NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Andexanet alfa for reversing anticoagulation [ID1101]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Andexanet alfa for reversing anticoagulation [ID1101]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from Portola Pharmaceuticals

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. British Society of Gastroenterology
   b. Royal College of Pathologists and British Society for Haematology
   c. Thrombosis UK

4. **Expert personal perspectives** from:
   a. Dr Deepa Jayakody Arachchillage, Consultant Haematologist & Honorary Senior Lecturer – clinical expert, nominated by the Royal College of Pathologists and British Society for Haematology
   b. Dr Andrew Veitch, Consultant Gastroenterologist, nominated by British Society of Gastroenterology
   c. Dr Elizabeth Warburton, Professor of Stroke Medicine nominated by British Association of Stroke Physicians

5. **Evidence Review Group report** prepared by BMJ-TAG

6. **Evidence Review Group report – factual accuracy check**

7. **Technical report**

8. **Technical engagement response from company**

9. **Technical engagement responses from experts:**
   a. Dr Deepa Jayakody Arachchillage – clinical expert, nominated by Royal College of Pathologists/British Society for Haematology
   b. Dr Elizabeth Warburton – clinical expert, nominated by British Association of Stroke Physicians

10. **Technical engagement responses from consultees and commentators:**
    a. British Society for Gastroenterology
    b. Thrombosis UK

11. Evidence Review Group critique of company response to technical engagement prepared by BMJ-TAG

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Andexanet alfa for reversing anticoagulation [ID1101]

Document B

Company evidence submission

23 September 2019

File name	Version	Contains confidential information	Date
ID1101 Andexanet Company Evidence Submission Document B [ACIC] 23 Sept 2019	**FINAL**	**Yes**	**23 September 2019**

Contents

Tables and figures

Abbreviations

3F-PCC	Three factor prothrombin complex concentrate
4F-PCC	Four factor prothrombin complex concentrate
ACC	American College of Cardiology
ACCP	American College of Chest Physicians
ACS	American College of Surgeons
ACT	Activated clotting time
AESI	Adverse Event of Special Interest
AF	Atrial fibrillation
AHA	American Heart Association
ALT	Alanine aminotransferase
ANNEXA	Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of FXa Inhibitors
ANNEXA-A	Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of FXa Inhibitors - Apixaban
ANNEXA-R	Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of FXa Inhibitors - Rivaroxaban
ANNEXA-4	Prospective, Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Have Acute Major Bleeding (apixaban, rivaroxaban, edoxaban, or enoxaparin)
aPCC	Activated prothrombin complex concentrate
aPTT	Activated partial thromboplastin time
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
AST	Aspartate aminotransferase
ATIII	Antithrombin

AUC	Area-under-the-curve
BLA	Biologics License Application
BMC	Below measurement capacity
BNF	British National Formulary
CC Score	Casemix companion score
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL	Clearance
Cmax	Maximum concentration
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CT	Computed tomography
dL	Decilitre
DOAC	Direct oral anticoagulant
DRG	Diagnosis-Related Group
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECH	Extracranial haemorrhage
EHRA	European Heart Rhythm Association
EMA	European Medicines Agency
ENGAGE AF-TIMI 48	Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48
EOB	End of bolus
EOI	End of infusion
EQ-5D	EuroQol 5 Dimension
ESC	European Society of Cardiology
ESO	European Stroke Organisation
ETP	Endogenous thrombin potential
EU	European Union
F1+2	Prothrombin fragments 1 and 2
FDA	(United States) Food and Drug Administration
FEIBA	Factor VIII Inhibitor Bypassing Activity
FFP	Fresh frozen plasma
FVII	Factor VII
FVIII	Factor VIII
FVIIa	Factor VIIa
FX	Factor X
FXa (anti-fXa)	Factor Xa (anti-factor Xa)
g	Gram

GCS	Glasgow Coma Scale
GI	Gastrointestinal
GIHP-NACO	Gestes Invasifs et Hémorragies chez les Patients Traités par les Nouveaux Anticoagulants Oraux
Hb	Haemoglobin
HR	Hazard ratio
hr	Hour
HRQOL	Health-related quality of life
HRT	Hormone replacement therapy
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
ICH	Intracranial haemorrhage
INMB	Incremental net monetary benefit
INR	International normalized ratio
ISTH	International Society on Thrombosis and Haemostasis
IU	International unit
IV	Intravenous
kg	Kilogram
L	Litre
LMWH	Low-molecular weight heparin
LOS	Length of stay
LYG	Life years gained
m	Metre
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Myocardial infarction
MIMS	Monthly Index of Medical Specialities
min	Minute
mL	Millilitre
mmHg	Millimetre of mercury
mmol	Millimoles
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
N/A	Not applicable
NE	North east
ng	Nanogram
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHSS	National Institutes of Health Stroke Scale
nM	Nanometre
NMB	Net monetary benefit

NOAC	Non–vitamin K antagonist oral anticoagulants
NR	Not reported
NSAID	Non-steroidal anti-inflammatory drugs
ONS	Office for National statistics
OR	Odds ratio
ORANGE	Oral Anticoagulant agent-associated bleeding events reporting system
OWSA	One-way sensitivity analysis
PCC	Prothrombin complex concentrate
PD	Pharmacodynamics
PE	Pulmonary embolism
P-gp	P-glycoprotein
PICOS	Population, interventions, comparators, outcomes and study type
PK	Pharmacokinetic
PRBCs	Packed red blood cells
PSA	Probabilistic sensitivity analysis
PSS	Prescribed Specialised Services
PSSRU	Personal Social Services Resource Use
PT	Prothrombin time
PT	Preferred term
QALY	Quality adjusted life year
RASUNOA	Registry of Acute Stroke Under New Oral Anticoagulants
RBC	Red blood cell
RCT	Randomised controlled trial
rFVIIa	Recombinant factor VIIa
ROC	Receiver operating characteristic
ROCKET-AF	Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SOC	System Organ Classification
SSC	Subcommittee on Control of Anticoagulation
STA	Single Technology Appraisal
TA	Technology Appraisal
TE	Thrombotic Event
TEAE	Treatment emergent adverse event
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor

THSNA	Thrombosis and Hemostasis Society of North America
TXA	Tranexamic acid
UK	United Kingdom
ULN	Upper limit of normal
UPRATE	Unactivated Prothrombin complex concentrates for the Reversal of Anti-factor TEn inhibitors
US	United States
USD	United States Dollars
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults requiring urgent reversal of anticoagulation in case of uncontrolled or life-threatening bleeding, after treatment with a factor Xa-inhibiting direct oral anticoagulant (DOAC)	Adults requiring urgent reversal of anticoagulation in case of uncontrolled or life-threatening bleeding, after treatment with a factor Xa-inhibiting DOAC	N/A
Intervention	Andexanet alfa	Andexanet alfa	N/A
Comparator(s)	Established clinical management of uncontrolled or life-threatening bleeding without andexanet alfa (including prothrombin complex concentrate with or without tranexamic acid)	Established clinical management of uncontrolled or life-threatening bleeding without andexanet alfa (including prothrombin complex concentrate with or without tranexamic acid)	N/A
Outcomes	The outcome measures to be considered include: • Requirement for blood products • Control of bleeding • Need for surgical control of bleeding or interventional radiology embolisation of bleeding vessel	The outcome measures presented are: • Requirement for blood products • Control of bleeding • Neurological outcomes (in people with intracranial bleeding) • Hospital stay • Mortality	The following outcome for ANNEXA-4 was not pre-specified and analyses are not yet available: • Need for surgical control of bleeding or interventional radiology embolisation of bleeding vessel The following pharmacodynamic outcomes are key in demonstrating the reversal of anticoagulation: • Anti-fXa activity, unbound anticoagulant plasma levels and thrombin generation

	• Neurological outcomes (in people with intracranial bleeding) • Hospital stay • Mortality • Adverse effects of treatment (including thrombotic events) • Health-related quality of life.	• Adverse effects of treatment (including thrombotic events) • Health-related quality of life • Reversal of anticoagulation effect as measured by anti-fXa activity, unbound anticoagulant plasma levels and thrombin generation	
Subgroups to be considered	If the evidence allows consideration will be given to subgroups with intracranial bleeding.	Evidence has been presented for the subgroup of patients with intracranial bleeding Evidence is also presented for patients with either ICH or gastrointestinal (GI) bleeding	ICH and GI bleeding events are frequent forms of FXa inhibitor-related bleeding, are life-threatening and are associated with significant morbidity. In addition to the high unmet need in these patients, the clinical benefit is more readily measured by objective clinical outcome measures, including outcomes utilised in the economic modelling.

B.1.2 Description of the technology being appraised

In appendix C include the summary of product characteristics or information for use, and the European public assessment report, scientific discussion or drafts.

Table 2. Technology being appraised

UK approved name and brand name	Ondexxya® (Andexanet alfa)
Mechanism of action	Andexanet alfa is a specific reversal agent for FXa inhibitors. The predominant mechanism of action is the binding and sequestration of the FXa inhibitor, although there may be a minor contribution from the inhibition of tissue factor pathway inhibitor (TFPI) activity through binding to TFPI. The interaction between andexanet alfa and TFPI has not been fully characterized. Andexanet alfa binds direct FXa inhibitors with high affinity, making them unavailable to exert their anticoagulant effects.[1]
Marketing authorisation/CE mark status	On 28 February 2019, the Committee for Medicinal Products for Human Use (CHMP) adopted a unanimous positive opinion, recommending the granting of a conditional marketing authorisation for andexanet alfa. On 26 April 2019 the European Commission granted conditional Marketing Authorisation.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The full indication is: For adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
Method of administration and dosage	Andexanet alfa is given intravenously. There are two dosing regimens: • Low dose: initial IV bolus 400 mg at a target rate of 30 mg/min, followed by a continuous IV infusion of 4 mg/min for 120 mins (480 mg)

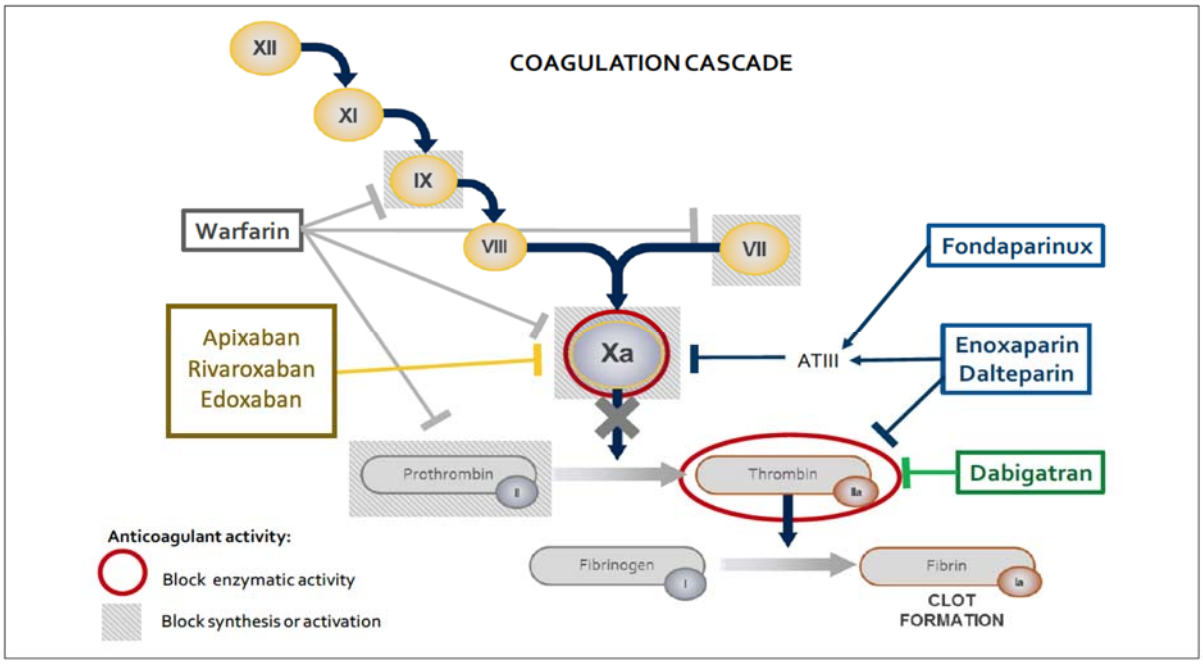
<table>
<tr><td></td><td>
High dose: initial IV bolus 800 mg at a target rate of 30 mg/min, followed by a continuous IV infusion of 8 mg/min for 120 mins (960 mg)
The recommended dosing of andexanet alfa is based on the specific FXa inhibitor (rivaroxaban or apixaban), dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor:
<table>
<tr><th>FXa Inhibitor</th><th>FXa Inhibitor Last Dose</th><th>< 8 Hours or Unknown</th><th>≥ 8 Hours</th></tr>
<tr><td>Rivaroxaban</td><td>≤ 10 mg</td><td>Low Dose</td><td rowspan="4">Low Dose</td></tr>
<tr><td>Rivaroxaban</td><td>> 10 mg/ unknown</td><td>High dose</td></tr>
<tr><td>Apixaban</td><td>≤ 5 mg</td><td>Low Dose</td></tr>
<tr><td>Apixaban</td><td>> 5 mg/ unknown</td><td>High dose</td></tr>
</table>
</td></tr>
<tr><td>Additional tests or investigations</td><td>None</td></tr>
<tr><td>List price and average cost of a course of treatment</td><td>Andexanet is a one-off treatment.
The list price is £11,100, for four 200 mg vials.
The average cost per course of treatment is £15,081.52 based on the proportion receiving each low and high dose with wastage.</td></tr>
<tr><td>Patient access scheme (if applicable)</td><td>None</td></tr>
</table>

B.1.3 Health condition and position of the technology in the treatment pathway

B1.3.1 Anticoagulants

Anticoagulants reduce the risk of clot formation in patients with underlying thrombotic conditions. Patients at high risk for thrombotic events, including those with atrial fibrillation (AF) or venous thromboembolism (VTE), generally receive long-term oral anticoagulation treatment to prevent thrombotic events. There are several classes of oral anticoagulation treatment. Warfarin is a vitamin K antagonist. The direct oral anticoagulants (DOACs), are a newer class of anticoagulants and include oral direct FXa inhibitors (rivaroxaban, apixaban and edoxaban) and direct thrombin inhibitors (dabigatran). Direct FXa inhibitors selectively block the active site of FXa, which plays a central role in the cascade of blood coagulation (Figure 1) and is the primary site of amplification in the coagulation cascade, where one molecule of FXa can facilitate the generation of more than 1,000 thrombin molecules.[2] Direct FXa inhibitors are used for the prevention of stroke in patients with nonvalvular AF, acute treatment and secondary long-term prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE), for patients at risk of venous thrombosis after orthopaedic surgery and for the prevention of atherothrombotic events in patients with acute coronary syndrome, coronary artery disease or symptomatic peripheral artery disease.[3-5]

Figure 1. Sites of Action for Anticoagulants



ATIII – antithrombin

B1.3.2 Risk and type of bleeding events

A serious risk associated with any anticoagulant treatment is the occurrence of unanticipated, serious bleeding episodes which may occur spontaneously or as a result of trauma,

complications from invasive procedures, or other illnesses or conditions. Although relatively rare, these events can be serious and life-threatening. The presence of anticoagulants may exacerbate the bleeding episode and complicate the treatment of these patients with bleeds (e.g., delays in urgent surgery).

Rapid assessment and initiation of the appropriate protocol is essential in the management of haemorrhage. While blood loss may sometimes be obvious, neither visual estimation nor physiological parameters are satisfactory guides to estimate the degree of bleeding. For trauma patients, knowledge about the mechanism of injury provides useful information to identify patients at risk of significant haemorrhage at an early stage, for example critical mechanisms such as a falling height above 6 metres, high-energy deceleration impact as well as penetrating injuries. The shock index, defined as the ratio of heart rate to systolic blood pressure, is advocated in recent guidelines by the European Task Force for Advanced Bleeding Care in Trauma to better risk-stratify patients for critical bleeding, increased transfusion requirements and early mortality.[6] The guidelines also cite the American College of Surgeons (ACS) Advanced Trauma Life Support classification system of blood loss as being useful as a rough estimation of sustained blood loss in patients with haemorrhagic shock.[7]

The International Society on Thrombosis and Haemostasis (ISTH) has published a recommendation for a harmonised definition of major bleeding in non-surgical studies (Table 3). This definition has been adopted by several regulatory agencies and is currently used widely in many trials.

Table 3. ISTH Major Bleeding Definition

Major bleed is defined as any one of the following:		
Haemoglobin	**Bleed site**	**Transfusion**
Drop of > 2g/dL	• Bleeding is expected to be fatal and/or • Symptomatic bleeding that is: – intracranial – intraspinal – intraocular – pericardial – intra-articular – intramuscular with compartment syndrome – retroperitoneal	> 2 units of blood or packed red blood cells

ISTH – International Society for Thrombosis and Haemostasis Source: Schulman et al, 2005[8]

Bleeding events constitute a complication of treatment with FXa inhibitors and are associated with significant morbidity and mortality. Data from clinical trials and real-world analyses have consistently shown major bleeding in approximately 2% to 4% of AF patients treated with FXa inhibitors.[9-13] In the Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) study, major bleeding associated with rivaroxaban was most frequently located in the upper GI tract (38%), and were less commonly intracranial (13%) and intraocular or retinal (4%).[12] This finding has been corroborated by other studies, which have shown that 30% to 50% of major bleeds occur in the GI, and 10% to 25% of major bleeding events are ICHs.[10-12,14,15] The risk of bleeding may vary among anticoagulants although, in general,

studies report lower rates of ICH with DOACs compared with warfarin; in a meta-analysis of RCTs in patients with AF the risk of ICH was 50% lower with DOACs.[16]

B1.3.3 Burden of major bleeding events

Patients on a FXa inhibitor, who experience a major bleeding event are at an increased risk of death and an increased risk of developing subsequent thrombotic events.[15] Thirty-day mortality rates are approximately 15% to 20% in FXa inhibitor-treated patients with AF who have a major bleeding event (Table 4). These risks are especially elevated in patients with ICH, where 30-day mortality rates after major bleeding are reported to be up to 45%.[15] Most recently, a large study that included 4918 patients with intracerebral haemorrhage who had received treatment with a DOAC reported an in-hospital mortality rate of 26.5%.[17]

Table 4. 30-day mortality rates after direct FXa inhibitor-associated major bleeding

	Rate of mortality at 30 days		Reference Source
	Patients with major bleeding	Patients who experienced an ICH	
ARISTOTLE clinical trial	15%	45%	Held et al, 2015[15]
ROCKET-AF clinical trial	20%[a]	43%	Piccini et al, 2014[18]; Hankey et al, 2014[19]
ORANGE observational study	21%	NR (33% overall including warfarin-related bleeds)	Green et al, 2018[20]

ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ORANGE: ORal ANticoagulant aGEnt-associated bleeding events reporting system; ROCKET-AF: Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
a Median time to all-cause death 60 days
NR, not reported

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial (N=18,201), the rate of mortality after major bleeding was about 15%.[15] The risk of 30-day mortality was substantially higher in patients with ICH, as 45% of patients treated with apixaban who experienced an ICH died within 30 days of the bleeding event. This corresponded to a 122-fold elevation in the risk of death during the 30 days following ICH compared with patients without a major bleed. Among patients with non-ICH major bleeding, 9% of those treated with apixaban died within 30 days of the bleeding event. This corresponded to a 12-fold elevation in the risk of death during the 30 days following major non-ICH bleeding compared with patients without major bleeding.

In the ROCKET-AF trial (N=14,264), among rivaroxaban-treated patients who experienced a major bleed, the rate of all-cause death for patients was 20%.[18] Among all patients with ICH, 43% did not survive the first 30 days after the bleeding event.[19]

Real-world observational studies have also shown high rates of bleeding-related mortality in patients being treated with direct FXa inhibitors. The UK study ORANGE (ORal ANticoagulant aGEnt-associated bleeding events reporting system) was a 3-year, prospective cohort study that collected information from multiple UK hospitals on the presentation and clinical outcomes of patients who were admitted for a major bleeding episode while on oral anticoagulant therapy.[20] The study included 2,192 patients, 372 of which were on a FXa inhibitor. The

mortality rate up to 30 days of follow up was 21% overall, and among DOAC treated patients (see Section 2.9.1).

Gastrointestinal bleeding also carries a risk of substantial morbidity and mortality. Among patients admitted to hospital with acute upper GI bleeding in the UK in 2007, the overall in-hospital mortality rate was 10%.[21] For lower GI bleeding in-hospital mortality has been reported at 3.4%, rising to 18% in patients who develop bleeding while already hospitalised, and 20% in patients with transfusion requirements of ≥4 units of red cells.[22] These studies included all patients with lower/upper GI bleeding, irrespective of severity, and the mortality rate is therefore expected to be higher in those with major bleeding events. However, it should be noted that the in-hospital mortality rate related to major GI bleeds in patients receiving DOAC therapy is reported to be lower than that with those in patients receiving Vitamin K antagonist or antiplatelet therapy.[23]

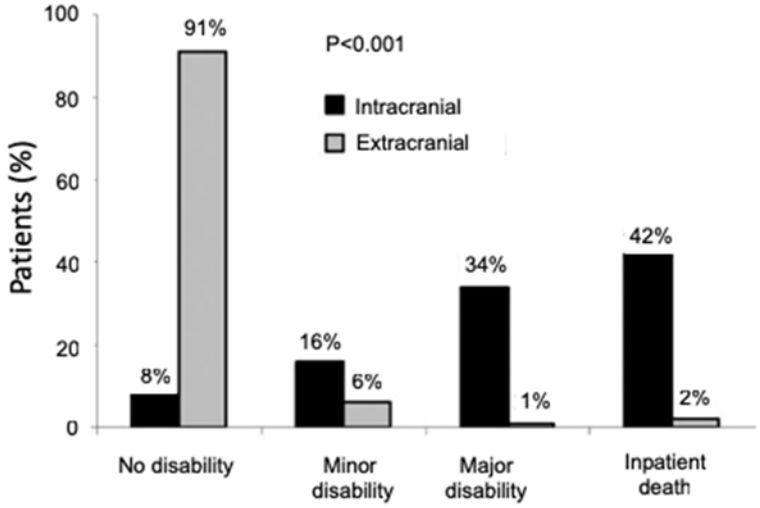
Data from clinical trials and real-world studies show that patients with major bleeding are also at increased risk of developing subsequent thrombotic events due to a procoagulant state and interruption of anticoagulation following a bleed.[14,15,18,24,25] Therefore, it is important to ensure timely reinstatement of anticoagulation in these patients.

Major bleeding events have a significant impact on health-related quality of life (HRQOL). Among edoxaban-treated patients with AF in the ENGAGE AF-TIMI 48 trial, all categories of bleeding events were associated with negative impacts on health-state utility as measured by the EuroQol 5 Dimension (EQ-5D) questionnaire.[26] The major bleeding events were associated with largest negative impacts in utility scores and relatively large immediate decreases that gradually diminished over 12 months.[26]

In addition to the high mortality risk, ICH may also result in severe disability. In the intracerebral haemorrhage substudy of the Registry of Acute Stroke Under New Oral Anticoagulants (RASUNOA), a prospective multicentre observational study, 65% (28 of 43) of the survivors had an unfavourable outcome at 3-month follow-up (mRS, 3-5, i.e. moderate to severe disability).[27] Fang et al (2007[28]) conducted an assessment of disability in warfarin-treated patients with AF. Functional disability was determined from a review of documentation from physician, nursing, physical/occupational therapy, and social work services, which was then categorised using a modified Rankin scale (mRS). The categories included fatal inpatient event, major disability (i.e., deficit that prevented independent living), minor disability (i.e., residual deficit that did not interfere with independent living), and no disability. This assessment of functional disability has been strongly associated with subsequent death within 30 days in patients admitted with AF-associated ischaemic stroke. Among patients with nonvalvular AF hospitalised for warfarin-associated intracranial and major extracranial haemorrhage, patients with ICH had far more severe functional deficits than did patients with major extracranial haemorrhage (Figure 2).[28] Among the 129 survivors at the time of discharge, 21 patients (61%) with ICH had major functional disability compared with only 1 patient (1%) with a major extracranial haemorrhage ($p < 0.001$). A more recent study has investigated functional outcome and predictors of severe disability or death following spontaneous ICH (N=452).[29] Median mRS score before the ICH was 1 (i.e. no significant disability). Among 275 survivors at 3 months, 52 (18.9%) were severe disabled (mRS 5), and

at 12 months, 12 (4.8%) had mRS 5. Prior to the ICH, 314 (69.5%) of the patients lived at home. Three months later, only 83 (26.4%) of these continued living at home.[29]

Figure 2. Functional Deficit from Warfarin-Associated Intracranial Haemorrhage vs Major Extracranial Haemorrhage in Patients with Atrial Fibrillation



Source: Adapted from Fang et al, 2007[28]

The need for an urgent reversal agent for FXa inhibitors in the setting of life-threatening bleeding events is a well-recognised, critical unmet medical need, particularly given that FXa inhibitors are being preferentially adopted over warfarin, so the number of bleeds associated with FXa inhibitors has been increasing over time.[30,31]

B1.3.4 Clinical pathway of care

Other than andexanet alfa, no other reversal agent is approved to reverse the anticoagulant effects of direct FXa inhibitors (Table 5).

Table 5. Anticoagulants and Their Reversal Agents

	Name	Mechanism of action	Approved reversal agent
DOAC	Rivaroxaban	Direct FXa inhibitor	Andexanet alfa
	Apixaban	Direct FXa inhibitor	Andexanet alfa
	Edoxaban	Direct FXa inhibitor	None
	Dabigatran	Direct FIIa (thrombin) inhibitor	Idarucizumab (Praxbind®)
LMWH	Enoxaparin	Indirect FXa inhibitor	Protamine (*partial reversal*)
	Dalteparin	Indirect FXa inhibitor	Protamine (*partial reversal*)
Others	Fondaparinux	Indirect FXa inhibitor	None
	Warfarin	Vitamin K antagonist	Vitamin K, PCC

DOAC – direct oral anticoagulant; LMWH – low molecular weight heparin; PCC – prothrombin complex concentrate

The current management of major bleeding due to anticoagulation with FXa inhibitors is primarily supportive and includes activated charcoal, fresh frozen plasma, and/or pro-haemostatic agents.[32] Fresh frozen plasmas containing normal levels of all coagulation factors have practical constraints for the rapid reversal of DOACs.[32] The lack of a specific reversal agent for FXa inhibitors has led to the off-label use of prothrombin complex concentrate (PCC) as a pro-haemostatic agent in some cases, to provide coagulation factors to bleeding patients

receiving FXa inhibitors, although there are several limitations to their use in reversing the anticoagulation effects of FXa inhibitors, as discussed below. PCCs are available as (1) non-activated three-factor PCCs (3F-PCC); (2) non-activated four-factor PCCs (4F-PCC) and (3) activated 4F-PCC (FEIBA®; Factor VIII Inhibitor Bypassing Activity)(Table 6). However, 3F-PCC is not generally used for this indication, and FEIBA is used very rarely. Although use of off-label recombinant factor VIIa (rFVIIa) is a potential option when other measures have failed, it is also used very rarely in clinical practice in the UK.[32,33]

Table 6. Pro-haemostatic agents

Pro-haemostatic agent	Components
4F-PCC (Beriplex®)	Heparin, factors II, VII, IX, X, proteins C and S, antithrombin III, and human albumin
4F-PCC (Octaplex®)	Factors II, VII, IX, X, proteins C and S
Activated 4F-PCC (FEIBA®)	Factors II, IX and X and activated FVII
rFVIIa (NovoSeven®)	FVIIa

PCCs were used as bypassing agents for bleeding episodes in inhibitor positive haemophilia patients, and then specifically developed for the reversal of acquired coagulation factor deficiency induced by vitamin K antagonists (VKAs). PCCs contain highly concentrated plasma-derived coagulation factors to replenish those that are missing in haemophilia or warfarin-treated patients in order to support clot formation.[34] These factors are all upstream of FXa and coagulation may remain suppressed in the presence of FXa inhibitors. FEIBA, containing factors II, IX and X and activated FVII was developed for use in haemophilia patients with Factor VIII inhibitors[35]. Another 4F- PCC (Beriplex®), containing heparin, factors II, VII, IX, X, proteins C and S, antithrombin III, and human albumin[36], was specifically developed and approved to reverse the effects of warfarin by replacing the depleted vitamin K-dependent coagulation factors. PCCs were developed for non-specific supplementation of coagulation factors; therefore, the mechanism of action of PCCs was not designed to reverse FXa inhibitors. Furthermore, evidence is lacking even for their licensed indication for management of vitamin K antagonist bleeding. In a Cochrane review of PCC for the reversal of vitamin K antagonist treatment, PCC was not found to reduce mortality compared to fresh frozen plasma, and no differences in blood loss were detected. All studies were of low quality, small population size and very heterogeneous.[37]

Recent evidence from an in vitro spike-in study showed that 4F-PCC (up to 1.0 IU/mL, equivalent to 50U/kg high dose) had no apparent reversal activity when the inhibitor (rivaroxaban or apixaban) concentration was greater than 75 ng/mL, as measured by correction of inhibition of thrombin generation to baseline levels. Endogenous thrombin potential (ETP) increased only when the FXa inhibitor concentration was sufficiently low (≤ 37.5 ng/mL, < 30% inhibition of ETP). This indicates that thrombin generation at presumably therapeutic levels of FXa inhibitors was limited by the level of active FXa, which limits the contribution of 4F-PCC to restoration of normal thrombin generation.[38]

There is a lack of robust clinical evidence on the efficacy of PCCs to reverse anticoagulation effects of FXa inhibitors.[39] PCCs have been studied in healthy subjects and in animal models in an attempt to demonstrate efficacy to reduce the anticoagulant effects of FXa inhibitors. Efficacy results from these studies in healthy subjects show that PCCs do not reverse anti-fXa

activity or affect unbound concentration of edoxaban, rivaroxaban, or apixaban.[40-43] In addition, PCC effects as assessed by other pharmacodynamic (PD) markers (e.g., PT, aPTT, thrombin generation) or reduced blood loss, have been largely inconsistent.[40-49] PCC studies have shown sustained elevation in PD markers for 1 to 2 days after the FXa inhibitors have cleared reflecting the half-lives of the various factors present in PCCs. The safety consequences of this prolonged pro-thrombotic state are unknown.

The majority of studies investigating the effectiveness of PCCs for reversal of FXa-inhibitor bleeding are retrospective, single-centre studies (see Appendix D). Two prospective observational cohort studies were recently published evaluating the effectiveness of PCCs in FXa inhibitor-related bleeding.[50,51] Although some of these studies concluded that PCCs may have a beneficial effect on FXa inhibitor-related bleeding, the findings are confounded due to the lack of rigorously adjudicated outcomes and because the level of FXa inhibitor present in the patients included in these studies was unknown, and in some cases likely to be very low. Furthermore, optimal dosing strategies are not known, unlike in the case of warfarin bleeds where dosing is based on knowledge of level of anticoagulation (e.g. INR). Of the 108 patients that received PCC in the ORANGE study, there was considerable variation in weight for selected fixed PCC doses.[52] Further observational studies have reported on outcomes in patients with DOAC-related major bleeding, although it should be noted that these studies generally also include patients who had received dabigatran. In the ORANGE study, that included use of 4F-PCC in 38% of patients being treated in UK hospitals for a DOAC-related bleed; the use of 4F-PCC was not predictive of the cumulative risk of death.[52] In the intra-cerebral haemorrhage substudy of RASUNOA, administration of 4F-PCC had no statistically significant effect on the early haematoma expansion (43% [12 of 28] for PCC vs 29% [5 of 17] for no PCC [p = 0.53]) or the functional outcome at 3 months.[27] The authors state that the finding may have been due to more severe haematoma in the PCC group at baseline. The GIHP-NACO registry (NCT02185027) (Gestes Invasifs et Hémorragies chez les Patients Traités par les Nouveaux Anticoagulants Oraux) is a large, prospective, multicentre registry that enrolled patients treated with a DOAC and hospitalised for spontaneous or posttraumatic bleeding or who needed urgent invasive procedures in France and Belgium. This study was not designed to address the haemostatic efficacy of PCC in specific bleeding sites, which was only assessed subjectively by local investigators.[53]

A recent meta-analysis has evaluated the safety and effectiveness of 4F-PCC for managing direct FXa inhibitor–related major bleeding.[54] Ten case series with 340 patients were included. Based on 2 studies (Majeed et al, 2017[50] and Schulman et al 2018,[51] discussed above) that used the ISTH criteria for effective bleeding management,[55] 69% of patients achieved successful bleeding management using 4F-PCCs. In a crude pooled mortality analysis that included 9 studies, 16% of patients died during the specified follow-up period (between 9 and 180 days across the studies included). On the basis of the evidence the authors were unable to conclude whether 4F-PCC was more effective than cessation on FXa-inhibitor alone.[54]

The activity of PCCs on thrombin generation is not rapid and varies among studies. The increase in thrombin generation to baseline with PCCs can be variable and may take more than 4 hours.[41,44-46,49] Some phase 1 randomised studies evaluating the reversal of rivaroxaban and edoxaban with the use of PCCs in healthy subjects showed that 4F-PCC did not rapidly

correct thrombin generation. Furthermore, due to the half-life mismatch between FXa inhibitors (7-12 hours) and PCCs (6-72 hours for the different factors), the effects of PCCs persist for days after the Xa inhibitors have cleared.[41,49]

Finally, PCCs have a risk for pro-thrombotic effects. This may potentially, to some extent, be due to the fact that when thrombin generation is returned to baseline due to clearance of FXa inhibitor, PCCs cause a sustained excess in thrombin generation for 24 to 72 hours.[41,49,56] The use of PCCs has been associated with thrombotic complications including VTE, disseminated intravascular coagulation, microvascular thrombosis, and myocardial infarction (MI).[57] The increase of thromboembolic events associated with the use of rFVIIa may be even higher.[32]

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that acts as an inhibitor of fibrinolysis by blocking the lysine binding sites on plasminogen molecules and inhibiting the formation of plasmin. TXA has been shown to reduce the need for a blood transfusion in adult patients undergoing surgery[58,59] and to reduce mortality in trauma patients who were bleeding or at risk of significant bleeding,[60] and is recommended in the NICE trauma guideline for patients with major trauma and active or suspected active bleeding (regardless of use of anticoagulation).[61] The efficacy of TXA in reversal of DOAC related bleeding is unknown. In a recent study in healthy volunteers given rivaroxaban (20 mg twice daily for 3 days), TXA did not have an effect on thrombin generation or punch biopsy bleeding.[47] Current guidelines do not include TXA as a method of DOAC reversal in patients with major bleeding.

With no evidence to guide treatment decisions and no treatment alternatives, clinicians in the UK may utilise PCCs in an attempt to manage major bleeding in patients receiving FXa inhibitors. Data from the ORANGE study provide additional information on the use of agents of reversal of bleeding in the UK.[20,52] For the management of bleeding, those patients on DOACs were given any blood transfusion (41%), 4F-PCC (39%, including 1% who were administered FEIBA), tranexamic acid (28%).[52] 3F-PCC is not used in the UK, and rFVIIa is used very rarely.[33,62]

In this submission, treatment with PCC (i.e. 4F-PCC, excluding FEIBA), is considered to be the comparator for andexanet alfa.

Guidelines

Guidelines or guidance for the reversal of the anticoagulant effects of DOACs have been published by several societies/groups including the British Society of Gastroenterology,[22] British Committee for Standards in Haematology,[63] the European Stroke Organisation (ESO),[64] the European Heart Rhythm Association (EHRA),[65] the European Society of Cardiology (ESC) Working Groups on Cardiovascular Pharmacotherapy and Thrombosis,[32] the pan-European, multidisciplinary Task Force for Advanced Bleeding Care in Trauma,[6] the Neurocritical Care Society/Society of Critical Care Medicine,[66] the American Heart Association (AHA),[67] the American College of Cardiology (ACC) Task Force on Expert Consensus Decision Pathways[68] and related Guidance for Anticoagulation Reversal,[69] the ACC/AHA Task Force on Clinical Practice Guidelines and the Heart Rhythm Society[70], the Subcommittee on Control of Anticoagulation (SSC) of the ISTH,[71] the Thrombosis and Hemostasis Society of North America (THSNA),[72] the Anticoagulation Forum.[73] The majority of guidelines were published prior to the FDA and EMA-approval of andexanet alfa; thus, they do not include the

use of andexanet alfa for the reversal of FXa inhibitors. However, the updated 2018 EHRA guidelines recommend the use of andexanet alfa for FXa inhibitor-treated patients, pending approval and availability.[65] In addition, the recent ESO, ACC and Anticoagulation Forum guidance for anticoagulation reversal both recommend andexanet alfa as a first line agent, whilst PCC is recommended when andexanet alfa is not available.[64,69,73] Recently, the first UK national guideline on acute lower GI bleeding was published, and recommends andexanet alfa for life-threatening bleeding in those on a direct oral anticoagulant.[22] It is anticipated that new guidelines will recommend the use of andexanet alfa. ESO guidelines recommend against the use of TXA and rFVIIa to reverse oral anticoagulation in patients with intracerebral haemorrhage.[64]

The guidelines are generally consistent in recommending that reversal of anticoagulation be restricted to severe/life-threatening bleeding or therapeutically treated patients in need of an invasive procedure or emergency surgery. Current treatment recommendations for life-threatening/emergency situations are based on several approaches as described in Table 7.

Table 7. Treatment Recommendations for Urgent Reversal of DOACs

1) General supportive measures	• Discontinue the DOAC • Mechanical compression • Support measures (hemodynamic support, volume replacement, blood transfusion) • Maintain diuresis
2) Antagonising the anticoagulant effects	• Reducing anticoagulant absorption via haemodialysis (for dabigatran only) or oral activated charcoal • Specific reversal of anticoagulant activity, if available (andexanet alfa when available and approved) • Non-specific reversal of anticoagulant activity if a specific antidote is not available or sufficient (this may include PCCs and/or rFVIIa)

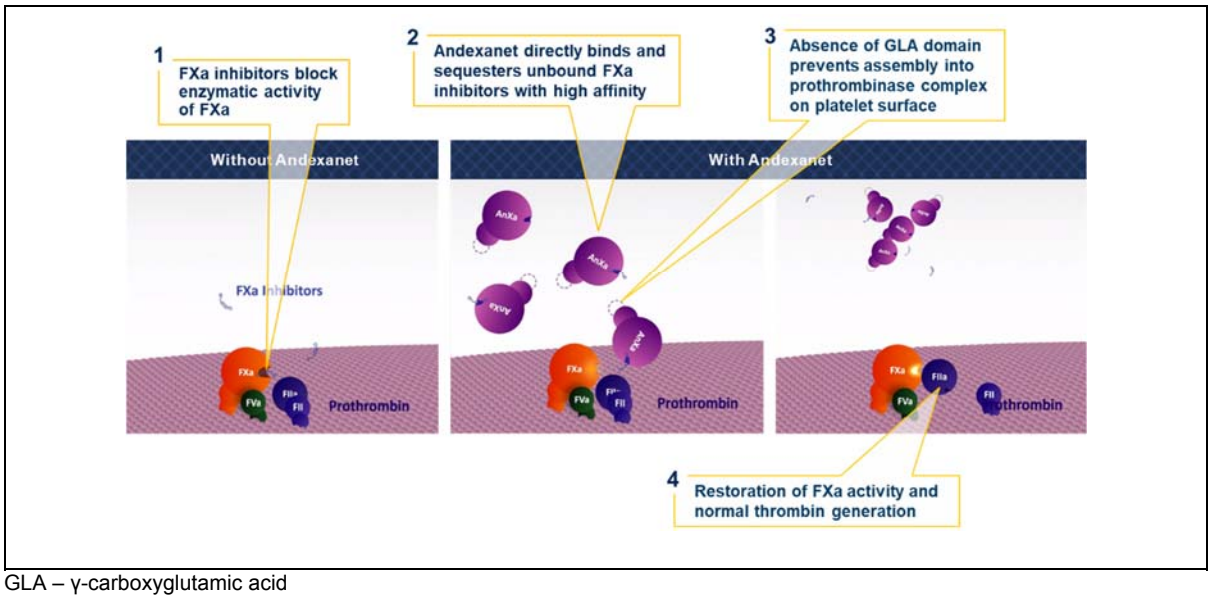
Source: Niessner, 2017[32], Steffel, 2018[65]; Makris, 2013[63]

The guidelines discuss the use of PCCs for FXa inhibitor-associated bleeding; however, they acknowledge the limited clinical evidence in this setting and recommend weighing the potential pro-thrombotic effects of PCCs against the potential benefits. Furthermore, these agents are not approved for the reversal of FXa inhibitors. The NICE trauma guideline only recommends PCC in patients with active bleeding that need emergency reversal of warfarin. The advice for adults who have active bleeding and need reversal of any anticoagulant agent other than a vitamin K antagonist is to consult a haematologist immediately.[61]

Andexanet alfa

Andexanet alfa is a recombinant modified human FXa protein that is catalytically inactive but rapidly binds and sequesters FXa inhibitors and reduces the concentration of the unbound (pharmacologically active) inhibitors, thereby neutralising the inhibitors' anticoagulant effects (Figure 3). This allows for the restoration of haemostasis via endogenous native FXa. Andexanet alfa is a specific reversal agent for the management of major FXa inhibitor-related bleeding and may address the existing significant unmet medical need.

Figure 3. Mechanism of Action of Andexanet Alfa for Direct FXa Inhibitors



GLA – γ-carboxyglutamic acid
Adapted from Yeh et al, 2013

Andexanet alfa is the only treatment approved in the EU for the reversal of the FXa inhibitors rivaroxaban and apixaban. In line with the licensed indication, the anticipated use of andexanet alfa is as a reversal agent for patients anticoagulated with the FXa inhibitors rivaroxaban or apixaban who experience a serious uncontrolled or life-threatening bleeding event.

For the purpose of this submission, the following definition for uncontrolled or life-threatening bleeding, aligned to the inclusion criteria in the ANNEXA-4 study,[74] is used:

- Life threatening bleeds (e.g. with signs or symptoms of haemodynamic compromise, such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise explained)
- Symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome
- Bleeding causing a fall in haemoglobin level of ≥ 20 g/L (2 g/dL or 1.24 mmol/L) OR a haemoglobin level ≤ 80 g/L if no baseline haemoglobin level is available OR in the opinion of the physician, the patient's haemoglobin will fall to ≤ 80 g/L with resuscitation OR leading to transfusion of two or more unit of whole blood or red cells

This broadly aligns with the International Society for Thrombosis and Haemostasis (ISTH) definition of major bleeding (Table 3).

All patients within the marketing authorisation for andexanet alfa are expected to benefit from treatment. However, there are two groups of patients that may derive greatest benefit:

1) Patients with GI bleeding: GI bleeding is the most frequent form of DOAC related major bleeding and also carries a substantial morbidity and mortality risk (see Section B1.3.3).

2) Patients with ICH: As defined in the scope for this assessment, evidence has been presented for the subgroup of patients with intracranial bleeding. Due to their anatomic location and spatial constraints, ICH bleeds have a markedly poor prognosis, even in relationship to other major bleeding events.[15] (see Section B1.3.3) Patients with ICH therefore have the greatest unmet medical need. Due to the high mortality rates in ICH patients, and since the evaluation of haemostatic efficacy in ICH patients is based on objective measures (CT/MRI measurements) this group of patients was proposed by the FDA as a group in which the treatment effect of andexanet alfa may be best determined. Accordingly, to more comprehensively evaluate the efficacy and safety of andexanet in this particularly vulnerable subset of bleeds, the ANNEXA-4 study population was enriched for ICH patients (See Section B2.3.1).

Studies report that 30% to 50% of major DOAC-related bleeds occur in the GI, and 10% to 25% of major bleeding events are ICHs.[10-12,14,15] Therefore these patients represent the majority of patients that are expected to be treated with andexanet alfa in practice. Due to the size of these groups, the high unmet need, and the ability to objectively measure outcomes in these patients, they represent key populations of interest. Therefore, this submission considers three populations:

1) The full population within the marketing authorisation: Patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.
3) Patients within the marketing authorisation who have either an ICH or GI bleed
4) Patients within the marketing authorisation who an ICH

B.1.4 Equality considerations

No issues have been identified regarding equality.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Please see appendix D for the literature search used to identify and select clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

Andexanet alfa studies

The efficacy and safety of andexanet alfa has been evaluated in multiple preclinical animal models, phase 1, 2 and 3 studies in healthy subjects, and a phase 3b/4 study in bleeding patients.

As a reversal agent, the evidence base for andexanet should be considered with the view that it acts as an antidote to FXa-inhibitors. In this respect, key evidence supporting regulatory approval of andexanet alfa was the overwhelming pharmacodynamic data, including evidence from randomised clinical trials (ANNEXA-A and ANNEXA-R), that support its mechanism of action and ability to rapidly reverse FXa-inhibitor anticoagulation, and formed the basis of the regulatory approval.

The ANNEXA-A and ANNEXA-R studies were not used to populate the economic model but are included in sections 2.2 to 2.6. These studies are the phase 3 randomised, placebo-controlled registration studies in healthy volunteers that provided key evidence supporting the Marketing Authorisation Application for andexanet alfa. The results, reported by Siegal et al (2015),[75] showed a rapid reduction in anti-fXa activity and unbound (pharmacologically active) inhibitor concentration within 2 to 5 minutes after administration of a bolus of andexanet alfa, and sustained reversal of anticoagulation during the 2-hour infusion of andexanet alfa. Based on the correlations between the risk of major bleeding and levels of both anti-fXa activity and unbound inhibitor concentrations, a reduction in these markers is expected to lead to clinical benefit. These studies were not included in the economic model because they only included healthy volunteers, whereas ANNEXA-4 included patients with acute major bleeding (reflecting the real world setting for this treatment).

Andexanet alfa also rapidly reversed the anticoagulant activity of FXa inhibitors in phase 2 studies in healthy subjects anticoagulated with apixaban, edoxaban, rivaroxaban, betrixaban, or enoxaparin.[76-81] Various concentrations of andexanet alfa administered as a bolus or bolus followed a 120-minute infusion (although some infusions were shorter) were investigated. Whilst these studies provide further supportive evidence for andexanet alfa, they were dose-ranging studies that did not include the licensed dose of andexanet alfa for reversal of rivaroxaban or apixaban anticoagulation and have not been presented in this submission.

The key study that provides clinical outcome data that is utilised in the economic model is ANNEXA-4, a phase 3b/4, open-label, single-arm study. ANNEXA-4 was designed to evaluate the efficacy and safety of andexanet alfa in patients receiving a FXa inhibitor (apixaban, rivaroxaban, edoxaban, or enoxaparin) who present with acute major bleeding.

Prior to the publication of the full study results,[74] two preliminary reports provided safety and efficacy data. Results from the first preliminary report by Connolly et al (2016) were published in New England Journal of Medicine (N = 67).[82] Subsequent to the first preliminary report, updated safety findings were published in response to a letter to the editor.[83] The second preliminary report included 227 patients and was presented at the American College of Cardiology Scientific Session in March 2018.[84] The full analysis included 352 patients; results were published in the New England Journal of Medicine by Connolly et al (2019).[74]

It should be noted that ANNEXA-4 is still ongoing. The timing of additional data regarding the completed study will depend on the enrolment rate, but will be available in approximately 2021 or 2022.

Table 8. Clinical effectiveness evidence

Study	ANNEXA-A				
Study design	Phase 3, randomized, double-blind, placebo-controlled study				
Population	Healthy volunteers 50 to 75 years of age, who received apixaban (5 mg orally twice daily for 3.5 days)				
Intervention(s)	Andexanet alfa administered as a 400-mg intravenous bolus (30 mg per minute) (part 1) or as a 400-mg intravenous bolus followed by a continuous infusion of 4 mg per minute for 120 minutes (480 mg in total) (part 2)				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	*x*	**Indicate if trial used in the economic model**	Yes	
	No			No	*x*
Rationale for use/non-use in the model	This study was in healthy volunteers and does not provide outcome data that could be used in the economic model.				
Reported outcomes specified in the decision problem	• Adverse effects of treatment (including thrombotic events)				
All other reported outcomes	• Reversal of anticoagulation effect as measured by anti-fXa activity, unbound anticoagulant plasma levels and thrombin generation				

Study	ANNEXA-R				
Study design	Phase 3, randomized, double-blind, placebo-controlled study				
Population	Healthy volunteers 50 to 75 years of age, who received rivaroxaban (20 mg orally once daily - the highest approved dose - for 4 days).				
Intervention(s)	Andexanet alfa administered as an 800-mg intravenous bolus (30 mg per minute) (part 1) or as an 800-mg intravenous bolus followed by a continuous infusion of 8 mg per minute for 120 minutes (960 mg in total) (part 2)				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	*x*	**Indicate if trial used in the economic model**	Yes	
	No			No	*x*
Rationale for use/non-use in the model	This study was in healthy volunteers and does not provide outcome data that could be used in the economic model.				
Reported outcomes specified in the decision problem	• Adverse effects of treatment (including thrombotic events)				
All other reported outcomes	• Reversal of anticoagulation effect as measured by anti-fXa activity, unbound anticoagulant plasma levels and thrombin generation				

Study	ANNEXA-4				
Study design	Multicentre, prospective, open-label, single-group study				
Population	Adults (at least 18 years of age), who received apixaban, rivaroxaban, edoxaban, or enoxaparin within the past 18 hours, and experienced acute overt major bleeding requiring urgent anticoagulation reversal.				
Intervention(s)	Andexanet alfa				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	Yes	*x*	**Indicate if trial used in the economic model**	Yes	*x*
	No			No	
Rationale for use/non-use in the model	This study investigated andexanet alfa in the population to be treated as per the licensed indication, and includes key outcomes that are utilised in the economic model				
Reported outcomes specified in the decision problem (outcomes in bold are incorporated into the economic model)	• Control of bleeding – occurrence of effective haemostasis (co-primary efficacy outcome), haemostatic efficacy as measured by haematoma expansion in intracranial haemorrhage and re-bleeding • Requirement for blood products • **Neurological outcomes (in people with intracranial bleeding) – as measured by Modified Rankin Score,** Glasgow Coma Scale (GCS) and National Institutes of Health Stroke Scale (NIHSS) • **Hospital stay** • **Mortality** • Adverse effects of treatment (including thrombotic events)				
All other reported outcomes	• Percent change from baseline in anti–FXa activity (co-primary outcome) • Reversal of anticoagulation effect as measured by thrombin generation				

Comparator studies

The literature search identified 17 studies that investigated the use of PCC in patients receiving a Factor Xa inhibitor requiring rapid reversal of anticoagulation due to major bleeding (see Appendix D, Table 14). The studies identified were all relatively small: considering the relevant population (i.e. patients receiving apixaban or rivaroxaban), 5 studies included fewer than 20 patients, 6 included fewer than 50 patients and the remaining 6 studies included fewer than 100 patients. Other than one study (Arachchillage et al, 2018[85]), all were carried out in countries other than the UK. Twelve of the studies identified were retrospective in design. Four prospective studies were identified (Majeed et al 2017[50]; Schenk et al 2018[86]; Schulman et al 2018[51] and Yoshimura et al 2017[87]) and one study (Bayer-Westendorf et al, 2014[14]) was a review of a prospective registry. Study methodology and results of the 17 studies are shown in Appendix D, tables 14 to 16.

Seven of the studies did not provide outcome data comparable to ANNEXA-4 or were not relevant for this submission (see Appendix D, Table 16, for detailed reasons). In summary:

- One study (Mao et al, 2016[88]) investigated FEIBA (a 3-factor/activated PCC), which is not commonly used as a reversal agent in the UK.
- Two studies (Berger et al, 2016[89]; Beyer-Westendorf et al, 2014[14]) did not report clinical outcomes comparable to the data available to ANNEXA-4, or did not report comparable outcomes relating only to the licensed population for andexanet alfa.
- Two studies reported hospital length of stay (Stratman et al. 2015[91]; Kaplan et al, 2018[92]) but were only reported in an abstract with limited information on the severity of bleeds in the included patients.
- Two studies reported thrombotic events, but no other outcomes of interest (Schenk et al, 2018[86]; Tao et al, 2018[93]). The decision of when to restart anti-coagulation, and the choice of anticoagulant is based on clinical opinion on a case to case basis. Since the occurrence of thrombotic events is thought to be greatly influenced by the timing of restarting anticoagulation, as well as pre-existing co-morbidities, comparing the rate of events observed in patients receiving PCC and andexanet was not thought to be appropriate.

Ten studies therefore provided outcome data that could be compared to the ANNEXA-4 study, although, other than categorising for ICH and non-ICH bleeds, baseline differences in the study populations cannot be accounted for. The outcome data in the studies included hospital length of stay (reported in 5 studies), 30-day mortality (4 studies), in-hospital mortality (4 studies) and haemostatic efficacy (2 studies) (Appendix D, Table 16). A quality assessment of these studies is provided in Appendix D, Table 21.

It should be noted that there were substantial differences in the way that major bleeding and haemostatic efficacy were defined and evaluated in these studies. Whilst in the study by Majeed et al[50], assessment was performed independently by two coagulation specialists, in the study by Schulman et al[51], assessment of haemostasis was by the treating physician was not adjudicated for, therefore potentially introducing inconsistency and bias. Another key difference compared to the ANNEXA-4 study is that patients undergoing an interventional procedure were automatically categorized as poor/none in ANNEXA-4, whereas they were not in the studies by Majeed and Schulman. The remaining studies reporting on haemostatic efficacy were retrospective studies and did not include predefined or standardised adjudicated methods for assessment of haemostasis.

Whilst mortality data from the nine relevant studies identified in the SLR could possibly have been used to inform the economic modelling, these studies were relatively small, generally including patients treated at one or two centres in the USA. One study was conducted in hospitals in Sweden[50] and one in Canada[51]. The study by Arachchillage et al[85], whilst conducted in the UK, is also a smaller retrospective study carried out at one centre, that only included 80 patients that had been treated with rivaroxaban or apixaban. In addition, inclusion criteria were not well defined in this study and there were no criteria to define 'major bleeding event', with these patients being identified retrospectively.

The ORANGE study[20,52] (described in sections B1.3.3 and B2.9.1) was excluded from the literature review as the available study publications did not report outcomes separately for

patients treated with rivaroxaban or apixaban (i.e. the licensed indication for andexanet alfa). However, to our knowledge the ORANGE study is the largest prospective study reporting on haematological management and outcomes of DOAC-related bleeding, and 372 patients included in the study had experienced major bleeding whilst receiving rivaroxaban or apixaban therapy. Importantly, the study was conducted in the UK between October 2013 to August 2016, and therefore is representative of current clinical practice. Since it was possible to obtain patient level data from this study, it was considered the most robust source of data for the economic analysis.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. Study methodology

ANNEXA-A/ANNEXA-R

The ANNEXA-A and ANNEXA-R studies were randomized, double-blind, placebo-controlled studies designed to evaluate the safety and reversal of apixaban (ANNEXA-A) or rivaroxaban (ANNEXA-R) anticoagulation with andexanet alfa (Table 9).[75] The studies enrolled older (aged 50 to 75 years) healthy subjects who were in reasonably good health. The studies were conducted at two clinical sites in the US. A total of 101 participants across both studies were randomly assigned to receive andexanet alfa from March 2014 through May 2015.

The studies were both performed in two consecutive parts: part 1 examined andexanet alfa IV bolus alone, and part 2 studied IV bolus followed by a continuous 120-minute infusion. The primary endpoint was percent reduction in anti-fXa levels. In addition, the study evaluated reversal of FXa inhibitor anticoagulation based on reductions in unbound (pharmacologically active) inhibitor concentration, increase in thrombin generation to pre-anticoagulant levels, and changes in other coagulation markers.

Table 9. ANNEXA-A/ANNEXA-R Study Design

Study Acronym/ I.D.	**ANNEXA-A/ANNEXA-R**
Primary study reference	Siegal et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity (NEJM, 2015)
Trial design	Randomized, double-blind, placebo-controlled trials designed to demonstrate the ability of andexanet alfa to reverse apixaban-induced (ANNEXA-A) or rivaroxaban-induced (ANNEXA-R) anticoagulation and evaluate safety in older subjects (ages 50 through 75 years). The studies consisted of 2 consecutive parts, each of which evaluated a different dosing regimen of andexanet alfa: bolus only (Part 1) and bolus followed by a continuous infusion (Part 2). In both Parts 1 and 2 of the study, randomization was 2:1 andexanet alfa: placebo.
Participants (Key Inclusion criteria)	Healthy volunteers 50 to 75 years of age

	• Good health as determined by the Investigator based on medical history, full physical examination (including blood pressure) and pulse rate measurement), 12-lead electrocardiogram (ECG), and clinical laboratory tests. Subjects with well-controlled, chronic, stable conditions (e.g., controlled hypertension, noninsulin dependent diabetes, osteoarthritis, hypothyroidism) could be enrolled based on the clinical judgment of the Investigator and if approved by the Medical Monitor. • Systolic blood pressure <160 mmHg and diastolic blood pressure <92 mmHg at Screening and Day -1. • The following laboratory values must be within the normal laboratory reference range within 28 days of Day -1: o Prothrombin time (PT), activated partial thromboplastin time (aPTT), and ACT; o Haemoglobin, haematocrit, and platelet count. • The following laboratory values must be equal to or below 2 times the upper limit of normal (ULN) range within 28 days of Day -1: o Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) and total bilirubin. • The Screening serum creatinine must be ≥50 ml/min using the Cockcroft-Gault equation within 28 days of Day -1 and on Day -1. • The subject has a body mass index of 19 to 32 kg/m^2, inclusive, and weighs at least 60 kg.
Participants (Key Exclusion criteria)	• Previously received andexanet alfa or participated in the current study or other andexanet alfa study (even if the subject received placebo). • History of abnormal bleeding, signs or symptoms of active bleeding, or risk factors for bleeding. • Past or current medical history of thrombosis, any sign or symptom that suggests an increased risk of a systemic thrombotic condition or thrombotic event, or recent events that may increase risk of thrombosis. • Absolute or relative contraindication to anticoagulation or treatment with rivaroxaban/apixaban. • Received any anticoagulant within 7 days prior to Day -1 or is anticipated to require such drugs during the study. • Receiving (by any route) hormonal contraception, post-menopausal hormone replacement therapy, or testosterone during the 4 weeks prior to Study Day -1 or is anticipated to require such drugs during the study • Family history of or risk factors for a hypercoagulable or thrombotic condition • History of adult asthma or chronic obstructive pulmonary disease or current regular or as-needed use of inhaled medications. • Use of any drugs that are combined P-glycoprotein (P-gp) and strong CYP3A4 inhibitors or combined P-gp and strong CYP3A4 inducers within 7 days prior to Study Day -1 or anticipated need for such drugs during the study.
Settings and locations	The studies were conducted at 2 clinical sites in the US.
Trial drugs, n, dose, duration, timing	Prior to treatment with andexanet alfa, participants were treated with apixaban/rivaroxaban, as follows: • ANNEXA-A: Apixaban, 5 mg orally twice daily for 3.5 days to achieve steady-state plasma levels at the highest approved dose. • ANNEXA-R: Rivaroxaban, 20 mg of rivaroxaban orally once daily (the highest approved dose) for 4 days. <u>Study interventions:</u> The study was performed in two consecutive parts: part 1 examined IV andexanet alfa bolus alone, and part 2 studied IV bolus followed by a continuous 120-minute infusion.

	• ANNEXA-A: Andexanet alfa (400-mg intravenous bolus [30 mg/minute] or a 400-mg intravenous bolus followed by a continuous infusion of 4 mg per minute for 120 minutes [480 mg in total)], or placebo. Given three hours after the last dose of apixaban on day 4 (at or near the time of the highest plasma concentration). • ANNEXA-R: Andexanet alfa (800-mg intravenous bolus [30 mg per minute] or as an 800-mg intravenous bolus followed by a continuous infusion of 8 mg per minute for 120 minutes [960 mg in total]), or placebo. Given 4 hours after the last dose of rivaroxaban (at or near the maximum plasma concentration).
Concomitant medications	Anticoagulant, antiplatelet (including aspirin and NSAIDs), and prothrombotic drugs (i.e., hormonal contraceptives and HRTs) were avoided during the entire study (i.e., until the Study Termination Visit) unless absolutely indicated to treat an emergent or urgent medical situation. Other than the subject's chronic medications and standard multivitamin or mineral supplements that were ongoing prior to Screening, the use of any new prescription, OTC, or herbal medication or nutritional supplement through the domiciled portion of the study was prohibited unless required as treatment for an adverse event.
Primary efficacy outcomes	Percent change in anti–FXa activity, measured with the use of a validated chromogenic assay of FXa enzymatic activity, from baseline (before administration of andexanet alfa or placebo) to nadir (after administration of andexanet alfa or placebo). For part 1, the nadir was defined as the value of anti–FXa activity at 2 minutes or 5 minutes (whichever value was smaller) after the end of the bolus; for part 2, it was defined as the smallest value between 10 minutes before and 5 minutes after the end of the continuous infusion.
Secondary efficacy outcomes	• Proportion of participants with an 80% or greater reduction in anti–FXa activity from baseline to the nadir after administration of andexanet alfa or placebo • The change in unbound inhibitor plasma concentration from baseline to the nadir after administration of andexanet alfa or placebo • The change in thrombin generation, measured as the change in endogenous thrombin potential, from baseline to peak after administration of andexanet alfa or placebo • The occurrence of an endogenous thrombin potential above the lower limit of the baseline-derived range at its peak after administration of andexanet alfa or placebo (between 2 and 10 minutes after the end of the bolus) or after the infusion. • For part 2, an additional secondary end point was the percent change in anti–FXa activity from baseline to the post-bolus nadir. • Patients were followed for evaluation of clinical outcomes, including symptomatic thrombosis and bleeding.
Safety outcomes	• Vital signs included temperature, respiratory rate, heart rate, and blood pressure • Oxygen saturation • Standard 12-lead ECG • Physical exams included at a minimum an examination of the head, ears, nose and throat, heart, lungs, abdomen, skin, extremities and peripheral pulses, and a brief neurologic exam • Specific scoring systems designed to detect risk of thromboembolic disease (VTE) included the Wells score for deep vein thrombosis and pulmonary embolism • Determination of the possible presence of antibodies to andexanet alfa, factor X (FX) (human), and FXa (human) using validated electrochemiluminescent methods; for any sample that was positive for antibodies against andexanet alfa, the potential for neutralizing antibody activity was further assessed by measuring the functional activity of andexanet alfa in plasma • Blood specimens for routine chemistry and haematology were obtained at selected time points • Urine samples for urinalysis; a microscopic urinalysis was performed only if protein, haemoglobin, leukocyte esterase, or nitrite was positive.

Pre-planned subgroups	None.
Duration of follow-up / loss to follow-up / cross over	For an individual subject, the study duration was approximately 8 to 12 weeks, depending on the length of Screening. The study periods were as follows: • Screening: Days -42 to -1 • Anticoagulant Dosing: Days 1 to 4 • Andexanet alfa/placebo Dosing: Day 4 • Safety Follow-Up: Days 5 to 43 (+3) Study subjects were domiciled from Day -1 to Day 8, then discharged from the inpatient facility on Day 8 to continue outpatient follow-up through approximately Day 43. One subject (ANNEXA-A, Part 1) received apixaban but was not treated with andexanet alfa due to inadequate IV access and was therefore excluded from both the efficacy and safety analyses. One subject (ANNEXA-A, Part 2) was withdrawn partway through the study drug infusion due to mild hives; this subject was excluded from the efficacy analysis due to not having anti-fXa values recorded after the infusion but was included in the safety population. In ANNEXA-R Part 2, one subject was lost to follow-up and one withdrew from the study. Both subjects completed study drug administration and were included in the efficacy and safety analyses.

ACT – Activated clotting time; ALT - Alanine aminotransferase; aPTT - Activated partial thromboplastin time; AST - Aspartate aminotransferase; ECG -Electrocardiogram; FXa – factor Xa; HRT - Hormone replacement therapy, NSAIDs – non-steroidal anti-inflammatory drugs; P-gp - P-glycoprotein; PT - Prothrombin time; VTE – venous thromboembolism
Sources: Siegal, 2015[75]; ANNEXA-A CSR, 2015[94]; ANNEXA-R CSR, 2015[95]

ANNEXA-4

ANNEXA-4 is a phase 3b/4 multicentre, prospective, open-label, single-group study designed to evaluate the efficacy and safety of andexanet alfa in patients receiving a FXa inhibitor (apixaban, rivaroxaban, edoxaban, or enoxaparin) and presenting with acute major bleeding (Table 10).[74]

This study included 83 centres in North America and Europe. Patients were enrolled from April 2015 through May 2018. After the complete enrolment of the primary cohort, an extension of the ANNEXA-4 study continued to enrol patients in Germany, and began to enrol patients in Japan in March 2019. The purpose of this extension is to gain experience with patients receiving edoxaban and with Japanese patients.

Patients received andexanet alfa administered as IV bolus, immediately followed by 2-hour continuous infusion. Two dosing regimens (low dose or high dose) were used based on the type and dose of FXa inhibitor and timing of the last dose received. The primary endpoints were the percent change from baseline in anti-fXa activity and the occurrence of “effective haemostasis” as judged by an independent endpoint adjudication committee (Table 11).

The efficacy analysis population included patients who retrospectively met both of two criteria: baseline anti-fXa activity ≥ 75 ng/mL (or ≥ 0.25 IU/mL for enoxaparin); and confirmed major bleeding at presentation.

There were 4 protocol amendments for the ANNEXA-4 study (detailed in the supplementary materials for Connolly et al 2019[74]). Amendment 1 was made in January 2015, prior to enrolment of any patients onto the study. Likewise, Amendment 2 was implemented in May 2015, after 1 patient had been enrolled in the study. Both amendments were enacted due to FDA feedback regarding the study design and population. Changes in these two amendments

were made to the efficacy objectives, including changing anti-fXa activity from a secondary to co-primary outcome; data points; and inclusion/exclusion criteria. Amendment 3 (October 2015) was a country-specific amendment regarding informed consent procedures, and was otherwise identical to Amendment 2.

Amendment 4 (January 2017) was the most substantive amendment made during the study, and, similar to the other amendments, was implemented largely in response to FDA feedback. The main changes were:

- To enrich the population for patients with ICH, a minimum of approximately 120 evaluable patients with ICH were to be enrolled in the study
- Inclusion/exclusion criteria:
    - Removed inclusion of patients with bleeding based on an investigator's opinion that the haemoglobin level will fall to ≤ 8 g/dL with resuscitation;
    - Added a requirement that for patients with ICH, there must be a reasonable expectation that andexanet treatment will commence within 2 hours of the baseline imaging evaluation;
    - Exclusion of patients with visible, musculoskeletal, or intra-articular bleeding;
    - Clarified that patients with a history of deep vein thrombosis or cerebral venous thrombosis within 2 weeks prior to Screening are excluded, as with other thrombotic events.
- Minor modification to the andexanet administration plan
- Additional exploratory objectives, including evaluation of re-bleeding, and for ICH patients, change in GCS, mRS and NIHSS
- Added requirement for repeat imaging at 12 hours when that was used for initial bleeding diagnosis in order to facilitate adjudication.

Table 10. ANNEXA-4 Study Design

Study Acronym/ I.D.	**ANNEXA-4**
Primary study reference	Connolly et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors (NEJM, 2019)
Trial design	Ongoing Phase 3b/4, open-label, single-arm, prospective, multicentre study of andexanet alfa in patients presenting with acute major bleeding who have recently received one of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin.
Participants (Key Inclusion criteria)	• At least 18 years old at the time of Screening. • The patient must have had an acute overt major bleeding episode requiring urgent reversal of anticoagulation. Acute major bleeding requiring urgent reversal of anticoagulation was defined by at least ONE of the following:

	a) Acute overt bleeding that is potentially life-threatening, e.g., with signs or symptoms of haemodynamic compromise, such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise explained. b) Acute overt bleeding associated with a fall in Hb level by ≥ 2 g/dL, OR a Hb ≤ 8 g/dL if no baseline Hb is available. c) Acute overt bleeding in a critical area or organ, such as pericardial, intracranial, or intraspinal. • The patient, for whom the bleeding is intracranial or intraspinal, must have undergone a head CT or MRI scan demonstrating the intracranial bleeding. • The patient received or was believed to have received one of the following anticoagulants within 18 hours prior to andexanet alfa administration: apixaban, rivaroxaban, edoxaban, or enoxaparin (dose of enoxaparin ≥ 1 mg/kg/day). • For patients with ICH, there must be a reasonable expectation that andexanet alfa treatment would commence within 2 hours of the baseline imaging evaluation. [Note: From July 2016 through August 2017, only patients with intracranial haemorrhage were enrolled to enrich the study with these patients.]
Participants (Exclusion criteria)	• Scheduled to undergo surgery in less than 12 hours with the exception of minimally invasive surgery/procedures (e.g., endoscopy, bronchoscopy, central lines, Burr holes) • A patient with ICH had any of the following: a) Glasgow Coma Score < 7 b) Estimated intracerebral haematoma volume > 60 cc as assessed by the CT or MRI • Visible, musculoskeletal, or intra-articular bleeding as the qualifying bleed (implemented with Protocol Amendment 4, therefore a small number of these patients were enrolled). • Expected survival of less than 1 month. • Recent history (within 2 weeks) of a diagnosed Thrombotic Event (TE) as follows: VTE (e.g., deep venous thrombosis, pulmonary embolism, cerebral venous thrombosis), myocardial infarction (MI), disseminated intravascular coagulation, cerebral vascular accident, transient ischaemic attack, unstable angina pectoris hospitalization, or severe peripheral vascular disease within 2 weeks prior to Screening. • Severe sepsis or septic shock at the time of Screening. • Pregnancy or a lactating female. • The patient had received any of the following drugs or blood products within 7 days of Screening: o VKA (e.g., warfarin). o Dabigatran. o Prothrombin complex concentrate (PCC) products (e.g., Kcentra®) or recombinant factor VIIa (rfVIIa) (e.g., NovoSeven®). o Whole blood, plasma fractions. [Note: Administration of platelets or packed red blood cells (PRBCs) was not an exclusion criterion.] • The patient was treated with an investigational drug < 30 days prior to Screening. • Planned administration of PCC, Fresh Frozen Plasma (FFP), or rfVIIa from Screening until within 12 hours after the EOI.
Settings and locations	Patients were enrolled at 83 centres in North America and Europe. Patients were hospitalised (At the time of informed consent 80% were in an emergency department, 13% were in an intensive care unit and 6% were on an inpatient or other ward). Patients were enrolled from April 2015 through May 2018.
Trial drugs, n, dose,	Two possible dosing regimens were used based on the type and timing of the last dose of FXa inhibitor received. The low dose regimen consisted of a 400 mg bolus, delivered at 30 mg/min, followed by a 4 mg/min infusion for 120 minutes. The high

<table>
<tr><td>duration, timing</td><td>dose regimen consisted of an 800 mg bolus, delivered at 30 mg/min, followed by an 8 mg/min infusion for 120 minutes.
Dosing and Administration of Andexanet Alfa*
<table>
<tr><th></th><th></th><th colspan="2">Timing of FXa Inhibitor Last Dose Before Andexanet alfa Initiation</th></tr>
<tr><th>FXa Inhibitor</th><th>FXa Inhibitor Last Dose</th><th>< 8 Hours or Unknown</th><th>≥ 8 Hours</th></tr>
<tr><td>Rivaroxaban</td><td>≤ 10 mg</td><td>Low dose</td><td rowspan="10">Low dose</td></tr>
<tr><td></td><td>> 10 mg/ unknown</td><td>High dose</td></tr>
<tr><td>Apixaban</td><td>≤ 5 mg</td><td>Low dose</td></tr>
<tr><td></td><td>> 5 mg/ unknown</td><td>High dose</td></tr>
<tr><td>Enoxaparin</td><td>≤ 40 mg</td><td>Low dose</td></tr>
<tr><td></td><td>> 40 mg/ unknown</td><td>High dose</td></tr>
<tr><td>Edoxaban</td><td>≤ 30 mg</td><td>Low dose</td></tr>
<tr><td></td><td>> 30 mg/ unknown</td><td>High dose</td></tr>
<tr><td>Unknown</td><td>Unknown</td><td>High dose</td></tr>
</table>
*Two changes were made in the Amendment 4 of the ANNEXA-4 study protocol which became effective in January 2017: 1) Threshold time to determine a low vs high dose was changed (7 to 8 hours); and 2) specific doses of the last FXa inhibitor were added to determine a low vs high dose of andexanet alfa. There were 139 patients enrolled under Amendment 4 of the study protocol.</td></tr>
<tr><td>Concomitant medications</td><td>See exclusion criteria for prior and concomitant medications that excluded patients.
Anticoagulant and antiplatelet drugs (e.g., clopidogrel, aspirin, and non-steroidal anti-inflammatory drugs [NSAIDs]) were avoided from the signing of the ICF until after the 12-hour haemostatic efficacy evaluation measurements were made.
To maintain uniformity in transfusion practices across study participants, it was strongly suggested that the trigger for PRBC transfusion be a Hb ≤ 8.0 g/dL (± 1 g/dL).
Systemic anti-fibrinolytic (e.g., aminocaproic acid, tranexamic acid) and other systemic haemostatic agents were administered according to standard institutional/local practices and/or guidelines.
Local haemostatic agents (e.g., microfibrillar collagen, chitosan-containing products) and topical vasoconstrictors (e.g., epinephrine) were used as deemed clinically appropriate.</td></tr>
<tr><td>Primary efficacy outcomes</td><td>The two co-primary outcomes were the percent change in the anti–FXa activity and the rate of excellent or good haemostatic efficacy 12 hours after the andexanet alfa infusion, with haemostatic efficacy assessed by an independent adjudication committee on the basis of prespecified criteria (Table 11).
Anti–fXa activity was measured by means of a validated chromogenic assay of FXa enzymatic activity.</td></tr>
<tr><td>Secondary/ tertiary efficacy outcomes</td><td>The secondary objective was to assess the relationship between two primary efficacy endpoints, anti-fXa activity and haemostatic efficacy, to establish change in anti-fXa activity as a predictor of achievement of haemostatic efficacy.
Exploratory efficacy endpoints included:
o The number of patients receiving one or more red blood cell transfusions from the start of the andexanet alfa bolus through 12 hours after the end of infusion (EOI).
o For patients receiving apixaban or rivaroxaban, the evaluation of the decrease in free fraction of the FXa inhibitor following andexanet alfa administration.
o The number of red blood cell (RBC) units transfused per patient from the start of the andexanet alfa bolus through 12 hours after the EOI.</td></tr>
</table>

	o The use of non-study-prescribed blood products and/or haemostatic agents. o The occurrence of re-bleeding following andexanet alfa treatment. Re-bleeding is defined as follows: bleeding from the same (or a different) anatomical site in patients within 24 hours of initial andexanet alfa treatment and after achieving initial good/excellent haemostasis. o Andexanet alfa reversal of anticoagulant effect as measured through thrombin generation parameters (with endogenous thrombin potential as the primary measure), for both the tissue factor-initiated assay and the non–tissue factor-initiated assay. o Tissue factor pathway inhibitor (TFPI) levels, both free and total, pre- and post-administration of andexanet alfa. o Antithrombin III (ATIII) levels, pre- and post-administration of andexanet alfa. o The achievement of haemostatic efficacy in intracranial haemorrhage (ICH) patients at high risk of haematoma expansion. o Change from baseline in Glasgow Coma Scale (GCS), modified Rankin Scale (mRS) and National Institute of Health Stroke Scale (NIHSS) at 1 hour, 12 hours, and 30 days (for ICH patients only).
Safety outcomes	Safety outcomes included overall safety (adverse events, vital signs, and clinical laboratory measurements), thromboembolic events, antibodies to FX, FXa, and andexanet alfa, and 30-day all-cause mortality. Thromboembolic events included the protocol-specified, independently-adjudicated events that were defined at the start of the study (i.e., cerebrovascular accidents, deep vein thromboses, myocardial infarctions (MI), pulmonary embolisms, and transient ischaemic attacks).
Pre-planned subgroups	The data was analysed according to the following pre-specified subgroups: • Age (<65 years, 65-75 years, >75 years) • Race (any race with at least 5 members, all other races combined) • Sex • Region (North America, Europe) • FXa inhibitor • Bleeding type (gastrointestinal, ICH, other) • Andexanet alfa dose • Renal function • Andexanet manufacturing process*
Duration of follow-up / loss to follow-up / cross over	Blood samples were obtained to measure anti–FXa activity and the unbound fraction of the plasma level of FXa inhibitor before and during andexanet alfa treatment and at 4, 8, and 12 hours after the end of treatment. For patients with ICH, CT or MRI of the head was expected to be performed within 2 hours before andexanet alfa treatment and at 1 hour and 12 hours after the end of andexanet alfa treatment. All patients included received andexanet alfa and were followed for at least 30 days or until death. Some patients had their final safety visit completed up to 45 days after andexanet alfa treatment; all analyses were censored at 30 days in the published analysis data set (Connolly et al, 2019), however analyses up to 45 days were included in the final clinical study report to be provided to the EMA.

ATIII- antithrombin III; CT – computed tomography; EOI – end of infusion; FFP – fresh frozen plasma; FXa – factor Xa; GCS – Glasgow Coma Scale; GI – gastrointestinal; EOI – end of infusion; ETP – endogenous thrombin potential; Hb – haemoglobin; ICH – intracranial haemorrhage; MI – myocardial infarction; MRI – magnetic resonance imaging; mRS – modified Rankin Scale; NIHSS - National Institute of Health Stroke Scale ; NSAIDs – non-steroidal anti-inflammatory drugs; PCC – prothrombin complex; PRBC – packed red blood cells; RBC – red blood cell; TE – thrombotic event; TFPI - tissue factor pathway inhibitor; VTE – venous thromboembolism

*In January 2017 a new manufacturing process for andexanet alfa was introduced (Generation 2). No substantial differences in efficacy or safety have been detected between Generation 1 and Generation 2.

Table 11. Rating System for Effective Haemostasis in ANNEXA-4

Excellent (effective)	• Visible: Cessation of bleeding ≤ 1 hour after end of infusion and no plasma, coagulation factor or blood products (excludes pRBCs)
	• Muscular/skeletal: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤1 hour after the end of infusion; and the condition has not deteriorated during the 12-hour period
	• ICH:
	  • Intracerebral haemorrhage: ≤ 20% increase in haematoma volume compared to baseline on a repeat CT or MRI scan performed at both the 1- and 12-hour post infusion time points.
	  • Subarachnoid bleeding: ≤ 20% increase in maximum thickness using the most dense area on the follow-up vs baseline at both the 1- and 12-hour post infusion time points.
	  • Subdural haematoma: ≤ 20% increase in maximum thickness at both the 1- and 12-hour post infusion assessments compared to baseline.
	• Pericardial bleed. No increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion.
	• Intra-spinal bleed. No increase in haematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion.
	• Other (e.g., gastrointestinal bleeding, genitourinary bleeding): ≤ 10% decrease in both corrected haemoglobin/haematocrit at 12 hours compared to baseline.

Good (effective)	• Visible: Cessation of bleeding between > 1 and ≤ 4 hours after end of infusion and ≤ 2 units plasma, coagulation factor or blood products (excludes pRBCs).
	• Muscular/skeletal: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding >1 and ≤4 hours after end of infusion; and the condition has not deteriorated during the 12-hour period
	• ICH:
	  • Intracerebral haematoma: > 20% but ≤ 35% increase in haematoma volume compared to baseline on a repeat CT or MRI scan at +12-hour time point.
	  • Subarachnoid bleeding: > 20% but < 35% increase in maximum thickness using the most dense area on the follow-up at +12 hours vs baseline.
	  • Subdural haematoma: > 20% but < 35% increase in maximum thickness at +12 hours compared to baseline.
	• Pericardial bleed. < 10% increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion.
	• Intra-spinal bleed. < 10% increase in haematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion.
	• Other: > 10% to ≤ 20% decrease in both corrected haemoglobin/haematocrit at 12 hours compared to baseline.

Poor/None (not effective)	• Visible: Cessation of bleeding > 4 hours after end of the infusion and /or >2 units plasma, coagulation factor or blood products (excludes pRBCs)
	• Muscular/skeletal: No improvement by 4 hours after end of infusion and/or condition has deteriorated during the 12-hour period
	• ICH:
	  • Intracerebral haematoma: > 35% increase in haematoma volume on a CT or MRI compared to baseline on a repeat CT or MRI scan at +12-hour time point.
	  • Subarachnoid bleeding: > 35% increase in maximum thickness using the most dense area on the +12 hours vs at baseline.
	  • Subdural haematoma: > 35% increase in maximum thickness at +12 hours compared to baseline.
	• Pericardial bleed. 10% or more increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion.
	• Intra-spinal bleed. 10% or more increase in haematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion.
	• Other: > 20% decrease in both corrected haemoglobin/haematocrit.

Criteria based on 14-405 Protocol Amendment 2
CT – computed tomography; GI – gastrointestinal; ICH – intracranial haemorrhage; MRI – magnetic resonance imaging
Source: Connolly 2019[74]

B.2.3.2. Baseline Characteristics

ANNEXA-A/ANNEXA-R

A total of 101 subjects (48 in the apixaban study and 53 in the rivaroxaban study) were randomly assigned to receive andexanet alfa, and 44 participants (17 in the apixaban study and 27 in the rivaroxaban study) were randomly assigned to receive placebo. The treatment groups were balanced with respect to baseline characteristics (Table 12).

Table 12. Baseline characteristics of patients in the ANNEXA-A/ANNEXA-R studies

	Apixaban				Rivaroxaban			
	Part 1 bolus only		Part 2 bolus + infusion		Part 1 bolus only		Part 2 bolus + infusion	
	Andexanet alfa	Placebo	Andexanet alfa	Placebo	Andexanet alfa	Placebo	Andexanet alfa	Placebo
n	24	9	24	8	27	14	26	13
Age, Year - median	60.0	58.0	56.0	58.5	56.0	53.5	56.0	57.0
Female (%)	45.8	33.3	29.2	37.5	33.3	42.9	42.3	46.2
BMI, Mean (SD)	26.7	27.4	27.5	27.8	27.0	25.9	27.8	27.6
Creatinine, Mean (SD) (mg/dL)	0.8 (0.2)	0.8 (0.1)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.8 (0.2)	0.9 (0.2)	0.9 (0.2)
Race (%) White	100	100	87.5	100	81.5	71.4	76.9	61.5

Source: Siegal, 2015[75]

ANNEXA-4

Patients enrolled in ANNEXA-4 represented a high-risk population (Table 13).[74] In ANNEXA-4 patients with life-threatening bleeding had to have signs or symptoms of haemodynamic compromise (e.g., severe hypotension, poor skin perfusion, mental confusion, or low cardiac output that could not otherwise be explained), reflecting a population at higher risk of mortality than a population enrolled solely based on ISTH criteria (Table 3). Furthermore, due to protocol-specified enrichment of patients with ICH, the ANNEXA-4 population included a high proportion of these particularly vulnerable patients with a high mortality risk.

A total of 352 patients were enrolled. All patients received andexanet alfa and were followed for 30 days or until death (note: one patient died before the continuous infusion could be initiated). There were 254 patients (72%) who met the criteria for the efficacy population (adjudicated to meet the criteria for bleeding severity and with baseline anti–FXa activity of ≥75 ng per millilitre, or ≥0.25 IU per millilitre for those receiving enoxaparin).

322 patients in the safety population received apixaban or rivaroxaban. Baseline characteristics of these patients, and the subgroups of patients with ICH or GI bleeds are shown in Table 14.

A number of patients enrolled prior to Amendment 4 had a last dose between 7-8 hours – (Table 16) in which case they received a low dose of andexanet but may have received a high dose starting with Amendment 4.

Table 13. Baseline characteristics of patients in the ANNEXA-4 study

	Safety Population (N = 352)	Efficacy Population (N = 254)
Age, years, mean (SD)	77.4 (10.8)	77.1 (11.1)
Male, n (%)	187 (53)	129 (51)
Body mass index (kg/m^2), mean (SD)	27.0 (5.9)	27.0 (6.2)
Estimated creatinine clearance (mL/min), n (%)		
< 30	33 (9)	27 (11)
30 - <60	137 (39)	104 (41)
≥ 60	167 (47)	113 (44)
Missing Data	15 (4)	10 (4)
Indication for anticoagulation, n (%) [a]		
Atrial fibrillation	280 (80)	201 (79)
Venous thromboembolism [b]	61 (17)	46 (18)
Other	11 (3)	7 (3)
Medical history, n (%)		
Myocardial infarction	48 (14)	36 (14)
Stroke	69 (20)	57 (22)
Deep vein thrombosis	67 (19)	53 (21)
Pulmonary embolism	41 (12)	28 (11)
Atrial fibrillation	286 (81)	204 (80)
Heart failure	71 (20)	56 (22)
Diabetes mellitus	107 (30)	80 (31)
FXa inhibitors, n (%)		
Rivaroxaban	128 (36)	100 (39)
Apixaban	194 (55)	134 (53)
Enoxaparin	20 (6)	16 (6)
Edoxaban	10 (3)	4 (2)
Site of bleeding, n (%)		
Intracranial	227 (64)	171 (67)
GI	90 (26)	62 (24)
Other	35 (10)	21 (8)

GI – gastrointestinal; SD – standard deviation
[a] For some patients, more than one primary indication was recorded. If atrial fibrillation was present, it was considered primary. Venous thromboembolism, if recorded, was considered primary in the remaining patients.
[b] Includes deep vein thrombosis treatment or prevention and/or pulmonary embolism
Source: Connolly, 2019[74]

Table 14. Baseline characteristics of patients treated with apixaban or rivaroxaban in the ANNEXA-4 study (overall and for those with ICH or GI bleeds, Safety population)

	All Patients (N=322)	Patients with ICH (N=209)	Patients with GI (N=82)
Age Distribution (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
CHADS2VASC Score			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Time from Hospitalisation to Treatment (hr)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Medical History			
Atrial Fibrillation	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Hyperlipidemia	[redacted]	[redacted]	[redacted]
Diabetes	[redacted]	[redacted]	[redacted]
Cancer	[redacted]	[redacted]	[redacted]
Evidence of Coronary Disease (CD)	[redacted]	[redacted]	[redacted]
Renal Dysfunction	[redacted]	[redacted]	[redacted]
Venous Thromboembolism[1]	[redacted]	[redacted]	[redacted]
Deep Vein Thrombosis	[redacted]	[redacted]	[redacted]
Pulmonary Embolism	[redacted]	[redacted]	[redacted]
Congestive Heart Failure	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]
Chronic Anemia	[redacted]	[redacted]	[redacted]
Myocardial Infarction	[redacted]	[redacted]	[redacted]
Bleeding	[redacted]	[redacted]	[redacted]
Transient Ischemic Attack	[redacted]	[redacted]	[redacted]
Diverticulitis	[redacted]	[redacted]	[redacted]
Severe Peripheral Vascular Disease	[redacted]	[redacted]	[redacted]
Peptic Ulcer	[redacted]	[redacted]	[redacted]
Helicobacter Pylori	[redacted]	[redacted]	[redacted]
Inflammatory Bowl Disease	[redacted]	[redacted]	[redacted]

	All Patients (N=322)	Patients with ICH (N=209)	Patients with GI (N=82)
GI Angiodysplasia	[redacted]	[redacted]	[redacted]
Disseminated Intravascular Coagulation	[redacted]	[redacted]	[redacted]
Region			
North America	[redacted]	[redacted]	[redacted]
EU	[redacted]	[redacted]	[redacted]
United Kingdom	[redacted]	[redacted]	[redacted]
Dose of Andexanet			
Low (400 mg bolus + 480 mg IV)	[redacted]	[redacted]	[redacted]
High (800 mg bolus + 960 mg IV)	[redacted]	[redacted]	[redacted]
Baseline Daily Dose (mg) of Apixaban or Rivaroxaban			
Apixaban (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Rivaroxaban (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Time from Last AC to Treatment (hr)			
Apixaban or Rivaroxaban (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Apixaban (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Rivaroxaban (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

	All Patients (N=322)	Patients with ICH (N=209)	Patients with GI (N=82)
Baseline Anti-fXa Activity (ng/mL)			
Apixaban (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Rivaroxaban (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Database lock date: 28Nov2018. The Safety Population included patients treated with any amount of andexanet.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
[1]Patients with deep vein thrombosis or pulmonary embolism are counted.
Source: Portola data on file[96]

Table 15. Sites of Other Bleeding Patients with Apixaban or Rivaroxaban (Safety Population)

	(N=31)
Retroperitoneal	[redacted]
Extracranial - Galeal	[redacted]
Respiratory tract – pulmonary/pleural	[redacted]
Urinary tract/ Urethra	[redacted]
Genital - vaginal	[redacted]
Pericardial	[redacted]
Intraspinal – epidural/intramedullary	[redacted]
Leg	[redacted]
Intra-articular	[redacted]
Nasal (nose bleed)	[redacted]
Mediastinal	[redacted]

Table 16. Numbers of Patients with Apixaban or Rivaroxaban Enrolled Prior to Amendment 4 by Time from Last Dose to Andexanet (Safety Population)

Protocol #	Time from Last Dose to Andexanet	All Patients (N=322)	Patients with ICH (N=209)	Patients with GI (N=82)
Prior to Protocol Amendment 4	<7 hour	[redacted]	[redacted]	[redacted]
	7-8 hour	[redacted]	[redacted]	[redacted]
	≥8 hour	[redacted]	[redacted]	[redacted]
Protocol Amendment 4	<7 hour	[redacted]	[redacted]	[redacted]
	7-8 hour	[redacted]	[redacted]	[redacted]
	≥8 hour	[redacted]	[redacted]	[redacted]

Database lock date: 28Nov2018. The Safety Population included patients treated with any amount of andexanet.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Source: Portola data on file[96]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Details of the numbers of participants eligible to enter the trials are provided in appendix D.

Table 17. ANNEXA-A/ANNEXA-R statistical analysis

Trial number (acronym)	ANNEXA-A/ANNEXA-R
Hypothesis	The primary efficacy objective was to compare andexanet alfa and placebo with respect to reversal of apixaban anticoagulation as measured by anti-fXa activity, both after a bolus and after a bolus followed by a continuous infusion.
Statistical analysis	The primary efficacy analysis compared the primary endpoint between the two treatment groups using an exact Wilcoxon rank-sum test. All hypothesis tests were 2-sided and performed at the 0.05 significance level. For both Part 1 and Part 2, the secondary efficacy analysis consisted of comparing the secondary endpoints between the 2 treatment groups. The dichotomous secondary endpoints were compared between treatment groups using Fisher's Exact Test. The secondary endpoints were defined as change from baseline (continuous measure) between treatment groups using an exact Wilcoxon rank-sum test. A sequentially closed testing procedure as a gate-keeping method was used to compare the secondary endpoints between the two treatment groups after the primary endpoint comparison was rejected in favour of the treatment group. The order of hypothesis testing for comparing the secondary endpoints follows the order of the secondary endpoints specified.
Sample size, power calculation	The samples were sufficient to provide greater than 99% power to detect a difference between andexanet alfa and placebo in the percent change in anti-fXa activity from baseline to the primary time point (nadir), at a two-sided alpha level of 5%, within each part of each study. The study was powered under the assumption that the differences relative to placebo that were observed in the previous studies of andexanet alfa represent the true differences. The sample size of 145 participants was sufficient to provide safety data on at least 100 participants treated with andexanet alfa and to retain power if the observed difference in previous studies overestimated the true difference.

Changes to the SAP	None
Interim analysis	There were no interim analyses.
Outcome populations, **Imputing of missing data**	The safety analysis population consisted of all subjects randomized and treated with study drug (andexanet alfa or placebo). All safety analyses were performed by actual treatment received. The primary efficacy analysis was performed with the modified intention-to-treat population, which included all participants who underwent randomization, who received any amount of andexanet alfa or placebo, and for whom a baseline measurement of anti–FXa activity (before administration of andexanet alfa or placebo) and at least one measurement of anti–FXa activity after administration of andexanet alfa or placebo were available for analysis.

Sources: Siegal, 2015[75]; ANNEXA-A CSR, 2015[94]; ANNEXA-R CSR, 2015[95]

Table 18. ANNEXA-4 statistical analysis

Trial number (acronym)	**ANNEXA-4**
Objectives	Primary objectives were: • To demonstrate a decrease in anti-fXa activity following andexanet alfa treatment. • To evaluate the haemostatic efficacy of andexanet alfa in patients receiving a FXa inhibitor who have acute major bleeding and reduced FXa activity.
Statistical analysis	Percent change from baseline in anti–FXa activity was computed with a two-sided nonparametric confidence interval for the median. Percentages of patients with effective haemostasis are presented with a 95% confidence interval calculated with the binomial test. The association between haemostatic efficacy and change in anti–FXa activity was examined with the use of receiver-operating-characteristic curves. All Confidence Intervals (CI) are two-sided and reported at the 95% confidence level. For continuous variable, distribution free non-parametric CIs are presented. For binary endpoints, Fisher exact CIs are presented.
Sample size, power calculation	Initially, a sample of 250 patients was planned, which would provide 80% power to show that the percentage of patients with excellent or good haemostatic efficacy was more than 50%. The sample was adjusted to 350 patients in protocol amendment 4 (January 2017) to meet new regulatory requirements for sufficient numbers of patients for each FXa inhibitor and to have at least 120 patients with intracranial haemorrhage in the efficacy analysis population.
Changes to the SAP	There were two SAPs during the conduct of the study. Both are listed (including a summary of changes) within the supplementary appendix for Connolly et al, 2019.[74]

Interim analysis	Formal interim analyses to evaluate the efficacy of andexanet alfa were not planned. However, interim summaries of safety data were performed approximately every six months to report safety data from the ongoing study to the independent data safety monitoring board for review. Prior to the publication of the final study results,[74] two preliminary reports provided safety and/or efficacy data. Results from the first preliminary report by Connolly et al (2016) were published in New England Journal of Medicine (N = 67).[82] Subsequent to the first preliminary report, updated safety findings were published in response to a letter to the editor.[83] The second preliminary report included 227 patients and was presented at the American College of Cardiology Scientific Session in March 2018.[84]
Outcome populations, **Imputing of missing data**	Safety analyses included all the patients who had received andexanet alfa. The efficacy analysis population included only patients who retrospectively met both of two criteria: baseline anti–FXa activity of at least 75 ng per millilitre (or ≥0.25 IU per millilitre for patients receiving enoxaparin) and confirmed major bleeding at presentation, as determined by the adjudication committee. Patients with a qualifying baseline anti-fXa activity but no end of bolus (EOB) or EOI anti-fXa activity were imputed to have had zero change in anti-fXa activity. If only one post-baseline sample is missing, the available sample (either EOB or EOI) will be used for the imputation (Last Observation Carried Forward). Patients that were adjudicated as having non-evaluable haemostatic efficacy for clinical reasons were imputed as poor/none. Patients that were adjudicated as having non-evaluable haemostatic efficacy for administrative reasons were excluded from the analysis. The adjudication committee determined whether the non-evaluables were administrative or clinical.

EOB - end of bolus; EOI - end of infusion
Source: Connolly, 2019[74]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A complete quality assessment for each trial is provided in Appendix D.

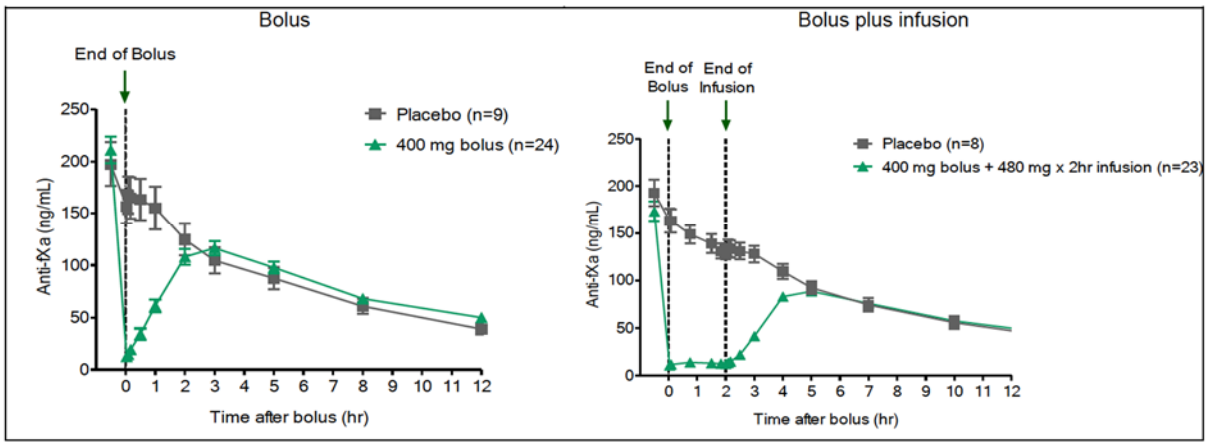
B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 ANNEXA-A/ANNEXA-R

Primary Efficacy Endpoint

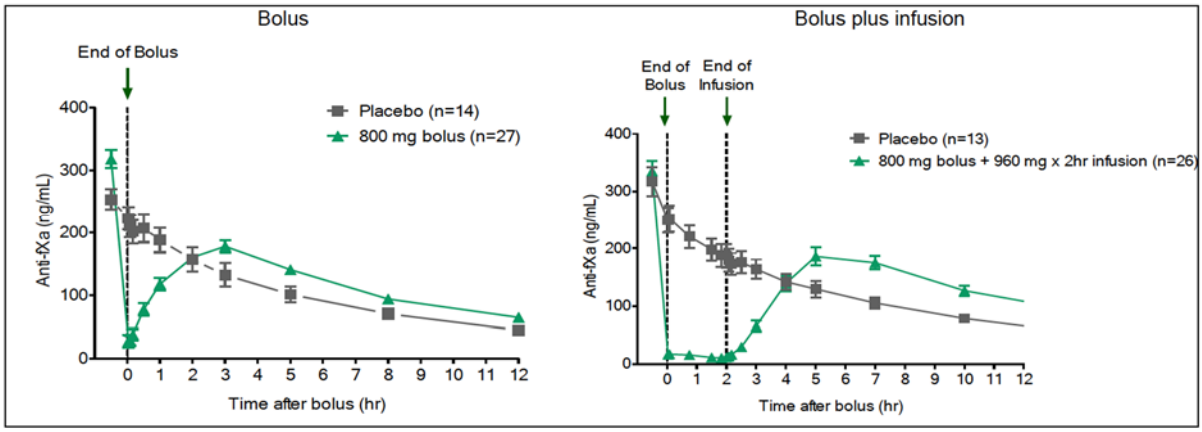
Anti-fXa activity was rapidly reduced (within 2 to 5 minutes) to a greater extent after administration of a bolus of andexanet alfa than after administration of placebo, both in the apixaban study (mean reduction, 94% vs 21%; p<0.001) and in the rivaroxaban study (92% vs 18%, p<0.001)(Figure 4 and Figure 5). When andexanet alfa was administered as a bolus plus a 2-hour infusion, it also reduced anti-fXa activity to a greater extent than did placebo, both in the apixaban study (92% vs 33%, p<0.001) and in the rivaroxaban study (97% vs 45%, p<0.001).

Figure 4. Anti-fXa Activity in Apixaban-Treated Healthy Subject



Source: Siegal, 2015[75]

Figure 5. Anti-fXa Activity in Rivaroxaban-Treated Healthy Subjects



Source: Siegal, 2015[75]

Secondary Efficacy Endpoints

Proportion of participants with an 80% or greater reduction in anti–FXa activity

All the participants who were treated with andexanet alfa had at least 80% reversal of anti–FXa activity, with the exception of one participant who did not receive the full dose of andexanet alfa because of a malfunction with the intravenous administration; none of participants who received placebo had an 80% or greater reversal of anti–FXa activity ($p<0.001$).

Change in unbound inhibitor plasma concentration

The mean concentration of unbound (pharmacologically active) apixaban and rivaroxaban in plasma was reduced by a significantly greater amount after administration of a bolus of andexanet alfa than after administration of placebo (apixaban reduction, 9.3 ng/mL vs 1.9 ng/mL, $p<0.001$; rivaroxaban reduction, 23.4 ng/mL vs 4.2 ng/mL, $p<0.001$). After administration of bolus plus an infusion of andexanet alfa; the mean plasma concentrations of unbound apixaban and rivaroxaban were reduced by a significantly greater amount with andexanet alfa than with placebo (apixaban reduction, 6.5 ng/mL vs 3.0 ng/mL, $p<0.001$; rivaroxaban reduction, 30.3 ng/mL vs 12.1 ng/mL, $p<0.001$).

Figure 6. Unbound (Pharmacologically Active) Apixaban Plasma Concentrations

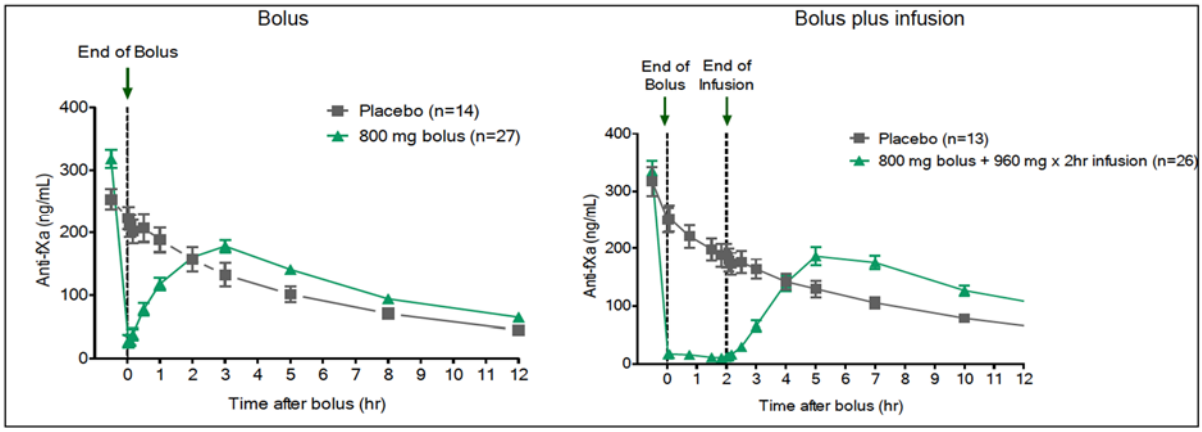
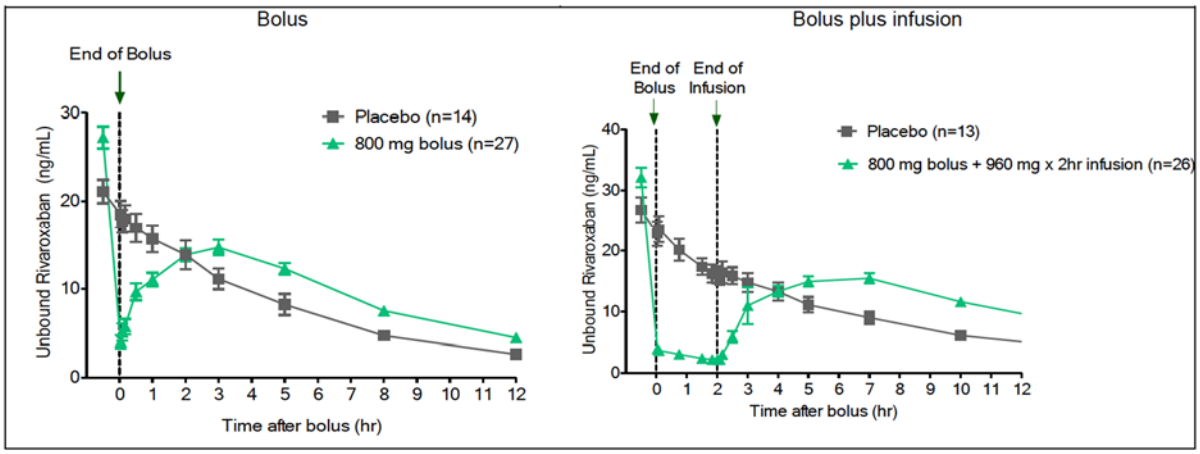


Figure 7. Unbound (Pharmacologically Active) Rivaroxaban Plasma Concentrations



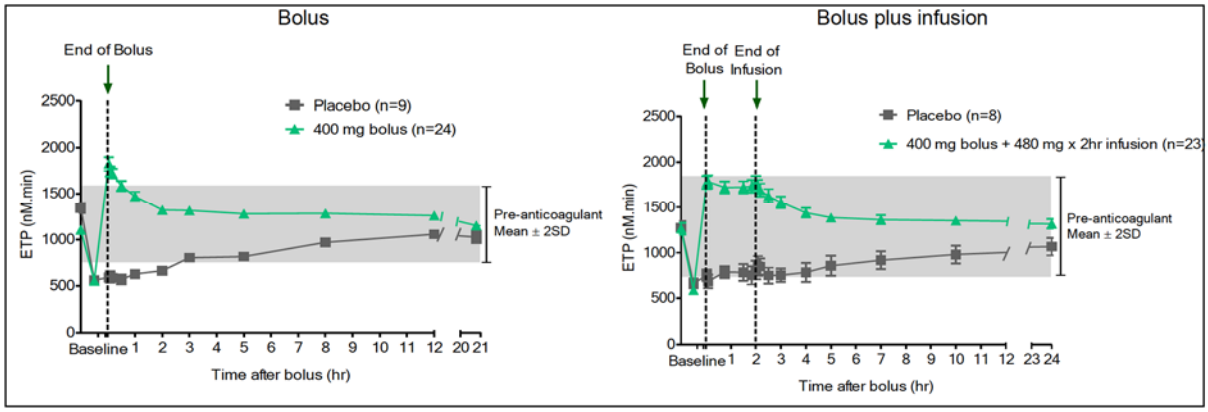
Thrombin generation

After the bolus alone, the mean change in thrombin generation was significantly greater among participants who received andexanet alfa than among those who received placebo, both in the apixaban study (1323.2 nM min vs 88.2 nM min, p<0.001) and in the rivaroxaban study (1314.2 nM min vs 173.9 nM min, p<0.001). After administration of bolus plus infusion, the mean change in thrombin generation was significantly greater among participants who received andexanet alfa than among those who received placebo, both in the apixaban study (1193.1 nM min vs 189.4 nM min, p<0.001) and in the rivaroxaban study (1510.4 nM min vs 264.4 nM min, p<0.001).

Thrombin generation increased to above the lower limit of the normal range within 2 to 10 minutes after bolus administration in 100% and 96% (26 of 27) of participants who received andexanet alfa in the apixaban and rivaroxaban studies, respectively, as compared with 11% (1 of 9) and 7% (1 of 14) of participants who received placebo in the apixaban and rivaroxaban studies, respectively (p<0.001 vs placebo for each comparison)(Figure 8 and Figure 9). The single andexanet alfa-treated participant in the rivaroxaban study who did not meet this end point did not receive the full dose of andexanet alfa (as above). After administration of bolus plus infusion andexanet alfa restored thrombin generation (to above the lower limit of the

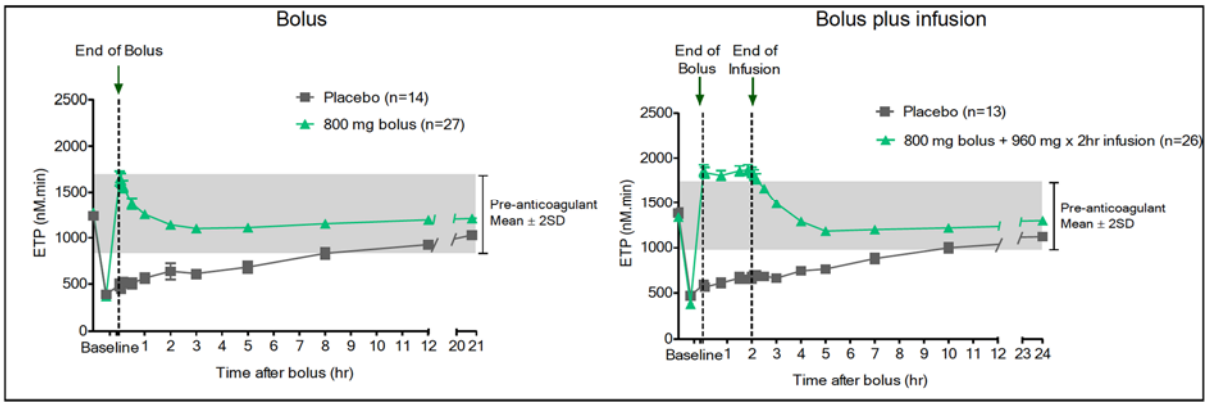
normal range) in all the participants in the apixaban study and in the rivaroxaban study; among participants who received placebo, thrombin generation was restored in 25% of participants in the apixaban study and in no participants in the rivaroxaban study (p<0.001 vs placebo for each comparison).

Figure 8. Thrombin Generation in Apixaban-treated Subjects



ETP – endogenous thrombin potential; hr – hour; SD – standard deviation
Source: Siegal, 2015[75]

Figure 9. Thrombin Generation in Rivaroxaban-treated Subjects



ETP – endogenous thrombin potential; hr – hour; SD – standard deviation
Source: Siegal, 2015[75]

B.2.6.2 ANNEXA-4

Patient disposition

Patient disposition is detailed in appendix D. The efficacy analysis population included 254 patients; 134 received apixaban, 100 received rivaroxaban, 16 received enoxaparin and 4 received edoxaban. In this respect, in addition to the overall results, where available the results presented below focus on the current licensed indication, i.e. those patients who received apixaban or rivaroxaban.

Of the 254 patients in the efficacy analysis, 249 could be evaluated for haemostatic efficacy.

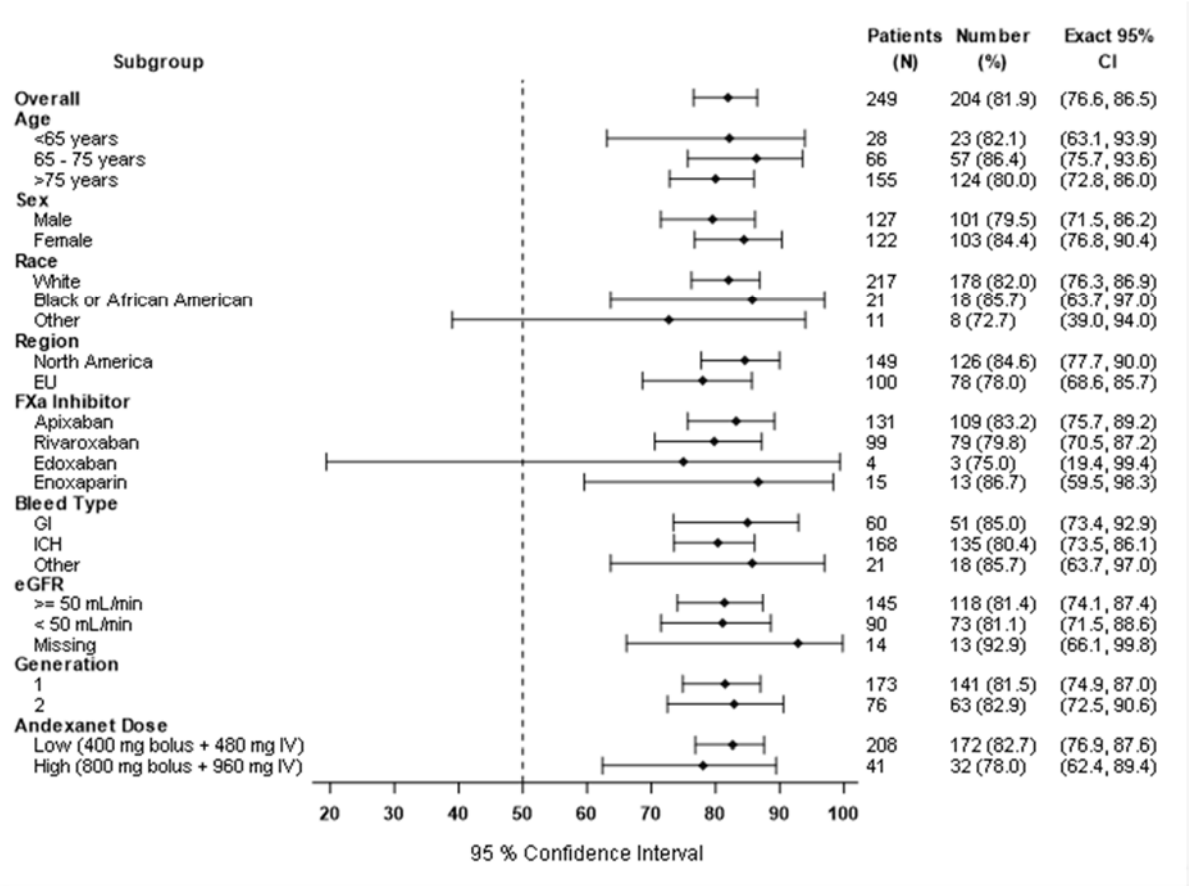
Primary Efficacy Outcomes

Haemostatic efficacy

Clinical haemostasis was adjudicated by an independent and blinded endpoint adjudication committee as excellent or good in 204 of 249 patients (82%; 95% CI, 77–87) 12 hours after

andexanet alfa infusion. Of these, 171 were adjudicated as excellent and 33 as good. Similar rates of haemostatic efficacy were observed in the pre-specified subgroups (Figure 10). The rates of excellent or good efficacy were 85% (95% CI, 76–94) for GI bleeding and 80% (95% CI, 74–86) for intracranial bleeding.[74] For the subgroup of patients who had received apixaban or rivaroxaban (n = 230), 82% (188 of 230) achieved excellent or good haemostatic efficacy.

Figure 10. Effective haemostasis at 12 hours post andexanet alfa (Efficacy Population)



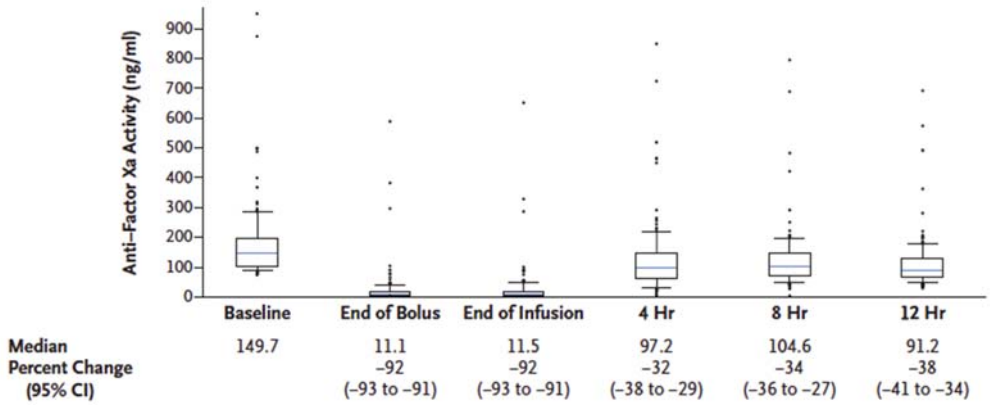
Shown are the percentages of patients in the efficacy analysis who had excellent or good haemostatic efficacy at 12 hours, as assessed by the independent adjudication committee on the basis of prespecified criteria. There were five patients in the efficacy population in whom haemostatic efficacy could not be adjudicated owing to administrative reasons.
Source: Connolly 2019[74] and ANNEXA-4 CSR[97]

Anti-fXa Activity

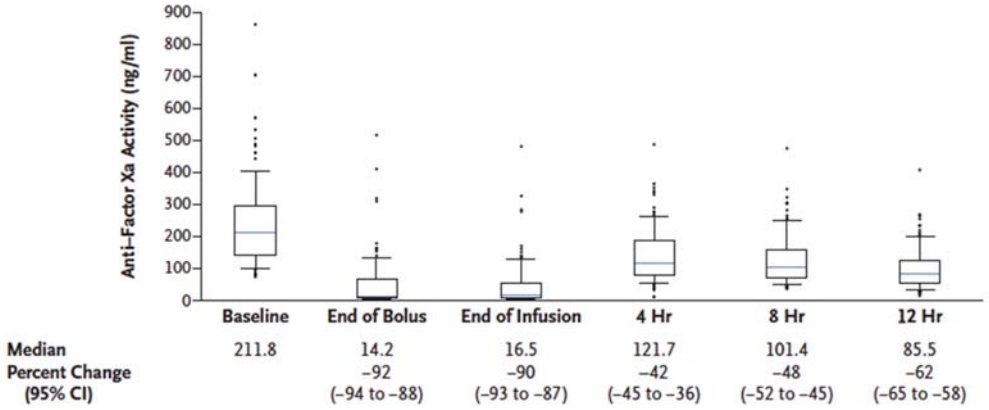
After the bolus administration of andexanet alfa, the median anti-fXa activity decreased by 92% (95% CI, 91–93) from baseline among patients receiving apixaban (n = 134) and by 92% (95% CI, 88–94) among patients receiving rivaroxaban (n = 100). In patients who received apixaban, the median anti-fXa activity value decreased from 149.7 ng/mL at baseline to 11.1 ng/mL after andexanet alfa bolus; in patients who received rivaroxaban, the median decreased from 211.8 ng/mL to 14.2 ng/mL. At 4, 8 and 12 hours after the end of infusion, there was a relative decrease from baseline of 32%, 34%, and 38% for apixaban and 42%, 48%, and 62% for rivaroxaban.[74]

Figure 11. Anti-fXa Activity by FXa Inhibitor (Efficacy Population)

A Patients Who Received Apixaban



B Patients Who Received Rivaroxaban

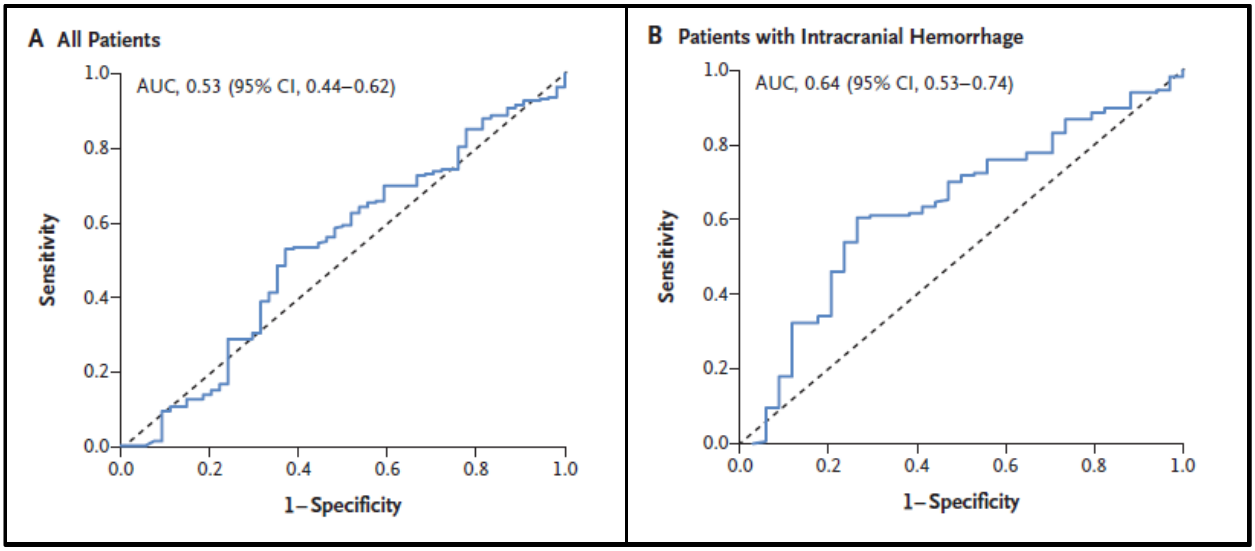


CI – confidence interval; Hr – hours
The median for each level of anti–FXa activity at each time point is marked as a horizontal line within the box. The top and bottom of the box denote the 75th and 25th percentiles, respectively, and the whiskers indicate the 90th and 10th percentiles. Outliers are shown as dots.
Source: Connolly et a, 2019[74]

Secondary Efficacy Objective: Relationship of Haemostatic Efficacy and Anti-fXa Activity

For patients with all bleed types, no relationship between haemostatic efficacy and reduction in anti-fXa activity was observed. For patients with ICH, the magnitude of the reduction in anti-fXa activity was a predictor of h**a**emostatic efficacy (area under the ROC curve, 0.64; 95% CI, 0.53−0.74).

Figure 12. Receiver-Operating-Characteristic (ROC) Curves for Haemostatic Efficacy in ANNEXA-4



AUC – area under the curve; CI – confidence interval; ROC – receiver operating characteristic
Patients are included in the analysis if assessment of haemostatic efficacy was available and if the level of anti-fXa activity was available at baseline and during andexanet alfa treatment (at the end of administration of either the bolus or the infusion). The dashed line is a reference line indicating chance prediction. AUC denotes area under the curve.
Source: Connolly 2019[74]

Exploratory Efficacy Endpoints

Haemostatic efficacy as measured by haematoma expansion in intracranial haemorrhage and re-bleeding

Re-bleeding was introduced as an endpoint in protocol amendment 4, and was defined as follows: bleeding from the same anatomical site in patients within 24 hours of initial andexanet treatment and after achieving initial good/excellent haemostasis. Re-bleeding was a rare event: [redacted] patients enrolled after the implementation of amendment 4 were adjudicated as having re-bleeding. [redacted]

Haematoma expansion in patients with intracerebral haemorrhages was explored in a post-hoc analysis. [redacted] efficacy evaluable patients had non-traumatic, single-compartment, intracerebral haemorrhages. Of these, [redacted] had volume expansion ≤ 35% from baseline at 1 hour. Of these, [redacted] had no additional haematoma expansion at 12 hours (haematoma volume remained ≤35% vs baseline).[97]

Red blood cell transfusions, non-study-prescribed blood products and haemostatic agents

Of the 352 patients in the Safety Population who completed the 30-day safety follow-up, [redacted] received red blood cell transfusions during the efficacy evaluation period. [redacted]

Of the 254 patients in the Efficacy Population, [redacted] received non-study-prescribed blood products and/or haemostatic agents between the start of andexanet treatment and 12 hours after the end of the infusion. [redacted]

[redacted]

[redacted]_Perhaps consistent with the fact that these patients received the supplemental therapies mentioned above, only [redacted]

[redacted][97]

Table 19. Blood product use (mL) and non-RBC blood product use of patients with apixaban or rivaroxaban (Safety Population)

	All Patients (N=322)	Patients with ICH (N=209)	Patients with GI (N=82)
Blood Product Use (mL)			
Before Andexanet Dosing (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
0-16 hour (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
>16 hour (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Coagulation Factor Transfusion (N)			
Before Andexanet Dosing	[redacted]	[redacted]	[redacted]
30 minutes before end of infusion	[redacted]	[redacted]	[redacted]
1 hour	[redacted]	[redacted]	[redacted]
4 hour	[redacted]	[redacted]	[redacted]
8 hour	[redacted]	[redacted]	[redacted]
12 hour	[redacted]	[redacted]	[redacted]
Haemostatic Treatments (N)			
Before Andexanet Dosing	[redacted]	[redacted]	[redacted]
30 minutes before end of infusion	[redacted]	[redacted]	[redacted]
1 hour	[redacted]	[redacted]	[redacted]
4 hour	[redacted]	[redacted]	[redacted]
8 hour	[redacted]	[redacted]	[redacted]
12 hour	[redacted]	[redacted]	[redacted]
Other Blood/Coagulation (N)			
Before Andexanet Dosing	[redacted]	[redacted]	[redacted]

30 minutes before end of infusion	[redacted]	[redacted]	[redacted]
1 hour	[redacted]	[redacted]	[redacted]
4 hour	[redacted]	[redacted]	[redacted]
12 hour	[redacted]	[redacted]	[redacted]

Database lock date: 28Nov2018. The Safety Population included patients treated with any amount of andexanet.
Bleed type was adjudicated by the Endpoint Adjudication Committee. 16 hours is 12 hours after EOI.
Source: Portola data on file[96]

Neurological function

[redacted] Note that NIHSS testing was not implemented and the additional GCS assessments were not added until Protocol Amendment 4; therefore, the number of patients evaluated was lower for the baseline NIHSS and the later time points for GCS.

[redacted]

Table 20. Clinical Neurologic Status (Glasgow Coma Scale & National Institutes of Health Stroke Scale) for Patients with ICH (Efficacy Population)

Assessment Time	Statistic	GCS	GCS Change	NIHSS	NIHSS Change
Baseline	Patients (N)	[redacted]		[redacted]	
	Mean (SD)	[redacted]		[redacted]	
	Median	[redacted]		[redacted]	
	Min, Max	[redacted]		[redacted]	
	Median 95% CI	[redacted]		[redacted]	
1 Hour	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]
12 Hour	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Day 30	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]

Database lock date: 28Nov2018.The Efficacy Population includes all patients who received any amount of andexanet, met clinical bleeding criteria, and had an anti-fXa level of ≥75 ng/mL (0.25 IU/mL for patients receiving enoxaparin).
Source: ANNEXA-4 CSR[97]

The results for the mRS at Day 30 are shown in Table 21 and Table 22. [redacted]

Table 21. Modified Rankin Score (mRS) of ICH patients with Apixaban or Rivaroxaban (Safety Population)

Timepoint	Statistic	Patients with ICH (N=209)
Screening	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	IQR	[redacted]
	Range	[redacted]
1 hour	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	IQR	[redacted]
	Range	[redacted]
12 hour	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	IQR	[redacted]
	Range	[redacted]
Day 30	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	IQR	[redacted]
	Range	[redacted]

Database lock date: 28Nov2018. The Safety Population included patients treated with any amount of andexanet.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Source: Portola data on file[96]

Table 22. The Modified Rankin Score of ICH Patients (Efficacy Population)

Modified Rankin Scale	Screening Assessment	Day 30 Assessment
No. Patients	[redacted]	[redacted]
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]

The efficacy population included all patients in the safety population who met the clinical bleeding criteria and had anti-fXa level of at least 75 ng/mL (0.25 IU/mL for patients receiving enoxaparin).
Study: Portola Data on FIIe[98] (Table 14.2.2.12, Date: 25JAN2019)

Duration of hospital stay

The median duration of hospital stay was [redacted] (Table 23).

Table 23. Hospitalisation Summary of Patients with Apixaban or Rivaroxaban (Safety Population)

Bleed Type	Statistic	Apixaban (N=194)	Rivaroxaban (N=128)	All Patients (N=322)
All Patients	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
GI	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
ICH	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Other	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]

Database lock date: 28Nov2018. The Safety Population includes all patients who received any amount of andexanet.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Study: Portola Data on FIIe[98] (Table 14.1.1.8b, Date: 16MAY2019)

Surgical control of bleeding of interventional radiology embolisation

The use of interventions to control bleeding was not an endpoint in the ANNEXA-4 study and these interventional procedures were recorded as free-text terms only. Analysis of this data was therefore carried out by searching each patient record by hand. As such, the data listed in Table 24 should be interpreted with caution.

Table 24. Surgical and other interventions for control of bleeding (Safety Population)

Bleed type Procedure	Apixaban (n=194)	Rivaroxaban (n=128)	Overall (n=322)
ICH			
Craniotomy/craniectomy	[redacted]	[redacted]	[redacted]
Ventricular drain	[redacted]	[redacted]	[redacted]
Evacuation of haematoma	[redacted]	[redacted]	[redacted]
Burr hole	[redacted]	[redacted]	[redacted]
Unidentified procedure	[redacted]	[redacted]	[redacted]
Other procedure	[redacted]	[redacted]	[redacted]
GI	[redacted]	[redacted]	[redacted]
Exploratory laparotomy	[redacted]	[redacted]	[redacted]
Intraluminal device	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Hemiathroplasty	[redacted]	[redacted]	[redacted]
Pleural drainage	[redacted]	[redacted]	[redacted]
Vaginal packing	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Source: Portola data on file[96]

Thrombin generation

In both nonclinical and clinical studies, increases in anti-fXa activity correlate with decreases in thrombin generation. Tissue factor (TF)-initiated thrombin generation is a well-accepted assay for assessing the level of anticoagulation in patients and a relevant PD marker for restoration of haemostasis downstream of FXa inhibition.

At baseline, thrombin generation was elevated in the majority of patients in the Efficacy Population, despite the fact that all patients were taking FXa inhibitors, possibly reflective of a general activation of the coagulation system in the setting of acute bleeding. [redacted] The time course profiles for the TF-initiated ETP are shown in Figure 13.

Figure 13. Time Course of Thrombin Generation in Patients Taking Rivaroxaban and Apixaban (Efficacy Population)

Database lock date: 28Nov2018. The Efficacy Population includes all patients who received any amount of andexanet, met clinical bleeding criteria, and had an anti-fXa level of ≥75 ng/mL (0.25 IU/mL for patients receiving enoxaparin).
Time course of ETP is shown as [median, 25th, 75th percentiles] at each time. -1 hour indicates the screening timepoint.
Endogenous Thrombin Potential values identified by the lab as “BMC (below measurement capacity)” were replaced with zeros.

The horizontal dashed line indicates the lower bound of the normal value for ETP of 1269 nM*min minus the SD of 230 as presented in the New England Journal of Medicine (2016), 375:1131-41.
Source ANNEXA-4 CSR[97]

In summary, baseline ETP levels in bleeding patients were higher compared to healthy subjects with therapeutic levels of FXa inhibition, as expected in patients with a major acute bleeding episode. Nevertheless, both mean and median ETP values at baseline were well below the normal ETP ranges established in healthy subjects, indicating these patients presented anticoagulated while bleeding. [redacted] These data are consistent with the mechanism of action of andexanet, and suggest that andexanet effectively modulates the activation of prothrombin to thrombin—an important intermediate step between reduction in anti-fXa activity and the achievement of clinical haemostatic efficacy.

B.2.7 Subgroup analysis

In ANNEXA-4, data were analysed according to the following pre-specified subgroups:

- Age (<65 years, 65-75 years, >75 years)
- Race (any race with at least 5 members, all other races combined)
- Sex
- Region (North America, Europe)
- FXa inhibitor
- Bleeding type (gastrointestinal, ICH, other)
- Andexanet alfa dose
- Renal function
- Andexanet manufacturing process

Results of for the subgroup with ICH are utilised in the economic model. Haemostatic efficacy for the subgroup of patients with ICH is shown in Table 25 below. Further results for this subgroup are presented in Section B2.10 (adverse events).

Table 25. Haemostatic Efficacy of ICH Patients by Subgroup (Efficacy Population)

		Haemostatic Efficacy		
Group	**Subgroup**	**Number of Patients**	**Excellent/Good n (%)**	**Poor/None n (%)**
Overall	Overall	[redacted]	[redacted]	[redacted]
FXa Inhibitor	Apixaban	[redacted]	[redacted]	[redacted]
	Rivaroxaban	[redacted]	[redacted]	[redacted]
	Enoxaparin	[redacted]	[redacted]	[redacted]
	Edoxaban	[redacted]	[redacted]	[redacted]
Andexanet alfa Dose	400 mg bolus + 480 mg IV	[redacted]	[redacted]	[redacted]
	800 mg bolus + 960 mg IV	[redacted]	[redacted]	[redacted]

Based on data transfer from 28NOV18. All patients who received any amount of andexanet, met clinical bleeding criteria, and have anti-fXa level of at least 75 ng/mL (0.25 IU/mL for patients receiving enoxaparin) are included. Site of Bleeding was adjudicated by the Endpoint Adjudication Committee. Five patients adjudicated as non-evaluable for clinical reasons are included in the All Efficacy Patients population and were considered as having Poor/None haemostatic efficacy.
Study: Portola Data on FIIe[98] (Table 14.2.2.4, Date: 25JAN2019)

B.2.8 Meta-analysis

A meta-analysis has not been completed. Whilst it may have been possible to combine the results of ANNEXA-A and ANNEXA-R, it was not considered necessary since the study outcomes are not directly utilised in the economic model.

B.2.9 Indirect and mixed treatment comparisons

Since ANNEXA-4 was a single arm study, population matching methods with a suitable observational study were considered to inform an indirect comparison of andexanet alfa compared to PCC.

As described in Section B2.2, comparator studies for PCC were limited in terms of evidence and relevance to the UK. However, the ORANGE study provides the largest prospective study reporting on haematological management and outcomes of DOAC-related bleeding, of which 40% of patients received PCC. Importantly, the study was conducted in the UK between October 2013 to August 2016, and therefore is representative of current clinical practice.

Since it was possible to obtain patient level data from this study, specifically to determine outcomes for PCC in licenced population, it was considered the most robust source of data for the economic analysis, and has been used in a propensity score matching analysis with ANNEXA-4 (Section B.2.9 Indirect and mixed treatment comparisons).

B2.9.1 ORANGE study overview

Methodology

The UK study ORANGE was a 3-year, prospective cohort study that collected information from multiple UK hospitals on the presentation and clinical outcomes of patients who were admitted for a major bleeding episode while on oral anticoagulant therapy.[20] An overview of the study methodology is provided in Table 26. A quality assessment is provided in Appendix D.

Table 26. ORANGE Study Methodology

Study Acronym/ I.D.	**ORANGE**
Primary study reference(s)	Green et al. A three-year prospective study of the presentation and clinical outcomes of major bleeding episodes associated with oral anticoagulant use in the UK (ORANGE study). Haematologica. 2018 Green et al. Haematological management of major bleeding associated with direct oral anticoagulants - UK experience. Br J Haematol. 2019
Trial design	Prospective cohort study that collected information across multiple UK hospitals on the presentation and clinical outcomes of patients who were admitted for a major bleeding episode whilst on oral anticoagulation therapy. Data on major bleeding events were submitted by multiple hospitals across England, Scotland, Wales and Northern Ireland between 1st October 2013 and 31st August 2016. Patients

	underwent the normal course of treatment as directed by their clinicians and hospital protocols; at no point was their care altered for the purpose of this study.
Participants (Key Inclusion criteria)	Any patient of 18 years or over on oral anticoagulation therapy at the time when they developed major bleeding was eligible for the study. The definition of major bleeding adopted was an augmented version of the ISTH criteria. It was defined as bleeding requiring hospitalisation and at least one of the following: a) resulting in death; b) transfusion of ≥2 units of red blood cell units or drop in haemoglobin of ≥20 g/L; c) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; d) transfusion of fresh frozen plasma; e) administration of prothrombin complex concentrate, recombinant FVIIa, factor VIII inhibitor bypassing activity or fibrinogen concentrate. The rationale for appending (d) and (e) was to ensure that the routes for case identification were as comprehensive as possible.
Settings and locations	32 hospitals across England, Scotland, Wales and Northern Ireland between 1st October 2013 and 31st August 2016. Cases were reported consecutively and identified by clinical and research staff in participating hospitals from the emergency department, transfusion laboratory, pharmacy (if they stored haemostatic agents) and haematology doctors who were called to give medical advice on the management of these patients.
Trial drugs, n, dose, duration, timing	Not applicable- observational study. Patients underwent the normal course of treatment as directed by their clinicians and hospital protocols; at no point was their care altered for the purpose of this study.
Outcomes	The study collected information on: patients' baseline characteristics; type of oral anticoagulation and indication(s), as well as co-morbidities and clinical outcomes at 30 days, death, or discharge, whichever occurred first. In a sub-study of patients on DOACs, Data comprised information on co-morbidities, bleeding sites, haematological laboratory results, management of bleeding and first outcome up to 30 days (death, discharge or continued hospitalisation).
Pre-planned subgroups	None.
Duration of follow-up / loss to follow-up / cross over	Patients were followed up for 30 days, death, or discharge, whichever occurred first. Outcomes up to 30 days were reported for 2,132 (97%) patients.

Baseline characteristics

The ORANGE study included 2,192 patients, 372 of whom had experienced major bleeding whilst receiving rivaroxaban or apixaban therapy. In a sub-study, bleeding characteristics and outcomes of patients on DOACs (i.e. rivaroxaban, apixaban, edoxaban and dabigatran) were analysed.[52]

Table 27. Baseline characteristics of patients in the ORANGE study (apixaban and rivaroxaban-treated patients)

	Apixaban (n = 89)	Rivaroxaban (n = 283)
Age, years, median (IQR)	81 (76-86)	82 (74-88)
Male, n (%)	54 (61%)	130 (46%)
Indication for anticoagulation, n (%) [a]		
Atrial fibrillation	76 (85%)	193 (68%)
Venous thromboembolism	11(12%)	89 (31%)
Other	12 (13%)	19 (7%)
Medical history, n (%)		
Chronic heart failure	14 (16%)	46 (16%)
Hypertension	50 (56%)	154 (54%)
Stroke/ transient ischaemic attack	23 (26%)	56 (20%)
Peripheral vascular disease	2 (2%)	13 (5%)
Ischemic heart disease	29 (33%)	69 (24%)
Alcohol dependence	1 (1%)	7 (2%)
Dementia	8 (9%)	35 (12%)
Recurrent falls	6 (7%)	24 (8%)
Liver failure	0	6 (2%)
Cancer	14 (16%)	55 (19%)
Diabetes mellitus	21 (24%)	62 (22%)
Site of bleeding, n (%)[#]		
Intracranial	43 (48%)	97 (34%)
Intracerebral	24 (27%)	59 (21%)
Subarachnoid	8 (9%)	10 (4%)
Subdural	11 (12%)	28 (10%)
GI	31 (35%)	127 (45%)
Upper GI	19 (21%)	75 (27%)
Lower GI	12 (14%)	52 (18%)
Other*	15 (17%)	59 (21%)
Visceral	4 (5%)	14 (5%)
Genitourinary	0	13 (5%)
Musculoskeletal	6 (7%)	26 (9%)
Miscellaneous	5 (6%)	6 (2%)

GI – gastrointestinal; IQR – inter quartile range
Patients reported to have more than one bleeding site were assigned to the clinically most severe, in descending order of priority as above.
*Explanation of Other
Visceral Haemoptysis; Pericardium; Retroperitoneal; Abdomen; Chest/Thoracic
Genitourinary Haematuria/Urethral; Vaginal
Musculoskeletal Epistaxis or mucosal; Cutaneous or soft tissue; Intra-articular; Oral/Pharyngeal
Miscellaneous Surgical site; Intraocular; Puncture site; Unknown; Other not covered above
(cases with more than 1 of the above classified in descending order of priority)
Source: Green at al, 2018[20]; Green et al, 2019[52]

Results

Table 28 details the interventions used to manage bleeding in the apixaban and rivaroxaban groups.

Table 28. Management of bleeding in the ORANGE study (apixaban and rivaroxaban-treated patients)

	Apixaban (n = 89)	Rivaroxaban (n = 283)
Received any intervention	75 (84%)	193 (68%)
PCC	45 (51%)	104 (37%)
Tranexamic Acid	29 (33%)	73 (26%)
Vitamin K	14 (16%)	41 (14%)
FEIBA	1 (1%)	1 (<1%)
Any blood transfusion	32 (36%)	117 (41%)
Red Blood Cells	29 (33%)	112 (40%)
Fresh Frozen Plasma	8 (9%)	18 (6%)
Platelets	5 (6%)	8 (3%)
Cryoprecipitate	2 (2%)	3 (1%)

DOAC: direct oral anticoagulant agents; PCC: prothrombin complex concentrate; FEIBA: factor eight inhibitor bypassing activity.

The mortality rate up to 30 days of follow up was 21% among DOAC treated patients (i.e. including patients who received apixaban, rivaroxaban, edoxaban and dabigatran). Of 413 (98%) patients who were followed-up until discharge, death or 30 days (whichever occurred first), 88 (21.3%; 95% CI: 17.5 – 25.6%) had died in hospital within 30 days, with no significant differences between the DOACs (p=0.66).[52] Based on the patient level data obtained, in patients treated with PCC (an indicator for a more severe bleed), who had received apixaban and rivaroxaban, the 30 day mortality rate was 32% in the Whole cohort, 43% in ICH patients, 23% in GI patients and 18% in Other major bleed patients.

Amongst discharged patients, the median (IQR) stay in hospital was 6 (3-11) days (data not shown); this was not different between DOACs (p=0.24).[52]

An analysis of reversal strategies and time to death showed that compared with not receiving PCC, getting ≤25 IU/kg, 26–49 IU/kg and ≥50 IU/kg of PCC were not significantly predictive of the cumulative risk of death. Type of DOAC, administration of tranexamic acid and total red cell+plasma transfusion were not found to be associated with risk of death.[52]

B2.9.2 Propensity score matching analysis

As discussed in Section B.2 Clinical effectiveness, the ANNEXA-4 and ORANGE studies provide the most robust real world outcomes for which to evaluate the efficacy and safety of andexanet alfa and PCC in the UK. However, given that both studies are single-arm observational studies, statistically adjusted estimates of effect could only be generated using population matching methods.

It is evident that 30-day mortality is the fundamental clinical outcome to determine the clinical effectiveness of andexanet alfa and would be a key driver of cost-effectiveness results.

Therefore, in order to calculate adjusted 30-day mortality estimates, a propensity score matching analysis was undertaken to replicate randomisation by identifying and drawing comparisons between similar patients based on one or more characteristics. The methods used were chosen to align with NICE DSU guidelines.[99]

When considering other outcomes listed in the NICE scope (see Table 1), only thrombotic events and hospital stay were captured across ANNEXA-4 and ORANGE. Neither were considered suitable for propensity score matching as treatment-emergent serious thrombotic events occurred in ≤2% across the ANNEXA-4 and ORANGE studies, and hospital stay is likely to be uninformative given the differences in the settings of care across the two studies.

Before conducting the propensity score matching analysis, the feasibility of generating controlled estimates of effect associated with andexanet alfa compared to PCC in patients within the licenced indication (i.e. adults experiencing life-threatening or uncontrolled bleeds receiving rivaroxaban and apixaban) were considered for the following populations:

- Whole population
- ICH subgroup
- GI subgroup
- Other major bleeds subgroup (non-ICH/GI)

This assessment comprised a comparison of: the sample sizes; the study settings; the inclusion and exclusion criteria; and the availability of patient baseline characteristics and other covariates in the two studies. To be able to generate robust propensity score matching results, the following assumptions had to be met:[99]

- 'Ignorability of treatment' or 'unconfoundedness' assumption, under which all patient characteristics which affect the outcome of interest (30-day mortality) and show statistically significant differences between treatment groups are included in the regression model and are therefore controlled for;
- 'Overlap assumption', under which no baseline characteristic included in the regression model is sufficient to cause patients to have a zero probability of being included in either treatment group. This ensures that an adequate sample of comparable patients is available between the two studies.

The patients in the ORANGE study were considered reflective of the population eligible for current standard of care (SoC) in the UK,[20] though it was noted that while all patients in the ORANGE study had major bleeds, they had not necessarily suffered life-threatening bleeds like the patients in the ANNEXA-4 trial. Only patients receiving PCC in the ORANGE dataset were considered, to reflect the use of PCC as the model comparator treatment in patients with life-threatening or uncontrolled bleeds (see Section B.3.2 Economic analysis). The use of PCC may also be a relevant proxy for determining the severity of the major bleed, and therefore more aligned to andexanet alfa's label.

The results of the feasibility assessment indicated that the ANNEXA-4 and ORANGE studies were comparable overall; however, two sources of potential bias were identified:

- Differences in the study populations, as determined by the inclusion and exclusion criteria. Several variables used to determine eligibility were not reported in both studies, so the populations could not be adjusted for these characteristics and the magnitude of differences could not be gauged.
- Omission of reported data on multiple key covariates in one or other of the studies.

Despite the limitations identified in the feasibility assessment, propensity score matching was undertaken to see if matches could be made between the patient-level datasets of ORANGE and ANNEXA-4. To ensure the methods and results were appropriately considered and interpreted to NICE standards, Portola worked in partnership with Kate Ren (https://www.sheffield.ac.uk/scharr/sections/heds/staff/ren_k), a statistician and lecturer specialised in network meta-analysis and indirect comparisons; Kate currently serves as a lead evidence reviewer in relation to these topics for Sheffield University's Evidence Review Group (ERG) – the School of Health and Related Research (ScHARR).

The first step of the propensity score matching was to specify the model for the propensity score regression equation. Matching was made to the ANNEXA-4 study, since this is reflective of the licenced indication for andexanet alfa. A logit model was used, on account of the binary treatment outcome (andexanet alfa or PCC). Covariates, chosen from baseline characteristics reported by either study, were selected based on UK clinical opinion regarding their effect on 30-day mortality and the strength of their association with treatment assignment. The covariates that fulfilled these criteria, for the Whole cohort included:

- Age
- Bleed type (i.e. location of bleeding – ICH, GI or other)
- Medical history of coronary artery disease
- Medical history of stroke
- Medical history of transient ischemic attack
- Medical history of deep vein thrombosis
- Medical history of venous thromboembolic disease
- Medical history of atrial fibrillation
- Medical history of hypertension
- Medical history of diabetes
- Medical history of renal dysfunction
- Medical history of cancer

Addition of other variables would have increased the number of dimensions on which observable characteristics were required for matching individuals.[100] This in turn would have reduced the pool of comparable individuals between the two studies. In addition, inclusion of inappropriate covariates would have unnecessarily increased the variance of results, and so reduced precision.

Following the selection of covariates, propensity score matching was conducted in R version 3.6.1 utilising the MatchIt package for a one-to-one nearest neighbour matching with replacement. Nearest neighbour matching will reduce the bias in the results, while recognising the difficulty in achieving matches with only a medium-sized sample. No trimming of the sample was conducted; however, replacement was undertaken to minimise bias.

The two patient level datasets were cleaned and combined to allow for analysis. Only individuals with complete response data (no missing data for baseline characteristics) were included in the analysis. Three patients were excluded from the subset of the ORANGE patient population receiving rivaroxaban and apixaban because data were not available for their age; a variable UK clinical experts indicated was a key driver of mortality outcomes. One patient was excluded from the subset of the ORANGE patient population receiving rivaroxaban and apixaban because they did not report whether they died.

The results of the propensity score matching are presented in Table 33.

Table 29. Summary of balanced for matched Whole cohort data

Whole cohort	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI bleed	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with other bleed types	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of stroke	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of CAD	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of TIA	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of AF	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of diabetes	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]

Medical history of cancer	[redacted]	[redacted]	[redacted]	[redacted]

Table 30. Summary of balanced for matched ICH cohort data

ICH cohort	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of stroke	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of CAD	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of TIA	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of AF	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of diabetes	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of cancer	[redacted]	[redacted]	[redacted]	[redacted]

Table 31. Summary of balanced for matched GI cohort data

Severe GI	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of stroke	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of CAD	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of TIA	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of AF	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of diabetes	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of cancer	[redacted]	[redacted]	[redacted]	[redacted]

Table 32. Summary of balanced for matched other major bleeds cohort data

Other major bleeds	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of stroke	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of CAD	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of TIA	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of AF	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of diabetes	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
Medical history of cancer	[redacted]	[redacted]	[redacted]	[redacted]

Table 33. Propensity score matching results for each cohort

Population	Number of matches	Adjusted 30-day mortality for PCC (%)	Adjusted 30-day mortality for andexanet alfa (%)
Whole population	[redacted]	[redacted]	[redacted]
ICH subgroup	[redacted]	[redacted]	[redacted]
GI subgroup	[redacted]	[redacted]	[redacted]
Other major bleeds (non-ICH/GI)	[redacted]	[redacted]	[redacted]

ICH – intracranial haemorrhage, GI – gastrointestinal

Several limitations were associated with the analysis:

- Firstly, the treatment effects apply to a wider population than the population with life-threatening bleeds, specified in the NICE scope. The ORANGE study collated data for patients who had experienced a major bleed, though it was not required for the bleed

to be life-threatening or uncontrolled as per andexanet alfa's licence. While an ICH may usually be considered life-threatening, and GI bleed particularly with the treatment of PCC, other major bleed categories have a wide range of severity which unsurprisingly results in higher mortality rates in the andexanet alfa arm.

- Secondly, the number of matches in the other major bleeds subgroup were low. This suggests several patients were not similar in their baseline characteristics and therefore were not comparable across the two studies. In addition, the two studies had different distributions of bleeds considered 'other major bleeds' which would have different baseline characteristics. Therefore, no possible adjustment using covariates was considered sufficient to ensure the comparability of patients in matched pairs for the 'other major bleeds' group only, making these results non-applicable to the economic model.
- Finally, a limitation of non-randomised data is that it is not possible to account for unobserved confounders and hence results are subject to inherent bias.

Acknowledging the limitations above, it is notable that in the ICH subgroup, for which the number of matches and applicability to the andexanet alfa licence is less of a concern, 30-day mortality for PCC ([redacted] is slightly higher than the naïve unadjusted results ([redacted]), and at the top end of mortality reported in the literature for all-cause ICH (range 33-45%,[15,19,20]). This is unsurprising given that the population consists of patients receiving PCC (an indicator of bleed severity) and matching has attempted to identify life threatening and uncontrolled bleeds, which presumably would seek to remove major bleeds which were not life-threatening or uncontrolled. Based on the adjusted or unadjusted results, andexanet alfa is associated with at least a 3-fold improvement in survival.

For the GI subgroup, 30-day mortality for PCC ([redacted]) is slightly higher than the naïve unadjusted results ([redacted]). This is unsurprising given that the population consists of patients receiving PCC (an indicator of bleed severity) and matching has attempted to identify life threatening and uncontrolled bleeds, which presumably would seek to remove major bleeds which were not life-threatening or uncontrolled. Based on the adjusted or unadjusted results, andexanet alfa is associated with a 2-fold improvement in survival.

For the other major bleed subgroup, the heterogeneity in other major bleed populations alongside the smaller sample size (<10 patients when matching) can be seen by the counter-intuitive results when comparing the adjusted 30-day mortality for PCC ([redacted] with the naïve unadjusted results ([redacted]). Given the heterogeneity between bleeds, the sample size and clinically counter-intuitive results, the propensity score matching analysis for the other major bleed subgroup is less informative.

B.2.10 Adverse reactions

B.2.10.1 ANNEXA-A/ANNEXA-R

All adverse events related to andexanet alfa administration were non-serious and mild (Table 34). One subject with a history of hives discontinued andexanet alfa infusion after 35 minutes due to developing mild hives (the patient was excluded from the efficacy population but

included in safety analyses). There were no serious or severe adverse events, and no thromboembolic events were reported. Antibodies to FX or FXa did not develop in any participants. Neutralising antibodies against andexanet alfa were not detected. Non-neutralising antibodies against andexanet alfa were detected in 1 of 44 participants (2%) who received placebo and in 17 of 101 participants (17%) who received andexanet alfa. There were transient elevations in D-dimer and prothrombin fragments 1 and 2 levels in a subset of subjects, but these generally returned to the normal range within 24 to 72 hours.

Table 34. Drug-Related Adverse Events (Adverse Events That Occurred ≥ 2 Times and More Frequently with Andexanet Alfa vs Placebo)

	Apixaban Group Treated with Andexanet Alfa		Rivaroxaban Group Treated with Andexanet Alfa		Placebo
Event	Bolus (n = 24)	Bolus + Infusion (n = 24)	Bolus (n = 27)	Bolus + Infusion (n = 26)	(n = 44)
GI disorders	2	2	0	0	0
Constipation	0	2	0	0	0
Dysgeusia	2	0	0	0	0
General disorders and administration-site conditions	3	4	2	0	1
Feeling hot	1	2	0	0	1
Flushing	2	2	2	0	0
Immune system disorders	0	1	1	0	0
Urticaria	0	1	1	0	0

CI – confidence interval; GI – gastrointestinal
Source: Siegal, 2015[75]

B.2.10.2 ANNEXA-4

Summary of Adverse Events

Of the 352 patients in the Safety Population, a total of [redacted] treatment-emergent adverse events (TEAEs) were reported by [redacted] patients (Table 35). The majority [redacted] of TEAEs were graded as mild or moderate, though [redacted] patients experienced at least one TEAE that was graded as at least severe on the severity scale.[97]

The majority ([redacted] of TEAEs were assessed by Investigator as unrelated/unlikely related to andexanet alfa. Overall, [redacted] patients experienced treatment-related TEAEs (Table 37). [redacted] patients experienced TEAEs resulting in premature discontinuation of the study drug, [redacted]

A total of [redacted] had an SAE that was considered possibly or probably related to andexanet alfa. [redacted].

There were [redacted]).

The most common TEAEs by primary System Organ Classification (SOC) are shown in Table 36. The most frequently reported TEAEs by preferred term (PT) (occurring in ≥ 3% of patients) were [redacted]

[redacted] The pattern and frequency of the adverse events are consistent with the background risk profile, underlying medical history, and severity of illness in the patients enrolled.

Table 35. Overall Summary of Adverse Events (Safety Population, Day 30/45* Safety Follow Up Visit)

	Overall
All Patients	352
Number of Patients with AT LEAST ONE	
Adverse Events	[redacted]
Treatment Emergent Adverse Event	[redacted]
Treatment-Related Adverse Event	[redacted]
Adverse Event Leading to Drug Discontinuation	[redacted]
Adverse Event Leading to Early Study Withdrawal	[redacted]
Adverse Event Special Interest	[redacted]
Infusion Reactions	[redacted]
Thrombotic Event	[redacted]
Serious TEAE	[redacted]
Fatal TEAE	[redacted]
Number of TEAEs	[redacted]

Database lock date: 28Nov2018. The Safety Population includes all patients who received any amount of andexanet.
Thrombotic event was adjudicated by the Endpoint Adjudication Committee.
Toxicity grade of seven AEs was imputed by fatal AE action outcome.
* NOTE: all patients enrolled under Amendment 1 or earlier had a day 45 visit in lieu of a day 30 visit. All patients enrolled under Amendment 2 or later had a day 30 visit and no Day 45 visit. No patient had both a Day 30 and a Day 45 visit. Thus, all adverse events cited in the tables were recorded to Day 45 for those patients that had a Day 45 visit, and Day 30 for those patients that had a Day 30 visit.
** 5 deaths occurred after 30 calendar days. 2 of these deaths occurred after the Day 30/45 visit and were mistakenly recorded by the investigators; as such they were counted in the final tabulations.
Source: ANNEXA-4 CSR[97]

Table 36. Most Common (≥ 10%) TEAE by MedDRA Primary System Organ Class (Safety Population)

MedDRA Primary System Organ Class	All Patients (N=352) n(%)
Patients with TEAE	[redacted]
Infections and infestations	[redacted]
Nervous system disorders	[redacted]
Vascular disorders	[redacted]
Gastrointestinal disorders	[redacted]
Cardiac disorders	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]
General disorders and administration site conditions	[redacted]

Database lock date: 28Nov2018. The Safety Population includes all patients who received any amount of andexanet.
Source: ANNEXA-4 CSR[97]

Table 37. Treatment-related Treatment-emergent Adverse Events by MedDRA Preferred Term (Safety Population)

MedDRA Preferred Term	All Patients (N=352) n (%)
Patients with Related TEAE	[redacted]
Ischaemic stroke	[redacted]
Pyrexia	[redacted]
Headache	[redacted]
Nausea	[redacted]
Cerebral infarction	[redacted]
Cerebrovascular accident	[redacted]
Myocardial infarction	[redacted]
Deep vein thrombosis	[redacted]
Infusion related reaction	[redacted]
Pulmonary embolism	[redacted]
Depressed level of consciousness	[redacted]
Intracranial venous sinus thrombosis	[redacted]
Transient ischaemic attack	[redacted]
Acute myocardial infarction	[redacted]
Bradycardia	[redacted]
Cardiac arrest	[redacted]
Cardiac failure	[redacted]
Tachycardia	[redacted]
Dry mouth	[redacted]
Flatulence	[redacted]
Vomiting	[redacted]
Sudden death	[redacted]
Iliac artery occlusion	[redacted]
Acute kidney injury	[redacted]
Haematuria	[redacted]
Pruritus	[redacted]

MedDRA = Medical dictionary for regulatory activities; TEAE = Treatment-emergent adverse event
Note: Database lock date: 28 Nov 2018. The Safety Population includes all patients who received any amount of andexanet.
Source: ANNEXA-4 CSR[97]

No patients developed antibodies to FX after andexanet alfa treatment, and no neutralising antibodies to FXa or andexanet alfa were observed.[74]

Deaths and Serious Adverse events

There were 49 deaths (14%) overall to Day 30, with 35 adjudicated as cardiovascular events, 12 as non-cardiovascular events, and 2 were of unknown cause (Table 38 and Table 40).[74] The Day-30 mortality rate in patients with ICH was 15%, and 11% in patients with GI bleeding.[101] For patients treated with rivaroxaban or apixaban, the Day-30 mortality rate was [redacted] in patients with ICH [redacted] in patients with GI bleeding). [redacted]

[redacted]

Table 38. Adjudicated Reason for Deaths (Safety Population)

		Patients with Apixaban or Rivaroxaban		
	All Patients (N=352)	**Patients (n=322)**	**Patients with ICH (n=209)**	**Patients with GI (n=82)**
Deaths [1], N	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for death, N (%)				
Cardiovascular: Not Related to Bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Patients had TEs	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular: Related to Bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Patients had TEs	[redacted]	[redacted]	[redacted]	[redacted]
Non-Cardiovascular	[redacted]	[redacted]	[redacted]	[redacted]
Patients had TEs	[redacted]	[redacted]	[redacted]	[redacted]
Uncertain	[redacted]	[redacted]	[redacted]	[redacted]
Unknown[2]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths within 30 days	[redacted]	[redacted]	[redacted]	[redacted]

Database lock date: 28Nov2018. The Safety Population includes all patients who received any amount of andexanet.
[1] [redacted]
[2] Deaths of two patients were not adjudicated (as they occurred after the Day 30/45 visit)
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Source: Portola data on file[96]

Of the 352 patients in the Safety Population, a total of [redacted] patients experienced at least one SAE. Twenty-three (6.5%) patients experienced at least one treatment-related SAE (Table 39). [redacted] No other event occurred in more than one patient. Overall, the burden, pattern, and frequency of SAEs were not unexpected, given the advanced age and acuity/severity of illness of the enrolled population.

Table 39. Serious treatment-emergent adverse events considered possibly or probably related to andexanet alfa treatment by MedDRA Primary System Organ Class and Preferred Term (Safety Population)

MedDRA Primary System Organ Class Preferred Term	All Patients (N=352) n (%)
Patients with Related SAE	[redacted]
Nervous System Disorders	[redacted]

MedDRA Primary System Organ Class Preferred Term	All Patients (N=352) n (%)
Ischaemic Stroke	[redacted]
Cerebral Infarction	[redacted]
Cerebrovascular Accident	[redacted]
Depressed Level Of Consciousness	[redacted]
Intracranial Venous Sinus Thrombosis	[redacted]
Transient Ischaemic Attack	[redacted]
Cardiac Disorders	[redacted]
Myocardial Infarction	[redacted]
Acute Myocardial Infarction	[redacted]
Cardiac Arrest	[redacted]
Cardiac Failure	[redacted]
Vascular Disorders	[redacted]
Deep Vein Thrombosis	[redacted]
Iliac Artery Occlusion	[redacted]
Respiratory, Thoracic and Mediastinal Disorders	[redacted]
Pulmonary Embolism	[redacted]
General Disorders and Administration Site Conditions	[redacted]
Sudden Death	[redacted]
Injury, Poisoning and Procedural Complications	[redacted]
Infusion Related Reaction	[redacted]
Renal and Urinary Disorders	[redacted]
Acute Kidney Injury	[redacted]

Database lock date: 28Nov2018. The Safety Population includes all patients who received any amount of andexanet.
Source: ANNEXA-4 CSR[97]

Thrombotic events

Thrombotic events included the protocol-specified, independently-adjudicated events that were defined at the start of the study (i.e., cerebrovascular accidents, DVTs, myocardial infarctions, PEs, and transient ischemic attacks). Thrombotic events occurred in 34 of 352 patients (10%) during the 30-day follow-up.[74]

There were 220 of 352 (62%) patients who received at least one dose of parenteral or oral anticoagulant therapy in the 30 days after andexanet alfa treatment; 8/352 (2%[1]) had a thrombotic event after restarting any anticoagulation. Only 100/352 (28%) patients were restarted on oral anticoagulation during follow-up; no thrombotic events were reported in these patients after restart of oral anticoagulation (Table 41).[74]

[1]The 2% rate of thromboembolic events was calculated using the total safety population (N = 352) as the denominator. If the number of patients restarting any anticoagulation is used as the denominator (N = 220), the rate of thromboembolic events is 3.6% (8/220).

Table 40. Timing of Thromboembolic Events and Deaths (N = 352)[a]

	Total N = 352	< 6 days after bolus	6-14 days after bolus	15-30 days after bolus
≥ 1 thrombotic event within 30 days, n (%) [b]	34 (10)	11	11	12
Myocardial infarction	7	6	1	0
Ischemic stroke or stroke of uncertain classification	14	5	6	3
Transient ischemic attack	1	0	0	1
Deep vein thrombosis	13	1	5	7
Pulmonary embolism	5	1	0	4
Death occurring within 30 days, n (%) [c]	49 (14)	8	21	20
Cardiovascular death	35	7	15	13
Non-cardiovascular death	12	1	5	6
Death of uncertain cause	2	0	1	1

a Thrombotic events that occurred on the day of restarting anticoagulation were considered to have occurred before the restart.
b Some patients had more than one thromboembolic event.
c Five deaths occurred during study follow-up, but after 30 calendar days
Source: Connolly 2019[74]

Table 41. Timing of Restarting of Anticoagulation (N = 352)

	Total N = 352	< 6 days after bolus	6−14 days after bolus	15−30 days after bolus
Restart of any anticoagulation, n (%) [a]	220 (62)	145 (41)	46 (13)	29 (8)
Thrombotic event before restart [c]	26 (7)			
Thrombotic event after restart	8 (2[d])			
Restart of oral anticoagulation, n (%) [c]	100 (28)	31 (9)	37 (11)	32 (9)
Thrombotic event before restart [b]	34 (10)			
Thrombotic event after restart	0			

a Restart of any anticoagulation includes use of any form of heparin or low molecular weight heparin, fondaparinux or argatroban; or any oral anticoagulant including vitamin K antagonists, and non-vitamin K antagonists (at any dose and for any duration).
b Restart of oral anticoagulation includes only use of Vitamin K antagonists or non-Vitamin K oral anticoagulants.
c Included are thrombotic events that occurred in patients who never restarted anticoagulation. Thromboembolic events occurring on the day of restarting anticoagulation are considered to have occurred before anticoagulation.
d The 2% rate of thromboembolic events was calculated using the total safety population (N = 352) as the denominator. If the number of patients restarting any anticoagulation is used as the denominator (N = 220), the rate of thromboembolic events is 3.6% (8/220).
Source: Connolly 2019[74]

Table 42. Timing of Restarting of Anticoagulation in Patients with Apixaban or Rivaroxaban (Safety Population, N = 322)

Anticoagulation Type	Days	All Patients (N=322)	Patients with ICH (N=209)	Patients with GI (N=82)
Patients who Restarted Any Anticoagulation	<30 days	[redacted]	[redacted]	[redacted]
	≥30 days	[redacted]	[redacted]	[redacted]
Patients who Restarted Non-oral Anticoagulation	<30 days	[redacted]	[redacted]	[redacted]
	≥30 days	[redacted]	[redacted]	[redacted]
Patients who Restarted Oral Anticoagulation[1]	<30 days	[redacted]	[redacted]	[redacted]
	≥30 days	[redacted]	[redacted]	[redacted]

Database lock date: 28Nov2018. The Safety Population included patients treated with any amount of andexanet.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
[1] Restart of oral anticoagulation includes only the use of vitamin K antagonists or non-vitamin K oral anticoagulants (at any dose and for any duration).
Source: Portola data on file[96]

B.2.11 Ongoing studies

No additional data from ongoing studies in bleeding patients are expected in the next 12 months.

Andexanet alfa is being investigated in a randomized, controlled clinical trial evaluating efficacy and safety versus usual standard of care in patients with ICH anticoagulated with a direct oral anticoagulant (NCT03661528). Estimated primary completion date is March 2023.

B.2.12 Innovation

Andexanet alfa is a highly innovative technology. Andexanet alfa has been granted conditional marketing authorisation by the European Commission, where the benefit to public health of immediate availability outweighs the risk of less comprehensive data than normally required. Andexanet alfa is also an FDA-designated breakthrough therapy. Andexanet alfa is the only agent that has been demonstrated to directly reverse the inhibitory effects of apixaban and rivaroxaban on FXa, their target.

In randomized clinical trials, FXa inhibitors have been shown to be effective for the treatment and prevention of VTE and for stroke prevention in patients with AF, with an acceptable safety profile, and compared to warfarin reduced rates of ICH.[16] Since their introduction use of DOACs has increased substantially[102] and will continue to do so with the increasingly elderly population and associated rates of AF.

However, FXa inhibitors are associated with major and even fatal bleeding events. These bleeding patients suffer poor outcomes and high mortality rates. Such episodes of acute major bleeding may be difficult to treat because there is no reversal agent. In addition, agents with no efficacy evidence to support their use are given in clinical practice; this is a consequence of the urgent nature of treatment and the high unmet need for a reversal agent. As the first agent specifically developed to reverse the effects of FXa inhibitors, andexanet alfa represents a step-change in therapy.

Despite FXa inhibitors having advantages over warfarin such as rapid onset and offset of action; fewer drug, disease state, and dietary interactions; fixed dosing and no need for routine monitoring of anticoagulant activity, the lack of a specific reversal agent may be used to justify adopting their use ahead of warfarin.[103] The availability of andexanet alfa as an innovative specific reversal agent for FXa inhibitors will encourage their use further and potentially decreases the overall risk of intracranial bleeding in the anticoagulated population. Whilst rare, intracranial bleeding can have catastrophic consequences to individual patients, as well as putting great costs on the NHS in resource use. This indirect benefit is unlikely to be picked up by the QALY calculation.[103]

The ability to have a standard of care which is effective in reversing FXa inhibiting DOACs will create a standardisation that will facilitate timely effective treatment and within hospital efficiencies. This change in service would not be captured in the QALY calculation but will represent significant benefits to patients and the NHS.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Key findings of the clinical evidence

As a reversal agent, the evidence base for andexanet should be considered with the view that it acts as an antidote to FXa-inhibitors. In this respect, key evidence supporting regulatory approval of andexanet alfa was the overwhelming pharmacodynamic data that included evidence from randomised clinical trials (ANNEXA-A and ANNEXA-R) that support its mechanism of action and ability to rapidly reverse FXa-inhibitor anticoagulation from randomized placebo-controlled trials in healthy people.

The phase 3 ANNEXA-A and ANNEXA-R studies showed a rapid and significant reduction in anti-fXa activity (above 90%) and unbound apixaban or rivaroxaban concentration within 2 to 5 minutes after administration of a bolus of andexanet alfa in healthy subjects, and the effects were sustained throughout a 2-hour infusion.[75] The studies also showed that andexanet (bolus + infusion) restored thrombin generation (to above the lower limit of the normal range) in all the apixaban-treated and rivaroxaban-treated subjects.

The duration of reversal after cessation of andexanet alfa administration is consistent with the half-life of andexanet alfa. This observation is relevant for situations in which re-anticoagulation is considered. Due to the risk of thrombotic events after direct FXa inhibitor-associated major bleeding, it is important to ensure timely reinstatement of anticoagulation in these patients.

Haemostatic efficacy with andexanet alfa was evaluated in a phase 3b/4 study in patients with major bleeding associated with FXa inhibitors (ANNEXA-4 [apixaban, rivaroxaban, edoxaban, or enoxaparin]).[74] The efficacy analysis population included 254 patients who met two additional eligibility criteria: baseline anti-fXa activity ≥ 75 ng/mL (apixaban and rivaroxaban); and independently adjudicated major bleeding at presentation. The 75 ng/mL threshold was chosen to ensure evaluable patients would be in the therapeutic range of the FXa inhibitors. After andexanet alfa bolus, the median anti-fXa activity decreased by 92% (95% CI, 91–93) from baseline among patients receiving apixaban (n = 134) and by 92% (95% CI, 88–94) among patients receiving rivaroxaban (n = 100).[74]

In ANNEXA-4, clinical haemostasis was adjudicated as excellent or good in 82% (95% CI, 77–87) of patients 12 hours after andexanet alfa infusion. The rates of excellent or good efficacy were 85% (95% CI, 76–94) for GI bleeding and 80% (95% CI, 74–86) for intracranial bleeding.[74] In a post-hoc analysis of ANNEXA-4, [redacted] efficacy evaluable patients had non-traumatic, single-compartment, intraparenchymal haemorrhages. Of these [redacted] patients [redacted] patients ([redacted] had volume expansion >35% (a threshold commonly used to define haematoma expansion). Of [redacted] with volume expansion ≤35% from baseline at 1 hour, [redacted] had no additional haematoma expansion at 12 hours (haematoma volume remained ≤35% vs baseline).[101] Expansion of the initial haematoma strongly influences morbidity and mortality. The hazard ratio of mortality goes up by 5% with every 10% increase in ICH volume. Numerous studies confirm the relationship of expansion with neurological deterioration, poor functional outcome, and death.[104]

Rapid specific reversal of FXa inhibition to hasten haemostatic control should improve clinical outcomes. Based on NIHSS and GCS data from ANNEXA-4, it can [redacted].

Studies of PCC to reverse FXa inhibitor bleeding have limitations in their comparability to ANNEXA-4. In a prospective evaluation, Majeed et al (2017)[50] reported on the use of 4F-PCC to reverse apixaban- or rivaroxaban-related major bleeding in patients attending 25 Swedish hospitals (N=84; ICH in 70% of patients). In this study, effective haemostasis occurred in 69% of patients. A further prospective study by Schulman et al (2018)[51] reported haemostatic effectiveness from a registry describing the use of PCC in patients with acute major bleeding associated with FXa inhibitors (N=66; ICH in 55% of patients). The effectiveness of the treatment with PCC on haemostasis was assessed by the treating physician as good for 43 patients (65%; 95% confidence interval [CI], 53–77), moderate for 13 (20%; 95% CI, 10–30). Comparison of outcomes observed in these studies to outcomes in the ANNEXA-4 study is not appropriate. There were substantial differences in the way that major bleeding and haemostatic efficacy were defined and evaluated in these studies. Whilst in the study by Majeed et al, assessment was performed independently by two coagulation specialists, in the study by Schulman et al, assessment of haemostasis was by the treating physician and was not adjudicated, therefore potentially introducing inconsistency and bias. There was no protocol-driven follow up CT imaging performed at specified timepoints, which is a critical component of the assessment of haemostatic efficacy in ICH patients in ANNEXA-4. The results may also be confounded because the level of FXa inhibitor present in the patients included in these studies was unknown, and in some cases likely to be very low, since the time from last FXa inhibitor was substantially greater (e.g., mean approximately 18 hours in the Schulman study compared to 12 hours in ANNEXA-4).

Cohort studies that enrolled patients receiving PCC have included haemostatic outcomes assessed by diverse methods. In the study by Schulman et al,[51] of 36 patients with ICH who underwent repeat brain imaging or had early death, 11 (31%) had an increase in haematoma volume of more than 35% or died. Gerner et al.[90] retrospectively measured haematoma expansion in 146 patients with ICH associated with a direct oral anticoagulant, and unlike the studies by Schulman et al and Majeed et al, utilised serial CT scans to assess haemostatic efficacy. 83% of bleeding episodes were associated with FXa inhibitors, and 71% of patients with a bleeding episode received PCC. Haematoma expansion (≥33% from baseline) occurred in 34% of the patients. There was no significant association of PCC administration with the occurrence of haematoma enlargement in patients with factor Xa inhibitor intake. In a further small study, of 9 patients with ICH, 5 (55%) showed haematoma expansion, and 4 (including 2 with haematoma expansion) required haematoma evacuation surgery.[87] In the intra-cerebral haemorrhage substudy of RASUNOA, administration of PCC had no statistically significant effect on the early haematoma expansion and the functional outcome at 3 months.[27] The authors state that the limited sample size, and the potential for confounding by indication did not allow any conclusions regarding a potential association between PCC treatment and outcome. It should be noted that the Gerner et al and RASUNOA studies enrolled only patients with intracerebral haemorrhage, whereas other studies (including ANNEXA-4) enrolled intracranial haemorrhage, of which intracerebral haemorrhage is a subtype). Intracerebral

haemorrhages tend to have a worse prognosis than other subtypes of intracranial haemorrhage, including subdural and subarachnoid bleeds.

Andexanet alfa was generally well-tolerated in healthy subjects and in patients with acute major bleeding. No deaths or serious/severe adverse events were reported in healthy subjects in phase 2 and 3 studies. The most common adverse reactions (≥ 5%) in patients receiving andexanet alfa were urinary tract infections and pneumonia. The most common adverse reactions (≥ 3%) in healthy volunteers treated with andexanet alfa were infusion-related reactions.[1] Clinical studies in healthy subjects have shown that andexanet alfa lacks inherent pro-thrombotic activity. In the phase 3 ANNEXA-A and ANNEXA-R studies in healthy subjects, transient elevations in coagulation markers, prothrombin fragments 1 and 2 and D-dimer, were observed but were not associated with the development of thromboembolic events.[75]

Patients receive FXa inhibitors because they are at high risk for thrombotic events. Abrupt discontinuation of anticoagulation, coincident with acute bleeding, accentuates this risk. Real-world studies and clinical trials have reported rates of thrombotic events after direct FXa inhibitor-associated major bleeding after 30 days ranging from 4% to 15%.[14,18,53,105,106] In the ANNEXA-4 study, 10% (34/352) of patients had a thromboembolic event (protocol-specified, independently-adjudicated events defined at the start of the study, such as cerebrovascular accidents, DVT, myocardial infarctions, PE, and transient ischaemic attacks) during the 30-day follow-up period.[74] Not surprisingly, the majority of thrombotic events (76%) in ANNEXA-4 occurred in patients in whom resumption of oral anticoagulation was delayed or in patients who did not restart anticoagulation. After restarting of oral anticoagulation, no patient had a thrombotic event during the 30-day follow-up.[74]

Overall, there were 49 deaths (14%) in ANNEXA-4 within 30 days of enrolment, with 35 adjudicated as cardiovascular events, 12 as non-cardiovascular events, and 2 were of unknown cause.[74] The mortality rate in patients with ICH was 15%. In studies of PCCs in patients with major bleeding who were receiving a direct FXa inhibitor, the rate of mortality 30 days after the bleeding event ranged from 14% to 33.5%,[50,51,107-109] and was higher in patients with ICH, ranging between 22% and 44%.[51,107,109] In addition, since the studies by Schulman et al[51] and Majeed et al[50] excluded patients with a Do Not Resuscitate order, the observed mortality rates would have been artificially reduced compared to those expected in practice. In clinical trials of FXa inhibitors in patients with AF, 30-day mortality rates after major bleeding are reported to be up to 20%, and up to 45% in patients with ICH.[15,18,19] Real-world observational studies have also shown high rates of bleeding-related mortality in patients being treated with direct FXa inhibitors. As described in Section B1.3.3, the UK study ORANGE was a 3-year, prospective cohort study that collected information from multiple UK hospitals on the presentation and clinical outcomes of patients who were admitted for a major bleeding episode (based on ISTH criteria) while on oral anticoagulant therapy.[20,52] It is the first and largest study of its kind in the UK. Data on major bleeding events were prospectively collected by over 30 hospitals across England, Scotland, Wales and Northern Ireland between October 1, 2013 and August 31, 2016, with information retrieved directly from patients' case notes. The study included 2,192 patients, of which 283 were on rivaroxaban and 89 were on apixaban. Patients underwent the normal course of treatment as directed by their clinicians and hospital protocols. For the management of bleeding, those patients on DOACs were given

any blood transfusion (41%), 4F-PCC (39%, including 1% who were administered FEIBA), tranexamic acid (28%).[52]

In the ORANGE study, the mortality rate up to 30 days of follow up was 21% among DOAC treated patients. Recently published analysis on the DOAC subgroup of this study did not find evidence of a benefit for 4F-PCC on in-hospital mortality.[52] In addition, administration of tranexamic acid was not found to be associated with risk of death in these patients.[52] The ORANGE study is the first and largest to report on the association between PCC use and mortality in patients who develop major bleeding on DOACs (note, this second report was published subsequent to the completion of the systematic literature review).

As with all therapeutic proteins, there is potential for immunogenicity. Andexanet alfa showed little immunogenicity in healthy subjects or in patients with acute major bleeding.

B.2.13.2 Strengths and limitations of the clinical evidence base

The strengths of the ANNEXA-A/ANNEXA-R studies include their randomized, double-blind, placebo-controlled design and the inclusion of older participants, who are more similar to those who receive FXa inhibitors in the community than younger people. The use of a dosing regimen of the FXa inhibitors that would achieve steady-state levels in plasma (leading to equilibrium with the extravascular space) and the use of widely accepted biomarkers of coagulation (anti–FXa activity, free anticoagulant concentrations, and thrombin generation) are additional strengths.

The evidence base for andexanet alfa could be compared to products use to reverse the effect of poisons or other toxic drugs. For example, glucarpidase, which is commissioned by NHS England for the urgent treatment of methotrexate-induced renal dysfunction to treat a variety of cancers and autoimmune conditions.[110] Efficacy of glucarpidase was based on reductions of plasma methotrexate concentration in addition to renal recovery from single-arm compassionate-use clinical trials.[110]

Healthy study participants anticoagulated to steady-state to investigate reversal of anticoagulation may not reflect the patient population who receive FXa inhibitors as prescribed. However, the use of an older volunteer population was deemed appropriate for demonstration of reversal of anticoagulation because blocking anticoagulation in the target patient population would expose these patients' underlying thromboembolic risk by reversing their medically necessary anticoagulation. It is possible to achieve therapeutic anticoagulation in a volunteer population and to directly measure the reversal of anticoagulation using clinically relevant assays for anti-fXa activity and other coagulation markers. In order to approximate the ultimate target patient population for andexanet alfa, the ANNEXA-A and ANNEXA-R studies enrolled older (ages 50 to 75 years) subjects, including those with existing but stable chronic medical conditions. Therefore, subjects with hypercholesterolemia, hypertension, diabetes, and osteoarthritis, conditions that are common amongst the population of patients taking FXa inhibitors, were not excluded in these studies.

ANNEXA-4 is the first prospective study of an intervention for the reversal of FXa inhibitors, including adjudicated outcomes for haemostatic efficacy, carried out to date. This trial did not include a randomized comparison with a control group. At the time of study initiation, it was

determined that a randomized, controlled trial would have logistic and ethical challenges, given the perceived risks of placebo assignment in this highly vulnerable population. However, continued use of unapproved agents including PCC, despite a lack of rigorous clinical data, and uncertainty regarding their efficacy and safety, has changed the equipoise for a trial. Thus, the sponsor has initiated a randomized trial (ClinicalTrials.gov number, NCT03661528). In the European Union, submission of the clinical study report for this post-authorisation study is an obligation of the conditional marketing authorisation.

In ANNEXA-4 an independent adjudication committee assessed whether patients met criteria for major bleeding and adjudicated haemostatic efficacy on the basis of pre-specified criteria as well as thrombotic events and cause of death.

The majority of patients enrolled in ANNEXA-4 were from US centres. However, the demographics, co-morbidities and range of indications for anticoagulation of patients in ANNEXA-4 were similar to that of patients in the UK receiving DOACs.[20,102] The mean age of the patients was 77 years and represented a high-risk population that will be receiving a FXa inhibitor and at risk for acute major bleeding events. In the ANNEXA-4 and ORANGE studies a similar proportion of patients had bleeding due to trauma (approximately 30%).[20]

B.2.13.2 End-of-life criteria

Andexanet alfa does not meet the criteria for ‘life-extending treatment at the end of life'.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

- In appendix G, describe and compare the methods and results of any published cost-effectiveness analyses available for the technology and/or the comparator technologies (relevant to the technology appraisal).
- See Section 3.1 of the user guide for full details of the information required in appendix G.

An economic systematic literature review (SLR) was conducted using a single search strategy to identify cost-effectiveness, health-related quality-of-life (HRQoL) (Section B.3.4 Measurement and valuation of health effects), and cost and resource use studies (Section B.3.5 Cost and healthcare resource use identification, measurement and valuation).

Please see Appendix G for the methods used to identify all relevant studies, and a description and quality assessment of the cost-effectiveness studies identified. The economic SLR identified relevant studies in adults receiving a direct or indirect FXa inhibitor requiring reversal of anticoagulation due to life-threatening or uncontrolled bleeding on the 14th December 2016 with an update performed on the 25th January 2019.

In line with guidance from the Centre for Reviews and Dissemination (CRD)[111], the population, interventions, comparators, outcomes and study type (PICOS) principal was used to define the following review question to identify relevant cost-effectiveness studies:

- What cost-effectiveness analyses have been conducted in individuals receiving a direct or indirect FXa inhibitor requiring rapid reversal of anticoagulation?

The economic SLR identified one publication which met the cost-effectiveness eligibility criteria and was considered for data extraction; Mangram et al. 2016.[112] The objective of this cost-effectiveness study was to compare the efficacy, safety and cost-effectiveness of 3-factor (3F)-PCC versus 4-factor (4F)-PCC in patients who had experienced trauma and required rapid reversal of either rivaroxaban or warfarin from a United States (US) perspective. Study outcomes assessed included induced normalised ratio (INR) reversal, adverse effects and cost-effectiveness. The time horizon of the cost-effectiveness study was 48 hours, with no reported discount rate applied.

The study evaluated the cost-effectiveness of PCC from a US perspective. Efficacy and safety data to inform the model were based on a retrospective study which was conducted in two affiliated American College of Surgeons-verified trauma centres. One of these was a level-I trauma centre and the other was a level-III trauma centre. Further details of this study are presented in Table 43 below.

Table 43. Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (USD) (intervention, comparator)	ICER (per QALY gained)
Mangram et al. (2016)	2016	48 hour time horizon; US perspective; outcomes include: successful INR reversal, adverse effects, cost-effectiveness	76 years	No quality-of-life data collected	Total cost of 46 patients receiving 3F-PCC: $2,691 ± $1,432 Total cost of 18 patients receiving 4F-PCC: $3,164 ± $870	ICER (per QALY gained) not reported Total cost per successful reversal: 3F-PCC: $5,382 ± $2,864 4F-PCC: $3,797 ± $1,044

3F – 3 factor; 4F – 4 factor; ICER – incremental cost-effectiveness ratio; INR – induced normalised ratio reversal; PCC – pro-thrombin complex concentrate; QALYs – quality-adjusted life years; USD – United states dollars.

B.3.2 Economic analysis

A cost-effectiveness SLR identified one cost-effectiveness study conducted in adults receiving a direct or indirect FXa inhibitor who require reversal of anticoagulation due to life-threatening or uncontrolled bleeding; Mangram et al. 2016.[112] Mangram et al. 2016 investigated patients receiving warfarin and rivaroxaban, though the analysis reported was simplistic and did not report utilities, quality adjusted life years (QALYs) or an incremental cost per QALY. In addition, it presented no clear structure which could be used to inform the cost-effectiveness model (CEM). As such, the cost-effectiveness analysis had little relevance for informing the economic analysis of andexanet alfa for the purpose of this NICE submission. Therefore, a de novo CEM was developed.

B.3.2.1 Patient population

The population entering the CEM are adults who have received a direct FXa inhibitor who are experiencing life-threatening or uncontrolled bleeding events and consequently require anticoagulant reversal, to reflect the anticipated indication shown in Table 2 for andexanet alfa.

Life-threatening or uncontrolled bleeding was defined by site of bleed in consultation with UK clinical experts. Specifically, patients entering the model had one of the following types of acute major bleeds:

- Intracranial haemorrhage (ICH): bleeding inside the skull
- Severe gastrointestinal (GI) bleed: hemodynamically unstable bleeding originating from the GI tract
- Intraocular bleed: bleeding of the eye
- Intraspinal bleed: bleeding within the spinal column
- Pericardial bleed: bleeding within the pericardial space
- Retroperitoneal bleed: bleeding within the retroperitoneal cavity

This broadly aligns with the inclusion criteria of the ANNEXA-4 study in terms of bleed sites. However, intra-articular bleeds and intramuscular bleeds with compartment syndrome were omitted as these bleeds were felt to be less severe than the other aforementioned bleeds.

Cost-effectiveness results have been calculated for three cohorts of patients:

1. Whole cohort: All patients with any of the bleed types above;
2. ICH and severe GI bleed cohort: All patients with either an ICH or a severe GI bleed;
3. ICH cohort: All patients with an ICH bleed only.

These populations were selected to support NICE in their decision making since the levels of evidence for each population differs in terms of demonstrating clinical effectiveness and cost effectiveness within the licenced indication.

The Whole cohort contains patients with all of the bleed types above, which is reflective of the licenced indication for andexanet alfa and the scope for NICE's appraisal. However, very limited evidence exists to assess the benefit of andexanet alfa in intraspinal ([redacted]), intraocular ([redacted]), pericardial ([redacted]), and retroperitoneal ([redacted]) patients since these bleed types were scarcely documented or captured in the ANNEXA-4 study. As such, the clinical effectiveness of andexanet alfa is assumption driven for these bleed types.

The ICH and severe GI bleed cohort captured patients with the bleed types carrying the greatest risk of mortality within the 30-day trial follow-up period, relative to the total population. The sample size for ICH and severe GI bleeds is sufficient to conduct propensity score matching however, severe GI bleeds have fewer objective measures to determine baseline severity of GI bleeds, making the evaluation of life-threatening or uncontrolled bleeding events challenging.

The ICH cohort carries the highest clinical unmet need since it has the greatest 30-day mortality risk of all the bleed types. The sample size provides enough bleeds to conduct propensity score matching and includes more objective measures for assessment of the severity of ICH (e.g. hematoma volume) and therefore, UK clinicians can more confidently determine life-threatening or uncontrolled bleeding events.

B.3.2.2 Model structure

A decision analytic model structure comprising a decision tree in the short-term and Markov model in the long-term was deemed most appropriate to estimate the cost-effectiveness of andexanet alfa for adult patients receiving direct anticoagulant therapy with FXa inhibitors who require reversal of anticoagulation due to life-threatening or uncontrolled bleeding. The CEM was constructed in Microsoft® Excel.

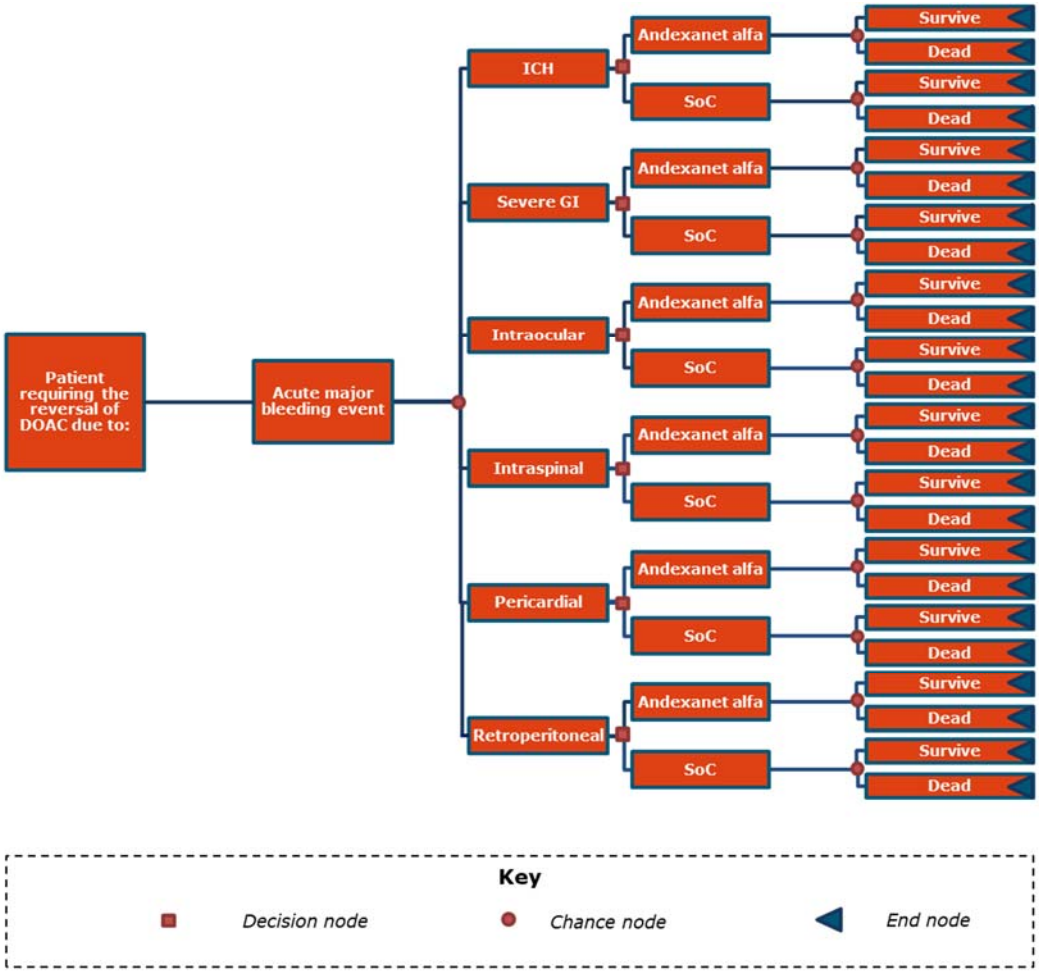
The decision tree was developed to reflect the first 30 days of bleed management, including treatment costs, acute bleed-related management costs, and the risk of death. Patients entering the decision tree were assigned to health states according to the bleed types: ICH, severe GI bleed, intraocular bleed, intraspinal bleed, pericardial bleed and retroperitoneal bleed. The model assumed patients have one bleed type and if a secondary bleed was experienced the mortality rate of the first bleed type remained unchanged. Two scenarios were considered in which a cohort of 1000 patients received andexanet alfa in one scenario and the same cohort received SoC in the other scenario. Following intervention, patients were assigned to survivor health states or the 'Dead' state. A diagram of the decision tree structure is presented in Figure 14.

For the remaining period from 30 days until death, a Markov structure was used to capture long-term mortality, morbidity and costs for the lifetime of patients surviving from the decision tree. Patients who survived the decision tree enter the Markov model in the corresponding 'survivor' state, whilst patients who die during the decision tree enter the 'Dead' state. All surviving patients remain in their respective state until death. A diagram of the Markov model structure is presented in Figure 15.

The mean age of patients entering the model was [redacted] years for the Whole cohort, [redacted] years for the ICH and severe GI cohort and [redacted] years for the ICH cohort based on patients receiving

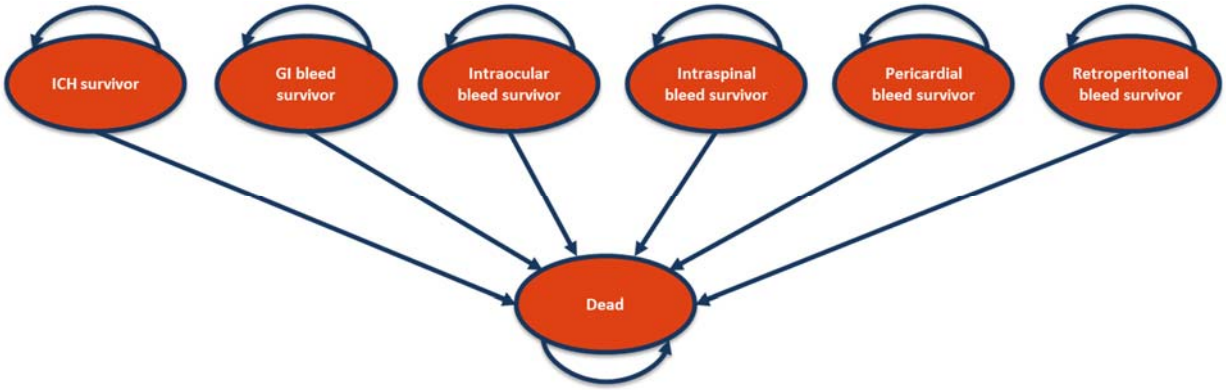
apixaban or rivaroxaban in the ANNEXA-4 study. Since data identified from the literature report the cost and quality-of-life impact of acute major bleeding in months,[113,114] a monthly cycle length was chosen for the CEM. A half-cycle correction was applied to both costs and health benefits in the Markov model to align with conventional modelling standards.

Figure 14. 30-day decision tree structure



DOAC - Direct oral anticoagulant; ICH – intracranial haemorrhage; GI – Gastrointestinal; SoC – standard of care.

Figure 15. Markov model structure



ICH – intracranial haemorrhage; GI – Gastrointestinal.

Table 44. Features of the economic analysis

	Current appraisal	
Factor	**Chosen values**	**Justification**
Time horizon (decision tree)	30 days	The follow-up period of the ANNEXA-4 trial was 30-days. In this period, mortality was captured as a result of a life-threatening or uncontrollable bleeding event.
Time horizon (Markov model)	Lifetime ([redacted])	The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.[115] Therefore, a lifetime horizon was chosen since patients accumulate differential costs and QALYs until death. Since the minimum mean age of patients receiving apixaban and rivaroxaban in the ANNEXA-4 study was [redacted] years, a time horizon of [redacted] years was chosen - assuming no patients survive beyond a mean age of 100 years.
Cycle length	1 month	Aligned with the age of patients and reported costs and quality-of-life data identified in the literature; see Appendices H and I for further information.
Discount of 3.5% for utilities and costs	Yes	NICE reference case. The impact of alternative discount rates has been tested in sensitivity analyses.
Perspective (NHS/PSS)	UK NHS/PSS	NICE reference case.
Treatment waning effect?	N/A	Treatment is applied at a single time in response to major bleeding. Consequently, no extrapolation is required.
Source of utilities	Fletcher et al 2015.[116] Øie et al 2018.[29] ANNEXA-4. Matza et al. 2014.[117] Miller JD, et al. 2016.[113] NICE 2015.[114] Kind et al. 1999.[118] Wittenborn et al. 2017.[119]	No quality-of-life data were available from the ANNEXA-4 study; therefore, utilities were sourced from published literature. Fletcher et al. reports utility score for each mRS score used for long-term utility and mRS score in populations suffering ICH were identified for SoC from Øie et al 2018 and from ANNEXA-4 for andexanet alfa. Kind et al. identified utility scores for a UK population for a subgroup aged 75 years and above. Matza et al. reports utility decrement for paralysis. Miller et al. reports utility decrements for life-threatening or uncontrolled bleeding events for acute bleeds. NICE 2015 reports the acute utility value for an ICH event. Wittenborn et al. reports utility decrement for monocular blindness.
Source of costs	BNF costs.[120] 2017/18 NHS Reference costs.[121] PSSRU costs.[122] MIMS.[123] Luengo-Fernandez 2013. [124]	Reflects the resources used by patients who are receiving anticoagulant treatment and experience a life-threatening or uncontrolled bleeding event; where possible, costs were obtained from UK national resources to reflect the UK NHS/PSS perspective.

BNF – British National Formulary; ICH – intracranial haemorrhage; N/A – Not Applicable; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PSS – personal social services; QALY – Quality Adjusted Life Year; SLR – systematic literature review; SoC – standard of care; UK – United Kingdom;

B.3.2.3 Intervention technology and comparators

As discussed in Section B.1.2 Description of the technology being appraised, no treatment is currently recommended by NICE for the reversal of direct FXa inhibitors in adults with a life-threatening or uncontrolled bleeding event. However, for patients suffering major trauma with haemorrhage using vitamin K anti-coagulants (VKA), NICE guidelines advise rapid anti-coagulant reversal using PCC. The potential of PCC medications for reversal of non-VKAs is under investigation. However, PCCs may be associated with an increased risk of thromboembolic events and their use in non-VKA recipients is not well supported by evidence as discussed in Section B.1.3 Health condition and position of the technology in the treatment pathway.

A clinical SLR sought to identify randomised controlled trials evaluating the safety and efficacy of andexanet alfa, clotting factor concentrates (PCCs, recombinant (r)FVIIa and activated pro-thrombin complex [aPCC]), fresh frozen plasma (FFP), vitamin K or protamine in both individuals requiring rapid anticoagulant reversal and healthy individuals. Findings from this SLR were used to inform the choice of comparator for the CEM. Of the 17 studies identified, one was the ANNEXA-4 trial exploring the effect of andexanet alfa, 11 investigated a four factor PCC (4F-PCC), four investigated an unspecified PCC, and one investigated an activated PCC (aPCC) (See Appendix D).

Therefore, aligned with the results of the clinical SLR and the NICE scope, off-label PCC (with or without tranexamic acid) was considered to be the base case comparator for the cost-effectiveness analysis. This aligns with UK clinical expert opinion, which suggests that despite the lack of clinical evidence, PCC is the most commonly used treatment representing SoC in this population.

Tranexamic acid was not included in the economic model, as according to UK clinicians, its use may be restricted to an ambulance setting and is unlikely to be used at all in ICH bleeds. As such, if it is received, there is unlikely to be any difference between patients receiving andexanet alfa or PCC, and the acquisition cost of tranexamic acid is so low its inclusion may only serve to over-complicate the decision problem.

In addition, UK clinical experts and market research[62] suggested that alternative, expensive treatments (FEIBA and NovoSeven) are also used in the UK, despite their lack of evidence in the population of interest. This market research estimated NovoSeven market uptake at 15% and FEIBA market uptake at 8%.[62] FEIBA is an anti-inhibitor coagulant complex indicated for the use in haemophilia A and B patients with inhibitors for control and prevention of bleeding episodes, perioperative management and routine prophylaxis to prevent and reduce the frequency of bleeding episodes. NovoSeven is a coagulation Factor VIIa (recombinant) used for treatment of bleeding and prevention of bleeding for surgeries and procedures in adults and children with haemophilia A or B with inhibitors, congenital Factor VIIa deficiency, people with Glanzmanns's thrombasthenia who have a decreased or absent response to platelet transfusions and treatment of bleeding and prevention of bleeding for surgeries and procedures in adults with acquired haemophilia.

It is important to note, and UK clinicians agree, that the use of PCCs, (including FEIBA as an activated 4F-PCC) and NovoSeven is not substantiated by robust clinical evidence, but driven by efficacy demonstrated in VKA-related bleeds (as opposed to FXa inhibitor bleeds) and the life-threatening emergency situation which requires immediate action.

Nevertheless, since the ORANGE study observed extremely minimal usage of FEIBA (1%) and no usage of NovoSeven, FEIBA and NovoSeven have not been included in the economic model. Given their lack of evidence in the reversal of Factor Xa inhibitor bleeds and their high cost, their inclusion

would only serve to improve the cost-effectiveness of andexanet alfa. As such, cost-effectiveness results may be viewed from this perspective as conservative.

B.3.3 Clinical parameters and variables

B.3.3.1 Key clinical studies

As discussed in Section B.2 Clinical effectiveness, as a reversal agent, the evidence base for andexanet alfa should be considered with the view that it acts as an ***antidote to FXa-inhibitors***. In this respect, key evidence supporting regulatory approval of andexanet alfa is the overwhelming pharmacodynamic data that support its mechanism of action and ability to rapidly reverse FXa-inhibitor anticoagulation from randomized placebo-controlled trials in healthy people (ANNEXA-A or ANNEXA-R).

The ANNEXA-4 study in patients with life-threatening or severe bleeding provides confirmation of the reversal effect in addition to important clinical outcome data, specifically for the enriched population of ICH patients for which objective measures for the population can be made.

Despite the RCTs confirming the substantial magnitude of effect in reversing FXa-inhibitor activity, these data cannot be used to populate a health economic model. As such, acknowledging the limitations of comparing across studies without a control arm, baseline demographics of the cohort and 30-day mortality following a life-threatening or uncontrolled bleeding event were sourced from:

- ANNEXA-4 [N=[redacted] patients taking rivaroxaban or apixaban]: multicentre, prospective, open-label, single-arm study enrolling patients on a FXa inhibitor with an acute major bleed. Patients received andexanet alfa as a bolus injection followed by a 2-hour infusion; follow-up of mortality was at 30-days.
- ORANGE [N=[redacted] patients taking rivaroxaban and apixaban and receiving PCC]: UK centre, prospective, open-label, single arm study enrolling patients on an oral anticoagulant with an acute major bleed. Patients received UK SoC comprising a mix of interventions including PCC, tranexamic acid, vitamin-K and blood transfusion; follow-up of mortality was at 30-days.

Patient level data were made available for the ORANGE study, and as such data from the rivaroxaban and apixaban population have been used, unless otherwise stated, to align with the licenced indication for andexanet alfa. Three patients were excluded from the subset of the ORANGE patient population receiving rivaroxaban and apixaban because data were not available for their age; a variable UK clinical experts indicated was a key driver of mortality outcomes. For the calculation of efficacy, only patients receiving PCCs were considered in line with the model comparator (see Section B.3.2.3 Intervention technology and comparators) and propensity score matching analysis (see Section B.2.9 Indirect and mixed treatment comparisons).

B.3.3.2 Baseline demographics

Patient demographics at baseline were based on the ANNEXA-4 study to align with the licenced population entering the model (Section B.3.2 Economic analysis) and are presented in Table 45. Baseline demographics were specified for the Whole cohort, ICH and severe GI bleed cohort, and the ICH cohort.

Table 45. Baseline demographics of each cohort entering the model (Safety Population Taking Apixaban or Rivaroxaban)

Baseline demographics	Whole cohort	ICH and severe GI bleed cohort	ICH cohort	Reference
N	[redacted]	[redacted]	[redacted]	ANNEXA-4
Mean age (years)	[redacted]	[redacted]	[redacted]	ANNEXA-4
% Male	[redacted]	[redacted]	[redacted]	ANNEXA-4
Mean weight (kg)	[redacted]	[redacted]	[redacted]	ANNEXA-4

ICH – intracranial haemorrhage; GI – gastrointestinal; N – number of patients; kg – kilograms

The ANNEXA-4 study was used to inform the proportion of patients suffering different types of a life-threatening or uncontrolled bleeds in the decision tree at baseline. Of the 322 acute major bleeding events recorded in ANNEXA-4 for patients who received apixaban or rivaroxaban; 209, 82 and 31 patients experienced an ICH, severe GI bleed and an 'other major bleed', respectively. As data were only available for ICH, severe GI bleeds and 'other major bleeds', it was assumed that intraspinal, intraocular, retroperitoneal and pericardial bleeds were captured within the 'other major bleeds' category in equal measure. The 'other major bleed' patients were considered to be too few to meaningfully reflect the distribution of each: intraocular, intraspinal, pericardial and retroperitoneal bleeds, within the 'other major bleed' category.

Hence, in order to stratify the 31 'other major bleed' patients from ANNEXA-4, the proportion of patients were split by bleed type from data collected in the entire safety population of the ORANGE study since only seven of the 369 patients who had received apixaban and rivaroxaban only in the ORANGE study recorded an 'other major bleed'. On the other hand, musculoskeletal (224) and miscellaneous (75) bleeding events were recorded in 299 patients in the total safety population of the ORANGE study. It was known that the critical areas for which bleeding was measured were: intracranial (known as ICH and recorded separately), intraspinal, intraocular, retroperitoneal, pericardial or intra-articular, or intramuscular with compartment syndrome (Green et al. 2018[20]). Only one of these is neither recorded in isolation nor musculoskeletal; intraocular bleeding. Hence, it was assumed that all of the miscellaneous bleeds reported in Green et al. 2018 were intraocular. As such, the proportion of 'other major bleed' patients in ANNEXA-4 who experienced an intraocular bleed was set at 25.08% (75/299). In order to assign proportions for intraspinal, pericardial and retroperitoneal bleeds within 'other major bleed', the 224 musculoskeletal bleeding events were divided equally between these categories; as such 24.97% (224/3/299) experienced an intraspinal, pericardial and retroperitoneal bleeding event (Table 46).

Table 46. Proportion of other major bleeds used in the decision tree

Event	N (%)	Reference	Calculation
ICH	[redacted]	ANEXXA-4	[redacted]
Severe GI bleed	[redacted]	ANEXXA-4	[redacted]
Intraocular	[redacted]	ANNEXA-4 & ORANGE[20]	[redacted]
Intraspinal	[redacted]	ANNEXA-4 & ORANGE[20]	[redacted]
Pericardial	[redacted]	ANNEXA-4 & ORANGE[20]	[redacted]
Retroperitoneal	[redacted]	ANNEXA-4 & ORANGE[20]	[redacted]

ICH – Intracranial haemorrhage; GI – Gastrointestinal. *Assumed to be one third of the total number of patients with musculoskeletal bleeding; **Assumed to represent 100% of the miscellaneous bleeds

B.3.3.3 Transitions in 30-day decision tree

The proportion of patients in the decision tree who died following an acute major bleeding event was taken from an indirect comparison of results from the ANEXXA-4 and ORANGE studies for andexanet alfa and SoC, respectively. Propensity score matching was considered to adjust results between the studies (see Section B.2.9 Indirect and mixed treatment comparisons).

In the ORANGE study, unadjusted mortality rates, among patients receiving rivaroxaban or apixaban, and treated with PCC were [redacted] for patients who experienced an ICH, GI bleed or other major bleed, respectively. As discussed in Section B.2.9 Indirect and mixed treatment comparisons, propensity score matching results gave slightly higher mortality rates for ICH ([redacted]) and GI ([redacted]), which is unsurprising given the differences in populations (ORANGE include all major bleeds whilst ANNEXA-4 including only life threatening or uncontrolled major bleeds). On the other hand, other major bleed results were considered uninformative ([redacted]).

In light of the lack of data from alternative data sources for UK SoC patients with life-threatening or uncontrolled bleeds, the propensity score matching results for the ORANGE study was used as the basis for 30-day mortality with SoC for ICH and severe GI bleeds.

The number of patients in the ORANGE study receiving DOACs was very small for intraocular ([redacted]), intraspinal ([redacted]), pericardial ([redacted]) and retroperitoneal ([redacted]) bleed survivors. Hence, mortality data for each of these bleed types were not thought reliable for use in the model. The mortality rate ([redacted]for all other major bleed types patients in ORANGE, among patients receiving rivaroxaban or apixaban, and treated with PCC, was used for survivors of pericardial or retroperitoneal bleeding. The mortality rate for all other major bleed types patients in andexanet alfa was an assumption of 25% reduction as the results were not reliable with only eight matches from ORANGE.

It was initially conceived that the mortality reported in the ORANGE study for ICH, severe GI bleeds and other major bleeds may be used for ICH, severe GI bleeds, and intraocular / intraspinal / pericardial / retroperitoneal bleeds, respectively (acknowledging the aforementioned limitations) for patients receiving SoC. However, upon validation from UK clinical experts, it was deemed that patients rarely die due to intraocular or intraspinal bleeds – although both are associated with severe morbidity - blindness and paralysis, respectively. Therefore, 30-day mortality rates for intraocular and intraspinal bleeds were set to zero for both SoC and andexanet alfa.

In the ANEXXA-4 study, the 30-day mortality rate following an acute major bleeding event with andexanet alfa was [redacted]) for apixaban and rivaroxaban patients who experienced an ICH. Based on the propensity score matching analysis (see Section B.2.9 Indirect and mixed treatment comparisons), treatment with andexanet alfa resulted in a relative reduction in mortality for ICH patients of [redacted] compared to SoC ([redacted] Acknowledging the limitations in the propensity score matching analysis (see Section B.2.9 Indirect and mixed treatment comparisons), the adjusted results were used in the base case given the ability to sufficiently match patient characteristics and associated outcomes.

In the ANEXXA-4 study, the 30-day mortality rate following an acute major bleeding event with andexanet alfa was [redacted]) for apixaban and rivaroxaban patients who experienced a severe GI bleed. Based on the propensity score matching analysis (see Section B.2.9 Indirect and mixed treatment comparisons), treatment with andexanet alfa resulted in a relative reduction in mortality for severe GI patients of [redacted] compared to SoC ([redacted]. Acknowledging the limitations in the propensity score matching analysis (see Section B.2.9 Indirect and mixed

treatment comparisons), the adjusted results were used in the base case given the ability to sufficiently match patient characteristics and associated outcomes.

Due to the paucity of data in ANNEXA-4 for other major bleeds ([redacted] unadjusted, N<10 adjusted), the heterogeneity of bleed types and this category and inherent difficulty in identifying and therefore comparing life-threatening or uncontrolled bleeds from the ORANGE study using propensity score matching techniques (see Section B.2.9 Indirect and mixed treatment comparisons), it was assumed that treatment with andexanet alfa would also lead to reduction in the risk of death observed in the ORANGE study.

The exact value for this reduction could not be estimated from data using ANNEXA-4 due to a limited number of deaths reported for other major bleeds. Therefore, a conservative assumption was made whereby treatment with andexanet alfa resulted in a relative reduction in mortality other major bleed patients of 25% compared to SoC. The justification for this value is as follows:

1. Half the relative reduction recorded for GI in ANNEXA-4 based on propensity score matching (~50%); this is conservative since the mechanism of action of andexanet alfa (see Table 2) would not cause treatment to behave differently by bleed type.
2. Half the relative reduction observed for ICH with PCC vs FFP in patients with warfarin bleeds (~50%),[125] given that PCC and FFP are both comparators with andexanet alfa; reductions in mortality have not been solely observed in warfarin bleed ICH patients, and it is not unreasonable to extrapolate this result to FXa bleeds

The mortality rates used to inform the transition into the Markov health state for andexanet alfa and SoC are described in Table 47. Patients who died transitioned to the 'Dead' state. Patients who survived transitioned into their respective survivor Markov health state.

Table 47. Decision tree mortality rates

Bleeding event	**Andexanet alfa 30-day mortality rate**	**Reference**
ICH	[redacted]	Propensity score matching; ANEXXA-4
Severe GI bleed	[redacted]	Propensity score matching; ANEXXA-4
Intraocular bleed	[redacted]	UK clinical opinion
Intraspinal bleed	[redacted]	UK clinical opinion
Retroperitoneal bleed	[redacted]	ORANGE * (1-0.25)
Pericardial bleed	[redacted]	ORANGE * (1-0.25)
Bleeding event	**SoC 30-day mortality rate**	**Reference**
ICH	[redacted]	Propensity score matching, ORANGE
Severe GI bleed	[redacted]	Propensity score matching, ORANGE
Intraocular bleed	[redacted]	UK clinical opinion
Intraspinal bleed	[redacted]	UK clinical opinion
Retroperitoneal bleed	[redacted]	Propensity score matching, ORANGE
Pericardial bleed	[redacted]	Propensity score matching, ORANGE

ICH – intracranial haemorrhage; GI – gastrointestinal

B.3.3.4 Transitions in the Markov Model

Surviving patients exiting the decision tree transitioned into their respective survivor health states: ICH survivor; severe GI bleed survivor; intraocular bleed survivor; intraspinal bleed survivor; pericardial bleed survivor; and retroperitoneal bleed survivor. The proportion of patients transitioning into the Markov model was calculated from the proportion of patients experiencing an acute major bleeding event (Table 46) and the mortality rate following administration of either intervention (Table 47). The proportion of patients entering the Markov model by health state are presented in Table 51.

Patients remained in their respective health state until they transitioned to the 'Dead' state. Since patients were receiving an FXa inhibitor and had survived an acute major bleeding event, patients were assumed to have a higher risk of death than the general population. However, no long-term survival data were available from the ANEXXA-4 or ORANGE studies and therefore a targeted literature search was undertaken to support with the estimation of long-term mortality for patients in the Markov model.

All-cause mortality

Firstly, all-cause mortality was estimated for the age-gender matched population in ANNEXA-4 from national life tables available from the Office for National Statistics (ONS). Mean life expectancy was calculated as [redacted] years based on an average age of [redacted] years (Whole cohort), [redacted] years based on an average age of [redacted] years (ICH and severe GI cohort) and [redacted] based on an average age of [redacted] years (ICH cohort), weighted by the proportion male and female recorded in the ANEXXA-4 trial.

ICH mortality

For the ICH long-term mortality, a study by Huybrechts et al. 2008[126] was identified which provided long-term mortality estimates for 1,276 stroke survivors. In Huybrechts et al. 2008, Kaplan Meier survival curves for ICH and by mRS scores for the whole population were recorded for surviving patients after 3 months. In order to extrapolate the long-term survival over a lifetime horizon, and obtain mean survival for each treatment, parametric distributions were fit to the Kaplan Meier data by treatment arm and mRS. The one month mRS baseline for andexanet alfa was from the ANNEXA-4 trial and the one month mRS baseline for SoC was from Øie et al. 2018 (Table 48).[29] NICE Decision Support Unit (DSU) guidelines were followed in selecting and fitting the following six parametric distributions to the Kaplan Meier data using R: Exponential, Weibull, Gompertz, Log-logistic, Lognormal and Generalised Gamma.[127]

Table 48. Number of patients with each mRS score, by treatment

mRS	Number of patients with score receiving andexanet alfa: N (%)*		Number of patients with score receiving SoC**	
	Actual value: N (%)	Redistributed value: %***	Actual value: N (%)	Redistributed value: %***
Total	[redacted]	[redacted]	452	100%
0	[redacted]	[redacted]	1%	2%
1	[redacted]	[redacted]	5%	8%
2	[redacted]	[redacted]	9%	15%
3	[redacted]	[redacted]	12%	20%
4	[redacted]	[redacted]	22%	36%
5	[redacted]	[redacted]	12%	20%
6	[redacted]	[redacted]	39%	N/A

mRS – modified Rankin score; SoC – standard of care. *Source: ANNEXA-4 patient level data; **Source: Øie et al. 2018; ***Redistributed to exclude death

The best fitting distribution between the treatment arms was chosen by statistical consideration (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]), visual inspection of the fitted curve against the Kaplan Meier data to ensure the survival distributions closely predicted the observed events and visual inspection of the fitted curve against the general population survival curve, which was based on age-specific all-cause mortality probabilities sourced from the ONS. The lower the AIC and BIC the better fit the distribution is to the observed data. Table 49 summarises the AIC and BIC scores for each survival distribution. The Kaplan Meier, parametric distributions and all-cause curve are presented in Figure 16 to Figure 21.

Upon visual inspection, the selected fitted curves in Table 50 were used. For mRS 0-3 and 5, the best or second best fitting curves that do not cross the general population survival line or each other were selected to be clinically plausible. For mRS 4, the best fitting curves based on AIC and BIC (see Table 49) were clinically implausible as they crossed the general population mortality line. Exponential and Weibull were the only curves considered clinically plausible for the group with this mRS score, as they did not cross the general population survival curve and yielded credible average life expectancy estimates. The Weibull distribution was selected for mRS 4 as it was the best fit of the two clinically plausible curves.

Table 49. Goodness of fit statistics for the mRS parametric distributions

Curve	mRS score											
	0		1		2		3		4		5	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	9993.2	9998.8	13301.9	13307.4	14752.1	14757.6	15253.8	15259.3	14422.2	14427.7	15056.2	15061.7
Weibull	9952.2	9963.2	13153.7	13164.7	14620.6	14631.6	15183.6	15194.7	14405.4	14416.4	15056.0	15067.0
Gompertz	9952.6	9963.6	13143.7	13154.7	14602.1	14613.1	15162.6	15173.6	14352.8	14363.8	15002.4	15013.4

Log-logistic	9964.8	9975.8	13207.0	13218.0	14710.4	14721.4	15281.4	15292.4	14322.8	14333.8	14859.8	14870.8
Lognormal	9983.2	9994.2	13274.2	13285.2	14760.6	14771.7	15250.4	15261.4	14257.1	14268.1	14748.1	14759.1
Generalised gamma	9950.2	9966.8	13132.1	13148.6	14597.5	14614.0	15150.2	15166.7	14223.9	14240.4	14272.9	14289.4

AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; mRS – modified Rankin Scale. Lower AIC/BIC indicates better fit. Best fitting curve.

Figure 16. Kaplan Meier, parametric distributions and all-cause survival for mRS 0 long-term survival

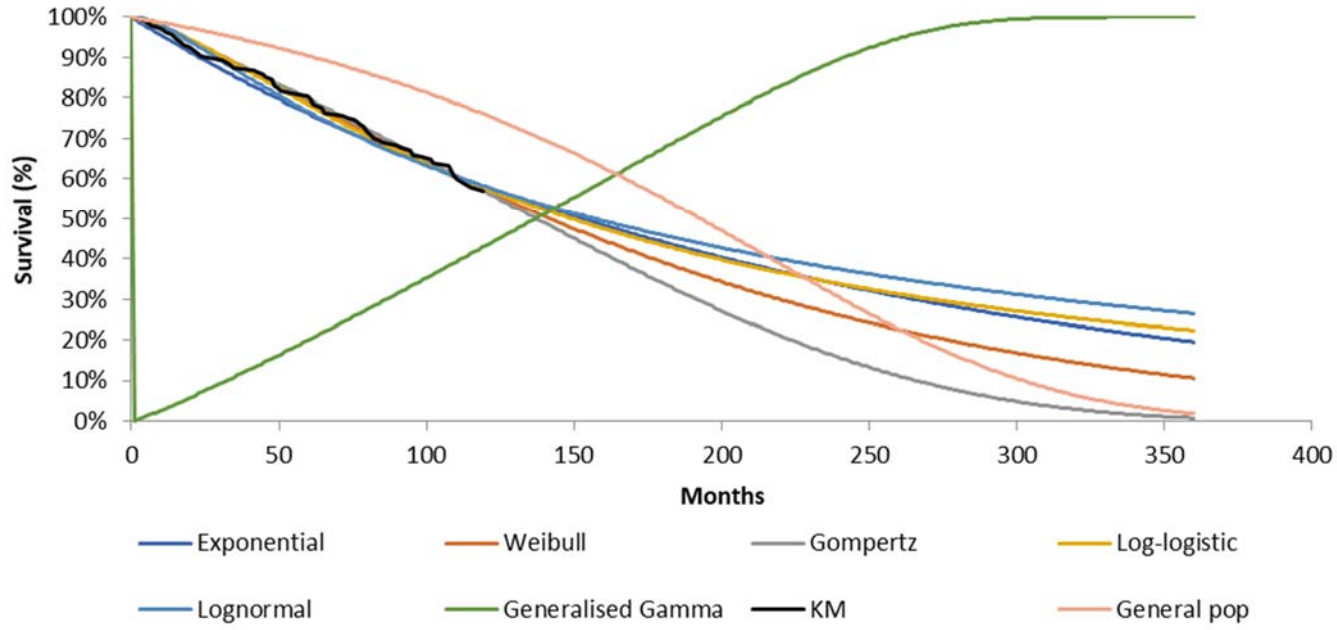


Figure 17. Kaplan Meier, parametric distributions and all-cause survival for mRS 1 long-term survival

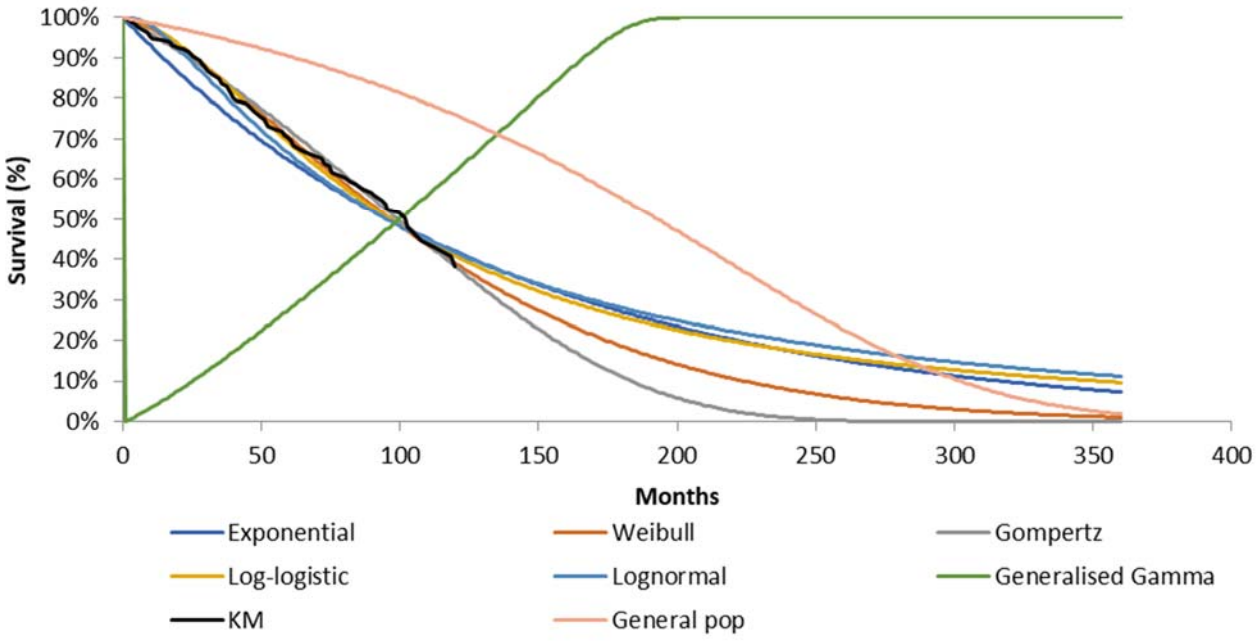


Figure 18. Kaplan Meier, parametric distributions and all-cause survival for mRS 2 long-term survival

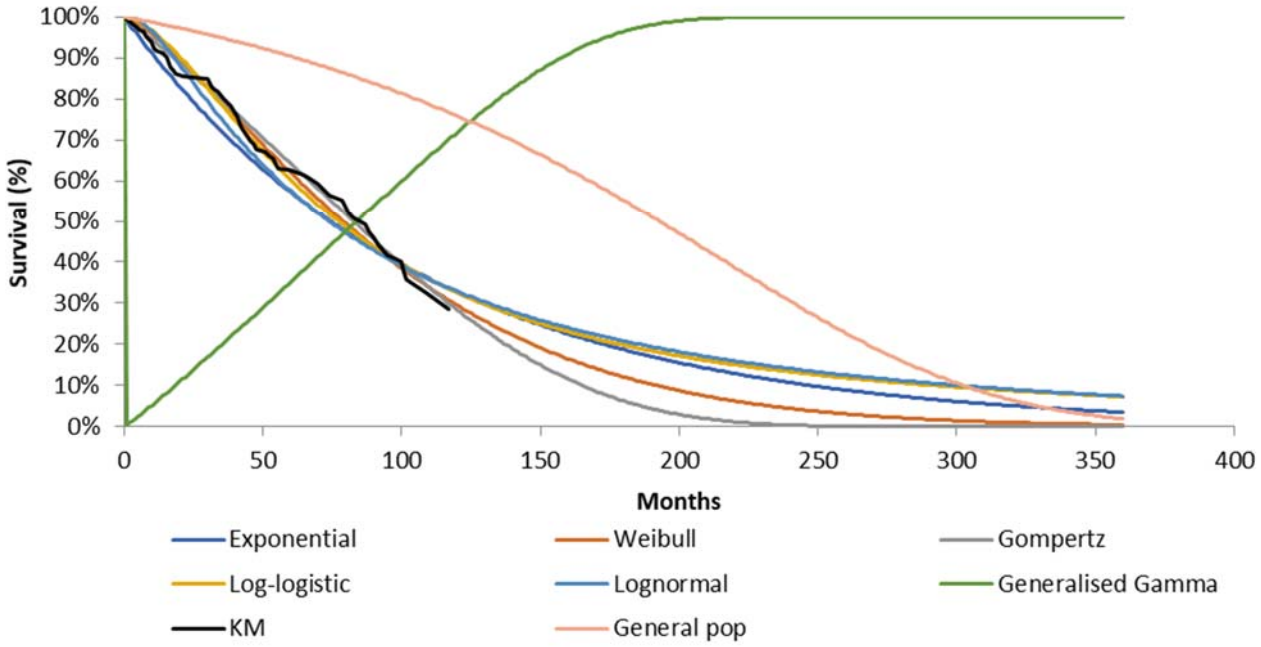


Figure 19. Kaplan Meier, parametric distributions and all-cause survival for mRS 3 long-term survival

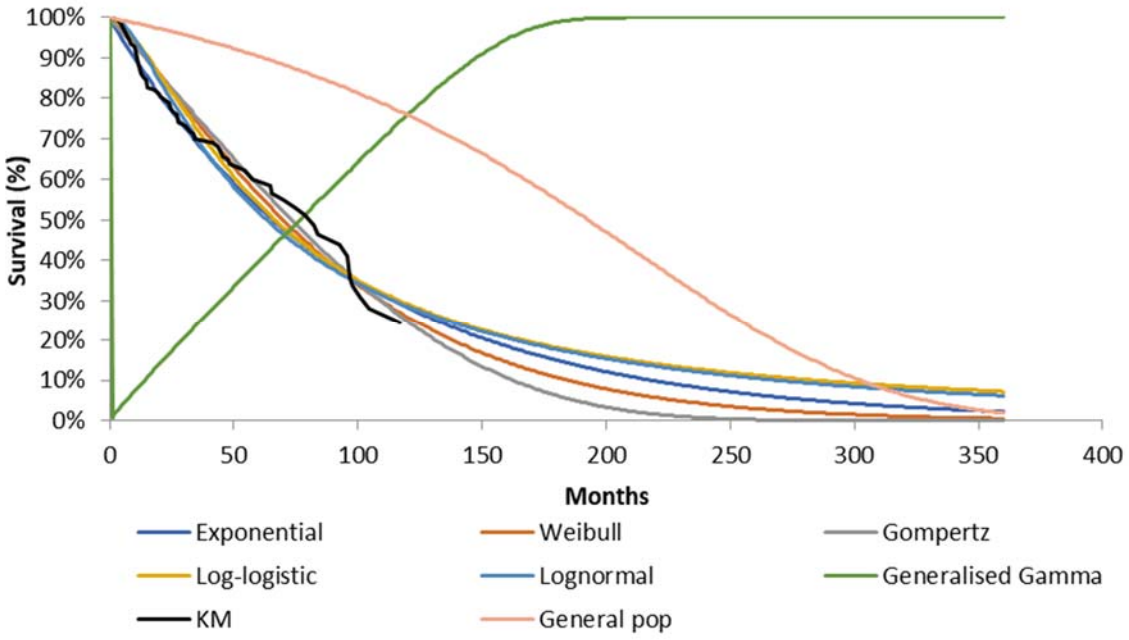


Figure 20. Kaplan Meier, parametric distributions and all-cause survival for mRS 4 long-term survival

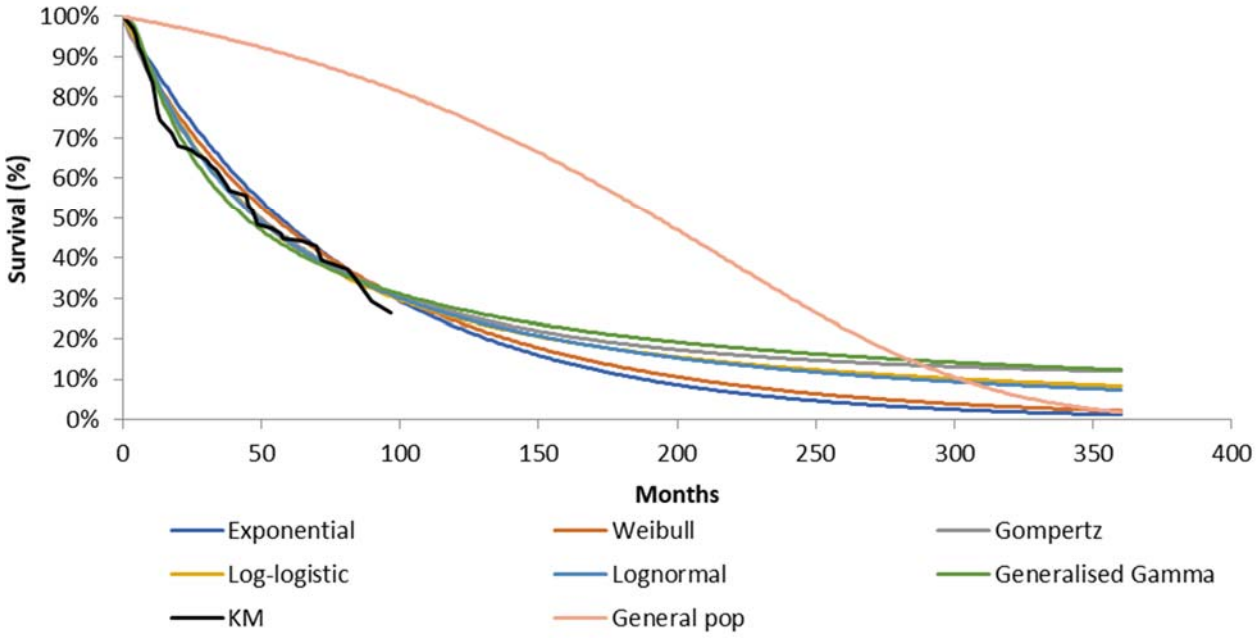
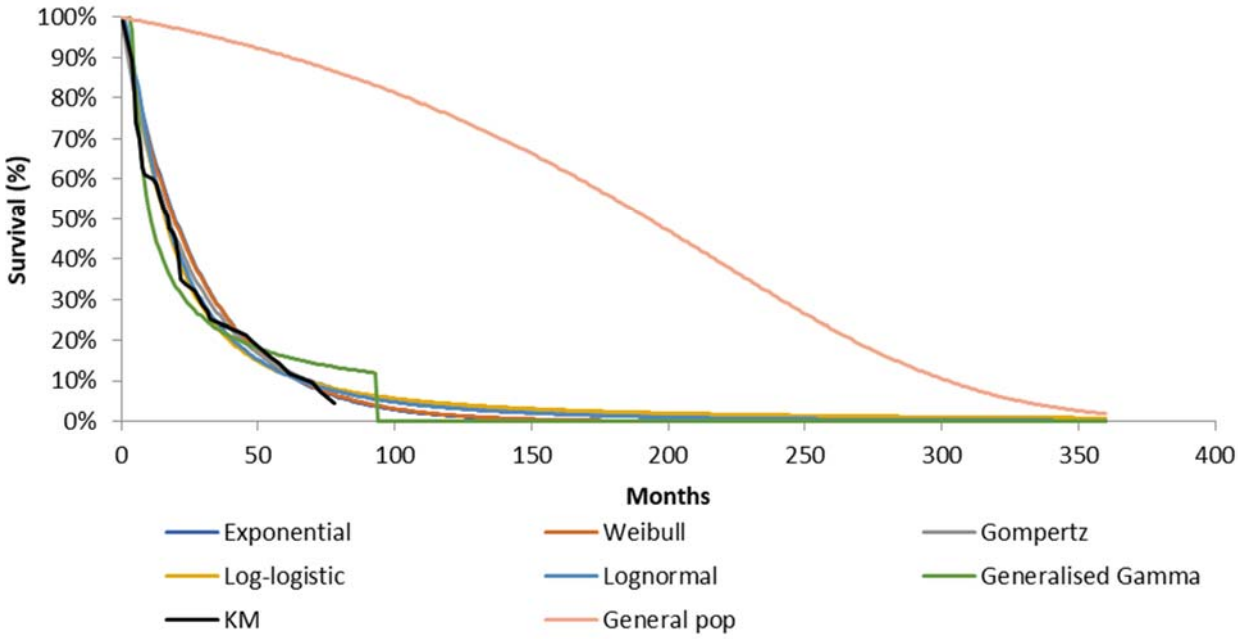


Figure 21. Kaplan Meier, parametric distributions and all-cause survival for mRS 5 long-term survival



Using the selected distributions in the base case (see Table 50), the mean survival for each mRS score was calculated as the area-under-the-curve (AUC) using the following trapezium rule:

$$\int_a^b f(x)\,dx \approx (b-a)\frac{f(a)+f(b)}{2}$$

The mean survival for each mRS score is shown in Table 50. Weighting these scores by the mRS distributions in Table 50, the survival mean equates to 7.38 years and 6.37 years for andexanet alfa and SoC, respectively.

Table 50. Calculated mean survival in years for each mRS score

mRS score	Distribution – parametric curve	Mean survival in years
0	Gompertz	12.03
1	Gompertz	8.53
2	Gompertz	7.33
3	Gompertz	6.84
4	Weibull	7.02
5	Log-logistic	2.63

mRS – modified Rankin Scale

The transition probabilities to the death state were calculated each month by applying hazard ratios (HRs) to national life tables for England and Wales from ONS such that mean undiscounted life years were 4.40 years and 3.80 years for ICH for andexanet alfa and SoC, respectively, for the Whole cohort. These survival estimates represent the life expectancies adjusted for the baseline model age (77.7 years) and take into account the ratio of years lost relative to the all-cause age-matched population from Huybrechts et al. 2008[126], multiplied by the all-cause age-matched population in the model [7.38 years / 17.21 years * 10.26 years]. The HRs leading to these life expectancies were 1.345 and 1.411 for andexanet alfa and SoC, respectively.

When applying the same method to the ICH and severe GI cohort, life expectancies were 4.17 and 3.60 for andexanet alfa and SoC, respectively. The HRs leading to these life expectancies were 1.343 and 1.409 for andexanet alfa and SoC. Finally, for the ICH only cohort, life expectancies were 3.87 and 3.34 for andexanet alfa and SoC, respectively. The HRs leading to these life expectancies were 1.340 and 1.406 for andexanet alfa and SoC.

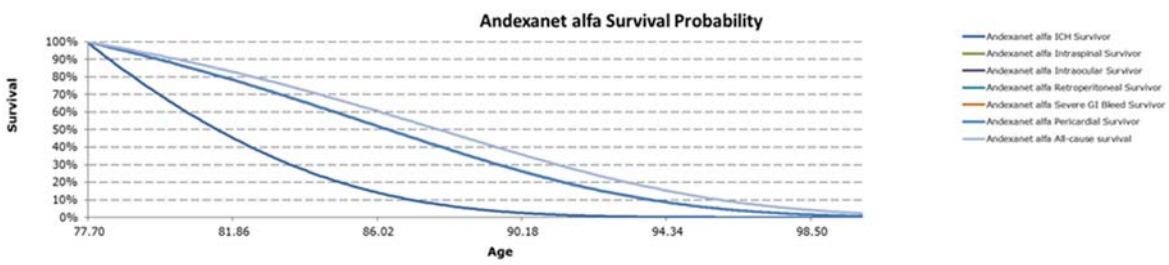
Severe GI mortality and other major bleeds

Advice from UK clinical experts suggested that unlike ICH, patients surviving severe GI bleeds and other major bleeds are unlikely to die as a consequence of the original bleed, and are more likely to die due to underlying comorbidities from a population of that age. Therefore, long-term mortality estimates for severe GI bleed and other major bleed survivors, were sourced from a study which assessed the risk of death in a cohort of 2,824 patients with atrial fibrillation (AF) compared with a matched general population, authored by Friberg et al. 2008.[128] The AF population was deemed to be representative of a cohort of patients receiving DOACs – i.e. the population of interest following survival of a life-threatening or uncontrolled bleeding event.

Friberg et al. 2008[128] reported the standardised mortality ratio of 1.3 for all AF compared with the general population. The all-cause mortality per cycle was multiplied by the standardised mortality rate for all AF to estimate the long-term survival of uncontrolled bleeding event for all non-ICH bleed types.

Figure 22 represents the mortality estimates over time for andexanet alfa and SoC.

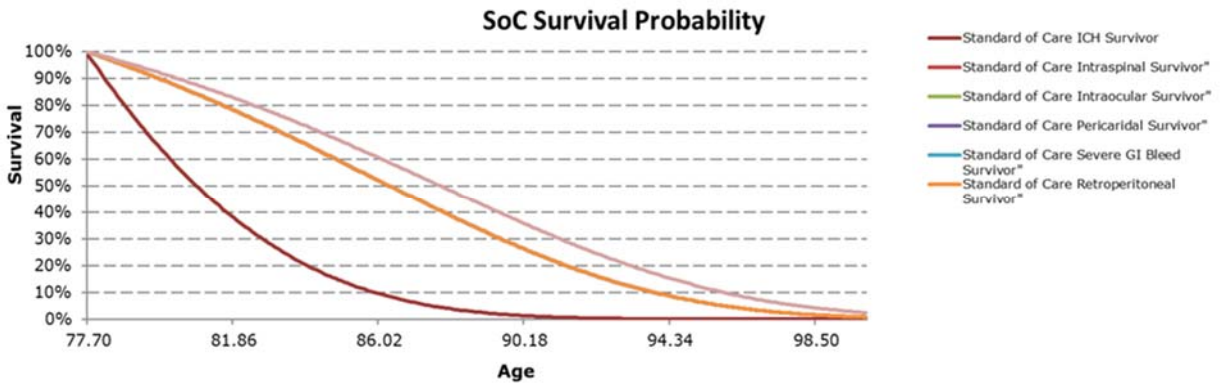
Figure 22. Long-term survival estimates by bleed type for patients receiving andexanet alfa



*NB curves for intraspinal survivor, intraocular survivor, retroperitoneal survivor, and pericardial survivor are overlapping

GI – gastrointestinal; ICH – Intracranial haemorrhage.

Figure 23. Long-term survival estimates by bleed type for patients receiving SoC



*NB curves for intraspinal survivor, intraocular survivor, retroperitoneal survivor, and pericardial survivor are overlapping

GI – gastrointestinal; ICH – Intracranial haemorrhage.

Table 51. Proportion of patients entering different states in the Markov Model (Whole cohort)

	ICH Survivor	Intraspinal Bleed Survivor	Intraocular Bleed Survivor	Retroperitoneal Bleed Survivor	Severe GI Bleed Survivor	Pericardial Bleed Survivor	Total
Andexanet alfa							
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC							
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 52. Proportion of patients entering different states in the Markov Model (ICH and severe GI Cohort)

	ICH Survivor	Intraspinal Bleed Survivor	Intraocular Bleed Survivor	Retroperitoneal Bleed Survivor	Severe GI Bleed Survivor	Pericardial Bleed Survivor	Total
Andexanet alfa							
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC							
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 53. Proportion of patients entering different states in the Markov Model (ICH Cohort)

	ICH Survivor	Intraspinal Bleed Survivor	Intraocular Bleed Survivor	Retroperitoneal Bleed Survivor	Severe GI Bleed Survivor	Pericardial Bleed Survivor	Total
Andexanet alfa							
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC							
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

No HRQoL data were collected in the ANNEXA-4 study. However, data for the mRS, a measure of the severity of ICH and stroke, were captured in ANNEXA-4 (see Section B.2.6 Clinical effectiveness results of the relevant trials). These data were extracted for use in the CEM since published literature indicates that mRS is correlated with EQ-5D utility score among patients with an ICH.[116] Hence, published literature and ANNEXA-4 mRS data were used to determine utility scores for patients receiving andexanet alfa and SoC.

B.3.4.2 Mapping

No HRQoL data were collected in the ANNEXA-4 study to map onto a generic outcome measure. However, mRS data were used to derive the impact of andexanet alfa on EQ-5D utility for ICH patients; this is further explained below.

B.3.4.3 Health-related quality-of-life studies

An economic SLR was conducted to identify existing studies investigating HRQoL in management of adults receiving direct or indirect FXa inhibitor who require reversal of anticoagulation due to life-threatening or uncontrolled bleeding event. The original search was run on the 14th December 2016, and an update was performed on the 25th January 2019. One search strategy was devised to identify cost-effectiveness, HRQoL and cost and resource use studies. The PICOS principle described in CRD guidance was used to develop the review question below, which guided the search for HRQoL studies only. For more details on the search strategies, the inclusion/ exclusion criteria, and HRQoL results please see Appendix G and H, respectively. The review question evaluated in the HRQoL SLR was:

- What quality-of-life studies have been conducted in the management of individuals receiving a direct or indirect FXa inhibitor requiring rapid reversal of anticoagulation which can inform utility and disutility estimates?

Using this search strategy and inclusion/exclusion criteria specified in Appendix G, 59 studies were found to be eligible for data extraction, none of which provided HRQoL data for interventions for the reversal of a direct or indirect FXa inhibitor-induced life-threatening bleeding events. Two sources were identified for use in the CEM (Miller 2016[113] and NICE TA 341 2015[114]).

Miller 2016[113] was a cost-effectiveness analysis which calculated a utility score in patients with nonvalvular AF from the population enrolled in the ENGAGE-AF TIMI 48 study.[129] No elicitation method was reported, though utilities were valued using EQ-5D for the health state representing people with nonvalvular atrial fibrillation, in alignment with the NICE reference case.

NICE TA 341 was a NICE technology appraisal of apixaban for the treatment and secondary prevention of DVT and/or PE included individuals with DVT, PE and VTE.[130] The appraisal provided a utility scores for ICH patients which was used in the CEM. In addition, Kind et al.

1999[118], a study evaluating EQ-5D in the UK norms in the UK, was identified as the original source used in the appraisal as way of calculating baseline utilities for patients with AF. During the appraisal, it was criticised that the population norms were not age stratified, and therefore age-stratified value from Kind et al. 1999 values were used from this source.

B.3.4.4 Adverse reactions

No adverse events have been included in economic analysis. 754 Treatment-Emergent adverse events (TEAEs) were observed among the 352 patients in the ANNEXA-4 safety population. Of these, 95.5% were assessed by investigators to be unrelated or unlikely related to andexanet alfa treatment. In addition, the majority (54.0%) of TEAEs were graded as mild or moderate. For these reasons, TEAEs were omitted from the CEM. The rationale for this decision is discussed in greater depth in Section B.2 Clinical effectiveness.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The quality-of-life of patients receiving andexanet or SoC following a life-threatening or uncontrolled bleeding event concurrent with use of FXa inhibitors, is expected to be significantly diminished during the acute period. Following successful anticoagulant reversal and survival of the original bleeding event, it is expected that long-term HRQoL will be impacted by the type and severity of bleed experienced by the patient. As such different HRQoL values were applied to patients in the acute period (30-day decision tree) and in the long-term period (life-time Markov model).

B.3.4.6 Acute HRQoL

The NICE 2015 reported an EQ-5D utility score of 0.33 for patients who suffered an ICH whilst on anticoagulant therapy.[114] In NICE 2015[114] this score was applied for duration of 3 months (3 cycles). As such a utility score of 0.33 was applied in the 30-day decision tree for patients who have suffered an ICH.

To calculate the acute HRQoL utility for severe GI bleed patients, an EQ-5D disutility decrement for an ECH major GI bleed of 0.1511 was subtracted from the baseline EQ-5D utility score of 0.73. This decrement was obtained from Miller et al. 2016[113], whilst the baseline utility score was based on EQ-5D UK population norms for people aged 75 years and over, in line with NICE TA 341.[114] Therefore, an acute utility score of 0.5789 was obtained for patients with a severe GI bleed and was applied in the 30-day decision tree.

To calculate the acute HRQoL utility for other major bleed patients, an EQ-5D disutility decrement for an ECH major non-GI bleed of 0.1511 was subtracted from the baseline EQ-5D utility score of 0.73. As before, this decrement was obtained from Miller et al. 2016[113], whilst the baseline utility score was based on EQ-5D UK population norms for people aged 75 years and over, in line with NICE TA 341.[114] Therefore, an acute utility score of 0.5789 was obtained for patients with an other major bleed and was applied in the 30-day decision tree.

B.3.4.7 Long-term HRQoL for ICH survivors

Life-threatening and uncontrollable bleeding events are associated with a long-term reduction in patient quality-of-life (See Section B.2 Clinical effectiveness), for patients who suffer an ICH.

Published literature reports an association between a measure of stroke/ICH severity, mRS scores, and EQ-5D utility scores. A score of 0 means no symptoms at all, a score of 5 means severe disability and 6 indicates death. As a consequence, a reduction in mRS score for ICH survivors correlates with an increase in quality-of-life. Fletcher et al. 2015[116] quantifies this relationship. The study used mRS score to define health states capturing ICH of different levels of severity in a decision analytic model. Hence, the study reports EQ-5D scores from another published source for each mRS score.

Table 54. EQ-5D scores associated with mRS score and weighted average score by treatment[116]

Variable	Value (range)
EQ-5D score for patients with mRS = 0	0.85 (0.8–1)
EQ-5D score for patients with mRS = 1	0.80 (0.75–0.9)
EQ-5D score for patients with mRS = 2	0.70 (0.53–0.75)
EQ-5D score for patients with mRS = 3	0.51 (0.45–0.65)
EQ-5D score for patients with mRS = 4	0.30 (0.25–0.55)
EQ-5D score for patients with mRS = 5	0.15 (0–0.32)
EQ-5D score for patients with mRS = 6	0 (0–0)

EQ-5D – EuroQoL-5 Dimensions; mRS – modified Rankin Score; SoC – standard of care

Clinical trial results from the ANNEXA-4 trial report mRS scores for ICH patients receiving andexanet alfa 30-days after the bleeding event, whilst a study reported by Øie et al. 2018[29] comprising 452 intracerebral haemorrhage patients reports mRS values for patients receiving SoC whilst on a non-VKA 90-days after the bleeding event (Table 48).

Redistributing these data to exclude death, Fletcher et al. 2015[116] reports the associated EQ-5D utility score for each mRS score. By combining the mRS score proportional split for SoC and andexanet alfa shown in Table 48, with the EQ-5D scores from Fletcher et al. 2015[116], a weighted average utility score for each treatment for ICH survivors was obtained (**Error! Reference source not found.**). The weighted mean EQ-5D scores were 0.53 and 0.42 for andexanet alfa and SoC respectively. The resulting mean EQ-5D score for andexanet alfa is 0.11 greater than that for SoC. This absolute increase was applied to the SoC utility score with acute care for patients with ICH (0.61) to calculate the andexanet alfa utility score of 0.72.

Table 55. Weighted mean EQ-5D scores derived from mRS score

Variable	Value
Weighted mean EQ-5D score for patients receiving andexanet alfa	0.53
Weighted mean EQ-5D score for patients receiving SoC	0.42

EQ-5D – EuroQoL-5 Dimensions; mRS – modified Rankin Score; SoC – standard of care

B.3.4.8 Long-term HRQoL for intraocular survivors

The long-term HRQoL for patients with intraocular bleeding was calculated using the mean utility score obtained using EQ-5D, reported in Kind et al. 1999, for people aged 75 and over, with a utility decrement applied for monocular blindness.[118] The utility decrement applied was obtained from a study by Wittenborn et al. (2017)[119] which assessed age-related macular degeneration utility decrement for patients with monocular blindness using a health economic model. This decrement was 0.036 for patients aged 75 years and older. The decrement was applied with a weighting based on the prevalence of monocular blindness among survivors of intraocular bleeding. This prevalence was based on UK clinical opinion and was estimated at a value of 25%. As such, the resulting long-term utility applied to SoC survivors of intraocular bleeding who received SoC was [0.730 – (0.25*0.036)] = 0.721.

Though data were not available on the differential effect of andexanet alfa on the proportion of patients suffering from monocular blindness as a result of intraocular bleeding or the severity of their monocular blindness, it was assumed that rapid reversal of anticoagulants to reduce bleeding would have some reductive effect on these variables. Hence, aligned with the assumption on mortality benefit where data is sparse for severe GI bleeds and other major bleeds, a 25% reduction in the proportion of patients experiencing monocular blindness in the andexanet alfa arm was applied relative to SoC.

As such, the resulting long-term utility applied to andexanet alfa survivors of intraocular bleeding was [0.730 – ((1-0.25)*0.25*0.036)] = 0.72325.

B.3.4.9 Long-term HRQoL for intraspinal survivors

The long-term HRQoL for patients with intraspinal bleeding was calculated using the mean utility score obtained using EQ-5D, reported in Kind et al. 1999, for people aged 75 and over, with a utility decrement applied for paralysis.[118] The utility decrement applied was obtained from a study by Matza et al. (2014)[117] which assessed 187 participants using the time trade off interviews for skeletal-related events. The associated decrement for spinal cord decompression with paralysis was 0.32. This was applied with a weighting based on the prevalence of paralysis among survivors of intraspinal bleeding. This prevalence was based on UK clinical opinion and was estimated at 50%. As such, the resulting long-term utility applied to survivors of intraocular bleeding who received SoC was [0.730 – (0.50*0.32)] = 0.57.

Though data were not available on the differential effect of andexanet alfa on the proportion of patients suffering from paralysis as a result of intraspinal bleeding or the totality of their paralysis, it was assumed that rapid reversal of anticoagulants to reduce bleeding would have some reductive effect on these variables. Hence, aligned with the assumption on mortality benefit where data is sparse for severe GI bleeds and other major bleeds, a 25% reduction in the proportion of patients experiencing paralysis in the andexanet alfa arm was applied relative to SoC.

As such, the resulting long-term utility applied to andexanet alfa survivors of intraspinal bleeding was [0.730 – ((1-0.25)*0.50*0.32)] = 0.61.

B.3.4.10 Long-term HRQoL for other survivors

The long-term HRQoL used for survivors of the remaining bleed types was the mean utility score obtained using EQ-5D, reported in Kind et al. 1999, for people aged 75 and over (0.73).[118] This was applied as UK clinical opinion did not indicate that long-term morbidity effects would be suffered by survivors of these bleed types.

Table 56. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)*	Reference in submission (section and page number)	Reference	Justification
ICH survivor - acute	0.33	Measurement and valuation of health effects, page 105	NICE 2015[114]	NICE 2015 baseline utility
Intraspinal bleed survivor – acute	0.58	Measurement and valuation of health effects, page 105	NICE 2015;[114] Kind et al. 1999;[118] Miller et al. 2016[113,115]	Using method from NICE 2015, Kind et al. 1999 total population utility among people aged over 75 less. Miller et al. 2016 reports disutility decrement for major non-GI extracranial haemorrhage (ECH) bleed
Intraocular bleed survivor - acute	0.58	Measurement and valuation of health effects, page 105	NICE 2015;[114] Kind et al. 1999;[118] Miller et al. 2016[113,115]	Using method from NICE 2015, Kind et al. 1999 total population utility among people aged over 75 less Miller et al. 2016 disutility decrement for major non-GI extracranial haemorrhage (ECH) bleed
Retroperitoneal bleed survivor - acute	0.58	Measurement and valuation of health effects, page 105	NICE 2015;[114] Kind et al. 1999;[118] Miller et al. 2016[113,115]	Using method from NICE 2015, Kind et al. 1999 total population utility among people aged over 75 less Miller et al. 2016 disutility decrement for major non-GI extracranial haemorrhage (ECH) bleed
Severe GI bleed survivor - acute	0.58	Measurement and valuation of health effects, page 105	NICE 2015;[114] Kind et al. 1999;[118] Miller et al. 2016[113]	Using method from NICE 2015, Kind et al. 1999 total population utility among people aged over 75 less Miller et al. 2016 disutility decrement for major GI haemorrhage bleed

State	Utility value: mean (standard error)*	Reference in submission (section and page number)	Reference	Justification
Pericardial bleed survivor - acute	0.58	Measurement and valuation of health effects, page 105	NICE 2015;[114] Kind et al. 1999;[118] Miller et al. 2016[113,115]	Using method from NICE 2015, Kind et al. 1999 total population utility among people aged over 75 less Miller et al. 2016 disutility decrement for major non-GI extracranial haemorrhage (ECH) bleed
ICH survivor - follow up – Andexanet alfa	0.72	Measurement and valuation of health effects, page 105	NICE 2015; ANNEXA-4, Fletcher et al. 2015;[116] Øie et al. 2018.[27]	NICE 2015 baseline utility used for SoC was combined with mRS data from ANNEXA-4 for andexanet alfa and from Øie et al. 2018 for SoC to determine level of HRQoL impact post bleed
ICH survivor - follow up - SoC	0.61	Measurement and valuation of health effects, page 105		
Intraspinal bleed survivor - follow up- Andexanet alfa	0.61	Measurement and valuation of health effects, page 105	Clinical opinion; Matza et al 2014;[117] Kind et al. 1999[118]	Kind et al. 1999 baseline utility combined with clinical opinion regarding the prevalence of paralysis, and a utility decrement for paralysis from Matza et al to determine the level of HRQoL impact of paralysis
Intraspinal bleed survivor – follow up - SoC	0.57	Measurement and valuation of health effects, page 105		
Intraocular bleed survivor - follow up – Andexanet alfa	0.723	Measurement and valuation of health effects, page 105	Clinical opinion; Wittenborn et al. 2017;[119] Kind et al. 1999[118]	Kind et al. 1999 baseline utility combined with clinical opinion regarding the prevalence of mono ocular blindness, and a utility decrement for blindness from Wittenborn et al., to determine the level of HRQoL impact of blindness
Intraocular bleed survivor - follow up – SoC	0.721	Measurement and valuation of health effects, page 105		
Retroperitoneal bleed survivor - follow up	0.73	Measurement and valuation of health effects, page 105	Miller et al. 2016; Kind et al. 1999[113,118]	HRQoL assumed by Miller et al. 2016 to return to baseline if patient survives non-ICH
Severe GI bleed survivor - follow up	0.73	Measurement and valuation of health effects, page 105	Miller et al. 2016; Kind et al. 1999[113,118]	HRQoL assumed by Miller et al. 2016 to return to baseline if

State	Utility value: mean (standard error)*	Reference in submission (section and page number)	Reference	Justification
				patient survives non-ICH
Pericardial bleed survivor - follow up	0.73	Measurement and valuation of health effects, page 105	Miller et al. 2016; Kind et al. 1999[113,118]	HRQoL assumed by Miller et al. 2016 to return to baseline if patient survives non-ICH

*Literature sources for health state utilities did not provide standard errors associated with the EQ-5D utility data values. Hence, no standard errors or confidence intervals are reported

Abbreviations: ACD – Appraisal Consultation Document; HRQoL – health-related quality of life; ICH – intracranial haemorrhage; SoC – standard of care

B.3.5 Cost and healthcare resource use identification, measurement and valuation

In appendix I describe how relevant cost and healthcare resource data were identified.

An economic SLR was conducted to identify existing studies reported cost and resource use data in the management of individuals receiving direct or indirect FXa inhibitor who require rapid reversal of anticoagulation due to life-threatening or uncontrolled bleeding event. The original search was run on the 14th December 2016, and an update was performed on the 25th January 2019. One search strategy was devised to identify cost-effectiveness, HRQoL and cost and resource use studies. The PICOS principle described in CRD guidance was used to develop the review question below, which guided the search for cost and resource use studies only. For more details on the search strategies and the inclusion/exclusion criteria, and cost and resource use SLR results please see Appendix G and I, respectively. The review question evaluated in the cost and resource use SLR was:

- What are the costs and resource use associated with the management of individuals receiving a direct or indirect FXa inhibitor requiring rapid reversal of anticoagulation?

Using this search strategy and inclusion/ exclusion criteria specified in Appendix I, 79 studies were found to be eligible for data extraction. Of these 79, the following was undertaken:

- Extraction of references reporting resource use and costs from a UK perspective was conducted following guidelines set out in the NICE STA user guide. Extraction was also undertaken for references reporting costs for reversing a pre-defined life-threatening or major bleed and/or non-UK perspective. (n=14) (Appendix I, Table 8)
- A summary was developed for references reporting resource use and costs from other countries (n=65) (Appendix I, Table 9)

Of the 14 studies extracted, 12 were from a UK perspective, while the remaining 2 studies were from a US perspective. Information from the following cost categories were extracted from the papers; treatment costs, clinical/adverse event costs, monitoring costs, resource costs (e.g. staff time, procedure cost, outpatient, and inpatient). Information from the following resource use categories were extracted from the papers; anticoagulant use, hospital time, time span for maintenance costs of bleeding events, follow-up visits, outpatient management, renal monitoring tests and resource use associated with clinical events.

Cost categories included in the CEM are: treatment costs; acute management costs of bleeding events; and long-term management costs for bleeding events. Several studies identified in the cost and resource SLR obtained costs for the acute management of bleeding events the National Health Service (NHS) reference costs tariff. As the perspective of this cost-effectiveness analysis is the NHS and PSS, the NHS reference costs was deemed an appropriate source for the cost inputs of acute management of bleeding events in the model. Two papers from the cost and resource use SLR were used to inform the long-term management cost of the bleeding events in the Markov model; Lanitis 2016[131] and Luengo-Fernandez 2012.[132] A targeted literature review was performed to identify alternative bleed management costs, which were used in a sensitivity analysis. Treatment costs were sourced from the British National Formulary via the NICE website and the Monthly Index of Medical Specialities (MIMS) database. Where necessary costs were inflated to the 2017/18 cost year using inflation indices published by Curtis et al. 2018.[122]

B.3.5.1 Intervention and comparators' costs and resource use

Treatment using andexanet alfa and SoC are provided in an emergency hospital setting. There is no additional infrastructure required to administer care within this setting. As a result, only treatment administration and acquisition costs were applied to fully represent the costs of treatment itself for both interventions.

B.3.5.2 Andexanet alfa acquisition cost

The cost for one 200 mg vial of andexanet alfa was £2,775.00. Andexanet alfa is administered intravenously as a one-off bolus and immediate subsequent infusion for the reversal of anticoagulant effects in patients who are experiencing a life-threatening or uncontrollable bleeding event. There are two dosing regimens for andexanet alfa:

- Low dose: initial IV bolus 400 mg at a target rate of 30 mg/min, followed by a continuous IV infusion of 4 mg/min for 120 mins (480 mg).
- High dose: initial IV bolus 800 mg at a target rate of 30 mg/min, followed by a continuous IV infusion of 8 mg/min for 120 mins (960 mg).

The recommended dose for andexanet alfa depends on which FXa inhibitor was received, the dose of that FXa inhibitor and the timing of the dose received (Table 57). In the ANNEXA-4 study, all patients treated at least 8 hours after their last FXa inhibitor received the low dose. For patients treated less than 8 hours after their last FXa inhibitor, a low andexanet dose was given if the last FXa inhibitor amount was 5 mg or less for apixaban, 10 mg or less for rivaroxaban, 40 mg or less for enoxaparin, or 30 mg or less for edoxaban. Patients less than

8 hours after FXa inhibitor treatment who had higher FXa doses received the high andexanet dose.

Table 57. Dosing regimens and weighted average bolus and infusion doses

Dosing regimen	Bolus dose (mg)	Infusion dose (mg)	Total dose on regimen (mg)
Low dose	400	480	880
High dose	800	960	1760

As a result of these rules being applied, 287 (89.1%) of the 322 patients in the ANNEXA-4 efficacy population received the low dose and 35 (10.9%) received the high dose. Given this, a weighted average cost of each the initial bolus injection and the subsequent infusion dose were calculated, respectively (Table 59). Under these dosing regimens the acquisition cost per patient for andexanet alfa was calculated as £15,081.52 when vial wastage was assumed (Table 59). The andexanet alfa acquisition costs were applied to all patients in the andexanet alfa cohort who enter the decision tree at the start of the 30-day time horizon.

Table 58. Andexanet alfa unit drug costs

Drug	Unit size (mg)	Cost (£)	Cost per unit (£)	Reference
Andexanet alfa	200	£2,775.00	£13.875	*Portola*

Table 59. Acquisition cost of andexanet alfa for the Whole cohort

Andexanet alfa	% Patients on regimen	No wastage		Wastage	
		Units	£	Units	£
Low dose	89.1	4.40	£12,210.00	5.00	£13,875.00
High dose	10.9	8.80	£24,420.00	9.00	£24,975.00
Weighted average		4.88	£13,537.17	5.43	£15,081.52

B.3.5.3 SoC acquisition cost

As discussed in Section B.3.2 Economic analysis, PCC was considered the most relevant SoC comparator to andexanet alfa in the base-case. Acquisition costs for PCC were sourced from MIMS (Table 60). The dosing regimen for PCC is presented in Table 61, where total dose for PCC is calculated as the product of mean body weight and the licensed dose of PCC per kilogram of body weight. Mean body weight at baseline is [redacted] kilograms for the Whole cohort, [redacted] kilograms for ICH and severe GI and [redacted] kilograms for ICH only, based on the ANNEXA-4 study. There are two available 4F-PCC regimens. The literature reports that the dosing regimen for PCCs is chosen depending on which FXa inhibitor the patient received. In a UK study, the average PCC dose received by patients who had been on rivaroxaban [n=40] was 26.8 units per kilogram and for apixaban [n=40] patients was 25.0 units per kilogram.[107] The weighted dose in Table 61 uses the proportion of patients receiving each rivaroxaban and apixaban to weight the two average PCC doses by anticoagulant.

Table 60. SoC unit drug costs

Drug	Unit size	Cost (£)	Cost per unit (£)	Reference
4F-PCC (500 UI) inflated to 2017/2018 prices	20 ml	£208.25	£0.42	*MIMS*[123]
4F-PCC (1000 UI) inflated to 2017/2018 prices	40 ml	£416.50	£0.42	*MIMS*[123]

MIMS – Monthly Index of Medical Specialities; PCC – prothrombin complex concentrate

Table 61. SoC dosage

Population	Drug	Dose (IU)	Calculation	Total dose	Proportion on dosing regimen (%)	Weighted dose modelled	Reference
Whole cohort	Rivaroxaban	26.8	77.32*26.8	2072.05	39.78	1988.25	MIMS[123]
	Apixaban	25.0	77.32*25.0	1932.89	60.22		
ICH and severe GI cohort	Rivaroxaban	26.8	77.34*26.8	2072.77	39.78	1988.94	MIMS[123]
	Apixaban	25.0	77.34*25.0	1933.56	60.22		
ICH cohort	Rivaroxaban	26.8	77.19*26.8	2068.82	39.78	1985.15	MIMS[123]
	Apixaban	25.0	77.19*25.0	1929.87	60.22		

MIMS – Monthly Index of Medical Specialities; PCC – prothrombin complex concentrate

Under these dosing regimens the acquisition costs per patient for PCC were calculated as £833.00, assuming wastage (Table 62). In the base-case analysis the cost of SoC was modelled for PCC as £833.00 per single use. The SoC acquisition cost was applied to all patients in the SoC cohort who enter the decision tree at the start of the 30-day time horizon.

Table 62. Acquisition cost for SoC

PCC	Cost per unit (£)	No wastage		Wastage	
Unit size		**Units**	**£**	**Units**	**£**
500	208.25	0.00	0.00	2.00	416.50
1000	416.50	1.99	828.11	1.00	416.50
	Total	**1.99**	**828.11**	**3.00**	**833.00**

PCC - prothrombin complex concentrate; SoC – standard of care

B.3.5.4 Administration

Administration cost for both andexanet alfa and SoC were sourced from 2017/18 NHS Reference costs (Table 63). NHS Reference Costs code SB14Z (Deliver Complex Chemotherapy, including Prolonged Infusion Treatment, at First Attendance) at a cost of £336.55 was modelled for andexanet alfa. NHS Reference Costs code SB12Z (Deliver Simple Parenteral Chemotherapy at First Attendance) at a cost of £228.99 was modelled for SoC. Codes were selected based on UK expert opinion and the time to administer the treatments for each of these costs.[121]

Table 63. Administration costs

Administration costs	Unit cost	Year	Reference
Andexanet alfa	336.55	2017/18	NHS Reference Costs 2017/18 Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (SB14Z)
SoC	228.99	2017/18	NHS Reference Costs 2017/18 Deliver Simple Parenteral Chemotherapy at First Attendance (SB12Z)

NHS – National Health Service; SoC – Standard of care.

B.3.5.5 Health-state unit costs and resource use

Acute bleed management

The 2017/18 NHS reference costs were used to source the costs of acute management of bleeding events in the CEM (see Table 64):

- A weighted average of costs associated with NHS Reference Costs code AA23C-G (Haemorrhagic Cerebrovascular Disorders with CC Score 0-2:14+) was the cost modelled for acute care of an ICH survivor.
- A weighted average of costs associated with NHS Reference Costs code FD03A-B (Gastrointestinal Bleed with Multiple Interventions) was the cost modelled for the acute care of patients surviving a severe GI bleed.
- The same cost for the acute care was applied to patients surviving intraspinal, intraocular, retroperitoneal, or pericardial bleeds since no specific HRG codes were available in the NHS Reference Costs. As such, a simplified assumption using a weighted average of cost associated with NHS Reference Costs code FE02B-C (Major Therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures, 19 years and over with CC Score > 0) was applied for the acute care of patients with these bleed types.

Costs of acute management were assumed to be the same between andexanet alfa and SoC, as there were no compelling evidence to suggest otherwise.

Table 64. Acute care hospitalisation cost by bleed type

Health state	Unit cost from NHS Reference costs 17/18 (£)
ICH Survivor	£4,099
Intraspinal Survivor	£2,447
Intraocular Survivor	£2,447
Retroperitoneal Bleed Survivor	£2,447
Severe GI Bleed Survivor	£4,516
Pericardial Bleed Survivor	£2,447

ICH – intracranial haemorrhage; GI – Gastrointestinal; LOS – length of stay; NHS – National Health Service; SoC – standard of care.

B.3.5.6 Long-term bleed management

Long-term bleed management costs were modelled as a direct consequence of the life-threatening or uncontrolled bleeding event. Other comorbid costs associated with other underlying conditions were not considered in the model as they lie outside of the decision problem for andexanet alfa. The ICH long-term management cost associated with healthcare by mRS score was sourced from published literature (Luengo-Fernandez 2013) and inflated to 2017/18 cost year.[122] The study by Luengo-Fernandez 2013[124] was a UK population-based cohort study called the Oxford Vascular Study, which reported resource use and associated hospital unit costs for 485 patients with transient ischaemic attack and 729 patients who experienced stroke. The inflated costs were calculated as £201.22, £392.55 and £596.04 for non-disabling (assumed mRS 0-2), moderately disabling (assumed mRS 3-4) and totally disabling (assumed mRS 5) stroke. Using the mRS distributions in Table 48, the monthly cycle cost for surviving ICH patients receiving SoC and andexanet alfa was £385.53 and [redacted], respectively.

Published literature by Persson et al. 2017[133] associates mRS scores of ICH survivors with how dependent or independent a survivor will be on a carer. A mRS score of 3-5 indicates that the individual would be dependent on a carer whereas a score of 0-2 indicates that the individual would be independent. It has been shown that a more dependent ICH survivor would incur more costs due to greater care costs, than an independent ICH survivor.

As previously demonstrated in Section B.3.4 Measurement and valuation of health effects, treatment with andexanet alfa was associated, in a naïve treatment comparison, with lower mRS scores for surviving ICH patients compared to patients receiving SoC. Specifically, Table 48 shows the redistributed proportions of patients with each mRS score below six, on each treatment. These proportions are derived from ANNEXA-4 for patients receiving andexanet alfa and from Øie et al. 2018[27] for patients receiving SoC.

The proportions of those receiving scores of 0-2 were added to estimate the number of patients who were independent and the remainder were categorised as dependent based on Persson et al. 2017 (Table 65). The proportion of dependent ICH survivors was [redacted] % and 52.3% for SoC and andexanet alfa, respectively. These proportions were applied to the ICH rehabilititation cost and added to the mRS weighted costs described above to provide a total cost of an ICH survivor for SoC and andexanet alfa. The total costs used in the long-term cost for ICH were £[redacted] and £542.53 for SoC and andexanet alfa, respectively.(Table 66).

Table 65. Proportion of ICH survivor patients categorised as independent or dependent following SoC and andexanet alfa

Category	SoC	Andexanet alfa
Dependent	75.4%	[redacted]
Independent	24.6%	[redacted]

ICH – intracranial haemorrhage; SoC – Standard of care

Table 66. Long-term ICH health state costs for SoC and andexanet alfa

	Total costs, SoC	Total costs, andexanet alfa
Long-term cost ICH	£677.83	[redacted]

ICH – intracranial haemorrhage; SoC – Standard of care

Further health state-specific long-term costs were applied to patients in the intraspinal bleed survivor and intraocular bleed survivor states. These were applied to the proportion of patients affected by paralysis and blindness in the intraspinal bleed survivor and intraocular bleed survivor states, respectively. In line with the assumptions regarding quality-of-life for intraocular and intraspinal bleeds, the proportion of patients experiencing paralysis and blindness was reduced by 25% for patients receiving andexanet alfa.

Costs applied for the care of patients with paralysis were sourced from an economic model of the cost impact of spinal cord injuries in the UK, which was the best available proxy for the costs of paralysis after intraspinal bleeding. Costs for care in the first year among patients aged 76 to 85 were presented for 133 patients suffering from either tetraplegia and paraplegia; 71% of costs were costs to personal and social services in the UK, and only these were included. In the 76 to 85 age group, the total cost during the first year was £5,421,553, and a per-patient monthly cost was calculated from this as £2,412.[134]

Table 67. Costs of care for patients with paralysis during the first year

Cost	Proportion of costs incurred to public and social services	Number of patients to whom cost applied	Cost (£)	Cost to the public (£)	Years over which costs incurred	Cost per patient (£)	Monthly cost (£)
Cost of first year of care – patients age 76-85	71%	133	5,421,553	3,849,303	1	28,942	2,412

For subsequent years, a 60-day cost for care in a spinal cord injury centre was sourced from Spinal UK and applied at a monthly rate.[135] The 60-day cost was £968 and hence the monthly cost applied was £495. This cost was inflated from a 2015 to a 2018 cost.

Life expectancy in the model for patients surviving intraspinal bleeds was 7.79 years. Hence, the average cost across this period of applying £2,412 per month during the first year and £495 per month subsequently, was £740.91 per month. This was the cost applied for long-term paralysis in the model to 50% of survivors of intraspinal bleed receiving SoC and to 50%*(1-0.25) = 37.5% of patients receiving andexanet alfa.

Costs applied to patients surviving an intraocular bleed and suffering monocular blindness were identified in a patient group response within the Appraisal Consultation document of a NICE appraisal of Pegaptanib and ranibizumab for treatment of age-related macular degeneration (AMD), which included cost estimates for age-related macular degeneration associated with monocular blindness.[136] The annual average cost per patient with AMD was £3,823.89, which was used to calculate a per-patient monthly cost of £318.66. These costs were inflated using PSSRU inflation data to 2017/18 costs, giving a final cost of £374.43. This was the cost applied for long-term monocular blindness in the model to 50% of survivors of intraocular bleed receiving SoC and to 25%*(1-0.25) = 18.75% of patients receiving andexanet alfa.

Finally, costs were added for re-initiation of anticoagulant treatment for this patient population, due to their heightened risk of recurrent bleeding events. A monthly weighted average of the costs of rivaroxaban and apixaban treatment regimens was calculated using the proportions of patients receiving each rivaroxaban and apixaban in the paper reporting on ANNEXA-4 by Connolly et al.[74]

The costs of each apixaban and rivaroxaban were sourced from the costs provided by the BNF.[120] The proportion of patients receiving tablets of each size was obtained from Prescription Cost Analysis data for the year 2017. Where each tablet size matched an indication for prophylaxis of recurrent deep-vein thrombosis or prophylaxis of recurrent pulmonary embolism, the dosing regimens described for these indications were used to calculate costs.[137] Table 68 shows the calculation of monthly costs for apixaban and rivaroxaban FXa inhibitors.

Table 69 shows the weighted average cost for each FXa inhibitor, where weighting was conducted using the prevalence of use of each tablet size. Finally, the weighted average cost of the two FXa inhibitors, with weighted conducted using the proportion of patients on each FXa inhibitor, sourced from Connolly et al. 2019.[74] The resulting weighted average monthly cost of FXa inhibitors was £55.81.

Table 68. FXa inhibitor long-term cost data

FXa inhibitor	Dose (mg)	Proportion of patients	Pack size (tablets)	Pack cost (£)	Tablet cost (£)	Frequency (per day)	Duration (days)	Cost
Rivaroxaban	10 mg	0.80%	10	18	1.80	1	30	54.00
	10 mg		30	54	1.80			
	10 mg		100	180	1.80			
	15 mg	11.00%	14	25.2	1.80	1	30	54.00
	15 mg		28	50.4	1.80			
	15 mg		42	75.6	1.80			
	15 mg		100	180	1.80			

	2.5 mg	0.20%	56	50.4	0.90	2	30	54.00
	20 mg	88.00%	28	50.4	1.80	1	30	54.00
	20 mg		100	180	1.80			
Apixaban	2.5 mg	34.40%	10	9.5	0.95	2	30	57.00
	2.5 mg		20	19	0.95	2	30	
	2.5 mg		60	57	0.95	2	30	
	5 mg	65.60%	28	26.6	0.95	2	30	57.00
	5 mg		56	53.2	0.95	2	30	

Table 69. Weighted average cost of FXa inhibitors

FXa inhibitor	Proportion of patients (%)	Average cost weighted by prevalence of each tablet size (£)	Weighted average monthly FXa inhibitor cost
Rivaroxaban	39.78	£54.00	£55.81
Apixaban	60.22	£57.00	

B.3.5.7 Adverse reaction unit costs and resource use

As stated above, in Section B.3.4 Measurement and valuation of health effects, adverse events were not included in the de novo CEM developed to inform this submission because 94.5% were assessed by investigators to be unrelated or unlikely related to andexanet alfa treatment.

B.3.5.8 Miscellaneous unit costs and resource use

No additional costs or resource use were used to informed this cost-effectiveness analysis.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Table 70 shows the base-case de novo analysis inputs. Further detail on these inputs can be found in other sections noted in the reference column.

Table 70. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Age	Whole cohort = [redacted] ICH+GI cohort = [redacted] ICH only cohort = [redacted]	GAMMA	B.3.3.2 Baseline demographics; Page 92
Percentage male	Whole cohort = 53.1% ICH + severe GI cohort = [redacted] ICH only cohort = [redacted]	BETA	B.3.3.2 Baseline demographics; Page 92

Weight (kg)	Whole cohort = [redacted] ICH + severe GI cohort = [redacted] ICH only cohort = [redacted]	GAMMA	B.3.3.2 Baseline demographics; Page 92
Andexanet alfa decision tree distribution	See Figure 14	N/A (fixed values)	B.3.2.2 Model structure; Page 87
SoC decision tree distribution	See Figure 14	N/A (fixed values)	B.3.2.2 Model structure; Page 87
Andexanet alfa relative mortality reduction	25.00%	BETA	B.3.3.3 Transitions in 30-day decision tree; Page 94
Discount rate costs	3.50%	N/A (fixed values)	B.3.2.2 Model structure; Page 89
Discount rate outcomes	3.50%	N/A (fixed values)	B.3.2.2 Model structure; Page 89
Andexanet alfa relative improvement of intraspinal bleed Survivor long-term utility	25.00%	BETA	B.3.4.9 Long-term HRQoL for intraspinal survivors; Page 107
Andexanet alfa relative improvement of intraocular bleed Survivor long-term utility	25.00%	BETA	B3.4; Page 104
SoC ICH acute care cost (£)	4099	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
SoC ICH long-term care cost (£)	733.64	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
Andexanet alfa ICH acute care cost (£)	4099	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards

Andexanet alfa ICH long-term care cost (£)	[redacted]	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
SoC Intraspinal bleed acute care costs (£)	2447	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
SoC Intraspinal bleed long-term care cost (£)	411	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
Andexanet alfa Intraspinal bleed acute care costs (£)	2447	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
Andexanet alfa Intraspinal bleed long-term care cost (£)	322	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
SoC Intraocular bleed acute care cost (£)	2447	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
SoC Intraocular bleed long-term care cost (£)	149	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
Andexanet alfa Intraocular bleed acute care cost (£)	2447	GAMMA	B.3.5 Cost and healthcare resource use

			identification, measurement and valuation; Page 110 onwards
Andexanet alfa Intraocular bleed long-term care cost (£)	126	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
SoC Retroperitoneal bleed acute care cost (£)	2447	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
SoC Retroperitoneal bleed long-term care cost (£)	56	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
Andexanet alfa Retroperitoneal bleed acute care cost (£)	2447	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
Andexanet alfa Retroperitoneal bleed long-term care cost (£)	56	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
SoC Severe GI bleed acute care cost (£)	4516	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
SoC Severe GI bleed long-term care cost (£)	56	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and

			valuation; Page 110 onwards
Andexanet alfa Severe GI bleed acute care cost (£)	4516	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
Andexanet alfa Severe GI bleed long-term care cost (£)	56	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
SoC Pericardial bleed acute care cost (£)	2447	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
SoC Pericardial bleed long-term care cost (£)	56	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
Andexanet alfa Pericardial bleed acute care cost (£)	2447	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
Andexanet alfa Pericardial bleed long-term care cost (£)	56	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
Andexanet alfa treatment cost (£)	15082	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards

Administration cost per cycle with andexanet alfa (£):	336.55	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
SoC treatment cost (£)	833	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
Administration cost per cycle with SoC (£):	228.99	GAMMA	B.3.5 Cost and healthcare resource use identification, measurement and valuation; Page 110 onwards
Andexanet alfa mortality HR: ICH Survivor	1.35	GAMMA	B.3.3.4 Transitions in the Markov Model; Page 95
SoC mortality HR: ICH survivor	1.41	GAMMA	B.3.3.4 Transitions in the Markov Model; Page 95
Standardised mortality ratio: non-ICH bleed Survivor	1.30	GAMMA	B.3.3.4 Transitions in the Markov Model; Page 95
Utility: ICH acute care	0.33	BETA	B3.4; Page 108
Utility: ICH follow-up care – Andexanet alfa	0.72	BETA	B3.4; Page 108
Utility: ICH follow-up care – SoC	0.61	BETA	B3.4; Page 108
Utility: Intraspinal bleed acute care	0.58	BETA	B3.4; Page 108
Utility: Intraspinal bleed follow-up care – Andexanet alfa	0.61	BETA	B3.4; Page 108
Utility: Intraspinal bleed follow-up care – SoC	0.57	BETA	B3.4; Page 108
Utility: Intraocular bleed acute care	0.58	BETA	B3.4; Page 108
Utility: Intraocular bleed follow-up care – Andexanet alfa	0.72	BETA	B3.4; Page 108
Utility: Intraocular bleed follow-up care - SoC	0.72	BETA	B3.4; Page 108

Utility: Retroperitoneal Bleed acute care	0.58	BETA	B3.4; Page 108
Utility: Retroperitoneal Bleed follow-up care	0.73	BETA	B3.4; Page 108
Utility: Severe GI Bleed acute care	0.58	BETA	B3.4; Page 108
Utility: Severe GI Bleed follow-up care	0.73	BETA	B3.4; Page 108
Utility: Pericardial Bleed acute care	0.58	BETA	B3.4; Page 108
Utility: Pericardial Bleed follow-up care	0.73	BETA	B3.4; Page 108
Abbreviations: CI, confidence interval			

B.3.6.2 Assumptions

Table 71 presents the assumptions underlying the de novo CEM created for this analysis.

Table 71. Assumptions underpinning cost effectiveness model

Variable	Assumed value	Justification
Time horizon	[redacted] years	Patients entering the model have a mean age of [redacted] years based on clinical trial baseline characteristics. Patients in the cohort are not expected to live beyond 100 years and therefore a [redacted] year time horizon was deemed appropriate ([redacted]
Markov assumption	NA	Following the occurrence of events in the decision tree, patients will either remain in their current health state, or die. This is a reasonable assumption as the health states describe the patients' history.
Half cycle correction applied	NA	A half-cycle correction was applied to both costs and health outcomes in the Markov model to align with conventional modelling standards.
Baseline characteristics of patients	Whole cohort: Age (years) = [redacted] % male = [redacted] Weight (kg) = [redacted]	The indicated population were enrolled in the ANNEXA-4 study, so it is suitable to use the baseline characteristics from ANNEXA-4 for both the andexanet alfa and SoC cohort.
ANNEXA4 'other major bleeds' definition	31 other major bleed events	Life-threatening or uncontrolled bleeding was defined by site of bleeding in consultation with UK clinical experts. The number of ICH and severe GI bleeds were known in ANNEXA-4; while 'other major bleeds' were grouped together. The model assumed that intraspinal, intraocular, retroperitoneal and pericardial bleeds were captured within the 'other major bleeds' category.

Musculoskeletal bleeds assumed to include intraspinal bleed, pericardial bleed and retroperitoneal bleed	224 musculoskeletal bleeding events of 229 events = 74.92%	Intraspinal bleed, pericardial bleed and retroperitoneal bleed are all musculoskeletal bleeding events. Other major bleeding events included in the model were non-musculoskeletal bleeding events. Therefore, the proportion of other major bleeding events attributable to these other major bleeding types was considered to mirror those observed in the ORANGE trial.
Miscellaneous bleeds assumed to include intraocular bleeds	75 miscellaneous bleeding events of 299 events = 25.08%	The only bleed type that was neither captured by the musculoskeletal bleed category nor reported separately (ICH or GI) was intraocular bleeding. Hence, all miscellaneous bleeds were assumed to be intraocular bleeding events.
Relative reduction of mortality for andexanet alfa for non-ICH/GI bleeds	25%	Due to the paucity of data in ANNEXA-4 for non-ICH/GI, and the difficulty in identifying and therefore comparing life-threatening or uncontrolled bleeds of these types in the ORANGE study, it was assumed that treatment with andexanet alfa would also lead to reduction in the risk of death. However, when conducting a naïve comparison of 30-day mortality in ANNEXA-4 versus ORANGE there was a limited number of deaths reported for other major bleeds in ANNEXA-4. Therefore, it was assumed that treatment with andexanet alfa results in a relative reduction in mortality for other major bleed patients of 25% compared to SoC. This assumption is conservative because a 50% relative reduction was observed for the ICH population.
Relative reduction of paralysis and blindness for andexanet alfa for intraspinal bleed and intraocular respectively	25% reduction of percentage of patients with paralysis 25% reduction of percentage of patients with blindness	Due to the paucity of data in ANNEXA-4 for intraspinal bleed and intraocular bleed, it was assumed that treatment with andexanet alfa would also lead to reduction in associated morbidities (paralysis and blindness). Based on UK clinical expert, the percentage of reduction is relative to the reduction of mortality for other major bleeds stated above. Therefore, it was assumed that treatment with andexanet alfa results in a relative reduction in paralysis for intraspinal bleeds and blindness in intraocular bleeds of 25% compared to SoC. This assumption is conservative because a 25% relative reduction was observed for the mortality rate.
Comparison of mRS between SoC and andexanet alfa	Andexanet alfa: ANNEXA4 (mRS for ICH at 30 days) SoC: Øie *et al.* 2018[29] (mRS for ICH at 90 days)	ANNEXA 4 study measured the mRS scores at day 30; while Øie *et al.* 2018 measured mRS scores at day 90. Due to the paucity of day 30 data for SoC, the model assumed the day 30 scores in ANNEXA4 were comparable to the day 90 scores from Øie *et al.* 2018. Upon consultation with UK clinical experts, this assumption would only serve to favour SoC since 90 day mRS would be improved compared to 30 day mRS in general. In being able to compare these populations, it is also assumed that the severity of patients are similar between ANNEXA-4 and Øie *et al.* 2018. This was confirmed by UK clinical experts as plausible since ANNEXA-4 only included patients

		with life-threatening or uncontrolled bleeds whilst Øie *et al.* 2018 included most cerebral bleed patients (a severe form of bleeding in the brain).
QoL for surviving retroperitoneal bleed, severe GI bleed and pericardial bleed patient equals baseline utility	Long-term utility = 0.73	Long-term reduction in patient quality-of-life was only identified for ICH, intraspinal bleed and intraocular in published literature. As such, patients with all other major bleed types were based on the baseline utility for patients aged 75 years old and above.
QoL for surviving intraocular bleed patients equals baseline utility less a weighted decrement for monocular blindness	Long-term utility = 0.72 (SoC)	Long-term reduction in patient quality-of-life is assumed to only be caused by monocular blindness as a result of intraocular bleeding. As such, a long-term utility value with a decrement for monocular blindness weighted by the proportion of intraocular bleed survivors suffering monocular blindness is applied to all patients surviving intraocular bleeds.
QoL for surviving intraspinal bleed equals baseline utility less a weighted decrement for paralysis	Long-term utility = 0.57 (SoC)	Long-term reduction in patient quality-of-life is assumed to only be caused by paralysis as a result of intraocular bleeding. As such, a long-term utility value with a decrement for paralysis weighted by the proportion of intraspinal bleed survivors suffering paralysis is applied to all patients surviving intraspinal bleeds.
Vials wastage assumption	NA	Wastage was included in the model as vial sharing is not expected.
No adverse events	NA	No adverse events have been included in economic analysis because 94.5% of events assessed by investigators were deemed to be unrelated or unlikely related to andexanet alfa treatment. In addition, the majority (52.1%) of TEAEs were graded as mild or moderate. In ORANGE, no adverse events were comparable to the ANNEXA-4 definitions. For these reasons, adverse events were omitted from the CEM.
Bleeds per patient	1	It was assumed that all patients had only one type of bleed and hence that if patients had more than one bleed type in clinical trial data, the additional bleeds did not make a change to mortality rates.
Acute care HRG costs for other bleeds	£2,447	Acute care management costs were assumed to be the same between treatments, as there were no other evidence to suggest otherwise. NHS Reference Costs for acute bleeding events were only identified for ICH and severe GI bleeds. It was assumed the same cost for the acute care was applied to patients surviving intraspinal, intraocular, retroperitoneal, or pericardial bleeds since no specific HRG codes were available in the NHS Reference Costs. As such, a simplified assumption using a weighted average of costs associated with NHS Reference Costs code FE02B-C (Major Therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures, 19 years and

		over with CC Score > 0) was applied for the acute care of patients with these bleed types.
Long-term ICH cost	Non-disabling stroke = mRS 0-2, moderately disabling stroke = 3-4, totally disabling stroke =5	UK clinical opinion

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

Base-case incremental cost-effectiveness analysis results are presented in Table 72. Andexanet alfa was associated with £19,782 incremental costs and 1.043 incremental QALYs, which corresponds to an ICER of £18,968.

Table 72. Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Whole cohort								
SoC	17,583	3.267	2.187	-	-	-	-	-
Andexanet alfa	37,365	4.563	3.230	19,782	1.296	1.043	18,968	18,968
ICH and severe GI cohort								
SoC	16,958	2.741	1.824	-	-	-	-	-
Andexanet alfa	37,392	4.100	2.909	20,434	1.359	1.085	18,832	18,832
ICH only cohort								
SoC	19,069	1.620	0.953	-	-	-	-	-
Andexanet alfa	41,122	3.058	2.121	22,053	1.438	1.169	18,871	18,871

GI – gastrointestinal; ICER – incremental cost-effectiveness ratio; ICH – intracranial haemorrhage LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

In appendix J please provide the following:

- **Clinical outcomes from the model**
  - Present the estimates of clinical outcomes included in the cost-effectiveness analysis (and compare with the clinical trial results).
  - See section 3.7 of the user guide for full details of the information required here.
- **Disaggregated results of the base-case incremental cost effectiveness analysis**

- Describe and tabulate the disaggregated results of the base-case incremental cost-effectiveness analysis.
- See section 3.7 of the user guide for full details of the information required here.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to explore the uncertainty around key model inputs. PSA was conducted by varying these inputs simultaneously by assigning distributions and recording the mean model results. 10,000 PSA iterations were run in order to obtain a stable estimate of the mean model results.

As shown in Table 73, the following parameters were kept fixed in the PSA: time horizon, cycle length, discount rates, average drug costs per day, decision tree distribution, and treatment costs. Dirichlet distributions were assigned to the baseline decision tree data for andexanet alfa and SoC. Beta distributions were used for the event probabilities, utilities, disutilities, andexanet alfa relative mortality reduction, andexanet alfa percentage increase in ICH utility score and andexanet alfa relative reduction in ICH long-term bleed management cost. Gamma distributions were used for age, weight, costs and mortality HRs by bleed type.

Mean incremental results were recorded and illustrated through an incremental cost-effectiveness plane (ICEP). In addition, a cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF) were plotted.

PSA results of andexanet alfa versus SoC the Whole cohort are presented in Table 73. The mean PSA results lie close to the deterministic base-case results (Table 72). The Whole cohort receiving andexanet alfa accrued 3.302 QALYs at a cost of £38,074. Patients receiving SoC accrued 2.188 QALYs at a cost of £17,533, respectively. This resulted in a mean PSA ICER of £18,441.

The ICEP showing the PSA results for the Whole cohort is presented in Figure 24. The CEAC and CEAF for the Whole cohort are presented in Figure 25 and Figure 26, respectively. The majority of simulations were when andexanet alfa had higher incremental costs and higher incremental QALYs.

Table 73. PSA results for Whole cohort

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
SoC	17,533	2.188	-	-	-
Andexanet alfa	38,074	3.302	20,540	1.1138	18,441

ICER – incremental cost-effectiveness ratio; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; SoC – standard of care.

Figure 24. Incremental Cost Effectiveness Plane for Whole cohort

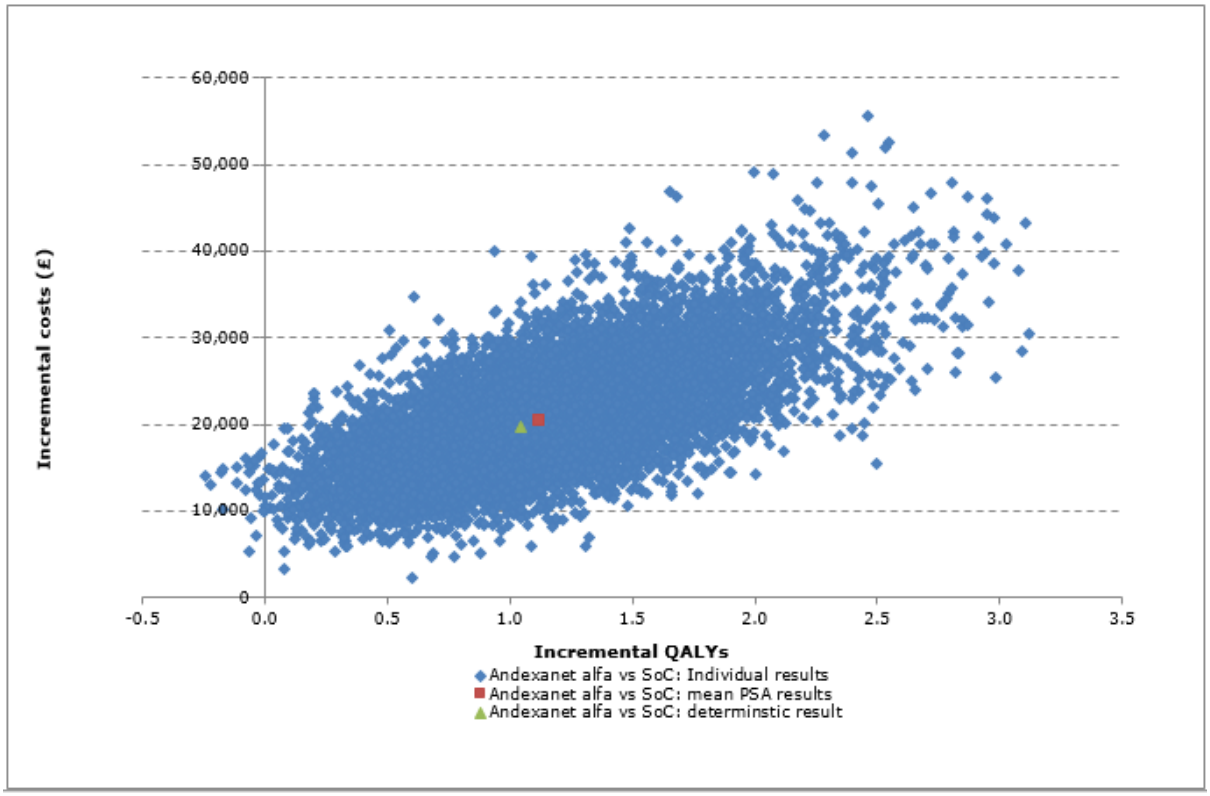


Figure 25. Cost Effectiveness Acceptability Curve for Whole cohort

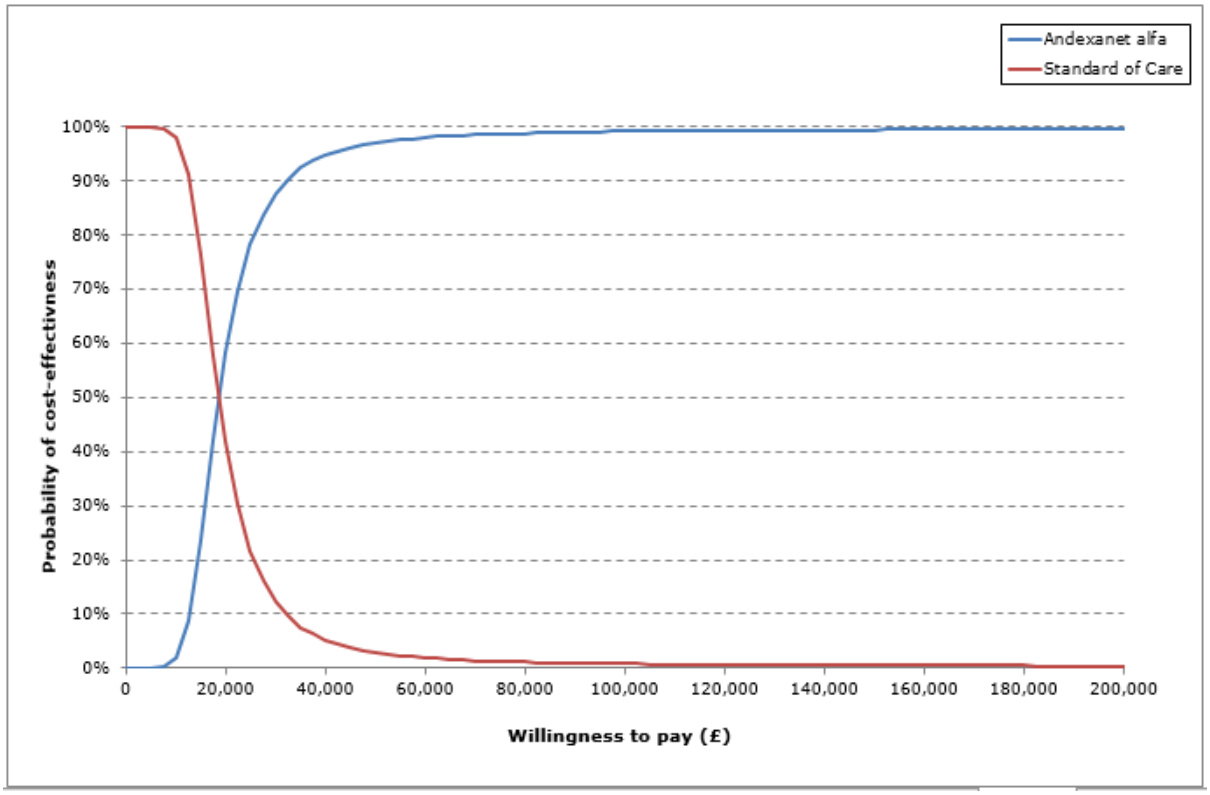
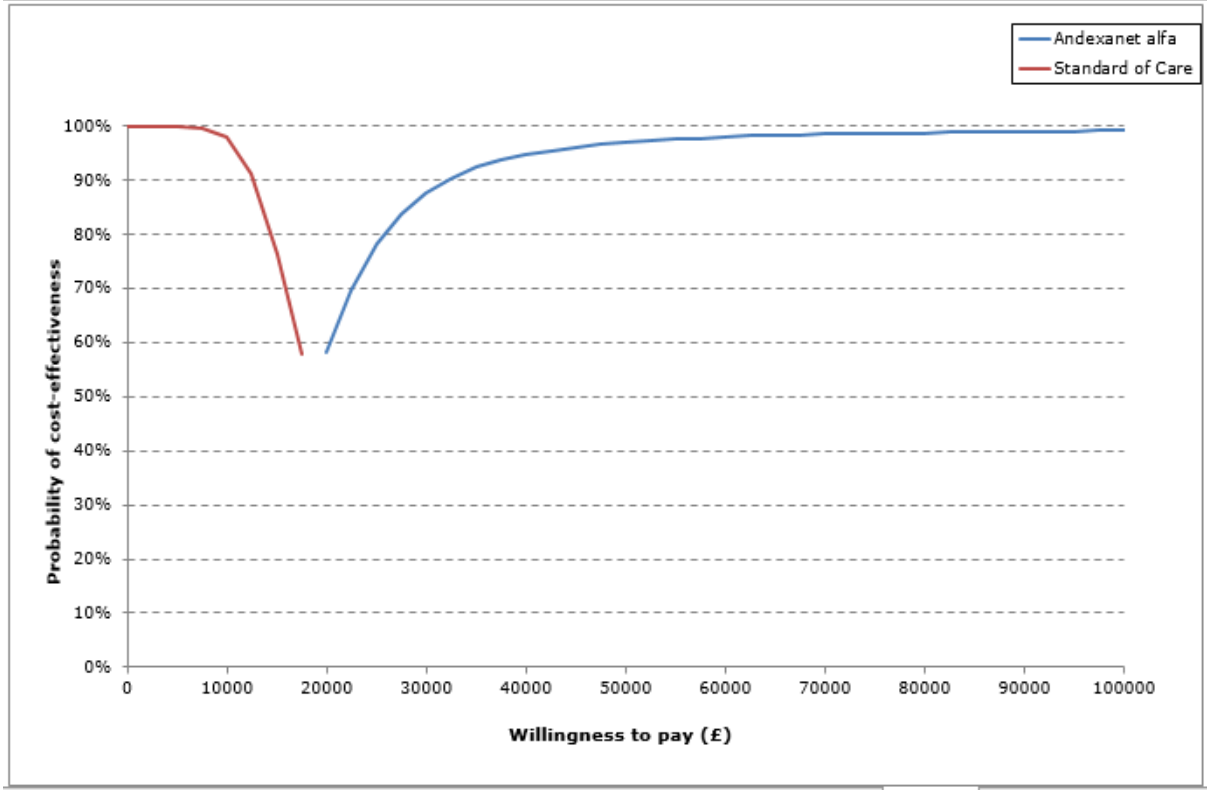


Figure 26. Cost Effectiveness Acceptability Frontier for Whole cohort



PSA results of andexanet alfa versus SoC for the ICH and severe GI cohort are presented in Table 74. The mean PSA results lie close to the deterministic base-case results (Table 72). The cohort receiving andexanet alfa accrued 2.979 QALYs at a cost of £38,152. Patients receiving SoC accrued 1.823 QALYs at a cost of £16,962, respectively. This resulted in a mean PSA ICER of £18,332.

The ICEP showing the PSA results for the total population is presented in Figure 27. The CEAC and CEAF for the total population are presented in Figure 28 and Figure 29, respectively. The majority of simulations were when andexanet alfa had higher incremental costs and higher incremental QALYs.

Table 74. PSA results for ICH and severe GI cohort

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
SoC	16,962	1.823	-	-	-
Andexanet alfa	38,152	2.979	21,190	1.1559	18,332

GI – gastrointestinal; ICER – incremental cost-effectiveness ratio; ICH – intracranial haemorrhage; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; SoC – standard of care.

Figure 27. Incremental Cost Effectiveness Plane for ICH and severe GI cohort

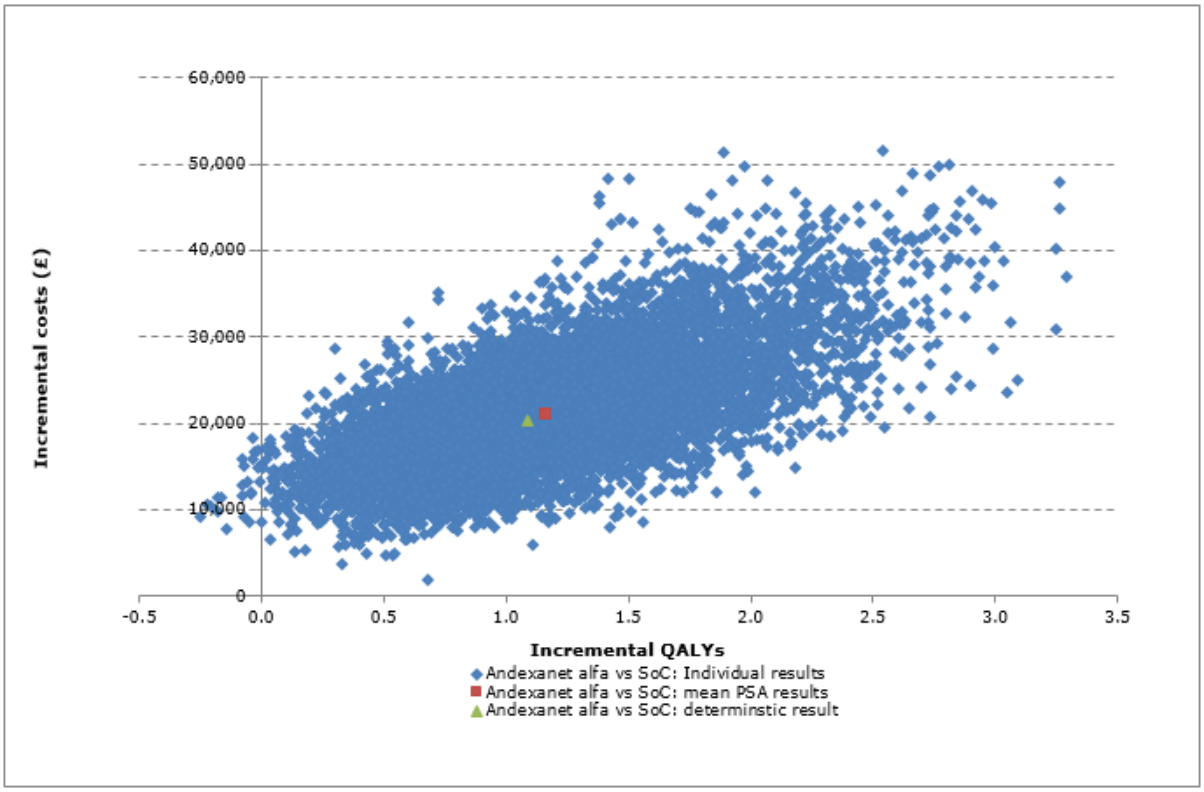


Figure 28. Cost Effectiveness Acceptability Curve for ICH and severe GI cohort

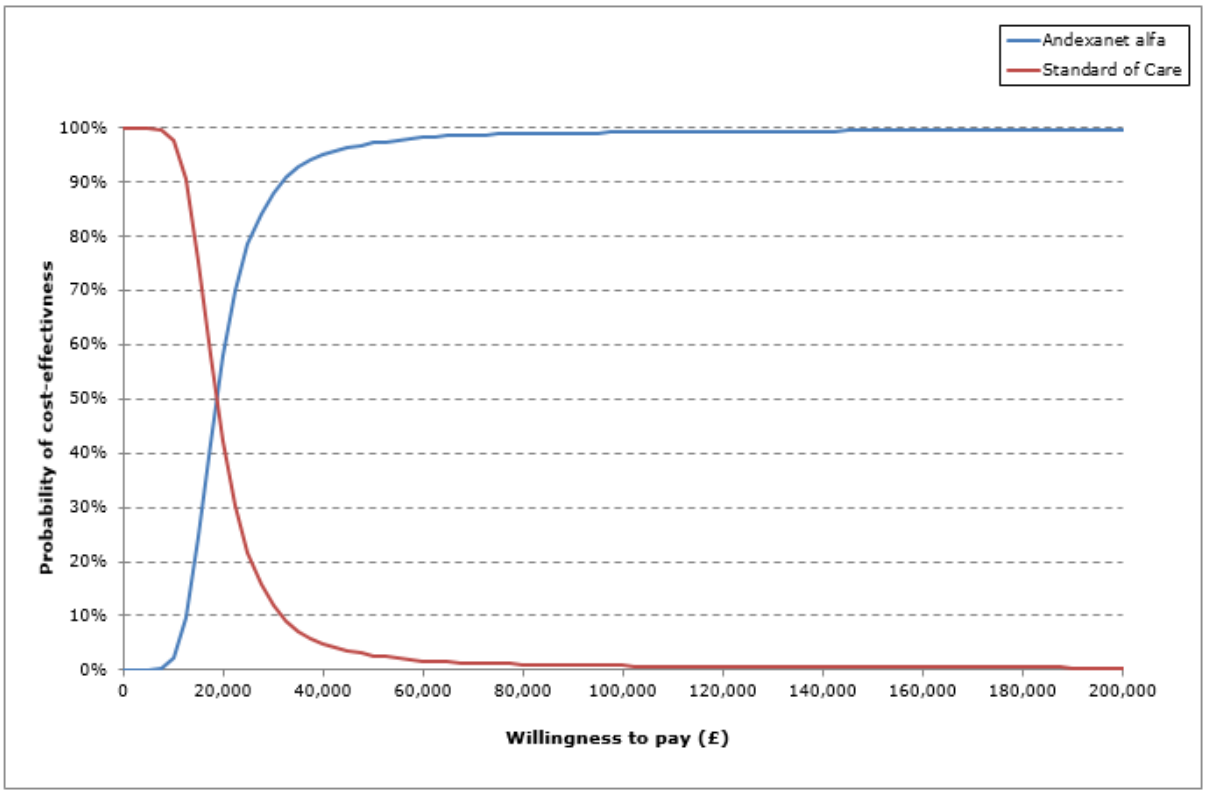
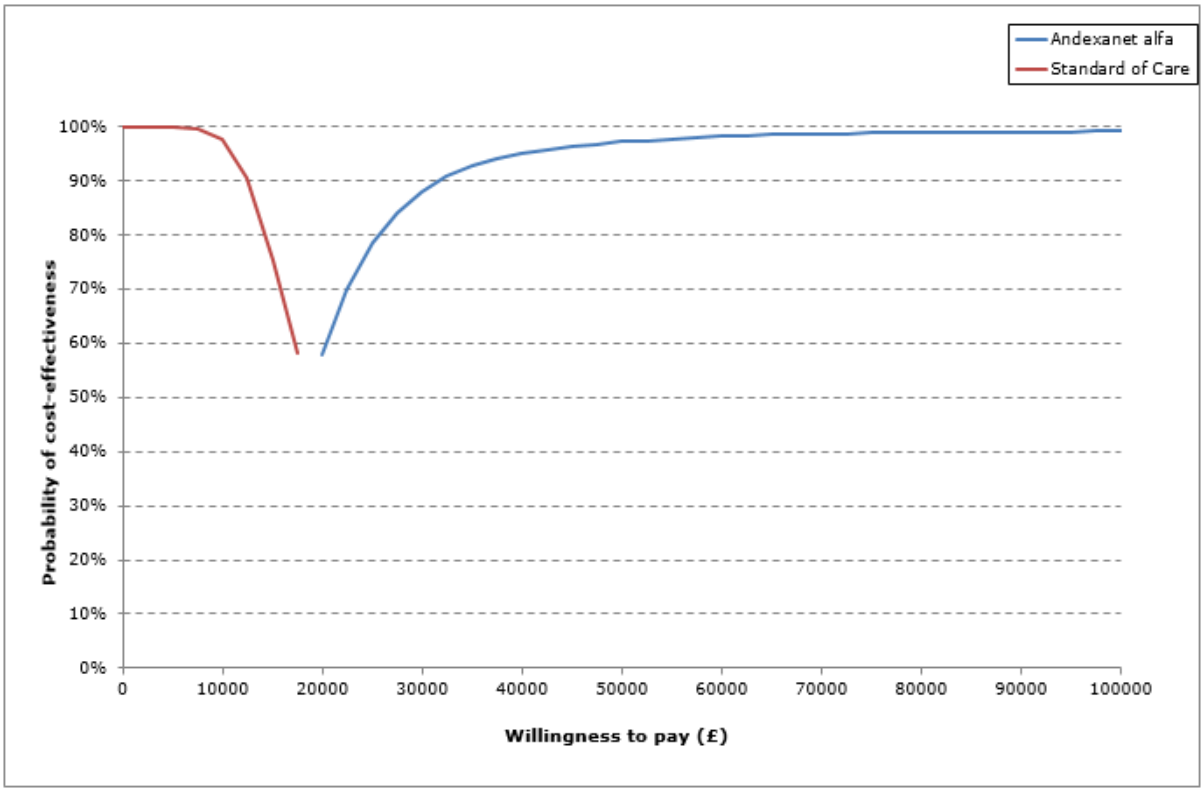


Figure 29. Cost Effectiveness Acceptability Frontier for ICH and severe GI cohort



PSA results of andexanet alfa versus SoC for the ICH cohort are presented in Table 75. The mean PSA results lie close to the deterministic base-case results (Table 72). The cohort receiving andexanet alfa accrued 2.230 QALYs at a cost of £42,198. Patients receiving SoC accrued 0.954 QALYs at a cost of £19,095, respectively. This resulted in a mean PSA ICER of £18,099.

The ICEP showing the PSA results for the total population is presented in Figure 30. The CEAC and CEAF for the total population are presented in Figure 31 and Figure 32, respectively. The majority of simulations were when andexanet alfa had higher incremental costs and higher incremental QALYs.

Table 75. PSA results for ICH cohort

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
SoC	19,095	0.954	-	-	-
Andexanet alfa	42,198	2.230	23,103	1.2765	18,099

ICER – incremental cost-effectiveness ratio; PSA – probabilistic sensitivity analysis; QALY – quality-adjusted life year; SoC – standard of care.

Figure 30. Incremental Cost Effectiveness Plane for ICH cohort

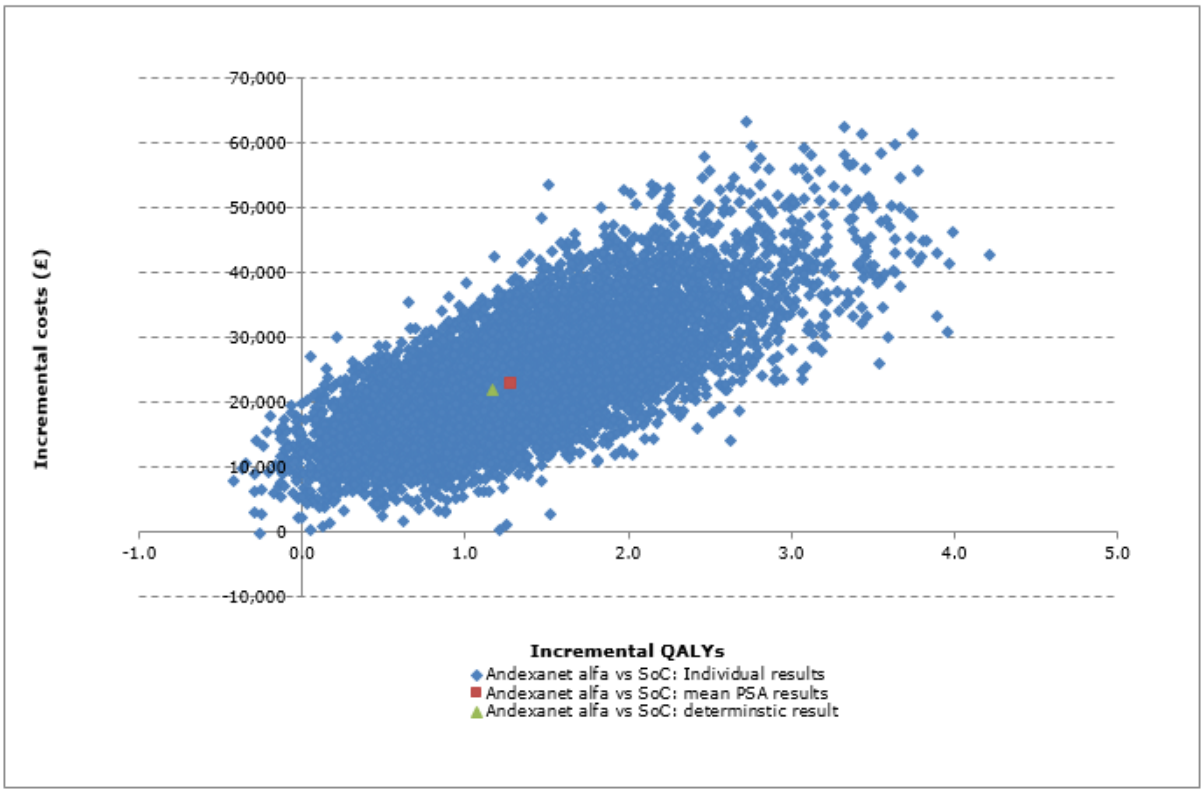


Figure 31. Cost Effectiveness Acceptability Curve for ICH cohort

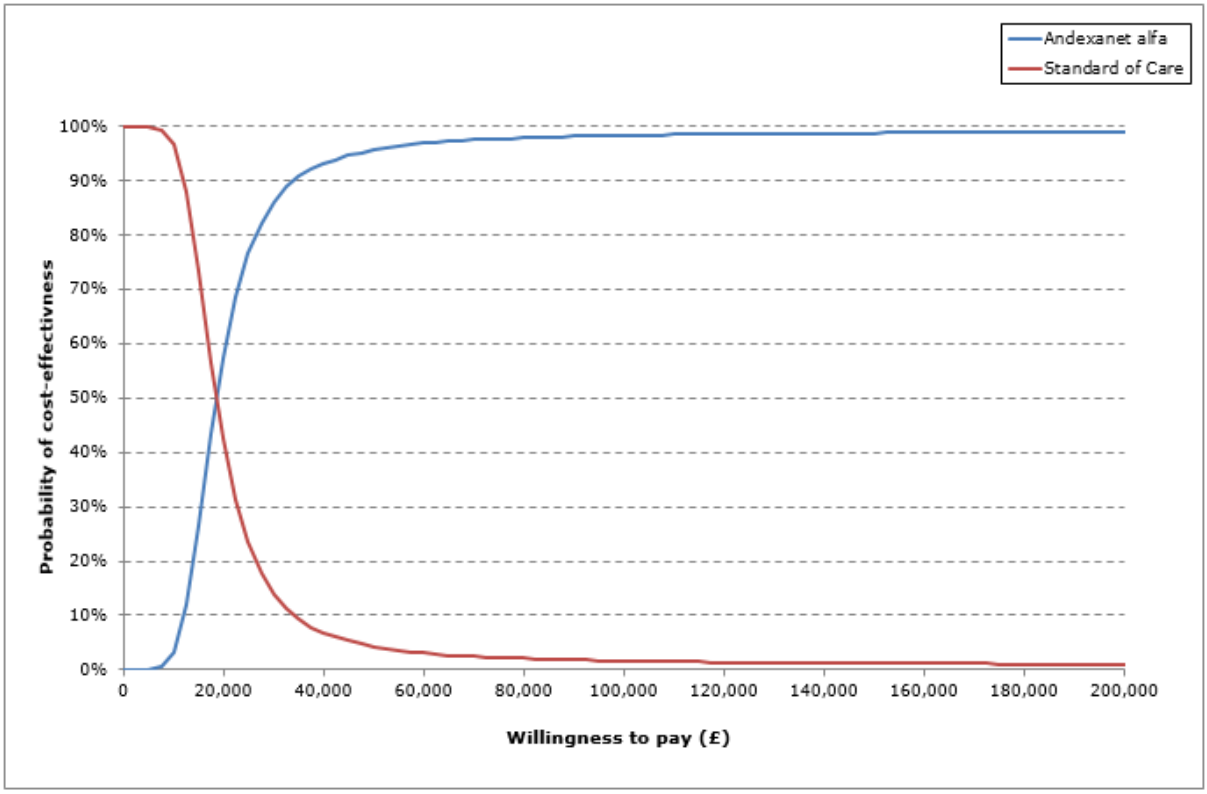
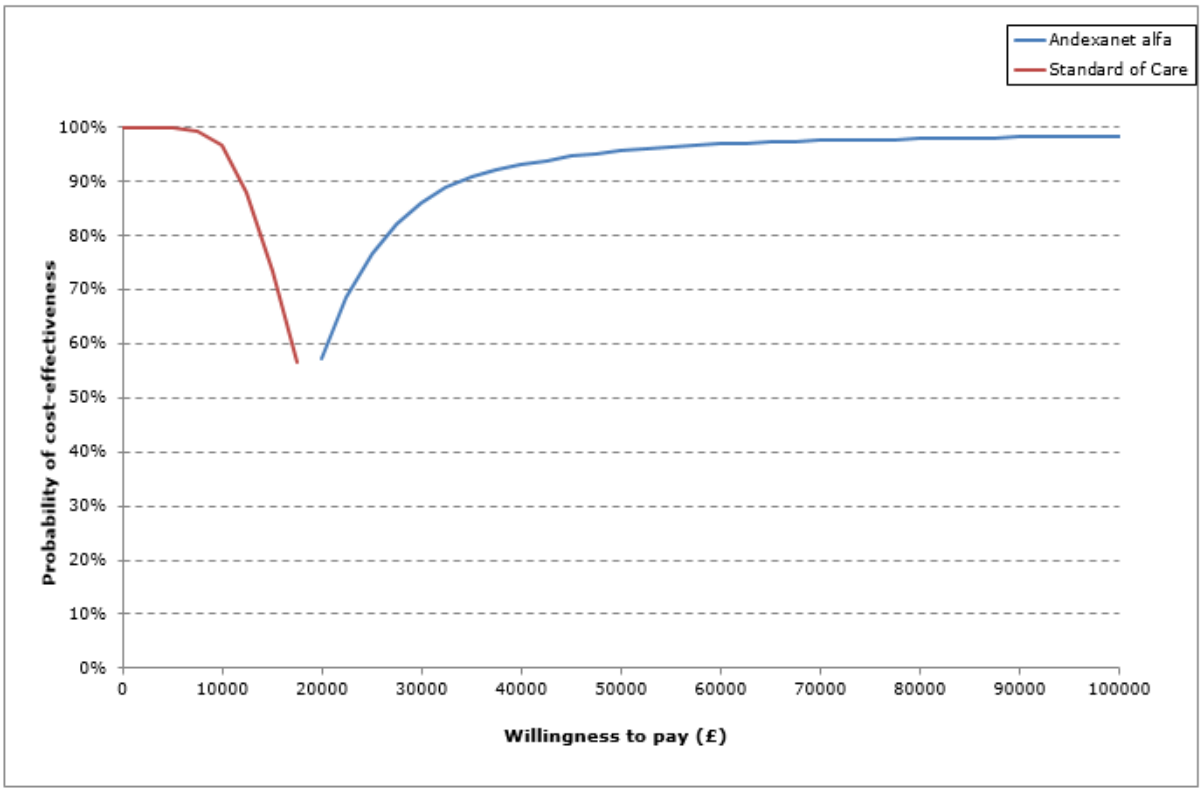


Figure 32. Cost Effectiveness Acceptability Frontier for ICH cohort



B.3.8.2 Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was performed to assess the impact of individual parameters on the model results. OWSA considered upper and lower CIs sourced from literature in the first instance or calculated from the pre-specified probabilistic distributions assigned to each parameter as an alternative. Where the standard error was unavailable to calculate upper and lower CIs, this was assumed to be 20% of the mean value. The mean values for the parameters included in the OWSA are shown in Table 70. The decision tree baseline data was varied by using 2.5% lower and 97.5% upper bounds of the Dirichlet distribution according to the number of people in each branch of the tree.

A tornado diagram is presented to illustrate the level of uncertainty considering the ICER. A tornado diagram is presented for andexanet alfa versus SoC for the Whole cohort, ICH and severe GI cohort and ICH cohort in Figure 33. The top 14 most sensitive parameters are presented. The associated results in tabular format for all relevant variables are presented in Table 76, Table 77 and Table 78 to illustrate the level of uncertainty.

The OWSA results demonstrated the model was most sensitive to the mortality, long-term care costs and utilities for patients with ICH receiving andexanet alfa.

Figure 33. Tornado Diagram of andexanet alfa versus SoC (ICER) for the Whole cohort

ICER – Incremental cost-effectiveness ratio; ICH – intracranial hemorrhage; GI – gastrointestinal; HR – hazard ratio; SoC – standard of care

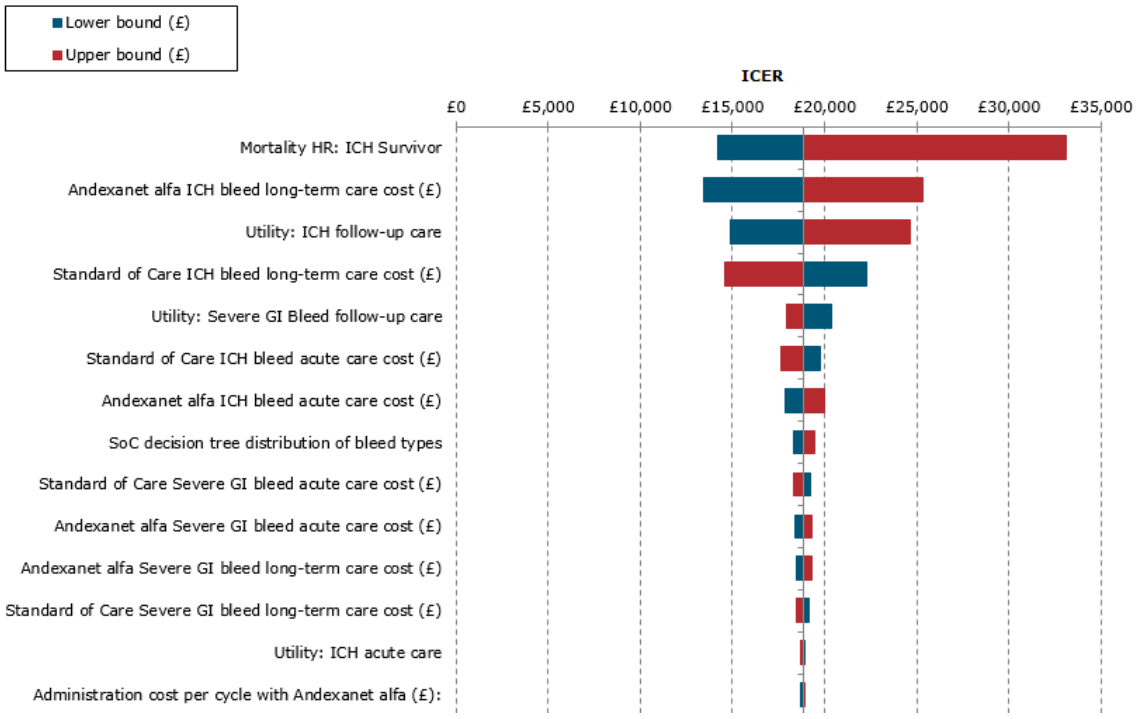
Table 76. OWSA results of andexanet alfa versus SoC for the Whole cohort

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Mortality HR: ICH Survivor	£14,352.11	£32,998.12	£18,646.01
Andexanet alfa ICH bleed long-term care cost (£)	£13,678.67	£25,388.76	£11,710.09
Utility: ICH follow-up care	£15,035.74	£24,707.39	£9,671.65
Standard of Care ICH bleed long-term care cost (£)	£22,396.82	£14,803.92	£7,592.90
Utility: Severe GI Bleed follow-up care	£20,505.76	£18,042.84	£2,462.92
Standard of Care ICH bleed acute care cost (£)	£19,867.58	£17,874.71	£1,992.87
Andexanet alfa ICH bleed acute care cost (£)	£18,067.43	£20,060.30	£1,992.87
SoC decision tree distribution of bleed types	£18,058.92	£20,042.17	£1,983.25
Utility: Intraocular follow-up care	£17,989.11	£19,721.89	£1,732.78
Utility: Intraspinal follow-up care	£18,262.88	£19,677.21	£1,414.33
Andexanet alfa Severe GI bleed acute care cost (£)	£18,578.39	£19,439.93	£861.54
Standard of Care Severe GI bleed acute care cost (£)	£19,356.61	£18,495.08	£861.53
Andexanet alfa Severe GI bleed long-term care cost (£)	£18,594.80	£19,420.01	£825.21
Standard of Care Severe GI bleed long-term care cost (£)	£19,285.87	£18,580.97	£704.90
Standard of Care Intraspinal long-term care cost (£)	£19,262.32	£18,609.56	£652.76
Andexanet alfa Intraspinal long-term care cost (£)	£18,736.37	£19,248.12	£511.75
Utility: ICH acute care	£19,088.34	£18,835.63	£252.71
Administration cost per cycle with Andexanet alfa (£):	£18,853.64	£19,105.75	£252.11
Andexanet alfa relative improvement of intraspinal bleed Survivor long-term utility	£19,080.45	£18,839.39	£241.06
Standard of Care Intraocular long-term care cost (£)	£19,075.28	£18,836.65	£238.63
Andexanet alfa Intraocular long-term care cost (£)	£18,876.61	£19,077.86	£201.25
Administration cost per cycle with Standard of Care (£):	£19,044.98	£18,873.45	£171.53
Andexanet alfa Retroperitoneal long-term care cost (£)	£18,931.19	£19,011.60	£80.41

Andexanet alfa Pericardial long-term care cost (£)	£18,931.19	£19,011.60	£80.41
Standard of Care Retroperitoneal long-term care cost (£)	£19,002.57	£18,924.93	£77.64
Standard of Care Pericardial long-term care cost (£)	£19,002.57	£18,924.93	£77.64
Utility: Retroperitoneal Bleed follow-up care	£19,000.36	£18,945.13	£55.23
Utility: Pericardial Bleed follow-up care	£19,000.36	£18,945.13	£55.23
Standard of Care Intraocular acute care cost (£)	£18,987.50	£18,943.23	£44.27
Andexanet alfa Intraocular acute care cost (£)	£18,947.51	£18,991.78	£44.27
Standard of Care Intraspinal acute care costs (£)	£18,987.41	£18,943.34	£44.07
Andexanet alfa Intraspinal acute care costs (£)	£18,947.60	£18,991.67	£44.07
Standard of Care Retroperitoneal acute care cost (£)	£18,987.41	£18,943.34	£44.07
Andexanet alfa Retroperitoneal acute care cost (£)	£18,947.60	£18,991.67	£44.07
Standard of Care Pericardial acute care cost (£)	£18,987.41	£18,943.34	£44.07
Andexanet alfa Pericardial acute care cost (£)	£18,947.60	£18,991.67	£44.07
Andexanet alfa relative improvement of intraocular bleed Survivor long-term utility	£18,987.60	£18,944.60	£43.00
Utility: Severe GI Bleed acute care	£18,978.97	£18,956.91	£22.06
Utility: Retroperitoneal Bleed acute care	£18,967.77	£18,967.26	£0.51
Utility: Pericardial Bleed acute care	£18,967.77	£18,967.26	£0.51

GI – gastrointestinal; HR – hazard ratio; ICER – incremental cost-effectiveness ratio; ICH – intracranial haemorrhage; OWSA – one-way sensitivity analysis; SoC – standard of care

Figure 34. Tornado Diagram of andexanet alfa versus SoC (ICER) for the ICH and severe GI cohort



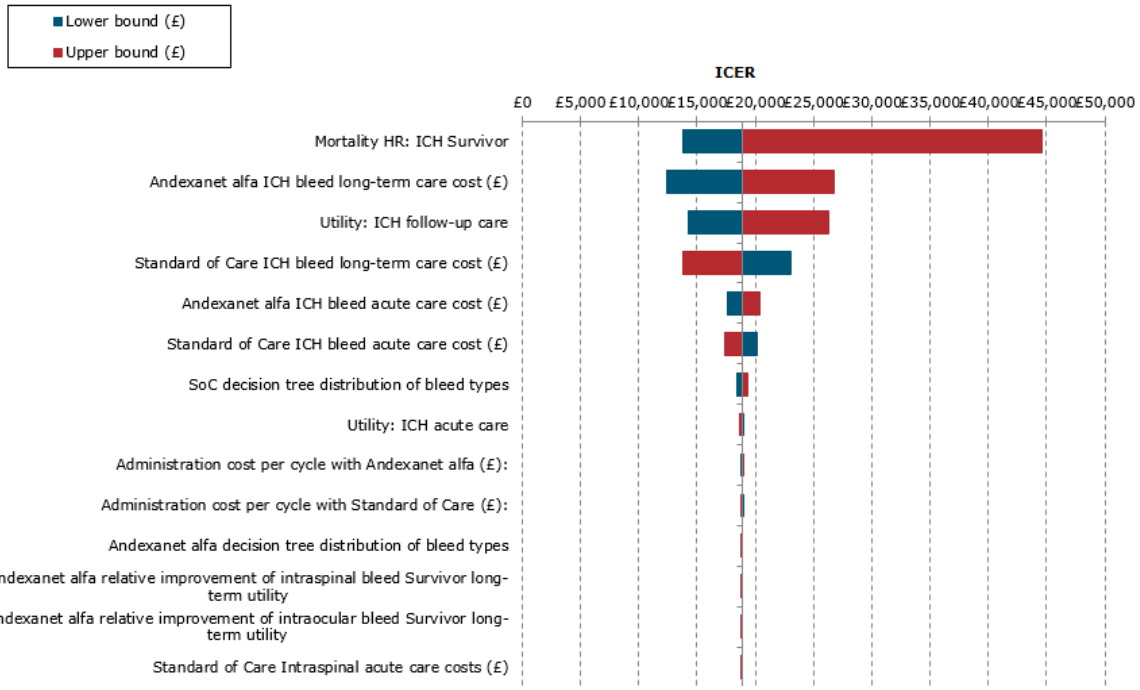
GI – gastrointestinal; HR – hazard ratio; ICER - incremental cost-effectiveness ratio; ICH – intracranial hemorrhage; SoC – standard of care

Table 77. OWSA results of andexanet alfa versus SoC for the ICH and severe GI cohort

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Mortality HR: ICH Survivor	£14,235.65	£33,078.88	£18,843.23
Andexanet alfa ICH bleed long-term care cost (£)	£13,464.67	£25,347.95	£11,883.28
Utility: ICH follow-up care	£14,894.01	£24,612.80	£9,718.79
Standard of Care ICH bleed long-term care cost (£)	£22,306.85	£14,612.53	£7,694.32
Utility: Severe GI Bleed follow-up care	£20,382.44	£17,901.30	£2,481.14
Standard of Care ICH bleed acute care cost (£)	£19,789.03	£17,669.46	£2,119.57
Andexanet alfa ICH bleed acute care cost (£)	£17,874.43	£19,994.00	£2,119.57
SoC decision tree distribution of bleed types	£18,291.83	£19,425.21	£1,133.38
Standard of Care Severe GI bleed acute care cost (£)	£19,245.58	£18,329.27	£916.31
Andexanet alfa Severe GI bleed acute care cost (£)	£18,417.88	£19,334.19	£916.31
Andexanet alfa Severe GI bleed long-term care cost (£)	£18,453.77	£19,290.62	£836.85
Standard of Care Severe GI bleed long-term care cost (£)	£19,154.59	£18,439.74	£714.85
Utility: ICH acute care	£18,959.33	£18,692.60	£266.73
Administration cost per cycle with Andexanet alfa (£):	£18,722.29	£18,964.61	£242.32
Administration cost per cycle with Standard of Care (£):	£18,906.19	£18,741.32	£164.87
Utility: Severe GI Bleed acute care	£18,843.84	£18,820.54	£23.30

GI – gastrointestinal; HR – hazard ratio; ICH – intracranial haemorrhage; NMB – net monetary benefit; OWSA – one-way sensitivity analysis; SoC – standard of care

Figure 35. Tornado Diagram of andexanet alfa versus SoC (ICER) for the ICH cohort



SoC – standard of care

Table 78. OWSA results of andexanet alfa versus SoC for the ICH cohort

Parameter	Lower bound (£) NMB	Upper bound (£) NMB	Difference (£) NMB
Mortality HR: ICH Survivor	£13,812.62	£44,599.44	£30,786.82
Andexanet alfa ICH bleed long-term care cost (£)	£12,384.27	£26,747.20	£14,362.93
Utility: ICH follow-up care	£14,315.07	£26,311.02	£11,995.95
Standard of Care ICH bleed long-term care cost (£)	£23,070.76	£13,772.56	£9,298.20
Andexanet alfa ICH bleed acute care cost (£)	£17,633.64	£20,373.86	£2,740.22
Standard of Care ICH bleed acute care cost (£)	£20,108.86	£17,368.65	£2,740.21
SoC decision tree distribution of bleed types	£18,398.39	£19,343.09	£944.70
Utility: ICH acute care	£19,036.77	£18,691.52	£345.25
Administration cost per cycle with Andexanet alfa (£):	£18,769.63	£18,994.63	£225.00
Administration cost per cycle with Standard of Care (£):	£18,940.39	£18,787.31	£153.08

HR – hazard ratio; ICH – intracranial haemorrhage; NMB – net monetary benefit; OWSA – one-way sensitivity analysis; SoC – standard of care

B.3.8.3 Summary of sensitivity analyses results

The results of sensitivity analyses showed andexanet alfa being more cost effective at willingness to pay thresholds above £20,000 for the Whole cohort, ICH and severe GI cohort and ICH cohort. In the majority of iterations also for all three cohorts, andexanet alfa was more costly and more effective than SoC.

Mean PSA results were lower than but similar to the base case result, with mean PSA results for all three cohorts showing that andexanet alfa increased patient benefit by one QALY at a cost at or below £18,441 (with mean PSA ICERs of £18,441, £18,332 and £18,099 for the Whole cohort, ICH and severe GI cohort and ICH cohort, respectively).

B.3.9 Scenario analysis

B.3.9.1 Scenario analysis for threshold benefit for intraspinal and intraocular bleeding events

A scenario analysis was conducted using different threshold of benefit levels for intraspinal and intraocular bleeding events for the Whole cohort. This analysis sought to test the sensitivity of model results to the assumed relative benefit reduction for intraspinal and intraocular bleed long-term utility and cost at baseline, of 25%, the rationale for which is presented in Section B.3.4 Measurement and valuation of health effects. In this analysis, the relative benefit reduction was varied between 0%, 12.5%, 25% (the base case), 37.5%, and 50%.

The resulting ICERs varied between £18,606 and £19,334 per QALY for the Whole cohort. For the Whole cohort, the highest ICER being obtained when relative benefit reduction was 0% for patients receiving andexanet alfa relative to patients receiving SoC, and the lowest being obtained when relative benefit reduction was 50%.

Table 79. Scenario analysis varying relative benefit reduction for the Whole cohort

Relative benefit reduction	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
0%	SoC	17,583	3.267	2.187	-	-	-	-	-
	Andexanet alfa	37,603	4.563	3.223	20,020	1.296	1.035	19,334	19,334
12.5%	SoC	17,583	3.267	2.187	-	-	-	-	-
	Andexanet alfa	37,484	4.563	3.227	19,901	1.296	1.039	19,150	19,150
25% (base case)	SoC	17,583	3.267	2.187	-	-	-	-	-
	Andexanet alfa	37,365	4.563	3.230	19,782	1.296	1.043	18,968	18,968
37.5%	SoC	17,583	3.267	2.187	-	-	-	-	-
	Andexanet alfa	37,246	4.563	3.234	19,663	1.296	1.047	18,786	18,786
50%	SoC	17,583	3.267	2.187	-	-	-	-	-
	Andexanet alfa	37,127	4.563	3.238	19,544	1.296	1.050	18,606	18,606

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

B.3.9.2 Scenario analysis varying relative mortality reduction of andexanet alfa relative to SoC for other major bleeds

A scenario analysis was conducted to vary the relative mortality reduction applied to the andexanet alfa treatment arm for other major bleeds. This analysis sought to test the sensitivity of model results to the assumed relative mortality reduction at baseline, of 25%, the rationale for which is presented in Section B.3.3 Clinical parameters and variables. In this analysis, the relative mortality reduction was varied between 0%, 12.5%, 25% (the base case), 37.5%, and 50%.

The resulting ICERs varied between £18,828 and £19,109 per QALY for the Whole cohort, with the highest ICER being obtained when relative mortality reduction was 0% for patients receiving andexanet alfa relative to patients receiving SoC, and the lowest being obtained when relative mortality reduction was 50%. The results for the Whole cohort are shown in Table 80. No results were presented for the ICH and GI cohort and ICH only cohort as the mortality reduction assumption does not apply to this group, given that more robust data were available.

Table 80. Results of varying relative mortality reduction for andexanet alfa patients for Whole cohort

Relative mortality reduction	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
0%	SoC	17,583	3.267	2.187	-	-	-	-	-
	Andexanet alfa	37,358	4.552	3.222	19,775	1.285	1.035	19,109	19,109
12.5%	SoC	17,583	3.267	2.187	-	-	-	-	-
	Andexanet alfa	37,361	4.557	3.226	19,779	1.290	1.039	19,038	19,038
25% (base case)	SoC	17,583	3.267	2.187	-	-	-	-	-
	Andexanet alfa	37,365	4.563	3.230	19,782	1.296	1.043	18,968	18,968
37.5%	SoC	17,583	3.267	2.187	-	-	-	-	-
	Andexanet alfa	37,369	4.568	3.234	19,786	1.301	1.047	18,897	18,897
50%	SoC	17,583	3.267	2.187	-	-	-	-	-
	Andexanet alfa	37,372	4.574	3.238	19,790	1.307	1.051	18,828	18,828

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

B.3.9.3 Scenario analysis varying long-term mortality hazard ratio source for ICH survivors

A scenario analysis was conducting by using two different sources for long-term hazard ratios for the ICH cohort. The sources explored were Lee et al. 2010 and Huybrechts et al. 2008 whole ICH mortality (not broken down by mRS score).

The results of this scenario analysis are shown in Table 81, Table 82 and Table 83 for the Whole cohort, ICH and GI cohort and ICH only cohort, respectively. ICERs were lower using alternative sources compared to the base case, suggesting that results in the base case may be conservative.

Table 81. Results of Scenario Analysis hazard ratio source for the Whole cohort

Long-term mortality HR (source)	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Base case	SoC	17,583	3.267	2.187	-	-	-	-	-
	Andexanet alfa	37,365	4.563	3.230	19,782	1.296	1.043	18,968	18,968
1.29 (Lee 2010)	SoC	20,313	3.577	2.376	-	-	-	-	-
	Andexanet alfa	39,138	4.809	3.408	18,825	1.233	1.032	18,247	18,247
1.21(Huybrechts 2008)	SoC	22,702	3.847	2.541	-	-	-	-	-
	Andexanet alfa	42,369	5.259	3.731	19,667	1.411	1.190	16,526	16,526

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

Table 82. Results of Scenario Analysis hazard ratio source for the ICH and GI cohort

Long-term mortality HR (source)	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Base case	SoC	16,958	2.741	1.824	-	-	-	-	-
	Andexanet alfa	37,392	4.100	2.909	20,434	1.359	1.085	18,832	18,832
1.29 (Lee 2010)	SoC	19,802	3.063	2.020	-	-	-	-	-
	Andexanet alfa	39,190	4.350	3.089	19,389	1.287	1.069	18,145	18,145
1.21(Huybrechts 2008)	SoC	22,375	3.355	2.198	-	-	-	-	-
	Andexanet alfa	42,672	4.834	3.438	20,297	1.479	1.239	16,378	16,378

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

Table 83. Results of Scenario Analysis hazard ratio source for the ICH cohort

Long-term mortality HR (source)	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Base case	SoC	19,069	1.620	0.953	-	-	-	-	-
	Andexanet alfa	41,122	3.058	2.121	22,053	1.438	1.169	18,871	18,871
1.29 (Lee 2010)	SoC	22,854	2.049	1.215	-	-	-	-	-
	Andexanet alfa	43,573	3.399	2.367	20,719	1.350	1.152	17,981	17,981
1.21(Huybrechts 2008)	SoC	26,155	2.423	1.443	-	-	-	-	-
	Andexanet alfa	48,038	4.019	2.814	21,883	1.596	1.371	15,960	15,960

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

B.3.9.4 Scenario analysis varying discount rate

A scenario analysis was conducted varying the discount rate, to explore the impact of applying a greater or lesser weight to future costs and benefits. The discount rates explored were: 0% and 5%, relative to a 3.5% discount rate at baseline for both costs and benefits.

The results of this scenario analysis are shown in Table 84, **Error! Reference source not found.** and Table 86 for the Whole cohort, ICH and GI cohort and ICH only cohort respectively.

Table 84. Results of Scenario Analysis varying Discount Rate for the Whole cohort

Discount rate	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
0%	SoC	19,218	3.845	2.587	-	-	-	-	-
	Andexanet alfa	39,814	5.339	3.789	20,596	1.495	1.202	17,130	17,130
3.5% (base case)	SoC	17,583	3.267	2.187	-	-	-	-	-
	Andexanet alfa	37,365	4.563	3.230	19,782	1.296	1.043	18,968	18,968
5%	SoC	16,996	3.068	2.050	-	-	-	-	-
	Andexanet alfa	36,487	4.294	3.037	19,491	1.226	0.986	19,758	19,758

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

Table 85. Results of Scenario Analysis varying Discount Rate for the ICH and severe GI cohort

Discount rate	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
0%	SoC	18,295	3.176	2.126	-	-	-	-	-
	Andexanet alfa	39,603	4.733	3.369	21,308	1.557	1.242	17,151	17,151
3.5% (base case)	SoC	16,958	2.741	1.824	-	-	-	-	-
	Andexanet alfa	37,392	4.100	2.909	20,434	1.359	1.085	18,832	18,832
5%	SoC	16,469	2.589	1.719	-	-	-	-	-
	Andexanet alfa	36,589	3.877	2.747	20,120	1.289	1.029	19,555	19,555

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

Table 86. Results of Scenario Analysis varying Discount Rate for the ICH only cohort

Discount rate	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
0%	SoC	20,449	1.776	1.048	-	-	-	-	-
	Andexanet alfa	43,525	3.392	2.362	23,077	1.616	1.314	17,565	17,565
3.5% (base case)	SoC	19,069	1.620	0.953	-	-	-	-	-
	Andexanet alfa	41,122	3.058	2.121	22,053	1.438	1.169	18,871	18,871
5%	SoC	18,554	1.561	0.917	-	-	-	-	-
	Andexanet alfa	40,237	2.935	2.033	21,682	1.373	1.116	19,436	19,436

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

B.3.9.5 Scenario analysis without wastage assumed in drug costs

The final scenario analysis was selecting 'no wastage' for the drug acquisition cost calculation. The ICER decreased to £17,491 per QALY for the Whole cohort, £17,421 per QALY for the ICH and severe GI bleed cohort, and £17,565 per QALY for the ICH only cohort. ICERs were lower assuming no wastage compared to the base case, suggesting that results in the base case may be conservative if vial sharing is possible in hospitals.

Table 87. Scenario analysis without wastage

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Whole cohort								
SoC	17,578	3.267	2.187	-	-	-	-	-
Andexanet alfa	35,821	4.563	3.230	18,243	1.296	1.043	17,491	17,491
ICH and severe GI bleed cohort								
SoC	16,953	2.741	1.824	-	-	-	-	-
Andexanet alfa	35,856	4.100	2.909	18,903	1.359	1.085	17,421	17,421
ICH cohort								
SoC	19,063	1.620	0.953	-	-	-	-	-
Andexanet alfa	39,590	3.058	2.121	20,527	1.438	1.169	17,565	17,565

ICER – incremental cost-effectiveness ratio; LY – life year; QALY – quality adjusted life year; SoC – standard of care

B.3.11 Validation

B.3.11.1 Validation of cost-effectiveness analysis

The model has undergone thorough internal and external validation. The model was developed internally by a health economist and checked for accuracy by two independent health economists. Clinical trial data underpinning the decision tree section of the model was taken from the propensity score matching where possible and methods and results were validated by Kate Ren, a lead evidence reviewer in relation to these topics for Sheffield University's Evidence Review Group (ERG) – ScHARR.

UK clinical experts from Kings College London and Guy's and St Thomas's NHS Foundation Trust and Cardiff and Vale University Health Board as well as the University College London informed the key aspects of the model design, data sources and assumptions.

All feedback and external ratification went into the final model and this written submission.

B.3.12 Interpretation and conclusions of economic evidence

Over a 22-year time horizon, for the Whole Population patients receiving andexanet alfa accrued 3.230 QALYs at a cost of £37,365, whilst patients receiving SoC accrued 2.187 QALYs at a cost of £17,583. The resulting ICER in the base case was £18,968 per QALY, well below the NICE threshold of £30,000 per QALY. Similar ICERs below £20,000 per QALY were found for the ICH and severe GI cohort, and the ICH only cohort.

Probabilistic results fell below the deterministic ICERs. OWSA found that results were most sensitive to ICH mortality, long-term care costs and utilities. Scenario analyses were all found to be well below a cost-effectiveness threshold of £30,000 per QALY. As such, andexanet alfa may be considered a cost-effective use of NHS resources.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Andexanet alfa for reversing anticoagulation [ID1101]

Clarification questions

November 2019

File name	Version	Contains confidential information	Date
ID1101 andexanet clarification questions v5.0_Response to ERG questions_26Nov2019	Version 5.0	Yes	26th November 2019

List of Tables

Table 1. Abbreviations

AF	Atrial fibrillation
CAD	Coronary artery disease
DSU	NICE Decision Support Unit
DVT	Deep vein thrombosis
ERG	Evidence Review Group
GI	Gastrointestinal
ICH	Intracranial haemorrhage
mRS	Modified Rankin score
NICE	National Institute for Health and Care Excellence
OWSA	One-way sensitivity analysis
PCC	Prothrombin complex concentrate
PSA	Probabilistic sensitivity analysis
ScHARR	School of Health and Related Research
SoC	Standard of care
TIA	Transient Ischemic Attack
UK	United Kingdom
ICER	Incremental cost-effectiveness ratio
CEM	Cost-effectiveness model
SMR	Standardised mortality ratio
PSA	Probabilistic sensitivity analysis
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
ICEP	Incremental cost-effectiveness plane
MIMS	Monthly Index of Medical Specialties
INR	International Normalized Ratio
SmPC	Summary of Product Characteristics

This document contains responses to all ERG Questions, following part 1 of the response submitted by the company on 30th November 2019 and part 2 of the response submitted by the company on 6th November 2019. In addition to the contents of part 2, this document:

- *Contains the results of the scenarios specified in Document B.3.9 of the latest submission to NICE for andexanet alfa;*
- *Presents results of scenarios not included in the updated base case as compared to the updated base case as indicated in the heading of each table in parentheses ('revised results' or 'original results').*

We have also provided details of the assumptions used to define an updated base case, as well as the cost effectiveness results and probabilistic and deterministic sensitivity analyses associated with the updated base case.

Section A: Clarification on effectiveness data

Propensity score matching

A1. Priority question. Please justify why the following baseline characteristics were not included as covariates in the propensity score matching between ANNEXA-4 and ORANGE:

a) **Site of bleed (e.g. upper GI, lower GI, intracerebral, subarachnoid etc.);**

b) **Severity of bleed (e.g. mRS score);**

c) **Volume of bleed.**

If only a limited number of covariates were chosen due to issues concerning overlap and resulting sample size, please can the company provide an explanation of why certain covariates were deemed more important than others? (Providing a rationale for each individual covariate as opposed to a more global rationale.)

Response

Choice of covariates

The selection of baseline characteristics to include as covariates in the propensity score matching analysis were made based on advice from two UK clinical experts in the field of haematology. Experts were consulted in particular regarding:

- The comparability of ORANGE and ANNEXA-4 studies in terms of their inclusion and exclusion criteria, study design and study setting.
- The effect of prospective covariates, sourced from ORANGE and ANNEXA-4 patient level data, on mortality within 30 days of a major bleed. This was examined in order to remove potential bias caused by imbalances between studies in potential confounding covariates, and required that all covariates included had a significant effect on both 30-day mortality and treatment assignment.
    - The effect on mortality was considered by clinical experts, while the effect on treatment assignment was determined using statistical testing (t-tests and Chi-squared tests).

In response to the ERG's query about limitations to the number of covariates due to issues of overlap and sample size, we can clarify that these were not the primary reasons for exclusion of any of the variables considered for use as covariates. The reasons for not including site of bleed (upper GI, lower GI, intracerebral, subarachnoid etc.), severity of bleed (e.g. mRS score), and volume of bleed are detailed below:

Site of bleed

We initially included site of bleed as a covariate but specified a less granular approach based on the populations considered of interest in the positioning of andexanet alfa. Namely, we considered ICH, severe GI bleeds and other major bleeds, all within the licensed indication of life-threatening or uncontrolled major bleeding events.

Following the ERG's suggestion, we consulted with the same UK clinical experts who agreed that defining a more granular approach to the site of bleed would be clinically appropriate – albeit appreciating that this runs the risk of different numbers of matches made across all covariates (as a greater number of covariates are specified) and potentially smaller sample sizes following matching.

Therefore, a new variable was generated considering a more granular approach to site of bleed for ICH and GI bleeds; results of which are presented in A3.

Additional granularity of site of bleed was not considered appropriate for other major bleeds because the ORANGE and ANNEXA-4 studies do not have a significant level of overlap in the specific bleed sites of patients matched within the broad 'other major bleed' category. This caused only eight patients to be matched from the ORANGE study to treated patients in ANNEXA-4, for other major bleeds following propensity score matching. Due to the small number of matches, and as discussed in the original submission, we deemed the results of this analysis unfit for inclusion in the model as an assessment of clinical benefit. Therefore, further specifying the bleed types in other major bleeds was thought unnecessary in the absence of a remedy to the existing limitations.

Severity of bleed and bleed volume

We did not include severity of bleed (e.g. mRS) or volume of bleed as covariates in the propensity score matching analysis as neither of these outcomes were collected in the ORANGE study. Consequently, no matching could be performed for these covariates.

A2. Priority question. For the propensity score matching analysis presented in the CS please provide the following:

a) **Details of any limit applied to restrict the maximum number of times an individual could be matched in the propensity score matching analysis;**

b) **A detailed breakdown of the frequency of matching of each individual in the propensity score matching analysis; and**

c) **The results for the subgroup of patients who were matched more than once in the analysis.**

Response

No limit was applied to restrict the maximum number of times an individual could be matched. We deemed it most appropriate to allow replacement as many times as required. This was a judgement made in mindfulness of the NICE Decision Support Unit (DSU) Document 17. This stated that poor matches may result from matching without replacement, though variance may be increased by making multiple matches with the same individual.[1]

Given that propensity score matching was intended to reduce the bias of model inputs for 30-day mortality, matching with replacement was chosen to achieve the best possible matches for every member of the treated group. This was to provide the greatest possible degree of adjustment to results using the propensity score matching. Any other approach was thought

inconsistent with the goal of propensity score matching, as this would result in comparisons being drawn between members of the treated group and less similar members of the control group.

Finally, as discussed in the original submission, to ensure the methods and results were appropriately considered and interpreted to NICE standards, we worked in partnership with Kate Ren (https://www.sheffield.ac.uk/scharr/sections/heds/staff/ren_k), a statistician and lecturer specialised in network meta-analysis and indirect comparisons. Kate currently serves as a lead evidence reviewer in relation to these topics for Sheffield University's Evidence Review Group (ERG) – the School of Health and Related Research (ScHARR). As such, we would expect the methods adopted to abide by the expectations of NICE and ERGs alike.

In response to the ERG's request, Table 53 in the appendix of this response shows the frequency with which individual patients from the ORANGE study were matched to treated patients. Table 2 below shows the mean frequency with which patients from ORANGE were matched to treated patients, among all patients who were matched at all, for each cohort for which propensity score matching was conducted. The proportion of patients matched more than once is also presented in Table 2.

Table 2. Table of mean frequencies with which individuals from ORANGE were matched

Cohort	Mean no. of matches with a treated patient (no. of matched individuals from ORANGE)	Proportion of patients matched more than once (%)
Whole cohort	[redacted]	[redacted]
ICH	[redacted]	[redacted]
Severe GI	[redacted]	[redacted]
Other major bleeds (non-ICH/GI	[redacted]	[redacted]
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; no. number		

Table 3 and Table 4 present the 30-day mortality and 30-day survival time for patients from the ORANGE study who were matched more than once and only once, respectively. For the Whole Population and patients with ICH, survival outcomes were similar between those matched more than once and those matched only once. Differences however were seen in patients with severe GI bleeding and patients with other major bleeds, where patients matched more than once have, on average, a better prognosis in terms of 30-day survival, than those only matched once.

Table 3. Table of mean survival time for only patients matched more than once in the ORANGE study

Cohort	Died within 30 days (%)	30-day survival time (days)
Whole cohort	[redacted]	[redacted]

ICH	[redacted]	[redacted]
Severe GI	[redacted]	[redacted]
Other major bleeds (non-ICH/GI)	[redacted]	[redacted]
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage		

Table 4. Table of mean survival time for only patients matched exactly once in the ORANGE study

Cohort	Died within 30 days (%)	30-day survival time (days)
Whole cohort	[redacted]	[redacted]
ICH	[redacted]	[redacted]
Severe GI	[redacted]	[redacted]
Other major bleeds (non-ICH/GI)	[redacted]	[redacted]
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage		

A3. Priority question. Please conduct propensity score matching analyses adjusting where possible for only the covariates specified below for all populations (Whole population, ICH subgroup and GI subgroup as defined in the propensity score matching analysis presented in the CS) as reported in Table 33, CS Document B for adjusted 30-day mortality:

a) **Age, site of bleed (e.g.intracerebral), bleed severity (e.g. mRS), volume of bleed, medical history of stroke or TIA and medical history of VT (including DVT);**

b) **All covariates adjusted for in the CS plus site of bleed and severity of bleed**

Response

As already highlighted in response to Question A1, outcomes for bleed severity and bleed volume were not collected in the ORANGE study and as such cannot be specified as covariates in propensity score matching analysis.

Whilst we appreciate the rationale for exploring a more granular approach to site of bleed as requested in Question A3 (b), with which UK clinical experts also agree, the request to exclude key covariates for medical history and comorbidity status as requested in Question A3 (a) appears to contradict the intention of adjusting for potential cofounding effects of covariates on 30-day mortality. See the response to Question A1 for further information regarding the basis for selecting covariates.

In particular, we are concerned by the request to omit coronary artery disease, atrial fibrillation, hypertension, diabetes, renal dysfunction and cancer, all of which were identified by UK clinical experts as variables with likely confounding effects on 30-day mortality. Furthermore, as shown in Table 5, there were statistically significant differences between the ORANGE study and ANNEXA-4 in these covariates, suggesting that rebalancing as much as possible using propensity score matching is essential in order to minimise confounding effects and obtain robust estimates for comparative mortality outcomes.

Table 5. Mean and differences between relevant variables for patients receiving apixaban and rivaroxaban FXa inhibitors, in the whole cohort

Characteristic	Means from ANNEXA-4 patient level data (N = 322)	Means from ORANGE patient level data (N = 372)	Chi-squared, if applicable	p-value (from Welch two sample t-test)
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]
Bleed type	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: DVT	[redacted]	[redacted]	[redacted]	[redacted]
MH: Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]
MH: Severe peripheral vascular disease	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Congestive heart failure	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]
History of bleeding	[redacted]	[redacted]	[redacted]	[redacted]

*Calculated using relevant FXa inhibitors only. Abbreviations: GI, gastro-intestinal; ICH, intracranial haemorrhage; MH, medical history; TIA, Transient Ischemic Attack; DVT, Deep vein thrombosis; CAD, Coronary artery disease; AF, Atrial fibrillation. *p-value <0.05; **p-value <0.01; ***p-value <0.001.*

For these reasons, we have focused on Question A3 (b) in this response.

The analysis in response to Question A3 (b) has consisted of propensity score matching for the whole cohort, ICH patients, and patients with severe GI bleeds using: medical history of cancer; medical history of renal dysfunction; medical history of diabetes; medical history of

hypertension; medical history of atrial fibrillation (AF); medical history of transient Ischemic Attack (TIA); medical history of coronary artery disease (CAD); medical history of stroke; age and specific bleed sites (intracerebral, subarachnoid, subdural/epidural, GI-lower, GI-upper, GI-unknown, other), as covariates, for a population anticoagulated using apixaban and rivaroxaban, and for which control patients all received prothrombin complex concentrates (PCCs).

The specification of the bleed site variable was conducted with UK clinical expert input, and considering where data were available on the site of bleed in the ANNEXA-4 and ORANGE studies.

Table 6 presents the results of propensity scoring as specified in Question A3 (b). Results are similar to the propensity score matching results previously reported in the original submission, albeit 30-day mortality is slightly higher in the adjusted 30-day mortality for PCC. This is unsurprising, as analysis by expert UK clinicians suggest that the distribution of bleed types in ANNEXA-4 are more severe than in ORANGE – with more intracerebral [redacted], subarachnoid [redacted] and subdural/epidural [redacted] bleeds.

Table 6. Propensity score matching results for each cohort for Question A3 (b) – additional suggested covariates with the addition of more specific site of bleed variable

Cohort	Number of matches	Adjusted 30-day mortality for PCC (%)	Adjusted 30-day mortality for andexanet alfa (%)
Whole cohort	PCC = [redacted] Andexanet alfa = [redacted]	[redacted]	[redacted]
ICH	PCC = [redacted] Andexanet alfa = [redacted]	[redacted]	[redacted]
Severe GI	PCC = [redacted] Andexanet alfa = [redacted]	[redacted]	[redacted]
Other major bleeds (non-ICH/GI)	PCC = [redacted] Andexanet alfa = [redacted]	[redacted]	[redacted]

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; PCC, Prothrombin complex concentrate.

Table 7, Table 8, and Table 9 show the balance between the covariates included in the propensity score matching undertaken in answer to Question A3 (b).

Table 7. Propensity score matching results showing the balance for whole cohort for Question A3 (b) – additional suggested covariates with the addition of more specific site of bleed variable

Whole cohort	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	N= [redacted]	N= [redacted]	N= [redacted]	N= [redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH - intracerebral	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH- subarachnoid	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH- subdural/epidural	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI- lower	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI- upper	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI- unknown	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with other bleed types	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH: TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; PCC, Prothrombin complex concentrate; MH, medical history; TIA, Transient Ischemic Attack; CAD, Coronary artery disease; AF, Atrial fibrillation

Table 8. Propensity score matching results showing the balance for ICH cohort for Question A3.b – additional suggested covariates with the addition of more specific site of bleed variable

ICH cohort	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	N= [redacted]	N= [redacted]	N= [redacted]	N= [redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH - intracerebral	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH-subarachnoid	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH-subdural/epidural	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH:TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICH, intracranial haemorrhage; PCC, Prothrombin complex concentrate; MH, medical history; TIA, Transient Ischemic Attack; CAD, Coronary artery disease; AF, Atrial fibrillation

Table 9. Propensity score matching results showing the balance for GI cohort for Question A3.b – additional suggested covariates with the addition of more specific site of bleed variable

Severe GI	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	N= [redacted]	N= [redacted]	N= [redacted]	N= [redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH:TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GI, gastrointestinal; PCC, Prothrombin complex concentrate; MH, medical history; TIA, Transient Ischemic Attack; CAD, Coronary artery disease; AF, Atrial fibrillation

A4. Priority question. Please provide the results of a propensity score matching analysis in ANNEXA-4 and the PCC patients in ORANGE for the subgroup of patients on apixaban or rivaroxaban at baseline for the outcome length of hospital stay using the covariates specified in question A2.

As this analysis was not conducted as part of the company submission, please explain what you consider are the limitations of the results.

Response

We have updated the base case after consideration of the ERG's questions. The assumptions underlying this updated base case and cost effectiveness results associated with it are detailed at the beginning of Section B. This change has meant that the propensity score matching results included in the model are now based on analysis using both the covariates defined in the CS, mentioned in Question A2, and the specific bleed type variable suggested by the ERG in Question A1. Hence, the same set of covariates as are used in the propensity score matching analysis in Question A3.b are used in this analysis in answer to Question A4.

Limitations of analysis

A feasibility assessment was conducted to assess the heterogeneity of the ORANGE and ANNEXA-4 studies with reference to the 30-day mortality outcomes. It was concluded that

some limitations remained with the analysis. One consideration was whether there would be differences in the care which patients could be assumed to have received at the UK sites in the ORANGE study and at the international sites in the ANNEXA-4 trial. A UK clinical expert in haematology was consulted on this issue, and it was concluded that international guidelines would ensure homogeneity to a great extent in the treatment of major bleeding in anticoagulated patients. This homogeneity was not thought to extend to hospital length of stay, as international guidelines were not expected to guarantee similar clinical decision making with respect to hospital length of stay, and health systems in the US and UK especially were known to differ with respect to use of secondary and tertiary healthcare.

Moreover, setting aside the infeasibility of adequately adjusting length of stay for setting using propensity score matching, as mentioned in response to Question B13, the impact of length of stay on the CEM was assumed to be relatively minor. This is because the cost of hospitalisation was included in the NHS Reference costs 2017/18 used in the model. Hence, only inclusion of the costs of excess bed days in the model could be justified in addition to the NHS reference costs. For survivors of ICH and severe GI bleeds, the mean numbers of bed days from the ANNEXA-4 and ORANGE studies both consistently fell within the range associated with each of the NHS Reference Costs 2017/18 so had zero excess bed days for both groups. Table 47 shows this.

Hence, the only cohort for which a differential in length of stay may have been observed was the other major bleeds category, and even the justifiability of including this depended on the choice of trimpoint, as discussed in response to Question B13. For these reasons, conducting propensity score matching to identify a persistent difference between ORANGE and ANNEXA-4 in length of stay, seemed unnecessary, in addition to being infeasible due to the limitations mentioned above.

Results of the analysis

Table 10 presents the results of the propensity score matching using length of stay. Table 11, Table 12, Table 13, and Table 14 present the balance between covariates before and after matching was conducted for the length of stay outcome.

Table 10. Propensity score matching results for each cohort for Question A4 – analysis for length of stay outcome using covariates specified in response to Question A3.b

Cohort	Number of matches	Adjusted LOS for PCC (days)	Adjusted LOS for andexanet alfa (days)
Whole cohort	PCC = [redacted] Andexanet alfa = [redacted]	[redacted]	[redacted]
ICH	PCC = [redacted] Andexanet alfa = [redacted]	[redacted]	[redacted]
Severe GI	PCC = [redacted] Andexanet alfa = [redacted]	[redacted]	[redacted]
Other major bleeds (non-ICH/GI)	PCC = [redacted] Andexanet alfa = [redacted]	[redacted]	[redacted]
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; PCC, Prothrombin complex concentrate; LOS – length of stay.			

Table 11. Propensity score matching results showing the balance for whole cohort for Question A4

Whole cohort	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	N=[redacted]	N=[redacted]	N=[redacted]	N=[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH - intracerebral	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH- subarachnoid	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH- subdural/epidural	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI- lower	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI- upper	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI- unknown	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with other bleed types	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH: TIA	[redacted]	[redacted]	[redacted]	[redacted]

Whole cohort	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; PCC, Prothrombin complex concentrate; MH, medical history; TIA, Transient Ischemic Attack; CAD, Coronary artery disease; AF, Atrial fibrillation				

Table 12. Propensity score matching results showing the balance for ICH cohort for Question A4

ICH cohort	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	N=[redacted]	N=[redacted]	N=[redacted]	N=[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH - intracerebral	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH-subarachnoid	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH-subdural/epidural	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH:TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]

ICH cohort	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICH, intracranial haemorrhage; PCC, Prothrombin complex concentrate; MH, medical history; TIA, Transient Ischemic Attack; CAD, Coronary artery disease; AF, Atrial fibrillation				

Table 13. Propensity score matching results showing the balance for severe GI bleed cohort for Question A4

Severe GI	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	N=[redacted]	N=[redacted]	N=[redacted]	N=[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI - unknown	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI - upper	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI - lower	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH:TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: GI, gastrointestinal; PCC, Prothrombin complex concentrate; MH, medical history; TIA, Transient Ischemic Attack; CAD, Coronary artery disease; AF, Atrial fibrillation				

Table 14. Propensity score matching results showing the balance for other major bleeds cohort for Question A4

Other bleeds	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	N= [redacted]	N= [redacted]	N= [redacted]	N= [redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH:TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GI, gastrointestinal; PCC, Prothrombin complex concentrate; MH, medical history; TIA, Transient Ischemic Attack; CAD, Coronary artery disease; AF, Atrial fibrillation

ORANGE

A5. Priority question. Please provide the following for the ORANGE study:

a) **Baseline characteristics for the subgroup of patients in the 'Whole cohort' after propensity score matching for the characteristics listed in question A1;**

b) **Baseline characteristics for the subgroup of patients in the 'matched ICH cohort' after propensity score matching for the characteristics listed in question A1;**

c) **Baseline characteristics for the subgroup of patients in the 'matched GI cohort' after propensity score matching for the characteristics listed in question A1;**

d) **Baseline characteristics for the subgroup of patients in the 'matched other major bleeds cohort' after propensity score matching for the characteristics listed in question A1; and.**

e) **A breakdown of the location of bleeds classified as other bleeds before propensity score matching.**

Response

As requested by the ERG, Table 15 presents the baseline characteristics after matching of the patients from the ORANGE study matched in the analysis requested using covariates listed in Question A1. Results are provided for each of the cohorts for which propensity score matching was conducted in our base case.

Table 15. Baseline characteristics of patients matched in ORANGE for characteristics specified in Question A1

Baseline characteristic	Cohort			
	Whole	ICH	Severe GI	Other major bleed
n	[redacted]	[redacted]	[redacted]	[redacted]
Age, mean (years)	[redacted]	[redacted]	[redacted]	[redacted]
Female, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Medical history	[redacted]	[redacted]	[redacted]	[redacted]
Indication for anticoagulation				
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]
Deep vein thrombosis	[redacted]	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]
Metal heart valve	[redacted]	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]
Medical history, n (%)				
Chronic renal disease	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Labile INR	[redacted]	[redacted]	[redacted]	[redacted]
Liver failure	[redacted]	[redacted]	[redacted]	[redacted]
Cancer	[redacted]	[redacted]	[redacted]	[redacted]
Peripheral vascular disease	[redacted]	[redacted]	[redacted]	[redacted]
Ischaemic heart disease	[redacted]	[redacted]	[redacted]	[redacted]
TIA/Stroke	[redacted]	[redacted]	[redacted]	[redacted]
Alcohol dependence	[redacted]	[redacted]	[redacted]	[redacted]
Dementia	[redacted]	[redacted]	[redacted]	[redacted]
Recurrent falls	[redacted]	[redacted]	[redacted]	[redacted]
Congestive heart failure	[redacted]	[redacted]	[redacted]	[redacted]
Diabetes mellitus	[redacted]	[redacted]	[redacted]	[redacted]
FXa inhibitors, n (%)				
Apixaban	[redacted]	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]	[redacted]	[redacted]	[redacted]
Site of bleed, n (%)				
ICH - subdural/epidural	[redacted]	[redacted]	[redacted]	[redacted]
ICH – intracerebral	[redacted]	[redacted]	[redacted]	[redacted]
ICH – subarachnoid	[redacted]	[redacted]	[redacted]	[redacted]
GI – upper GI	[redacted]	[redacted]	[redacted]	[redacted]
GI – lower GI	[redacted]	[redacted]	[redacted]	[redacted]
Other major bleed	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FXa, factor 10 a; GI, gastrointestinal; ICH, intracranial haemorrhage.
Stroke, pulmonary embolism, atrial fibrillation, metal heart valve and deep vein thrombosis calculated using indicators; Patients may have experienced more than one site of bleeding.

Table 16 below presents the breakdown of other major bleed types in ANNEXA-4 and ORANGE for only patients receiving apixaban or rivaroxaban who went on to receive PCC during the ORANGE study period.

Table 16. Breakdown of other types of major bleeding before matching in ANNEXA-4 and ORANGE

Specific bleed type from ORANGE patient level data	Frequency (of the other major bleed types) in ORANGE	Frequency (of the other major bleed types) in ANNEXA-4
Retroperitoneal	[redacted]	[redacted]
Extracranial - Subgaleal	[redacted]	[redacted]
Intramuscular with compartment syndrome	[redacted]	[redacted]
Intraarticular	[redacted]	[redacted]
Intraocular	[redacted]	[redacted]
Haematuria/urethral	[redacted]	[redacted]
Urinary tract – unknown site	[redacted]	[redacted]
Urinary tract – urinary bladder	[redacted]	[redacted]
Oral/pharyngeal	[redacted]	[redacted]
Puncture site	[redacted]	[redacted]
Vaginal	[redacted]	[redacted]
Epistaxis/mucosal	[redacted]	[redacted]
Cutaneous/soft tissue	[redacted]	[redacted]
Haemoptysis	[redacted]	[redacted]
Pericardium	[redacted]	[redacted]
Surgical site	[redacted]	[redacted]
Intraspinal – epidural	[redacted]	[redacted]
Intraspinal - intramedullary	[redacted]	[redacted]
Mediastinal	[redacted]	[redacted]
Respiratory tract – pleural	[redacted]	[redacted]
Respiratory tract - pulmonary	[redacted]	[redacted]
Visible bleeding – leg	[redacted]	[redacted]
Other	[redacted]	[redacted]

A6. Priority question. Please provide the results from the ORANGE study for the PCC apixaban or rivaroxaban subgroup and the ICH and GI bleed subgroups of this population for the following outcomes:

a) **Length of hospital stay (Please provide the equivalent data in Table 23 of Document B for the duration of hospital stay in the ORANGE study subgroup of patients on rivaroxaban or apixaban who received PCC);**

b) **Re-bleeding;**

c) **Thrombotic events; and**

d) **Restart of oral anticoagulation (Please provide the equivalent data provided for ANNEXA-4 in Table 41, CS Document B).**

Response

Re-bleeding, thrombotic events and restart of oral anticoagulation

Patient level data for re-bleeding, thrombotic events and restart of oral anticoagulation were not provided as part of the ORANGE patient level dataset. As such, we cannot provide the requested information for parts (b) – (d) of this question.

Length of hospital stay

Length of hospital stay data from ORANGE were available. Table 17 below provides the requested information on hospital length of stay for the ORANGE patient population receiving rivaroxaban or apixaban and PCC treatment.

Table 17. Hospital Length of Stay Summary for Patients anticoagulated with Apixaban or Rivaroxaban (ORANGE)

Bleed Type	Statistic	Apixaban (N=45)	Rivaroxaban (N=104)	All Patients (N=149)
All Patients	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
GI	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
ICH	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Other	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SD, standard deviation

A7. Please provide the number of patients in ORANGE for each of the propensity score matching analyses who received:

a) Tranexamic acid; and

b) Blood products (with a breakdown of type of blood product).

Response

The information requested is presented in Table 18.

Table 18. Summary of products received by the 145 patients in the full before matching population in ORANGE

Product	Number of patients (N=145)
Tranexamic acid	[redacted]
Red blood cells (transfusion)	[redacted]
Fresh frozen plasma	[redacted]
Platelets	[redacted]
Cryoprecipitate	[redacted]

ANNEXA-4

A8. Priority question. Please provide a breakdown of the types of ICH patients in ANNEXA-4 experienced at baseline (e.g. intracerebral, subarachnoid etc.) and all clinical results for each subtype for the subgroup of the safety population who received apixaban or rivaroxaban.

Response

Table 19. Baseline Hematoma Compartment and Clinical Results in Patients (who received Apixaban or Rivaroxaban) with ICH (Safety Population)

Parameter	Haemostatic Efficacy (N=167)	Thrombotic Events (N=20)	Death (N=35)	All Patients (N=209)
Haematoma Compartment				
Intracerebral/ intraventricular	[redacted]	[redacted]	[redacted]	[redacted]
Multiple	[redacted]	[redacted]	[redacted]	[redacted]
Subarachnoid	[redacted]	[redacted]	[redacted]	[redacted]
Subdural	[redacted]	[redacted]	[redacted]	[redacted]
Primary Location of Multiple Bleeding				
Intracerebral	[redacted]	[redacted]	[redacted]	[redacted]
Subarachnoid	[redacted]	[redacted]	[redacted]	[redacted]
Subdural	[redacted]	[redacted]	[redacted]	[redacted]
cannot be determined	[redacted]	[redacted]	[redacted]	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet.
Study: ANNEXA4 (14-505), Program: Table A8.sas, Output: Table A8.rtf, Date: 25OCT2019

A9. Priority question. Please provide data for the efficacy endpoints as specified below in the following subgroups:

a) **the subgroup of the safety population who received apixaban or rivaroxaban (in line with the eligible population for andexanet alfa according to the European marketing authorisation)**

    I. **Haemostatic efficacy/effective haemostasis at 12 hours post-andexanet;**

    II. **Anti-FXa activity for the time points presented in Figure 11, CS Document B;**

b) **the subgroup of the safety population who received apixaban or rivaroxaban and had an ICH**

    I. **Haemostatic efficacy/effective haemostasis at 12 hours post-andexanet;**

    II. **Anti-FXa activity for the time points presented in Figure 11, CS Document B;**

    III. **Haematoma expansion at 1 hour and 12 hours post-andexanet;**

    IV. **GCS and NIHSS scores for the time points detailed in Table 20.**

c) **the subgroup of the safety population who received apixaban or rivaroxaban and had a GI bleed.**

    I. **Haemostatic efficacy/effective haemostasis at 12 hours post andexanet;**

    II. **Anti-FXa activity for the time points presented in Figure 11, CS Document B.**

Response

Table 20. (Response to A9a-c, Part I) Haemostatic Efficacy at 12 Hours Post Andexanet of Apixaban and Rivaroxaban (Safety Population)

Cohort	Statistic	All Patients
Overall	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
Bleed Type		
GI	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
ICH	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
Other	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet. Bleed type was adjudicated by the Endpoint Adjudication Committee.
Patients adjudicated as non-evaluable for administrative reasons were excluded.
Study: ANNEXA4 (14-505), Program: Table A9A1.sas, Output: Table A9A1.rtf, Date: 25OCT2019

Table 21. (Response to A9a-c, Part II) Summary for Anti-FXa Activity by FXa Inhibitor (Apixaban & Rivaroxaban) and Bleed Type (Safety Population)

		Apixaban (ng/mL)				Rivaroxaban (ng/mL)			
Assessment Time	**Statistic**	**GI**	**ICH**	**Other**	**All Patients**	**GI**	**ICH**	**Other**	**All Patients**
Baseline	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	25th, 75th Percentile	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of bolus	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	25th, 75th Percentile	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of infusion	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	25th, 75th Percentile	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 Hours	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Apixaban (ng/mL)				Rivaroxaban (ng/mL)			
Assessment Time	**Statistic**	**GI**	**ICH**	**Other**	**All Patients**	**GI**	**ICH**	**Other**	**All Patients**
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	25th, 75th Percentile	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8 Hours	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	25th, 75th Percentile	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 Hours	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	25th, 75th Percentile	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet. Bleed type was adjudicated by the Endpoint Adjudication Committee.
Values >950 ng/mL were replaced with 950 ng/mL (the upper limit of quantitation). Values <4 ng/mL (or <0.10 IU/mL for enoxaparin) were replaced with 4 ng/mL (or 0.10 IU/mL) (the lower limit of quantitation), respectively.
The 95% CI for the median is based on distribution free method.
Patient 204002 was in the apixaban group, but was reported as the rivaroxaban group in the laboratory results. The patient is summarized in the apixaban group.
Study: ANNEXA4 (14-505), Program: Table A9A2.sas, Output: Table A9A2.rtf, Date: 24OCT201

Table 22. (Response to A9b, Part III) Analysis of Hematoma Expansion in Patients Received Apixaban or Rivaroxaban with Intracerebral Volume (Safety Population)

Status of Hematoma Expansion	N (%) with Intracerebral Volume > 35% Increase from Baseline to 1 hour (N=124)	Number at 1 hour Mean (SD)	N (%) with Intracerebral Volume > 35% Increase from Baseline to 1 & 12 hour (N=119)	Number at 12 hour Mean (SD)
Hematoma Expansion	[redacted]	[redacted]	[redacted]	[redacted]
No Hematoma Expansion	[redacted]	[redacted]	[redacted]	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients treated with any amount of andexanet.
Patients who didn't have intracerebral volumes at baseline, 1 hour assessment, and/or 12 hour assessment were excluded.
Hematoma expansion defined as volume increase from baseline greater than 35%.
Study: ANNEXA4 (14-505), Program: Table A9B3.sas, Output: Table A9B3.rtf, Date: 24OCT2019

Table 23. (Response to A9b Part IV) Clinical Neurologic Status (Glasgow Coma Scale & National Institutes of Health Stroke Scale) for Patients, who Received Apixaban or Rivaroxaban, with ICH (Safety Population)

Assessment Time	Statistic	GCS	GCS Change	NIHSS	NIHSS Change
Baseline	Patients (N)	[redacted]		[redacted]	
	Mean (SD)	[redacted]		[redacted]	
	Median	[redacted]		[redacted]	
	Min, Max	[redacted]		[redacted]	
	Median 95% CI	[redacted]		[redacted]	
1 Hour	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]
12 Hour	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]

Day 30	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Study: ANNEXA4 (14-505), Program: Table A9B4.sas, Output: Table A9B4.rtf, Date: 24OCT2019

A10. Please provide details of the baseline medications used in ANNEXA-4 for each of the three subgroups detailed in Table 14, CS Document B, including details of antiplatelets, anticoagulants, NSAIDs and PPIs.

Response

Table 24. Concomitant Medication Use of Patients Received Apixaban or Rivaroxaban by Bleed Type (Safety Population)

Type of Medication	Generic Name	GI (N=82) n (%)	ICH(N=209) n (%)	All Patients(N=322) n (%)
Anticoagulants	Apixaban	[redacted]	[redacted]	[redacted]
	Warfarin	[redacted]	[redacted]	[redacted]
Antiplatelet	Aspirin	[redacted]	[redacted]	[redacted]
	Clopidogrel	[redacted]	[redacted]	[redacted]
NSAIDs	Ibuprofen	[redacted]	[redacted]	[redacted]
	Naproxen/Naproxen sodium	[redacted]	[redacted]	[redacted]
ACE Inhibitors		[redacted]	[redacted]	[redacted]
Alpha Blockers		[redacted]	[redacted]	[redacted]
Angiotensin Receptor Blockers		[redacted]	[redacted]	[redacted]
Antidepressant		[redacted]	[redacted]	[redacted]
Beta Blockers		[redacted]	[redacted]	[redacted]
Bisphosphonates		[redacted]	[redacted]	[redacted]
Calcium Channel Blockers		[redacted]	[redacted]	[redacted]

Type of Medication	Generic Name	GI (N=82) n (%)	ICH(N=209) n (%)	All Patients(N=322) n (%)
Cholinesterase Inhibitor		[redacted]	[redacted]	[redacted]
Digitalis		[redacted]	[redacted]	[redacted]
Diuretics		[redacted]	[redacted]	[redacted]
Estrogen Replacement		[redacted]	[redacted]	[redacted]
Fibrates		[redacted]	[redacted]	[redacted]
Insulin		[redacted]	[redacted]	[redacted]
Nitrates		[redacted]	[redacted]	[redacted]
Oral Hypoglycemics		[redacted]	[redacted]	[redacted]
PDE5 Inhibitor		[redacted]	[redacted]	[redacted]
Statins		[redacted]	[redacted]	[redacted]

Bleed type was adjudicated by the Endpoint Adjudication Committee.
Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet.
Study: ANNEXA4 (14-505), Program: Table A10.sas, Output: Table A10.rtf, Date: 24OCT2019

Clinical outcomes

A11. Priority Question. Please clarify what treatments fall into each of the following categories in Table 19, CS Document B:

a) **Blood product use;**

b) **Coagulation factor transfusion;**

c) **Haemostatic treatments; and**

d) **Other blood coagulation.**

Response

Table 25. Blood Products and Haemostatic Agents Use of Patients Received Apixaban or Rivaroxaban After Andexanet Treatment (Safety Population)

Group	Blood Products Hemostatic Agents	All Patients (N=322) n (%)
Coagulation Factor Products	4-Factor PCC	[redacted]
Blood products	Fresh Frozen Plasma	[redacted]
	Plasma	[redacted]
	Platelets	[redacted]
Haemostatic Treatment	Aminocaproic Acid	[redacted]
	Tranexamic Acid	[redacted]
Other	Thrombin	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet.
Study: ANNEXA4 (14-505), Program: Table A11.sas, Output: Table A11.rtf, Date: 24OCT2019

A12. Priority Question. Please provide the number of patients who received tranexamic acid for each of the study populations detailed in Table 19, CS Document B.

Response

There were a total of [redacted] patients in the entire ANNEXA-4 dataset that received tranexamic acid. Given the low number, a listing of all [redacted] patients, including their bleed type, FXa inhibitor, haemostatic outcome, and safety outcomes, are provided below (Table 26).

Table 26. ANNEXA-4 Patients Receiving Tranexamic Acid

Patient Number	Country	Bleed Type	FXa Inhibitor	Hemostatic Efficacy Outcome	Thrombotic Event?	Mortality?
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

A13. Please provide the interquartile ranges for the median duration of hospital stay data provided in Table 23 of Document B for ANNEXA-4.

Response

Table 27. Details of Hospitalisation (Days) Post Treatment in Patients Received Apixaban or Rivaroxaban by Bleed Type (Safety Populations)

Bleed Type	Parameter	Apixaban (N=194)	Rivaroxaban (N=128)	All Patients (N=322)
All Patients	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
GI	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
ICH	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Other	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]

Database lock date: 28NOV2018. The Safety Population included all patients who received any amount of andexanet.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Study: ANNEXA4 (14-505), Program: Table A13c.sas, Output: Table A13c.rtf, Date: 04NOV2019

A14. Please provide a clinical rationale for the variation in mean duration of hospital stay depending on DOAC (apixaban or rivaroxaban) received (Table 23, CS Document B).

Response

The differences in the mean values are due to the presence of significant outliers in subgroups with relatively small numbers of patients. Of note, the median values in the respective groups (6.9 and 7.4) are not particularly different, suggesting further that the difference in means is driven by the outliers.

A15. Please provide the number of patients who had a length of stay of 30 days or greater in the populations in Table 23 of Document B for Annexa-4 and for the ORANGE patients for the PCC apixaban or rivaroxaban subgroup and the ICH and GI bleed subgroups of this population.

Response

Table 28. Summary of Hospitalization ≥30 Days by Bleed Type in Patients Received Apixaban or Rivaroxaban (Safety Population)

FXa Inhibitor	Statistic	GI	ICH	All Patients
Apixaban	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Rivaroxaban	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet. Bleed type was adjudicated by the Endpoint Adjudication Committee.
Study: ANNEXA4 (14-505), Program: Table A15.sas, Output: Table A15.rtf, Date: 25OCT2019

[redacted] patients had a length of stay of 30 days exactly in ORANGE, with length of stay above 30 days not recorded.

A16. Please provide data on haemostatic efficacy as measured by haematoma expansion in the ORANGE study subgroup of patients on rivaroxaban or apixaban who received PCC who had an ICH.

Response

Unfortunately, the ORANGE study did not systematically collect imaging data in the ICH population, so it is impossible to determine how many patients had haematoma expansion.

Adverse events and mortality

A17. Priority question. Please provide details of the thrombotic events as presented in Table 40, CS Document B for the following subgroups:

a) **the subgroup of the safety population who received apixaban or rivaroxaban (in line with the eligible population for andexanet alfa according to the European marketing authorisation);**

b) **the subgroup of the safety population who received apixaban or rivaroxaban and had an ICH; and**

c) **the subgroup of the safety population who received apixaban or rivaroxaban and had a GI bleed.**

Response

Table 29. Characteristics of Thrombotic Events and Re-anticoagulation Stratified by Bleed Type (Safety Population)

Group	GI (N=82)	ICH (N=209)	All Patients (N=322)
TE, n(%)	[redacted]	[redacted]	[redacted]
Age (years)			
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
FXa Inhibitor			
Apixaban	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]	[redacted]	[redacted]
TE Type[1]			
CVA	[redacted]	[redacted]	[redacted]
DVT	[redacted]	[redacted]	[redacted]
PE	[redacted]	[redacted]	[redacted]
MI	[redacted]	[redacted]	[redacted]
TIA	[redacted]	[redacted]	[redacted]
Indication for Anticoagulation			
Arterial Thromboembolism	[redacted]	[redacted]	[redacted]

Group	GI (N=82)	ICH (N=209)	All Patients (N=322)
Atrial Fibrillation	[redacted]	[redacted]	[redacted]
VTE	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Time to First TE (median, days)[2]	[redacted]	[redacted]	[redacted]
First TE Onset within	[redacted]	[redacted]	[redacted]
0-12 hours (inclusive)	[redacted]	[redacted]	[redacted]
>12 hours and <4 days	[redacted]	[redacted]	[redacted]
4-30 days (inclusive)	[redacted]	[redacted]	[redacted]
Number of Patient Re-anticoagulated[3]	[redacted]	[redacted]	[redacted]
Within 30 days since TE onset	[redacted]	[redacted]	[redacted]
Prior to TE onset	[redacted]	[redacted]	[redacted]
Days to Re-anticoagulation (median)	[redacted]	[redacted]	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet.
Thrombotic event and bleed type were adjudicated by the Endpoint Adjudication Committee.
[1] TE type is summarized at subject level. A patient may have multiple TE type.
[2] Time to first TE is inclusive of the dosing day.
[3] A patient could have multiple indications for the initial anti-coagulation.
CVA: Stroke Ischemic/Uncertain Classification, DVT: Deep Vein Thromboembolism , MI: Myocardial Infarction, PE: Pulmonary Embolism, TIA: Transient Ischemic Attack
Study: ANNEXA4 (14-505), Program: Table A17.sas, Output: Table A17.rtf, Date: 25OCT2019

A18. Please clarify how many patients:

a) were enrolled under amendment 1 or earlier and were therefore scheduled to have a 45 day follow-up visit

b) were enrolled under amendment 2 or later and were therefore scheduled to have a 30 day follow-up visit

c) did not reach their final follow-up visit in the:

I. 30 day subgroup

II. 45 day subgroup.

Response

Table 30. Patient Enrolment by Protocol Version (Safety Population)

	Patients Enrolled (N=352)		<30 Day Follow-up Visit		30-45 Day Follow-up Visit	
Protocol Version	**n (%)**	**No 30 or 45 day follow-up visit**	**Death**	**Withdrawn Consent**	**Death**	**Lost to Follow-up**
Original dated 30 July 2014	[redacted]					
Protocol Amendment 1 dated 30 January 2015	[redacted]					
Protocol Amendment 2 dated 7 May 2015	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Protocol Amendment 3 dated 27 October 2015	[redacted]					
Protocol Amendment 4 dated 6 January 2017	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet.
Study: ANNEXA4 (14-505), Program: Table A18.sas, Output: Table A18.rtf, Date: 28OCT2019

A19. Please provide details on the location, severity and number of patients who had a treatment-emergent adverse event bleeding episode in ANNEXA-4 for the three populations as defined in the propensity score matching analysis presented in the CS (Whole population, ICH subgroup and GI subgroup).

Response

It is difficult to define what constitutes a treatment-emergent adverse event bleeding episode, because in some cases a “bleeding” event merely reflects the natural course of the disease (e.g. worsening ICH). In other cases, bleeding events occur along a timeframe well after (e.g., > 1 week) the expected duration of effect of the drug and the elimination of the FXa inhibitor. In such cases patients are often re-anticoagulated prior to the new bleeding event. Due to issues such as these, any systematic attempt to compile bleeding treatment-emergent adverse event as requested will grossly overestimate the true risk of re-bleeding after andexanet treatment. We would suggest this analysis is not appropriate.

Anticoagulation

A20. Priority question: Please provide details of the drugs used as non-oral anticoagulation and oral anticoagulation reported in Table 42, CS Document B.

Response

Table 31. Non-Oral or Oral Anticoagulation Drug Post Andexanet Treatment in Patients Received Apixaban or Rivaroxaban (Safety Population)

Anticoagulation	GI (N=82) n (%)	ICH (N=209) n (%)	All Patients (N=322) n (%)
Non-Oral Anticoagulation			
ACD-A Solution	[redacted]	[redacted]	[redacted]
Certoparin/ Certoparine	[redacted]	[redacted]	[redacted]
Dabigatran	[redacted]	[redacted]	[redacted]
Dalteparin	[redacted]	[redacted]	[redacted]
Enoxaparin	[redacted]	[redacted]	[redacted]
Fraxiparine/Nadroparin/Nadroparine	[redacted]	[redacted]	[redacted]
Heparin/Heparin Flush/Heparin Sodium	[redacted]	[redacted]	[redacted]
Oral Anticoagulation	[redacted]	[redacted]	[redacted]
Apixaban	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]	[redacted]	[redacted]
Warfarin	[redacted]	[redacted]	[redacted]
Oral Anticoagulation Different Than Their Initial FXa Inhibitor	[redacted]	[redacted]	[redacted]
Apixaban	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]	[redacted]	[redacted]
Warfarin	[redacted]	[redacted]	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet.
Study: ANNEXA4 (14-505), program: Table A20.sas, Output: Table A20.rtf, Date: 31OCT2019

A21. Please provide the number of patients who restarted on a different oral anticoagulant to the one they were on at baseline in ANNEXA-4 for each of the three subgroups detailed in Table 42.

Response

For those patients who had previously received apixaban or rivaroxaban, [redacted] patients restarted on a different oral anticoagulant, [redacted] of these had a GI bleed and [redacted] had an ICH. See Table 31.

Subgroups

A22. Please provide the results for haemostatic efficacy at 12 hours post-andexanet alfa in ANNEXA-4 for each of the three populations as defined in the propensity score matching analysis presented in the CS (Whole population, ICH subgroup and GI subgroup) for the following subgroups:

a) Type of bleed (e.g. ICH, GI etc.) [for the combined apixaban and rivaroxaban subgroup only];

b) Site of bleed (e.g. upper GI, lower GI etc.);

c) Dose of DOAC; and

d) Severity of bleed (e.g. mRS score).

Response

Table 32. Haemostatic Efficacy at 12 Hours Post Andexanet by Bleeding Type (Safety Population)

Subgroup	Statistic	All Patients
ICH	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
ICH/IVH	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
SDH	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
SAH	Patients (N)	[redacted]

	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
Multiple	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
GI	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
GI Upper	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
GI Lower	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
GI Unknown	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet. Bleed type was adjudicated by the Endpoint Adjudication Committee.
Patients adjudicated as non-evaluable for administrative reasons were excluded.
Study: ANNEXA4 (14-505), Program: Table A22B.sas, Output: Table A22B.rtf, Date: 29OCT2019

Table 33. Haemostatic Efficacy at 12 Hours Post Andexanet by FXa Inhibitor (Safety Population)

Subgroup	Statistic	All Patients
Overall	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
FXa Inhibitor		
Apixaban	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
Low Apixaban	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
High Apixaban	Patients (N)	[redacted]

Subgroup	Statistic	All Patients
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
Rivaroxaban	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
Low Rivaroxaban	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
High Rivaroxaban	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet. Bleed type was adjudicated by the Endpoint Adjudication Committee.
Patients adjudicated as non-evaluable for administrative reasons were excluded.
Study: ANNEXA4 (14-505), Program: Table A22C.sas, Output: Table A22C.rtf, Date: 25OCT2019

Table 34. Haemostatic Efficacy at 12 Hours Post Andexanet by Clinical Neurologic Status (Modified Rankin Score [mRS]) in Patients with ICH (Safety Population)

mRS	Patients (N)	n (%)	Exact 95% CI
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Study: ANNEXA4 (14-505), Program: Table A22D.sas, Output: Table A22D.rtf, Date: 29OCT2019

Section B: Clarification on cost-effectiveness data

Please note that if as a result of the responses to the cost-effectiveness clarification questions the company base case analyses are revised, please indicate what assumptions are considered for the revised base case and provide updated results, probabilistic sensitivity analyses and deterministic sensitivity analyses in the response document. Please provide all requested scenario analyses as options in the economic model.

Revised base case

Portola thanks the ERG for their questions. It has considered each of these and defined a new base case in the cost-effectiveness model (CEM), including the following assumptions:

1) As requested in Question A3 (b) and B1 (b), we conducted propensity score matching using the original covariates identified with the input of UK clinical experts and statistical testing, in addition to a new covariate for more granular site of bleed. The estimated 30-day mortality results from this analysis are now used in the revised base case for individuals with ICH and severe GI bleeds.
2) The change specified in Question B9 (a) has been made to the model and has been adopted as part of the revised base case. We agree that this is a desirable way to make use of the survival probabilities associated with the best fitting parametric curves derived from the survival data in Huybrechts *et al.* 2008.[2]
3) The costs incurred by intraspinal bleed survivors are applied as specified in Question B14, with the first 12 model cycles reflecting the monthly cost sourced from McDaid *et al.* 2019 and the monthly cost for all subsequent cycles reflecting the monthly cost sourced from the Spinal UK report for 60 days of spinal care unit care.[3]
4) The long term cost of an intraspinal bleed per month, as suggested by the ERG in their email on the 24th of October 2019, is defined using half of the £58,080 cost of care for 60 days, provided by Spinal UK.[3]

Given these assumptions in the CEM, Table 35 shows the results of the revised base case for the whole cohort, ICH and severe GI bleed, and ICH only subgroups. The results of the re-submission to which the ERG's questions pertain are also presented in Table 35 for comparison.

Throughout the response to questions in Section B, the results of the re-submission are provided for reference relative to the results of each scenario, since the impact each change proposed by the ERG on the original results was thought to be the most meaningful.

Results of probabilistic sensitivity analysis (PSA) and one-way sensitivity analysis (OWSA) for the revised base case are provided in Table 54 to Table 59, and Figure 1 to Figure 12, of the Appendix.

Table 35. Cost effectiveness results for updated base case

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Results included in original submission – whole cohort								
SoC	17,583	3.267	2.187	-	-	-	-	-
Andexanet alfa	37,365	4.563	3.230	19,782	1.296	1.043	18,968	18,968
Results for revised base case – whole cohort								
SoC	48,108	3.242	2.173	-	-	-	-	-
Andexanet alfa	60,430	4.564	3.232	12,322	1.322	1.059	11,636	11,636
Results included in original submission – ICH and GI cohort								
SoC	16,958	2.741	1.824	-	-	-	-	-
Andexanet alfa	37,392	4.100	2.909	20,434	1.359	1.085	18,832	18,832
Results for revised base case – ICH and GI cohort								
SoC	16,736	2.715	1.809	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.913	20,691	1.390	1.104	18,741	18,741
Results included in original submission – ICH only cohort								
SoC	19,069	1.620	0.953	-	-	-	-	-
Andexanet alfa	41,122	3.058	2.121	22,053	1.438	1.169	18,871	18,871
Results for revised base case – ICH only cohort								
SoC	18,780	1.586	0.933	-	-	-	-	-

Andexanet alfa	41,199	3.068	2.130	22,419	1.482	1.196	18,738	18,738

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

B1. Priority question. Please provide an economic analysis based on the clinical effectiveness analysis requested in clarification questions:

a) **A3a**

b) **A3b**

c) **A4**

Response

Aligned with the response to Question A3, the results of the scenario incorporating the analyses undertaken in Question A3 (b) into the CEM are presented in Table 36.

The results across all scenarios run indicate that andexanet alfa remains cost-effective compared to standard of care (SoC) across all three cohorts, with the incremental cost-effectiveness ratio (ICER) remaining below £20,000 for all scenarios conducted across all three populations.

Incorporation into the revised base case

Given the clinical validity of specifying the site of bleed into more granular detail, this has been incorporated into the revised base case.

Table 36. Results of using 30-day estimated mortality using propensity score matching from Question A3.b (original results)

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Results included in original submission – for whole cohort								
SoC	17,583	3.267	2.187	-	-	-	-	-
Andexanet alfa	37,365	4.563	3.230	19,782	1.296	1.043	18,968	18,968
Scenario using 30-day estimated using propensity score matching from Question A3.b – whole cohort								
SoC	17,372	3.242	2.173	-	-	-	-	-
Andexanet alfa	37,365	4.563	3.230	19,993	1.320	1.057	18,908	18,908
Results included in original submission – ICH and GI cohort								
SoC	16,958	2.741	1.824	-	-	-	-	-
Andexanet alfa	37,392	4.100	2.909	20,434	1.359	1.085	18,832	18,832
Scenario using 30-day estimated using propensity score matching from Question A3.b – ICH and GI cohort								
SoC	16,736	2.715	1.809	-	-	-	-	-
Andexanet alfa	37,392	4.100	2.909	20,656	1.385	1.100	18,773	18,773
Results included in original submission – ICH only cohort								
SoC	19,069	1.620	0.953	-	-	-	-	-
Andexanet alfa	41,122	3.058	2.121	22,053	1.438	1.169	18,871	18,871
Scenario using 30-day estimated using propensity score matching from Question A3.b – ICH only cohort								

SoC	18,780	1.586	0.933	-	-	-	-	-
Andexanet alfa	41,122	3.058	2.121	22,342	1.472	1.188	18,800	18,800

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio
Note: the switch to find these results from the original base case is in cell C20 of sheet 'Decision Tree SoC' in the CEM

B2. Priority question. mRS data obtained from the study by Øie *et al.* 2018 and implemented in the economic model indicate that patients who receive standard care experience more severe ICH events (Table 48 of the CS, Document B) naïvely compared with ANNEXA-4 mRS data used for andexanet alfa.

a) **Please clarify why a study in patients with intracerebral hemorrhage (Øie *et al.* 2018) was considered appropriate to inform the severity of patients with intracranial haemorrhage (ICH).**

b) **Please provide a clinical rationale for why patients on andexanet alfa would experience less severe ICH events compared with standard care.**

Response

We believe there may have been a misunderstanding regarding the severity of ICH events in ANNEXA-4 versus the Øie et al. 2018 study. In particular, there is no evidence to suggest that patients in the Øie et al. 2018 study experienced more severe ICH events compared to ANNEXA-4.

Table 48 of the CS, Document B presents the mRS scores following discharge from hospital 30 days post bleed in ANNEXA-4 and 90 days post bleed in Øie et al. 2018, which are not intended to indicate the level of severity of the ICH on the day of the event.

Appropriateness of Øie et al. 2018 to inform severity of SoC ICHs

We have conducted a targeted literature review of academic journal articles and other materials to provide a distribution of mRS for patients with ICH. The paper by Øie et al. 2018 was chosen for use in the CEM, because its entire patient population had intracranial bleeds, albeit of one sub-type, and because it had a reasonable sample size of 452 patients at baseline. Other papers were excluded mainly due to patient population, as most had patient populations who had experienced stroke of any type. Intracranial haemorrhage patients were known to be a minority of this wider group, and it was deemed inappropriate to use results for a population most of whom would not be included in the CEM.

Following the identification of the Øie et al 2018 study, we sought clinical expert opinion from UK clinicians specialising in haematology to validate the choice of source for the mRS distribution of patients in the SoC arm of the CEM. It was concluded that Øie et al 2018 was an appropriate source to represent SoC patients with life threatening or uncontrolled major

bleeding events because intracerebral haemorrhage is one of the most likely bleed sites to be considered as life-threatening or uncontrolled.

However, clinicians did note that not all intracerebral haemorrhage bleeds are life threatening, and as shown in the response to A8, [redacted]% of patients in ANNEXA-4 had ICH bleeding across multiple sites, whilst Øie et al. 2018 concentrated solely on intracerebral bleeding.[2] Furthermore, evaluation of the Øie et al. 2018 population suggests the population is younger in age compared to ANNEXA-4 whilst only [redacted]% of patients were receiving anti-coagulants; this is of particular importance as the study reports that older age and use of anti-coagulants were significant predictors of severe disability or death.[4] This evidence suggests that the ANNEXA-4 study represents a more severe group of ICH patients in terms of expected outcomes compared to Øie et al 2018.

Therefore, without a SoC population with life threatening or uncontrolled major bleeding ICH events, as with the ANNEXA-4 study, Øie et al 2018 was considered to adequately represent the potential outcomes in a SoC population as patients all suffered a relatively severe sub-type of ICH. Nevertheless, given the UK clinical advice received and analysis of the patient populations across the Øie *et al*. 2018 and ANNEXA-4 studies, mRS scores are likely to be higher for SoC than those reported in Øie *et al.* 2018 were this an anti-coagulated, life threatening or uncontrolled bleeding population like the ANNEXA-4 patient population. Cost-effectiveness estimates may be deemed conservative in light of this.

Clinical rationale for treatment effect of andexanet alfa on ICH morbidity outcomes

As previously discussed, patients with life-threatening or uncontrolled major bleeding events would not be expected to have differential ICH severity upon presentation of the event when treated with andexanet alfa or SoC. However, the prognosis for surviving ICH patients is expected to be different, which is what the difference in mRS scores from Øie et al 2018 and ANNEXA-4 seeks to represent.

According to UK expert clinicians specialising in haematology, andexanet alfa would be associated with improved ICH morbidity outcomes in surviving patients compared to SoC because by rapidly reversing the effects of anticoagulation caused by rivaroxaban or apixaban, the likelihood that the ICH bleed volume will cease expanding is substantially improved. This thereby prevents further irreparable damage to the brain caused by uncontrolled bleeding. The risk of haematoma expansion is well known to be associated with the risk of morbidity and mortality in patients with ICH[5]; therefore, any intervention aimed at reducing the risk of haematoma expansion will also impact ICH morbidity outcomes in a similar manner.

Finally, haemostatic efficacy in intracerebral patients in ANNEXA-4 was not substantially different to the total group of patients with ICH in ANNEXA-4, indicating that treatment efficacy is similar with andexanet alfa across all types/compartments of ICHs (Table 19).

B3. Priority question. Please explain why any additional benefits from reductions in haematoma expansion in patients with intracerebral haemorrhages were not considered by modelling patients with intracerebral haemorrhages separately to the other subtypes of ICH.

a) **Please provide a scenario where the proportion provided in clarification question A8 have intracerebral-specific mRS scores (mRS scores reported in Øie *et al.* 2018 applied to standard care and mRS scores reported in ANNEXA-4 applied to andexanet alfa) and the remaining proportion of patients in both treatment arms have mRS scores equal to ANNEXA-4**

b) **Please provide a scenario where mRS values obtained from ANNEXA-4 are used for both andexanet alfa and standard care arms, thus feeding into long-term ICH mortality, HRQoL and costs calculations**

Response

Haematoma expansion was not reported in ORANGE, nor explicitly in ANNEXA-4. We appreciate that andexanet alfa will provide benefits in terms of haematoma expansion, and as discussed in the response to Question B2, the mRS score post discharge represents an accurate reflection of morbidity status in ICH survivors, and has been utilised in the CEM.

For both scenarios B3 (a) and B3 (b) the underlying assumption being tested is that andexanet alfa would not affect mRS score (i.e. morbidity status) post ICH compared to SoC for some patients (either non-intracerebral [a] or all [b]). However, as already discussed in B2, expert clinical opinion in the UK would suggest that the Øie *et al*. 2018 study can be considered generalisable to a cohort of patients with life threatening or uncontrolled major bleeding events as identified in the ANNEXA-4 study, and if anything, may represent a slightly healthier ICH population – as not all patients entering Øie et al. 2018 necessarily had life-threatening or uncontrolled bleeds. As such, we would consider both scenarios to be extreme, based on the haemostatic efficacy observed for andexanet alfa across all ICH types (Table 19). Nevertheless, the requested scenarios are presented below.

Scenario – B3 (a)

Table 37 presents the results of a scenario in which the distribution of mRS scores among patients who had an intracerebral haemorrhage in ANNEXA-4 was applied to the proportion of patients with an intracerebral haemorrhage in ANNEXA-4 ([redacted] = [redacted]%), whilst the distribution of mRS scores as per Øie et al. 2018 was applied to the same proportion of patients in the SoC arm. The distribution of mRS scores for the remaining patients ([redacted]%) in both treatment arms was set equal to ANNEXA-4 (rivaroxaban + apixaban population, as per original submission); thereby assuming no treatment effect with andexanet alfa on morbidity status for the [redacted]% of patients who did not have an intracerebral bleed. The results indicate that the ICERs remain below £30,000 across all scenarios modelled.

Scenario – B3 (b)

Table 38 presents the results of a scenario in which the mRS score distributions from ANNEXA-4 for all patients with ICH were used for both patients receiving andexanet alfa and patients receiving SoC; thereby assuming no treatment effect with andexanet alfa on morbidity status for all ICH patients. The results indicate that the ICERs remain below £30,000 across all scenarios modelled, except for the ICH only cohort which remains below £32,100.

Table 37. Results of scenario using intracerebral haemorrhage-specific mRS scores for intracerebral haemorrhage patients (revised results)

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Results included in updated base case – for whole cohort								
SoC	48,108	3.242	2.173	-	-	-	-	-
Andexanet alfa	60,430	4.564	3.232	12,322	1.322	1.059	11,636	11,636
Scenario using intracerebral haemorrhage-specific mRS scores for intracerebral haemorrhage patients – whole cohort								
SoC	48,108	3.242	2.173	-	-	-	-	-
Andexanet alfa	60,430	4.564	3.050	12,322	1.322	0.877	14,044	14,044
Results included in updated base case – ICH and GI cohort								
SoC	16,736	2.715	1.809	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.913	20,691	1.390	1.104	18,741	18,741
Scenario using intracerebral haemorrhage-specific mRS scores for intracerebral haemorrhage patients – ICH and GI cohort								
SoC	16,736	2.715	1.809	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.721	20,691	1.390	0.913	22,675	22,675
Results included in updated base case – ICH only cohort								
SoC	18,780	1.586	0.933	-	-	-	-	-
Andexanet alfa	41,199	3.068	2.130	22,419	1.482	1.196	18,738	18,738
Scenario using intracerebral haemorrhage-specific mRS scores for intracerebral haemorrhage patients – ICH only cohort								

SoC	18,780	1.586	0.933	-	-	-	-	-
Andexanet alfa	41,199	3.068	1.881	22,419	1.482	0.948	23,659	23,659

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; MRs, Modified Rankin score
Note: the switch to apply this scenario from the revised base case is in cell E27 of the sheet 'Quality Of Life Inputs'

Table 38. Results of scenario using the distribution of mRS score from ANNEXA-4 for both treatment arms (revised results)

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Results included in updated base case – for whole cohort								
SoC	48,108	3.242	2.173	-	-	-	-	-
Andexanet alfa	60,430	4.564	3.232	12,322	1.322	1.059	11,636	11,636
Scenario using mRS score from ANNEXA-4 for all patients – whole cohort								
SoC	47,419	3.401	2.270	-	-	-	-	-
Andexanet alfa	60,430	4.564	3.001	13,011	1.163	0.732	17,785	17,785
Results included in updated base case – ICH and GI cohort								
SoC	16,736	2.715	1.809	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.913	20,691	1.390	1.104	18,741	18,741
Scenario using mRS score from ANNEXA-4 for all patients – ICH and GI cohort								
SoC	16,036	2.886	1.913	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.669	21,391	1.219	0.756	28,277	28,277

Results included in updated base case – ICH only cohort								
SoC	18,780	1.586	0.933	-	-	-	-	-
Andexanet alfa	41,199	3.068	2.130	22,419	1.482	1.196	18,738	18,738
Scenario using mRS score from ANNEXA-4 for all patients – ICH only cohort								
SoC	17,890	1.812	1.071	-	-	-	-	-
Andexanet alfa	41,199	3.068	1.814	23,309	1.257	0.743	31,377	31,377

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio
Note: the switch to apply this scenario from the revised base case is in cell E29 of sheet 'Quality Of Life Inputs'

B4. Priority question. The ERG considers the short-term economic model (the 30-day decision tree component of the model) provides the most robust estimates of the cost-effectiveness of andexanet alfa as it is directly informed by the key trials (ANNEXA-4 and ORANGE).Therefore, please provide a scenario that is based only on the outcomes of the 30-day decision tree model.

Response

Following the clarification call with the ERG, we understand that this question seeks to explore the sensitivity of the time horizon on the model results, and is not suggesting that a 30-day time horizon is more appropriate to evaluate the cost-effectiveness of andexanet alfa (for which the benefits are experienced in the long-term) compared to a lifetime horizon.

This is because excluding long term costs and consequences of improving mortality and morbidity following a life-threatening bleeding event is not in keeping with NICE's reference case for selecting a model time horizon:

"The time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared" [6]

We would add that a number of life-saving and quality of life-enhancing interventions would not have been made available to UK patient populations if only short term costs and benefits had been considered. Notable examples include direct-acting antiviral agents for the treatment of hepatitis C virus and CAR T-cell therapies for cancers.

Nevertheless, as requested, the scenario for a 30-day time horizon is provided below. Unsurprisingly, the cost-effectiveness results increase well above NICE acceptable thresholds, as the full cost of treatment is incurred whilst no benefits after 30 days (including extended survival and improved morbidity) are recognised.

The results highlight the need to evaluate the long-term costs and benefits of andexanet alfa when considering its cost-effectiveness.

Table 39. Time horizon scenario: incremental results at 30 days (revised results)

Cohort	Inc. Costs (£)	Inc. QALYs	ICER (£)
Whole cohort	14,356	0.008	1,834,587
ICH and GI	14,446	0.009	1,683,816
ICH only	14,477	0.010	1,520,070

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio
Note: these results can be found from the revised base case in the table C48:F50 of sheet 'Results' in the CEM

B5. Priority question. Please provide a scenario using the 30-day mortality rates for other major bleeds obtained from propensity score matching

Response

We provided the results of the scenario in which the 30-day mortality rates for other major bleeds are adopted in the CEM (Table 40). The results show that the ICER rises from £18,968 per quality-adjusted life year (QALY) to £19,277 per QALY, as a result of the higher mortality for andexanet alfa relative to SoC.

As discussed in the original submission, a higher mortality with andexanet alfa compared to SoC is clinically illogical and inconsistent with the known mechanism of action for andexanet alfa – as an antidote for reversing anticoagulation in life-threatening or uncontrolled major bleeding events. The results from the propensity score matching analysis are, as discussed in the original submission, a consequence of small sample sizes in the other major bleeds and heterogeneity both in terms of site of bleed and severity (ANNEXA-4 mandating that it must be life-threatening or uncontrolled, whilst ORANGE not having such a mandate). Evidence of this heterogeneity is outlined in Table 16.

Even with this increased mortality compared to SoC, andexanet alfa remains cost-effective with an ICER below £20,000 compared to SoC in the Whole cohort population.

Table 40. Results of scenario using the results of the propensity score matching for the other major bleeds cohort included in the original submission (revised results)

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Results included in revised base case – for whole cohort								
SoC	48,108	3.242	2.173	-	-	-	-	-
Andexanet alfa	60,430	4.564	3.232	12,322	1.322	1.059	11,636	11,636
Scenario using 30-day estimated using propensity score matching for the other major bleeds cohort included in the original submission – whole cohort								
SoC	48,108	3.242	2.173	-	-	-	-	-
Andexanet alfa	60,414	4.540	3.214	12,306	1.298	1.041	11,817	11,817

Abbreviations: SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio
Note: the switch to apply this scenario from the revised base case is in cell C20 of sheet 'Decision Tree Andexanet alfa'

B6. Priority question. Please provide a scenario that applies the unadjusted 30-day mortality rate for other major bleeds from ANNEXA-4 to both treatment arms.

Response

We have provided the results of the scenario in which the unadjusted 30-day mortality rate for other major bleeds from ANNEXA-4 were adopted in the CEM (Table 41). The results indicate that the ICER increases from £18,968 per QALY to £19,109 per QALY, as a result of the higher mortality for andexanet alfa relative to SoC.

As discussed in the original submission, a higher mortality associated with andexanet alfa compared to SoC is clinically illogical and inconsistent with the known mechanism of action for andexanet alfa – as an antidote for reversing anticoagulation in life-threatening or uncontrolled major bleeding events. The results from the naïve comparison are unadjusted and, as discussed in the original submission, a consequence of the heterogeneity in populations between the ANNEXA-4 and ORANGE studies. In particular, heterogeneity is problematic in terms of site of bleed and severity, which are key drivers of 30-day mortality risk. For example, in ANNEXA-4, all included patients experienced a life-threatening or uncontrolled bleed to warrant their inclusion, whilst within ORANGE, life threatening bleeding was not a requirement. Evidence of this heterogeneity is outlined in Table 16.

Even with this increased mortality compared to SoC, andexanet alfa remains cost-effective with an ICER below £20,000 compared to SoC the Whole cohort population.

Table 41. Results of scenario using 30-day mortality from ANNEXA-4 for both andexanet alfa and SoC patients (revised results)

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Results included in updated base case – for whole cohort								
SoC	48,108	3.242	2.173	-	-	-	-	-
Andexanet alfa	60,430	4.564	3.232	12,322	1.322	1.059	11,636	11,636
Scenario using 30-day mortality from ANNEXA-4 for both andexanet alfa and SoC patients – whole cohort								
SoC	48,108	3.242	2.173	-	-	-	-	-
Andexanet alfa	60,411	4.536	3.211	12,303	1.294	1.038	11,848	11,848

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; SoC, standard of care
Note: the switch to apply this scenario from the revised base case is in cell C32 of sheet 'Decision Tree SoC'

B7. The ERG does not consider the following assumptions sufficiently justified in the economic model, please provide additional supporting evidence and a comprehensive clinical rationale for:

a) Why the long-term cost and HRQoL decrements of paralysis and blindness was applied to 25% and 50% of intraspinal and intraocular bleeding survivors, respectively, in the standard care arm; and

b) Why a 25% reduction was assumed for andexanet alfa patients.

Response

The assumptions for the proportion of patients with paralysis and blindness were based on UK clinical expert opinion since there were no evidence identified from the literature to provide these values.

The percentage reduction assumed for andexanet alfa patients was based on observations seen in the populations for which propensity score matching was conducted for mortality at 30 days. A ≥[redacted]% reduction in mortality was observed at 30 days in the propensity score matching results for the Whole population ([redacted]%[redacted]), ICH subgroup ([redacted]%[redacted]), and GI subgroup ([redacted]%[redacted]). UK clinical experts believed that applying a 50% reduction for paralysis and blindness would be consistent with mortality findings, and perhaps even conservative. However, given that we do not have the necessary data to substantiate this value, [redacted] the benefit observed for reductions in mortality was applied to the reduction in paralysis and blindness – hence 25%. A similar assumption was also observed for other major bleed mortality reduction.

We acknowledge that the point estimates are highly uncertain, as these are based on clinical experience in the UK as opposed to a database of patients. As such, the value of 25% has been tested extensively in scenario analyses:

- From assuming no benefit with andexanet alfa ([redacted]), which would be surprising given the outcomes observed for ICH and GI – as well as the mechanism of action with treatment;
- To assuming an even greater benefit with andexanet alfa ([redacted]), in keeping with mortality benefits observed for both ICH and GI.

See Section B3.9 in the original submission for the results of these scenarios. The results across all scenarios run indicate that andexanet alfa remains cost-effective compared to SoC across all three cohorts, with the ICER remaining below £20,000 for all scenarios conducted across all three populations.

Long-term mortality

B8. Priority question. The ERG is concerned that the hazard ratio (HR) for ICH survivors has been erroneously mis-interpreted as a HR when it is in fact a risk ratio

a) Please provide a step-by-step calculation of the HRs for ICH survivors. If the "goal seek" function is used, please provide the "set cell", "to value" and "by changing cell" values and cells.

Response

We appreciate the ERG is seeking further information regarding the method for calculating long-term mortality for ICH patients and an explanation for the decisions made. We would highlight that following the ERG's recommendation in B9 for an alternative method for calculating long-term survival in ICH, we have now revised the base case to follow this recommendation.

However, the original methodology used is important when considering alternative scenarios and data sources for calculating long-term ICH mortality.

We wish to clarify that in the original submission, mean survival was calculated using the best fitting curves fitted to digitised data obtained from Huybrechts *et al* 2008*,* a paper provided by the ERG in its draft clarification questions. The calculation undertaken to find the hazard ratio applied to ICH survivors is described below.

1. **Mean survival** Parametric curves were fitted using digitised data from the six mRS-score specific survival curves presented in Figure 3 of Huybrechts *et al.* 2008.[2] Mean survival time in years was calculated using the best fitting parametric curve for each mRS score. Overall mean survival was then calculated as the average of all six mRS score-specific mean survival times, weighted by the distribution of mRS scores for each andexanet alfa and SoC. The resulting weighted mean survival times were [redacted] and [redacted] years for andexanet alfa and SoC, respectively. Full data from best fitting curves shown are in the 'Survival curves (mRS)' sheet of the cost-effectiveness model.

2. **Adjustment for age** Among those surviving to 3 months with mRS score observed in Huybrechts *et al.* 2008, the mean age was 68.0 years.[2] Mean age in the CEM instead reflected the ANNEXA-4 mean age for whole cohort, ICH and GI, and ICH only groups, at [redacted], [redacted], and [redacted] years respectively. To adjust for this, mean survival using all-cause mortality for the general population was calculated for people aged 68.0 years and for each of the modelled ages. Following this, the risk ratio relating to these values was applied to the weighted mean survival for andexanet alfa and SoC described in step 1. This gave mean survival as shown in cells L167:M169 of 'Data Store' in the CEM.

3. **Goal seek** Goal seek was run to find the hazard ratio required to make the mean survival for ICH survivors equal to the mean ICH survival values in cells L167:M169 for their respective treatments and groups.

- For all iterations of this calculation, the cell which was changed was L151 of Data Store.
- To calculate the hazard ratios for the three groups of patients receiving andexanet alfa (whole cohort, ICH and GI, and ICH only), the 'set cell' was AR56 in Clinical Inputs. This was set alternately to L167, L168 and L169 to give values L174, L175 and L176. Likewise, BA56 was set to M167, M168 and M169 to give values M174, M175 and M176.
- For example, L151 was varied to a value which would set AR56 to [redacted] (cell L167), for the whole cohort patients who received andexanet alfa. The resulting hazard ratio was [redacted].

4. **Model calculations** The HR is then applied in the model to the per-cycle transitions to the death health state for ICH survivors. This occurs in the 'Clinical Inputs' sheet in cells F58:325 and P58:325, where the all-cause mortality probability of death each month is exponentiated to the inverse of the HR. The HRs applied are shown in cells F49:G49. The application of these HRs has been validated by ensuring that the mean survival (years) in cells AR56 and BA56 match the andexanet alfa- and SoC-specific mean survival values derived from the literature, shown in cells L167:M169 in 'Data Store' after the HR is applied in this way.

B9. Priority question. Given the availability of mRS-related data and the assumption of treatment effect on mRS scores, the ERG is unclear why the

company chose not to split the ICH health state into six health states for each level of mRS severity (0, 1, 2, 3, 4 and 5).

a) **To accurately combine the six levels of mRS severity into one health state, without relying on proportional hazards, please produce a weighted survival curve for each treatment arm. For example, the calculation for month 1 in the standard care arm would be: SUMPRODUCT(B11:G11,$J$28:$O$28) in worksheet 'Survival curves (mRS)'. Please use the per cycle transitions estimated from the weighted curves to inform the model. The ERG acknowledges that this approach does not account for differences in the starting age. As a solution, please consider applying the HR from the general population that compares survival at [redacted] years of age and 68 years of years to the mRS weighted survival curve.**

b) **Please provide a scenario using the overall survival curve for ICH in Figure 1 of Huybrechts *et al.* 2008 for both treatment arms. Please use the per cycle transitions estimated from the best fitting distribution to inform the model.**

Response

We can confirm that the primary reasons for not considering health states for ICH based on mRS score were:

1) To keep the model simple and easier to interpret;

2) Because the mRS data obtained were observed at the time of presentation with bleeding in ANNEXA-4, rather than observed during the pre-morbid period. Hence, these were not thought appropriate for use in the model;

3) To accommodate the absence of cost data split by mRS score in the literature, since any attempts to estimate these would have required more assumptions and uncertainty in the economic analysis.

Response to B9 (a)

We have provided the results of the scenario (Table 42) requested by the ERG, using survival curves sourced from Huybrechts *et al.* 2008 to provide per-cycle transitions in the model. In

the scenario, for every cycle, the survival probabilities taken from the parametric curve fitted to the mRS score-specific curve derived from Huybrechts *et al.* 2008 were weighted by the mRS distributions used in the base case for andexanet alfa and SoC. These provide a weighted survival probability for every cycle.

As suggested, a hazard ratio was found relating all-cause mortality mean survival at age 68.0 to mean survival with all-cause mortality risk for populations at the ages of the whole, ICH and GI and ICH only cohorts. The survival probabilities obtained as described above were then used in the model to inform the probability of death, with changes made to the 'Clinical inputs' sheet and 'Survival curves (mRS)' sheets.

Unsurprisingly the results are similar to the original submission base case, since mean overall survival is similar between the two methods. Andexanet alfa remains cost-effective compared to SoC across all three cohorts, with the ICER remaining below £20,000 for all scenarios conducted across all three populations.

Response B9 (b)

We have provided the results of the scenario (Table 43) requested by the ERG, using survival curves sourced from Huybrechts *et al.* 2008 to inform the hazard ratio. The goal seek method used to do this is described in the response to Question B8. When considering this alternative source for informing survival, the ICERs decrease and cost-effectiveness is improved compared to the original base case.

Incorporation into the revised base case

Given the desire not to rely on the assumption of proportional hazards, we have adopted the ERG's suggested methodology in B9 (a) as part of the revised base case.

Table 42. Results of a scenario in which mRS score-specific survival curves informed transition probabilities to death (original results)

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Results included in original submission – for whole cohort								
SoC	17,583	3.267	2.187	-	-	-	-	-
Andexanet alfa	37,365	4.563	3.230	19,782	1.296	1.043	18,968	18,968
mRS-weighted probabilities of mortality – for whole cohort								
SoC	17,583	3.267	2.187	-	-	-	-	-
Andexanet alfa	37,378	4.564	3.232	19,795	1.298	1.044	18,952	18,952
Results included in original submission – ICH and GI cohort								
SoC	16,958	2.741	1.824	-	-	-	-	-
Andexanet alfa	37,392	4.100	2.909	20,434	1.359	1.085	18,832	18,832
mRS-weighted probabilities of mortality – ICH and GI cohort								
SoC	16,958	2.741	1.824	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.913	20,469	1.364	1.089	18,799	18,799
Results included in original submission – ICH only cohort								
SoC	19,069	1.620	0.953	-	-	-	-	-
Andexanet alfa	41,122	3.058	2.121	22,053	1.438	1.169	18,871	18,871

mRS-weighted probabilities of mortality – ICH only cohort								
SoC	19,069	1.620	0.953	-	-	-	-	-
Andexanet alfa	41,199	3.068	2.130	22,130	1.449	1.177	18,807	18,807

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; MRs, Modified Rankin score
Note: the switch to apply this scenario from the original base case is in cell I5 of sheet 'Survival curves (mRS)'

Table 43. Scenario showing using the overall survival curve for ICH in Figure 1 of Huybrechts et al. 2008 for both treatment (revised results)

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Results for revised base case – for whole cohort								
SoC	48,108	3.242	2.173	-	-	-	-	-
Andexanet alfa	60,430	4.564	3.232	12,322	1.322	1.059	11,636	11,636
Using the overall survival curve for ICH in Figure 1 of Huybrechts et al. 2008 for both treatment arms – for whole cohort								
SoC	53,121	3.811	2.520	-	-	-	-	-
Andexanet alfa	65,421	5.259	3.731	12,300	1.448	1.212	10,150	10,150
Results for revised base case – ICH and GI cohort								
SoC	16,736	2.715	1.809	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.913	20,691	1.390	1.104	18,741	18,741
Using the overall survival curve for ICH in Figure 1 of Huybrechts et al. 2008 for both treatment arms – ICH and GI cohort								
SoC	22,041	3.317	2.175	-	-	-	-	-
Andexanet alfa	42,672	4.834	3.438	20,631	1.517	1.262	16,345	16,345
Results for revised base case – ICH only cohort								
SoC	18,780	1.586	0.933	-	-	-	-	-
Andexanet alfa	41,199	3.068	2.130	22,419	1.482	1.196	18,738	18,738
Using the overall survival curve for ICH in Figure 1 of Huybrechts et al. 2008 for both treatment arms – ICH only cohort								
SoC	25,719	2.373	1.413	-	-	-	-	-

Andexanet alfa	48,038	4.019	2.814	22,319	1.646	1.401	15,930	15,930

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; MRs, Modified Rankin score
Note: the switch to apply this scenario from the revised base case is in cell F46 of sheet 'Clinical Inputs'

B10. Priority question. Please clarify why survivors of non-ICH bleeds have a mortality ratio (1.3) associated with paroxysmal AF and a 0-1 CHADS2 score

a) **Please provide a scenario using a mortality ratio in Friberg *et al.* 2007 that aligns with the CHADS2 score (4.5) and types of AF (paroxysmal, persistent and permanent) included in ANNEXA-4.**

Response

We would like to clarify that the standardised mortality ratio (SMR) for survivors of non-ICH bleeds was chosen from Friberg *et al.* 2007 for a population receiving warfarin and having any type of atrial fibrillation (paroxysmal, persistent or permanent), shown in Table 5 of Friberg *et al.* 2007.[7] It was not the SMR associated with paroxysmal AF and a 0-1 CHADS2 score as suggested by the ERG, although we note both groups have the same SMR, and can understand how this confusion has come about.

The rationale for choosing the SMR based on the subgroup of patients receiving warfarin was because the patients included in the calculation of this SMR were as similar as possible to the modelled patients with a severe GI or other major bleed, since they were anticoagulated and had a range of types of atrial fibrillation; both of which are significant predictors for mortality.

Table 44 presents the results for the requested scenario analysis for the whole cohort and the 'ICH and GI' cohort. Please note that the ICH only cohort has not been presented as this change impacts non-ICH survivors only. The SMR of 2.7 was sourced from Table 2 of Friberg *et al.* 2007 and reflects the SMR for a population with any type of atrial fibrillation.

The results indicate that for both the whole cohort and the 'ICH and GI' cohort, andexanet alfa remains cost-effective with both ICERs remaining below £20,200 per QALY gained, and the ICER for the whole cohort remaining below £20,000 per QALY gained.

Table 44. Scenario showing the effect of using the SMR proposed by the ERG, sourced from Friberg Table 2 (revised results)

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Results for revised base case – for whole cohort								
SoC	48,108	3.242	2.173	-	-	-	-	-
Andexanet alfa	60,430	4.564	3.232	12,322	1.322	1.059	11,636	11,636
SMR from Friberg et al. 2007 Table 2 for CHADS2 score of 4-6 and all types of AF – for whole cohort								
SoC	37,710	2.593	1.708	-	-	-	-	-
Andexanet alfa	52,470	3.836	2.707	14,760	1.243	0.999	14,773	14,773
Results for revised base case – ICH and GI cohort								
SoC	16,736	2.715	1.809	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.913	20,691	1.390	1.104	18,741	18,741
SMR from Friberg et al. 2007 Table 2 for CHADS2 score of 4-6 and all types of AF – ICH and GI cohort								
SoC	16,417	2.239	1.461	-	-	-	-	-
Andexanet alfa	37,053	3.547	2.505	20,636	1.308	1.045	19,753	19,753

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; SMR, standardised mortality ratio
Note: the switch to apply this scenario from the revised base case is in cell J51 of sheet 'Clinical Inputs'

Health-related quality of life (HRQoL)

B11. Priority question. The utility value for acute care of patients in the standard care arm (0.61) was derived from a paper by Pickford *et al.* 2004 which measure HRQoL in a cohort of 124 patients (mean age 68 years) hospitalised after ischemic stroke with 6 month follow up. The utility value of 0.61 is for the 3 month follow up assessment. However, a one-month utility value of 0.55 is also presented.

a) **Please justify why the 3-month utility value was considered appropriate to use for the post one-month Markov model.**

b) **Please provide a scenario where the utility value of 0.55 is used instead of 0.61 (company base case).**

Response

An acute utility value of 0.33 was sourced for ICH patients from NICE TA341 2015. This utility was applied in the original cost-effectiveness model for 3 months, in keeping with how the utility was applied in TA341. Post 3-months, the 3 month utility from Pickford et al. 2004[9] was used (0.61). We appreciate it may also be a plausible scenario to apply the post 1-month value from Pickford *et al.* 2004[9] to month 2 of the model. Results are similar to the revised base case analysis (see Table 45).

Table 45. Scenario showing results using Pickford *et al.* 2004 utility of 0.55 as baseline utility for ICH survivors in month 2 (revised results)

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Results for revised base case – for whole cohort								
SoC	48,108	3.242	2.173	-	-	-	-	-
Andexanet alfa	60,430	4.564	3.232	12,322	1.322	1.059	11,636	11,636
Using utility of 0.55 as baseline long term ICH survivor utility – for whole cohort								
SoC	48,108	3.242	2.179	-	-	-	-	-
Andexanet alfa	60,430	4.564	3.241	12,322	1.322	1.063	11,593	11,593
Results for revised base case – ICH and GI cohort								
SoC	16,736	2.715	1.809	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.913	20,691	1.390	1.104	18,741	18,741
Using utility of 0.55 as baseline long term ICH survivor utility – ICH and GI cohort								
SoC	16,736	2.715	1.815	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.923	20,691	1.390	1.108	18,667	18,667
Results included in updated base case – ICH only cohort								
SoC	18,780	1.586	0.933	-	-	-	-	-
Andexanet alfa	41,199	3.068	2.130	22,419	1.482	1.196	18,738	18,738
Using utility of 0.55 as baseline long term ICH survivor utility – ICH only cohort								
SoC	18,780	1.586	0.942	-	-	-	-	-

Andexanet alfa	41,199	3.068	2.144	22,419	1.482	1.203	18,643	18,643

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio
Note: the switch to apply this scenario from the revised base case is in cell E33 of sheet 'Quality Of Life Inputs'

B12. Priority question. Please explain the rationale for not directly using the utility values in Table 55 to estimate QALYs for the ICH survivor health state for andexanet alfa and standard care?

a) **Please perform a scenario where the utility values in Table 55 are used to estimate QALYs for the ICH survivor health state for andexanet alfa and standard care.**

Response

The utility values used for ICH survivors in the model receiving SoC were sourced from the NICE appraisal 'Apixaban for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism´.[8] Given that this was accepted by NICE, it was assumed to be an appropriate utility value for patients receiving SoC after a major bleed in a United Kingdom (UK) population. To determine a utility value for andexanet alfa, the absolute difference between SoC and andexanet alfa utilities was calculated by weighting mRS score-specific EQ-5D scores from Fletcher et al. 2015[8] using the distribution of patients between mRS scores provided in Øie et al. 2018.

Although utilities may be calculated using Øie et al. 2018, this study was conducted in Norway.[4] Therefore, we believed that the values calculated directly by weighting EQ-5D scores by the mRS distribution from Øie et al. 2018 would not be a true representation of utilities appropriate for patients in a UK population. Hence, the absolute difference in utility between SoC and andexanet alfa calculated from Øie et al. 2018, was applied to the utility accepted in NICE TA341 for use in the post-acute period among UK patients receiving SoC.

The results of a scenario using utility values of 0.42 for SoC and 0.53 for andexanet alfa are presented in Table 46. The results indicate that the ICERs remain below £30,000 across all scenarios modelled.

Table 46. Scenario showing the effect of using mRS-adjusted utilities (revised results)

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Results for revised base case – for whole cohort								
SoC	48,108	3.242	2.173	-	-	-	-	-
Andexanet alfa	60,430	4.564	3.232	12,322	1.322	1.059	11,636	11,636
mRS-adjusted utilities – for whole cohort								
SoC	48,108	3.242	1.970	-	-	-	-	-
Andexanet alfa	60,430	4.564	2.837	12,322	1.322	0.867	14,209	14,209
Results for revised base case – ICH and GI cohort								
SoC	16,736	2.715	1.809	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.913	20,691	1.390	1.104	18,741	18,741
mRS-adjusted utilities – ICH and GI cohort								
SoC	16,736	2.715	1.595	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.496	20,691	1.390	0.901	22,963	22,963
Results for revised base case – ICH cohort								
SoC	18,780	1.586	0.933	-	-	-	-	-
Andexanet alfa	41,199	3.068	2.130	22,419	1.482	1.196	18,738	18,738
mRS-adjusted utilities – ICH cohort								
SoC	18,780	1.586	0.656	-	-	-	-	-

Andexanet alfa	41,199	3.068	1.588	22,419	1.482	0.932	24,053	24,053

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; MRs, Modified Rankin score
Note: the switch to apply this scenario from the revised base case is in cell E31 of sheet 'Quality Of Life Inputs'

Resource use and costs

B13. Priority question. In the original model and submission, the company included the cost of excess hospital bed days in the acute bleed management cost calculations. Furthermore in the resubmitted model (September 2019) worksheet 'Change log', the company states that the average length of stay is longer for andexanet alfa compared to standard care from the ORANGE study.

a) **Please explain the rationale for why costs for excess hospital bed days were removed from the revised economic model.**

b) **Using the mean unadjusted durations, please provide a scenario where the costs for excess bed days are included in the acute bleed management costs, ensuring that the ANNEXA-4 data is not capped to 30 days, as stated in the worksheet 'Change log'.**

c) **Using the results from propensity score matching (provided in clarification question A4), please provide a scenario where the costs for excess bed days are included in the acute bleed management costs, ensuring that the ANNEXA-4 data is not capped to 30 days, as stated in the worksheet 'Change log'.**

Response[10]

As discussed in the response to Question A4, there are two key reasons why length of stay was not considered comparable for inclusion in the economic model.

Firstly, the length of stay outcome in the ORANGE study is likely to have been inherently underestimated as some proportion of the [redacted] patients who had a length of stay of at least 30 days likely had their length of stay capped to 30 days. As such, any comparison of mean length of stay would be biased in favour of SOC. Propensity score matching analysis capping ANNEXA-4 at 30 days provided identical results to those obtained without capping ANNEXA-4, as the ANNEXA-4 patients with length of stay over 30 days did not receive rivaroxaban or apixaban. However, the potential capping of length of stay for [redacted] patients in ORANGE limits the interpretation of any comparison, and its relevance for evaluating differences in an economic model.

Secondly, the ORANGE study was conducted in the UK, whereas numerous sites at which patients were observed in the ANNEXA-4 study were in North America. Due to fundamental differences in the structures of, and treatment pathways within, the health systems in these countries, we believed that the length of stay in hospital was non-comparable between the two studies. We recognise that the ERG seeks to better understand the impact of varying hospital length of stay between the andexanet alfa and SoC patients, but would argue that given fundamental differences in the study settings, even propensity score matching cannot adequately adjust for country-specific differences in hospital resource use.

Secondly, we wish to highlight that the cost of hospital bed days is already included in the average NHS Reference Costs 2017/18 tariffs applied to patients in the acute period. We understand that trimpoints are the bounds between excess and 'inlier' bed days, where inlier bed day costs are included for reimbursement under the NHS reference costs 2017/18 code and excess bed days are not.[11] Trimpoints can apply to a spell or an episode, with a spell being the period from hospital admission to hospital discharge, possibly encompassing many episodes of treatment. We believed that a spell timeframe was likely more applicable to many patients in the CEM as many patients would have remained hospitalised for rehabilitation in addition to hospitalisation during the acute period. In the absence of more information to provide certainty on this issue, both timeframes were considered in this exploration.

Within the base-case, weighted average costs are applied from codes AA23C – G, FD03A – B and FE02B – C for ICH, severe GI and other major bleeds respectively, within the decision-tree. The costs were weighted by the proportion of all finished consultant episodes (FCEs) attributed to that cost category, which were incurred by patients of that bleed type. When exploring the possibility of the inclusion of length of stay the model, the same approach was used to weight the trimpoints for both spell and episode timeframes identified for each code from NHS Digital.[11] Regardless of whether the spell or episode trimpoint is used for the ICH or GI cohorts, which constitute the majority of patients in the CEM, the weighted average trimpoint exceeds both:

- The length of stay estimated using propensity score matching in Question A4;
- The length of stay presented in Table 23 of the submission for ANNEXA-4 and in Table 17 for ORANGE.

For survivors of other major bleeds in the model, the weighted episode trimpoint is exceeded by the figures from both sources above, for both treatment arms. However, the naïve

comparison of the length of stay from the sources above only differed by 0.3 days so was expected to have a near-negligible impact on the ICER.

Moreover, as the propensity score matching was deemed inappropriate for 30-day mortality for the other major bleeds group, we would discourage the use of the length of stay output from propensity score matching for the other major bleed group for the same reasons. For both 30-day mortality and length of stay analyses, only eight members of the control group were matched to patients from the treated group. Details of our reservations regarding the use of this cohort's results from propensity score matching were provided in Section B2.9.2 of the submission.

For these reasons, we feel that the inclusion of length of stay in the model is not appropriate. Therefore, a scenario in which length of stay is included in the model has not been conducted.

Table 47. Trimpoints and length of stay by bleed type and NHS Reference Cost 2017/18 code used

Bleed type with which acute care cost is associated	NHS Reference Cost 2017/18 code used	Proportion of patients in category with this code (%)	Trimpoint for spell of care	Trimpoint for episode of care	Weighted average trimpoint for spell of care	Weighted average trimpoint for episode of care	Propensity score matching LOS (estimated in Question A4) andexanet alfa (days)	Propensity score matching LOS (estimated in Question A4) SoC (days)	Length of stay from Table 23 of submission – andexanet alfa	Length of stay from Table 17 – SoC
ICH survivor	AA23C	16.44	199	52	67.96	22.79	[redacted]	[redacted]	[redacted]	[redacted]
	AA23D	20.71	80	29						
	AA23E	29.03	44	16						
	AA23F	20.45	19	11						
	AA23G	13.36	15	10						
Severe GI bleed	FD03A	52.56	33	41	24.93	27.24	[redacted]	[redacted]	[redacted]	[redacted]
	FD03B	47.44	16	12						
Other major bleed	FE02B	57.89	29	6	18.47	5.16	[redacted]	[redacted]	[redacted]	[redacted]
	FE02C	42.11	4	4						

Abbreviations: NHS – National Health Service; LOS – length of stay.

B14. Priority question. The ERG considers the calculation of long-term costs for intraspinal survivors to invalid as it unnecessarily averages the lifetime costs of paralysis using mean life expectancy, which is then applied per model cycle and also incorporates transitions to death (thus double-counting mortality) and does not reflect the high first year cost presented in the submission. As a result of the use of an average cost, discounting is not captured appropriately. Therefore, please provide a scenario where:

a) **The first 12 model cycles reflect the estimated monthly cost of care for patients with paralysis presented in Table 67; and**

b) **The remainder of the model cycles reflect the 60-day cost of care in a spinal cord injury unit, adjusted to reflect a 30-day model cycle (£495).**

Response

We have provided the results of the scenario requested with the adjustments described in Question B14.a & b. In addition, the ERG has provided further information since sending these questions, stating that the company misinterpreted the 60-day cost of care in the Spinal UK 2015 source. Consequently, a cost of £968 per day, or £58,080 per 60 days, has been applied in the new base case and in this scenario, as a correction to the previous interpretation.[3] The results of these amends are presented in Table *48*. The results indicate that the ICER for the Whole Population falls, given that andexanet alfa is assumed to reduce the proportion of patients paralysed – while paralysis is now is associated with a much larger cost.

We made one additional change after re-examining the survival costs, to apply an inflated first year cost of paralysis based on the cost to the public shown in Table 67 of Document B in the latest submission divided by the number of patients to whom the cost applied (those between 76 and 85 years of age). This change has also been included in this scenario, as it is a more appropriate way of applying the first year cost.

Incorporation into the revised base case

Given this reflects a more appropriate way for capturing intraspinal bleed costs, this has been incorporated into the revised base case.

Table 48. Scenario showing the effect of modifying intraspinal costs (original results)

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Results included in original submission – for whole cohort								
SoC	17,583	3.267	2.187	-			-	- -
Andexanet alfa	37,365	4.563	3.230	19,782	1.296	1.043	18,968	18,968
Adjusted intraspinal costs – for whole cohort								
SoC	48,237	3.267	2.187	-	-	-	-	-
Andexanet alfa	60,356	4.563	3.230	12,119	1.296	1.043	11,620	11,600

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio
Note: the switches to apply this scenario from the original base case are in: cell F44 of sheet 'Cost Inputs' and celsl L140:L141 of sheet 'Data Store'

B15. Please clarify why the requirement for blood products was not costed in the economic model. Please provide a scenario including the appropriate costs.

Response

We did not have access to data on the volume of blood products used in ANNEXA-4, and hence could not conduct any comparison of the quantities of blood products used for patients receiving SoC or andexanet alfa.

Expert opinion from a UK clinical expert in haematology was sought to understand any expected differences in the use of blood products between patients in the two treatment arms of the model. It was concluded that if any difference existed between treatment arms, blood product use would likely be higher for patients receiving SoC. The clinical expert stated that clinicians would replace any blood lost by patients receiving any treatment, but that reversal of anticoagulation achieved with andexanet alfa would be expected to reduce blood loss in patients who received it. Hence, patients receiving andexanet alfa would require a relatively lower quantity of blood products to replace blood lost.

For this reason, the omission of blood products from the model was thought to be a conservative assumption, in the absence of adequate data to provide any comparison between treatment arms.

B16. Please provide a scenario using the mean dose of 4F-PCC from the ORANGE study to cost standard care treatment.

a) If the mean dose of 4F-PCC is not available please calculate the cost of using 4F-PCC based on mean pre-treatment INR as recommended in the SmPC guidance for octaplex and beriplex.

b) If the requested information from ORANGE is not available, please justify the rationale for using mean doses from Arachchillage *et al.* 2019, which represents doses at the lower end of the range.

Response

Part a

The mean dose of 4F-PCC was not available from the ORANGE study patient level data received; we are seeking to obtain this data from the investigators in the ORANGE study. As requested by the ERG, the company has used the Electronic Medicines Consortium Summary

of Product Characteristics (SmPC) as an alternative source from which to derive mean dose of 4F-PCC for patients receiving this treatment in the SoC arm of the CEM.[12,13]

Among the participants in the ORANGE study who were included in the propensity score matching analysis, [redacted]% and [redacted]% received Beriplex and Octaplex, respectively. Among those who received Beriplex, the first observed mean International Normalised Ratio (INR) was [redacted], at the time of bleeding. This is lower than any of the pre-treatment INR values shown in the table in the Posology section of the SmPC for Beriplex. Though no dose was recommended at an INR of this level, it was evident in the ORANGE patient level data that patients with such an INR were still treated with Beriplex. Hence, the [redacted] approximate dose per kilogram of body weight from this table has been chosen as the nearest to this INR ([redacted]).[12] This was a conservative assumption as it attributed the lowest cost to the treatment for patients receiving SoC.

Among those who received Octaplex, the first observed mean INR was [redacted], at the time of bleeding. This falls into the [redacted] shown in the table in the Posology section of the SmPC, and hence corresponds to an approximate dose of [redacted] mL of Octaplex per kilogram of body weight.[13] The footnote to the table providing approximate dose according to initial INR for Octaplex stated that [redacted] of Octaplex. Hence, the IU per kilogram range associated with an INR [redacted] was assumed to be [redacted]. In the interests of time, a conservative assumption was made that the lower of these approximate doses applied to patients in the model.

Wastage was assumed, in accordance with the company base case. The costs applied were sourced from the Monthly Index of Medical Specialties (MIMS) to match the costs originally applied to Octaplex only in the model.[14,15] The cost with wastage for each drug was calculated using the MIMS vial sizes and costs, and an average of these was used in the model, weighted by the proportion from the ORANGE study receiving each of these treatments.

Results are presented in Table 49, showing a slight decrease in the ICER on account of the slightly elevated cost of 4F-PCC in the scenario. This is thought to be a conservative estimate of the decrease in the ICER, since the lowest doses of Octaplex and Beriplex were used.

Part b

We identified Arachchillage *et al*. 2019 as a potential source of dose information for patients receiving SoC at the time of the first submission, in the absence of patient level data providing any dosing information from ORANGE. At the time of the resubmission, we reconsidered the

use of Arachchillage *et al.* 2019 and felt that given the [redacted] observed for patients receiving 4F-PCC in ORANGE, the relatively low dose remained appropriate. No patient level data was obtained from ORANGE to use in place of this, so we continued to use Arachchillage *et al.* 2019.

Table 49. Scenario showing the effect of using SmPC-derived doses for 4F-PCC (revised results)

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Results for revised base case – for whole cohort								
SoC	48,108	3.242	2.173	-	-	-	-	-
Andexanet alfa	60,430	4.564	3.232	12,322	1.322	1.059	11,636	11,636
SmPC 4F-PCC dose – for whole cohort								
SoC	48,217	3.242	2.173	-	-	-	-	-
Andexanet alfa	60,430	4.564	3.232	12,213	1.322	1.059	11,534	11,534
Results for revised base case – ICH and GI cohort								
SoC	16,736	2.715	1.809	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.913	20,691	1.390	1.104	18,741	18,741
SmPC 4F-PCC dose – ICH and GI cohort								
SoC	16,845	2.715	1.809	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.913	20,582	1.390	1.104	18,642	18,642
Results for revised base case – ICH cohort								
SoC	18,780	1.586	0.933	-	-	-	-	-
Andexanet alfa	41,199	3.068	2.130	22,419	1.482	1.196	18,738	18,738
SmPC 4F-PCC dose – ICH cohort								
SoC	18,889	1.586	0.933	-	-	-	-	-

Andexanet alfa	41,199	3.068	2.130	22,310	1.482	1.196	18,647	18,647

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; SmPC – summary of product characteristics; PCC – prothrombin complex concentrate
Note: the switch to apply this scenario from the revised base case is in cell C44 of sheet 'Cost Inputs'

Section C: Textual clarification and additional points

C1. Priority question. Please comment on the worksheet ‘Change log’ in the economic model

Response

The worksheet ‘Change log’ has no relevance to the final submission, this worksheet was intended for internal quality checking purposes prior to submission and was left in the model submitted in error.

C2. Priority question. Please include and vary 30-day mortality rates in one-way sensitivity analysis and probabilistic sensitivity analysis. Please ensure the 30-day mortality rates are added and called from the tab ‘Model parameters’ and not within the calculations made in the decision tree worksheets cells (‘Decision Tree Andexanet alfa’ and ‘Decision Tree SoC’)

Response

We acknowledge the ERG’s question and can confirm that rows 68-79 in tab ‘Model parameters’ have been added to include the updated base case 30-day mortality rates for all bleed types in the one-way sensitivity analysis. The probabilistic sensitivity analysis already includes the 30-day mortality rates, in column T of each ‘Decision Tree SoC’ and ‘Decision Tree Andexanet alfa’.

C3. As indicated in the company submission on page 70, please can the company confirm that no attempt was made to adjust for unobserved confounders, e.g. using an instrumental variable, despite this being advocated in NICE DSU TSD 17.

Response

Portola can confirm that no attempt was made to adjust for unobserved confounders. We assumed when the clinical trials used were designed that investigators would have observed all variables of importance as determinants of key outcomes, including 30-day mortality. Therefore, it was assumed that there were no unobserved cofounders.

C4. Please validate the generalised gamma curves produced for mRS scores 0, 1, 2 and 3 (Figures 16, 17, 18 and 19 of the CS in Document B). Please make corrections if necessary**.**

Response

We have checked the current function in the model for the Generalised Gamma and believe that it is correct. We believe that the appearance of Figures 16,17,18 and 19 is due to non-convergence, which indicates that the data is too limited to support estimation of the three parameters required to define generalised gamma curves; mu, sigma and Q.

C5. Please confirm if the life-years reported in the Excel model tab "Results" are undiscounted. If not, please provide the undiscounted life-years.

Response

The value of life-years provided in the Excel model tab 'Results' have been discounted. The undiscounted total life-years are provided in Table 50.

Table 50. Undiscounted life years for original submission and updated base cases

Cohort	Total undiscounted LYs			
	Original submission base case		Updated base case	
	Andexanet alfa	SoC	Andexanet alfa	SoC
Whole cohort	5.34	3.85	5.41	3.82
ICH and GI	4.73	3.18	4.81	3.15
ICH	3.39	1.78	3.49	1.74
Abbreviations GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life-years				

C6. The ERG has identified a discrepancy between the proportion of bleeds used in the decision tree (tabs 'Decision Tree Andexanet alfa' and 'Decision Tree SoC', cells H15:51) and the values in Table 46 of the CS in Document B, please clarify if the calculations and values in the model are correct and amend Table 46 of the CS where necessary.

Response

Table 46 of the CS document B provides calculations used to calculate the proportion of patients with each type of other major bleed from the two studies. In the CEM, we used a population of 1,000 rather than the true population provided in each study. To determine the number of individuals for each bleed type in the CEM, the proportions described in Section

B.3.3.2 of the resubmission were applied to a population of 1000. This is reflected in the agreement between the percentages in Table 46 of the CS document B and the proportions used in the decision tree (tabs 'Decision Tree Andexanet alfa' and 'Decision Tree SoC', cells H15:51).

C7. The ERG has identified a discrepancy between the monthly cost of paralysis used in the model (£709.48) [tab 'Data Store' cell L138] and the value in the CS, page 117 of Document B(£740.91). Please clarify which value is correct and make amendments where necessary.

Response

Please see our response to Question B14 and the updated model; the discrepancy has since been resolved.

C8. The ERG has identified a discrepancy between the number, proportion and total of pericardial bleeds for standard care used in the model (tab 'Clinical Inputs' cells I19:I20 and J19) and the values in Table 51 of the CS in Document B. Please clarify which values are correct and make amendments where necessary.

Response

We acknowledge the ERG's question and we can confirm that the values in the model are correct. Therefore, Table 51 of the CS in Document B should be amended to read:

	ICH Survivor	Intraspinal Bleed Survivor	Intraocular Bleed Survivor	Retroperitoneal Bleed Survivor	Severe GI Bleed Survivor	Pericardial Bleed Survivor	Total
Andexanet alfa							
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SoC							
Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care							

C9. Of the 145 patients from ORANGE included in the economic analysis, please report how many received PCC alone, or in combination with tranexamic acid.

Response

All 145 patients from ORANGE included in the economic analysis were either taking PCC alone, or in combination with tranexamic acid. Of the 145 patients, 53 patients were taking PCC in combination with tranexamic acid.

C10. Please clarify the study design for the exclusion of the 6 studies excluded based on 'study type' from Review Question 1 in Appendix D, and for any that are randomised controlled trials, non-randomised studies, observational studies (including patient registries) or retrospective analyses please explain why they were excluded when these study designs are listed as part of the inclusion criteria for Review Question 1.

Response

Table 51. References excluded at the full text review stage from the original review of studies of individuals receiving a Factor Xa inhibitor requiring rapid reversal of anticoagulation (n=24)

Bouget et al, 2015	Bouget J, Oger E, Nicolas N. Emergency admissions for major haemorrhage associated with antithrombotics: A cohort study. Thrombosis research. 2015 Jan 1;135(1):84-9	The reason for exclusion of this study should have been population. Only 2 patients were treated with a NOAC (both dabigatran) No patients treated with LMWH (relevant to original review) received reversal therapy.
Pahs et al, 2015	Pahs L, Beavers C, Schuler P. The real-world treatment of hemorrhages associated with dabigatran and rivaroxaban: a multicenter evaluation. Critical pathways in cardiology. 2015 Jun 1;14(2):53-61	Fewer than 10 patients in the population of interest, presented as a case series
Ingerslev et al, 2007	Ingerslev J, Vanek T, Culic S. Use of recombinant factor VIIa for emergency reversal of anticoagulation. Journal of postgraduate medicine. 2007 Jan 1;53(1):17-22	Fewer than 10 patients in the population of interest.
Dibu et al, 2015	Dibu JR, Weimer JM, Dexter K, Ahrens C, Manno E, Frontera JA. Role of feiba in reversing novel oral anticoagulants in intracerebral hemorrhage. Neurocritical care. 2015;23(1):S76	Fewer than 10 patients in the population of interest (presented in full paper Dibu et al, 2016)
Dibu et al, 2016	Dibu JR, Weimer JM, Ahrens C, Manno E, Frontera JA. The role of FEIBA in reversing novel oral anticoagulants in intracerebral hemorrhage. Neurocritical care. 2016 Jun 1;24(3):413-9	Fewer than 10 patients in the population of interest, presented as a case series
Stevens et al, 2015	Stevens CA, Dell'Orfano H, Reardon DP, Matta L, Greenwood B, Atay J. Retrospective analysis of management of bleeding complications in patients taking target specific oral anticoagulants at a large tertiary academic medical center. Journal of the American College of Cardiology. 2015;65(10):A439	Fewer than 10 patients in the population of interest. In addition, reversal treatment unclear and outcomes not presented separately.

Table 52. References excluded at the full text review stage from the update review of studies of individuals receiving Factor Xa inhibitor requiring rapid reversal of anticoagulation (n=44)

Helin et al, 2018	Helin TA, Zuurveld M, Manninen M, Meijers JC, Lassila R, Brinkman HJ. Hemostatic profile under fluid resuscitation during rivaroxaban anticoagulation: an in vitro survey. Transfusion. 2018 Dec;58(12):3014-26	Study type	In vitro study
Kaur et al, 2017	Kaur H, Yeang SH, See E, Grant D, Tan CW, Wong WH, Tan D, Ng HJ, Lee LH. Reversal of rivaroxaban using Prothromplex Total, a 4-factor prothrombin complex. Research and Practice in Thrombosis and Haemostasis. 2017;1:940-941	Study type	Case series – 8 patients

C11. On page 152 of the CS it states, "*Clinical trial data underpinning the decision tree section of the model was taken from the propensity score matching where possible and methods and results were validated by Kate Ren, a lead evidence reviewer in relation to these topics for Sheffield University's Evidence Review Group (ERG) – ScHARR.*" Please provide further details on the communication between the company and Kate Ren regarding the validation, including any checklists or questions that were asked. Also clarify if Kate Ren reviewed and approved the results of the propensity score matching as they appear in the submission and how they are used in the submitted economic model.

Response

[redacted]

[redacted]

C12. Please provide the full text papers for the following references, which are missing from the reference pack:

a) Allison T, Hartman H, Gass J, et al. Low-dose four-factor prothrombin complex concentrate in reversal of XA inhibitors in a neuro-ICU. Crit. Care Med. 2016;44(12):275.

b) Allison TA, Lin PJ, Gass JA, et al. Evaluation of the Use of Low-Dose 4-Factor Prothrombin Complex Concentrate in the Reversal of Direct Oral Anticoagulants in Bleeding Patients. Journal of Intensive Care Medicine. 2018:[Epub ahead of print].

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Response

These references have been provided in the reference pack.

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Appendices

Table 53. Frequency of patients matched from ORANGE for all cohorts matched in propensity score matching

Number of matches	Frequency of individuals matched in whole cohort	Frequency of individuals matched in ICH cohort	Frequency of individuals matched in GI cohort	Frequency of individuals matched in other bleeds cohort
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]	[redacted]
7	[redacted]	[redacted]	[redacted]	[redacted]
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10+	[redacted]	[redacted]	[redacted]	[redacted]

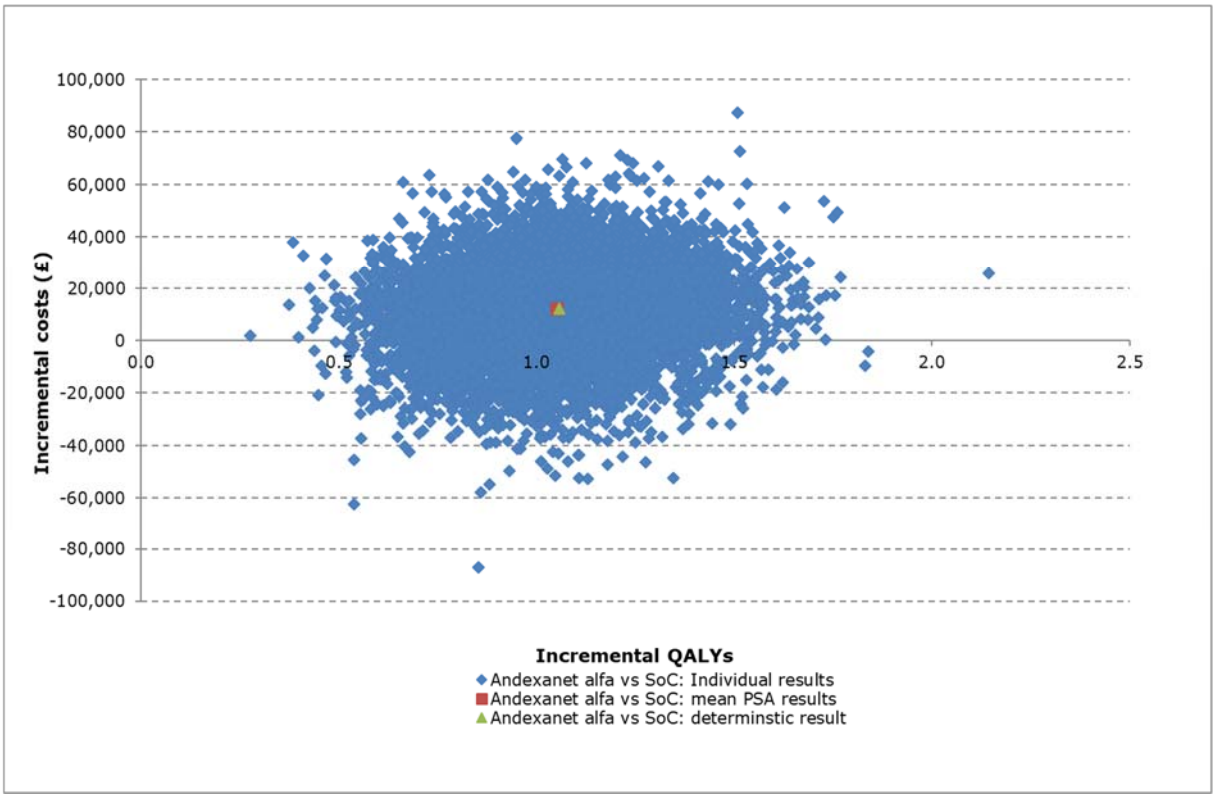
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage

Table 54. PSA results for Whole cohort

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
SoC	48,169	2.179	-	-	-
Andexanet alfa	60,437	3.232	12,268	1.0528	11,653

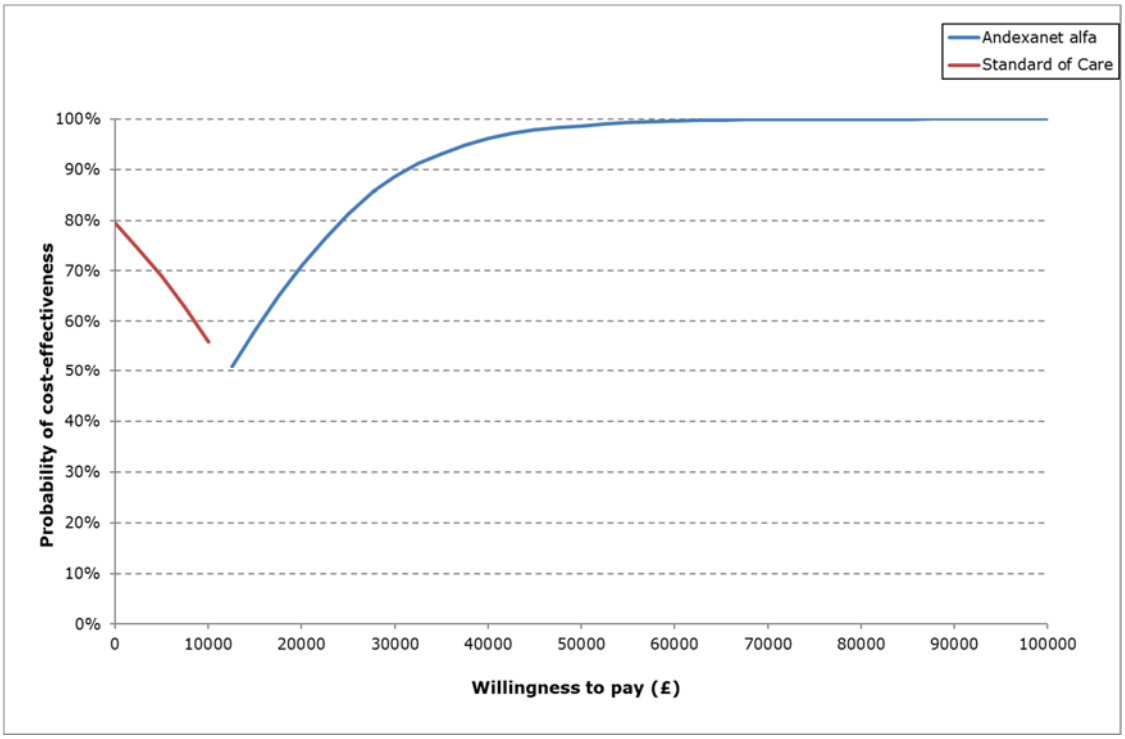
Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SoC, standard of care

Figure 1. ICEP for whole cohort



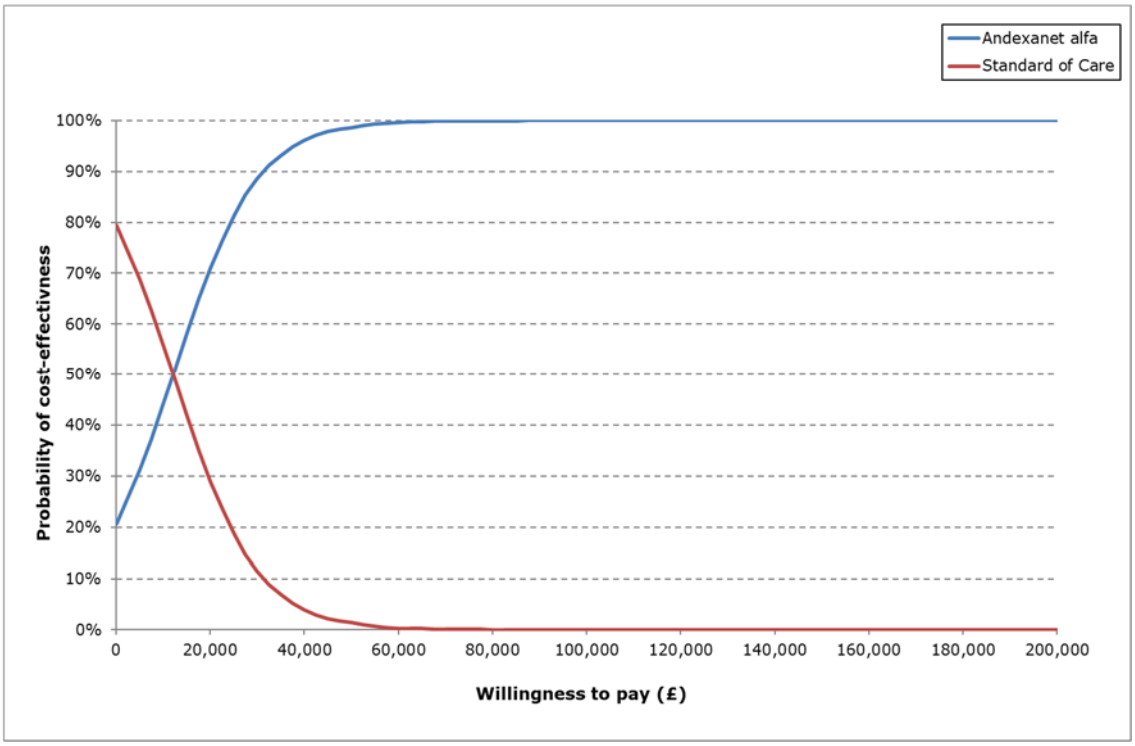
Abbreviations: ICEP, incremental cost-effectiveness plane; PSA, probabilistic sensitivity analysis; SoC, standard of care

Figure 2. CEAF for whole cohort



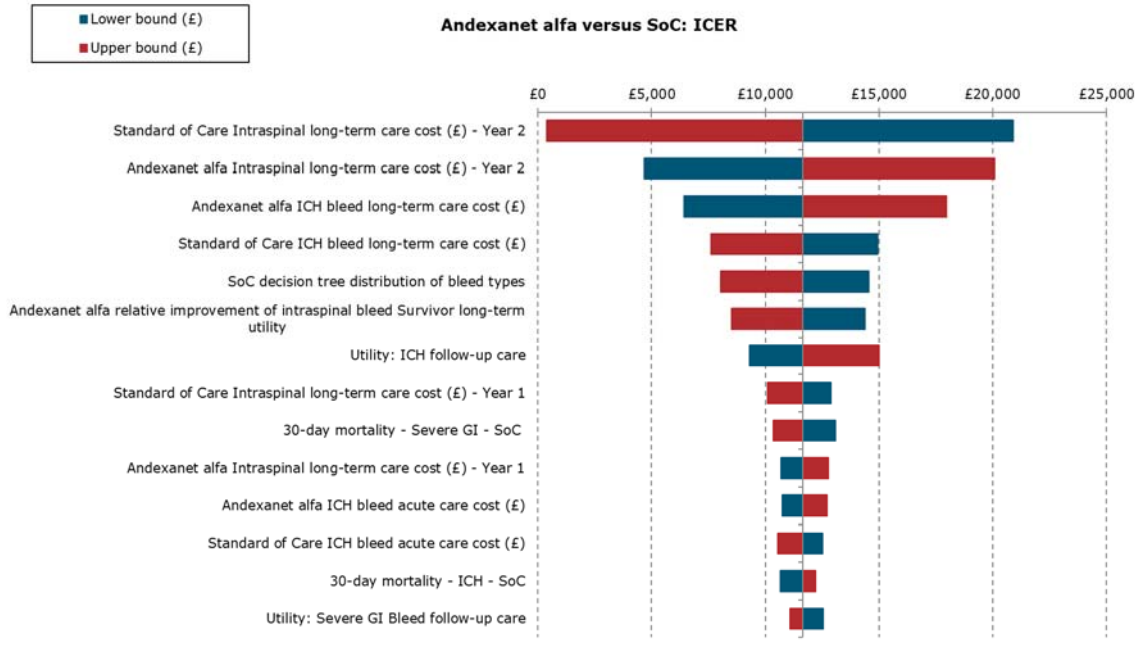
Abbreviations: CEAF, Cost-effectiveness acceptability frontier

Figure 3. CEAC for whole cohort



Abbreviations: CEAC, Cost-effectiveness acceptability curve

Figure 4. Tornado Diagram of andexanet alfa versus SoC (ICER) for the Whole cohort



Abbreviations: ICER, incremental cost-effectiveness ratio; GI, gastrointestinal; ICH, intracranial haemorrhage; HR, hazard ratio; SoC, standard of care

Table 55. OWSA results of andexanet alfa versus SoC for the Whole cohort (top 20 parameters)

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Standard of Care Intraspinal long-term care cost (£) - Year 2	£20,909.23	£377.77	£20,531.46
Andexanet alfa Intraspinal long-term care cost (£) - Year 2	£4,672.82	£20,090.64	£15,417.82
Andexanet alfa ICH bleed long-term care cost (£)	£6,422.81	£17,965.95	£11,543.14
Standard of Care ICH bleed long-term care cost (£)	£14,943.71	£7,620.59	£7,323.12
SoC decision tree distribution of bleed types	£14,546.91	£8,044.64	£6,502.27
Andexanet alfa relative improvement of intraspinal bleed Survivor long-term utility	£14,382.16	£8,521.35	£5,860.81
Utility: ICH follow-up care	£9,292.61	£14,996.32	£5,703.71
Standard of Care Intraspinal long-term care cost (£) - Year 1	£12,895.22	£10,107.70	£2,787.52
30-day mortality - Severe GI - SoC	£13,079.92	£10,358.21	£2,721.71
Andexanet alfa Intraspinal long-term care cost (£) - Year 1	£10,690.83	£12,784.09	£2,093.26
Andexanet alfa ICH bleed acute care cost (£)	£10,749.74	£12,712.56	£1,962.82
Standard of Care ICH bleed acute care cost (£)	£12,522.74	£10,559.93	£1,962.81
30-day mortality - ICH - SoC	£10,657.24	£12,224.13	£1,566.89
Utility: Severe GI Bleed follow-up care	£12,564.56	£11,077.12	£1,487.44
30-day mortality - Severe GI - AA	£11,059.78	£12,408.87	£1,349.09
Utility: Intraocular follow-up care	£11,044.61	£12,091.79	£1,047.18
Utility: Intraspinal follow-up care	£11,210.25	£12,064.83	£854.58
Standard of Care Severe GI bleed acute care cost (£)	£12,019.48	£11,170.94	£848.54
Andexanet alfa Severe GI bleed acute care cost (£)	£11,253.00	£12,101.54	£848.54
Andexanet alfa Severe GI bleed long-term care cost (£)	£11,269.16	£12,081.93	£812.77

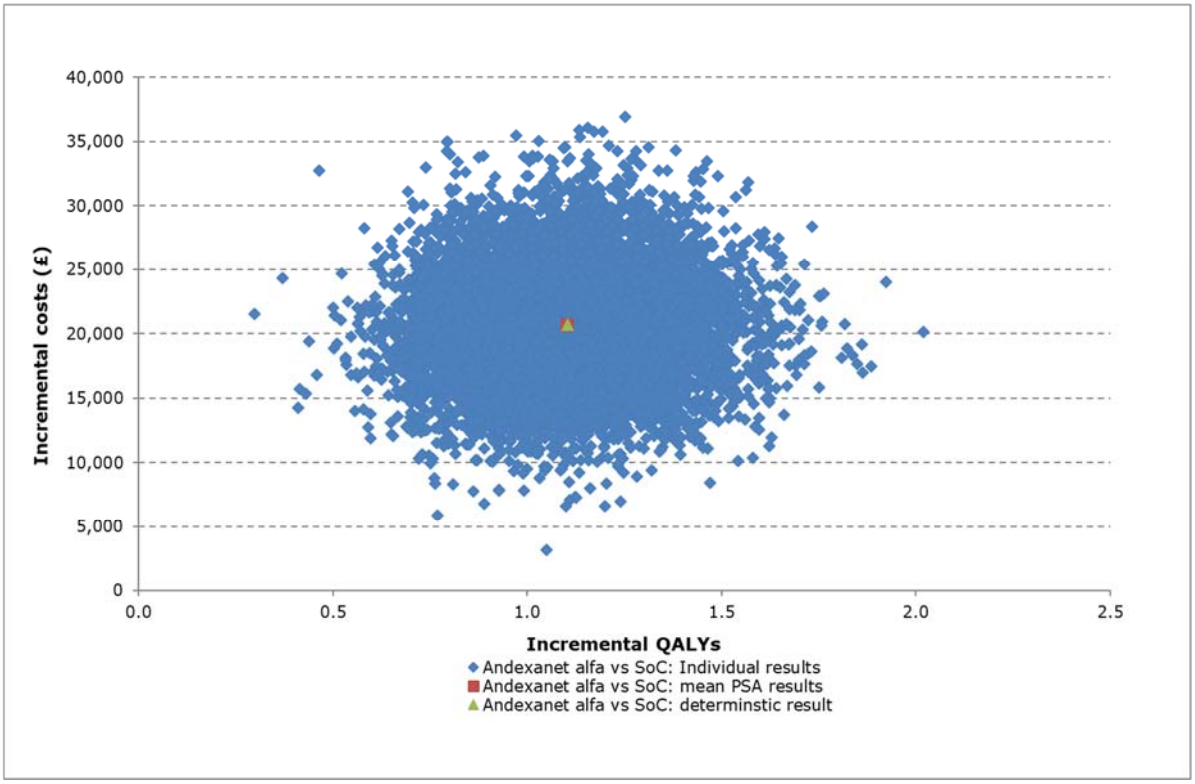
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care

Table 56. PSA results for ICH and GI cohort

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
SoC	16,715	1.811	-	-	-
Andexanet alfa	37,396	2.914	20,681	1.1028	18,753

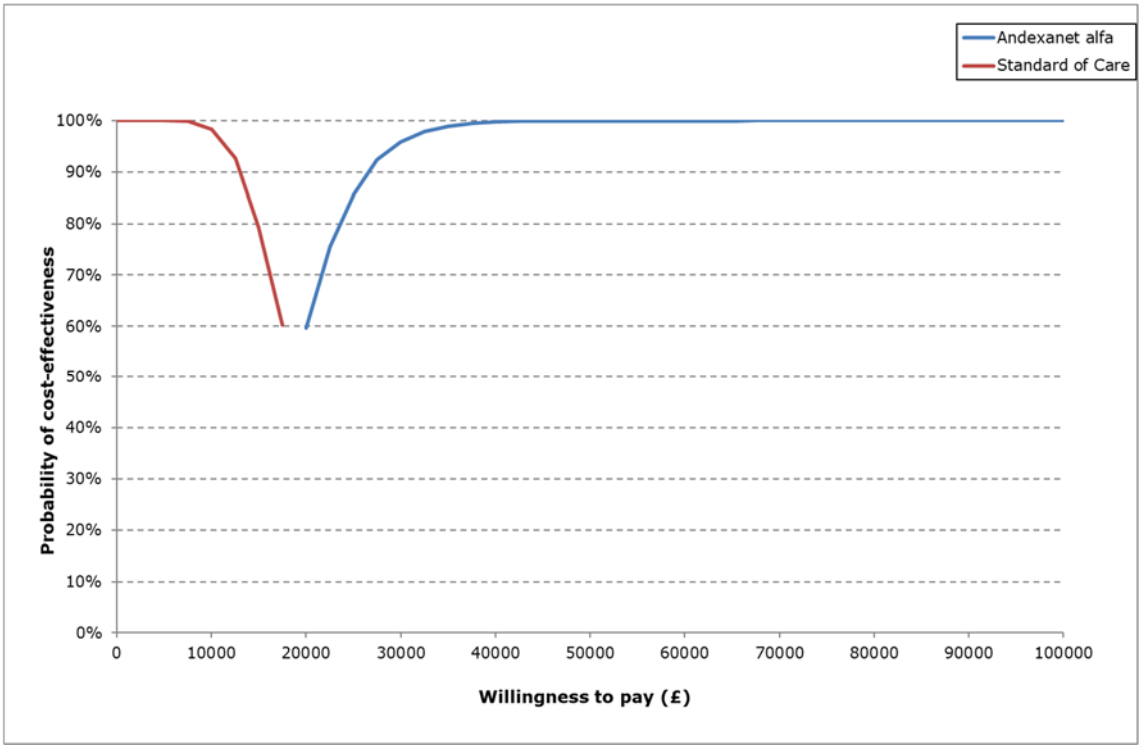
Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SoC, standard of care

Figure 5. ICEP for ICH and GI cohort



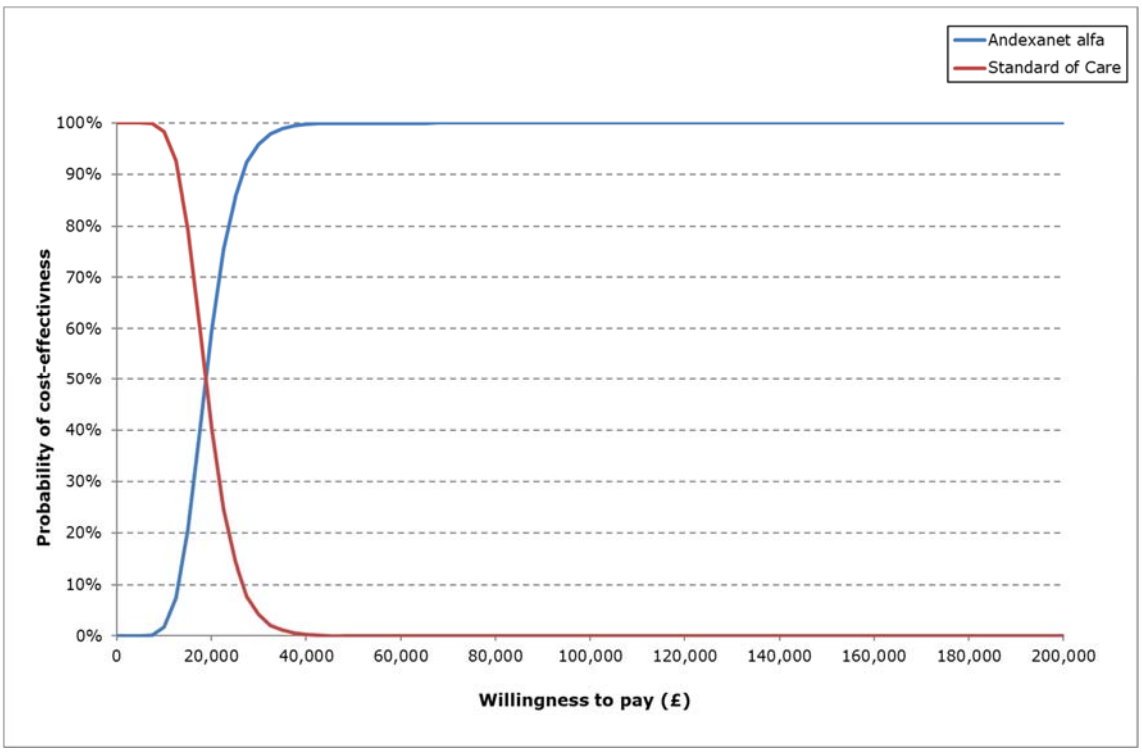
Abbreviations: ICEP, incremental cost-effectiveness plane; PSA, probabilistic sensitivity analysis; SoC, standard of care; GI, gastrointestinal; ICH, intracranial haemorrhage

Figure 6. CEAF for ICH and GI cohort



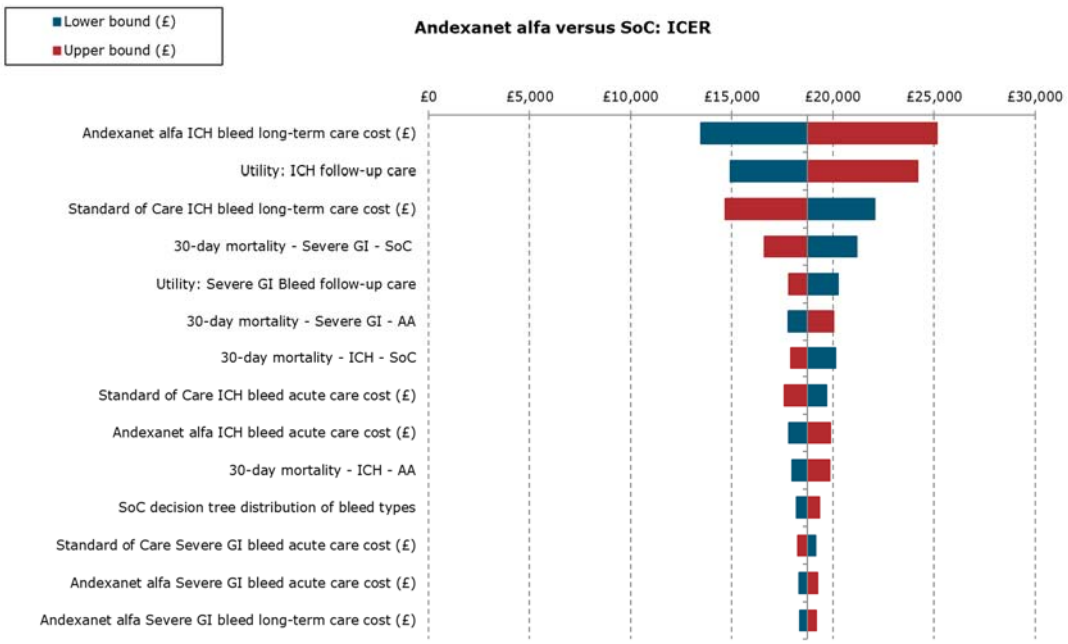
Abbreviations: CEAF, Cost-effectiveness acceptability frontier; GI, gastrointestinal; ICH, intracranial haemorrhage

Figure 7. CEAC for ICH and GI cohort



Abbreviations: CEAC, Cost-effectiveness acceptability curve; GI, gastrointestinal; ICH, intracranial haemorrhage

Figure 8. Tornado Diagram of andexanet alfa versus SoC (ICER) for the ICH and GI cohort



Abbreviations: ICER, incremental cost-effectiveness ratio; GI, gastrointestinal; ICH, intracranial haemorrhage; HR, hazard ratio; SoC, standard of care

Table 57. OWSA results of andexanet alfa versus SoC for the ICH and GI cohort (top 20 parameters)

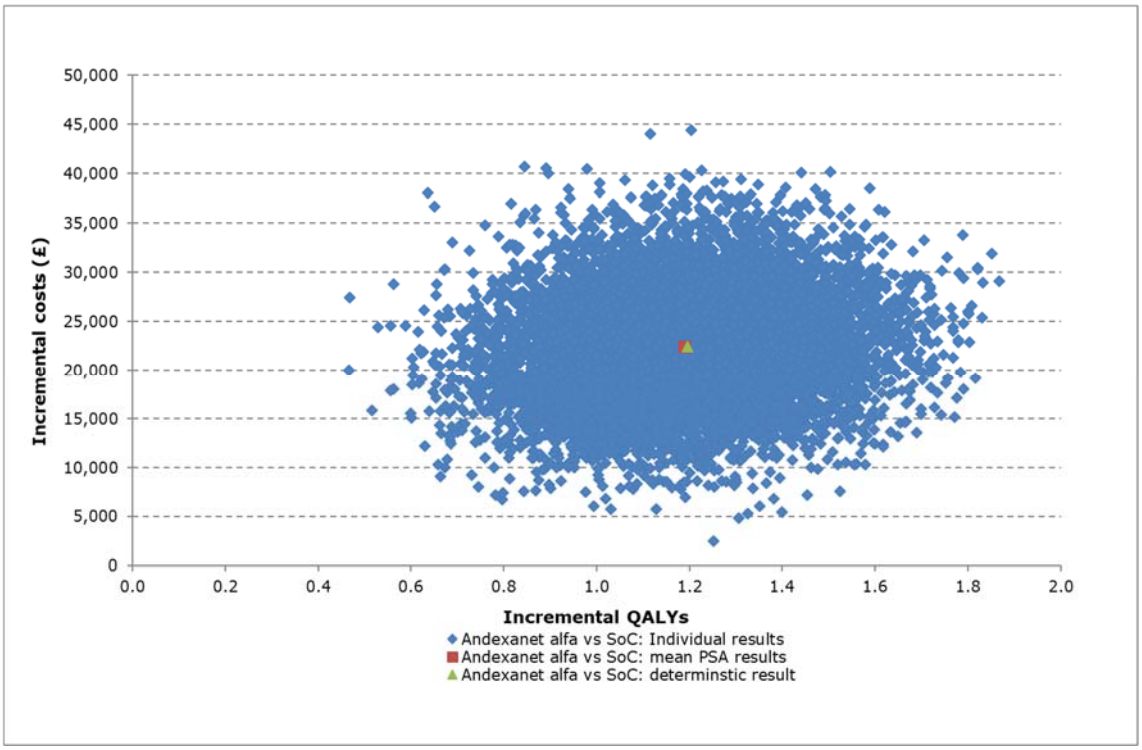
Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Andexanet alfa ICH bleed long-term care cost (£)	£13,454.86	£25,158.79	£11,703.93
Utility: ICH follow-up care	£14,939.57	£24,214.77	£9,275.20
Standard of Care ICH bleed long-term care cost (£)	£22,085.45	£14,680.27	£7,405.18
30-day mortality - Severe GI - SoC	£21,174.99	£16,592.94	£4,582.05
Utility: Severe GI Bleed follow-up care	£20,255.50	£17,830.10	£2,425.40
30-day mortality - Severe GI - AA	£17,771.27	£20,042.56	£2,271.29
30-day mortality - ICH - SoC	£20,143.97	£17,903.27	£2,240.70
Standard of Care ICH bleed acute care cost (£)	£19,681.77	£17,598.61	£2,083.16
Andexanet alfa ICH bleed acute care cost (£)	£17,800.06	£19,883.22	£2,083.16
30-day mortality - ICH - AA	£17,983.75	£19,839.16	£1,855.41
SoC decision tree distribution of bleed types	£18,205.81	£19,328.52	£1,122.71
Standard of Care Severe GI bleed acute care cost (£)	£19,147.66	£18,247.09	£900.57
Andexanet alfa Severe GI bleed acute care cost (£)	£18,334.18	£19,234.75	£900.57
Andexanet alfa Severe GI bleed long-term care cost (£)	£18,369.45	£19,191.92	£822.47
Standard of Care Severe GI bleed long-term care cost (£)	£19,058.23	£18,355.66	£702.57
Utility: ICH acute care	£18,868.32	£18,602.00	£266.32
Administration cost per cycle with Andexanet alfa (£):	£18,633.35	£18,871.51	£238.16
Administration cost per cycle with Standard of Care (£):	£18,814.10	£18,652.06	£162.04
Utility: Severe GI Bleed acute care	£18,752.76	£18,729.97	£22.79
Andexanet alfa decision tree distribution of bleed types	£18,740.92	£18,740.92	£0.00
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care			

Table 58. PSA results for ICH cohort

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
SoC	18,820	0.939	-	-	-
Andexanet alfa	41,291	2.129	22,471	1.1902	18,881

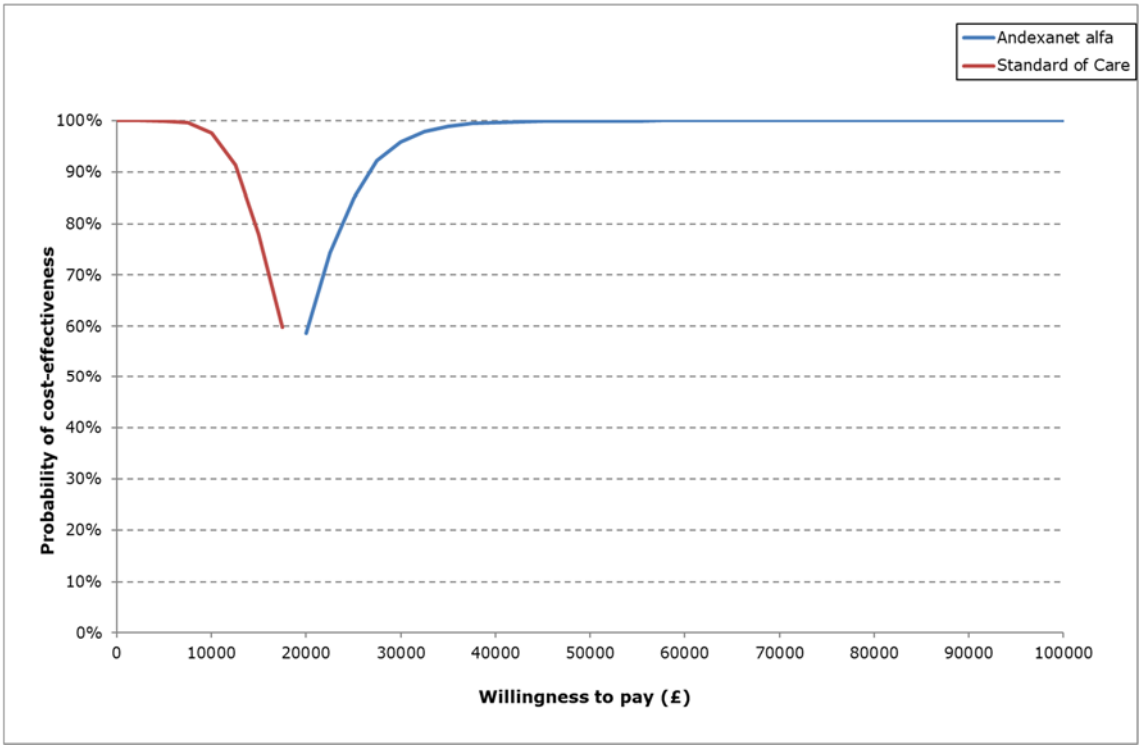
Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SoC, standard of care

Figure 9. ICEP for ICH cohort



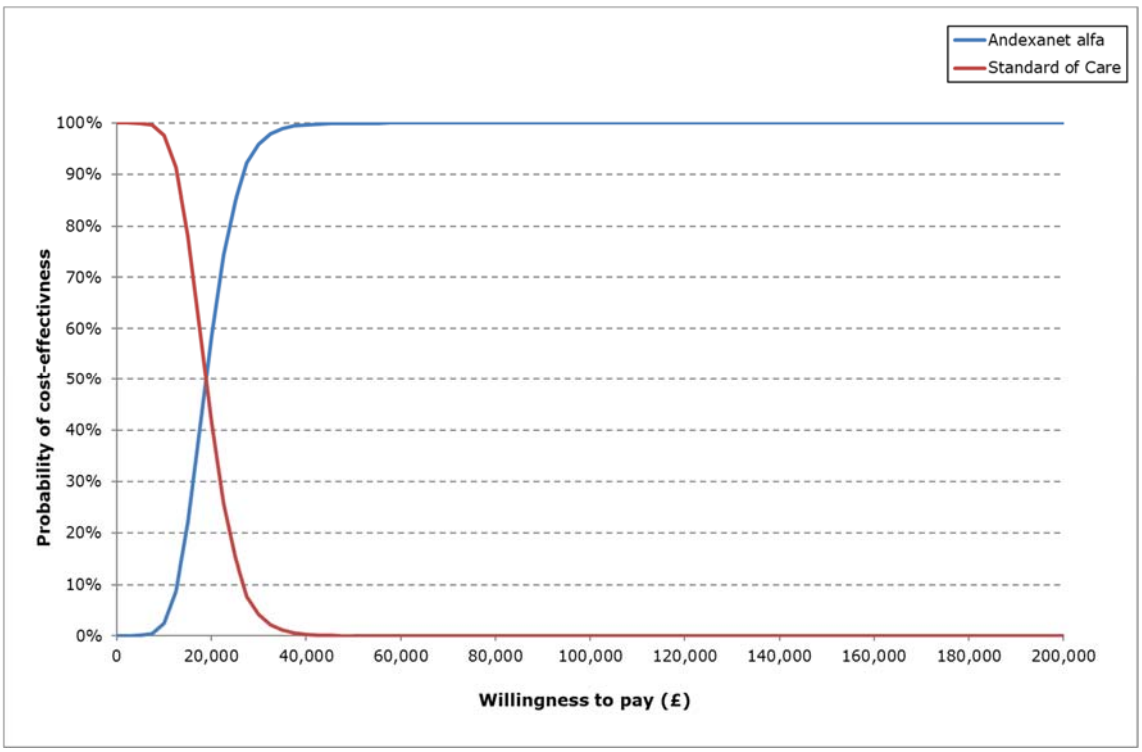
Abbreviations: ICEP, incremental cost-effectiveness plane; PSA, probabilistic sensitivity analysis; SoC, standard of care; ICH, intracranial haemorrhage

Figure 10. CEAF for ICH cohort



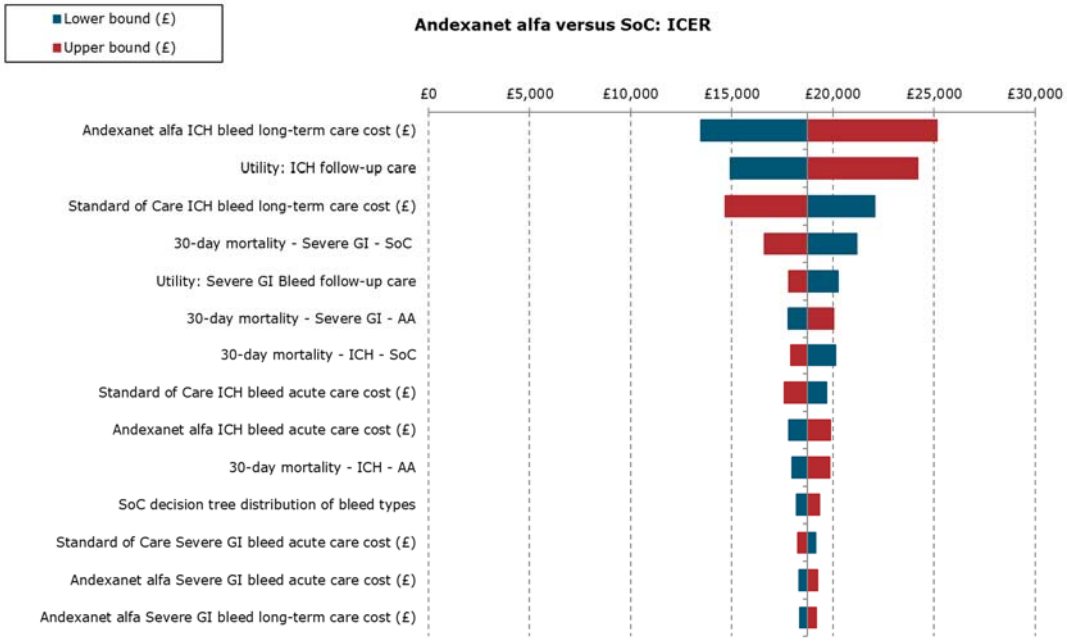
Abbreviations: CEAF, Cost-effectiveness acceptability frontier; ICH, intracranial haemorrhage

Figure 11. CEAC for ICH cohort



Abbreviations: CEAC, Cost-effectiveness acceptability curve; ICH, intracranial haemorrhage

Figure 12. Tornado Diagram of andexanet alfa versus SoC (ICER) for the ICH cohort



Abbreviations: ICER, incremental cost-effectiveness ratio; ICH, intracranial haemorrhage; HR, hazard ratio; SoC, standard of care

Table 59. OWSA results of andexanet alfa versus SoC for the Whole cohort (top 20 parameters)

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Andexanet alfa ICH bleed long-term care cost (£)	£12,378.95	£26,457.78	£14,078.83
Utility: ICH follow-up care	£14,364.70	£25,683.83	£11,319.13
Standard of Care ICH bleed long-term care cost (£)	£22,754.28	£13,860.93	£8,893.35
30-day mortality - ICH - SoC	£20,536.20	£17,775.07	£2,761.13
Standard of Care ICH bleed acute care cost (£)	£19,946.44	£17,269.97	£2,676.47
Andexanet alfa ICH bleed acute care cost (£)	£17,528.80	£20,205.26	£2,676.46
30-day mortality - ICH - AA	£17,845.16	£20,089.70	£2,244.54
SoC decision tree distribution of bleed types	£18,272.66	£19,201.35	£928.69
Utility: ICH acute care	£18,901.32	£18,559.85	£341.47
Administration cost per cycle with Andexanet alfa (£):	£18,638.36	£18,858.12	£219.76
Administration cost per cycle with Standard of Care (£):	£18,805.15	£18,655.63	£149.52
Andexanet alfa decision tree distribution of bleed types	£18,737.62	£18,737.62	£0.00
Andexanet alfa relative improvement of intraspinal bleed Survivor long-term utility	£18,737.62	£18,737.62	£0.00
Andexanet alfa relative improvement of intraocular bleed Survivor long-term utility	£18,737.62	£18,737.62	£0.00
Standard of Care Intraspinal acute care costs (£)	£18,737.62	£18,737.62	£0.00
Standard of Care Intraspinal long-term care cost (£) - Year 1	£18,737.62	£18,737.62	£0.00
Standard of Care Intraspinal long-term care cost (£) - Year 2	£18,737.62	£18,737.62	£0.00
Andexanet alfa Intraspinal acute care costs (£)	£18,737.62	£18,737.62	£0.00
Andexanet alfa Intraspinal long-term care cost (£) - Year 1	£18,737.62	£18,737.62	£0.00
Andexanet alfa Intraspinal long-term care cost (£) - Year 2	£18,737.62	£18,737.62	£0.00
Abbreviations: SoC, standard of care; ICH, intracranial haemorrhage			

Results of scenarios presented in Document B.3.9 for updated base case

Scenario analysis for threshold benefit for intraspinal and intraocular bleeding events

A scenario analysis was conducted using different threshold of benefit levels for intraspinal and intraocular bleeding events for the Whole cohort. This analysis sought to test the sensitivity of model results to the assumed relative benefit reduction for intraspinal and intraocular bleed long-term utility and cost at baseline, of 25%, the rationale for which is presented in Section 3.4 of Document B. In this analysis, the relative benefit reduction was varied between 0%, 12.5%, 25% (the base case), 37.5%, and 50%.

The resulting ICERs varied between £4,126 and £19,253 per QALY for the Whole cohort. For the Whole cohort, the highest ICER being obtained when relative benefit reduction was 0% for patients receiving andexanet alfa relative to patients receiving SoC, and the lowest being obtained when relative benefit reduction was 50%.

Table 60. Scenario analysis varying relative benefit reduction for the Whole cohort

Relative benefit reduction	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
0%	SoC	48,108	3.242	2.173	-	-	-	-	-
	Andexanet alfa	68,352	4.564	3.224	20,244	1.322	1.051	19,253	19,253
12.5%	SoC	48,108	3.242	2.173	-	-	-	-	-
	Andexanet alfa	64,391	4.564	3.228	16,283	1.322	1.055	15,431	15,431
25% (base case)	SoC	48,108	3.242	2.173	-	-	-	-	-
	Andexanet alfa	60,430	4.564	3.232	12,322	1.322	1.059	11,636	11,636
37.5%	SoC	48,108	3.242	2.173	-	-	-	-	-
	Andexanet alfa	56,469	4.564	3.236	8,361	1.322	1.063	7,868	7,868
50%	SoC	48,108	3.242	2.173	-	-	-	-	-
	Andexanet alfa	52,508	4.564	3.239	4,400	1.322	1.066	4,126	4,126

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

B.3.9.2 Scenario analysis varying relative mortality reduction of andexanet alfa relative to SoC for other major bleeds

A scenario analysis was conducted to vary the relative mortality reduction applied to the andexanet alfa treatment arm for other major bleeds. This analysis sought to test the sensitivity of model results to the assumed relative mortality reduction at baseline, of 25%, the rationale for which is presented in Section 3.3**Error! Reference source not found.** of Document B. In this analysis, the relative mortality reduction was varied between 0%, 12.5%, 25% (the base case), 37.5%, and 50%.

The resulting ICERs varied between £11,555 and £11,719 per QALY for the Whole cohort, with the highest ICER being obtained when relative mortality reduction was 0% for patients receiving andexanet alfa relative to patients receiving SoC, and the lowest being obtained when relative mortality reduction was 50%. The results for the Whole cohort are shown in Table 61. No results were presented for the ICH and GI cohort and ICH only cohort as the mortality reduction assumption does not apply to this group, given that more robust data were available.

Table 61. Results of varying relative mortality reduction for andexanet alfa patients for Whole cohort

Relative mortality reduction	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
0%	SoC	48,108	3.242	2.173	-	-	-	-	-
	Andexanet alfa	60,422	4.553	3.224	12,315	1.311	1.051	11,719	11,719
12.5%	SoC	48,108	3.242	2.173	-	-	-	-	-
	Andexanet alfa	60,426	4.559	3.228	12,318	1.317	1.055	11,678	11,678
25% (base case)	SoC	48,108	3.242	2.173	-	-	-	-	-
	Andexanet alfa	60,430	4.564	3.232	12,322	1.322	1.059	11,636	11,636
37.5%	SoC	48,108	3.242	2.173	-	-	-	-	-
	Andexanet alfa	60,434	4.570	3.236	12,326	1.328	1.063	11,595	11,595
50%	SoC	48,108	3.242	2.173	-	-	-	-	-
	Andexanet alfa	60,437	4.576	3.240	12,329	1.333	1.067	11,555	11,555

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

B.3.9.3 Scenario analysis varying long-term mortality hazard ratio source for ICH survivors

A scenario analysis was conducting by using two different sources for long-term hazard ratios for the ICH cohort. The sources explored were Lee et al. 2010 and Huybrechts et al. 2008 whole ICH mortality (not broken down by mRS score).

The results of this scenario analysis are shown in Table 62, Table 63 and Table 64 for the Whole cohort, ICH and GI cohort and ICH only cohort, respectively. ICERs were lower using alternative sources compared to the base case, suggesting that results in the base case may be conservative.

Table 62. Results of Scenario Analysis hazard ratio source for the Whole cohort

Long-term mortality HR (source)	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Base case	SoC	48,108	3.242	2.173	-	-	-	-	-
	Andexanet alfa	60,430	4.564	3.232	12,322	1.322	1.059	11,636	11,636
1.29 (Lee 2010)	SoC	50,782	3.546	2.358	-	-	-	-	-
	Andexanet alfa	60,430	4.564	3.232	9,648	1.019	0.874	11,039	11,039
1.21(Huybrechts 2008)	SoC	53,121	3.811	2.520	-	-	-	-	-
	Andexanet alfa	60,430	4.564	3.232	7,309	0.754	0.712	10,262	10,262

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

Table 63. Results of Scenario Analysis hazard ratio source for the ICH and GI cohort

Long-term mortality HR (source)	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Base case	SoC	16,736	2.715	1.809	-	-	-	-	-
	Andexanet alfa	37,427	4.105	2.913	20,691	1.390	1.104	18,741	18,741
1.29 (Lee 2010)	SoC	19,579	3.037	2.005	-	-	-	-	-
	Andexanet alfa	39,270	4.361	3.097	19,692	1.324	1.092	18,035	18,035
1.21(Huybrechts 2008)	SoC	22,041	3.317	2.175	-	-	-	-	-
	Andexanet alfa	42,672	4.834	3.438	20,631	1.517	1.262	16,345	16,345

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

Table 64. Results of Scenario Analysis hazard ratio source for the ICH cohort

Long-term mortality HR (source)	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Base case	SoC	18,780	1.586	0.933	-	-	-	-	-
	Andexanet alfa	41,199	3.068	2.130	22,419	1.482	1.196	18,738	18,738
1.29 (Lee 2010)	SoC	22,487	2.006	1.189	-	-	-	-	-
	Andexanet alfa	43,573	3.399	2.367	21,086	1.392	1.177	17,908	17,908
1.21(Huybrechts 2008)	SoC	25,719	2.373	1.413	-	-	-	-	-
	Andexanet alfa	48,038	4.019	2.814	22,319	1.646	1.401	15,930	15,930

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

B.3.9.4 Scenario analysis varying discount rate

A scenario analysis was conducted varying the discount rate, to explore the impact of applying a greater or lesser weight to future costs and benefits. The discount rates explored were: 0% and 5%, relative to a 3.5% discount rate at baseline for both costs and benefits.

The results of this scenario analysis are shown in Table 65, Table 66 and Table 67 for the Whole cohort, ICH and GI cohort and ICH only cohort respectively.

Table 65. Results of Scenario Analysis varying Discount Rate for the Whole cohort

Discount rate	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
0%	SoC	56,416	3.817	2.571	-	-	-	-	-
	Andexanet alfa	68,376	5.407	3.839	11,960	1.589	1.267	9,436	9,436
3.5% (base case)	SoC	48,108	3.242	2.173	-	-	-	-	-
	Andexanet alfa	60,430	4.564	3.232	12,322	1.322	1.059	11,636	11,636
5%	SoC	45,276	3.045	2.036	-	-	-	-	-
	Andexanet alfa	57,724	4.277	3.024	12,448	1.232	0.988	12,598	12,598

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

Table 66. Results of Scenario Analysis varying Discount Rate for the ICH and severe GI cohort

Discount rate	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
0%	SoC	18,050	3.148	2.109	-	-	-	-	-
	Andexanet alfa	40,130	4.807	3.422	22,080	1.659	1.312	16,826	16,826
3.5% (base case)	SoC	16,736	2.715	1.809	-	-	-	-	-
	Andexanet alfa	37,427	4.105	2.913	20,691	1.390	1.104	18,741	18,741
5%	SoC	16,255	2.564	1.704	-	-	-	-	-
	Andexanet alfa	36,479	3.862	2.737	20,224	1.298	1.033	19,582	19,582

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

Table 67. Results of Scenario Analysis varying Discount Rate for the ICH only cohort

Discount rate	Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
0%	SoC	20,131	1.739	1.026	-	-	-	-	-
	Andexanet alfa	44,219	3.488	2.432	24,087	1.749	1.405	17,140	17,140
3.5% (base case)	SoC	18,780	1.586	0.933	-	-	-	-	-
	Andexanet alfa	41,199	3.068	2.130	22,419	1.482	1.196	18,738	18,738
5%	SoC	18,276	1.529	0.898	-	-	-	-	-
	Andexanet alfa	40,128	2.920	2.022	21,852	1.391	1.124	19,439	19,439

ICER – incremental cost-effectiveness ratio; LYG – life years gained; QALYs – quality-adjusted life years; SoC – standard of care

B.3.9.5 Scenario analysis without wastage assumed in drug costs

The final scenario analysis was selecting 'no wastage' for the drug acquisition cost calculation. The ICER decreased to £10,182 per QALY for the Whole cohort, £17,354 per QALY for the ICH and severe GI bleed cohort, and £17,462 per QALY for the ICH only cohort. ICERs were lower assuming no wastage compared to the base case, suggesting that results in the base case may be conservative if vial sharing is possible in hospitals.

Table 68. Scenario analysis without wastage

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Whole cohort								
SoC	48,103	3.242	2.173	-	-	-	-	-
Andexanet alfa	58,885	4.564	3.232	10,783	1.322	1.059	10,182	10,182
ICH and severe GI bleed cohort								
SoC	16,731	2.715	1.809	-	-	-	-	-
Andexanet alfa	35,891	4.105	2.913	19,160	1.390	1.104	17,354	17,354
ICH cohort								
SoC	18,774	1.586	0.933	-	-	-	-	-
Andexanet alfa	39,667	3.068	2.130	20,893	1.482	1.196	17,462	17,462

ICER – incremental cost-effectiveness ratio; LY – life year; QALY – quality adjusted life year; SoC – standard of care

NICE National Institute for Health and Care Excellence

Professional organisation submission

Andexanet alfa for reversing anticoagulation [ID1101]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Society of Gastroenterology**

3. Job title or position	**Consultant Gastroenterologist** [redacted]
4. Are you (please tick all that apply):	☐ ✓ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ ✓ a specialist in the treatment of people with this condition? ☐ ✓ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Society of Gastroenterology is an organisation focused on the promotion of gastroenterology within the United Kingdom. It has over three thousand members drawn from the ranks of physicians, surgeons, pathologists, radiologists, scientists, nurses, dietitians, and others interested in the field. The organisation is a registered charity and is funded primarily by membership subscriptions.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or	The main aim of this treatment is to reverse the anticoagulant effect of certain Direct Oral Anticoagulants (DOACs) in patients taking these drugs who present with life-threatening haemorrhage. With regard to our professional specialty this would apply to gastrointestinal haemorrhage.

disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The immediate significant response would be to reduce the level of anticoagulation to a level which would enable haemostasis to be achieved, either spontaneously or with intervention (endoscopy, interventional radiology or surgery). Endpoints to be considered would include mortality, reduction in transfusion requirements, or reduction in need for surgery.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, DOACs are widely prescribed, and increase the risk of gastrointestinal haemorrhage in patients taking them. When haemorrhage occurs it is difficult to reverse the effects of these drugs. The previous lack of a reversal agent for the factor Xa inhibitors has hindered efforts to treat patients presenting with severe haemorrhage. This may have increased the mortality from haemorrhage of these patients, though I am unaware of specific data.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Acute gastrointestinal haemorrhage is treated with resuscitation, transfusion if required, and intervention including endoscopy. Anticoagulant drugs are discontinued at presentation. Warfarin can be reversed with Prothrombin Complex Concentrate, but this is ineffective for DOACs. Currently severe life-threatening haemorrhage on factor Xa inhibitors is managed with resuscitation, transfusion and intervention while awaiting the effects of the DOAC to diminish (they have relatively short half lives.). Idarucizumab is licenced for severe life threatening haemorrhage on dabigatran.
• Are any clinical guidelines used in the	Veitch AM, Vanbiervliet G, Gershlick AH, Boustiere C, Baglin TP, Smith LA, Radaelli F, Knight E, Gralnek IM, Hassan C, Dumonceau JM. Endoscopy in patients on antiplatelet or anticoagulant therapy, including direct oral anticoagulants: British Society of Gastroenterology (BSG) and European Society of Gastrointestinal Endoscopy

treatment of the condition, and if so, which?	(ESGE) guidelines. *Gut.* 2016;65(3):374-89. Tripathi D, Stanley AJ, Hayes PC, et al. U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. Gut 2015;64:1680-704. Acute upper gastrointestinal bleeding in over 16s: management NICE Clinical guideline [CG141]. 2012
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes the pathway for management is well defined, and there are no significant differences of opinion. National guidelines are generally well adhered to in my experience. The specific management of haemorrhage on DOACs is referred to in Veitch et al 2016, but a management algorithm Is not defined.
• What impact would the technology have on the current pathway of care?	Widespread provision of a reversal of agent for DOACs would improve the management (and probably outcomes) of patients with severe life-threatening haemorrhage who are taking these drugs.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This drug would be an addition to the current management algorithm for gastrointestinal haemorrhage.
• How does healthcare resource use differ between the technology	This drug would be an addition to the current management algorithm for gastrointestinal haemorrhage.

and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care as part of Major Haemorrhage protocols.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Resource for the drug costs, education and training in its use (including appropriate indications).
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, currently there is no effective antidote for factor Xa inhibitor DOACs, and use of an antidote is likely to be superior to current care (described above in section 9)
• Do you expect the technology to increase length of life more than current care?	Yes, but this needs to be prospectively tested and may vary according to the site of haemorrhage and comorbidties.
• Do you expect the technology to increase health-related quality of life more than current	Yes, but this needs to be prospectively tested and may vary according to the site of haemorrhage and comorbidties.

care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients presenting with life-threatening haemorrhage who have advanced age or multiple co-morbidties; there is very good evidence that these factors increase mortality.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	If used as part of a Major Haemorrhage Protocol with appropriate advice regarding indication and administration, then I foresee no difficulties in implementing this treatment.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	These could be incorporated into a Major Haemorrhage Protocol.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I do not have the information to respond to this question.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current	Yes.

need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Thrombotic side effects may impact adverse on morbidity or mortality outcomes. These need to be balanced against the immediate benefits.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Clinical trials have evaluated andexanet in acute haemorrhage, including gastrointestinal haemorrhage. The drug was given in addition to best current practice for the conditions, and that would be similar to current UK practice
• If not, how could the results be extrapolated to	

the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Mortality, reduction in transfusion requirements, or reduction in need for surgery are the most important clinical outcomes. Although mortality has been measured, I am not aware of any prospective randomised comparative trials which would indicate whether this is different from current practice.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Factor Xa activity has been measured as an outcome, but this does not seem to be predictive of mortality
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I am not aware of any.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the	This needs to be tested.

trial data?	
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	None that I am aware of.
21b. Consider whether these issues are different from issues with current care and why.	N/A
Key messages	
22. In up to 5 bullet points, please summarise the key messages of your submission. • Gastrointestinal haemorrhage has a substantial mortality despite current best practice, and the incidence of gastrointestinal haemorrhage is increased on DOACs. • The anticoagulant effect of DOACs is not effectively reduced using measures other than the new DOAC reversal agents • Andexanet is a promising treatment for the management of life threatening haemorrhage in patients on DOACs, but prospective randomised comparative data using clinically significant outcomes is required. • •	

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]

2. Name of organisation	**Royal College of Pathologists and British Society for Haematology**
3. Job title or position	**Consultant haematologist**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Pathologists is a professional membership organisation, whose mission is to maintain the internationally renowned standards and reputation of British pathology, through training, assessments, examinations and professional development, to the benefit of the public. It is a registered charity with over 11,000 members work in hospital laboratories, universities and industry worldwide. The British Society for Haematology is the UK professional organisation for doctors specialising in haematology. In addition to representing the interests of its members, it publishes the British Journal of Haematology and issues BSH Guidelines on haematological conditions
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	Prevent progression or disability

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Cessation of bleeding with reduction in death and morbidity
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Use of DOACs including factor Xa inhibitors is increasing for various indications. At present, there is no specific antidote for patients on factor Xa inhibitors presenting with major or life-threatening bleeding or requiring urgent surgery. Therefore, this proposal is very important and addresses an urgent clinical need.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	In the absence of a specific antidote, prothrombin complex concentrate (PCC) with tranexamic acid is considered to be the best care for patients presenting with major or life-threatening bleeding whilst on a DOAC. Activated factors such as FEIBA and rfVIIa are also used in some circumstances.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes 1) 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways 2) BSH Guideline on the management of bleeding in patients on antithrombotic agents, 2012
• Is the pathway of care well defined? Does it vary or are there	Yes. Most NHS Trusts have developed their own local guidelines/ policies on pathway and management on patients presenting with major/life threatening bleeding whilst on DOACs based on national guidelines (BSH

differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	guidelines). However, there is some variation in practice between professionals across the NHS in terms of dose of PCC or using activated PCC with or without tranexamic acid
• What impact would the technology have on the current pathway of care?	1. Cost will increase. The proposed cost of andexanet is significantly more than the cost of current standard of care and is also significantly higher than the cost of the dabigatran thrombin inhibitor antidote idarucizumab 2. May increase concern regarding development of thrombosis after the acute event.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	If Andexanet alfa is approved by NICE it may be incorporated in to the clinical care pathway for patients presenting with major /life threatening bleeding whilst on DOAC.
• How does healthcare resource use differ between the technology and current care?	As noted above, this may replace the current practice of using PCC/aPCC with or without tranexamic acid in patients presenting with major /life threatening bleeding whilst on DOAC An infusion is required rather than a single injection It is possible to measure the effect using a standard laboratory assay, although this was not shown to correlate with clinical effect.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Financial investment, education and training because the regimens for use of Andexanet alfa are different depending on the timing and the type of direct factor Xa inhibitor and also the first bolus dose is followed by infusion of the drug
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	No. There was no comparison with current care and so there is no evidence of any benefit compared with current care. Moreover, as a result of the 'Haemostatic efficacy' criteria used, (as in previous studies) it is not possible to conclude that Andexanet resulted in a decrease in bleeding. Use of Andexanet was also associated with a 10% incidence of thrombosis. Whilst there is no control group for comparison, this is not lower than seen in comparable reports of current therapy.
• Do you expect the technology to increase length of life more than current care?	No. Again, because there is no control group there ~~are~~ is no data demonstrating a survival benefit. The study showed a14% 30-day mortality rate. This is lower than is seen in reports of current therapy (PCC) but it is important to note that the study excluded patients with an expected survival of less than 30 days. So a fairer interpretation is that 14% of patients that were expected to survive beyond 30 days died within 30 days following treatment with this drug.
• Do you expect the technology to increase health-related quality of life more than current care?	No. It is not possible to conclude this in the absence of a control group receiving current care. Treatment with andexanet markedly reduced anti–factor Xa activity. However, this was variable and was followed by a return to therapeutic levels in many patients after 4 hours. Furthermore, the study concluded that *"Overall, there was no significant relationship between hemostatic efficacy and a reduction in anti–factor Xa activity during andexanet treatment."* We note that of the 352 patients enrolled in the study 92 (28%) were excluded from the final analysis because they had low anti-Xa levels (i.e. no significant DOAC activity at the point of study entry). At present

	this test is not likely to be available prior to treatment so the analysis tends to falsely ~~elevated~~elevate the estimation of efficacy likely to be achieved in practice. This may alter when the assay becomes more widely available. The effectiveness of a treatment at stopping bleeding is assessed by the change in the size of the bleed. It is not clear from the main paper whether any patients had a reduction in bleed size or even that the bleed stopped increasing in size after treatment. For intracranial haemorrhage (the largest group) the authors report that 80% of the evaluated patients had an increase in bleed volume of 35% or less. It is debatable whether this is a good outcome or not. As there was no comparator arm it is quite possible that this would have been the outcome without andexanet treatment.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology may be beneficial to patients presenting with major/life threatening bleeding whilst on rivaroxaban or apixaban and with anti-Xa levels in the range expected for the specific DOAC. This range varies for each DOAC and it is generally not possible to determine the level in an acute setting in most hospitals.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	It may be more difficult use the technology than current practice due to the complexity of administration regimens for Andexanet alfa (bolus followed by 2-hour infusion). The study reports the benefit only in patients with a clinically significant level of anti-Xa activity due to DOAC treatment. It will not be feasible to measure this in an acute setting in most hospitals

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes. There will be protocol/policy on starting treatment with Andexanet alfa. As Andexanet alfa is not irreversibly inhibiting the direct factor inhibitors, monitoring of drug levels (drug specific anti-Xa levels) may be required after treatment with Andexanet alfa. It will not be feasible to measure this in an acute setting in most hospitals
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	It is an innovative approach but it is not possible to conclude that it has any beneficial impact in the absence of a comparative study with current treatments. The published data do not establish any clear benefit. It may be of benefit in patients with acute major bleeding in association with a clinically significant level of anti-Xa activity due to DOAC treatment. However, there is 10% risk of thrombosis following the treatment with Andexanet alfa.
• Is the technology a 'step-change' in the	No

management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	There is an unmet need for better therapy to reverse the new anticoagulants but it is not clear that this is met by Andexanet.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There was a 10% thrombosis rate following the treatment with the majority of patients developing thrombosis within first 2 weeks of treatment with Andexanet alfa. This has the potential to reduce the patient's quality of life and it is not established that this adverse effect is offset by any clinical benefit.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Clinical trials may differ from standard clinical practice as the patients for the trials are selected more carefully than in clinical practice and there are sets of inclusion and exclusion criteria. In clinical practice we may have to deviate from these based on individual patient risk and benefits.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Safety (mainly thrombosis) and efficacy (recurrent bleeding, improvement in the intracranial bleeding) or death and survival benefit. Most of these were measured except survival benefit as there was no comparison with current standard practice

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The surrogate measure of anti-Xa activity did not correlate with the important clinical outcomes.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, this is possible e.g. there were no antibodies against Andexanet alfa detected during the follow up period of up to 45 days in the trial but, long term effects especially if a patient is exposed to the drug for the second time remain unknown.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	Real world patients are managed with PCC/aPCC with or without tranexamic acid. However, there is limited information on this management regimen from prospective clinical studies. Retrospective data shows a lower thrombotic rate and higher 30-day mortality than seen in this study. However, the ANEXA-4 trial did not include patients with low GCS (<7) or expected life expectancy < 30 days into the study which may affect the 30-day mortality rate of the study compared to real life data.
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- The ANNEXA-4 study does not establish that andexanet results in a reduction in bleeding compared with standard care (PCC).
- Safety following Andexanet alfa is of concern because the thrombotic rate (10% at 30 days) is higher than in comparable studies of current care and the observed mortality was 14% in patients expected to survive.
- The cost of Andexanet alfa treatment per person following a major/life threatening bleeding is likely to be much higher than current alternatives
- There are no studies directly comparing andexanet with PCC or with placebo.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Andexanet alfa for reversing anticoagulation [ID1101]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Thrombosis UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Thrombosis UK is a leading UK charity working to raise awareness, extend understanding and support research into thrombosis (blood clots) often known as deep vein thrombosis (DVT) – blood clots most commonly in a limb, or pulmonary embolism (PE) – blood clots in the lungs. The charity works with patients, carers, relatives and bereaved as well as health care and allied professionals and all interested parties. From provision of a help line, information resources, educational conferences and support for research, our aim is to improve awareness and understanding of thrombosis in order to prevent avoidable events, improve early detection leading to early diagnosis and support implementation of best management of thrombosis to safeguard and improve patient outcomes. Thrombosis UK does not have a formal 'membership' but works freely with individuals. We currently have over five thousand active followers and supporters across patient, general public and health care professionals. Approximately 92-94% of the charity's annual income comes from individual donations, fundraising and successful applications to independent foundations and trusts. Annually the charity runs national accredited and endorsed conferences for healthcare professionals (HCPs) and at these the charity offers exhibition space to purchase. Companies, including although not solely, pharmaceutical and device companies, purchase exhibition space for HCP educational conferences. This accounts for 6-8% of the charity's annual income. Our annual reports and full summary of support can be found: http://www.thrombosisuk.org/our-partnerships.php

4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	1. Personal contact via the telephone help line. 2. Interaction with patients via our peer support group on Facebook and social media platforms. 3. Via the sharing of patient and carer/family case accounts posted or emailed to us from individuals. 4. During face to face meetings, in particular our national and regional patient education and support meetings. 5. Through responses gathered in on-line surveys.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	VTE can have a huge physical and psychological impact on patient's lives. Many patients are left with long-term, on-going physical and/or psychological problems associated with the condition. Diagnosis, in particular after a prolonged delay, is often initially, a relief. However, the impact of suffering a thrombotic event, in particular when there has been a delay in diagnosis or the blood clots have caused a medical, life threatening emergency, frequently has long term physical and psychological effects For everyone, treatment can impact on employment, future family planning, travel, work and social life. Almost everyone we hear from who has had one or more thrombotic events highlight their difficulty in finding information and understanding 'what is next' after diagnosis and discharge from hospital. In a recent talk by a 37 year old patient who first suffered an unprovoked PE when in his late twenties, he highlighted how 'alone' he felt – in the anticoagulation clinics he was not only considerably younger than almost everyone else, but he had no 'common group' he could link up with and felt isolated and the 'abnormal' one, stood apart from peers and also from others prescribed anticoagulation as the vast majority were older and being treated for mechanical valve / AF. He very much felt 'the odd one out' with

	no interaction with anyone taking the same therapy that was a similar age. Many patients speak of the fear of further blood clots, especially when their symptoms had initially been missed, disregarded or attributed to psychological issues. Females often highlight the lack of information (verbal or other forms) on the impact treatment has on menstruation, with excessively heavy periods, and the physical as well as social issues this causes. Furthermore, after suffering a thrombotic event, females need to be aware of the risk factors in future life, such as options in contraception, pregnancy and postpartum and in the menopause when HRT might be considered. These are long reaching affects that few people are aware before suffering blood clots or informed about or readily access information about, after diagnosis. On reflecting, many patients wish that after diagnosis, they had been offered a follow up appointment to ask 'how are *you*?' Because they may look well, everyone presumes they feel well, but many suffer prolonged pain / post thrombotic syndrome and anxiety. Many non-specialist healthcare professionals have few answers and a general low awareness of this issues and referral is either not offered or comes very late when the problem is harder to treat. There is an overwhelming feeling from almost all people we hear from, of the lack of information in any format, opportunity to have discuss 'what to expect' and 'how they might feel'. Practical guidance on common affects such as breathlessness and loss of fitness – which can too often be mistaken for a further clot and cause considerable anxiety. The Thrombosis UK website has a range of personal case stories and patient films, which help share insight on how it can be 'normal' to feel, and some of the reasons for this: http://www.thrombosisuk.org/share-tell.php http://www.thrombosisuk.org/media-patient-films.php
Current treatment of the condition in the NHS	

7. What do patients or carers think of current treatments and care available on the NHS?	Current treatments are mostly accepted by patients because they are life-saving but concerns about safely managing anticoagulation and how medication may impact on life-style, opportunities and physicality, does raise many questions and for some, anxieties. While some treatment options may appear to have a reversable agent (eg warfarin), the impact, in particular on any one in work / with family and commitments / who enjoys travel and eating out, is considerable. More recent, anticoagulation options (DOACs) if clinically appropriate, reduce multiple medical appointments and the impact on diet, restricted choice and lifestyle, however many worry if a problem or emergency should occur, how to quickly reverse this therapy.
8. Is there an unmet need for patients with this condition?	Yes. Patients diagnosed with a DVT or PE need not only effective treatments, but also safe treatments that can be managed should an emergency occur. Currently there is an unmet need in provision. Many patients contact Thrombosis UK anxious about bleeding and what would happen if this occurred; this causes some to feel very anxious. Recommendations that could allay these fears would be very positive for every patient.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	1. Reassurance. DOAC therapies that reduce risk of further blood clots and enable greater flexibility in diet, reduced requirement for regular tests and medical appointments and is given in a standard tablet dose is able to be safely managed are welcomed; **BUT** there needs to be reassurance that should a bleed or emergency occur, this medication can be safely managed. 2. Safety DOACs were a welcomed innovative treatment therapy after the life-style impact from injectable and Vit K options. However, in the case of an unavoidable emergency such as an accident, bleed or similar, there needs to be a safe, fast acting and effective reversal therapy.

	3.Access An effective reversal agent that can be administered by healthcare professionals who are not necessarily specialists in haematology means that in most settings, this can be accessed and administered quickly and safely by a range of healthcare providers. This avoids delay and improves access to a potential life-saving therapy. 4. Reduced time in hospital Potential reduction in hospital stay, which may be in a centre away from their local area because previously complex blood products needed to be administered and closely monitored were not always available at smaller centres. Any technology that can reverse the effects of DOACs would be seen as a huge advantage by patients.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so,	Patients who may live away from major hospitals where access to specialist haematology teams is not always immediate. The new therapy would alleviate the need for current complex reversal actions. Those patients whose anxiety about fear of a bleed while on a DOAC, and so have declined any of the more modern anticoagulation treatment options, would have reassurance and be able to now access choice.

please describe them and explain why.	Those whose cultural or religious beliefs may cause issues accepting treatment that include complex blood products.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No
Other issues	
13. Are there any other issues that you would like the committee to consider?	No

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • 1. DOAC therapy has enabled many patients to avoid frequent medical appointments, cost in finance and time for travel /absence from work /support to attend anticoagulation clinics. • 2. DOAC therapy has relieved worry on regularity of diet / interaction with other medications / change in dose. • 3. However currently patients have to face serious considerations when attempting to weigh up the benefits of a DOAC with the risk factors should a bleed occur. Currently the option only is access to specialist hospital teams who can provide and manage complex blood products to try to reverse treatment. • 4. Immediate access to specialist care and reversal blood product therapy, may not always be instantly or locally available. • 5. Patients who have suffered a thrombotic event frequently experience anxiety and fear. Reassurance that the anticoagulation therapy is not only effective in reducing their risk of further blood clots but can also be safely managed should an emergency arise, would be welcomed.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Andexanet alfa for reversing anticoagulation [ID1101]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

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Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	Dr Deepa Jayakody Arachchillage
2. Name of organisation	Imperial College Healthcare NHS Trust (on behalf of British Society for Haematology and Royal College of Pathologists)
3. Job title or position	Consultant Haematologist & Honorary senior lecturer

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Andrew Veitch**
2. Name of organisation	**British Society of Gastroenterology**
3. Job title or position	**Consultant Gastroenterologist**

4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
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NICE National Institute for Health and Care Excellence

Clinical expert statement

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Elizabeth Warburton**
2. Name of organisation	**Cambridge University Hospitals NHS Foundation trust**
3. Job title or position	**Consultant in stroke medicine**

4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? x☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	x☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	x☐ yes
The aim of treatment for this condition	

7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	In my sphere of clinical practice the main aim of the treatment would be to try and limit the brain damage caused by a brain haemorrhage in people who are taking the relevant anticoagulants. People are most often prescribed these for atrial fibrillation. Limiting the brain damage caused by the haemorrhage would impact on the death rate and also the eventual outcome measured in terms of 'return of function' –whether that be physical (mobility), cognitive, ability to speak, return to work/person's own home, dependency on others and overall quality of life. The most common subtype of brain haemorrhage I encounter is a spontaneous intracerebral haemorrhage. (haemorrhagic stroke), abbreviated to ICH However, other subtypes that are relevant are subdural haematoma which can be spontaneous or precipitated by a fall/trauma (abbreviated to SDH) And Sub arachnoid haemorrhage (abbreviated to SAH) – most often spontaneous I have very little clinical experience of these as they are managed by neurosurgery in the UK
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In ICH mortality rate are high. Best predictors of mortality and poor outcome are the initial volume of the brain haemorrhage as measured on the initial CT brain scan and initial stroke severity as measured by the NIHSS stroke scale. Other predictors are intraventricular blood, site of bleed (brain stem and thalamus with mortality and posterior limb of internal capsule with poor eventual outcome) and heamatoma expansion with clinical worsening (exact mechanism of this is unknown) A clinically significant treatment response would be as follows 1. Change in mortality rate 2. Change in major disability as assessed by the modified Rankin Scale (mRS) (death, score of 6; major disability, score of 3–5) 3. Improvement in the Health-related quality of life (HRQoL) as self-assessed by the patient or by a proxy responder using a scale such as the European Quality of Life Scale EQ5D 4. Reduction in clinical worsening (as measured by rise in NIHSS stroke scale - > 2 points) and haematoma expansion/growth (IVH) either mean or absolute on a CT scan at 24hours. (Estimate by 10mls.)

	In people with SAH 1 to 3 would apply. Also a determinant of mortality and poorer outcome would be a rebleed (associated with clinical worsening and demonstrated on repeat CT scan) and evidence of vasospasm (ischemia) and clinical worsening. So a reduction in rebleed rates and fewer ischemic events would be objective measures. In people with SDH; Main determinants of outcome are GCS at presentation, midline shift on CT scan, haematoma 'thickness'. 1 to 3 would apply. Change in midline shift or measured heamatoma thickness on CT scan would be surrogate measures of effectiveness.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Currently there are no proven treatment options for reversal of these anticoagulants.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Acute ICH is treated as an emergency with triage to immediate CT scanning and rapid blood pressure reduction. The role of neurosurgery is largely reserved for complications such as hydrocephalus. People are managed on specialist stroke units. There is no available national protocol in place that I know of for reversal of these DOACS if a person has an ICH. Ad hoc management may be with
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE guidelines - NG 128 (updated from CG68) May 2019.
• Is the pathway of care well defined? Does it vary or are there	For ICH: Pathways of care are well defined and involve triage of suspected stroke patients (ischemic or haemorrhagic) by ambulance to specialist acute stroke services. National targets are that people should be seen and have a CT head scan within one hour of arrival and that if an ICH is diagnosed then if a person is

differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	taking a DOAC with a licensed reversal agent this should be given within the first hour or as soon as possible. Protocols for acute blood pressure reduction are as documented in the NICE stroke guidelines. Differences of opinion exist mainly about the acute blood pressure reduction (clinical qualifiers) and choice of agent(s). There are variations in rates of neurosurgery for ICH across the NHS. Management of SAH and SDH is done by neurosurgery or after neurosurgical advice by general physicians in non neurosurgical centres
• What impact would the technology have on the current pathway of care?	Immediate impact. Currently we have a licensed reversal agent for those people taking dabigatran but no reversal for those on other DOACS. This technology if approved would go straight into the 'first hour' care bundle for ICH as above.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	yes
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	This would be used in secondary care within ED departments by stroke teams caring for people with acute ICH taking DOAC
• What investment is needed to introduce the	Already exist

technology? (For example, for facilities, equipment, or training.)	
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Not proven in my opinion as no RCT but no other option for these people.
• Do you expect the technology to increase length of life more than current care?	yes
• Do you expect the technology to increase health-related quality of life more than current care?	yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	People on relevant DOAC requiring urgent major surgery

The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	None as we are already using dabigatran reversal agent
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not sure

16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	no
• Does the use of the technology address any	yes

particular unmet need of the patient population?	
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	None identified
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	
• If surrogate outcome measures were used, do they adequately predict	

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance	
22. How do data on real-world experience compare with the trial data?	

Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
24. Are the criteria used to define haemostasis efficacy in ANNEXA-4 trial appropriate? How is haemostasis efficacy defined in the UK clinical practice?	
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- People taking DOACS who have either ICH, SAH and SDH have high mortality rates and often poor eventual outcomes. Costs to the health economy are largely taken up by ongoing care of disabled survivors rather than hospital costs.
- Currently there is no licensed reversal agent for this DOAC whereas one has been licensed for dabigatran creating differences in management if there is a brain bleed depending on which particular DOAC a person is prescribed
- ICH, SAH and SDH are different in terms of outcome predictors and pathways of care within the NHS. The evidence provided has grouped these together making interpretation difficult. The evidence also contains no control group and is not an RCT. There are differences in the inclusions between the cohort utilised to act as the comparator group – particularly people with bleeds with very poor prognosis. This is a potential source of bias in the conclusions drawn and conclusions should contain major caveats with limitations acknowledged.
- If Andexanet was licensed it could go into the current management pathways for the above almost immediately with no implications for a change in pathway or more staffing resource.
- Andexanet would likely be widely used within neurosciences practice as there is 'nothing else'. It also may be helpful in those people requiring emergency surgery who are taking the specific DOAC.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Andexanet alfa for reversing anticoagulation

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 16/168/04T

BMJ Technology Assessment Group

Title: Andexanet alfa for reversing anticoagulation

Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
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Declared competing interests of the authors:
No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Edwards SJ, Wakefield V, Marceniuk G, Jhita T, Karner C. Andexanet alfa for reversing anticoagulation: A Single Technology Appraisal. BMJ Technology Assessment Group, 2019.

Contributions of authors:

Steve Edwards	Critical appraisal of the company's submission; provided feedback on all versions of the report. Guarantor of the report.
Victoria Wakefield	Clinical lead for the critical appraisal of the company's submission and clinical evidence; drafting of the clinical effectiveness sections and summaries.
Charlotta Karner	Clinical support for the critical appraisal of the company's submission and clinical evidence; and reviewing all other clinical sections of the report.
Gemma Marceniuk	Economic lead. Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections.
Tracey Jhita	Economic support. Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections.

All authors read and commented on draft versions of the ERG report.

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Abbreviation	In full
ACC	American College of Cardiology
AIC	Akaike information criterion
aPCC	activated pro-thrombin complex concentrates
AF	Atrial fibrillation
AHA	American Heart Association
ASH	American Society of Hematology
BIC	Bayesian information criterion
BSH	British Society for Haematology
BMI	Body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CAD	Coronary artery disease
CASP	Critical Appraisal Skills Programme
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
$CHA_2DS_2VAS_C$	Congestive heart failure, hypertension, age ≥75, diabetes, stroke, vascular disease, age between 65-74, and female sex category
CI	Confidence interval
CHMP	Committee for Medicinal Products for Human Use
Cr Cl	Creatinine Clearance
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CT	Computed tomography
CVA	Stroke Ischemic/Uncertain Classification
DOAC	Direct oral anticoagulant
DVT	Deep venous thrombosis
EHRA	European Heart Rhythm Association
EMA	European Medicines Agency
EOI	End of infusion
EQ-5D	EuroQoL-5 Dimensions
ERG	Evidence Review Group
ESC	European Society of Cardiology
ESO	European Stroke Organisation
ETP	Endogenous thrombin potential
FDA	Food and Drug Administration
FEIBA	Factor eight inhibitor bypassing activity
FFP	Fresh frozen plasma
FXa	Factor Xa
GCS	Glasgow Coma Scale
GI	Gastrointestinal
GLA	γ-carboxyglutamic acid
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment

ICEM	International Conference on Emergency Medicine
ICER	Incremental cost effectiveness ratio
ICH	Intracranial haemorrhage
INR	Induced normalised ratio
IPD	Individual patient-level data
IQR	Interquartile range
IS	Ischaemic stroke
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISTH	International Society on Thrombosis and Haemostasis
IU	International unit
IVH	Intraventricular
Kg	Kilograms
KM	Kaplan Meier
LoS	Length of stay
LMWH	Low molecular weight heparin
LY	Life years
LYG	Life years gained
MI	Myocardial infarction
Mg	Milligram
mRS	modified Rankin Score
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHSS	National Institute of Health Stroke Scale
NOAC	Novel oral anticoagulant
ORANGE	ORal ANticoagulant aGEnt-associated bleeding events reporting system
OWSA	One-way sensitivity analyses
PSA	Probabilistic sensitivity analysis
PBS	Pharmaceutical Benefits Scheme
PE	Pulmonary embolism
PCC	Prothrombin complex concentrate
PRBC	Packed red blood cells
QA	Quality assessment
QALY	Quality adjusted life year
RBC	Red blood cell
RCT	Randomised controlled trial
rFVIIa	Recombinant factor VIIa
SAE	Serious adverse event
SAH	Subarachnoid haemorrhage
SAP	Statistical analysis plan
ScHARR	School of Health and Related Research
SD	Standard deviation
SDH	Subdural haemorrhage
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics

SoC	Standard of care
SR	Systematic review
SSC	Subcommittee on Control of Anticoagulation
STA	Single technology appraisal
TEAE	Treatment-emergent adverse events
TE	Thrombotic event
TFPI	Tissue factor pathway inhibitor
TIA	Transient ischemic attack
THSNA	Thrombosis and Hemostasis Society of North America
TSD	Technical Support Document
TTO	Time trade off
TXA	Tranexamic acid
VTE	Venous thromboembolism
WICH	World Intracranial Hemorrhage Conference

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company (Portola Pharmaceuticals) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the safety and effectiveness of andexanet alfa (Ondexxya®) for adults requiring urgent reversal of anticoagulation in case of uncontrolled or life-threatening bleeding, after treatment with the factor Xa-inhibiting direct oral anticoagulant (DOAC) apixaban or rivaroxaban. The company provided an overview of the role of factor Xa (FXa) in the clotting cascade (of blood coagulation), role of anticoagulants, risk and type of bleeding events and the burden of anticoagulant associated bleeding events in the company submission (CS). The evidence review group (ERG) notes that the most common major bleeds with DOACs are gastrointestinal (GI) bleeds and intracranial haemorrhages (ICH).

Andexanet alfa is a recombinant modified human FXa protein that binds to FXa inhibitors (e.g. apixaban) and reduces the concentration of the unbound (pharmacologically active) inhibitors. Andexanet alfa received conditional marketing authorisation from the European Medicines Agency (EMA) on 26 April 2019 for use in adult patients treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. The ERG notes that andexanet alfa is the only FXa inhibitor reversal agent for apixaban and rivaroxaban to be approved for use in the UK and that it is authorised for use at two different doses (high dose and low dose) with a key criterion for deciding on the dose being the time since last dose of FXa inhibitor.

The comparators listed in the NICE final scope were established clinical management of uncontrolled or life-threatening bleeding without andexanet alfa (including prothrombin complex concentrate with or without tranexamic acid). The ERG's clinical experts reported that 4-factor pro-thrombin complex concentrates (4F-PCCs) are the most commonly used treatments in patients whom would likely be eligible for andexanet alfa and that other supportive treatments including red cell transfusions may also be given concomitantly.

The company's clinical evidence is based on ANNEXA-4 an ongoing phase 3b/4, prospective, open-label, single-arm study. ANNEXA-4 was designed to evaluate the efficacy and safety of andexanet alfa in patients receiving a FXa inhibitor (apixaban, rivaroxaban, edoxaban, or enoxaparin) who present with acute major bleeding. In total, 352 patients were enrolled in ANNEXA-4; all patients received andexanet alfa and were followed for 30 days or until death. In the safety population for the whole cohort of ANNEXA-4, 9% of patients had received enoxaparin or edoxaban. However, only apixaban and rivaroxaban patients (n = 322) are of relevance to this STA given the European Marketing authorisation and so the population whom will be eligible for andexanet alfa in the UK. The mean age

of patients in the apixaban and rivaroxaban subgroup of ANNEXA-4 was [redacted] years. UK patients represented only [redacted]% of the subgroup with [redacted] patients from North America (n = [redacted]%). Clinical experts considered patients in ANNEXA-4 relevant to the NICE final scope and representative of patients likely to require andexanet alfa in the UK. However, the ERG notes that the criteria for determining the andexanet alfa dose were changed during the enrolment for ANNEXA-4 resulting in some patients who may not have received the marketing authorisation recommended dose of andexanet alfa. However, the impact of the likely bias resulting from this dose amendment on the efficacy results of ANNEXA-4 is unclear.

ANNEXA-4 had co-primary outcomes which were the percent change in anti–FXa activity and the rate of excellent or good haemostatic efficacy 12 hours after the andexanet alfa infusion. The ERG notes that the change in anti-FXa activity is a laboratory measure and not of direct relevance to the NICE final scope. However, the ERG considers the rate of excellent or good haemostatic efficacy to be relevant in relation to the control of bleeding outcome listed in the NICE scope.

The company conducted a systematic literature review (SLR) and identified 17 PCC studies suitable for inclusion. The ORANGE study, which had been previously excluded, was deemed to be the most suited for comparison with ANNEXA-4 in propensity score matching analyses. The ERG has some concerns about the transparency of study inclusion and the identification of the ORANGE study as it is not clear why data from the other 17 PCC studies were restricted to an appendix of the CS. The ERG is therefore uncertain whether ORANGE is the only appropriate study to inform the analysis of the clinical efficacy of andexanet alfa compared with 4F-PCC but the ERG acknowledges that it is the largest study with UK-based data and had individual patient-level data (IPD) available. The ERG also considers it important to highlight that there were no RCTs suitable for inclusion and that all included studies relate to single-arm cohort studies.

The ORANGE study (n = 2,192) was a UK-based, 3-year, prospective cohort study that collected data from multiple UK hospitals on the presentation and clinical outcomes of patients admitted for a major bleeding episode while on oral anticoagulant therapy. However, as for ANNEXA-4, only the apixaban and rivaroxaban subgroup of ORANGE (n = 372) is of relevance to this STA and within this subgroup only patients on 4F-PCC (n = 149) were deemed suitable for matching with ANNEXA-4.

Data on andexanet alfa were submitted for all outcomes listed in the NICE final scope with the exception of health related quality of life (HRQoL) which was not collected in ANNEXA-4. The ERG also notes that data from the propensity score matching analyses for the comparison of andexanet alfa with 4F-PCC were only reported for length of hospital stay and 30-day mortality.

1.2 Summary and critique of the clinical effectiveness evidence submitted by the company

The ERG notes that the efficacy analysis population in ANNEXA-4 included only patients who retrospectively met both of two criteria: baseline anti-FXa activity of at least 75 ng per millilitre (or ≥0.25 IU per millilitre for patients receiving enoxaparin) and confirmed major bleeding at presentation, as determined by the adjudication committee. The safety analyses included all the patients who had received andexanet alfa (i.e. all of the patients included in ANNEXA-4). The ERG's preferred analysis set is therefore the safety population of the subgroup of patients who were taking apixaban or rivaroxaban at baseline. This is because in clinical practice patients will not be required to have a minimum pre-specified baseline anti-FXa activity prior to treatment with andexanet alfa. Unless specified otherwise all results relate to this subgroup of ANNEXA-4.

In the apixaban and rivaroxaban subgroup of ANNEXA-4, the site of bleed was intracranial haemorrhage (ICH) for 209 patients, gastrointestinal (GI) bleed for 82 patients, [redacted] for [redacted] patients and other sites for the remaining [redacted] patients. Most patients received [redacted] The ERG also notes from the company's response to clarification, that [redacted]% of patients in the apixaban or rivaroxaban subgroup of ANNEXA-4 received concomitant aspirin and [redacted]% received concomitant clopidogrel, both of which may impact on the results for haemostatic efficacy. However, the ERG acknowledges that this proportion of patients on concomitant aspirin and clopidogrel may be reflective of UK clinical practice and reversal of the antiplatelet agent should also be considered as part of the treatment of a major bleed.

Haemostatic efficacy was adjudicated by an independent and blinded endpoint adjudication committee as excellent or good in [redacted]% ([redacted]) of the safety population subgroup of patients who had received apixaban or rivaroxaban ([redacted]), 12 hours after andexanet alfa infusion. Similar rates of haemostatic efficacy were seen in both the ICH and GI bleed subgroups. The ERG notes that a total of [redacted]% of patients in the apixaban or rivaroxaban subgroup received blood products within the first 16 hours of treatment with andexanet and only [redacted]% of patients received blood products beyond 16 hours.

The ERG considers the modified Rankin Scale (mRS) data in ANNEXA-4 suggest [redacted] The ERG also notes that there was [redacted]

The data on surgical or other interventions to control bleeding in ANNEXA-4 suggest that [redacted]% of patients required surgical or other interventional procedures for control of their bleeding and [redacted]

[redacted] The non-standardised recording of these data and small patient numbers limits their power and generalisability and so both the company and ERG considers that these results should be interpreted with caution.

Adverse effect data were presented by the company for the full ANNEXA-4 study population and not just the apixaban and rivaroxaban subgroup which the ERG considers reasonable. A total of [redacted] patients were deemed to have experienced treatment-related adverse events (AEs). There were [redacted] patients who experienced a serious adverse event (SAE) [redacted] patients experienced TEAEs resulting in premature discontinuation of andexanet alfa and there was a total of [redacted] deaths during ANNEXA-4. In terms of thrombotic events, data for the population receiving apixaban or rivaroxaban were also presented and these data showed [redacted] patients had a first thrombotic event by 30 days [redacted]. The data on the restart of anticoagulation after andexanet alfa in ANNEXA-4 showed that [redacted] of patients restarted oral anticoagulation, [redacted]

The results of the propensity score matching analysis between ANNEXA-4 and ORANGE for the outcome of length of hospital stay suggest [redacted] The results of the propensity score matching analyses for 30-day mortality suggest that [redacted] The ERG recommends caution when interpreting the results of the propensity score matching for both length of hospital stay and 30-day mortality for reasons detailed in Section1.1.

1.3 Summary of cost effectiveness evidence submitted by the company

The company submitted a single *de novo* economic model developed in Microsoft Excel© to assess the cost-effectiveness of andexanet alfa compared with standard care (4F-PCC with or without tranexamic acid). The patient population considered by the company for the cost-effectiveness analysis is based on the condition marketing authorisation, which includes patients who received a direct FXa inhibitor (apixaban or rivaroxaban) and are experiencing a life-threatening or uncontrolled bleeding event, which consequently requires anticoagulant reversal. The cost-effectiveness analysis was split into three cohorts including the whole cohort (all patients with either an ICH, GI bleed, or 'other major bleed'), ICH plus GI cohort and ICH cohort. In the whole cohort, the company assumed 'other major bleeds' included intraocular bleeds, intraspinal bleeds, pericardial bleeds and retroperitoneal bleeds.

The model structure implemented by the company consisted of a short-term decision tree, which modelled the first 30 days of the acute major bleeding event; defined as either an ICH, GI bleed, intraocular bleed, intraspinal bleed, pericardial bleed or retroperitoneal bleed, and a long-term Markov

model for patients who survive the acute bleeding event. When patients transition into their respective survivor health states in the Markov model, they remain there until death. A cycle length of one month was implemented in the Markov model with a half cycle correction applied. The company did not include treatment-related adverse events, or thrombotic events in the economic model.

The proportion of patients in the decision tree who died following an acute major bleeding event was taken from an indirect comparison of results from the ANEXXA-4 and ORANGE studies for andexanet alfa and standard care, respectively. The 30-day ICH and GI bleed mortality for andexanet alfa was obtained from the propensity score matching results for ANNEXA-4, while the 30-day ICH and GI bleed mortality for standard care was obtained from the propensity score matching results for ORANGE. Mortality for intraocular and intraspinal bleeds was set to 0% in both treatment arms based on UK clinical expert opinion, while it was assumed there would a 25% reduction in the andexanet alfa 30-day mortality for pericardial bleeds and retroperitoneal bleeds compared to standard care.

In the long-term model, the company assumed that patients who survive an uncontrolled or life-threatening bleed will have a decreased life expectancy compared to the general population. Long-term mortality for ICH survivors is based on the mRS distribution of patients from ANNEXA-4 for andexanet alfa patients and Øie *et al.* 2018 for standard care patients. The company fitted parametric distributions to the Kaplan Meier (KM) overall survival data reported in Huybrechts *et al*. 2008 for each mRS category and produced a weighted survival curve for each treatment arm. As for non-ICH survivors, the company adjusted all-cause general population mortality using evidence (a hazard ratio) in patients with atrial fibrillation (Friberg *et al*. 2007).

Utility values implemented in the model are based on EQ-5D data or time trade off (TTO) data identified in the literature. The utility decrement used in the short-term model for an acute non-ICH bleed event was -0.1511 and this was applied to the general population (75 years and over) baseline utility of 0.73. For an acute ICH, the company directly applied a utility of 0.33. In the long-term model, the company assumed that survivors of GI, retroperitoneal and pericardial bleeds will not suffer long-term morbidity and as such HRQoL will return to baseline levels. For survivors of intraspinal bleeds, the company assumed that 50% will suffer from paralysis and incur a utility decrement, and 25% of intraocular bleed survivors will have monocular blindness and incur a utility decrement. The company also assumed a 25% reduction in paralysis and monocular blindness for intraspinal and intraocular bleed survivors who received andexanet alfa, aligned with the assumption on mortality benefit. Long-term HRQoL for ICH survivors is based on the mRS distribution of patients from ANNEXA-4 for andexanet alfa patients and Øie *et al.* 2018 for standard care patients. The company obtained utility values by mRS from Fletcher *et al.* 2015 and calculated weighted utilities for andexanet alfa (0.53) and standard care (0.42). The company then applied the difference in utility (0.11) to the TA341 baseline assumed for standard care (0.61) to obtain the utility value for andexanet alfa. Thus, the health state utility values used in the

economic model for ICH survivors in the standard care arm and andexanet alfa arm are 0.61 and 0.72, respectively.

The costs considered in the economic model consist of: intervention and comparator acquisition and administration costs; acute bleed management costs; long-term bleed management costs; and, re-initiation of FXa inhibitor costs. The list price of a 200 mg vial of andexanet alfa is £2,775 and the company have not proposed a patient access scheme (PAS) discount. Long-term bleed management costs were incurred by ICH survivors and the proportion of patients affected by paralysis and blindness in the intraspinal bleed survivor and intraocular bleed survivor states, respectively. In line with the assumptions regarding HRQoL for intraocular and intraspinal bleeds, the proportion of patients experiencing paralysis and blindness was reduced by 25% for patients receiving andexanet alfa. Long-term costs for ICH survivors was based on the mRS distribution of patients from ANNEXA-4 for andexanet alfa patients and Øie *et al.* 2018 for standard care patients. The company mapped these mRS data to the disability categories reported in Luengo-Fernandez *et al*. 2013 to calculate weighted hospital costs (assuming mRS 0-2 is non-disabling, mRS 3-4 is moderately-disabling and mRS 5 is totally-disabling strokes) and in Persson *et al*. 2017 to calculate weighted rehabilitation costs (assuming mRS 3-5 is dependent and mRS 0-2 is independent).

The company base case deterministic incremental cost-effectiveness ratio (ICER) is £11,636, £18,741 and £18,738 per quality-adjusted life year (QALY) gained in the whole cohort, ICH plus GI cohort and ICH cohort, respectively. The company also carried out one-way sensitivity analyses, scenario analyses and probabilistic analyses to test the robustness of cost-effectiveness results.

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

- The patients in ANNEXA-4 are considered generally reflective of patients who are likely to be eligible for treatment with andexanet alfa in the UK.

- The company provided results for the ERG's preferred analysis set from ANNEXA-4, the safety population of the subgroup of patients on apixaban or rivaroxaban at baseline.

- Methods used for the propensity score matching analysis appeared to be mostly in line with guidance from the NICE Decision Support Unit and justification was provided where the limits of the evidence base prevented all effect modifiers being included as covariates (e.g. severity of bleed using mRS data was omitted due to the absence of data from the ORANGE study).

- The company included alternative clinically relevant covariates in response to clarification questions to adjust the study populations in the propensity score matching analyses to compare andexanet alfa with 4F-PCC.

- Data for the co-primary clinical outcome of haemostatic efficacy were adjudicated by an independent and blinded endpoint adjudication committee.

- Subgroup results were provided for the GI bleed subgroup in addition to the ICH subgroup specified in the final scope issued by NICE which is also of relevance in the UK and therefore gives a more granular breakdown of the efficacy of andexanet alfa.

Economic

- The economic model was straightforward and easy to navigate. The ERG did not encounter any major difficulty validating the methodologies applied in the economic model. In addition, the model was built to be flexible, allowing key assumptions to be changed easily. The company also included all requested scenario analysis in the model with drop down options to enable immediate use in the analysis.

1.4.2 Weaknesses and areas of uncertainty

Clinical

As previously discussed in Section 1.1, there were limitations in the available data from ANNEXA-4: HRQoL was not reported and data on surgical or other interventions to control bleeding were collated through hand searching each patient record. Due to the non-standardised recording of data on surgical or other interventions to control bleeding, the ERG considers that these results should be interpreted with caution. The ERG also has some concerns about the transparency of study inclusion of studies relating to 4F-PCC from the company's SLR and the identification of the ORANGE study for the propensity score matching. In addition to ANNEXA-4 and ORANGE, the company included, and data extracted 17 studies on PCC in the SLR but did not discuss why they were only reported in appendix D of the CS. The ERG is therefore uncertain whether ORANGE is the only appropriate study to inform the analysis of the clinical efficacy of andexanet alfa compared with 4F-PCC but the ERG acknowledges that it is the largest study with UK-based data and had IPD available.

Due to the absence of direct head to head studies or RCTs for the comparison of andexanet alfa with 4F-PCC, comparative data presented in the CS are limited to the propensity score matching of the single-arm cohort studies ANNEXA-4 and ORANGE. In addition, limited outcome data suitable for analysis between andexanet alfa and 4F-PCC were available with only analyses conducted by the company for 30-day mortality and length of hospital stay. The ERG considers length of hospital stay is

likely to be intrinsically linked with mortality as the longer hospital stay a patient has, the lower their risk of dying within 30 days is likely to be (assuming similar risk of death between both ANNEXA-4 and ORANGE). In addition, the ERG notes that data used from ORANGE for the propensity score matching analysis of length of hospital stay were censored at 30-days but there was longer follow-up in ANNEXA-4 and it was not censored to match that from ORANGE despite the company having access to the IPD for both studies. The ERG also acknowledges the company's concern that length of hospital stay may be impacted by differences in study location between ANNEXA-4 ([redacted] UK) and ORANGE (100% UK). The ERG therefore recommends caution when interpreting the results of the propensity score matching for length of hospital stay particularly if they are viewed independently to the mortality data.

Despite the availability of data, treatment-emergent serious thrombotic events were deemed unsuitable for propensity score matching as they only occurred in ≤2% of patients across the ANNEXA-4 and ORANGE studies, which the ERG considers reasonable.

In terms of comparability of the study populations of ANNEXA-4 and ORANGE, the ERG notes that ORANGE did not require bleeds to be life-threatening or uncontrolled, but this was a requirement in ANNEXA-4 and is a requirement for treatment with andexanet alfa. The ERG's clinical experts reported that the patients on 4F-PCC in ORANGE were however likely to be similar to those in ANNEXA-4 and so the impact of this difference in inclusion is likely to be minimal.

The company reported that the covariates selected for use in the propensity score matching analyses were those deemed important based on UK clinical expert opinion regarding their effect on 30-day mortality and the results of statistical testing (t-tests and Chi-squared tests) regarding the strength of their association with treatment assignment. In response to clarification questions, the company revised their selection of covariates to include additional covariates suggested by the ERG's clinical experts and removing some relating to baseline medical history that were not associated with statistically significant differences between ANNEXA-4 and ORANGE. However, the company reported that they were unable to include severity of bleed (e.g. as assessed by mRS) or volume of bleed as covariates in the propensity score matching analysis as these data weren't collected in the ORANGE study. The ERG considers bleed severity to be of particular importance as clinical experts reported it was likely to be a prognostic indicator and the use of the mRS in the economic model is a key driver in the cost-effectiveness analysis (see below).

The ERG also notes that the company presented subgroup data for patients with other major bleeds from the propensity score matching analysis in addition to data for the ICH and GI bleed subgroups. However, the ERG notes that site of bleed wasn't included as a covariate in the other bleeds subgroup analysis [redacted]. The ERG does not consider

this appropriate as there was wide variation in the site of bleed in ANNEXA-4 compared to ORANGE and the ERGs clinical experts reported that the different sites of bleeds classed as other is likely to result in differences in mortality and length of hospital stay, the outcomes in the propensity score matching analyses. In fact, the ERG does not consider the data on other major bleeds to be suitable for propensity score matching analysis or any other analysis given [redacted]. The ERG therefore recommends caution when interpreting the results for the other bleeds population in the propensity score matching analyses.

Finally, the ERG notes that [redacted]. In addition, the ERG notes that a matching with replacement method was used and in the 30-day mortality analyses [redacted]. The ERG also considers that unobserved confounders are likely to be present due to the non-randomised study design of ANNEXA-4 and ORANGE, and so the results of the propensity score matching analyses are subject to inherent bias.

Economic

As mentioned throughout this report, the ERG has concerns with the modelling of 'other major bleeds' in the economic model as it is primarily driven by assumptions based on the company's clinical expert opinion in the absence of outcomes data. Moreover, the NICE final scope does not limit 'other major bleeds' to the four types included in the company's economic analysis, and the ERG would emphasise that the results of the company's model only relate to intraocular, intraspinal, pericardial and retroperitoneal bleeds as opposed to the wider range of 'other major bleeds' seen in ANNEXA-4. Furthermore, the ERG's clinical experts highlighted that the 'other major bleeds' observed in ANNEXA-4 would generally be managed outside of an ambulatory setting using alternative reversal strategies such as cessation of the FXa inhibitor alone. As such, the ERG considers the most robust estimates for cost-effectiveness are for the ICH plus GI and ICH only cohorts as it removes the uncertainty of assumptions needed to model 'other major bleeds'. However, the ERG acknowledges the NICE final scope is for the full population covered by the marketing authorisation and therefore considers it important to point out the flaws in the company's analysis of 'other major bleeds' rather than focus this report on its preferred population.

With regards to the company's main outcome measure, the company considered the 30-day mortality rate for 'other major bleeds' obtained from propensity score matching to be counterintuitive (adjusted 30-day mortality rate of [redacted] for standard care versus [redacted] for andexanet alfa) and therefore did not use it to inform the economic analysis. Instead, the company assumed that treatment with andexanet alfa would reduce the risk of death observed in ORANGE by 25% for pericardial and retroperitoneal

bleeds. Although the company highlighted that this was a conservative estimate compared to the relative reductions observed in the propensity score matching for ICH and GI bleeds [redacted] compared to standard care; the company did not provide a clinical rational why any relative reduction would be seen in 'other major bleeds'. Thus, the ERG considers that in the absence of any evidence to substantiate the 25% relative reduction in 30-day mortality associated with andexanet alfa compared to standard care, the company's scenario of no reduction is a more appropriate scenario. This also lies in-between the results from propensity score matching and the company's base case assumption (a relative reduction of 25%).

In addition, the use of the mRS for estimating the impact of andexanet alfa on ICH survivors has been a central issue for the cost-effectiveness analysis as it affects the estimation of costs, quality of life and mortality. In short, the ERG is concerned that the study used to inform the severity of ICH survivors in the standard care arm represents patients with a severe subtype of ICH (intracerebral haemorrhage) and therefore overestimates the severity of the mRS in the standard care arm. To account for the proportion of patients that would experience one of the most severe subtypes of ICH (intracerebral haemorrhage) in the economic analysis, the ERG asked the company to explore a scenario where intracerebral-specific mRS results (recorded in Øie *et al*. 2018 for standard care and ANNEXA-4 for andexanet alfa) are applied to the proportion of patients that experienced an intracerebral haemorrhage in ANNEXA-4, and the remaining proportion of patients in both treatment arms have mRS results equal to ANNEXA-4. However, when the ERG looked into the intracerebral-specific mRS results from ANNEXA-4, the ERG found them to include the largest proportion of patients with a mRS of 5 ([redacted]). A smaller proportion of patients with a mRS of 5 were seen in Øie *et al*. 2018 for intracerebral-specific patients (19.7%) and this finding lacks face validity according to both the ERG and the company experts. However, the ERG would like to caveat this finding with the fact the company undertook a naïve comparison and did not provide baseline data for intracerebral-specific patients in ANNEXA-4 and therefore it is unclear how the distribution of patients in the different mRS categories changed over the 30 days. Nonetheless, the ERG considers this to be a key scenario that accurately attributes intracerebral-specific mRS results to patients with intracerebral haemorrhages. As an alternative, the ERG also requested the company to provide a scenario where mRS results recorded in ANNEXA-4 are used in both treatment arms to remove all uncertainty associated with mRS.

An additional and related area of concern with ICH survivors is the company's estimation of long-term HRQoL. The company initially performed calculations using published utility and mRS data to calculate weighted utilities for andexanet alfa and standard care, which only serve the purpose of estimating the potential utility increment associated with andexanet alfa. The utility increment is applied to another utility value (0.61) obtained from TA341, which is used to represent standard care. The final calculated utility for andexanet alfa, applying the utility increment to the NICE TA341 utility value is

0.72, which is 0.01 less than the UK general population norms for people aged 75 years and above. The company argue that using the weighted utility values directly, instead of applying the utility increment to another baseline, is not appropriate as the mRS distribution for standard care are obtained from *Øie* et al. *2018* a study, which is a study conducted in Norway. However, as *Øie* et al. *2018* has been used to inform mRS distributions throughout the economic model, the ERG considers the company's argument is inconsistent. The ERG considers the weighted utility values for standard care and andexanet alfa (0.42 and 0.53, respectively) are more appropriate to use in the model as the source utilities are based on a population closer in age to the ANNEXA-4 population (mean age of 77 years) and it eliminates the introduction of another utility from a different source, resulting in an unnecessary calculation step. Furthermore, the ERG considers 0.01 utility difference for ICH survivors of varying degrees of severity, compared with the general population lacks face validity.

With regards to the long-term costs for ICH survivors, the ERG is concerned that the company overestimated the duration of rehabilitation. The ERG verified whether ICH patients would receive rehabilitation on the NHS for a lifetime with its clinical experts. The ERG's clinical experts stated that rehabilitation provided by the NHS would, at most, be given for a matter of months rather than years. To address this, the ERG explored scenarios where the rehabilitation cost for dependent ICH survivors was applied for six and 12 months.

An additional concern for the costs implemented in the economic model, was the company's estimation of vial wastage for andexanet alfa. The ERG considers the company's approach underestimates vial wastage and so the cost of treatment. The company's uses rounded-up units for low and high dose of andexanet alfa and weights these based on the proportion of patients receiving each dose. The ERG considers this approach does not accurately reflect vial wastage, as the number of units estimated from the weighting calculation (5.43 or 5.48, depending on the cohort) should have been rounded up to 6 units.

Finally, aside from the ERG's concerns related to the 30-day mortality for 'other major bleeds', the ERG identified several issues with the long-term complications of intraspinal and intraocular bleeds. In particular, the company assumed that treatment with andexanet alfa would reduce the instances of paralysis and monocular blindness by 25% compared to standard care, thus increasing HRQoL and reducing costs for intraspinal and intraocular survivors in the andexanet alfa arm compared to the standard care arm. In their clarification response, the company justified this assumption by stating that andexanet alfa [redacted] 30-day mortality by [redacted] compared with standard care for all three cohorts and clinical experts advised that reduction in paralysis and monocular blindness would be consistent with the mortality findings. The ERG considers that this adds another layer of uncertainty to the whole cohort cost-effectiveness results and so considers the company's scenario of a 0% reduction

in paralysis and monocular blindness for patients on andexanet alfa is an appropriate, if conservative, scenario.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a series of exploratory analyses in addition to the scenarios provided by the company during the clarification stage, to test the impact of changes in the data and assumptions used by the company on the ICER. The choice of scenarios was driven by key issues found by the ERG around the modelling of treatment effectiveness, HRQoL, and costs. The scenarios which replaced inappropriate assumptions were incorporated into the ERG base case, and were as follows:

- Treatment with andexanet alfa results in a relative reduction in 30-day mortality for other major bleed patients of 0% compared to standard care. The ERG considers that in the absence of any evidence to substantiate the company's base case assumption (a relative reduction of 25%), no reduction is more appropriate. The ERG's assumption also lies in-between the results obtained from the company's propensity score matching and the company's base case assumption.

- Treatment with andexanet alfa results in a relative reduction for paralysis in intraspinal bleeds and blindness in intraocular bleeds of 0% compared to standard care The ERG considers that in the absence of any evidence to substantiate a relative reduction of 25%, no reduction is more appropriate, if, conservative.

- Applying alternative mRS distributions. The ERG's base case employs intracerebral-specific mRS results to [redacted] of patients thus feeding into long-term mortality, HRQoL and cost calculations, while the ERG's alternative base case employs mRS distributions from ANNEXA-4 to patients receiving andexanet alfa and patients receiving standard care.

- An alternative and more accurate approach to calculate vial wastage for andexanet alfa. The ERG considers the company's approach underestimates the cost of treatment.

- Reducing the duration of rehabilitation for ICH survivors from lifetime to 12 months. The ERG verified whether ICH patients would receive rehabilitation in the NHS for a lifetime with its clinical experts. The ERG's clinical experts stated that lifetime rehabilitation provided by the NHS would, at most, be given for a matter of months rather than years.

- Applying the weighted utility values by mRS directly, instead of applying the utility increment to the TA341 baseline. This eliminates the introduction of another utility from a different source, resulting in an unnecessary calculation step.

Incorporating the assumptions above, the ERG produced six different base case ICERs for the three cohorts, ranging from £27,834 to £37,311. These include one preferred base case ICER (using intracerebral-specific mRS distributions) and one alternative base case ICER (assuming no treatment benefit in mRS) for each cohort. The highest ICER corresponds to the ICH cohort where intracerebral-specific mRS results are applied to [redacted] of ICH patients. Conversely, the lowest ICER corresponds to the ICH plus GI cohort where mRS distributions from ANNEXA-4 are applied to both treatment arms. Table A presents a summary of the ERG preferred base case ICERs in each cohort, while Table B presents the ERG's alternative base case ICERs.

Overall, all six ICERs produced by the ERG are above NICE's lower threshold of £20,000 which may be a cause for concern given the uncertainty in the underlying comparison of treatment effectiveness. In addition, using either the ERG's preferred (using intracerebral-specific mRS distributions) or alternative base case assumptions (assuming no treatment benefit in mRS), the benefits of andexanet alfa are derived from reductions in 30-day mortality compared to standard care for ICH and GI bleeds.

Table A. Summary of ERG ICERs by population, ERG base case

Population	Company's corrected base case ICER, deterministic	ERG ICER, deterministic	ERG ICER, probabilistic (10,000 simulations)
Whole cohort	£12,489	£33,541	£33,735
ICH plus GI cohort	£18,663	£32,352	£32,217
ICH cohort	£18,640	£37,311	£37,216
Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin score; QALYs, quality adjusted life years.			

Table B. Summary of ERG ICERs by population, ERG alternative base case

Population	Company's corrected base case ICER, deterministic	ERG ICER, deterministic	ERG ICER, probabilistic (10,000 simulations)
Whole cohort	£12,489	£28,997	£29,297
ICH plus GI cohort	£18,663	£27,834	£27,754
ICH cohort	£18,640	£30,193	£30,037
Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin score; QALYs, quality adjusted life years.			

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

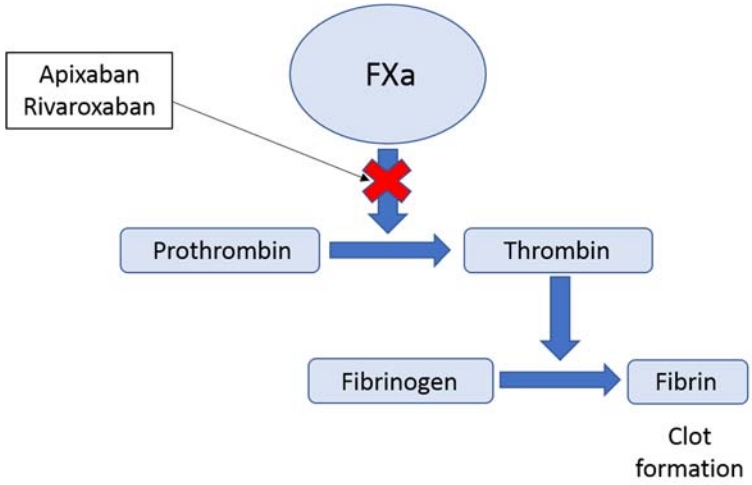
The company provided an overview of the role of factor Xa (FXa) in the clotting cascade (of blood coagulation), role of anticoagulants, risk and type of bleeding events and the burden of anticoagulant associated bleeding events in Section B.1.3.1 to B.1.3.3 of the company submission (CS). The final scope issued by the National Institute for Health and Care Excellence (NICE) for this Single Technology Appraisal (STA) defines the population of interest as adults requiring urgent reversal of anticoagulation in case of uncontrolled or life-threatening bleeding, after treatment with a factor Xa-inhibiting direct oral anticoagulant (DOAC).[1] The Evidence Review Group (ERG) notes that the conditional European marketing authorisation for andexanet alfa restricts it's use to patients who have received either apixaban or rivaroxaban rather than the full spectrum of factor Xa inhibitors.[2]

The ERG considers the overviews of the clotting cascade, role of anticoagulants and bleeding events associated with DOACs presented by the company appropriate and relevant to the decision problem. A synopsis is provided below with supplementary information from the ERG's clinical experts:

- Patients at high risk for thrombotic events, including those with atrial fibrillation (AF) or venous thromboembolism (VTE), generally receive long-term oral anticoagulation treatment to prevent thrombotic events. There are several classes of oral anticoagulation treatment, of which DOACs are one. The DOACs include rivaroxaban, apixaban and edoxaban, which are oral direct Factor Xa (FXa) inhibitors, and dabigatran which is a direct thrombin inhibitor.

- Direct FXa inhibitors selectively block the active site of FXa, which is the primary site of amplification in the coagulation cascade, where one molecule of FXa can facilitate the generation of more than 1,000 thrombin molecules (Figure 1).[3]

Figure 1. Site of action of apixaban and rivaroxaban (adapted from CS Document B, Figure 1)



- A serious complication associated with any anticoagulant treatment is the occurrence of unanticipated, serious or life-threatening bleeding episodes which may occur spontaneously or as a result of trauma, complications from invasive procedures, or other illnesses or conditions.

- The International Society on Thrombosis and Haemostasis (ISTH) definition of major bleeding in non-surgical studies is presented in Table 1. This definition is frequently used in clinical trials and was used in ANNEXA-4, the study providing the clinical effectiveness data for andexanet alfa that underpins the company submission (CS).[4]

Table 1. ISTH major bleeding definition[4] (adapted from CS Document B, Table 3)

Major bleed is defined as any one of the following:		
Haemoglobin	**Bleed site**	**Transfusion**
Drop of > 2g/dL	• Bleeding is expected to be fatal and/or • Symptomatic bleeding that is: – intracranial – intraspinal – intraocular – pericardial – intra-articular – intramuscular with compartment syndrome – retroperitoneal	> 2 units of blood or packed red blood cells
Abbreviations: CS, company's submission; ISTH, International Society on Thrombosis and Haemostasis.		

- Bleeding events resulting from complications of treatment with FXa inhibitors are associated with significant morbidity and mortality. Data from clinical trials and real-world analyses have shown major bleeding in approximately 2% to 4% of AF patients treated with FXa inhibitors.[5-9] Data on the location of DOAC associated bleeds suggest that the majority of the major bleeds occur in the gastrointestinal (GI) tract (30% to 50% of major bleeds), and 10% to 25% of major bleeding events are intracranial haemorrhages (ICHs).[6-8, 10, 11]

- Patients on a FXa inhibitor, who experience a major bleeding event are at an increased risk of death. [11] Thirty-day mortality rates are approximately 15% to 20% in FXa inhibitor-treated patients with AF who have a major bleeding event. [11-13] When the major bleeding event is an ICH, 30-day mortality rates can be up to 45%. [11] In addition, ICH survivors are at risk of long term severe disability. [14-16] The UK study ORANGE (ORal ANticoagulant aGEnt-associated bleeding events reporting system)[17], a real-world observational study demonstrated a similar 30-day rate of bleeding-related mortality in patients being treated with direct FXa inhibitors (21%) compared to the ARISTOTLE[11] and ROCKET-AF[12] randomised controlled trials in patients with AF (15% and 20%, respectively).

- Data from clinical trials and real-world studies show that patients with major bleeding are also at increased risk of developing subsequent thrombotic events due to a procoagulant state and interruption of anticoagulation following a bleed. [10-12, 18, 19] Therefore, it is important to ensure timely reinstatement of anticoagulation in patients with major bleeding where clinically appropriate.

2.2 Critique of company's overview of current service provision

The company provided an overview of existing guidelines and treatment options for patients on DOACs who experience major or life-threatening bleeding events (CS Section B.1.3.4). The ERG notes that andexanet alfa has conditional marketing approval in the EU for the reversal of the FXa inhibitors rivaroxaban and apixaban and that the marketing authorisation does not include the DOAC edoxaban.[2] Other than andexanet alfa, no other reversal agent is approved to reverse the anticoagulant effects of rivaroxaban or apixaban.

The company reported that the current management of major bleeding attributed to anticoagulation with FXa inhibitors is primarily supportive and treatment options include activated charcoal, fresh frozen plasma, and pro-haemostatic agents such as prothrombin complex concentrate (PCC).[20] PCC is available as non-activated three-factor PCC (3F-PCC), non-activated four-factor PCC (4F-PCC) and activated 4F-PCC (FEIBA®; Factor VIII Inhibitor Bypassing Activity). However, both the company and the ERGs clinical experts considers that only 4F- PCC tends to be used in FXa attributed bleeding events in UK clinical practice and that the use of any of the PCC formulations for treatment of FXa related bleeding events is off-label. The two main types of 4F-PCC used in the UK and their components are summarised in Table 2.

Table 2. 4F-PCCs used in the UK (adapted from CS Document B, Table 6)

Pro-haemostatic agent	Components
4F-PCC (Beriplex®)	Heparin, factors II, VII, IX, X, proteins C and S, antithrombin III, and human albumin
4F-PCC (Octaplex®)	Factors II, VII, IX, X, proteins C and S

Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; CS, company's submission; UK, United Kingdom.

PCCs contain highly concentrated plasma-derived coagulation factors to replenish those that are missing in haemophilia or warfarin-treated patients in order to support clot formation.[21] These factors are all upstream of FXa in the clotting cascade and therefore PCCs do not directly reverse the effects of FXa inhibitors instead they provide non-specific supplementation of coagulation factors. PCCs have been studied in healthy subjects and the results confirm that PCCs do not reverse anti-FXa activity or affect unbound concentration of edoxaban, rivaroxaban, or apixaban.[22-25] However, due to the longer half-live of PCCs (6-72 hours for the different factors) compared to FXa inhibitors (7-12 hours) the effects of PCCs can persist for a few days after the Xa inhibitors have cleared thus resulting in a pro-thrombotic state.[23, 26, 27] PCCs cause a sustained excess in thrombin generation and have been associated with thrombotic complications including VTE, disseminated intravascular coagulation, microvascular thrombosis, and myocardial infarction (MI).[28]

A further potential pro-haemostatic treatment option is off-label recombinant factor VIIa (rFVIIa), although this is rarely used in clinical practice in the UK.[20, 29] Tranexamic acid (TXA) is an anti-fibrinolytic and has been shown to reduce mortality in trauma patients who were bleeding or at risk of significant bleeding,[30] and is recommended in the NICE trauma guideline for patients with major trauma and active or suspected active bleeding (irrespective of the use of anticoagulation).[31] However, the efficacy of TXA in reversal of DOAC related bleeding is unknown, although the ERG's clinical experts report that it is in some local guidelines as a treatment option that can be used alongside other interventions.

There are numerous guidelines and guidance documents published on the reversal of the anticoagulant effects of DOACs including:

- the British Society of Gastroenterology,[32]
- British Committee for Standards in Haematology,[33]
- the European Stroke Organisation (ESO),[34]
- the European Heart Rhythm Association (EHRA),[35]
- the European Society of Cardiology (ESC) Working Groups on Cardiovascular Pharmacotherapy and Thrombosis,[20]

- the pan-European, multidisciplinary Task Force for Advanced Bleeding Care in Trauma,[36]
- the Neurocritical Care Society/Society of Critical Care Medicine,[37]
- the American Heart Association (AHA),[38]
- the American College of Cardiology (ACC) Task Force on Expert Consensus Decision Pathways[39] and related Guidance for Anticoagulation Reversal,[40]
- the ACC/AHA Task Force on Clinical Practice Guidelines and the Heart Rhythm Society[41]
- the Subcommittee on Control of Anticoagulation (SSC) of the ISTH,[42]
- the Thrombosis and Hemostasis Society of North America (THSNA),[43]
- the Anticoagulation Forum.[44]

The guidelines generally recommend restricting the reversal of anticoagulation to patients with severe or life-threatening bleeding, or those patients in need of an invasive procedure or emergency surgery. Many of the guidelines were published prior to the regulatory approval of andexanet alfa but the key treatment approaches for major or life-threatening bleeding are summarised in Table 3.

Table 3. Treatment recommendations for urgent reversal of DOACs (adapted from CS Document B, Table 7)

Treatment option	Treatment
1) General supportive measures	Discontinue the DOAC Mechanical compression Support measures (haemodynamic support, volume replacement, blood transfusion) Maintain diuresis
2) Antagonising the anticoagulant effects	Reducing anticoagulant absorption via haemodialysis (for dabigatran only) or oral activated charcoal Specific reversal of anticoagulant activity, if available (andexanet alfa when available and approved) Non-specific reversal of anticoagulant activity if a specific antidote is not available or sufficient (this may include PCCs and/or rFVIIa)
Abbreviations: DOAC, direct oral anticoagulant; PCC, prothrombin complex concentrate; rFVIIa, recombinant factor VIIa. Source: Niessner, 2017[20], Steffel, 2018[35]; Makris, 2013[33]	

Despite the numerous guidelines, there is no consensus on the most effective treatment pathway for managing bleeding in patients receiving FXa inhibitors. PCCs are a treatment option although they are not specifically approved for use in FXa inhibitor related bleeding and they are associated with a potential risk of pro-thrombotic effects. Data from a UK based registry study, the ORANGE study,[17, 45] showed that for the management of bleeding in patients on DOACs the most commonly used treatments were blood transfusion (41%), 4F-PCC (39%, including 1% who were administered FEIBA), and

tranexamic acid (28%).[45] The ERG's clinical experts confirmed that generally 3F-PCC is not used in the UK, and rFVIIa is not routinely used.[29, 46]

In line with the licensed indication, the company reported that the anticipated use of andexanet alfa is as a reversal agent for patients anticoagulated with the FXa inhibitors rivaroxaban or apixaban who experience a serious uncontrolled or life-threatening bleeding event. Based on clinical advice, the ERG agrees with the company that 4F-PCC is likely to be the most appropriate comparator for andexanet alfa.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company provided an outline of the decision problem addressed in the company's submission (CS) in relation to the final scope issued by the National institute for Health and Care Excellence (NICE)[1], including a rationale for any deviations (reproduced in Table 4). The Evidence Review Group's (ERG's) critique is provided in the sections that follow.

Table 4. Summary of decision problem as outlined in the company submission with ERG comments (adapted from CS Document B, Table 1)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comments
Population	Adults requiring urgent reversal of anticoagulation in case of uncontrolled or life-threatening bleeding, after treatment with a factor Xa-inhibiting direct oral anticoagulant (DOAC)	Adults requiring urgent reversal of anticoagulation in case of uncontrolled or life-threatening bleeding, after treatment with a factor Xa-inhibiting DOAC	N/A	Only apixaban and rivaroxaban of relevance due to the conditional European marketing authorisation for andexanet alfa
Intervention	Andexanet alfa	Andexanet alfa	N/A	-
Comparator(s)	Established clinical management of uncontrolled or life-threatening bleeding without andexanet alfa (including prothrombin complex concentrate with or without tranexamic acid)	Established clinical management of uncontrolled or life-threatening bleeding without andexanet alfa (including prothrombin complex concentrate with or without tranexamic acid)	N/A	4F-PCC the most relevant comparator according to ERG's clinical experts
Outcomes	The outcome measures to be considered include: • Requirement for blood products • Control of bleeding • Need for surgical control of bleeding or interventional radiology embolisation of bleeding vessel • Neurological outcomes (in people with intracranial bleeding) • Hospital stay	The outcome measures presented are: • Requirement for blood products • Control of bleeding • Neurological outcomes (in people with intracranial bleeding) • Hospital stay • Mortality • Adverse effects of treatment (including thrombotic events) • Health-related quality of life	The following outcome for ANNEXA-4 was not pre-specified and analyses are not yet available: • Need for surgical control of bleeding or interventional radiology embolisation of bleeding vessel The following pharmacodynamic outcomes are key in demonstrating the reversal of anticoagulation: • Anti-fXa activity, unbound anticoagulant	The ERG considers data were presented by the company for the outcome • Need for surgical control of bleeding or interventional radiology embolisation of bleeding Health-related quality of life for andexanet alfa was not collected in the key trial, ANNEXA-4.

	• Mortality • Adverse effects of treatment (including thrombotic events) • Health-related quality of life.	• Reversal of anticoagulation effect as measured by anti-fXa activity, unbound anticoagulant plasma levels and thrombin generation	plasma levels and thrombin generation	
Subgroups to be considered	If the evidence allows consideration will be given to subgroups with intracranial bleeding.	Evidence has been presented for the subgroup of patients with intracranial bleeding Evidence is also presented for patients with either ICH or gastrointestinal (GI) bleeding	ICH and GI bleeding events are frequent forms of FXa inhibitor-related bleeding, are life-threatening and are associated with significant morbidity. In addition to the high unmet need in these patients, the clinical benefit is more readily measured by objective clinical outcome measures, including outcomes utilised in the economic modelling.	ERG agrees ICH and GI bleeds are the most common and relevant. Other major bleeds are rarer and data is limited on them due to small patient numbers in ANNEXA-4
Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; DOAC, direct oral anticoagulant; ERG, evidence review group; FXa, factor Xa; GI, gastrointestinal; ICH, intracranial haemorrhage; N/A, not applicable; NICE, National Institute for Health and Care Excellence.				

3.1 Population

The final scope issued by NICE specifies the population of interest to be adults requiring urgent reversal of anticoagulation in case of uncontrolled or life-threatening bleeding, after treatment with a factor Xa-inhibiting direct oral anticoagulant (DOAC).

The key clinical effectiveness data for andexanet alfa in the submission are derived from the ANNEXA-4 clinical study[47] and the company has used a definition for uncontrolled or life-threatening bleeding that is directly aligned to the inclusion criteria in ANNEXA-4:

- Life threatening bleeds (e.g. with signs or symptoms of haemodynamic compromise, such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise explained);

- Symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome;

- Bleeding causing a fall in haemoglobin level of ≥ 20 g/L (2 g/dL or 1.24 mmol/L) OR a haemoglobin level ≤ 80 g/L if no baseline haemoglobin level is available OR in the opinion of the physician, the patient's haemoglobin will fall to ≤ 80 g/L with resuscitation OR leading to transfusion of two or more unit of whole blood or red cells.

The definition broadly aligns with the International Society for Thrombosis and Haemostasis (ISTH) definition of major bleeding (Table 1) and the ERG's clinical experts report the ANNEXA-4 inclusion criteria are consistent with the population in which andexanet alfa is likely to be used in UK clinical practice.

The ERG is concerned that the use of the full ANNEXA-4 patient population is not consistent with the population in which andexanet alfa has received conditional European marketing authorisation. The marketing authorisation restricts the use of andexanet alfa to bleeding related to apixaban or rivaroxaban, whereas ANNEXA-4 also allowed the inclusion of patients with bleeds related to edoxaban and enoxaparin, which accounted for 9% of the safety population. The company has provided data for the apixaban and rivaroxaban (as an individual subgroup) along with the full efficacy population within the CS. The ERG restricts its critique to the apixaban and rivaroxaban subgroup as it considers this to be the most relevant population to the NICE final scope.

The company also provides subgroup data for patients with GI bleeding and patients with ICH for the apixaban and rivaroxaban subgroup in ANNEXA-4. The ERG notes that only ICH bleeds were a pre-specified subgroup in the NICE final scope but considers the data for the GI bleed subgroup to also be of relevance as GI bleeds account for 30% to 50% of major DOAC-related bleeds (Section 2.1).

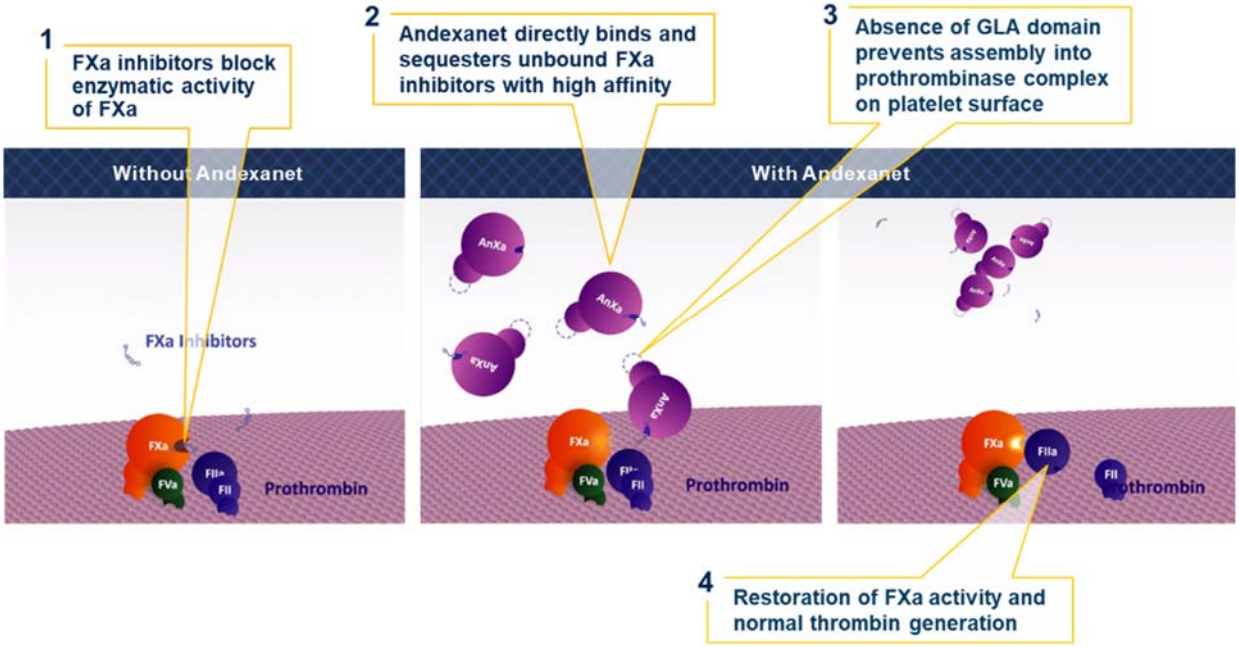
Subgroup data for other major bleeds are also provided for ANNEXA-4 although the relevance of these subgroup data is unclear to the ERG as the ERGs clinical experts report that some of the bleeds captured as 'other bleeds' are extremely rare in UK clinical practice and [redacted]. In addition, the ERGs clinical experts reported that the different sites of bleeds classed as 'other' is likely to result in differences in outcomes including mortality and length of hospital stay. The ERG notes that data from ANNEXA-4 on other bleeds was not used in the company's economic model although some of the types of bleeds captured in the 'other bleeds' category of ANNEXA-4 were included in the model (Section 5.3.5).

In summary, the ERG considers the data presented within the submission to be representative of patients in England and Wales with uncontrolled or life-threatening bleeding after treatment with apixaban or rivaroxaban, and to be relevant to the decision problem that is the focus of this STA.

3.2 Intervention

Andexanet alfa is a recombinant modified human FXa protein that binds to FXa inhibitors and reduces the concentration of the unbound (pharmacologically active) inhibitors, resulting in a reduction to the FXa inhibitors' anticoagulant effects (Figure 3). The blockade of the FXa inhibitor activity allows the restoration of normal haemostasis via endogenous FXa.

Figure 2. Mechanism of action of andexanet alfa for direct FXa Inhibitors (reproduced from CS Document B, Figure 3)



Abbreviations: CS, company's submission; FXa, factor Xa; GLA, γ-carboxyglutamic acid.
Adapted from Yeh *et al.* 2013

Andexanet alfa (Ondexxya®) was granted conditional marketing authorisation by the European Medicines Agency (EMA) on 26 April 2019 for use in adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Andexanet alfa is administered intravenously at either a low dose or high dose depending on the specific FXa inhibitor (rivaroxaban or apixaban), dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor (Table 5). The low dose of andexanet alfa comprises of a 400 mg IV bolus at a target rate of 30 mg/min, followed by a continuous IV infusion of 4 mg/min for 120 mins (480 mg). The high dose regimen comprises of an 800 mg IV bolus at a target rate of 30 mg/min, followed by a continuous IV infusion of 8 mg/min for 120 mins (960 mg).

Table 5. Andexanet alfa dosing regimen (adapted from CS Document B, Table 10)

FXa Inhibitor	FXa Inhibitor Last Dose	< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
Rivaroxaban	> 10 mg/ unknown	High dose	
Apixaban	≤ 5 mg	Low Dose	
Apixaban	> 5 mg/ unknown	High dose	
Abbreviations: CS, company's submission; FXa, Factor Xa.			

The ERG notes that in ANNEXA-4 there was a protocol amendment that affected the selection of the dose of andexanet alfa for patients, who had received their last dose of FXa inhibitor between 7 and 8 hours, that reflects the marketing authorisation approved dosing regimen. Prior to the protocol amendment, the cut-off for all patients to receive low dose was last FXa inhibitor dose ≥ 7 hours, but

this threshold was changed to ≥ 8 hours as part of the changes in protocol amendment 4 and became effective in January 2017. In addition, specific doses of the last FXa inhibitor were added to determine a low vs high dose of andexanet alfa for patients who had received their last dose at less than 8 hours. The company reported that 139 patients were enrolled under amendment 4 of the study protocol, although the ERG notes that only [redacted] patients were in the apixaban or rivaroxaban subgroup. The company provided a detailed breakdown of the number of patients enrolled at different timepoints after their last FXa inhibitor dose in relation to protocol amendment 4 (Table 6) and the ERG considers it likely that some of the [redacted] patients enrolled at <8 hours after last dose and prior to amendment 4 would have received different doses of andexanet alfa. Some of the patients enrolled at 7-8 hours may have been eligible for high dose of andexanet alfa after protocol amendment 4 (patients on apixaban > 5 mg or rivaroxaban > 10 mg or unknown dose of either apixaban or rivaroxaban) and some patients may have been eligible for low dose andexanet alfa rather than high dose (e.g. patients on low dose of apixaban (≤ 5 mg) or on rivaroxaban (≤ 10 mg) and enrolled at <7 hours). The number of patients enrolled prior to protocol amendment 4 who may have received a different dose of andexanet alfa in line with the marketing authorisation and protocol amendment 4 in ANNEXA-4 is unclear but the ERG considers that it is likely to be small. The ERG is unable to comment on the likely direction of any bias due to insufficient detail on the FXa inhibitor and dose for patients enrolled prior to protocol amendment 4.

Table 6. Numbers of patients with apixaban or rivaroxaban enrolled prior to amendment 4 by time from last dose to andexanet alfa (Safety Population) (adapted from CS Document B, Table 16)

Protocol #	Time from Last Dose to Andexanet alfa	All Patients (N=322)	Patients with ICH (N=209)	Patients with GI (N=82)
Prior to Protocol Amendment 4	<7 hour	[redacted]	[redacted]	[redacted]
	7-8 hour	[redacted]	[redacted]	[redacted]
	≥8 hour	[redacted]	[redacted]	[redacted]
Protocol Amendment 4	<7 hour	[redacted]	[redacted]	[redacted]
	7-8 hour	[redacted]	[redacted]	[redacted]
	≥8 hour	[redacted]	[redacted]	[redacted]

Abbreviations: CS, company's submission; GI, gastrointestinal; ICH, intracranial haemorrhage.
Database lock date: 28Nov2018. The Safety Population included patients treated with any amount of andexanet alfa.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Source: Portola data on file[48]

The company reported that no additional tests or investigations are likely to be required prior to administration of andexanet alfa, which the ERGs clinical experts agreed with. However, the ERG notes that patients are likely to have blood tests such as a full blood count, clotting screen and FXa inhibitor drug levels taken as part of their routine management of major or life-threatening bleeding.

3.3 Comparators

The comparator specified in the NICE final scope is established clinical management of uncontrolled or life-threatening bleeding without andexanet alfa (including prothrombin complex concentrate with or without tranexamic acid). The clinical data for andexanet alfa in the population specified in the NICE final scope is limited to data from the ANNEXA-4 single arm prospective study and therefore there are no head-to-head trial data for andexanet alfa compared to any other treatments. As discussed in Section 2.2, the ERG agrees with the company's decision that 4F-PCC is likely to be the most relevant comparator in current UK clinical practice. The ERG also considers that the ORANGE study selected by the company for use in the propensity score matching analysis is likely to be the most appropriate study to provide comparator data for andexanet alfa compared with 4F-PCC. The ERG does however note that there were only suitable data for comparison between andexanet alfa and 4F-PCC from ORANGE for two outcomes listed in the NICE final scope. The ERG also notes that there were other studies identified and included in the company's systematic literature review (SLR) that could potentially be used to enable comparisons for some of the other outcomes in the NICE final scope. However, the ERG acknowledges that due to the likely absence of IPD, small patient numbers and event rates any analysis might be either unfeasible or unlikely to generate reliable estimates and therefore maybe restricted to naïve comparison.

In addition, the ERG notes that there are limited data reported in the ORANGE study on the concomitant treatments received by patients and that there may be differences in the populations of ORANGE and ANNEXA-4 along with differences in care resulting from the differences in study locations (ANNEXA-4 was [redacted]% North America based and only [redacted]% of patients were in the UK whereas ORANGE is 100% UK based) thus limiting the comparability of the studies. These concerns are discussed further in Section 4.4.

The ERG notes that site of bleed was not included as a covariate in the propensity score matching analyses for the subgroup of patients with other major bleeds as there was already a small sample size after matching for the other covariates ([redacted]). The ERG does not consider this omission appropriate as there was wide variation in site of bleed in ANNEXA-4 compared to ORANGE (Table 33) and the ERG's clinical experts reported that the different sites of bleeds classed as other is likely to result in differences in mortality and length of hospital stay, which are the outcomes analysed using propensity score matching. In fact, the ERG does not consider the subgroup data on other major bleeds to be suitable for propensity score matching analysis or any other analysis given the [redacted] in both ORANGE and ANNEXA-4 for each type of other bleed. The ERG therefore recommends caution when interpreting the results for the other bleeds population in the propensity score matching analyses (Section 4.4.2).

3.4 Outcomes

Data on andexanet alfa from ANNEXA-4 for the apixaban and rivaroxaban subgroup were presented for the following outcomes specified in the NICE final scope:

- Requirement for blood products – red blood cell transfusions, non-study-prescribed blood products and haemostatic agents were exploratory efficacy endpoints. Data are provided for different timepoints but aggregate data for the total number of patients who received each group of products during the study were not provided for the apixaban and rivaroxaban subgroup.

- Control of bleeding – data were provided on haemostatic efficacy, adjudicated by an independent and blinded endpoint adjudication committee, as excellent or good 12 hours after andexanet alfa infusion. In addition, data on the exploratory efficacy endpoints of haemostatic efficacy as measured by haematoma expansion in intracranial haemorrhage (clarification response) and re-bleeding from the same anatomical site in patients within 24 hours of initial andexanet alfa treatment and after achieving initial good/excellent haemostasis were provided by the company.

- Neurological outcomes (in people with intracranial bleeding) – the mean and median modified Rankin Score (mRS) of ICH patients at screening, 1-hour, 12-hours and day 30 post andexanet alfa were presented in the CS. Data on Glasgow Coma Scale(GCS) and National Institute of Health Stroke Scale (NIHSS) were provided in the company response to clarification questions.

- Hospital stay – mean and median duration of hospital stay.

- Mortality – 30-day mortality, and mortality during follow-up (includes deaths beyond 30 days) and cause of death.

- Adverse effects of treatment (including thrombotic events) – data are presented for the whole ANNEXA-4 safety population and not just the apixaban and rivaroxaban subgroup.

- Need for surgical control of bleeding or interventional radiology embolisation of bleeding vessel – the company reported that the use of interventions to control bleeding was not an endpoint in ANNEXA-4 but data were identified through manual searches of each patient record for relevant free-text terms and the results were presented in the CS.

In addition, the company presented data on the reversal of anticoagulation effect as measured by anti-FXa activity, unbound anticoagulant plasma levels and thrombin generation and data on the timing of restart of anticoagulation. The ERG considers the anti-FXa activity, unbound anticoagulant plasma levels and thrombin generation data not to be of direct clinical relevance but provides an overview and

critique of the data in Appendix 10.1. Additional data to that supplied in the CS on the timing of restart of oral anticoagulation were provided by the company in their clarification question response document. Due to the relevance of this outcome to the economic model the ERG discusses the data in Section 4.3.

The ERG notes that, in Table 1 of the CS, the company reports that health-related quality of life (HRQoL) are presented in the CS. However, the ERG notes that HRQoL data were not captured in ANNEXA-4 and does not consider there to be alternative data on HRQoL for andexanet alfa to be presented in the CS.

The co-primary efficacy outcomes in ANNEXA-4 were the percent change in anti–FXa activity and the rate of excellent or good haemostatic efficacy 12 hours after the andexanet alfa infusion. The ERG considers that neither of the co-primary efficacy outcomes in ANNEXA-4 were used to inform the economic model in the CS. The ERG notes that anti-FXa activity was measured using a validated chromogenic assay of FXa enzymatic activity and as such is a laboratory measure that doesn't directly inform any of the clinical outcomes of interest in the NICE final scope. Haemostatic efficacy was assessed by an independent adjudication committee on the basis of prespecified criteria and to be classed as satisfactory it had to be graded as good or excellent. The ERGs clinical experts reported that neither anti-FXa activity nor haemostatic efficacy could be used as reliable predictors of the final clinical outcome (e.g. long-term severity of ICH or risk of death) and so they can't be directly associated with costs and quality adjusted life-years (QALYs). Therefore, the ERG considers the omission of haemostatic efficacy and anti-FXa activity from the economic analysis to be reasonable.

In summary, the company presents evidence for andexanet alfa for most of the outcomes listed in the final scope issued by NICE for the apixaban and rivaroxaban subgroup. However, the only data presented in the CS for andexanet alfa in comparison with 4F-PCC were for 30-day mortality and these were derived from a propensity score matching analysis. Data on mortality beyond 30 days were not captured in ORANGE and therefore it was not possible for the company to perform any analysis of longer-term mortality outcomes that would have been particularly useful for informing later timepoints in the economic model. Data for the outcome of length of hospital stay were provided by the company during the clarification stage and like the 30-day mortality data were derived from a propensity score matching analysis of ANNEXA-4 and ORANGE. The ERG considers that mortality and length of hospital stay are likely to be linked as, the longer hospital stay a patient has, the lower their risk of dying within 30 days is likely to be (assuming similar risk of death between both ANNEXA-4 and ORANGE). The ERG therefore considers length of hospital stay likely to be intrinsically linked with 30-day mortality and so it would be inappropriate to only include one outcome in the propensity score matching analysis. However, the ERG has concerns about the censoring of patients in ORANGE at 30 days in the analysis of length of hospital stay with no equivalent restriction on patients in ANNEXA-4. The ERG are unclear why length of hospital stay data in ANNEXA-4 weren't censored at 30-days given that the

company has access to the IPD. In addition, the ERG notes the company's concerns regarding differences in study location between ANNEXA-4 and ORANGE that may have impacted on the length of hospital stay of patients as 60% of ANNEXA-4 patients were located in North America and only 7% in the UK whereas ORANGE was a UK based study. The ERG therefore recommends caution when interpreting the results of the propensity score matching for length of hospital stay particularly if they are viewed independently to the mortality data. The ERG acknowledges that there was insufficient data from the ORANGE study and ANNEXA-4 to enable comparisons between andexanet alfa and 4F-PCC for the other outcomes listed in the NICE final scope.

Based on advice from clinical experts, the ERG considers that the outcomes presented in the submission are clinically relevant to the decision problem although there are extremely limited data to enable the comparison of andexanet alfa with 4F-PCC and the co-primary efficacy outcomes of ANNEXA-4 are not used in the economic model.

3.5 Other relevant factors

The company and the ERG's clinical experts reported that there are no known issues regarding equality.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

The company conducted a clinical systematic literature review (SLR) to identify studies investigating the efficacy and safety of andexanet alfa and clotting factor concentrates (pro-thrombin complex concentrates [PCCs], recombinant (r)FVIIa and activated pro-thrombin complex concentrates [aPCC]), fresh frozen plasma (FFP), vitamin K or protamine in patients who had received a direct or indirect Factor Xa (FXa) inhibitor and required rapid reversal of anticoagulation. The company reported that the wording of the licensed indication for andexanet alfa was not known when the original SLR was undertaken and so its scope was wider than that required by the NICE final scope.[1] The company also conducted a second SLR to identify studies investigating the efficacy and safety of interventions to reverse anticoagulation in healthy volunteers receiving a direct or indirect FXa inhibitor. The ERG considers the data and SLR relating to healthy volunteers not to be relevant to the NICE final scope and therefore does not critique this SLR or its results.

The company's SLRs are summarised in Table 7 with a comment from the evidence review group (ERG) about the appropriateness of the methods adopted. Further critique is provided in Sections 4.1.1 to 4.1.4.

Table 7. ERG critque of company's clinical SLR

Review step	CS Section	ERG critique
Data sources	CS Appendix D.1.1.1, pages 5-18	**The ERG considers the sources and dates searched comprehensive.** MEDLINE and MEDLINE (R) In-Process, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched with an update search conducted on 25 January 2019. In addition, grey literature searches were conducted, and reference lists of reviews were searched.
Search strategies	CS Appendix D.1 .1.1, pages 5-18	**The ERG is satisfied that searches would have identified all evidence relevant to the decision problem although the ERG considers the population and comparator terms were broader than the NICE final scope.** Database searches combined terms for the population of interest , study design, and either terms for andexanet alfa or a comparator.
Inclusion criteria	CS Appendix D.1.1.1, table 1	**The ERG considers the SLR eligibility criteria are wider than necessary and that it is unclear why included studies in Appendix D are not discussed in the CS and ORANGE was initially excluded.** In addition to ANNEXA-4 and ORANGE, the company included and data extracted 17 studies on PCC in the SLR but does not discuss why they were not discussed further in the CS and only reported in appendix D of the CS.
Screening and data extraction	CS Appendix D.1.1.1, pages 19-21	**The ERG has some concerns about the transparency of study inclusion and the identification of the ORANGE study for the propensity score matching.** Otherwise the methods described were robust (independent duplicate screening by two reviewers with predefined criteria; discrepancies resolved by consensus or with involvement of a third reviewer; data extracted by a single reviewer and verified by a second).
Quality assessment	CS Appendix D.1.3 pages 69-95	**The ERG considers the company's choice of quality assessment tool satisfactory.**

		The company provided quality assessments of all 19 included studies (including ORANGE and ANNEXA-4) using the NICE Quality Appraisal Checklist for Quantitative Intervention Studies.
Abbreviations: CS, company's submission; ERG, evidence review group; NICE, National Institute for Health and Care Excellence; SLR, systematic literature review.		

4.1.1 Searches

The company reported that the following databases were searched on 28 February 2017 and 10 March 2017 with update searches conducted on 25 January 2019 (applying limits from February 2017):

- MEDLINE and MEDLINE (R) In-Process (via Embase.com);
- EMBASE (via Embase.com);
- The Cochrane Central Register of Controlled Trials (CENTRAL).

The ERG is unclear why searches were conducted in both February and March 2017 but considers the choice of databases and search dates to be comprehensive. The ERG notes that the company's search strategies were provided in Appendix D and the database searches combined terms for the population of interest and either andexanet alfa or a comparator with terms for study design. Search terms were also applied to exclude studies in animals and letters, editorials and other non-relevant publications. The ERG considers the search strategies to be appropriate although the population and comparator terms were broader than specified in the NICE final scope.

The company also reported that supplementary searches of "grey" literature were performed to complement the literature database searches and to provide data from recent or ongoing trials. Sources for the supplementary searches included clinicaltrials.gov, searches of the manufacturer's repository of evidence and relevant conference proceedings from 2014 to 2019, which included the American College of Cardiology (ACC), ACCP Conference on Antithrombotic and Thrombolytic Therapy, American Heart Association (AHA), American Society of Hematology (ASH), British Society for Haematology (BSH), European Hematology Association (EHA), European Society of Cardiology (ESC), International Society of Thrombosis and Haemostasis (ISTH), Thrombosis, Hemostasis Societies of North America (THSNA), and the World Intracranial Hemorrhage Conference (WICH), International Symposium on Intensive Care and Emergency Medicine, International Conference on Emergency Medicine (ICEM). In addition, the bibliographies of identified reviews were hand searched. The ERG considers the company's searches of electronic databases and grey literature to be comprehensive and likely to have identified all key studies of relevance.

4.1.2 Inclusion criteria

The eligibility criteria used in the SLR of clinical effectiveness studies are detailed in Table 8. The ERG notes that studies published as abstracts or conference presentations were eligible if adequate data were provided although non-English language articles were excluded if they didn't have an abstract in English. The ERG also notes that the interventions in the inclusion criteria were amended during the SLR to align with the NICE final scope.

Table 8. Eligibility criteria used to identify clinical effectiveness studies in patients requiring rapid reversal of anti-coagulation (adapted from CS Appendix D, Table 1)

Selection criteria	Inclusion	Exclusion
Population	•Adults treated with a direct or indirect Factor Xa inhibitor who require rapid reversal of anticoagulation due to an acute major bleed that meets one or more of the following criteria: •Life threatening bleeds (e.g. with signs or symptoms of haemodynamic compromise, such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise explained) •Symptomatic bleeding in a critical area of organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome •Bleeding causing a fall in haemoglobin level of ≥ 20 g/L (2 g/dL or 1.24 mmol/L) OR a haemoglobin level ≤ 80 g/L if no baseline haemoglobin level is available OR in the opinion of the physician, the patient's haemoglobin will fall to ≤ 80 g/L with resuscitation OR leading to transfusion of two or more unit of whole blood or red cells •Adults due to have urgent/emergency surgery within the next 12 hours who have been treated with a direct or indirect Factor Xa inhibitor and require rapid reversal of anticoagulation*.	•Entirely comprised of individuals aged under 18 years •Entirely comprised of individuals who are pregnant and/or breastfeeding •Entirely comprised of individuals not receiving a direct or indirect Factor Xa inhibitor •Entirely comprised of individuals experiencing non-major bleeds
Intervention/ Comparator	•Andexanet alfa •PCC •rFVIIa* •aPCC* •Fresh frozen plasma* •Vitamin K* •Protamine*	•Other methods such as activated charcoal, haemodialysis, activated charcoal haemoperfusion, unless given concomitantly with an intervention of interest
Outcomes	•Change in anti-Factor Xa activity •Haemostatic efficacy •Blood transfusions •Haemoglobin change •Morbidity •Mortality •Modified Rankin Scale •Thrombin generation •Quality of life •Adverse events (e.g. thrombotic events, re-bleeding)	

Study type	•Randomised controlled trials •Non-randomised studies •Observational studies (including patient registries) •Retrospective analyses	•Meta-analyses •Systematic literature reviews •Modelling studies •Economic analyses •Narrative literature reviews, expert opinions, letters to the editor, editorials, or consensus reports •Case reports or case series of fewer than 10 patients •In vitro, animal, or foetal studies
Language	•Article or abstract available in English	•Non-English language articles (no abstract available in English)

Abbreviations: aPCC, activated prothrombin complex concentrate; CS, company's submission; PCC, prothrombin complex concentrate; rFVIIa.
*Text in italics indicates where the eligibility changed following the availability of the licence indication and NICE scope. Studies meeting these criteria have not been presented/extracted due to the scope of this report but are included in the review results.

Overall, the ERG considers that the clinical-effectiveness SLR is likely to have identified all clinical efficacy studies that were relevant to the decision problem outlined in the NICE final scope.

4.1.3 Critique of data extraction

The company reported that the results of the electronic database searches were de-duplicated and the resulting records were independently assessed for relevance by two reviewers based on title and abstract (1st pass) and full text (2nd pass) using the inclusion criteria in Table 8. Data for included studies were extracted by one reviewer and checked for accuracy by a second reviewer with any discrepancies resolved through discussion or by consulting a third reviewer if necessary. Disagreements were discussed and a third reviewer involved if required. The ERG notes that only studies relevant to the licensed indication for andexanet alfa and the comparators specified in the NICE scope were extracted despite the wider selection criteria used in the company's SLR.

The company presented Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagrams in Figures 1 and 2 of Appendix D to illustrate the inclusion and exclusion of studies and publications in the SLR and the update search. There were 1,354 titles and abstracts screened in the original review, which resulted in 15 references that met the eligibility criteria and were considered for extraction. Only 11 references met the eligibility criteria for data extraction, and they related to 7 studies. For the update search, a further 770 titles and abstracts were screened. A total of 30 references met the eligibility criteria, although only 23 publications met the criteria for data extraction and these related to 14 studies (note, three studies were also included in the original review). The combined original and update search resulted in the inclusion of 45 publications on 29 studies, of which 34 publications on 18 studies met the criteria for data extraction. Based on the company's reasons for not data extracting 11 studies that were included, the ERG considers they have been appropriately excluded. The company's reasons for the exclusion (i.e. not performing data extraction) of the 11 studies comprised among other things, that the FXa inhibitor was unknown and that the population included patients scheduled for urgent surgery. The ERG notes only apixaban and rivaroxaban are of relevance

to the NICE final scope and that patients expected to undergo surgery within 12 hours were excluded from ANNEXA-4 (with the exception of minimally invasive surgery or procedures).

The 18 data extracted studies were all uncontrolled cohort studies: five of the studies were prospective studies,[47, 49-52] one was an analysis of a prospective registry,[53] and the remaining 12 studies were retrospective studies. One study investigated andexanet alfa,[54] 11 investigated 4F-PCC,[50, 51, 55-63] 1 investigated FEIBA,[64] and in 5 the PCC wasn't specified.[52, 53, 65-67] The published study of andexanet alfa relates to the ANNEXA-4 study. The ERG notes that the ORANGE study,[17, 45] which was selected by the company to provide the comparator data on 4F-PCC in the CS, was originally excluded based on outcome. The ORANGE study publication doesn't report outcomes separately for patients treated with rivaroxaban or apixaban (the licensed population for andexanet alfa) and therefore does not form one of the 18 data extracted studies. The ERG considers that the company decision to subsequently include ORANGE was reasonable given its UK patient population, prospective study design and the availability of IPD suitable for conducting propensity score matching. The ERG's clinical experts also agreed that the ORANGE study is most likely to be the best source of comparator data for andexanet alfa particularly given that ORANGE was conducted in the UK between October 2013 to August 2016 and therefore is likely to be the most representative of current clinical practice.

However, the ERG does not consider the company to have provided suitable justification for the exclusion of all 17 of the other data extracted included studies for review question 1 reported in Appendix D of the CS. The ERG notes that the company excludes 7 of the studies later in the CS as not being relevant or not having suitable outcome data but that leaves 10 studies remaining. The company reports that other than categorising for ICH and non-ICH bleeds, baseline differences in the study populations cannot be accounted for between the 10 studies and ANNEXA-4 and that there are a variety of sources of potential clinical heterogeneity among the studies. In addition, the ERG is concerned that the ORANGE study does not provide comparator data for all of the outcomes specified in the NICE final scope and that other included studies may have suitable data to enable comparisons of andexanet alfa for some of the missing outcomes. Due to time constraints the ERG is unable to provide a comprehensive assessment of all 17 studies but the ERG provides a summary of the study designs, company assessment of the potential comparability with ANNEXA-4 and an ERG critique of the company's assessment in Appendix 10.2. The ERG notes that there is a large amount of clinical heterogeneity in the 17 included PCC studies due to differences in the type or brand of PCC, the dose of PCC, the study inclusion criteria and the underlying indication for the use of PCC. The ERG also acknowledges that the relevant study population in terms of patients on apixaban or rivaroxaban in the 17 PCC studies was less than 100 patients with five studies having less than 20 patients and so ORANGE has a larger population with 149 PCC patients who have had prior apixaban or rivaroxaban.

The ERG does, however, note that there were only suitable data for comparison between andexanet alfa and 4F-PCC from ORANGE for two outcomes listed in the NICE final scope. The ERG also notes that data for the outcomes of haemostatic efficacy, haematoma expansion, re-bleeds, surgical control of bleeding and use of blood products were reported in some of the 17 PCC studies. Nevertheless, the ERG considers that due to clinical heterogeneity and the small patient numbers in the available studies any analyses are unlikely to generate reliable estimates and therefore maybe restricted to naïve comparisons.

In summary, the ERG is uncertain whether ORANGE is the only appropriate study to inform the analysis of the clinical efficacy of andexanet alfa compared with 4F-PCC but the ERG notes that it is the largest study with UK-based data and had IPD available. The ERG considers it important to highlight that there were no RCTs of relevance to the NICE final scope identified in the SLR that were suitable for inclusion and that all included studies relate to single-arm cohort studies.

4.1.4 Quality assessment

The company used the NICE Quality Appraisal Checklist for Quantitative Intervention Studies to assess the quality of ANNEXA-4 and the ORANGE study. The ERG considers it important to highlight that observational studies have implicit biases resulting from their study design and notes that there is no standard tool for assessing non-RCTs or single arm study's. The ERG does, however, consider the quality assessment tool used by the company to be reasonable.

The ERG independently validated the company's quality assessments of ANNEXA-4 and ORANGE and these assessments are presented in Appendix 10.3. The ERG's quality assessment were broadly similar to the company's assessment although for ANNEXA-4 the ERG noted that the intention-to-treat (ITT) population were not used for the primary efficacy outcomes, instead a refined efficacy population was used. However, the company also provided outcome data for the safety population, which is more aligned with an ITT population, at the clarification stage. For further description of the statistical analyses in ANNEXA-4 please see Section 4.2.3. The ERG also noted that the ANNEXA-4 study population was enriched in the proportion of ICH bleeds compared to the proportion expected in UK clinical practice, therefore, whilst the results of the subgroups based on bleed location are reflective of the equivalent groups in UK clinical practice, the full trial population is less so.

In terms of the quality assessment of ORANGE, the ERG considers the company to have inappropriately downgraded the rating of few items on the checklist given the company's rationale for some of the ratings, but notes that the nature of the tool may lead to subjective differences. The items the ERG considers should have been higher rated (++) were relating to whether an ITT analysis was conducted as 98% of patients were followed up until discharge, and relating to the estimates of effect size and to the reporting of meaningful precision of intervention effect sizes as estimates including

hazard ratios with associated 95% confidence intervals were reported for different interventions including PCC.

In summary, the ERG considers ANNEXA-4 and ORANGE to both be of reasonable quality albeit they are non-comparative studies.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

The key clinical safety and efficacy data for andexanet alfa of relevance to the NICE final scope are those derived from ANNEXA-4. The ERG notes that the company also provided clinical safety and efficacy data in the CS from two phase 3 RCTs in healthy volunteers, the ANNEXA-A and ANNEXA-R studies.

The ANNEXA-A and ANNEXA-R studies were both placebo-controlled studies designed to evaluate the safety and reversal of apixaban (5 mg orally twice daily for 3.5 days; ANNEXA-A) or rivaroxaban (20 mg orally once daily for 4 days; ANNEXA-R) compared with andexanet alfa. ANNEXA-A and ANNEXA-R enrolled healthy adults aged 50 to 75 years and were conducted at two clinical sites in the USA. A total of 101 people (48 in ANNEXA-A and 53 in ANNEXA-R) were randomised to receive andexanet alfa, and 44 people (17 in ANNEXA-A and 27 in ANNEXA-R) were randomised to receive placebo. The RCTs were both performed in two consecutive parts with patients entering either part 1 or part 2. In ANNEXA-A only low dose andexanet alfa was administered as a 400 mg intravenous bolus (30 mg per minute) in part 1 and as a 400 mg intravenous bolus followed by a continuous infusion of 4 mg per minute for 120 minutes (480 mg in total) in part 2. In ANNEXA-R only high dose andexanet alfa was administered, with part 1 comprising only an 800 mg intravenous bolus (30 mg per minute) and part 2 comprised an 800 mg intravenous bolus followed by a continuous infusion of 8 mg per minute for 120 minutes (960 mg in total).

ANNEXA-A and ANNEXA-R provided key evidence supporting the Marketing Authorisation Application for andexanet alfa but given that the NICE final scope for andexanet alfa is in patients with uncontrolled major or life-threatening bleeding, the ERG does not consider these two studies in healthy volunteers to be relevant to the decision problem. In addition, the ERG notes that the efficacy outcomes reported from ANNEXA-A and ANNEXA-R were laboratory measures including reversal of anticoagulation effect as measured by anti-FXa activity, unbound anticoagulant plasma levels and thrombin generation and that these were not outcomes specified in the NICE final scope. The ERG does not therefore discuss or critique the results from ANNEXA-A or ANNEXA-R; only efficacy and safety data for andexanet alfa from ANNEXA-4 are discussed below.

4.2.1 Trial conduct

ANNEXA-4 is an ongoing phase 3b/4, prospective, open-label, single-arm study designed to evaluate the efficacy and safety of andexanet alfa in patients receiving a FXa inhibitor (apixaban, rivaroxaban, edoxaban, or enoxaparin) who present with acute major bleeding.[47] The ERG notes that the company reported in the CS that the data from the completed study is estimated to be available in 2021 or 2022 and that it is dependent on the enrolment rate. The ERG also notes that enrolment of the primary cohort is complete and that there are extensions of the ANNEXA-4 study, which are enrolling patients in Germany, and more recently in March 2019 in Japan. The purpose of the extensions is to gain experience with patients receiving edoxaban and with Japanese patients although the ERG is uncertain whether either of these have been mandated by regulatory agencies. Nevertheless, the ERG considers the primary cohort of ANNEXA-4 to be the most relevant to the decision problem.

There were two primary outcomes in ANNEXA-4: the percentage change in anti-FXa activity and the rate of excellent or good haemostatic efficacy 12 hours after the andexanet alfa infusion. Anti-FXa activity was measured by means of a validated chromogenic assay of FXa enzymatic activity and haemostatic efficacy was assessed by an independent adjudication committee on the basis of pre-specified criteria (Appendix 10.4, Table 91). The secondary objective in ANNEXA-4 was to assess the relationship between the two primary efficacy endpoints, anti-FXa activity and haemostatic efficacy, to establish change in anti-FXa activity as a predictor of achievement of haemostatic efficacy. There was also a number of exploratory efficacy endpoints which included further outcomes of relevance to the decision problem specified in the NICE final scope. The safety outcomes included overall safety (adverse events, vital signs, and clinical laboratory measurements), thromboembolic events, antibodies to FX, FXa, and andexanet alfa, and 30-day all-cause mortality. Thromboembolic events were independently-adjudicated events that were pre-defined at the start of the study and included stroke, deep vein thrombosis, myocardial infarction (MI), pulmonary embolism, and transient ischaemic attacks. As discussed in Section 3.4, the laboratory measure efficacy outcomes are not of relevance to the decision problem although the results are presented in Appendix 10.1.

ANNEXA-4 included 83 centres in North America and Europe and patients were enrolled between April 2015 and May 2018. All patients were in hospital with 80% in an emergency department, 13% in an intensive care unit and 6% on an inpatient or other ward at the time of informed consent for participation in the study. The inclusion and exclusion criteria for ANNEXA-4 are summarised in Table 9 and the ERGs clinical experts report they are reasonable in comparison to the patients seen in UK clinical practice whom are likely to be eligible for andexanet alfa. The ERG notes that for patients with ICH, a CT or MRI of the head was expected to be performed within 2 hours before andexanet alfa treatment and at 1 hour and 12 hours after the end of andexanet alfa treatment. The ERG's clinical experts reported that in UK clinical practice not all patients would be expected to have scans this

frequently and it would depend on the individual patient's clinical status. The ERG's clinical experts reported that all patients with suspected ICH would have a scan to confirm diagnosis and post-treatment scans would only be carried out if clinically indicated.

Andexanet alfa was administered as IV bolus, immediately followed by 2-hour continuous infusion to all patients. The type and dose of FXa inhibitor and timing of the last dose received were used to determine whether the high or lose dose regimen of andexanet alfa was given. The high dose regimen consisted of an 800 mg bolus, delivered at 30 mg/min, followed by an 8 mg/min infusion for 120 minutes and the low dose regimen consisted of a 400 mg bolus, delivered at 30 mg/min, followed by a 4 mg/min infusion for 120 minutes. The criteria for determining the andexanet alfa dose were changed midway through enrolment as part of protocol amendment 4 and these changes are discussed further in Section 3.2. In summary, the ERG considers it likely that some of the earlier enrolled patients may not have received the marketing authorisation recommended dose of andexanet alfa, although the impact of the likely resulting bias on the efficacy results of ANNEXA-4 is unclear. The company also reported that a new manufacturing process for andexanet alfa was introduced in January 2017 (Generation 2) and that no substantial differences in efficacy or safety have been detected in subgroup analyses of Generation 1 compared with Generation 2.

Concomitant medications in terms of other treatments to treat the bleeding event were mostly down to local practice and clinician preference, although the ANNEXA-4 protocol recommended that the trigger for packed red blood cell (PRBC) transfusion was a Hb $\leq$ 8.0 g/dL ($\pm$ 1 g/dL). Systemic anti-fibrinolytic (e.g., tranexamic acid) and other systemic haemostatic agents were administered according to standard local practices or guidelines. Local haemostatic agents (e.g., microfibrillar collagen, chitosan-containing products) and topical vasoconstrictors (e.g., epinephrine) were also permitted for use as deemed clinically appropriate.

The ERG notes that there were a total of four protocol amendments for the ANNEXA-4 study (detailed in the supplementary appendix for Connolly *et al.* 2019[47]) with the most significant changes resulting from amendment 4. Amendment 1 was made in January 2015, prior to enrolment of any patients onto the study and amendment 2 was implemented in May 2015, after 1 patient had been enrolled in the study. Both amendments 1 and 2 were in response to Food and Drug Administration (FDA) feedback and resulted in changes to: the efficacy objectives, including changing anti-FXa activity from a secondary to co-primary outcome; data points; and inclusion/exclusion criteria. Amendment 3 (October 2015) was a country-specific amendment regarding informed consent procedures.

Amendment 4 (January 2017) was reported by the company to be implemented largely in response to FDA feedback and the main resulting changes were:

- To enrich the population for patients with ICH, a minimum of approximately 120 evaluable patients with ICH were to be enrolled in the study;

- Inclusion/exclusion criteria:

    - Removed inclusion of patients with bleeding based on an investigator's opinion that the haemoglobin level will fall to ≤ 8 g/dL with resuscitation;

    - Added a requirement that for patients with ICH, there must be a reasonable expectation that andexanet alfa treatment will commence within 2 hours of the baseline imaging evaluation;

    - Exclusion of patients with visible, musculoskeletal, or intra-articular bleeding;

    - Clarified that patients with a history of deep vein thrombosis or cerebral venous thrombosis within 2 weeks prior to screening are excluded, as with other thrombotic events.

- Minor modification to the andexanet alfa administration plan including changes to the criteria for high and low dose andexanet alfa;

- Additional exploratory objectives, including evaluation of re-bleeding, and for ICH patients, change in GCS, mRS and NIHSS;

- Added requirement for repeat imaging at 12 hours when that was used for initial bleeding diagnosis in order to facilitate adjudication.

The ERG's clinical experts reviewed the protocol amendments and confirmed that there are no major concerns regarding the comparability of the ANNEXA-4 population with the equivalent UK patient population likely to receive andexanet alfa. The ERG therefore considers that despite the single-arm nature of ANNEXA-4 it was a reasonably well conducted study and applicable to the decision problem.

Table 9. ANNEXA-4 inclusion and exclusion criteria (adapted from CS Document B, Table 9)

Participants (Key Inclusion criteria)	• At least 18 years old at the time of Screening. • The patient must have had an acute overt major bleeding episode requiring urgent reversal of anticoagulation. Acute major bleeding requiring urgent reversal of anticoagulation was defined by at least ONE of the following: a) Acute overt bleeding that is potentially life-threatening, e.g., with signs or symptoms of haemodynamic compromise, such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise explained. b) Acute overt bleeding associated with a fall in Hb level by ≥ 2 g/dL, OR a Hb ≤ 8 g/dL if no baseline Hb is available. c) Acute overt bleeding in a critical area or organ, such as pericardial, intracranial, or intraspinal. • The patient, for whom the bleeding is intracranial or intraspinal, must have undergone a head CT or MRI scan demonstrating the intracranial bleeding.

	• The patient received or was believed to have received one of the following anticoagulants within 18 hours prior to andexanet alfa administration: apixaban, rivaroxaban, edoxaban, or enoxaparin (dose of enoxaparin ≥ 1 mg/kg/day). • For patients with ICH, there must be a reasonable expectation that andexanet alfa treatment would commence within 2 hours of the baseline imaging evaluation. [Note: From July 2016 through August 2017, only patients with intracranial haemorrhage were enrolled to enrich the study with these patients.]
Participants (Exclusion criteria)	• Scheduled to undergo surgery in less than 12 hours with the exception of minimally invasive surgery/procedures (e.g., endoscopy, bronchoscopy, central lines, Burr holes) • A patient with ICH had any of the following: a) Glasgow Coma Score < 7 b) Estimated intracerebral haematoma volume > 60 cc as assessed by the CT or MRI • Visible, musculoskeletal, or intra-articular bleeding as the qualifying bleed (implemented with Protocol Amendment 4, therefore a small number of these patients were enrolled). • Expected survival of less than 1 month. • Recent history (within 2 weeks) of a diagnosed Thrombotic Event (TE) as follows: VTE (e.g., deep venous thrombosis, pulmonary embolism, cerebral venous thrombosis), myocardial infarction (MI), disseminated intravascular coagulation, cerebral vascular accident, transient ischaemic attack, unstable angina pectoris hospitalization, or severe peripheral vascular disease within 2 weeks prior to Screening. • Severe sepsis or septic shock at the time of Screening. • Pregnancy or a lactating female. • The patient had received any of the following drugs or blood products within 7 days of Screening: o VKA (e.g., warfarin). o Dabigatran. o Prothrombin complex concentrate (PCC) products (e.g., Kcentra®) or recombinant factor VIIa (rfVIIa) (e.g., NovoSeven®). o Whole blood, plasma fractions. [Note: Administration of platelets or packed red blood cells (PRBCs) was not an exclusion criterion.] • The patient was treated with an investigational drug < 30 days prior to Screening. • Planned administration of PCC, Fresh Frozen Plasma (FFP), or rfVIIa from Screening until within 12 hours after the EOI.
Abbreviations: ATIII, antithrombin III; CS, company's submission; CT, computed tomography; EOT, end of infusion; FFP, fresh frozen plasma; FXa, factor Xa; GCS, Glasgow Coma Scale; GI, gastrointestinal; EOI, end of infusion; ETP, endogenous thrombin potential; Hb, haemoglobin; ICH, intracranial haemorrhage; MI, myocardial infarction; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale ; NSAIDs, non-steroidal anti-inflammatory drugs; PCC, prothrombin complex; PRBC, packed red blood cells; RBC, red blood cell; TE, thrombotic event; TFPI, tissue factor pathway inhibitor; VTE, venous thromboembolism.	

4.2.2 Baseline characteristics

In total 352 patients were enrolled in ANNEXA-4 and all patients received andexanet alfa and were followed for 30 days or until death (one patient died before the andexanet alfa continuous infusion was initiated). However, the ERG notes that only 254 patients (72%) were included in the efficacy analyses as they were required to meet the criteria for bleeding severity and have a baseline anti-FXa activity of ≥75 ng per millilitre, or ≥0.25 IU per millilitre for those receiving enoxaparin. The ERGs preferred analysis set is the safety population as in clinical practice patients will not be required to have a minimum pre-specified baseline anti-FXa activity prior to treatment with andexanet alfa. Also, as discussed in Section 3.1, not all patients in ANNEXA-4 were on apixaban or rivaroxaban; only 322 patients in the safety population received apixaban or rivaroxaban (9% of patients in the safety population received enoxaparin or edoxaban). Baseline characteristics of the apixaban and rivaroxaban safety population, and the subgroups of patients with ICH or GI bleeds are shown in Appendix 10.5, Table 92.

The company reported that patients enrolled in ANNEXA-4 represented a high-risk population because there was an artificially high proportion of patients with ICH which they claim is associated with a high mortality. In addition, patients in ANNEXA-4 were required to have ISTH defined life-threatening bleeding and also signs or symptoms of haemodynamic compromise (e.g., severe hypotension, poor skin perfusion, mental confusion, or low cardiac output that could not otherwise be explained). The company reported that the additional requirement for signs or symptoms defines a higher risk population, although the ERG's clinical experts report that patients with life threatening bleeding would be expected to have additional signs and symptoms as defined in ANNEXA-4. The ERG's clinical experts also reported that ICHs are one of the most common life-threatening bleeds seen with apixaban and rivaroxaban.

The ERG also notes that [redacted] patients were enrolled prior to amendment 4 and had a last dose between 7-8 hours so under the protocol amendment they may have been eligible for the high dose of andexanet alfa but received the low dose due to the timing of their enrolment. The impact of this potential difference in treatment dose on the efficacy results is unknown.

In the apixaban and rivaroxaban subgroup of ANNEXA-4, the site of bleed was ICH for 209 patients, GI bleed for 82 patients, [redacted] for [redacted] patients and other sites for the remaining [redacted] patients (detailed in Table 51). The mean age of patients was [redacted] years and mean CHA_2DS_2VASC (Congestive heart failure, hypertension, age ≥75, diabetes, stroke, vascular disease, age between 65-74, and female sex category) score was [redacted]. UK patients represented [redacted]% of the subgroup population, and [redacted]% of patients were from other EU sites and [redacted] patients from North America (n = [redacted]%). The majority of patients received [redacted] The ERG notes that both the mean and median anti-FXa inhibitor levels in the blood were [redacted] in patients [redacted] (Table 92), although the ERG is unsure whether there is any clinical rationale for this observed difference. The ERG also notes from the company's response to clarification, that [redacted]% of patients in the apixaban or rivaroxaban subgroup of ANNEXA-4 received concomitant aspirin and [redacted]% received concomitant clopidogrel – the ERG considers that this may impact on the results for haemostatic efficacy. However, the ERG acknowledges that this proportion of patients on concomitant aspirin and clopidogrel may be reflective of clinical practice; the ERG's clinical experts reported that concomitant antiplatelet use with a DOAC is probably seen in up to 20% of patients and reversal of the antiplatelet agent would also need to be considered as part of the treatment of a major bleed.

4.2.3 Description and critique of statistical approach used

The sample size in ANNEXA-4 was initially planned to be 250 patients and this was estimated to provide 80% power to show that the percentage of patients with excellent or good haemostatic efficacy

was more than 50%. The required sample size was increased to 350 patients in protocol amendment 4, which the company reported was to meet new regulatory requirements for sufficient numbers of patients for each FXa inhibitor and also in an attempt to ensure there were at least 120 patients with intracranial haemorrhage (ICH) in the efficacy analysis population. The final efficacy analysis population included 254 patients; 134 received apixaban, 100 received rivaroxaban, 16 received enoxaparin and 4 received edoxaban. The results discussed in Section 4.3 relate only to the apixaban and rivaroxaban patients (unless otherwise specified) as this reflects the European Marketing authorisation and the population whom will be eligible for andexanet alfa in the UK. The ERG notes that the efficacy analysis population included only patients who retrospectively met both of two criteria: baseline anti-FXa activity of at least 75 ng per millilitre (or ≥0.25 IU per millilitre for patients receiving enoxaparin) and confirmed major bleeding at presentation, as determined by the adjudication committee, whereas the safety analyses included all the patients who had received andexanet alfa (i.e. all of the patients included in ANNEXA-4). The ERGs preferred analysis set is the safety population as in clinical practice patients will not be required to have a minimum pre-specified baseline anti-FXa activity prior to treatment with andexanet alfa.

For the primary efficacy outcome of haemostatic efficacy, patients that were adjudicated as having non-evaluable haemostatic efficacy for clinical reasons were imputed as poor/none. Patients that were adjudicated as having non-evaluable haemostatic efficacy for administrative reasons were excluded from the analysis. An adjudication committee determined whether the non-evaluable patients were administrative or clinical. The ERG notes that the power calculation was done for the full study population and the apixaban and rivaroxaban was a post hoc subgroup analysis.

There were no formal planned interim analyses to evaluate the efficacy of andexanet alfa although interim summaries of safety data were performed approximately every six months. The results discussed in Section 4.3 all relate to the final analyses.

Patients in ANNEXA-4 were planned to be followed up for at least 30 days or until death although some patients had their final safety visit completed up to 45 days after andexanet alfa treatment. The company reported that all analyses were censored at 30 days in the published analysis data set[47] although analyses up to 45 days were to be included in the final clinical study report provided to the EMA.

In terms of statistical analysis, results are reported alongside two-sided confidence intervals (CI) that are reported at the 95% confidence level. For continuous variables, distribution free non-parametric CIs are presented and for binary endpoints, Fisher exact CIs are presented. For the primary outcome of effective haemostasis, percentages of patients with effective haemostasis are presented with a 95% confidence interval calculated with the binomial test.

Data in ANNEXA-4 were analysed for the following pre-specified subgroups:

- Age (<65 years, 65-75 years, >75 years);
- Race (any race with at least 5 members, all other races combined);
- Sex;
- Region (North America, Europe);
- FXa inhibitor;
- Bleeding type (gastrointestinal, ICH, other);
- Andexanet alfa dose;
- Renal function;
- Andexanet alfa manufacturing process*.

In summary, the ERG considers the statistical analysis plan for ANNEXA-4 to be appropriate. However, the ERG considers it important to highlight that based on the European marketing authorisation for andexanet alfa, the data of relevance to the decision problem specified in the NICE final scope are from the apixaban and rivaroxaban subgroup of the safety analysis population and relates to *post hoc* subgroup analyses that were not specifically powered for the primary outcomes.

4.2.4 Summary statement

The key clinical safety and efficacy data for andexanet alfa of relevance to the NICE final scope are those derived from ANNEXA-4, an ongoing phase 3b/4, prospective, open-label, single-arm study. ANNEXA-4 was designed to evaluate the efficacy and safety of andexanet alfa in patients receiving a FXa inhibitor (apixaban, rivaroxaban, edoxaban, or enoxaparin) who present with acute major bleeding.[47] The ERG notes that data from the completed study is estimated to be available in 2021 or 2022 dependent on the enrolment rate for the current extensions to ANNEXA-4, and that the extensions aim to gain more data in patients on edoxaban and those from Japan.

ANNEXA-4 included 83 hospitals in North America and Europe and for the analysis of relevance provided by the company, patients were enrolled between April 2015 and May 2018. The ERGs clinical experts reported that the inclusion and exclusion criteria for ANNEXA-4, are reasonable in comparison to the patients seen in UK clinical practice whom are likely to be eligible for andexanet alfa. However, the ERG notes that the criteria for determining the andexanet alfa dose were changed midway through enrolment for ANNEXA-4 resulting in some patients who may not have received the marketing

authorisation recommended dose of andexanet alfa, although the impact of the likely resulting bias on the efficacy results of ANNEXA-4 is unclear.

In total 352 patients were enrolled in ANNEXA-4 and all patients received andexanet alfa and were followed for 30 days or until death (one patient died before the andexanet alfa continuous infusion was initiated) although 9% of patients in the safety population received enoxaparin or edoxaban. The results discussed in Section 4.3 relate only to the apixaban and rivaroxaban patients (n = 322, unless otherwise specified) as this reflects the European Marketing authorisation and the population whom will be eligible for andexanet alfa in the UK. The ERG notes that the efficacy analysis population included only patients who retrospectively met both of two criteria: baseline anti-FXa activity of at least 75 ng per millilitre (or ≥0.25 IU per millilitre for patients receiving enoxaparin) and confirmed major bleeding at presentation, as determined by the adjudication committee, whereas the safety analyses included all the patients who had received andexanet alfa (i.e. all of the patients included in ANNEXA-4). The ERGs preferred analysis set is the safety population of patients who were taking apixaban or rivaroxaban at baseline as in clinical practice patients will not be required to have a minimum pre-specified baseline anti-FXa activity prior to treatment with andexanet alfa.

The company reported that patients enrolled in ANNEXA-4 represented a high-risk population because there was an artificially high proportion of patients with ICH which they claim is associated with a high mortality. In addition, patients in ANNEXA-4 were required to have ISTH defined life-threatening bleeding and also signs or symptoms of haemodynamic compromise (e.g., severe hypotension, poor skin perfusion, mental confusion, or low cardiac output that could not otherwise be explained). The company reported that the additional requirement for signs or symptoms defines a higher risk population, although the ERG's clinical experts report that patients with life threatening bleeding would be expected to have additional signs and symptoms as defined in ANNEXA-4. The ERG's clinical experts also reported that ICHs are one of the most common life-threatening bleeds seen with apixaban and rivaroxaban.

In the apixaban and rivaroxaban subgroup of ANNEXA-4, the site of bleed was ICH for 209 patients, GI bleed for 82 patients, [redacted] for [redacted] patients and other sites for the remaining [redacted] patients (detailed in Table 51). The mean age of patients was [redacted] years and UK patients represented only [redacted]% of the apixaban and rivaroxaban subgroup population with [redacted] patients from North America (n = [redacted]%). In addition, most patients received [redacted] The ERG also notes from the company's response to clarification, that [redacted]% of patients in the apixaban or rivaroxaban subgroup of ANNEXA-4 received concomitant aspirin and [redacted]% received concomitant clopidogrel, both of which may impact on the results for haemostatic efficacy. However, the ERG acknowledges that this proportion of patients on

concomitant aspirin and clopidogrel may be reflective of UK clinical practice and reversal of the antiplatelet agent should also be considered as part of the treatment of a major bleed.

Patients in ANNEXA-4 were planned to be followed up for at least 30 days or until death although some patients had their final safety visit completed up to 45 days after andexanet alfa treatment. The company reported that all analyses were censored at 30 days in the published analysis data set[47] although analyses up to 45 days were to be included in the final clinical study report provided to the EMA. The ERG notes that some of the analysis in the CS are post hoc such as length of hospital stay and that this outcome does not appear to of been censored at 30 or 45 days as patients with much longer follow-up are also included in the analyses.

4.3 ANNEXA-4 clinical effectiveness results

Please note all results presented below relate to the safety population analysis of the apixaban and rivaroxaban subgroup of ANNEXA-4 unless reported otherwise.

4.3.1 Haemostatic efficacy (control of bleeding)

Haemostatic efficacy was one of the co-primary outcomes and clinical haemostasis was adjudicated by an independent and blinded endpoint adjudication committee as excellent or good in [redacted]% ([redacted]) of the safety population subgroup of patients who had received apixaban or rivaroxaban ([redacted]), 12 hours after andexanet alfa infusion. The proportion of patients in the ICH and GI bleed subgroups with good or excellent haemostatic efficacy at 12 hours post andexanet alfa [redacted] (Table 10).

Table 10. Haemostatic efficacy at 12 hours post andexanet alfa of apixaban and rivaroxaban (Safety Population) (adapted from company response to clarification question A9a-c, Table 20)

Cohort	Statistic	All Patients
Overall	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
Bleed Type		
GI	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
ICH	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
Other	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]

Abbreviations: CI, confidence interval; GI, gastrointestinal; ICH, intracranial haemorrhage; N, number.

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet alfa.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Patients adjudicated as non-evaluable for administrative reasons were excluded.

4.3.2 Re-bleeding

Re-bleeding was introduced as an exploratory endpoint in protocol amendment 4 and was defined as bleeding from the same anatomical site within 24 hours of initial andexanet alfa treatment and after achieving initial good/excellent haemostasis. Re-bleeding [redacted] patients enrolled after the implementation of amendment 4 and [redacted]

A *post hoc* analysis of haematoma expansion in patients with ICH was conducted in the [redacted] patients in the safety population of the apixaban and rivaroxaban subgroup with suitable data (ERG assumes same criteria as for full study population analysis applied; i.e. non-traumatic, single-compartment, intracerebral haemorrhages; Table 11). The ERG are unclear what the mean and SD data reported in Table 11 relate to and therefore is unable to critique these data but the proportion of patients shows that [redacted] had volume expansion > 35% from baseline at 1 hour. Out of 119 patients, [redacted] had no haematoma expansion when defined as intracerebral volume >35% increase from baseline to 1 and 12 hours.

Table 11. Analysis of hematoma expansion in patients received apixaban or rivaroxaban with intracerebral volume (Safety Population) (adapted from company response to clarification question A9b, Table 22)

Status of Hematoma Expansion	N (%) with Intracerebral Volume > 35% Increase from Baseline to 1 hour (N=124)	Number at 1 hour Mean (SD)	N (%) with Intracerebral Volume > 35% Increase from Baseline to 1 & 12 hour (N=119)	Number at 12 hours Mean (SD)
Hematoma Expansion	[redacted]	[redacted]	[redacted]	[redacted]
No Hematoma Expansion	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: N, number; SD, standard deviation.
Database lock date: 28NOV2018. The Safety Population includes all patients treated with any amount of andexanet alfa.
Patients who didn't have intracerebral volumes at baseline, 1 hour assessment, and/or 12 hour assessment were excluded.
Hematoma expansion defined as volume increase from baseline greater than 35%.
Study: ANNEXA4 (14-505), Program: Table A9B3.sas, Output: Table A9B3.rtf, Date: 24OCT2019

4.3.3 Requirement for blood products (red blood cell transfusions, non-study-prescribed blood products and haemostatic agents)

The company reported that for the full study safety population (N = 352) who completed the 30-day safety follow-up, [redacted] received red blood cell transfusions during the efficacy evaluation period. [redacted] Equivalent data were not provided for the apixaban or rivaroxaban subgroup although data broken down by time of blood product use was provided (Table 12). The ERG considers it important to highlight that patients included in the data at the different timepoints in Table 12 may

have received blood products at more than one of the time points and it is not clear how many patients received multiple blood products over the follow-up period in ANNEXA-4. The results for blood product use show that [redacted].

Table 12. Blood product use (mL) and non-RBC blood product use of patients with apixaban or rivaroxaban (Safety Population) (adapted from CS Document B, Table 19)

	All Patients (N=322)	**Patients with ICH (N=209)**	**Patients with GI (N=82)**
Blood Product Use (mL)			
Before andexanet alfa dosing (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]		[redacted]
Median	[redacted]		[redacted]
IQR	[redacted]		[redacted]
Range	[redacted]		[redacted]
0-16 hour (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
>16 hour (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Coagulation Factor Transfusion (N)			
Before andexanet alfa dosing	[redacted]	[redacted]	[redacted]
30 minutes before end of infusion	[redacted]	[redacted]	[redacted]
1 hour	[redacted]	[redacted]	[redacted]
4 hour	[redacted]	[redacted]	[redacted]
8 hour	[redacted]	[redacted]	[redacted]
12 hour	[redacted]	[redacted]	[redacted]
Haemostatic Treatments (N)			
Before andexanet alfa dosing	[redacted]	[redacted]	[redacted]
30 minutes before end of infusion	[redacted]	[redacted]	[redacted]
1 hour	[redacted]	[redacted]	[redacted]
4 hour	[redacted]	[redacted]	[redacted]
8 hour	[redacted]	[redacted]	[redacted]
12 hour	[redacted]	[redacted]	[redacted]
Other Blood/Coagulation (N)			
Before andexanet alfa dosing	[redacted]	[redacted]	[redacted]
30 minutes before end of infusion	[redacted]	[redacted]	[redacted]
1 hour	[redacted]	[redacted]	[redacted]
4 hour	[redacted]	[redacted]	[redacted]
12 hour	[redacted]	[redacted]	[redacted]

Abbreviations: CS, company's submission; GI, gastrointestinal; ICH, intracranial haemorrhage; IQR, interquartile range; N, number; RBC, red blood cell; SD, standard deviation.
Database lock date: 28Nov2018. The Safety Population included patients treated with any amount of andexanet alfa.
Bleed type was adjudicated by the Endpoint Adjudication Committee. 16 hours is 12 hours after EOI.
Source: Portola data on file[48]

In the company's response to clarification questions, a further table was provided which gave a breakdown of the number of patients who received concomitant 4F-PCC, fresh frozen plasma, plasma, platelets, aminocaproic acid, tranexamic acid or thrombin during ANNEXA-4 in the apixaban or rivaroxaban subgroup (Table 13). The use of non-packed red blood cell (RBC) blood products including coagulation factor products and haemostatic products in ANNEXA-4 was [redacted] of patients in the apixaban or rivaroxaban subgroup receiving any individual product. The ERG notes that [redacted] patients received 4F-PCC, [redacted] Table 13. Blood products and haemostatic agents use of patients received apixaban or rivaroxaban after andexanet alfa treatment (Safety Population) (adapted from company response to clarification question A11, Table 25)

Group	Blood Products Haemostatic Agents	All Patients (N=322) n (%)
Coagulation Factor Products	4-Factor PCC	[redacted]
Blood products	Fresh Frozen Plasma	[redacted]
	Plasma	[redacted]
	Platelets	[redacted]
Haemostatic Treatment	Aminocaproic Acid	[redacted]
	Tranexamic Acid	[redacted]
Other	Thrombin	[redacted]

Abbreviations: 4-Factor PCC, 4-Factor prothrombin complex concentrate; N, number.
Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet alfa.

4.3.4 Neurological outcomes (in people with ICH)

Data for GCS and NIHSS in the apixaban and rivaroxaban subgroups were provided during the clarification stage but the ERG notes [redacted] patients had a post-baseline GCS assessment and [redacted] patients had post-baseline NIHSS assessments. NIHSS testing and the GCS assessments post-baseline were not added or implemented until Protocol Amendment 4, [redacted] The ERG therefore considers the outcome data for mRS to be more robust and reliable as it was captured from the study outset until day 30 follow-up for all ICH patients. Data on GCS and NIHSS are presented in Table 14 and show GCS score to [redacted]

Table 14. Clinical neurologic status (Glasgow Coma Scale & National Institutes of Health Stroke Scale) for patients, who received apixaban or rivaroxaban, with ICH (Safety Population) (adapted from company response to clarification question A9b, Table 23)

Assessment Time	Statistic	GCS	GCS Change	NIHSS	NIHSS Change
Baseline	Patients (N)	[redacted]		[redacted]	

	Mean (SD)	[redacted]		[redacted]	
	Median	[redacted]		[redacted]	
	Min, Max	[redacted]		[redacted]	
	Median 95% CI	[redacted]		[redacted]	
1 Hour	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]
12 Hour	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]
Day 30	Patients (N)	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
	Median 95% CI	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; GCS, Glasgow Coma Scale; ICH, intracranial haemorrhage; N, number; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.
Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet alfa.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Study: ANNEXA4 (14-505), Program: Table A9B4.sas, Output: Table A9B4.rtf, Date: 24OCT2019

The company provided data on the mean and median mRS at baseline, 1-hour post andexanet alfa, 12 hours post andexanet alfa and 30 days, which are useful in showing the change in mRS over time (Table 15). The ERG considers the mRS data suggest [redacted] (Table 15).

Table 15. Modified Rankin Score (mRS) of ICH patients with apixaban or rivaroxaban (Safety Population) (adapted from CS Document B, Table 21)

Timepoint	**Statistic**	**Patients with ICH (N=209)**
Screening	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	IQR	[redacted]
	Range	[redacted]
1 hour	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	IQR	[redacted]
	Range	[redacted]
12 hours	N	[redacted]
	Mean (SD)	[redacted]

	Median	[redacted]
	IQR	[redacted]
	Range	[redacted]
Day 30	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	IQR	[redacted]
	Range	[redacted]

Abbreviations: CS, company's submission; ICH, intracranial haemorrhage; IQR, interquartile range; N, number; SD, standard deviation.
Database lock date: 28Nov2018. The Safety Population included patients treated with any amount of andexanet alfa.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Source: Portola data on file[48]

The ERG notes that Table 22 in the CS presents a breakdown of the number of patients with each of the mRS scores (0 to 6) at baseline and day 30 for the whole ANNEXA-4 efficacy population rather than just the apixaban and rivaroxaban subgroup, whereas, Table 48 in the cost-effectiveness section of the CS provides the day 30 mRS for the apixaban and rivaroxaban subgroup of relevance. The ERG also notes that further subgroup data for the intracerebral bleed patients at day 30 are available within the company model which the ERG assumes also relate to the apixaban or rivaroxaban subgroup and may also include intraventricular haemorrhages. The ERG considers only the apixaban or rivaroxaban subgroup data of relevance, however, unfortunately as baseline data aren't provided for these patients it is unclear how the distribution of patients in the different mRS categories have changed over the 30 days (Table 16). The 30-day data suggest [redacted]

Table 16. The Modified Rankin Score of ICH patients at Day 30 (apixaban and rivaroxaban subgroup) (adapted from CS Document B, Table 48 and company model)

Modified Rankin Scale	All ICH	Intracerebral bleeds
No. Patients	[redacted]	[redacted]
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]

Abbreviations: CS, company's submission; ICH, intracranial haemorrhage.

4.3.5 Duration of hospital stay

The company provided the mean and median duration of hospital stay for the apixaban and rivaroxaban subgroup along with the respective standard deviation and interquartile ranges for all patients and

broken down by direct oral anticoagulant (DOAC; apixaban or rivaroxaban). The ERG notes that [redacted] (Table 17). The ERG also notes that rivaroxaban [redacted]

Table 17. Details of hospitalisation (days) post treatment in patients received apixaban or rivaroxaban by bleed type (Safety Populations)(adapted from company clarification response A13, Table 27)

Bleed Type	Parameter	Apixaban (N=194)	Rivaroxaban (N=128)	All Patients (N=322)
All Patients	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
GI	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
ICH	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Other	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]

Abbreviations: N, number; Q, quartile; SD, standard deviation.
Database lock date: 28NOV2018. The Safety Population included all patients who received any amount of andexanet alfa.
Bleed type was adjudicated by the Endpoint Adjudication Committee.

The company also provided a breakdown of the number of patients who had hospital stays lasting for 30 days or longer and these data suggest that [redacted] (Table 18). The median hospital stays were [redacted] (Table 18).

Table 18. Summary of hospitalization ≥30 days by bleed type in patients received apixaban or rivaroxaban (Safety Population) (adapted from company clarification response A15, Table 28)

FXa Inhibitor	Statistic	GI	ICH	All Patients
Apixaban	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Rivaroxaban	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]

Abbreviations: FXa, Factor Xa; GI, gastrointestinal; ICH, intracranial haemorrhage; N, number; Q, quartile; SD, standard deviation.
Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet alfa. Bleed type was adjudicated by the Endpoint Adjudication Committee.
Study: ANNEXA4 (14-505), Program: Table A15.sas, Output: Table A15.rtf, Date: 25OCT2019

4.3.6 Need for surgical control of bleeding or interventional radiology embolisation of bleeding vessel

The use of interventions to control bleeding was not a prespecified endpoint in the ANNEXA-4 study, although it was an outcome specified in the NICE final scope. The company reported that data on surgical or other interventions to control bleeding were captured as free-text terms in patients notes and the data were collated through hand searching each patient record. The results suggest that [redacted] of patients required surgical or other interventional procedures for control of their bleeding and [redacted] (Table 19). The non-standardised recording of these data and small patient numbers limits their power and generalisability and so both the company and ERG considers that these results should be interpreted with caution.

Table 19. Surgical and other interventions for control of bleeding (Safety Population of apixaban and rivaroxaban subgroup) (adapted from CS Document B, Table 24)

Bleed type & Procedure	Apixaban (n=194)	Rivaroxaban (n=128)	Overall (n=322)
ICH			
Craniotomy/craniectomy	[redacted]	[redacted]	[redacted]
Ventricular drain	[redacted]	[redacted]	[redacted]
Evacuation of haematoma	[redacted]	[redacted]	[redacted]
Burr hole	[redacted]	[redacted]	[redacted]
Unidentified procedure	[redacted]	[redacted]	[redacted]
Other procedure	[redacted]	[redacted]	[redacted]
GI			
Exploratory laparotomy	[redacted]	[redacted]	[redacted]
Intraluminal device	[redacted]	[redacted]	[redacted]

Other			
Hemiarthroplasty	[redacted]	[redacted]	[redacted]
Pleural drainage	[redacted]	[redacted]	[redacted]
Vaginal packing	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Abbreviations: CS, company's submission; GI, gastrointestinal; ICH, intracranial haemorrhage.

4.3.7 Subgroup analyses

In ANNEXA-4, data were analysed according to the pre-specified subgroups (Section 4.2.3) for the full efficacy population rather than the apixaban and rivaroxaban subgroup and the ERG notes that similar rates of haemostatic efficacy were observed in the pre-specified subgroups (CS document B, Figure 10). In terms of subgroup analysis data for the apixaban and rivaroxaban subgroup, the company provided data by FXa inhibitor and FXa inhibitor dose (high/low dose) in their response to clarification questions which suggested [redacted] (Company response to clarification question A22, Table 33).

The subgroup of interest in the NICE final scope was ICH and the company provided data based on bleed type (ICH or GI) including a breakdown for the location of ICH and GI bleeds for the primary efficacy outcome of haemostatic efficacy in the apixaban and rivaroxaban subgroup in the company response to clarification Table 20. The data suggest [redacted] The intracerebral haemorrhage and IVH bleeds were associated with [redacted]

Table 20. Haemostatic efficacy at 12 hours post andexanet alfa by bleeding type (Safety Population, apixaban and rivaroxaban subgroup) (adapted from company clarfication response A22, Table 32)

Subgroup	Statistic	All Patients
ICH	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
Intracerebral haemorrhage/IVH	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
SDH	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
SAH	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
Multiple	Patients (N)	[redacted]

	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
GI	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
GI Upper	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
GI Lower	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
GI Unknown	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]

Abbreviations: CI, confidence interval; GI, gastrointestinal; ICH, intracranial haemorrhage; IVH, intraventricular haemorrhage; N, number; SAH, subarachnoid haemorrhage; SDH, subdural haemorrhage.
Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet alfa.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Patients adjudicated as non-evaluable for administrative reasons were excluded.
Study: ANNEXA4 (14-505), Program: Table A22B.sas, Output: Table A22B.rtf, Date: 29OCT2019

Data provided by the company during clarification response suggested [redacted] (Table 21).

Table 21. Haemostatic efficacy at 12 hours post andexanet alfa by clinical neurologic status (Modified Rankin Score [mRS]) in patients with ICH (Safety Population)(adapted from company response to clarification question A22, Table 34)

mRS	Patients (N)	n (%)	Exact 95% CI
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; N, number; ICH, intracranial haemorrhage; mRS, Modified Rankin Scale.
Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet alfa.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Study: ANNEXA4 (14-505), Program: Table A22D.sas, Output: Table A22D.rtf, Date: 29OCT2019

4.3.8 Adverse effects

As discussed in Section 4.2.3, adverse effect data are discussed for the full ANNEXA-4 study population and not just the apixaban and rivaroxaban subgroup. Treatment-emergent adverse events (TEAEs) occurred in [redacted] patients (Table 22) with [redacted] patients experiencing at least one TEAE that was graded as at least severe on the severity scale.[69] The most frequently reported TEAEs (occurring in ≥ 3% of patients) were [redacted]

[redacted]

A total of [redacted] patients were deemed to have experienced treatment-related TEAEs (Table 23) and [redacted] patients experienced TEAEs resulting in premature discontinuation of the study drug. There were [redacted] during the study (the causes of mortality are discussed in Section 4.3.8.2) and [redacted] patients who experienced a serious adverse event (SAE; discussed further in Section 4.3.8.1).

Table 22. Overall summary of adverse events (Safety Population, Day 30/45* safety follow up visit) (adapted from CS Document B, Table 35)

Adverse event	Overall
All Patients	352
Number of Patients with AT LEAST ONE	
Adverse Events	[redacted]
Treatment Emergent Adverse Event	[redacted]
Treatment-Related Adverse Event	[redacted]
Adverse Event Leading to Drug Discontinuation	[redacted]
Adverse Event Leading to Early Study Withdrawal	[redacted]
Adverse Event Special Interest	[redacted]
Infusion Reactions	[redacted]
Thrombotic Event	[redacted]
Serious TEAE	[redacted]
Fatal TEAE	[redacted]
Number of TEAEs	[redacted]

Abbreviations: CS, company's submission; TEAE, treatment-emergent adverse event.
Database lock date: 28Nov2018. The Safety Population includes all patients who received any amount of andexanet alfa.
Thrombotic event was adjudicated by the Endpoint Adjudication Committee.
Toxicity grade of seven AEs was imputed by fatal AE action outcome.
* NOTE: all patients enrolled under Amendment 1 or earlier had a day 45 visit in lieu of a day 30 visit. All patients enrolled under Amendment 2 or later had a day 30 visit and no Day 45 visit. No patient had both a Day 30 and a Day 45 visit. Thus, all adverse events cited in the tables were recorded to Day 45 for those patients that had a Day 45 visit, and Day 30 for those patients that had a Day 30 visit.
** 5 deaths occurred after 30 calendar days. 2 of these deaths occurred after the Day 30/45 visit and were mistakenly recorded by the investigators; as such they were counted in the final tabulations.
Source: ANNEXA-4 CSR[69]

Table 23. Summary of treatment-related adverse events occurring in more than one patient by MedDRA preferred term (Safety Population) (adapted from CS Document B, Table 37)

MedDRA Preferred Term	All Patients (N=352) n (%)
Patients with Related TEAE	[redacted]
Ischaemic stroke	[redacted]
Pyrexia	[redacted]
Headache	[redacted]
Nausea	[redacted]
Cerebral infarction	[redacted]
Cerebrovascular accident	[redacted]
Myocardial infarction	[redacted]

Deep vein thrombosis	[redacted]
Infusion related reaction	[redacted]
Pulmonary embolism	[redacted]

Abbreviations: CS, company's submission; MedDRA, Medical dictionary for regulatory activities; TEAE, Treatment-emergent adverse event
Note: Database lock date: 28 Nov 2018. The Safety Population includes all patients who received any amount of andexanet alfa.
Source: ANNEXA-4 CSR[69]

The company reported that no patients in ANNEXA-4 developed antibodies to FX after andexanet alfa treatment, and no neutralising antibodies to FXa or andexanet alfa were observed during the study.[47]

4.3.8.1 Serious Adverse events

In the ANNEXA-4 safety population (full study population), a total of [redacted] patients experienced at least one SAE and [redacted] patients experienced at least one treatment-related SAE (Table 24). [redacted]

Table 24. Serious treatment-emergent adverse events considered possibly or probably related to andexanet alfa treatment by MedDRA primary system organ class and preferred term (Safety Population, full ANNEXA-4 study population) (adapted from CS Document B, Table 39)

MedDRA Primary System Organ Class Preferred Term	All Patients (N=352) n (%)
Patients with Related SAE	[redacted]
Nervous System Disorders	[redacted]
Ischaemic Stroke	[redacted]
Cerebral Infarction	[redacted]
Cerebrovascular Accident	[redacted]
Depressed Level Of Consciousness	[redacted]
Intracranial Venous Sinus Thrombosis	[redacted]
Transient Ischaemic Attack	[redacted]
Cardiac Disorders	[redacted]
Myocardial Infarction	[redacted]
Acute Myocardial Infarction	[redacted]
Cardiac Arrest	[redacted]
Cardiac Failure	[redacted]
Vascular Disorders	[redacted]
Deep Vein Thrombosis	[redacted]
Iliac Artery Occlusion	[redacted]
Respiratory, Thoracic and Mediastinal Disorders	[redacted]
Pulmonary Embolism	[redacted]
General Disorders and Administration Site Conditions	[redacted]
Sudden Death	[redacted]
Injury, Poisoning and Procedural Complications	[redacted]
Infusion Related Reaction	[redacted]

Renal and Urinary Disorders	[redacted]
Acute Kidney Injury	[redacted]

Abbreviations: CS, company's submission; MedDRA, Medical dictionary for regulatory activities; SAE, serious adverse event.
Database lock date: 28Nov2018. The Safety Population includes all patients who received any amount of andexanet alfa.
Source: ANNEXA-4 CSR[69]

4.3.8.2 Mortality

[redacted] The ERG notes that 30-day mortality data was used in the company's economic model which the ERG considers reasonable as this was an adjudicated end-point in ANNEXA-4. There were [redacted] deaths ([redacted]) to day 30 in the apixaban and rivaroxaban subgroup, with [redacted] adjudicated as cardiovascular events, [redacted] as non-cardiovascular events, and [redacted] were of unknown cause (Table 25).[47] The day 30-mortality rate in the apixaban and rivaroxaban subgroup of patients with ICH was [redacted], and [redacted] in the patients with GI bleeds.

Table 25. Adjudicated reason for deaths (Safety Population) (adapted from CS Document B, Table 38)

		Patients with Apixaban or Rivaroxaban		
	[redacted]	[redacted]	[redacted]	[redacted]
Deaths [1], N	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for death, N (%)				
Cardiovascular: Not Related to Bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Patients had TEs	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular: Related to Bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Patients had TEs	[redacted]	[redacted]	[redacted]	[redacted]
Non-Cardiovascular	[redacted]	[redacted]	[redacted]	[redacted]
Patients had TEs	[redacted]	[redacted]	[redacted]	[redacted]
Uncertain	[redacted]	[redacted]	[redacted]	[redacted]
Unknown[2]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths within 30 days	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CS, company's submission; TE, thrombotic event.
Database lock date: 28Nov2018. The Safety Population includes all patients who received any amount of andexanet alfa.
[1] [redacted]
[2] Deaths of two patients were not adjudicated (as they occurred after the Day 30/45 visit)
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Source: Portola data on file[48]

The ERG notes from data provided by the company in their clarification response that [redacted]

4.3.8.3 Thrombotic events

Thrombotic events were defined as the protocol-specified, independently-adjudicated cerebrovascular accidents, deep vein thromboses (DVTs), myocardial infarctions, pulmonary embolisms (PEs), and transient ischemic attacks. Thrombotic events occurred in 34 of 352 patients (10%; full ANNEXA-4 study population) during the 30-day follow-up (Table 26). The ERG notes that thrombotic events in the 5 days after andexanet alfa were most frequently due to myocardial infarction or stroke whereas the later thrombotic events that occurred beyond 5 days were most frequently due to DVT, stroke or PE (Table 26)

Table 26. Timing of thromboembolic events and deaths (N = 352)[a] (adapted from CS Document B, Table 40)

	Total N = 352	< 6 days after bolus	6-14 days after bolus	15-30 days after bolus
≥ 1 thrombotic event within 30 days, n (%) [b]	34 (10)	11	11	12
Myocardial infarction	7	6	1	0
Ischemic stroke or stroke of uncertain classification	14	5	6	3
Transient ischemic attack	1	0	0	1
Deep vein thrombosis	13	1	5	7
Pulmonary embolism	5	1	0	4
Death occurring within 30 days, n (%) [c]	49 (14)	8	21	20
Cardiovascular death	35	7	15	13
Non-cardiovascular death	12	1	5	6
Death of uncertain cause	2	0	1	1

Abbreviations: CS, company's submission; n, number.
a Thrombotic events that occurred on the day of restarting anticoagulation were considered to have occurred before the restart.
b Some patients had more than one thromboembolic event.
c Five deaths occurred during study follow-up, but after 30 calendar days
Source: Connolly 2019[47]

Details of the thrombotic events that occurred in the subgroup of patients on apixaban or rivaroxaban were provided in the company's clarification responses (Table 27).

Table 27. Characteristics of thrombotic events and re-anticoagulation stratified by bleed type (Safety Population)(adapted from company response to clarification question A17, Table 29)

Group	GI (N=82)	ICH (N=209)	All Patients (N=322)
TE, n(%)	[redacted]	[redacted]	[redacted]
Age (years)			
Mean	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
FXa Inhibitor			
Apixaban	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]	[redacted]	[redacted]
TE Type[1]			
CVA	[redacted]	[redacted]	[redacted]
DVT	[redacted]	[redacted]	[redacted]
PE	[redacted]	[redacted]	[redacted]

MI	[redacted]	[redacted]	[redacted]
TIA	[redacted]	[redacted]	[redacted]
Indication for Anticoagulation			
Arterial Thromboembolism	[redacted]	[redacted]	[redacted]
Atrial Fibrillation	[redacted]	[redacted]	[redacted]
VTE	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Time to First TE (median, days)[2]	[redacted]	[redacted]	[redacted]
First TE Onset within			
0-12 hours (inclusive)	[redacted]	[redacted]	[redacted]
>12 hours and <4 days	[redacted]	[redacted]	[redacted]
4-30 days (inclusive)	[redacted]	[redacted]	[redacted]
Number of patients re-anticoagulated[3]	[redacted]	[redacted]	[redacted]
Within 30 days since TE onset	[redacted]	[redacted]	[redacted]
Prior to TE onset	[redacted]	[redacted]	[redacted]
Days to Re-anticoagulation (median)	[redacted]	[redacted]	[redacted]

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; MI, myocardial infarction; TE, thrombotic event; TIA, transient ischemic attack; VTE, venous thromboembolism.
Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet alfa. Thrombotic event and bleed type were adjudicated by the Endpoint Adjudication Committee.
[1] TE type is summarized at subject level. A patient may have multiple TE type.
[2] Time to first TE is inclusive of the dosing day.
[3] A patient could have multiple indications for the initial anti-coagulation.
CVA: Stroke Ischemic/Uncertain Classification, DVT: Deep Vein Thromboembolism , MI: Myocardial Infarction, PE: Pulmonary Embolism, TIA: Transient Ischemic Attack
Study: ANNEXA4 (14-505), Program: Table A17.sas, Output: Table A17.rtf, Date: 25OCT2019

4.3.8.3.1 Restart of Anticoagulation

Data on the restart of anticoagulation after andexanet alfa in ANNEXA-4 show that [redacted] of patients restarted oral anticoagulation, although the ERG notes limited data were collected beyond 30 days [redacted] (Table 28). [redacted] during ANNEXA-4. The most frequently used non-oral anticoagulants were [redacted] The oral anticoagulants patients restarted on are summarised in Table 29 and includes [redacted] No patient who recommenced oral anticoagulation had a thrombotic event during ANNEXA-4 after restart of oral anticoagulation.

Table 28. Timing of restarting of anticoagulation in patients with apixaban or rivaroxaban (Safety Population, N = 322) (adapted from CS Document B, Table 42)

Anticoagulation Type	Days	All Patients (N=322)	Patients with ICH (N=209)	Patients with GI (N=82)
Patients who Restarted Any Anticoagulation	<30 days	[redacted]	[redacted]	[redacted]
	≥30 days	[redacted]	[redacted]	[redacted]
	<30 days	[redacted]	[redacted]	[redacted]

Patients who Restarted Non-oral Anticoagulation	≥30 days	[redacted]	[redacted]	[redacted]
Patients who Restarted Oral Anticoagulation[1]	<30 days	[redacted]	[redacted]	[redacted]
	≥30 days	[redacted]	[redacted]	[redacted]

Abbreviations: CS, company's submission; GI, gastrointestinal; ICH, intracranial haemorrhage.
Database lock date: 28Nov2018. The Safety Population included patients treated with any amount of andexanet alfa.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
[1] Restart of oral anticoagulation includes only the use of vitamin K antagonists or non-vitamin K oral anticoagulants (at any dose and for any duration).
Source: Portola data on file[48]

Table 29. Oral anticoagulation drug post andexanet alfa treatment in patients who received apixaban or rivaroxaban (Safety Population) (adapted from company response to clarification question A20, Table 31)

Anticoagulation	[redacted]	[redacted]	[redacted]
Oral Anticoagulation			
Apixaban	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]	[redacted]	[redacted]
Warfarin	[redacted]	[redacted]	[redacted]
Oral Anticoagulation Different Than Their Initial FXa Inhibitor			
Apixaban	[redacted]	[redacted]	[redacted]
Rivaroxaban	[redacted]	[redacted]	[redacted]
Warfarin	[redacted]	[redacted]	[redacted]

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage.
Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet alfa.
Study: ANNEXA4 (14-505), program: Table A20.sas, Output: Table A20.rtf, Date: 31OCT2019

4.4 Critique of the indirect comparison

As described in Section 4.1.3, the ORANGE study was included to provide comparator data on 4F-PCC and it was used in a propensity score matching analysis with ANNEXA-4 to enable an adjusted indirect comparison of andexanet alfa with PCC.

4.4.1 Critique of the ORANGE study

The ORANGE study was a UK-based, 3-year, prospective cohort study that collected data from multiple UK hospitals on the presentation and clinical outcomes of patients admitted for a major bleeding episode while on oral anticoagulant therapy.[17] An overview of the ORANGE study methodology including its inclusion and exclusion criteria is provided in Table 30. The ORANGE study (n = 2,192) included patients on warfarin and other oral anticoagulants including apixaban and rivaroxaban, although as for ANNEXA-4, only the apixaban and rivaroxaban subgroup (n = 372) is of relevance to this STA and within this subgroup only patients on 4F-PCC (n = 149) were deemed suitable for matching with ANNEXA-4. Therefore, the discussion of data from ORANGE is restricted to this subgroup from here on unless otherwise specified. The ERG notes that four patients from ORANGE receiving rivaroxaban

and apixaban were excluded from the propensity score matching analysis because data were not available for their age (3 patients) or it was not clear whether they died (1 patient). The company's concerns around age were that it was an important covariate likely to affect mortality outcomes which the ERG agrees with.

Table 30. ORANGE study methodology (adapted from CS Document B, Table 26)

Study Acronym/ I.D.	**ORANGE**
Primary study reference(s)	Green et al. A three-year prospective study of the presentation and clinical outcomes of major bleeding episodes associated with oral anticoagulant use in the UK (ORANGE study). Haematologica. 2018 Green et al. Haematological management of major bleeding associated with direct oral anticoagulants - UK experience. Br J Haematol. 2019
Trial design	Prospective cohort study that collected information across multiple UK hospitals on the presentation and clinical outcomes of patients who were admitted for a major bleeding episode whilst on oral anticoagulation therapy. Data on major bleeding events were submitted by multiple hospitals across England, Scotland, Wales and Northern Ireland between 1st October 2013 and 31st August 2016. Patients underwent the normal course of treatment as directed by their clinicians and hospital protocols; at no point was their care altered for the purpose of this study.
Participants (Key Inclusion criteria)	Any patient of 18 years or over on oral anticoagulation therapy at the time when they developed major bleeding was eligible for the study. The definition of major bleeding adopted was an augmented version of the ISTH criteria. It was defined as bleeding requiring hospitalisation and at least one of the following: a) resulting in death; b) transfusion of ≥2 units of red blood cell units or drop in haemoglobin of ≥20 g/L; c) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; d) transfusion of fresh frozen plasma; e) administration of prothrombin complex concentrate, recombinant FVIIa, factor VIII inhibitor bypassing activity or fibrinogen concentrate. The rationale for appending (d) and (e) was to ensure that the routes for case identification were as comprehensive as possible.
Settings and locations	32 hospitals across England, Scotland, Wales and Northern Ireland between 1st October 2013 and 31st August 2016. Cases were reported consecutively and identified by clinical and research staff in participating hospitals from the emergency department, transfusion laboratory, pharmacy (if they stored haemostatic agents) and haematology doctors who were called to give medical advice on the management of these patients.
Trial drugs, n, dose, duration, timing	Not applicable- observational study. Patients underwent the normal course of treatment as directed by their clinicians and hospital protocols; at no point was their care altered for the purpose of this study.
Outcomes	The study collected information on: patients' baseline characteristics; type of oral anticoagulation and indication(s), as well as co-morbidities and clinical outcomes at 30 days, death, or discharge, whichever occurred first. In a sub-study of patients on DOACs, Data comprised information on co-morbidities, bleeding sites, haematological laboratory results, management of bleeding and first outcome up to 30 days (death, discharge or continued hospitalisation).
Pre-planned subgroups	None.
Duration of follow-up / loss to follow-up / cross over	Patients were followed up for 30 days, death, or discharge, whichever occurred first. Outcomes up to 30 days were reported for 2,132 (97%) patients.

Abbreviations: DOAC, direct oral anticoagulant; ISTH, International Society on Thrombosis and Haemostasis.

Treatments given to manage the major bleeding episodes in ORANGE for the apixaban and rivaroxaban subgroups are summarised in Table 31. As discussed in Section 3.3, only PCC is deemed to be a relevant comparator for andexanet alfa and only the patients who received 4F-PCC are used in the propensity score matching analysis.

Table 31. Management of bleeding in the ORANGE study (apixaban and rivaroxaban-treated patients) (adapted from CS Document B, Table 28)

	Apixaban (n = 89)	**Rivaroxaban (n = 283)**
Received any intervention	75 (84%)	193 (68%)
PCC	45 (51%)	104 (37%)
Tranexamic Acid	29 (33%)	73 (26%)
Vitamin K	14 (16%)	41 (14%)
FEIBA	1 (1%)	1 (<1%)
Any blood transfusion	32 (36%)	117 (41%)
Red Blood Cells	29 (33%)	112 (40%)
Fresh Frozen Plasma	8 (9%)	18 (6%)
Platelets	5 (6%)	8 (3%)
Cryoprecipitate	2 (2%)	3 (1%)

Abbreviations: DOAC, direct oral anticoagulant agents; PCC, prothrombin complex concentrate; FEIBA, factor eight inhibitor bypassing activity.

All 145 patients from ORANGE included in the propensity score matching analysis were either taking [redacted] (Table 32).

Table 32. Summary of products received by the 145 PCC patients in the full before matching population in ORANGE (adapted from company response to clarification question A7, Table 18)

Product	**Number of patients (N=145)**
Tranexamic acid	[redacted]
Red blood cells (transfusion)	[redacted]
Fresh frozen plasma	[redacted]
Platelets	[redacted]
Cryoprecipitate	[redacted]

Abbreviations: CS, company's submission; PCC, prothrombin complex concentrate.

A breakdown of other major bleed types in ORANGE (n = [redacted]) for only patients receiving apixaban or rivaroxaban who went on to receive PCC, suggests no clear pattern in location of bleed. The ERG also notes that the location of the other major bleeds in ORANGE varied compared to the location of the other major bleeds seen in ANNEXA-4 (n = [redacted]; Table 33). The ERG notes that 1 patient is missing from the other major bleeds column for ANNEXA-4 in Table 33 and assumes it is a typological error by the company as all [redacted] patients were included in the propensity score matching analyses reported by the company for this subgroup.

Table 33. Breakdown of other types of major bleeding before matching in ANNEXA-4 and ORANGE (adapted from company response to clarification question A5, Table 16)

Specific bleed type from ORANGE patient level data	Frequency (of the other major bleed types) in ORANGE	Frequency (of the other major bleed types) in ANNEXA-4
Retroperitoneal	[redacted]	[redacted]
Extracranial – Subgaleal	[redacted]	[redacted]
Intramuscular with compartment syndrome	[redacted]	[redacted]
Intraarticular	[redacted]	[redacted]
Intraocular	[redacted]	[redacted]
Haematuria/urethral	[redacted]	[redacted]
Urinary tract – unknown site	[redacted]	[redacted]
Urinary tract – urinary bladder	[redacted]	[redacted]
Oral/pharyngeal	[redacted]	[redacted]
Puncture site	[redacted]	[redacted]
Vaginal	[redacted]	[redacted]
Epistaxis/mucosal	[redacted]	[redacted]
Cutaneous/soft tissue	[redacted]	[redacted]
Haemoptysis	[redacted]	[redacted]
Pericardium	[redacted]	[redacted]
Surgical site	[redacted]	[redacted]
Intraspinal – epidural	[redacted]	[redacted]
Intraspinal – intramedullary	[redacted]	[redacted]
Mediastinal	[redacted]	[redacted]
Respiratory tract – pleural	[redacted]	[redacted]
Respiratory tract – pulmonary	[redacted]	[redacted]
Visible bleeding – leg	[redacted]	[redacted]
Other	[redacted]	[redacted]
Abbreviations: none.		

4.4.1.1 ORANGE results

Based on the patient level data obtained from ORANGE in patients treated with PCC who had received apixaban and rivaroxaban:

- the 30-day mortality rate was [redacted] in the whole cohort, [redacted] in ICH patients, [redacted] in GI patients and 18% in other major bleed patients;
- length of stay of 30 days or more was captured in ANNEXA-4; however, length of stay above 30 days was not recorded in ORANGE as patients were censored at 30-days. [redacted] patients had a length of hospital stay of 30 days exactly in ORANGE;
- median length of hospital was [redacted] days in the whole cohort, [redacted] days in ICH patients, [redacted] days in GI patients and [redacted] days in other major bleed patients (Table 34);

- data for re-bleeding (including haematoma expansion), thrombotic events and restart of oral anticoagulation were not available.

Table 34. Hospital length of stay summary for PCC patients anticoagulated with apixaban or rivaroxaban in ORANGE (adapted from company response to clarification question A6, Table 17)

Bleed Type	Statistic	Apixaban (N=45)	Rivaroxaban (N=104)	All Patients (N=149)
All Patients	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
GI	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
ICH	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Other	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; PCC, prothrombin complex concentrate; SD, standard deviation.

4.4.2 Propensity score matching analysis

Population matching methods were used to generate statistically adjusted estimates of effect to enable a comparison of the single-arm ANNEXA-4 and ORANGE studies. The company conducted a propensity score matching analysis to replicate randomisation by identifying and drawing comparisons between similar patients based on one or more characteristics. The company reported that the methods used were chosen to align with NICE DSU Technical Support Document (TSD) 17.[70]

In terms of outcomes for propensity score matching, only 30-day mortality and length of hospital stay were deemed suitable for analysis. However, the company flagged concerns regarding differences in care settings between ORANGE and ANNEXA-4 that may impact on the results for length of hospital stay. The company reported that, based on clinical expert advice, they considered that international guidelines would ensure homogeneity between ANNEXA-4 and ORANGE in the treatment of major bleeding in anticoagulated patients and so 30-day mortality rates were likely to be suitable for comparison between the studies. However, the differences in healthcare systems between the UK and USA in particular were deemed likely to impact on length of hospital stay and so the company did not consider it appropriate to compare these.

The ERG notes that 60% of patients in ANNEXA-4 were from sites in North America and only 7% of the study population were from the UK, whereas in ORANGE all patients were treated in UK sites. However, the ERG considers that mortality and length of hospital stay are likely to be linked as, the

longer hospital stay a patient has, the lower their risk of dying within 30 days is likely to be (assuming similar risk of death between both ANNEXA-4 and ORANGE). The ERG therefore considers length of hospital stay likely to be intrinsically linked with mortality and so it would be inappropriate to only include one outcome in the propensity score matching analysis. Nevertheless, the ERG also has concerns about the censoring of patients in ORANGE at 30 days in the analysis of length of hospital stay, with no equivalent restriction on patients in ANNEXA-4. The ERG is unclear why length of hospital stay data in ANNEXA-4 weren't also censored at 30-days for the propensity score matching analysis given that the company has access to the IPD. The ERG therefore recommends caution when interpreting the results of the propensity score matching for length of hospital stay particularly if they are viewed independently to the mortality data. Treatment-emergent serious thrombotic events were deemed unsuitable for propensity score matching as they only occurred in ≤2% of patients across the ANNEXA-4 and ORANGE studies.

A feasibility assessment was conducted prior to any analysis and that comprised a comparison of: the sample sizes; the study settings; the inclusion and exclusion criteria; and the availability of patient baseline characteristics and other covariates in ANNEXA-4 and ORANGE for the comparison of andexanet alfa with PCC in patients within the marketing authorisation (i.e. adults experiencing life-threatening or uncontrolled bleeds receiving rivaroxaban and apixaban). The following ANNEXA-4 populations were considered:

- Whole population;
- ICH subgroup;
- GI subgroup; and
- Other major bleeds subgroup (non-ICH/GI).

The results of the feasibility assessment indicated that the ANNEXA-4 and ORANGE studies were comparable overall; however, two sources of potential bias were identified:

- Differences in the study populations, as determined by the inclusion and exclusion criteria for characteristics that could not be adjusted for as they were not reported in both studies;
- Omission of reported data on covariates in one of the studies.

Nevertheless, propensity score matching was deemed feasible and was undertaken with advice sought from a senior research fellow from the University of Sheffield to help inform the methods. Matching of ORANGE was made to the ANNEXA-4 study, which the ERG agrees was the best option given that it

comprises of patients suitable for andexanet alfa. A logit model was used due to the binary treatment outcome (andexanet alfa or PCC).

The company reported that adjustment was made for covariates deemed important based on UK clinical opinion regarding their effect on 30-day mortality and the results of statistical testing (t-tests and Chi-squared tests) regarding the strength of their association with treatment assignment. In response to clarification questions the company revised their selection of covariates to include additional covariates suggested by the ERG's clinical experts and removing some relating to baseline medical history that were not associated with statistically significant differences between ANNEXA-4 and ORANGE (Table 35). The ERG also notes that the addition of other variables would have increased the number of dimensions on which data on characteristics were required for matching individuals[71] and that this would then have reduced the pool of comparable individuals between the two studies. The ERG therefore considers it reasonable for the company to exclude baseline characteristics that are not prognostic indicators but does not consider the use of statistical significance testing to select covariates appropriate.

Table 35. Mean and differences between relevant variables for patients receiving apixaban and rivaroxaban FXa inhibitors, in the whole cohort (adapted from company response to clarification question A3, Table 5)

Characteristic	Means from ANNEXA-4 patient level data (N = 322)	Means from ORANGE patient level data (N = 372)	Chi-squared, if applicable	p-value (from Welch two sample t-test)
Age (years)	[redacted]	[redacted]	[redacted]	[redacted]
Bleed type	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: DVT	[redacted]	[redacted]	[redacted]	[redacted]
MH: Pulmonary embolism	[redacted]	[redacted]	[redacted]	[redacted]
MH: Severe peripheral vascular disease	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Congestive heart failure	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]
History of bleeding	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; DVT, deep vein thrombosis; MH, medical history; TIA, transient ischemic attack.
Calculated using relevant FXa inhibitors only. *p-value <0.05; **p-value <0.01; ***p-value <0.001.

The company reported that they were unable to include severity of bleed (e.g. as assessed by mRS) or volume of bleed as covariates in the propensity score matching analysis as these data weren't collected

in the ORANGE study. However, the ERG's clinical experts reported that they are potentially important prognostic indicators. The ERG considers it important that all relevant covariates are included where possible, so the resulting efficacy estimates are as accurate as possible and considers the company's resulting choice of covariates likely to be reasonable given the available data.

The resulting covariates chosen for the analyses of the whole cohort, ICH patients, and patients with severe GI bleeds included:

- Age;
- Site of bleed (intracerebral, subarachnoid, subdural/epidural, GI-lower, GI-upper, GI-unknown, other;
- Medical history of coronary artery disease;
- Medical history of stroke;
- Medical history of transient ischemic attack;
- Medical history of atrial fibrillation;
- Medical history of hypertension;
- Medical history of diabetes;
- Medical history of renal dysfunction;
- Medical history of cancer.

The ERG notes that site of bleed was not included as a covariate in the propensity score matching analyses for the subgroup of patients with other major bleeds as there was already a small sample size after matching ([redacted]). The ERG does not consider this appropriate as there was wide variation in site of bleed in ANNEXA-4 compared to ORANGE (Table 33) and the ERGs clinical experts reported that the different sites of bleeds classed as other is likely to result in differences in mortality and length of hospital stay, which are the outcomes in the propensity score matching analyses. In fact, the ERG does not consider the data on other major bleeds to be suitable for propensity score matching analysis or any other analysis given [redacted] in both ORANGE and ANNEXA-4 for each type of other bleed. The ERG therefore recommends caution when interpreting the results for the other bleeds population in the propensity score matching analyses.

Following the selection of covariates, propensity score matching was conducted in R version 3.6.1 using the MatchIt package for a one-to-one nearest neighbour matching with replacement. The ERG notes that no limit was applied to restrict the maximum number of times an individual could be matched, although the company acknowledged that variance may be increased by making multiple matches with the same individual. The company provided details of the mean frequency with which patients from ORANGE were matched to patients in ANNEXA-4 and also the proportion of patients who were matched more than once in the analysis of 30-day mortality (Table 36). The ERG notes that [redacted] The impact of this matching with replacement approach on the results by frequency of matching for 30-day mortality are discussed in Section 4.4.2.2

Table 36. Table of mean frequencies with which individuals from ORANGE were matched in the 30-day mortality analysis (adapted from company response to clarification question A2, Table 2)

Cohort	Mean no. of matches with a treated patient (no. of matched individuals from ORANGE)	Proportion of patients matched more than once (%)
Whole cohort	[redacted]	[redacted]
ICH	[redacted]	[redacted]
Severe GI	[redacted]	[redacted]
Other major bleeds (non-ICH/GI	[redacted]	[redacted]

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; no. number

The ERG notes that no attempt was made to adjust for unobserved confounders in the propensity score matching analysis despite this being advocated in NICE DSU TSD 17. The company reported that they had assumed that there were no unobserved cofounders. The ERG is uncertain of what impact this decision has had on the results of the propensity score matching analyses presented below and considers it a potential flaw in the analyses.

4.4.2.1 Propensity score matching analysis results – length of hospital stay

The balance between the covariates for the ANNEXA-4 and the ORANGE populations in the analyses before and after propensity score matching for the analysis of length of hospital stay are presented in Table 37 (whole cohort), Table 38 (ICH subgroup), Table 39 (GI bleed subgroup) and Table 40 (other bleeds subgroup). The ERG notes [redacted]

Table 37. Propensity score matching results showing the balance for whole cohort for length of hospital stay (adapted from company response to clarification question A4, Table 11)

Whole cohort	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH – intracerebral	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH-subarachnoid	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH-subdural/epidural	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI- lower	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI- upper	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI-unknown	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with other bleed types	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH: TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GI ,gastrointestinal; ICH, intracranial haemorrhage; PCC, Prothrombin complex concentrate; MH, medical history; TIA, Transient Ischemic Attack; CAD, Coronary artery disease; AF, Atrial fibrillation

Table 38. Propensity score matching results showing the balance for ICH cohort for length of hospital stay (adapted from company response to clarification question A4, Table 12)

ICH cohort	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH – intracerebral	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH-subarachnoid	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH-	[redacted]	[redacted]	[redacted]	[redacted]

subdural/epidural				
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH:TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICH, intracranial haemorrhage; PCC, Prothrombin complex concentrate; MH, medical history; TIA, Transient Ischemic Attack; CAD, Coronary artery disease; AF, Atrial fibrillation				

Table 39. Propensity score matching results showing the balance for severe GI bleed cohort for length of hospital stay (adapted from company response to clarification question A4, Table 13)

Severe GI	**Before propensity score matching**		**After propensity score matching**	
	Andexanet alfa	**PCC**	**Andexanet alfa**	**PCC**
Total	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI – unknown	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI – upper	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI – lower	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH:TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: GI ,gastrointestinal; PCC, Prothrombin complex concentrate; MH, medical history; TIA, Transient Ischemic Attack; CAD, Coronary artery disease; AF, Atrial fibrillation				

Table 40. Propensity score matching results showing the balance for other major bleeds cohort for length of hospital stay (adapted from company response to clarification question A4, Table 14)

Other bleeds	**Before propensity score matching**		**After propensity score matching**	
	Andexanet alfa	**PCC**	**Andexanet alfa**	**PCC**
Total	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]

MH:TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: GI ,gastrointestinal; PCC, Prothrombin complex concentrate; MH, medical history; TIA, Transient Ischemic Attack; CAD, Coronary artery disease; AF, Atrial fibrillation				

The results of the propensity score matching analysis for the outcome of length of hospital stay suggest [redacted] (Table 41). The results for the GI bleed subgroup are [redacted] With regards to other bleeds, [redacted] however, the ERG does not consider these results reliable due to the variation in site of bleed in ANNEXA-4 compared to ORANGE, the studies informing the analysis. In fact, the ERG does not consider the data on other major bleeds to be suitable for propensity score matching analysis or any other analysis [redacted] in both ORANGE and ANNEXA-4 for each type of other bleed.

As discussed in Section 4.4.2, the ERG considers length of hospital stay is likely to be intrinsically linked with mortality. Therefore, it would be inappropriate to ignore the results of the propensity score matching analysis for length of hospital stay. The ERG also acknowledges the company's concern that length of hospital stay may be impacted by differences in study location between ANNEXA-4 and ORANGE. In addition, the ERG has concerns about the censoring of patients in ORANGE at 30 days in the analysis of length of hospital stay with no equivalent restriction on patients in ANNEXA-4 despite the availability of IPD for both studies. The ERG therefore recommends caution when interpreting the results of the propensity score matching for length of hospital stay particularly if they are viewed independently to the mortality data.

Table 41. Propensity score matching results for each cohort for length of hospital stay (Adapted from company response to clarification question A4, Table 10)

Cohort	Number of matches	Adjusted LOS for PCC (days)	Adjusted LOS for andexanet alfa (days)
Whole cohort	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]
Severe GI	[redacted]	[redacted]	[redacted]
Other major bleeds (non-ICH/GI)	[redacted]	[redacted]	[redacted]

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; PCC, Prothrombin complex concentrate; LOS, length of stay.

4.4.2.2 Propensity score matching analysis results – 30-day mortality

The company provided a detailed breakdown of the balance between the covariates for the ANNEXA-4 and ORANGE populations in the analyses before and after propensity score matching for the whole cohort (Table 42), ICH subgroup (Table 43) and GI bleed subgroup (Table 44). No breakdown of the balance of covariates before and after co-variate matching for the analysis of 30-day mortality were provided for the other bleeds subgroup although results were provided for the propensity score matching analysis in this subgroup (Table 45). The ERG notes that there was a [redacted]

Table 42. Propensity score matching results showing the balance for whole cohort for 30-day mortality (adapted from company response to clarification question A3b, Table 7)

Whole cohort	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH – intracerebral	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH-subarachnoid	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH-subdural/epidural	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI- lower	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI- upper	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with GI-unknown	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with other bleed types	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH: TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GI ,gastrointestinal; ICH, intracranial haemorrhage; PCC, Prothrombin complex concentrate; MH, medical history; TIA, Transient Ischemic Attack; CAD, Coronary artery disease; AF, Atrial fibrillation

Table 43. Propensity score matching results showing the balance for ICH cohort for 30-day mortality (adapted from company response to clarification question A3b, Table 8)

ICH cohort	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH – intracerebral	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH-subarachnoid	[redacted]	[redacted]	[redacted]	[redacted]
% of patients with ICH-subdural/epidural	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH:TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICH, intracranial haemorrhage; PCC, Prothrombin complex concentrate; MH, medical history; TIA, Transient Ischemic Attack; CAD, Coronary artery disease; AF, Atrial fibrillation

Table 44. Propensity score matching results showing the balance for GI cohort for 30-day mortality (Adapted from company response to clarification question A3b, Table 9)

Severe GI	Before propensity score matching		After propensity score matching	
	Andexanet alfa	PCC	Andexanet alfa	PCC
Total	[redacted]	[redacted]	[redacted]	[redacted]
Age	[redacted]	[redacted]	[redacted]	[redacted]
MH: Stroke	[redacted]	[redacted]	[redacted]	[redacted]
MH: CAD	[redacted]	[redacted]	[redacted]	[redacted]
MH:TIA	[redacted]	[redacted]	[redacted]	[redacted]
MH: AF	[redacted]	[redacted]	[redacted]	[redacted]
MH: Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
MH: Diabetes	[redacted]	[redacted]	[redacted]	[redacted]
MH: Renal dysfunction	[redacted]	[redacted]	[redacted]	[redacted]
MH: Cancer	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GI ,gastrointestinal; PCC, Prothrombin complex concentrate; MH, medical history; TIA, Transient Ischemic Attack; CAD, Coronary artery disease; AF, Atrial fibrillation

The results of the propensity score matching analyses for 30-day mortality suggest that 30-day mortality rates are [redacted]

[redacted]

Table 45. Propensity score matching results for each cohort for for 30-day mortality (adapted from company response to clarification question A3b, Table 6)

Cohort	Number of matches	Adjusted 30-day mortality for PCC (%)	Adjusted 30-day mortality for andexanet alfa (%)
Whole cohort	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]
Severe GI	[redacted]	[redacted]	[redacted]
Other major bleeds (non-ICH/GI)	[redacted]	[redacted]	[redacted]

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; PCC, Prothrombin complex concentrate.

The ERG notes from the 30-day mortality results for patients in ORANGE, that based on the frequency of matching of patients in the propensity score matching analyses, the results [redacted] (Table 46). [redacted] The ERG also notes that the number of patients in the analysis [redacted] and so the analysis is not particularly robust.

Table 46. Table of mean survival time compared to frequency of matching for patients in the ORANGE study (Adapted from company response to clarification question A2, Table's 3 and 4)

Cohort	Patients only matched once		Patients matched more than once	
	Died within 30 days (%)	30-day survival time (days)	Died within 30 days (%)	30-day survival time (days)
Whole cohort	[redacted]	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]	[redacted]
Severe GI	[redacted]	[redacted]	[redacted]	[redacted]

Other major bleeds (non-ICH/GI)	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage				

4.4.3 Limitations of the propensity score matching analysis

In summary, the ERG considers that the key limitations of the propensity score matching analysis are:

- bleed severity and volume couldn't be included as covariates due to the absence of baseline data in ORANGE;
- ORANGE did not require bleeds to be life-threatening or uncontrolled – this was a requirement in ANNEXA-4 and is a requirement for treatment with andexanet alfa;
- the other major bleeds subgroup [redacted]
- length of hospital stay is likely to be intrinsically linked with mortality;
- differences in healthcare systems between the UK and USA, and the 30-day censoring of patients in ORANGE may have impacted on length of hospital stay therefore the results of the analysis may be unreliable.
- matching with replacement was used and in the 30-day mortality analyses over [redacted] of individuals in the PCC group were matched multiple times;
- unobserved confounders due to the non-randomised study design are likely to be present and so the results of the propensity score matching analyses are subject to inherent bias.

4.5 Summary and conclusions of the clinical effectiveness section

- The key clinical safety and efficacy data for andexanet alfa of relevance to the NICE final scope are those derived from ANNEXA-4, an ongoing phase 3b/4, prospective, open-label, single-arm study. ANNEXA-4 was designed to evaluate the efficacy and safety of andexanet alfa in patients receiving a FXa inhibitor (apixaban, rivaroxaban, edoxaban, or enoxaparin) who present with acute major bleeding.
- The ERG considers the key comparator for andexanet alfa to be 4F-PCCs and notes that the key study providing data on 4F-PCC in the CS is the ORANGE study; ORANGE is used in propensity score matching to generate adjusted estimates of efficacy to enable comparison between andexanet alfa and 4F-PCC.

- The ERG has some concerns about the transparency of study inclusion and the identification of the ORANGE study for the propensity score matching. In addition to ANNEXA-4 and ORANGE, the company included and data extracted 17 studies on PCC in the SLR but does not discuss why they were only reported in appendix D of the CS. The ERG is therefore uncertain whether ORANGE is the only appropriate study to inform the analysis of the clinical efficacy of andexanet alfa compared with 4F-PCC but the ERG notes that it is the largest study with UK-based data and had IPD available.

- Despite the NICE final scope specifying the relevant population to be adults requiring urgent reversal of anticoagulation in case of uncontrolled or life-threatening bleeding, after treatment with a factor Xa-inhibiting direct oral anticoagulant, only the FXa inhibitors apixaban and rivaroxaban are of relevance given the European Marketing authorisation for andexanet alfa.

- In the apixaban and rivaroxaban subgroup of ANNEXA-4, the site of bleed was ICH for 209 patients, GI bleed for 82 patients, [redacted] for [redacted] patients and other sites for the remaining [redacted] patients. The mean age of patients in the apixaban and rivaroxaban subgroup of ANNEXA-4 was [redacted] years and UK patients represented only [redacted]% of the subgroup with [redacted] patients from North America (n = [redacted]%).

- Most patients received [redacted] The ERG also notes from the company's response to clarification, that [redacted]% of patients in the apixaban or rivaroxaban subgroup of ANNEXA-4 received concomitant aspirin and [redacted]% received concomitant clopidogrel, both of which may impact on the results for haemostatic efficacy. However, the ERG acknowledges that this proportion of patients on concomitant aspirin and clopidogrel may be reflective of UK clinical practice and reversal of the antiplatelet agent should also be considered as part of the treatment of a major bleed.

- Haemostatic efficacy was a co-primary outcome in ANNEXA-4 and was adjudicated by an independent and blinded endpoint adjudication committee as excellent or good in [redacted]% ([redacted]) of the safety population subgroup of patients who had received apixaban or rivaroxaban ([redacted]), 12 hours after andexanet alfa infusion. [redacted] haemostatic efficacy were seen in both the ICH and GI bleed subgroups. The ERG notes that a total of [redacted]% of patients in the apixaban or rivaroxaban subgroup received blood products within the first 16 hours of treatment with andexanet and only [redacted]% of patients received blood products beyond 16 hours.

- The ERG considers the mRS data in ANNEXA-4 suggest [redacted]

[redacted] The ERG also notes that there was [redacted]

- [redacted]% of patients required surgical or other interventional procedures for control of their bleeding and [redacted] The non-standardised recording of these data and small patient numbers limits their power and generalisability and so both the company and ERG considers that these results should be interpreted with caution.

- Adverse effect data were presented by the company for the full ANNEXA-4 study population and not just the apixaban and rivaroxaban subgroup which the ERG considers reasonable. A total of [redacted] patients were deemed to have experienced treatment-related TEAEs. There were [redacted] patients who experienced a serious adverse event (SAE) [redacted] patients experienced TEAEs resulting in premature discontinuation of andexanet alfa. There were a total of [redacted] deaths during the ANNEXA-4.

- In terms of thrombotic events at 30-days post andexanet alfa, [redacted] patients in the apixaban or rivaroxaban subgroup had a first thrombotic event by 30 days [redacted]. The data on the restart of anticoagulation after andexanet alfa in ANNEXA-4 showed that [redacted] of patients restarted oral anticoagulation, [redacted]

- Population matching methods were used to generate statistically adjusted estimates of effect to enable a comparison of the single-arm ANNEXA-4 and ORANGE studies. The ORANGE study (n = 2,192) was a UK-based, 3-year, prospective cohort study that collected data from multiple UK hospitals on the presentation and clinical outcomes of patients admitted for a major bleeding episode while on oral anticoagulant therapy. However, as for ANNEXA-4, only the apixaban and rivaroxaban subgroup of ORANGE (n = 372) is of relevance to this STA and within this subgroup only patients on 4F-PCC (n = 149) were deemed suitable for matching with ANNEXA-4.

- Data suitable for analysis between andexanet alfa and 4F-PCC were restricted to the outcomes of 30-day mortality and length of hospital stay. The ERG considers length of hospital stay is likely to be intrinsically linked with mortality as the longer hospital stay a patient has, the lower their risk of dying within 30 days is likely to be (assuming similar risk of death between both ANNEXA-4 and ORANGE). In addition, the ERG notes that data used from ORANGE for the

propensity score matching analysis of length of hospital stay were censored at 30-days but there was longer follow-up in ANNEXA-4 and it was not censored to match that from ORANGE despite the company having access to the IPD for both studies. The ERG also acknowledges the company's concern that length of hospital stay may be impacted by differences in study location between ANNEXA-4 ([redacted] UK) and ORANGE (100% UK). The ERG therefore recommends caution when interpreting the results of the propensity score matching for length of hospital stay particularly if they are viewed independently to the mortality data.

- The company reported that adjustment was made for covariates deemed important based on UK clinical opinion regarding their effect on 30-day mortality and the results of statistical testing (t-tests and Chi-squared tests) regarding the strength of their association with treatment assignment. In response to clarification questions the company revised their selection of covariates to include additional covariates suggested by the ERG's clinical experts and removing some relating to baseline medical history that were not associated with statistically significant differences between ANNEXA-4 and ORANGE. The company reported that they were unable to include severity of bleed (e.g. as assessed by mRS) or volume of bleed as covariates in the propensity score matching analysis as these data weren't collected in the ORANGE study. However, the ERG considers bleed severity in particular to be of importance as clinical experts reported it was likely to be a prognostic indicator and the use of the mRS in the economic model is a key driver in the cost-effectiveness analysis (see Section 5.3.8).

- The ERG does not consider the data on other major bleeds to be suitable for propensity score matching analysis or any other analysis given [redacted]. The ERG therefore recommends caution when interpreting the results for the other bleeds population in the propensity score matching analyses.

- The ERG notes that [redacted]. In addition, the ERG notes that a matching with replacement method was used and in the 30-day mortality analyses [redacted]. The ERG also considers that unobserved confounders are likely to be present due to the non-randomised study design of ANNEXA-4 and ORANGE, and so the results of the propensity score matching analyses are subject to inherent bias.

- The results of the propensity score matching analysis for the outcome of length of hospital stay suggest [redacted] The results of the propensity score matching analyses for 30-

day mortality suggest that [redacted]

5 COST EFFECTIVENESS

5.1 Introduction

Due to changes made to the company's economic analysis in reply to the clarification stages, the company provided revised versions of the Microsoft Excel®-based economic model. The focus of the Evidence Review Group (ERG) report is therefore on the final, revised, economic model.

5.2 ERG comment on company's review of cost-effectiveness evidence

The company carried out a systematic literature review (SLR), using a single search strategy, to identify existing cost-effectiveness evidence, health-related quality of life (HRQoL) evidence, and cost and resource use evidence of direct or indirect Factor Xa (FXa) inhibitors in adults who require rapid reversal of anticoagulation. A summary of the ERG's critique of the methods implemented by the company to identify relevant evidence is presented in Table 47.

Table 47. Summary of ERG's critique of the methods implemented by the company to identify health economic evidence

Systematic review step	Section of CS in which methods are reported			ERG assessment of robustness of methods
	Cost-effectiveness evidence	HRQoL evidence	Cost and resource use evidence	
Data sources	Section 1.4 of Appendix G	Section 1.4 of Appendix G	Section 1.4 of Appendix G	Appropriate. Electronic databases included: EMBASE, Medline, Medline (R) In-Process, HTA, NHS EED, EconLit, ScHARRHUD and EuroQol. Other sources for "grey" literature included: HTA websites (NICE, PBS, CADTH and SMC), Google Scholar and ISPOR
Search terms	Section 1.4 of Appendix G	Section 1.4 of Appendix G	Section 1.4 of Appendix G	Appropriate. Published filters used to identify economic evidence and HRQoL evidence.[72, 73] Comprehensive terms used to identify the relevant the interventions. Additional terms for the population related to the critical area of the bleeding site such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular could have increased the sensitivity of the searches.

Inclusion criteria	Table 1 in Section 1.3 of Appendix G	Table 2 in Section 1.3 of Appendix G	Table 3 in Section 1.3 of Appendix G	Appropriate. The company considered any intervention for the treatment of patients who require rapid reversal of anticoagulation and the ERG considers this to be inclusive.
Screening	Section 1.4 of Appendix G	Section 1.4 of Appendix G	Section 1.4 of Appendix G	Appropriate.
Data extraction	Table 13 in Section 1.5 of Appendix G	Appendix H	Studies reporting costs and resource use from a UK perspective or studies reporting costs and resource use for reversal of life threatening or major bleed and/ or non-UK cost specific are extracted in Table 8 of Appendix I. Studies from other countries are summarised in Table 9 of Appendix I.	Appropriate. Due to the high volume of relevant cost and resource use studies, the ERG considers that appropriate and pragmatic decisions were made regarding their extraction. Given the availability of EQ-5D data in the studies providing HRQoL evidence and NICE's preference for EQ-5D data, the company could have also restricted HRQoL extractions to primary sources of EQ-5D data.
QA of included studies	Table 14 in Section 1.5 of Appendix G using the Drummond and Jefferson criteria[74]	No QA checklist completed, but report the uncertainty around values, consistency with reference case and appropriateness of the study for cost-effectiveness analysis within data extractions.	No QA checklist completed.	Checklists such as the Drummond checklist or Philip's checklist would be preferred for cost-effectiveness evidence.[75, 76] Checklists such as CASP (recommended in DSU TSD 9) would be preferred for HRQoL evidence. Although no QA checklists are recommended for cost and resource use evidence, the company could have considered the cost-related questions in the Drummond checklist or Philip's checklist.

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CASP, Critical Appraisal Skills Programme; CS, company submission; ERG, Evidence Review Group; HRQoL, health-related quality of life; HTA, health technology assessment; INR, induced normalised ratio; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; PBS, Pharmaceutical Benefits Scheme QA, quality assessment; SMC Scottish Medicines Consortium

The SLR identified a total of 2,639 papers after de-duplication and based on title and abstract, a total of 448 papers were identified as potentially relevant to one or more of the three types of evidence the SLR

aimed to identify, and were obtained for full text review. Overall, a total of one cost-effectiveness study, 59 HRQoL studies and 79 resource and cost use studies were included.

The single cost-effectiveness study by Mangram *et al.* 2016 compared three-factor prothrombin complex concentrate (3F-PCC) and four-factor prothrombin complex concentrate (4F-PCC) in patients who had experienced trauma and required rapid reversal of either rivaroxaban or warfarin from a US perspective.[77] In addition, successful international normalised ratio (INR) reversal was used as the measure of effectiveness rather than quality-adjusted life years (QALYs). For these reasons, the company considered the study to be of little relevance for informing the economic analysis of andexanet alfa. However, the ERG notes that the time horizon of the cost-effectiveness study was 48 hours which is considerably shorter than the time horizon considered in the company's analysis (lifetime). The implications surrounding the time horizon of the economic analysis are discussed further in Section 5.3.4.1.

None of the 59 HRQoL studies included in the HRQoL SLR reported any interventions for the reversal of a direct or indirect FXa inhibitor induced life threatening bleeding event. Even so, the company employed two of those studies (Miller *et al.* 2016[78] and NICE TA341[79]) in their cost-effectiveness analysis because they included utility values that were relevant to the bleeds included in the economic model (described in Section 5.3.9).

Finally, none of the 79 included studies that reported cost and resource use evidence were used to inform the economic model. However, the ERG does not consider this to be a major issue as the company employed other sources of high-quality evidence in the model (described in Section 5.3.10).

5.3 Overview and critique of company's economic evaluation

5.3.1 NICE reference case checklist

Table 48 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE final scope outlined in Section 3.1. [1, 80]

Table 48. NICE reference checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The final scope developed by NICE	Yes.
Comparator(s)	Alternative therapies routinely used in the NHS	Yes, 4F-PCC with or without tranexamic acid.
Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.

Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes (lifetime), although many assumptions based on the company's clinical expert opinion are made in the long-term Markov model resulting in an uncertain ICER.
Synthesis of evidence on outcomes	Systematic review	Partly. The company undertook SLRs to identify relevant data, but many assumptions based on the company's clinical expert opinion are made in the long-term Markov model resulting in an uncertain ICER.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes.
Benefit valuation	Time-trade off or standard gamble	Yes.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes.
Abbreviations: 4F-PCC, 4 factor prothrombin complex concentrate; CS, company submission; EQ-5D, EuroQoL-5 Dimensions; ERG, Evidence Review Group; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; SLR, systematic literature review.		

5.3.2 Population

The population considered in the company's economic analysis is based on the conditional marketing authorisation for andexanet alfa, which includes adults treated with a direct FXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding events. In line with the NICE final scope, the company provided a separate analysis for patients with intracranial bleeding (intracranial haemorrhage, ICH).[1] In addition, the company also included an analysis for patients with an ICH or GI bleed. Thus, three cohorts are considered for the economic analysis:

1. Whole cohort (all patients with either an ICH, GI bleed, or 'other major bleed');
2. ICH plus GI cohort (all patients with either an ICH or a GI bleed);
3. ICH cohort (all patients with an ICH bleed only).

In the whole cohort, the company assumed 'other major bleeds' included intraocular bleeds (bleeding within the eye), intraspinal bleeds (bleeding within the spinal column), pericardial bleeds (bleeding within the pericardial space) and retroperitoneal bleeds (bleeding within the retroperitoneal cavity).

However, the ERG considers it important to note that the NICE final scope does not limit 'other major bleeds' to the four types included in the company's economic analysis.[1]

The ANNEXA-4 study, described in detail in Section 4.2, included adults in North America and Europe, who received a direct FXa inhibitor and experienced acute major bleeding requiring urgent anticoagulation reversal. As such, the company deemed the ANNEXA-4 study as the most representative population describing life threatening and uncontrolled bleeding events for patients receiving a direct FXa inhibitor. Therefore, patient demographics at baseline in the company's model were based on the safety population in the ANNEXA-4 study. Baseline demographics for all three cohorts are presented in Table 49.

Table 49. Baseline demographics of each cohort entering the model (Safety Population Taking Apixaban or Rivaroxaban) (adapted from CS Document B, Table 45)

Baseline demographics	Whole cohort	ICH plus GI cohort	ICH cohort
N	[redacted]	[redacted]	[redacted]
Mean age (years)	[redacted]	[redacted]	[redacted]
% Male	[redacted]	[redacted]	[redacted]
Mean weight (Kg)	[redacted]	[redacted]	[redacted]
Abbreviations: ICH, intracranial haemorrhage; GI, gastrointestinal; Kg, kilograms			

5.3.2.1 Proportion of bleeds used in the decision tree

Of the 322 bleed events recorded in ANNEXA-4 for patients who received apixaban or rivaroxaban; 209, 82 and 31 patients experienced an ICH, GI bleed and an 'other major bleed', respectively. The company used the ANNEXA-4 study to inform the proportion of patients who suffer ICH and GI bleed events entering the decision tree. However, the company considered that there were too few intraocular, intraspinal, pericardial and retroperitoneal bleeds, within the 'other major bleed' category of ANNEXA-4 to inform the economic model.

In order to stratify the remaining 31 patients with 'other major bleeds' in ANNEXA-4, the proportion of patients were split by bleed type from data collected in the entire safety population of the ORANGE study (not limited to patients who received apixaban and rivaroxaban as 'other major bleeds' were only recorded for seven out of 369 patients who received these treatments).

In short, based on the ORANGE study, the company assumed that intraspinal, intraocular, retroperitoneal and pericardial bleeds were captured within the 'other major bleeds' category in equal measure. The company's justification for this assumption were that 229 patients in the entire safety population of the ORANGE study experienced 224 musculoskeletal-related bleed events and 75 miscellaneous bleed events, then:

- All 75 miscellaneous bleed events were assumed to include intraocular bleeds; as such, intraocular bleeds represent 25.08% (75/229) of 'other major bleeds'; and,

- The 224 musculoskeletal bleed events were divided equally between intraspinal, pericardial and retroperitoneal bleed events; as such, intraspinal, pericardial and retroperitoneal bleed events each represent 24.97% (224/3/299) of 'other major bleeds'.

Table 50 below summarises the proportion of bleeds used in the decision tree when the whole cohort (all patients with either an ICH, GI bleed, or 'other major bleed') is considered. For the ICH plus GI bleed cohort, the proportions were re-weighted to exclude 'other major bleeds'. This resulted in proportions of [redacted] and [redacted] for ICH and GI bleeds, respectively. For the ICH cohort, the proportion of ICH was set to 100% while the proportion of GI bleeds and 'other major bleeds' were set to 0%.

Table 50. Proportion of bleeds used in the decision tree (adapted from CS Document B, Table 46)

Event	N (%*)	Reference	Calculation*
ICH	[redacted]	ANEXXA-4	[redacted]
GI bleed	[redacted]	ANEXXA-4	[redacted]
Intraocular	[redacted]	ANNEXA-4 & ORANGE	[redacted]
Intraspinal	[redacted]	ANNEXA-4 & ORANGE	[redacted]
Pericardial	[redacted]	ANNEXA-4 & ORANGE	[redacted]
Retroperitoneal	[redacted]	ANNEXA-4 & ORANGE	[redacted]
Abbreviations: ICH, intracranial haemorrhage; GI, gastrointestinal *updated by the ERG, using the values in the economic model			

5.3.2.2 ERG critique

The ERG sought clinical expert opinion to ascertain if the types of 'other major bleeds' included in the economic analysis (intraocular, intraspinal, pericardial and retroperitoneal bleeds) reflect the uncontrolled or life-threatening bleeds they see in UK clinical practice. Although clinical experts considered the 'other major bleeds' included in the economic analysis to be important, they had only treated a small proportion of these patients in clinical practice. Furthermore, the ERG's clinical experts highlighted that the 'other major bleeds' observed in ANNEXA-4 (Table 51) would generally be managed outside of an ambulatory setting using alternative reversal strategies such as cessation of the FXa inhibitor alone. As such, the ERG considers it important to reiterate that the NICE final scope does not limit 'other major bleeds' to the four types included in the company's economic analysis, and would emphasise that the results of the company's model only relate to intraocular, intraspinal, pericardial and retroperitoneal bleeds as opposed to the wider range of 'other major bleeds' seen in ANNEXA-4.

Table 51. Sites of Other Bleed Patients with Apixaban or Rivaroxaban, Safety Population (reproduced from CS Document B, Table 15)

Other bleed site	N=31
Retroperitoneal	[redacted]
Extracranial - Galeal	[redacted]
Respiratory tract – pulmonary/pleural	[redacted]
Urinary tract/ Urethra	[redacted]

Other bleed site	N=31
Genital - vaginal	[redacted]
Pericardial	[redacted]
Intraspinal – epidural/intramedullary	[redacted]
Leg	[redacted]
Intra-articular	[redacted]
Nasal (nose bleed)	[redacted]
Mediastinal	[redacted]

The ERG also has concerns regarding the number of intraocular bleeds and intraspinal bleeds recorded in ANNEXA-4 compared with the number applied in the economic analysis. In ANNEXA-4, [redacted] intraocular bleeds ([redacted] of 'other major bleeds' in ANNEXA-4) and [redacted] intraspinal bleeds ([redacted] of 'other major bleeds' in ANNEXA-4) were recorded (Table 51). In the economic analysis, based on the stratification described earlier, the company included [redacted] intraocular bleeds (25% of 'other major bleeds' in the model) and [redacted] intraspinal bleeds (25% of 'other major bleeds' in the model) (Table 50). Furthermore, intraocular bleeds and intraspinal bleeds are associated with complications (blindness and paralysis, respectively) in the economic analysis and these complications incur larger long-term cost and quality of life decrements in patients who receive standard care compared to patients who receive andexanet alfa (see Sections 5.3.9.2 and 5.3.10.3). For these reasons, the ERG considers that the company has inflated the incidence of intraocular bleeds and intraspinal bleeds in the economic analysis and subsequently favoured andexanet alfa.

Overall, the ERG considers that including 'other major bleeds' in the economic analysis is of limited benefit as it causes unnecessary "noise" (due to the number of assumptions that need to be made to supplement the lack of outcome data for this subgroup) and distracts from the population most likely to be treated with andexanet alfa in UK clinical practice (patients with life threatening or uncontrolled ICH or GI bleeds). As such, the ERG's preferred population is the ICH plus GI cohort. However, in order to adhere to the NICE final scope,[1] the ERG considers it important to point out the fundamental flaws in the company's analysis of 'other major bleeds' rather than focus the remainder of this report on its preferred population.

5.3.3 Interventions and comparators

The intervention under consideration in the economic analysis is andexanet alfa, formulated as a 200 mg vial, delivered intravenously. The company modelled the two dosing regimens reported in the summary of product characteristics (SmPC) for andexanet alfa, low or high, depending on the type and timing of the last does of FXa inhibitor received.[2] The low dose regimen consists of a 400 mg bolus, delivered at 30 mg/min, followed by a 4 mg/min infusion for 120 minutes, while the high dose regimen consisted of an 800 mg bolus, delivered at 30 mg/min, followed by an 8 mg/min infusion for 120 minutes.

Currently, there are no specific agents available for the reversal of anticoagulation effect of FXa inhibitors. As a result, the NICE final scope lists the comparator as established clinical management of uncontrolled or life-threatening bleeding without andexanet alfa (including off-label PCC with or without tranexamic acid).[1] However, the company highlighted that three types of PCCs are available in UK clinical practice: non-activated 3F-PCC; non-activated 4F-PCC (Beriplex® and Octaplex®); and, activated 4F-PCC (FEIBA®; Factor VIII Inhibitor Bypassing Activity). Based on findings from the clinical SLR on the safety and efficacy of PCCs (described in Section 4.1) and clinical expert advice, the company stated that treatment with non-activated 4F-PCC (excluding FEIBA) is the most appropriate comparator for andexanet alfa; 3F-PCC is not generally used for this indication and activated 4F-PCC (FEIBA) is used very rarely. The company also noted that off-label recombinant factor VIIa (rFVIIa; NovoSeven®) is a relatively expensive treatment that is considered as an option by some clinicians when other measures have failed.

As described in Section 4.4, the clinical efficacy of the comparator given by the 30-day mortality rate was sourced from the ORANGE study. The ORANGE study was a 3-year, prospective cohort study in multiple UK hospitals where patients received the UK standard of care comprising a mix of interventions including 4F-PCC, tranexamic acid, vitamin-K and blood transfusion. Since the ORANGE study observed extremely minimal usage of FEIBA (1%) and no usage of NovoSeven, the company did not include these two treatments in the economic analysis. The company also omitted the cost of tranexamic acid from the economic analysis because it is a low-cost drug that is not generally used in UK clinical practice. During the clarification stage, the company clarified that of the 145 patients from ORANGE taking 4F-PCC and included in the economic analysis, 53 of those patients were taking 4F-PCC in combination with tranexamic acid.

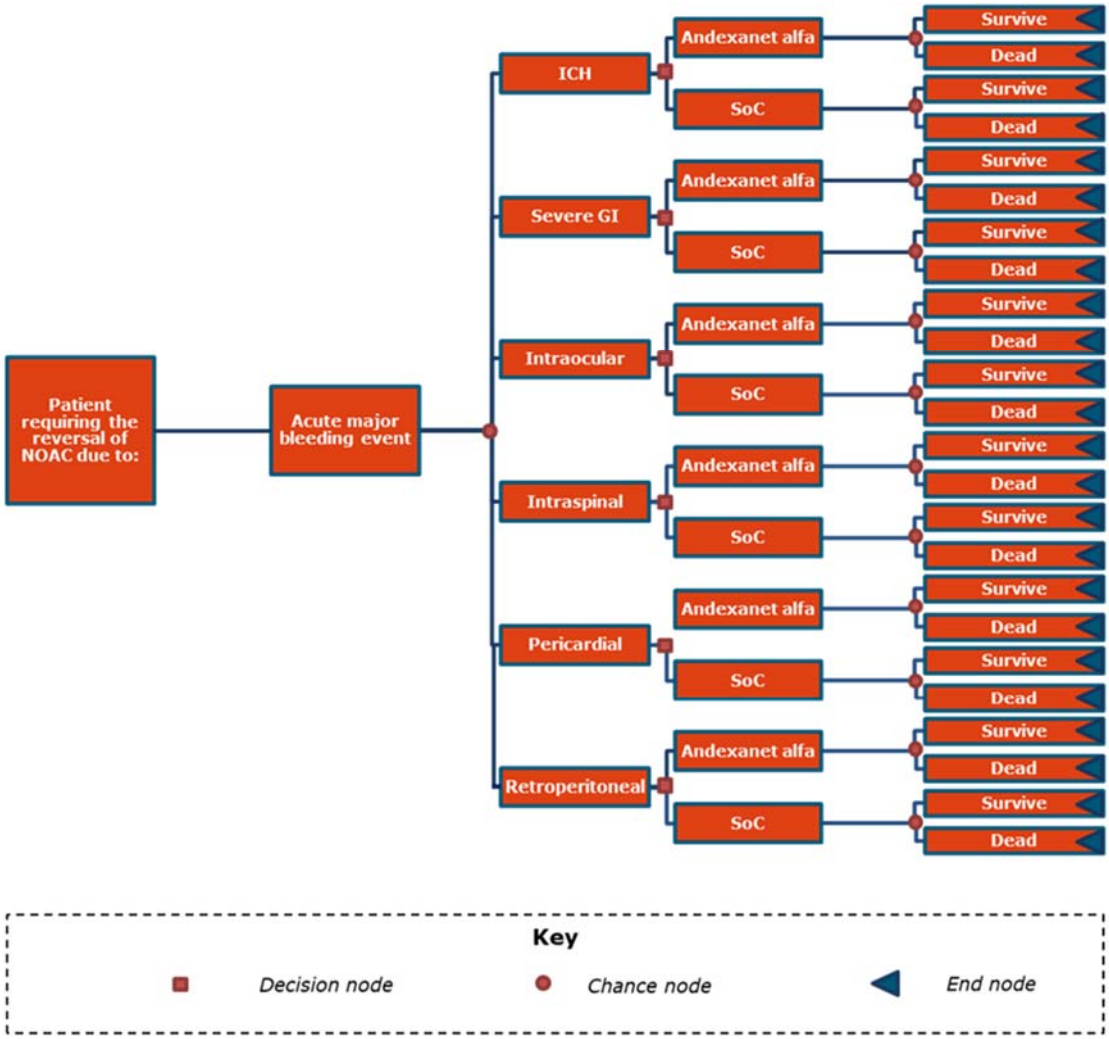
The ERG also consulted with its clinical experts who confirmed that non-activated 4F-PCC (Beriplex and Octaplex) is the most commonly used treatment representing standard care in this population and is an appropriate comparator. However, they considered that tranexamic acid should be given to all patients (regardless of whether they are on andexanet alfa or 4F-PCC) with the caveat that in UK clinical practice, less than half of patients receive tranexamic acid.

Overall, the ERG is satisfied that non-activated 4F-PCC (with or without tranexamic acid) is the most appropriate comparator and is in line with the NICE final scope.[1] The ERG also considers that the omission of NovoSeven, FEIBA and tranexamic acid is appropriate.

5.3.4 Modelling approach and model structure

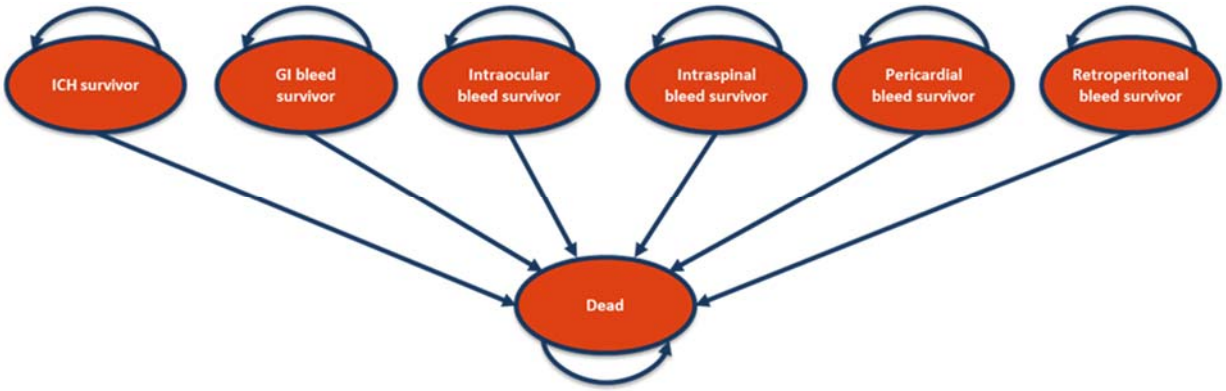
A *de novo* cost-effectiveness model was developed in Microsoft Excel comprising a short-term decision tree (Figure 3) followed by a long-term Markov model (Figure 6).

Figure 3. 30-day decision tree structure (Figure 14 of the CS Document B)



Abbreviations: CS, company submission; GI, gastrointestinal; ICH, intracranial haemorrhage; NOAC, noval oral anticoagulant; SoC, standard or care

Figure 4. Markov model structure (Figure 15 of the CS Document B)



Abbreviations: CS, company submission; GI, gastrointestinal; ICH, intracranial haemorrhage

The decision tree estimates costs and quality adjusted life years (QALYs) for the first 30 days of a bleed event; defined as either an ICH, GI bleed, intraocular bleed, intraspinal bleed, pericardial bleed or retroperitoneal bleed. The proportion of patients by type of bleed event entering the decision tree is

provided in Table 50 of Section 5.3.2.1. For simplicity, the company assumed that all patients had only one type of bleed and if a secondary bleed was experienced the mortality rate of the first bleed type remained unchanged. One of the outcomes observed in the ANNEXA-4 and ORANGE studies and modelled in the decision tree included the 30-day mortality rate.

Patients surviving their bleed event in the decision tree transition to their respective survivor health states in the Markov model and remain there until death. Within the 'Intraocular bleed survivor' and 'Intraspinal bleed survivor' health states, a proportion of patients are assumed to experience complications (blindness and paralysis, respectively) which are associated with health care costs and quality of life decrements. Within the 'ICH survivor' health state the company considered neurological outcomes as measured by mRS in ANNEXA-4 (and by mRS in Øie *et al.* 2018[16] for the standard care arm), thus feeding into long-term mortality, HRQoL and cost calculations. No other outcomes observed in ANNEXA-4 were modelled by the company in the Markov model.

A cycle length of one month was implemented in the Markov model with a half cycle correction applied. The mean age at entry in the decision tree for the whole cohort was [redacted] years and the model time horizon was [redacted] years as patients in the cohort are not expected to live beyond 100 years. For the ICH plus GI cohort and ICH cohort, the mean starting age was [redacted] years and [redacted] years with a time horizon of [redacted] years and [redacted] years, respectively. The perspective of the analysis is based on the UK national health service (NHS), with costs and benefits discounted using a rate of 3.5% as per the NICE reference case.[80]

5.3.4.1 ERG critique

The one-month cycle length used in the long-term Markov model is suitable to capture important changes in the health state of patients, allowing for robust estimates of costs and benefits to be calculated for each treatment. Half-cycle correction has been appropriately applied in the long-term Markov model to prevent over or under-estimation of costs and QALYs.

The company assumed additional bleeds did not change mortality rates and consequently omitted additional bleeds from the economic model. Clinical experts consulted by the ERG agreed with this assumption as additional bleeds are usually seen within the first week of the first bleed, and at the same site as the first bleed. Moreover, because patients are already in hospital receiving treatment, subsequent bleeds will be caught a lot earlier than the first bleed, and are therefore, likely to be less severe. Combined with the fact that only [redacted] patients enrolled after the implementation of protocol amendment 4 in ANNEXA-4 experienced a second bleed, the ERG considers that this represents a reasonable simplification.

Overall, the ERG has three primary concerns relating to the model structure including the time horizon, subtypes of ICH and disaggregation of 'other major bleeds'. A summary of these issues is given below.

Time horizon

As mentioned in Section 5.2, the cost effectiveness search identified one relevant study (Mangram *et al.* 2016) and a time horizon of 48 hours was considered in that study.[77] Moreover, the key outcome of andexanet alfa recorded in the clinical studies and employed in the economic analysis is the 30-day mortality rate (described in Section 5.3.5.1). There is no evidence to suggest that a patient's bleed event will recover any quicker or be any less severe compared with standard care. As such, the need for a lifetime horizon is somewhat questionable.

Although the ERG agrees with the company that a lifetime time horizon would capture all the long-term benefits of treatment, because andexanet alfa could be considered a lifesaving treatment; all the costs to obtain the long-term benefits are captured by the decision tree. Moreover, the base case ICER is uncertain given the number of assumptions in the long-term Markov model. Therefore, the ERG considers that the results from the short-term economic model (the 30-day decision tree component of the model), informed by the 30-day mortality rate recorded in the key studies (ANNEXA-4 and ORANGE), involves minimum extrapolation beyond study data, thus reducing the number of assumptions in the long-term Markov model. As such, the ERG asked the company to explore the impact of a 30-day time horizon as a conservative estimate of the ICER. These additional scenarios were provided by the company at the clarification stage and the ICER for each cohort increased well above the NICE standard threshold of £20,000 – £30,000 (£1,834,587, £1,683,816 and £1,520,070 for the whole cohort, ICH plus GI cohort and ICH cohort, respectively). However, given that andexanet alfa results in reductions in 30-day mortality compared to standard care (relative reductions of [redacted] and [redacted] for GI and ICH bleeds, respectively), the ERG reiterates that these scenarios using a 30-day time horizon are only exploratory.

ICH survivor health state

Clinical expert opinion sought by the ERG considered that andexanet alfa may have the largest effect on intracerebral bleeds as it could prevent haematoma expansion. Following this, the ERG asked the company to explain why any additional benefits from reductions in haematoma expansion in patients with intracerebral haemorrhages were not considered by modelling patients with intracerebral haemorrhages separately to the other subtypes of ICH. In response to the ERG's clarification question, the company agreed that andexanet alfa will provide benefits in terms of ceasing haematoma expansion, but since the ORANGE study did not collect data on haematoma expansion, the mRS was utilised in the economic analysis, across all subtypes of ICH. However, the ERG notes that the ORANGE study

did not collect data on mRS either and applying the same treatment effect (mRS) to all subtypes of ICH potentially overestimates the benefits of andexanet alfa in non-intracerebral haemorrhages.

Furthermore, aside from the 30-day mortality rate, the mRS is where the long-term benefits of treatment are derived in the economic analysis (described in Section 5.3.5.2). As such, the ERG is unclear why the company chose not to split the ICH survivor health state into six health states for each level of mRS severity (0, 1, 2, 3, 4 and 5). In response to the ERG's clarification question, the company explained that the primary reasons for not considering health states for ICH based on mRS categories were to keep the model simple and easier to interpret and to accommodate the absence of cost data split by mRS in the literature. However, the ERG disagrees with the company's rationale since the company calculated weighted averages from long-term mortality data, HRQoL data and bleed management data, split by mRS. Nonetheless, changing how mRS is implemented in the model is likely to have a minimal impact on the ICER.

Other major bleeds

As noted in Section 5.3.2.2, the types and proportions of 'other major bleeds' included in the economic model (intraspinal, intraocular, retroperitoneal, and pericardial, in equal measure) are based on a series of assumptions and do not reflect the 'other major bleeds' observed in ANNEXA-4, or the indefinite types of 'other major bleeds' included in the NICE final scope.[1] The ERG considers that the company did not need to disaggregate the 'other major bleeds' into specific bleed types as this resulted in layers of assumptions adding a substantial amount of uncertainty to the whole cohort cost-effectiveness results. Instead, the company could have analysed 'other major bleeds' as a whole, rather than breaking it down into their chosen specific bleeds, for which there is a lack of outcome data. However, given that clinical experts consulted by the ERG do not consider patients with 'other major bleeds' to be eligible for andexanet alfa, the ERG does not see the value in exploring this scenario.

5.3.5 Treatment effectiveness

The two primary efficacy outcomes in ANNEXA-4 (haemostatic efficacy and anti-FXa activity) were not used to inform the economic analysis. Instead, the structure of the model was based on the 30-day mortality rate following a life-threatening or uncontrolled bleeding event from the ANNEXA-4 and ORANGE studies (described in Section 5.3.5.1). The company also considered neurological outcomes (in people with ICH) in the long-term Markov model as measured by mRS in ANNEXA-4 for andexanet alfa patients and Øie *et al*. 2018[16] for standard care patients (described in Section 5.3.5.2).

Another efficacy endpoint recorded in ANNEXA-4 included the length of hospital stay (see Section 3.4). According to the company, the length of stay was unlikely to be informative given the differences in the settings of care across the ANNEXA-4 (North America and Europe) and ORANGE (UK) studies.

For this reason, the company did not consider the length of hospital stay when calculating the cost to treat the acute bleed in the economic analysis. This outcome is discussed and explored further in Section 5.3.10 on resources and costs.

5.3.5.1 30-day mortality

As described in Section 4.4, propensity score matching was used to adjust the 30-day mortality rate between the ANEXXA-4 and ORANGE studies for andexanet alfa and standard care, respectively. The propensity score matching results were used to inform the 30-day mortality rate for ICH and GI bleeds in the short-term economic model (the 30-day decision tree component of the model).

For 'other major bleeds' the number of matches using propensity score matching was low (8 patients in ORANGE) and the company considered the results to be counterintuitive (adjusted 30-day mortality rate of [redacted] for standard care versus [redacted] for andexanet alfa) and therefore did not use it to inform the economic analysis.

To address this, the company set the 30-day mortality rate for intraocular and intraspinal bleeds to zero in both treatment arms, based on clinical expert opinion. For pericardial and retroperitoneal bleeds, the company assumed treatment with andexanet alfa would lead to a 25% reduction in the risk of death observed in ORANGE. The company stated that this reduction was conservative as relative reductions of [redacted] and [redacted] were recorded for ICH events and GI bleeds in ANNEXA-4 based on propensity score matching.

Table 52 summarises the 30-day mortality data applied in the decision tree for each bleed type.

Table 52. Decision tree mortality rates

Bleed event	30-day mortality rate	Reference
Andexanet alfa		
ICH	[redacted]	Propensity score matching; ANEXXA-4
GI bleed	[redacted]	Propensity score matching; ANEXXA-4
Intraocular bleed	[redacted]	UK clinical opinion
Intraspinal bleed	[redacted]	UK clinical opinion
Retroperitoneal bleed	[redacted]	Propensity score matching, ORANGE * (1-0.25)
Pericardial bleed	[redacted]	Propensity score matching, ORANGE * (1-0.25)
Standard care		
ICH	[redacted]	Propensity score matching, ORANGE
GI bleed	[redacted]	Propensity score matching, ORANGE
Intraocular bleed	[redacted]	UK clinical opinion
Intraspinal bleed	[redacted]	UK clinical opinion
Retroperitoneal bleed	[redacted]	Propensity score matching, ORANGE
Pericardial bleed	[redacted]	Propensity score matching, ORANGE
Abbreviations: ICH, intracranial haemorrhage; GI, gastrointestinal		

5.3.5.2 modified Rankin score (mRS)

The ANNEXA-4 study collected mRS data for ICH patients receiving andexanet alfa 30-days after the bleed event, while a study reported by Øie *et al*. 2018[16], collected mRS data for 452 intracerebral haemorrhage patients receiving standard care 90-days after the bleed event. The company assumed the 30-day scores in ANNEXA-4 were comparable to the 90-day scores in Øie *et al.* 2018, due to the paucity of data in patients receiving standard care. Subsequently, treatment with andexanet alfa was associated with lower mRS results for surviving ICH patients compared to patients receiving standard care (Table 53). In the economic analysis, mRS results feed into the long-term ICH mortality, HRQoL and cost calculations. These calculations are described in Sections 5.3.8, 5.3.9 and 5.3.10, respectively.

Table 53. Number of patients in each mRS category, by treatment (adapted from CS Document B, Table 48)

mRS category	Number of patients receiving andexanet alfa taken from ANNEXA-4		Number of patients receiving standard care taken from Øie *et al*. 2018	
	Actual value: N (%)	Redistributed % excluding death	Actual value: N, %	Redistributed % excluding death
Total	[redacted]	[redacted]	452	100%
0	[redacted]	[redacted]	1%	2%
1	[redacted]	[redacted]	5%	8%
2	[redacted]	[redacted]	9%	15%
3	[redacted]	[redacted]	12%	20%
4	[redacted]	[redacted]	22%	36%
5	[redacted]	[redacted]	12%	20%
6	[redacted]	[redacted]	39%	NA
Abbreviations: mRS, modified Rankin score; NA, not applicable				

5.3.5.3 ERG critique

The two primary efficacy outcomes in ANNEXA-4 (haemostatic efficacy and anti-FXa activity), mentioned in Section 3.4, were not included in the economic analysis. However, given that these are intermediate endpoints, the ERG considers that their inclusion would be meaningless unless they could be linked to final outcomes (associated with costs and QALYs). The ERG explored potential links with its clinical experts who explained that haemostatic efficacy and anti-FXa activity would not be reliable predictors of the severity of long-term ICH, or risk of death. The ERG's clinical experts also added that they were not aware of any robust evidence that has established a predictive relationship between these outcomes. Furthermore, anti-FXa activity does not directly inform any of the clinical outcomes of interest in the NICE final scope. Therefore, the ERG considers the omission of haemostatic efficacy and anti-FXa activity from the economic analysis to be reasonable.

However, the ERG has several concerns regarding the company's estimation of 30-day mortality in the economic model including the appropriateness of the covariates included in propensity score matching and the rationale for why a 25% reduction was assumed for andexanet alfa patients with 'other major

bleeds' compared to standard care. Furthermore, the ERG does not consider the reasons why patients on andexanet alfa would have a better prognosis following an ICH event (in terms of lower a mRS) compared with standard care to be sufficiently justified. Each of these issues is described in turn below.

30-day mortality

As noted in Section 4.4, the ERG did not consider the covariates included in the company's first propensity score matching analysis to be appropriate given the large focus on irrelevant medical histories and the omission of important covariates including the site of bleed, severity of bleed and volume of bleed. In response to the ERG's clarification questions, the company reported that they were unable to include severity of bleed or volume of bleed as covariates in the propensity score matching analysis as these outcomes weren't collected in the ORANGE study. However, the company revised their selection of covariates to include additional covariates suggested by the ERG's clinical experts and removing some relating to baseline medical history that were not associated with statistically significant differences between ANNEXA-4 and ORANGE. These results were used to inform the company's revised base case analysis.

As for 'other major bleeds', the ERG is concerned that the 30-day mortality rates are driven by assumptions in the absence of robust evidence. Thus, the ERG prefers to focus on the ICH and GI, and ICH only cohorts to determine the cost-effectiveness of andexanet alfa, as it limits the uncertainty associated with 'other major bleeds'. However, the ERG acknowledges the NICE final scope is for the full population covered by the marketing authorisation and so considers it important to comment on the company's flaws. In particular, the company assumed that treatment with andexanet alfa would reduce the risk of death observed in ORANGE by 25% for pericardial and retroperitoneal bleeds. Although the company highlighted that this was a conservative estimate compared to the relative reductions [redacted] observed in the propensity score matching results, the company did not provide a clinical rational why any relative reduction would be seen in 'other major bleeds'. During the clarification stage, the ERG invited the company to provide additional justifications in support of their assumption. In their clarification response, the company stated the relative reduction was verified by clinical expert opinion and tested extensively in scenario analysis using relative reductions that ranged from [redacted] to [redacted] (see Section 5.4.2). However, the ERG considers that in the absence of any evidence to substantiate the 25% reduction in 30-day mortality associated with andexanet alfa, the company's scenario of no relative reduction is a more appropriate scenario. The results of the ERG's base case analysis incorporating this assumption are reported in Section 6.3.

The ERG would also like to add that the risk of death taken from ORANGE was not limited to pericardial and retroperitoneal bleeds as the company employed the propensity score matching result ([redacted]) based on all 'other major bleeds'. Therefore, the ERG considers that the company has

potentially underestimated the risk of death associated with pericardial and retroperitoneal bleeds given that the other types of 'other major bleeds' "*were felt to be less severe than the other aforementioned bleeds*" (page 85 of the CS, Document B). Although increasing the risk of death associated with pericardial and retroperitoneal bleeds had a negligible impact on the ICER in the ERG's exploratory scenario analysis, the company's approach has added to the uncertainty surrounding 'other major bleeds'.

Finally, the ERG considers a scenario that replaces the company's 30-day mortality rates for 'other major bleeds' with the 30-day mortality rates obtained from propensity score matching ([redacted] for standard care and [redacted] for andexanet alfa) is important. Nonetheless, the scenario analysis provided by the company at the clarification stage led to a small increase in the ICER (from £11,636 to £11,817) due to the small proportion of 'other major bleeds' (<10%) within the whole cohort.

modified Rankin score (mRS)

The ERG is concerned that the study used to inform the severity of ICH survivors in the standard care arm (Øie *et al.* 2018) represents patients with one of the most severe subtypes of ICH (intracerebral haemorrhage) and therefore overestimates the mRS in the standard care arm.[16] In response to the ERG's clarification question the company explained that Øie *et al.* 2018 was chosen to inform the economic analysis because of the reasonable sample size (452 patients) and because alternative sources did not define the stroke type and site. The company also went on to discuss how reversing the effects of anticoagulation will cease haematoma expansion and prevent further damage to the brain. However, the company referred to supporting evidence undertaken in patients with intracerebral haemorrhage (Davis *et al.* 2006).[81] As such, the company's assumption that reducing the risk of haematoma expansion will also impact ICH morbidity outcomes (mRS) in a similar manner is purely speculative.

During the clarification stage, the ERG was also made aware of the company's concerns using Øie *et al.* 2018 to inform utility calculations (discussed in Section 5.3.9.3), leading to the inconsistent use of Øie *et al.* 2018 in the model.[12] Even so, the ERG considers Øie *et al.* 2018 to represent the best available evidence for mRS in people with intracerebral haemorrhage.

As explained in Section 5.3.4, the company chose not to model the subtypes of ICH. Therefore, to account for the proportion of patients that would experience one of the most severe subtypes of ICH (intracerebral haemorrhage), the ERG asked the company to explore a scenario where intracerebral-specific mRS results (recorded in Øie *et al.* 2018 for standard care) are applied to the proportion of patients that experienced an intracerebral haemorrhage in ANNEXA-4, and the remaining proportion of patients in both treatment arms have mRS results equal to ANNEXA-4. In response to the ERG's clarification question, the company applied intracerebral-specific mRS results to [redacted] of

patients and assumed no treatment effect for the remaining [redacted] of patients. The three sets of mRS results applied in this scenario are given in Figure 3.

Figure 5. Intracerebral-specific mRS results (redistributed to exclude death)

Abbreviations: ICH, intracerebral; mRS, modified Rankin Score; SoC, standard of care

However, the ERG considers it important to note that the company combined intracerebral and intraventricular haemorrhages (IVHs) in this analysis. Consequently, the ERG sought clinical expert opinion to assess if intracerebral haemorrhages and IVHs are similar. The ERG's clinical experts noted that intraventricular haemorrhages (in association with intracerebral haemorrhage, rather than in isolation) are common and associated with a poor prognosis and should be considered separate to subdural and extradural haemorrhages. Thus, it could be considered reasonable to combine intracerebral haemorrhages and IVHs given that they are both severe subtypes of ICH.

In addition, the company only fed the proportion of intracerebral-specific patients into HRQoL calculations when HRQoL, cost and long-term mortality calculations needed to be adjusted. Furthermore, when the ERG compared the mRS distributions in Figure 7, the ERG found a larger proportion of patients with a mRS of 5 in ANNEXA-4 for intracerebral-specific patients ([redacted]) and a much smaller proportions in Øie *et al.* 2018 for intracerebral-specific patients (19.7%).[16] This finding concerns the ERG as the company and the ERG's clinical experts expected andexanet alfa to lead to greater reductions in haematoma expansion (and subsequently lower mRS results) in patients with intracerebral haemorrhage compared with standard care.

The ERG caveats this finding with the fact that this was a naïve comparison and so no reliable conclusions can be drawn. Moreover, baseline data aren't provided for intracerebral-specific patients in ANNEXA-4 and therefore it is unclear how the distribution of patients in the different mRS categories have changed over the 30 days. Also, the Øie *et al*. 2018 population is [redacted] (74.8 years versus [redacted] years) and has a lower use of anticoagulants than ANNEXA-4 (22% versus 100%), which

suggests that ANNEXA-4 could represents a more severe group of patients. Thus, either Øie *et al*. 2018 is not a representative population for standard care, or the treatment benefit in terms of the prognosis for survivors of intracerebral haemorrhages is negligible. However, the ERG acknowledges that in the absence of head-to-head trial data, Øie *et al.* 2018 is likely to represent the best available evidence on mRS in people with intracerebral haemorrhage receiving standard care.

The ERG also considers it important to add that the mRS results from ANNEXA-4 applied to non-intracerebral ICH survivors encompass all subtypes of ICH. In spite of this, these scores are applied to both treatment arms, thereby reducing the impact of this inaccuracy on the ICER. Overall, the ERG considers this to be a key scenario that accurately attributes intracerebral-specific mRS results to patients with intracerebral haemorrhages. As such, the ERG ran a scenario where the proportion of intracerebral patients fed into utility, cost and long-term mortality calculations. Results of the ERG's analysis are reported in Section 6.

As an alternative scenario, the ERG also requested the company to provide a scenario where mRS values recorded in ANNEXA-4 are used in both treatment arms. The scenario analysis provided by the company included adjustments to HRQoL, cost and long-term mortality calculations and these led to large increases in the ICER for each cohort (£17,785, £28,277 and £31,377 for the whole cohort, ICH plus GI cohort and ICH cohort, respectively).

5.3.6 Treatment-related adverse events

No treatment-related adverse events have been included in the economic analysis, as the company states that 94.5% of adverse events in the ANNEXA-4 safety population were deemed to be unrelated or unlikely related to andexanet alfa treatment by study investigators. The ERG consulted with its clinical experts who agreed that it was reasonable to exclude treatment-related adverse events from the economic analysis as there are no relevant side effects of andexanet alfa or 4F-PCC that could affect the management of the condition, or patients' quality of life.

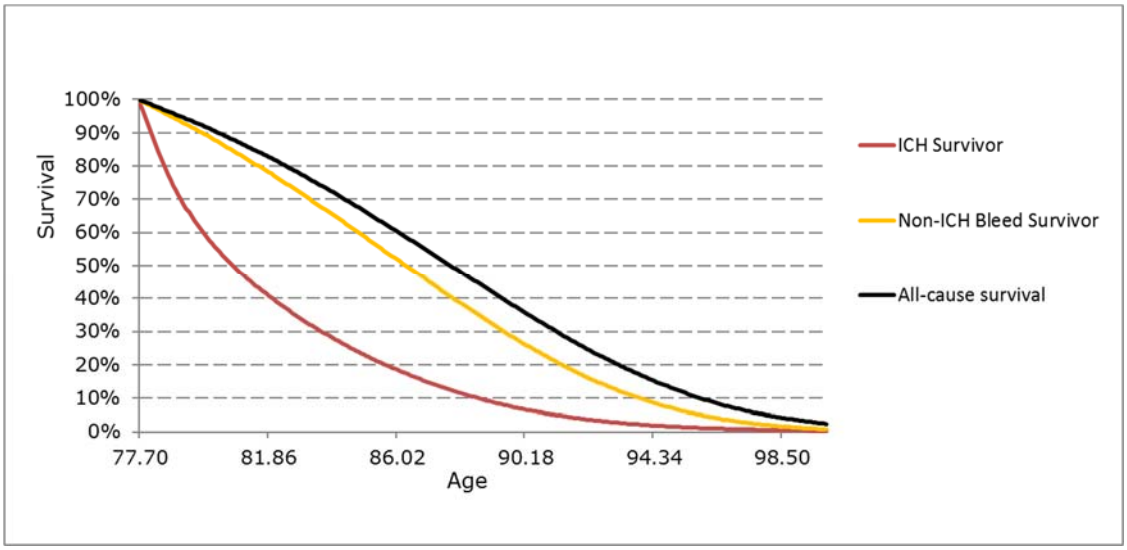
5.3.7 Thrombotic events

Thrombotic events were listed in the NICE final scope for inclusion.[1] However, the company choose not to model this outcome given that treatment-emergent serious thrombotic events occurred in ≤2% across the ANNEXA-4 and ORANGE studies. Moreover, given that the risk of thrombotic events would reduce as soon as patients restarted their anticoagulation, the ERG considers that modelling the small incidence of events would not make meaningful differences to the cost-effectiveness results.

5.3.8 Long-term mortality

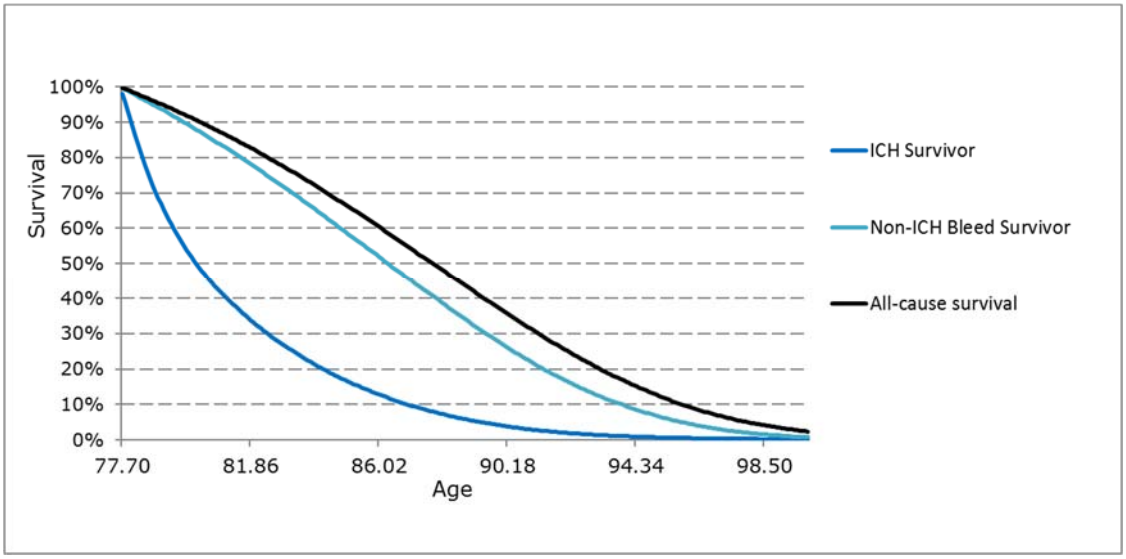
In the long-term model, the company assumed that patients who survive an uncontrolled or life-threatening bleed will have a decreased life expectancy compared to the general population. The company obtained all-cause general population mortality from national life tables provided by the Office of National Statistics (ONS).[82] The methods used to estimate the long-term mortality of ICH survivors and non-ICH survivors is described in Section 5.3.8.1 and 5.3.8.2, respectively. The resulting long-term survival curves by bleed type for patients receiving andexanet alfa and standard care are given in Figure 6 and Figure 7, respectively.

Figure 6.Long-term survival curves, andexanet alfa (produced by the ERG)



Abbreviations: ERG, Evidence Review Group; ICH, intracerebral

Figure 7. Long-term survival curves, standard care (produced by the ERG)



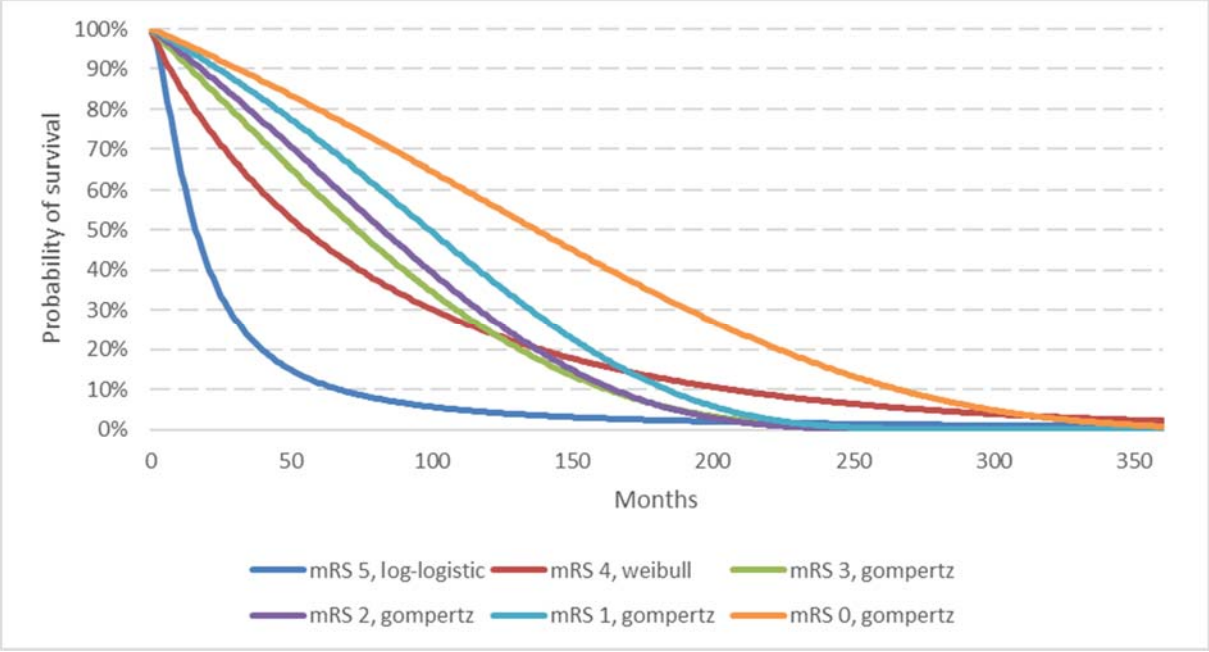
Abbreviations: ERG, Evidence Review Group; ICH, intracerebral

5.3.8.1 *Long-term survival estimates for ICH survivors*

Long-term mortality for ICH survivors is based on the mRS distribution of patients from ANNEXA-4 for andexanet alfa patients and Øie *et al.* 2018[16] for standard care patients (described in Section 5.3.5.2). The company obtained mortality estimates for each mRS category from a study by Huybrechts *et al.* 2008 in 1,276 stroke survivors in Athens.[83]

The company fitted parametric distributions to the Kaplan Meier (KM) overall survival data reported in Huybrechts *et al.* 2008 for each mRS category.[83] The company states it implemented the process of parametric curve selection recommended in the NICE decision support unit technical support document (DSU TSD) 14 to select an appropriate distribution for the extrapolation of each survival curve.[84] The company assessed the fit of each modelled curve against the observed KM data using statistical goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics, visual inspection of the curves and clinical plausibility. The KM data, parametric distributions and all-cause mortality curves are presented in Figures 16 to 21 of the CS, for each mRS category while the selected distributions for each mRS category are presented below in Figure 8.

Figure 8. Survival curves by mRS category



Abbreviations: mRS, modified Rankin Score

In response to a clarification request from the ERG, the company revised its next steps to estimate the long-term mortality associated with ICH survivors. As mentioned in Section 5.3.4, the company included one 'ICH survivor' health state in the model, encompassing all subtypes and severities. Therefore, to accurately combine the six levels of mRS severity into one health state (without relying on proportional hazards), the ERG requested the company produced a weighted survival curve for each

treatment arm (using the mRS proportions outlined in Section 5.3.5.2), applying the per cycle transitions estimated from the weighted curves. Furthermore, to account for the difference in starting age between Huybrechts *et al.* 2008[83] (68 years) and patients entering the model ([redacted] years in the whole cohort, ICH plus GI cohort and ICH cohort, respectively), the ERG suggested applying a hazard ratio that compares the all-cause mortality mean survival at 68 years to the age of the cohort entering the model. The company agreed with the ERG's approach and revised its base case to reflect this.

5.3.8.2 Long-term survival estimates for non-ICH survivors

For patients surviving GI bleeds and 'other major bleeds' (i.e. non-ICH bleeds), the company considered that patients would be unlikely to die because of the original bleed, and more likely to die due to underlying comorbidities from a population of that age (a population with atrial fibrillation, AF). Following this, the company identified Friberg *et al.* 2007 who assessed the risk of death in a cohort of 2,824 patients in Sweden with AF compared with a matched general population.[85] The company obtained a HR of 1.3 from Friberg *et al.* 2007 and multiplied the rate of all-cause mortality per cycle by 1.3 to estimate transition probabilities from the 'GI bleed survivor', 'Intraocular bleed survivor', 'Intraspinal bleed survivor', 'Pericardial bleed survivor' and 'Retroperitoneal bleed survivor' health states to the death state.

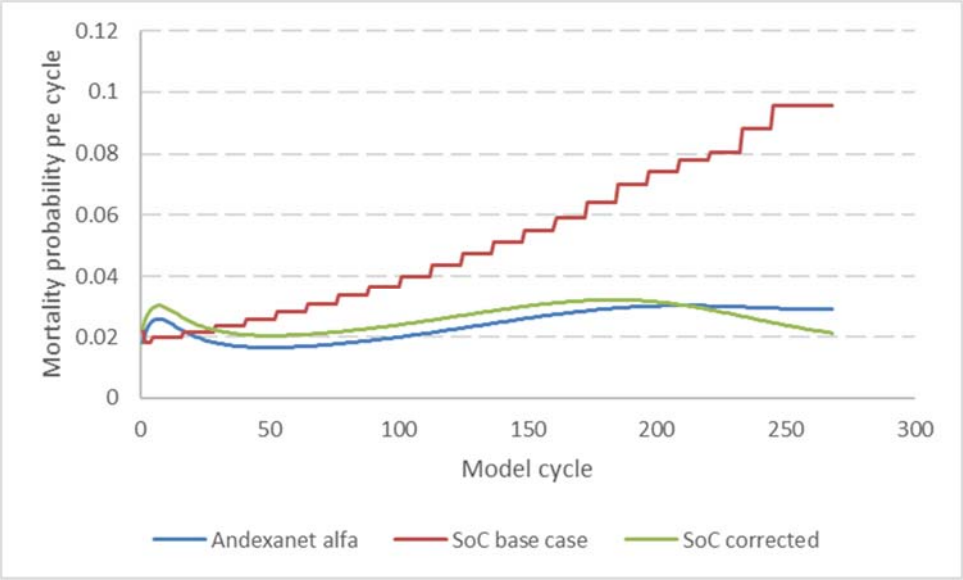
5.3.8.3 ERG critique

The ERG considers the parametric distributions chosen for each mRS category to be generally sound, though for mRS 4, the selected distribution (Weibull) appears to be overly optimistic. For instance, mRS 4 is associated with a larger mean survival (7.02 years) than mRS 3 (6.84 years). To address this, the ERG explored the impact of selecting the Exponential distribution. This distribution also produced a curve that was considered clinically plausible by the company and yielded a credible mean survival of 6.76 years. However, as shown in Section 6.2, the impact on the ICER in each cohort was minimal.

Furthermore, when the ERG reviewed the implementation of long-term mortality in the revised economic model, the ERG identified an error in the mortality probability per cycle estimated for ICH survivors in the standard care arm. As shown in Figure 9, the company applied a cumulative probability in place of a monthly probability Nonetheless, when the ERG corrected this error the impact on the ICER in each cohort was negligible given the small number of patients that are affected. Model corrections undertaken by the ERG are presented in Section 6.1.

Finally, as mentioned throughout this report, the ERG has concerns with the company's use of mRS distributions from Øie *et al.* 2018 in the standard care arm.[16] Scenarios that explore alternative mRS distributions which feed into long-term mortality calculations are given in Section 5.3.5.3.

Figure 9. ICH mortality probability per cycle correction



Abbreviations: ICH, intracerebral; SoC, standard of care

5.3.9 Health-related quality of life

No HRQoL data were collected in either the ANNEXA-4 or ORANGE studies. Instead, the company used data obtained from the HRQoL SLR to populate the model. As mentioned in Section 5.2, the HRQoL search identified two relevant papers as a source of utilities estimates for the economic model, TA341 and Miller *et al*. 2016.[78, 79] A baseline utility value of 0.73 was implemented in the model for the three cohorts. The baseline utility value was obtained from a paper by Kind *et al.* 1999 which reported general population EQ-5D values for people aged 75 years and older.[86]

5.3.9.1 HRQoL for acute events

HRQoL values for acute events in the decision tree part of the model (1 month) were estimated to quantify the short-term impact of a life-threatening or uncontrolled bleeding event. The utility decrement used in the model for an acute non-ICH bleed event was -0.1511 and this was applied to the baseline utility of 0.73. As for an acute ICH, the company directly applied the utility value obtained from TA341.[79] As such, two utility values were estimated for five types of bleed events, outlined in Table 54.

Table 54. Health-related quality of life values for acute events used in the economic model

Health state	Utility value/ utility decrement	Utility measurement	Source
ICH	0.33	TTO	TA341[79]
GI bleed [a]	-0.1511	EQ-5D	Miller *et al*. 2016[78]
Intraspinal bleed [b]	-0.1511	EQ-5D	Miller *et al*. 2016[78]
Intraocular bleed [b]			
Retroperitoneal bleed [b]			

Pericardial bleed [b]			
Abbreviations: ECH, extracranial haemorrhage; GI, gastrointestinal; ICH, intracranial haemorrhage; TTO, time-trade off a Major GI utility value extracted from source. b Major non-GI ECH utility value extracted from source.			

5.3.9.2 HRQoL for survivor health states

Long-term HRQoL for survivors of each bleed type implemented in the economic model are estimated based on data obtained from published literature.[79, 86-90] Table 55 presents the utility values used in the long-term (lifetime) Markov model. Based on clinical expert opinion, the company assumed that survivors of GI, retroperitoneal and pericardial bleeds will not suffer long-term morbidity and as such HRQoL will return to baseline levels.

Table 55. Health-related quality of life values for acute events used in the economic model

Health state	Utility value – standard care	Utility value – andexanet alfa	Utility measurement	Source
ICH survivor	0.61	0.72	EQ-5D TTO	TA341[79] Pickard *et al.* 2004[88] Fletcher *et al.* 2015[89]
Intraspinal bleed survivor [a]	0.57	0.61	TTO	Matza *et al*. 2014[87]
Intraocular bleed survivor [b]	0.721	0.723	TTO	Wittenborn *et al*. 2017[90]
GI bleed survivor	0.73	0.73	EQ-5D	Kind *et al*. 1999[86]
Retroperitoneal bleed survivor				
Pericardial bleed survivor				
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; TTO, time trade-off a Weighted by prevalence of paralysis and assumed effectiveness of andexanet alfa (treatment arm only). b Weighted by prevalence of monocular bleeding and assumed effectiveness of andexanet alfa (treatment arm only)				

For survivors of intraspinal bleeds, the company assumed that 50% will suffer from paralysis. The company also assumed that 25% of intraocular bleed survivors will have monocular blindness. Both assumptions were informed by clinical expert opinion. Utility decrements used in the model for paralysis and monocular blindness are -0.32 and -0.036, respectively and are applied to the baseline utility of 0.73.[86, 87, 90] Furthermore, the company assumed a 25% reduction in paralysis and monocular blindness for intraspinal and intraocular bleed survivors who received andexanet alfa, aligned with the assumption on mortality benefit discussed in Section 5.3.8.

Long-term HRQoL for ICH survivors is based on the mRS distribution of patients from ANNEXA-4 for andexanet alfa patients and Øie *et al*. 2018 for standard care patients (described in Section 5.3.5.2) and the associated utility value for each score.[16] The company obtained utility values by mRS from a paper by Fletcher *et al*. 2015, presented in Table 56.[89] The utility values were measured by the time-trade off method and are not EQ-5D scores, as stated by the company. Using the proportions of patients in each mRS category, presented in Section5.3.5.2 of this report, the company calculated weighted

utilities of 0.53 and 0.42, for andexanet alfa and standard care, respectively. Based on the calculated weighted utilities for andexanet alfa and standard care, the company applied the difference (0.11) to a 3-month post-acute care utility value of 0.61 obtained from NICE TA341[79] for the standard care arm to estimate the andexanet alfa utility value of 0.72. Thus, the utility values used in the economic model for standard care and andexanet alfa are 0.61 and 0.72, respectively.

Table 56. Utility values by mRS (adapted from CS Document B, Table 54)

mRS category[89]	Proportion – andexanet alfa (ANNEXA-4)	Proportion – standard care (Øie *et al*. 2018)[16]	Utility value (range)
0	[redacted]	2%	0.85 (0.8-1)
1	[redacted]	8%	0.80 (0.75-0.9)
2	[redacted]	15%	0.70 (0.53-0.75)
3	[redacted]	20%	0.51 (0.45-0.65)
4	[redacted]	36%	0.30 (0.25-0.55)
5	[redacted]	20%	0.15 (0-0.32)
Abbreviations: mRS, modified Rankin Scale.			

5.3.9.3 ERG critique

The ERG considers that the company's approach to estimating HRQoL in the absence of direct trial data for acute events to be reasonable and appropriate. Given the age and likely co-morbidities of the population, the EQ-5D UK population norms for people aged 75 and above will capture the impact of the co-morbidities on HRQoL. The published sources for the utility decrements for the health states are robust and relevant for the population under consideration.

However, the ERG is concerned with the company's estimation of long-term HRQoL for ICH stroke survivors. The company initially performed calculations using published utility and mRS data to calculate weighted utilities for andexanet alfa and standard care (Table 56), which only serve the purpose of estimating the utility increment associated with andexanet alfa.[16, 86, 89] The utility increment is then applied to another utility value (0.61) obtained from NICE TA341, which is used to represent post-acute care (3-months) for standard care. The final calculated utility for andexanet alfa, applying the utility increment to the NICE TA341 utility value is 0.72, which is 0.01 less than the UK general population norms for people aged 75 years and above. Both the utility value from NICE TA341[79] and the source utility values used for the weighted utility value calculation (Fletcher *et al.* 2015[89], primary source Gage *et al.* 1998[91]) are based on 3-month follow-up of patients who have had an ICH. Utility values obtained from Fletcher *et al.* 2015, employ the TTO method and the mean age of respondents was 70 years.[89] From NICE TA341, the utility value is based on the EQ-5D, but the mean age of respondents is 68 years.[79]

The company's justification for their approach is that the 3-month utility value from NICE TA341 represents a 3-month utility value is that it is appropriate to predict the long-term quality of life for an

ICH survivor following hospitalisation episode and that it was accepted by NICE as an appropriate value for patients receiving standard care after an intracranial bleed.[79] Furthermore, the company argue that using the weighted utility values directly, instead of applying the utility increment to the TA341 baseline, is not appropriate as the mRS distribution for standard care are obtained from Øie *et al*. 2018, which is a study conducted in Norway, but did not elaborate further.[16] As Øie *et al*. 2018 has been used throughout the economic model, the ERG considers the company's argument is inconsistent, as the source has been deemed appropriate for other aspects of the economic model, as well as for the increment applied to the utility value from NICE TA341.

The ERG considers the weighted utility values for standard care and andexanet alfa (0.42 and 0.53, respectively) are more appropriate to use in the model as the source utilities are based on a population closer in age to the ANNEXA-4 population (mean age of [redacted] years) and it eliminates the introduction of another utility from a different source, resulting in an unnecessary calculation step. Furthermore, the ERG considers 0.01 utility difference for ICH survivors of varying degrees of severity, compared with the general population lacks face validity. Scenarios using the weighted utility values for andexanet alfa and standard care were provided by the company at the clarification stage and cause an upward shift in the ICER for all three cohorts (£14,209, £22,963 and £24,053 for the whole cohort, ICH plus GI cohort and ICH cohort, respectively).

As mentioned throughout this report, the ERG has concerns with the modelling of 'other major bleeds' in the economic model as it is primarily driven by assumptions based on the company's clinical expert opinion in the absence of outcomes data. In particular, the company assumed that treatment with andexanet alfa would reduce the instances of paralysis and monocular blindness by 25%, thus increasing HRQoL for intraspinal and intraocular survivors compared with standard care. In their clarification response, the company justified this assumption by stating that andexanet alfa reduced 30-day mortality by greater than [redacted] for all three cohorts and clinical experts advised that reduction in paralysis and monocular blindness would be consistent with the mortality findings. However, the company chose a 25% reduction as they do not have direct evidence from ANNEXA-4 to substantiate the findings. The ERG considers that in the absence of any evidence to substantiate the 25% reduction in paralysis and monocular blindness associated with andexanet alfa, the company's scenario of no relative reduction is a more appropriate, if, conservative scenario. The results of the company's scenario analysis using a 0% relative reduction is reported in Section 5.4.2. However, as mentioned previously, the ERG considers the most robust estimates for cost-effectiveness are for the ICH and GI and ICH only cohorts as it removes the uncertainty of assumptions needed to model 'other major bleeds'. The results of the ERG's base case analysis incorporating this assumption are reported in Section 6.3.

5.3.10 Resources and costs

The costs included in the economic analysis are listed below and discussed in detail in the following sub-sections:

- Intervention and comparator acquisition and administration costs (Section 5.3.10.1);
- Acute bleed management health state costs (Section 5.3.10.20);
- Long term bleed management health state costs (Section 5.3.10.3);
- Re-initiation of FXa inhibitor (Section 5.3.10.4).

5.3.10.1 Intervention and comparator acquisition and administration costs

Andexanet alfa is administered intravenously as a one-off bolus, followed by an infusion. The list price of a 200 mg vial of andexanet alfa is £2,775. The company have not proposed a patient access scheme (PAS) discount. Two dosing regimens (Table 58) are recommended depending on the FXa inhibitor treatment taken by the patient (apixaban or rivaroxaban) and the timing of the last dose, presented in Table 57. Based on the proportions either receiving low or high dose, presented in Table 59 for each cohort, the company calculated the weighted average cost of andexanet alfa. In the weighted cost calculations, the company assumed vial wastage.

Table 57. Recommended andexanet alfa dose based on FXa inhibitor and timing of last dose (adapted from CS Document B, Table 2)

FXa inhibitor and last dose	**Recommended andexanet alfa dosing regimen**	
	< 8 hours or unknown	**≥8 hours**
Apixaban ≤5mg	Low dose	Low dose
Apixaban >5mg or unknown	High dose	
Rivaroxaban ≤10mg	Low dose	
Rivaroxaban >10mg	High dose	
Abbreviations: mg, milligram		

Table 58. Andexanet alfa dosing regimens and vials (adapted from CS Document B, Table 57)

Dosing regimen	**Bolus dose (mg)**	**Infusion dose (mg)**	**Total dose (mg)**	**Number of vials (incl. wastage)**
Low dose	400	480	880	5
High dose	800	960	1,760	9
Abbreviations: incl., including; mg, milligram				

Table 59. Andexanet alfa acquisition costs

Cohort	**Proportion on low dose**	**Proportion on high dose**	**Weighted number of vials**	**Weighted cost**
Whole	89.1%	10.9%	5.43	£15,082
ICH and GI	88.3%	11.7%	5.47	£15,172

ICH only	88.0%	12.0%	5.48	£15,203
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage.				

As mentioned in Section 5.3.3, non-activated 4F-PCC was considered by the company to be the most appropriate treatment to represent standard care. Two types of non-activated 4F-PCC are available in the NHS, Octaplex and Beriplex. The company used the costs associated with Octaplex for the economic analysis. According to the monthly index of medical specialities (MIMS) database, the unit cost of non-activated 4F-PCC (1000 IU) 40ml is £416.50.[92] As non-activated 4F-PCC is used off-label for the reversal of anticoagulant effects of FXa inhibitors, there is no official dosing regimen. However, the company state, based on information obtained from the literature, dosing of non-activated 4F-PCC is dependent on the type of FXa inhibitor the patient has taken and body weight.[93] Based on the study by Arachchillage *et al.* 2019, the dose for a rivaroxaban patient was found to be 26.8 units per kilogram and 25.0 units for an apixaban patient.[93] Data on mean weight and proportions of patients receiving apixaban or rivaroxaban were obtained from ANNEXA-4. For all three cohorts, mean weight was [redacted]kg and the proportions of patients on apixaban and rivaroxaban was 60.2% and 39.8%, respectively. Table 60 presents the weighted cost for 4F-PCC (including vial wastage) used for each cohort in the economic model.

Table 60. Treatment cost of non-activated 4F-PCC used in economic model based on patient data from ANNEXA-4

FXa inhibitor	Proportion	Dose per KG (IU)[93]	Mean body weight (kg)	Weighted dose (IU) (incl. wastage)	Number of vials (1000 IU)	Non-activated 4F-PCC Cost
Apixaban	60.2%	25.0	[redacted]	2000	2	£833
Rivaroxaban	39.8%	26.8				
Abbreviations: GI, gastrointestinal; incl, including; ICH, intracranial haemorrhage; IU, international unit						

Andexanet alfa and 4F-PCC are intravenous therapies and the company have included administrations costs to deliver the treatment, presented in Table 61. In the economic model, the company added that the currency codes from NHS Reference Costs were chosen according to the duration of the infusion.

Table 61. Treatment administration costs (adapted from CS Document B, Table 63)

Treatment	Unit cost	Source
Andexanet alfa	£336.55	NHS Reference Costs 2017/18 SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance
4F-PCC	£228.99	NHS Reference Costs 2017/18 SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance
Abbreviations: 4F-PCC, four factor prothrombin complex concentrate.		

5.3.10.2 Acute bleed management health state costs

Acute bleed management costs by survivor health state were sourced from NHS Reference Costs, presented in Table 62.[94] The company applied the same cost for acute care to patients surviving intraspinal, intraocular, retroperitoneal, or pericardial bleeds since no specific HRG codes were available in the NHS Reference Costs. The company also assumed the cost of a fatal bleed was equal to the acute bleed management cost. For instance, if an ICH patient died, the cost of the fatal bleed in the model is £4,099.

Table 62. Acute health state costs

Health state	Unit cost	Source
ICH Survivor	£4,099	NHS Reference Costs 2017/18[94] AA23C-G (weighted) - Haemorrhagic Cerebrovascular Disorders with CC Score 0-2:14+
GI Bleed Survivor	£4,516	NHS Reference Costs 2017/18[94] FD03A-B (weighted) - Gastrointestinal Bleed with Multiple Interventions
Intraspinal Survivor	£2,447	NHS Reference Costs 2017/18[94] FE02B-C (weighted) - Major Therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures, 19 years and over with CC Score > 0
Intraocular Survivor		
Retroperitoneal Bleed Survivor		
Pericardial Bleed Survivor		
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage		

5.3.10.3 Long term bleed management health state costs

As mentioned in Section 5.3.9.2 the company assumed no long-term morbidity effects for survivors of GI bleeds, retroperitoneal and pericardial bleeds, based on clinical expert opinion and as such, no long term bleed management costs were included in the economic model for these patients.

Long-term ICH management costs were based on a combination of mRS (discussed in Section 5.3.5.2) mapped to published hospital cost data from Luengo-Fernandez *et al*. 2013.[95] Annual post-acute hospital cost data in Luengo-Fernandez *et al*. 2013 were estimated for non-disabling, moderately-disabling and totally-disabling strokes. The company mapped the mRS data from Øie *et al.* 2018[16] (standard care) and ANNEXA-4 (andexanet alfa) to the disability categories to calculate a weighted cost for long-term ICH management, assuming the following: mRS 0-2 is non-disabling, mRS 3-4 is moderately-disabling and mRS 5 is totally-disabling. Table 63 presents the weighted long-term ICH management cost per cycle for standard care and andexanet alfa.

Table 63. Long-term ICH management costs based on Luengo-Fernandez *et al*. 2013 (taken from the company's economic model)

mRS	Cost per cycle (uplifted to 2017/18 prices)	Standard of Care		Andexanet alfa	
		Proportion	Weighted cost	Proportion	Weighted cost
0-2	£201	24.6%	£49.48	[redacted]	[redacted]
3-4	£393	55.7%	£218.80	[redacted]	[redacted]
5	£596	19.7%	£117.25	[redacted]	[redacted]
Total weighted cost per cycle	-	-	**£385.53**	**-**	[redacted]
Abbreviations: mRS, modified Rankin Scale.					

In addition to the hospital costs, the company estimated the costs associated with stroke rehabilitation, based on the level of dependency of a patient. The company used data presented in Persson *et al*. 2017, which reported patients with mRS categories of three to five to be dependent stroke survivors to estimate the percentage of ICH survivors in each arm of the model that would be classed as either dependent or independent.[96] As such, the company estimated that 75.4% of standard care patients and [redacted] of andexanet alfa patients are dependent based on mRS results, previously discussed in Section 5.3.5.2. The company applied the proportion of dependent stroke survivors to a stroke rehabilitation cost (£388) obtained from NHS reference costs (VC04Z)[94] to estimate a cost per cycle for standard care of £292 and £203 for andexanet alfa patients, which was added to the weighted hospital costs. Thus, the overall ICH survivor health state cost per cycle in the model is £678 and [redacted] for standard care and andexanet alfa, respectively.

As with the assumptions made for HRQoL, the company assumed 50% of survivors of an intraspinal bleed would suffer from paralysis and 25% of intraocular bleed survivors would suffer from monocular blindness. Furthermore, the company assumed that in the andexanet arm of the model, there would be a 25% reduction in patients suffering from paralysis and monocular blindness.

The company sourced cost data for paralysis from an economic analysis of spinal cord injuries in the UK[97] and Spinal UK[98]. The economic analysis of spinal cord injuries in the UK estimated the first-year total cost of care for 133 patients aged 76-85 suffering from either tetraplegia or paraplegia was £5.42million, of which 71% relate to personal and social services in the UK. Thus, the adjusted total costs were used to calculate the annual cost per patient (£29,582), which was applied to the first 12 cycles of the long-term economic model.

For subsequent years, the company used a 60-day cost for care in a spinal cord injury centre from Spinal UK, inflated to 2018 prices and converted it into a monthly (per cycle) cost. In the company's original submission, the day cost of £968 was taken from the Spinal UK report and used as the 60-day cost. During the clarification stage, the ERG highlighted this error and asked the company to revise their analysis using the cost of £58,080, which represents the 60-day cost presented in the Spinal UK report.

Using the correct cost, the company estimated the per cycle cost for care in a spinal cord injury centre to be £29,682, which was applied for the remainder of the long-term model after the first year.

The per-cycle cost for monocular blindness was sourced from TA155 (pegaptanib and ranibizumab for treatment of age-related macular degeneration [AMD])[99]. In TA155, the estimated annual average cost of for AMD associated with monocular blindness was £3,823.89, which the company uplifted to 2018 prices and converted to a per-cycle cost of £374.43.

Table 64 summaries the long-term bleed management costs applied in the economic model.

Table 64. Long-term bleed management costs per cycle used in the economic model

Parameter	Markov model per-cycle cost
ICH care – standard care	£678
ICH care – andexanet alfa	[redacted]
Paralysis – year 1	£29,582
Paralysis – year 2 and beyond	£29,682
Monocular blindness	£374
Abbreviations: ICH, intracranial haemorrhage	

5.3.10.4 Re-initiation of FXa inhibitor

Costs of FXa inhibitor were sourced from the British National Formulary. The per-cycle (one month) cost of apixaban and rivaroxaban, for any dose, was £57 and £54, respectively.[100] As presented in Table 60, the proportion of patients on apixaban in ANNEXA-4 was estimated to be 60.44%, with the remaining 39.56% on rivaroxaban. The company assumed that all patients restarted on the FXa inhibitor they were taking before their bleeding event. Based on the proportions on each FXa inhibitor and the per cycle treatment cost, the company calculated the weighted average cost per cycle of FXa inhibitors to be £56. This cost was applied each cycle in the Markov model (one month after the bleed event) until death.

5.3.10.5 ERG critique

During the clarification stage, the ERG highlighted to the company that the original methodology used to estimate long-term intraspinal costs was flawed, as initially the company calculated a lifetime average cost based on the first-year cost of paralysis (£29,582) and the subsequent 60-day costs of care in a spinal cord injury unit (£968, subsequently changed to £58,080 due to error highlighted by the ERG in the clarification stage). The ERG suggested that the rather than estimate an average cost per cycle, a per-cycle cost based on the first-year cost of paralysis is used for the first 12 cycles and then the per-cycle cost of care in a spinal cord injury unit is applied for the remainder of the economic model time horizon. The company revised their base case using ERG methodology, but did not convert the first-year cost of paralysis into a monthly per-cycle cost, which the ERG considers a modelling error and has corrected. Corrected company base case results can be found in Section 6.1.

Aside from the modelling error and as mentioned previously, the ERG considers the assumptions made for the modelling of other bleeds is not founded in robust evidence. The company acknowledges that the evidence base does not exist to estimate the percentage of intraspinal and intraocular bleeds that would result in paralysis and monocular blindness, respectively, and the impact that andexanet alfa has on these outcomes and thus rely on clinical expert opinion. Thus, the ERG prefers to focus on the ICH and GI, and ICH only cohorts to determine the cost-effectiveness of andexanet alfa, as it limits the uncertainty associated with other bleeds. However, the ERG acknowledges the NICE final scope is for the full population covered by the marketing authorisation and so considers the company's scenario of a 0% reduction in paralysis and monocular blindness for patients on andexanet alfa is an appropriate, if, conservative scenario.

As mentioned throughout this report, the use of mRS for estimating the impact of andexanet alfa on ICH survivors has been a central issue for the cost-effectiveness analysis as it affects both the estimation of costs and of benefits. For costs, mRS distributions based on ANNEXA-4 and Øie *et al.* 2018[16] for andexanet alfa and standard care, respectively, have been used to weight the unit costs of long-term ICH bleed management and rehabilitation. Whilst the ERG considers that the underlying unit costs used for the ICH survivor health state are appropriate, the implementation of mRS data in the economic model is not. This issue is discussed in depth in Section 5.3.5.3 and scenarios exploring the impact of changing mRS assumptions in the model is provided in Section 6.

With regards to the rehabilitation cost for ICH survivors used in the model, the ERG is concerned with how this has been implemented in the long-term Markov model. ICH survivors in both arms of the model are categorised as dependent based on an mRS category three to five. Subsequently, the proportion of patients classed as dependent are used to weight the per-cycle unit cost of rehabilitation, which is then added to the per-cycle long-term weighted ICH bleed management cost and applied for a lifetime in the economic model. The ERG verified whether ICH patients would receive rehabilitation on the NHS for a lifetime with its clinical experts. The ERG's clinical experts stated that lifetime rehabilitation provided by the NHS would, at most, be given for a matter of months rather than years. The ERG ran two scenarios testing the impact on the ICER of applying the rehabilitation cost for dependent ICH survivors for six and 12 months, respectively. Results of the scenarios can be found in Section 6.

Treatment costs in the model for standard care are considered appropriate by the ERG. During the clarification stage, the ERG requested several scenarios from the company exploring the use of INR data from the ORANGE study to estimate the vial requirements based on the SmPC dosing guidelines for Beriplex® and Octaplex®. However, all scenarios resulted in only two vials for non-activated 4F-PCC required, which is reflective of the company's base case. In addition, the company's base case employs the cost of the cheapest treatment option, Octaplex® and appropriately captures vial wastage.

However, the company stated that vial wastage was also included for andexanet alfa for the base case analysis, but the ERG considers the company's approach underestimates the cost of treatment. The company's uses rounded-up units for low and high dose of andexanet alfa and weights these based on the proportion of patients receiving each dose (see Table 59). The ERG considers this approach does not accurately reflect vial wastage, as the number of units estimated from the weighting calculation (5.43-5.48, depending on the cohort) should have been rounded up to 6 units. Implementing 6 units for the acquisition cost of andexanet alfa results in a consistent cost for the three cohorts of £16,650, which is a difference of between £1,447 and £1,568 per patient, depending on the cohort. The impact of the change in the wastage assumption on the ICER is presented in Section 6.

Finally, the company's resubmission of the economic model excluded an assumption around length of hospital stay that was present in the original model. The ERG considers it is important to highlight this change, even though it is satisfied with the company's revised position as including length of hospital stay in the original analysis only served to increase costs for standard of care and thus positively influence the cost-effectiveness of andexanet alfa.

In the company's original submitted economic model, analysis on length of hospital stay was included for resource use and costs. In the analysis, the company estimated that patients on standard care stayed in hospital longer after a life-threatening bleed than patients on andexanet alfa and as such included excess hospital bed day costs for the standard care arm of the model. The ERG requested clarification from the company on the clinical rationale for length of hospital stay being longer for standard care and why in the company's resubmission, length of hospital stay was excluded from the economic analysis.

During the second round of clarification, the company performed additional analysis on length of hospital stay between andexanet alfa and standard care using propensity score matching (described in Section 4.4.2) and found that instead, andexanet alfa was associated with [redacted] in the whole cohort and ICH cohort compared with standard care. The company stated that the reason for these results was that patients in the ORANGE study that had a hospital stay longer than 30 days were censored, whereas in ANNEXA-4 patients were not censored at 30 days.

The company also provided additional analysis on the NHS reference costs used for acute bleeds and determined that length of stay associated with certain bleed types is included in the unit costs. The company compared the length of hospital stay for both treatment arms against the length of hospital stay included in the NHS reference costs and found that neither treatment arm exceeded the NHS average. Thus, the company concluded that it is inappropriate to include excess hospital days in the economic analysis, which contradicts the company's initial position for modelling the costs of standard care.

Nonetheless, as discussed in Section 4.4.2, the ERG acknowledges the company's concern that length of hospital stay may be impacted by differences in study location between ANNEXA-4 and ORANGE. However, the ERG considers that length of hospital stay is likely to be intrinsically linked with 30-day mortality. Therefore, it would be inappropriate to ignore the results of the propensity score matching analysis. Although the ERG acknowledges that this would make no difference from a costing perspective (given that neither treatment arm exceeded the average number of hospital days included in the NHS tariff) it would make a difference in terms of patient throughput by [redacted] for ICH bleeds.

5.4 Results included in company's submission

5.4.1 Base case results

The results of the company's revised base case analysis (discounted at 3.5%) are presented in Table 65 to Table 67, using list prices. According to the company's analysis for the three cohorts, andexanet alfa is expected to extend patients' lives by around 1.3 to 1.5 years compared to standard care. This translates to an incremental QALY gain for andexanet alfa of between 1.06 to 1.20 QALYs, and an incremental cost-effectiveness ratio (ICER) of £11,636 to £18,741 per QALY gained.

Table 65. Company's revised deterministic base case results (discounted at 3.5%) – Whole cohort (adapted from Table 35 of the company's clarification response)

Therapy	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Standard care	£48,108	3.24	2.17	-	-	-	-
Andexanet alfa	£60,430	4.56	3.23	£12,322	1.32	1.06	£11,636
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.							

Table 66. Company's deterministic base case results (discounted at 3.5%) – ICH and GI cohort (adapted from Table 35 of the company's clarification response)

Therapy	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Standard care	£16,736	2.72	1.81	-	-	-	-
Andexanet alfa	£37,427	4.11	2.91	£20,691	1.39	1.10	£18,741
Abbreviations: GI, gastrointestinal; ICER, incremental cost-effectiveness ratio; ICH, intracranial haemorrhage; LYG, life years gained; QALY, quality-adjusted life year.							

Table 67. Company's deterministic base case results (discounted at 3.5%) – ICH cohort (adapted from Table 35 of the company's clarification response)

Therapy	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Standard care	£18,780	1.59	0.93	-	-	-	-
Andexanet alfa	£41,199	3.07	2.13	£22,419	1.48	1.20	£18,738

Abbreviations: ICER, incremental cost-effectiveness ratio; ICH, intracranial haemorrhage; LYG, life years gained; QALY, quality-adjusted life year.

5.4.2 Deterministic sensitivity analysis

The company carried out one-way sensitivity analyses (OWSAs) to assess the impact of varying the values of parameters using upper and lower confidence intervals (CIs) sourced from the literature where available or calculated from the pre-specified distributions assigned to each parameter. Where a standard error was unavailable to calculate a lower or upper CI, the company assumed it to be ±20% of the mean value. For the decision tree baseline data, the company varied the parameters using 2.5% lower and 97.5% upper bounds of the Dirichlet distribution according to the number of people in each branch of the tree. The results of the OWSA are reproduced from the company's clarification response.

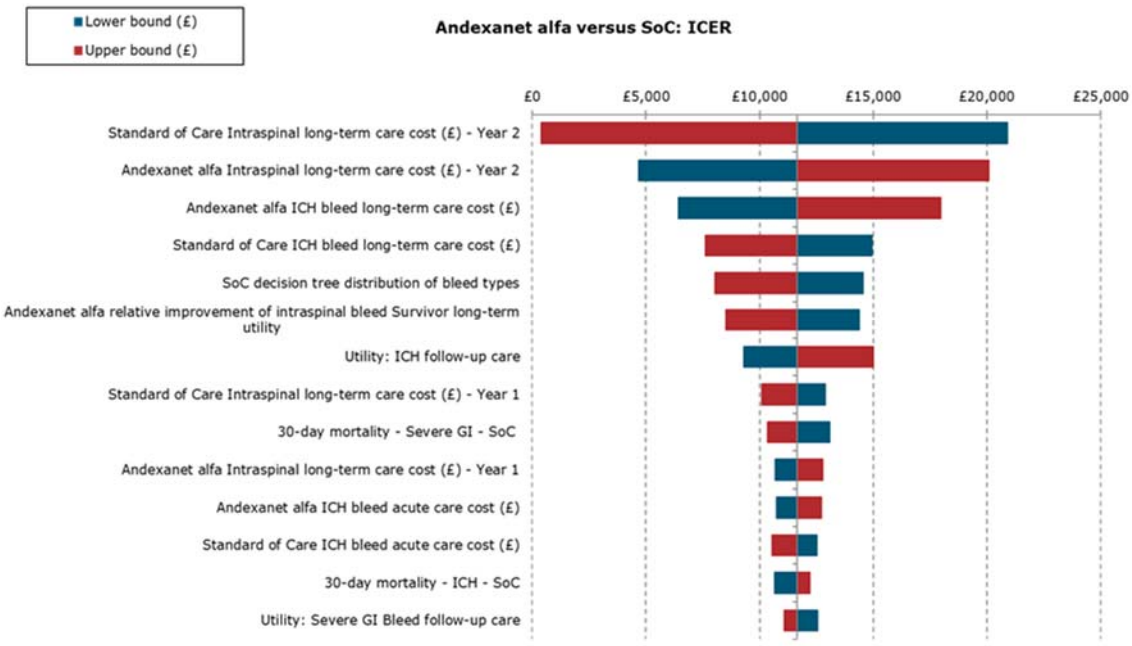
Furthermore, the company ran a number of scenarios changing the assumptions of the following parameters:

- Threshold benefit for intraspinal and intraocular bleeding events;
- Relative mortality reduction of andexanet alfa relative to standard care for other major bleeds;
- Long-term mortality hazard ratio source for ICH survivors;
- Discount rate for costs and benefits;
- Exclusion of wastage assumption for drug costs.

Whole cohort

The results of the OWSA and scenario analysis carried out by the company for the whole cohort are presented in Figure 10 for the 14 most influential parameters and Table 68, respectively. According to the scenario analysis, the results were most sensitive to the threshold benefit of intraspinal and intraocular bleeds, producing ICERs of between £4,126 (50% benefit) and £19,253 (0% benefit). As for OWSA, the main driver of the model was the long-term bleed management cost for standard care intraspinal survivors, producing an ICER of £20,909 when the low value is used to inform the model.

Figure 10. Tornado diagram of andexanet alfa versus standard care for the whole cohort (Figure 4 of the company's clarification response)



Abbreviations: ICER, incremental cost-effectiveness ratio; GI, gastrointestinal; ICH, intracerebral; mRS, modified Rankin Score; SoC, standard of care

Table 68. Results of scenario analyses for the whole cohort

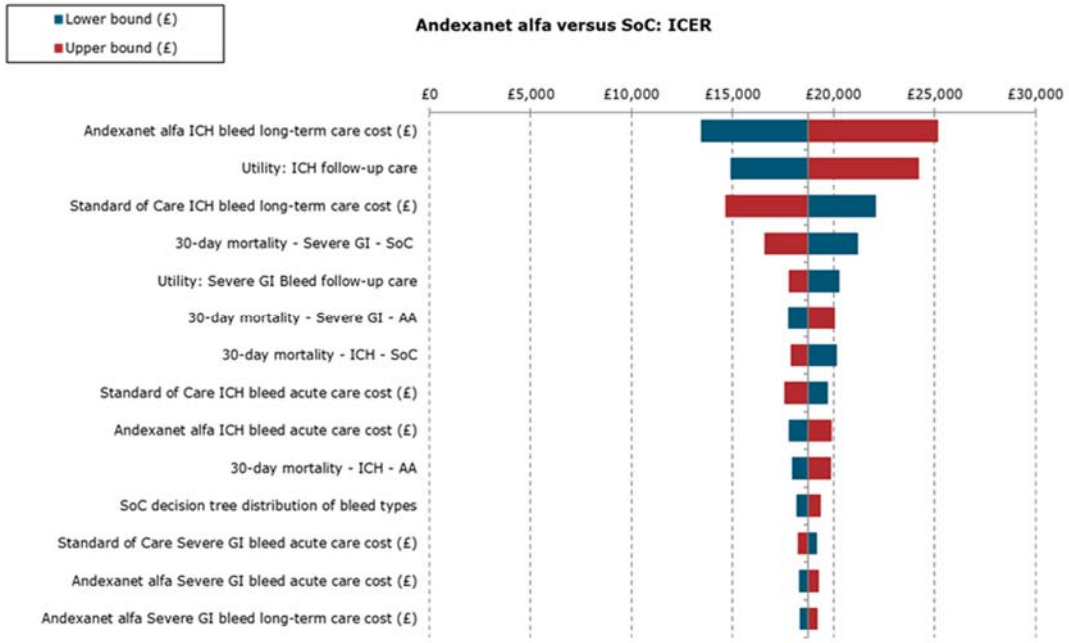
Parameter	Base case	Scenario	Andexanet alfa		Standard care		ICER (£)
			Costs (£)	QALYS	Costs (£)	QALYS	
Base case			60,430	3.23	48,108	2.17	11,636
Threshold benefit for intraspinal and intraocular bleeds	25%	0%	68,352	3.224	48,108	2.173	19,253
		12.5%	64,391	3.228	48,108	2.173	15,431
		37.5%	56,469	3.236	48,108	2.173	7,868
		50%	52,508	3.239	48,108	2.173	4,126
Relative mortality reduction of andexanet alfa versus standard care for other major bleeds	25%	0%	60,422	3.224	48,108	2.173	11,719
		12.5%	60,426	3.228	48,108	2.173	11,678
		37.5%	60,434	3.236	48,108	2.173	11,595
		50%	60,437	3.24	48,108	2.173	11,555
Long-term mortality hazard ratio		1.29 (Lee *et al*. 2010)[101]	60,430	3.232	50,782	2.358	11,039
		1.21 (Huybrechts *et al*. 2008)[83]	60,430	3.232	53,121	2.52	10,262
Discount rate	3.5%	0%	68,376	3.839	56,416	2.571	9,436
		5%	57,724	3.024	45,276	2.036	12,598
No vial wastage for drug costs	Vial wastage included	Vial wastage not included	58,885	3.232	48,103	2.173	10,182

Abbreviations: ICER, incremental cost-effectiveness ratio; ICH, intracranial haemorrhage; LYG, life years gained; QALY, quality-adjusted life year

ICH and GI cohort

The results of the OWSA and scenario analysis carried out by the company for the ICH and GI cohort are presented in Figure 11 for the 14 most influential parameters and Table 69, respectively. According to the scenario analysis, the results were most sensitive to the Huybrechts *et al*. 2008,[83] source used for the long-term mortality hazard, producing an ICER of £16,345. As for OWSA, the main driver of the model was the long-term bleed management cost for andexanet alfa ICH survivors, producing an ICER of £25,159 when the high value is used to inform the model.

Figure 11. Tornado diagram of andexanet alfa versus standard care for the whole cohort (Figure 8 of the company's clarification response)



Abbreviations: ICER, incremental cost-effectiveness ratio; GI, gastrointestinal; ICH, intracerebral; mRS, modified Rankin Score; SoC, standard of care

Table 69. Results of scenario analyses for the ICH and GI cohort

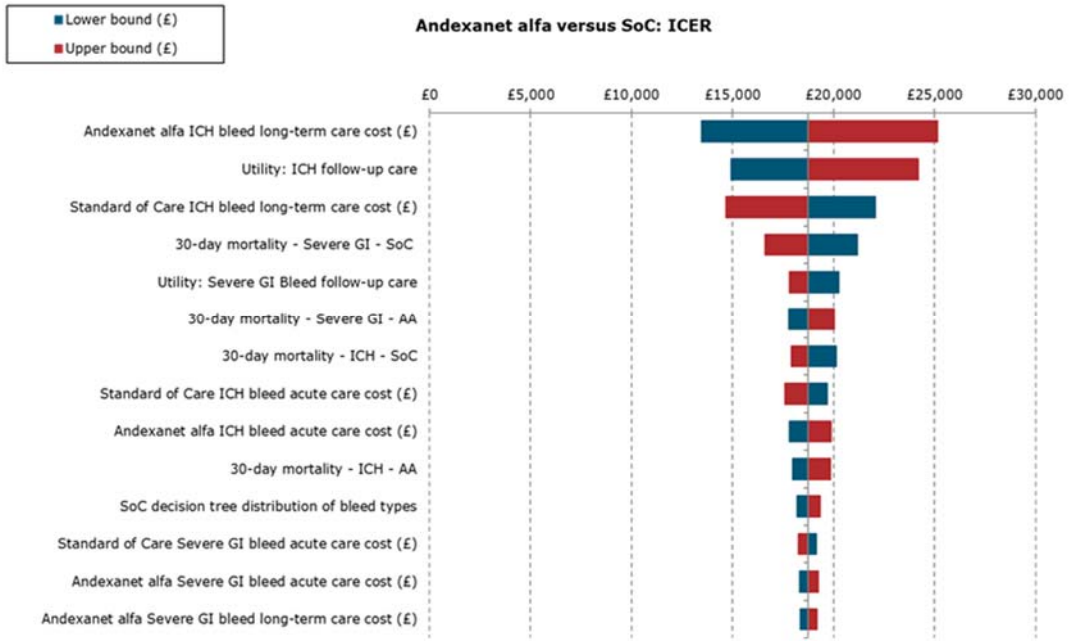
Parameter	Base case	Scenario	Andexanet alfa		Standard care		ICER (£)
			Costs (£)	QALYS	Costs (£)	QALYS	
Base case			37,427	2.91	16,736	1.81	18,741
Long-term mortality hazard ratio		1.29 (Lee *et al.* 2010)[101]	39,270	3.097	19,579	2.005	18,035
		1.21 (Huybrechts *et al*. 2008)[83]	42,672	3.438	22,041	2.175	16,345
Discount rate	3.5%	0%	40,130	3.422	18,050	2.109	16,826
		5%	36,479	2.737	16,255	1.704	19,582

No vial wastage for drug costs	Vial wastage included	Vial wastage not included	35,891	2.913	16,731	1.809	17,354
Abbreviations: ICER, incremental cost-effectiveness ratio; ICH, intracranial haemorrhage; LYG, life years gained; QALY, quality-adjusted life year							

ICH cohort

The results of the OWSA and scenario analysis carried out by the company for the ICH cohort are presented in Figure 12 for the 14 most influential parameters and Table 70, respectively. According to the scenario analysis, the results were most sensitive to Huybrechts *et al*. 2008,[83] source used for the long-term mortality hazard, producing an ICER of £15,930. As for OWSA, the main driver of the model was the long-term bleed management cost for andexanet alfa ICH survivors, producing an ICER of £26,458 when the high value is used to inform the model.

Figure 12. Tornado diagram of andexanet alfa versus standard care for the whole cohort (Figure 12 of the company's clarification response



Abbreviations: ICER, incremental cost-effectiveness ratio; GI, gastrointestinal; ICH, intracerebral; mRS, modified Rankin Score; SoC, standard of care

Table 70. Results of scenario analyses for the ICH cohort

Parameter	Base case	Scenario	Andexanet alfa		Standard care		ICER (£)
			Costs (£)	QALYS	Costs (£)	QALYS	
Base case			41,199	2.13	18,780	0.93	18,738
Long-term mortality hazard ratio		1.29 (Lee *et al.* 2010)[101]	43,573	2.367	22,487	1.189	17,908
		1.21 (Huybrechts *et al*. 2008)[83]	48,038	2.814	25,719	1.413	15,930

Discount rate	3.5%	0%	44,219	2.432	20,131	1.026	17,140
		5%	40,128	2.022	18,276	0.898	19,439
No vial wastage for drug costs	Vial wastage included	Vial wastage not included	39,667	2.13	18,774	0.933	17,462
Abbreviations: ICER, incremental cost-effectiveness ratio; ICH, intracranial haemorrhage; LYG, life years gained; QALY, quality-adjusted life year							

5.4.3 Probabilistic sensitivity analysis

The company performed probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results. The results are based on 10,000 PSA iterations. Table 71 presents the parameter distributions used in the PSA.

Table 71. Parameter distributions used in PSA

Distribution	Parameter
Fixed	• Time horizon • Cycle length • Discount rate • Average drug costs per day • Decision tree distribution • Treatment costs
Dirichlet	• Baseline decision tree data for andexanet alfa and standard care
Beta	• Event probabilities • Utilities • Disutilities • Andexanet alfa relative mortality reduction • Andexanet alfa relative reduction in ICH long-term bleed management cost
Gamma	• Age • Weight • Costs • Mortality HRs by bleed type • 30-day mortality
Abbreviations: HR, hazard ratio; PSA, probabilistic sensitivity analysis.	

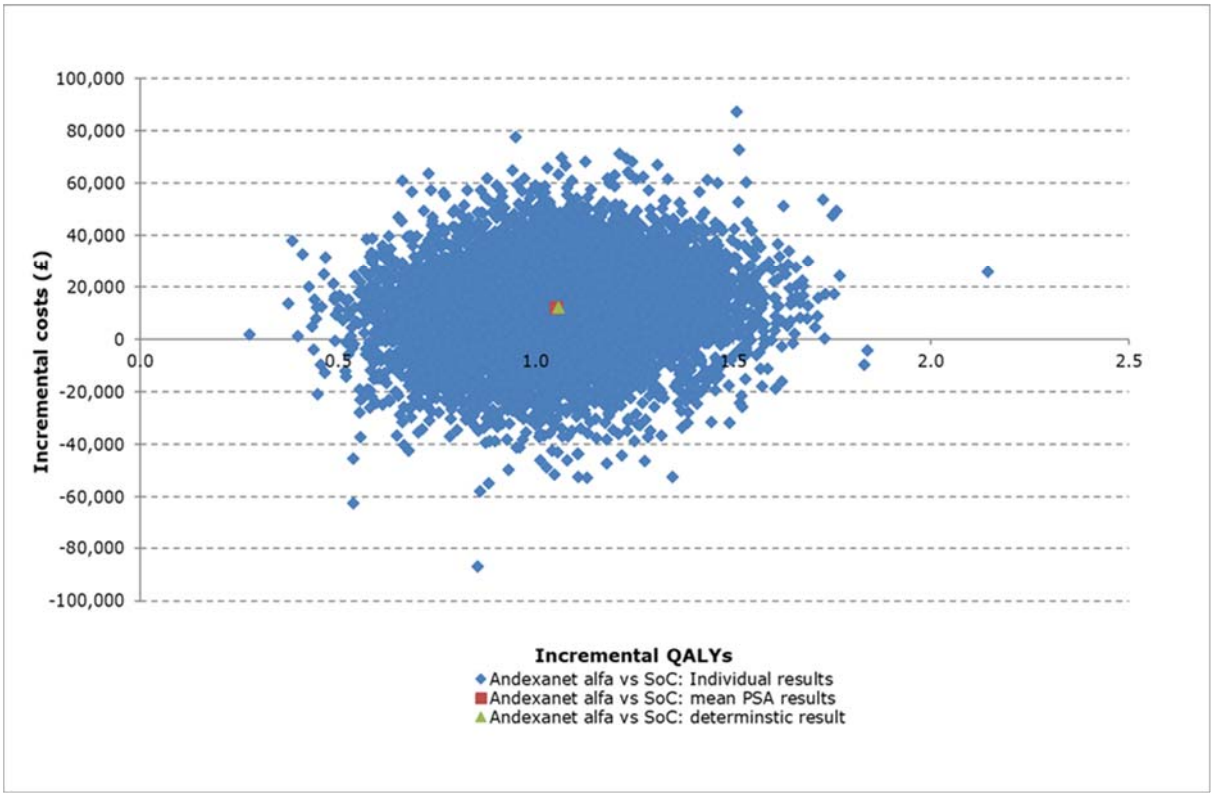
Whole cohort

The mean probabilistic ICER for the whole cohort is presented in Table 72. The PSA results produced a mean ICER of £11,653 per QALY gained for andexanet alfa compared to standard care which the ERG considers to be comparable to the deterministic base case results. The scatterplots, cost-effectiveness frontier (CEAF) and cost-effectiveness curve (CEAC) are presented in Figure 13, Figure 14 and Figure 15, respectively.

Table 72. Company's probabilistic base case results – Whole cohort (reproduced from Table 54 of the company's clarification response)

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Standard care	£48,169	2.179	-	-	-
Andexanet alfa	£60,437	3.232	£12,268	1.0528	£11,653
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.					

Figure 13. Incremental cost-effectiveness plane of andexanet alfa versus standard care for the whole cohort (Figure 1 of the company's clarification response)



Abbreviations: PSA, probabilistic sensitivity analysis; QALYS, quality-adjusted life years; SoC, standard of care

Figure 14. Cost-effectiveness frontier for andexanet alfa versus standard care for the whole cohort (Figure 2 of the company's clarification response)

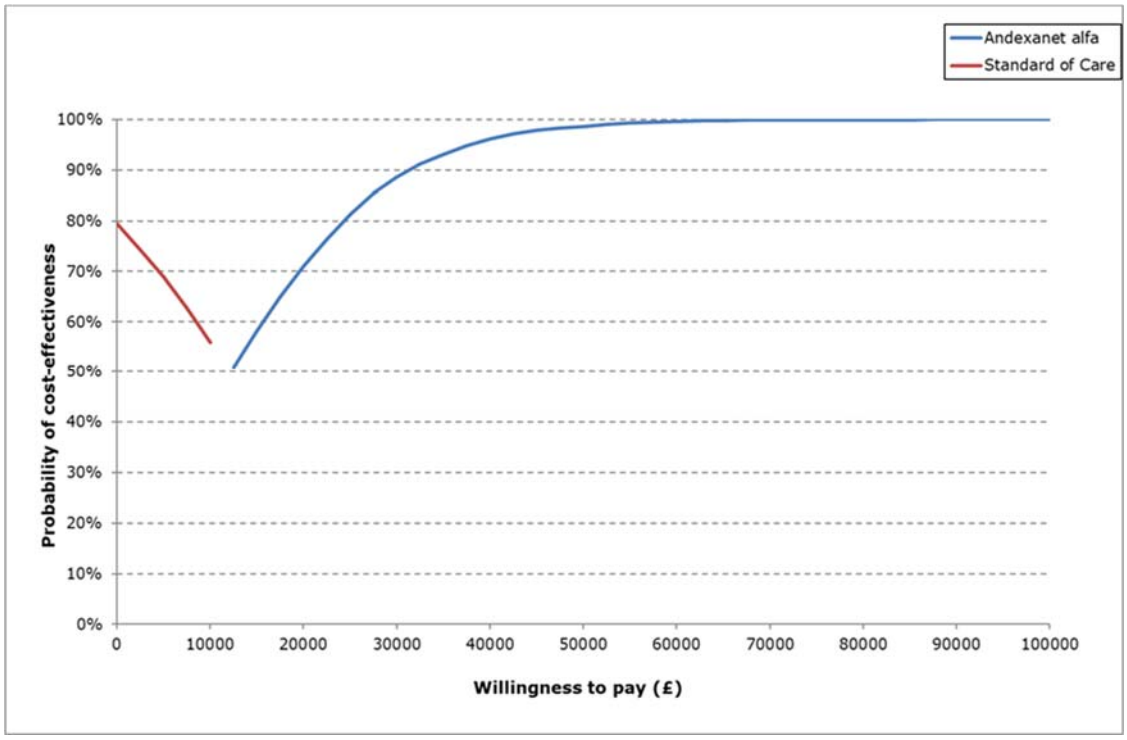
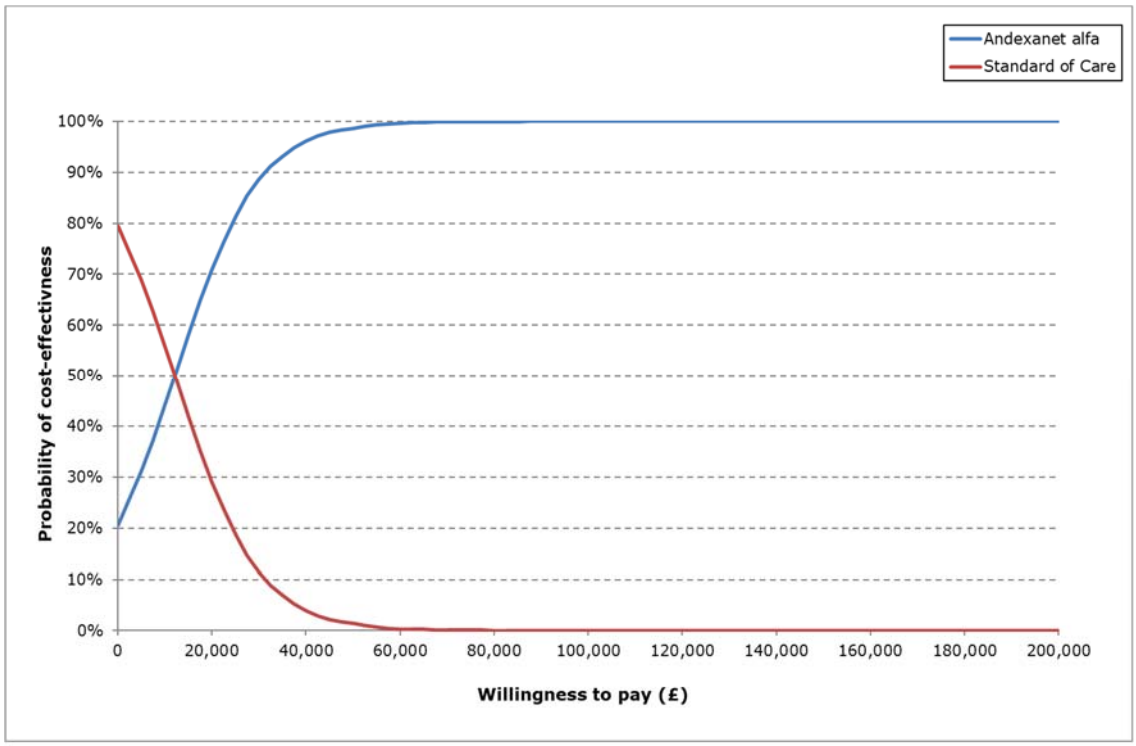


Figure 15. Cost-effectiveness curve for andexanet alfa versus standard care for the whole cohort (Figure 3 of the company's clarification response)



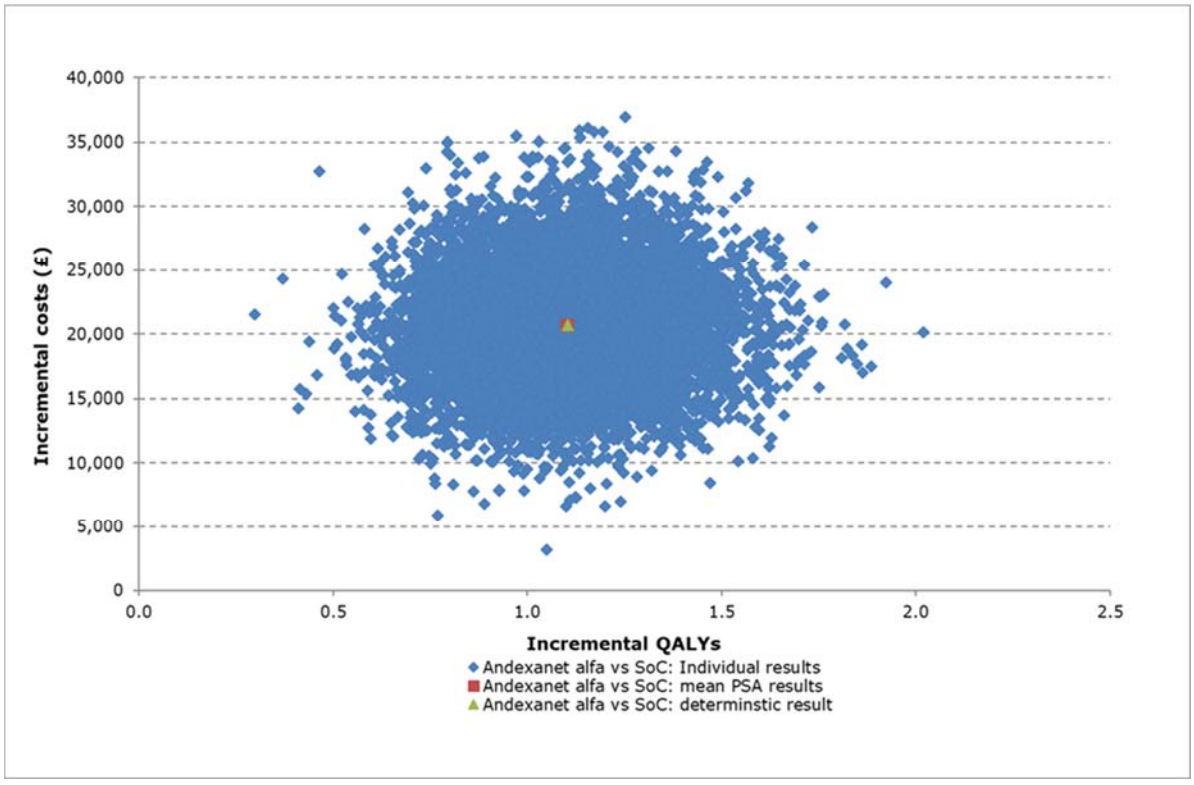
ICH and GI cohort

The mean probabilistic ICER for the ICH and GI cohort is presented in Table 73. The PSA results produced a mean ICER of £18,753 per QALY gained for andexanet alfa compared to standard care which the ERG considers to be comparable to the deterministic base case results. The scatterplots, CEAF and CEAC are presented in Figure 16, Figure 17 and Figure 18, respectively.

Table 73. Company's probabilistic base case results – ICH and GI cohort (reproduced from Table 56 of the company's clarification response)

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Standard care	£16,715	1.811	-	-	-
Andexanet alfa	£37,396	2.914	£20,681	1.1028	£18,753
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.					

Figure 16. Incremental cost-effectiveness plane of andexanet alfa versus standard care for the ICH and GI cohort (Figure 5 of the company's clarification response)



Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; PSA, probabilistic sensitivity analysis; QALYS, quality-adjusted life years; SoC, standard of care

Figure 17. Cost-effectiveness frontier for andexanet alfa versus standard care for the ICH and GI cohort (Figure 6 of the company's clarification response)

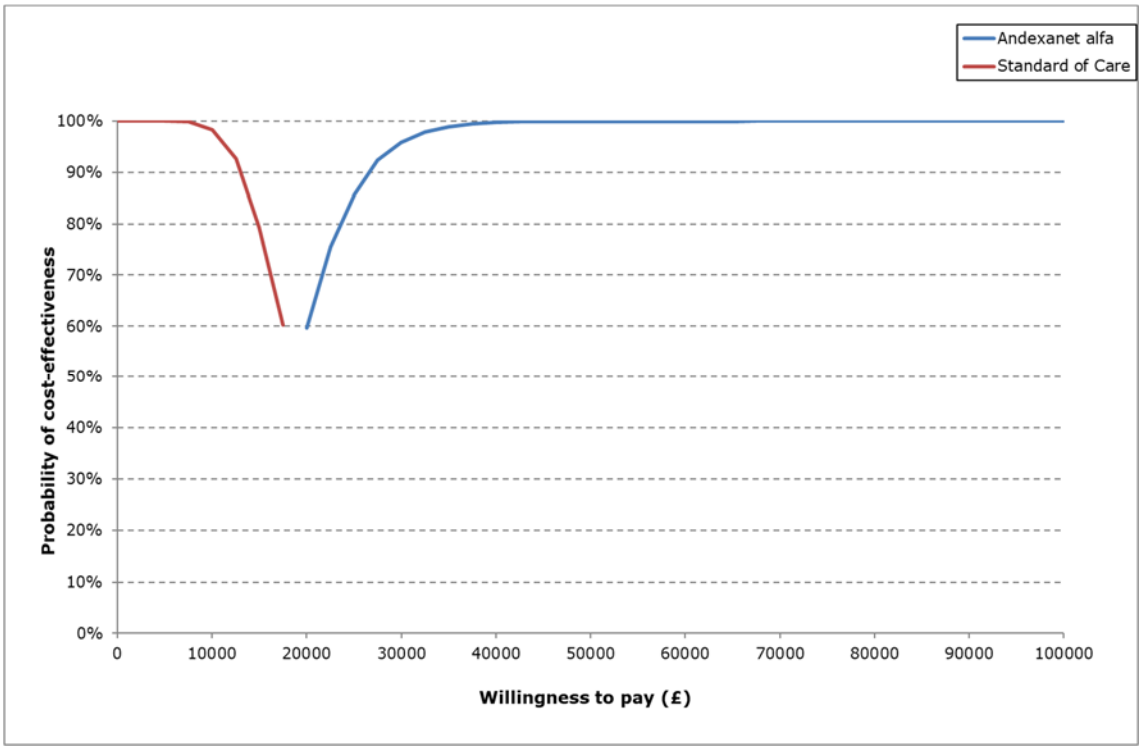
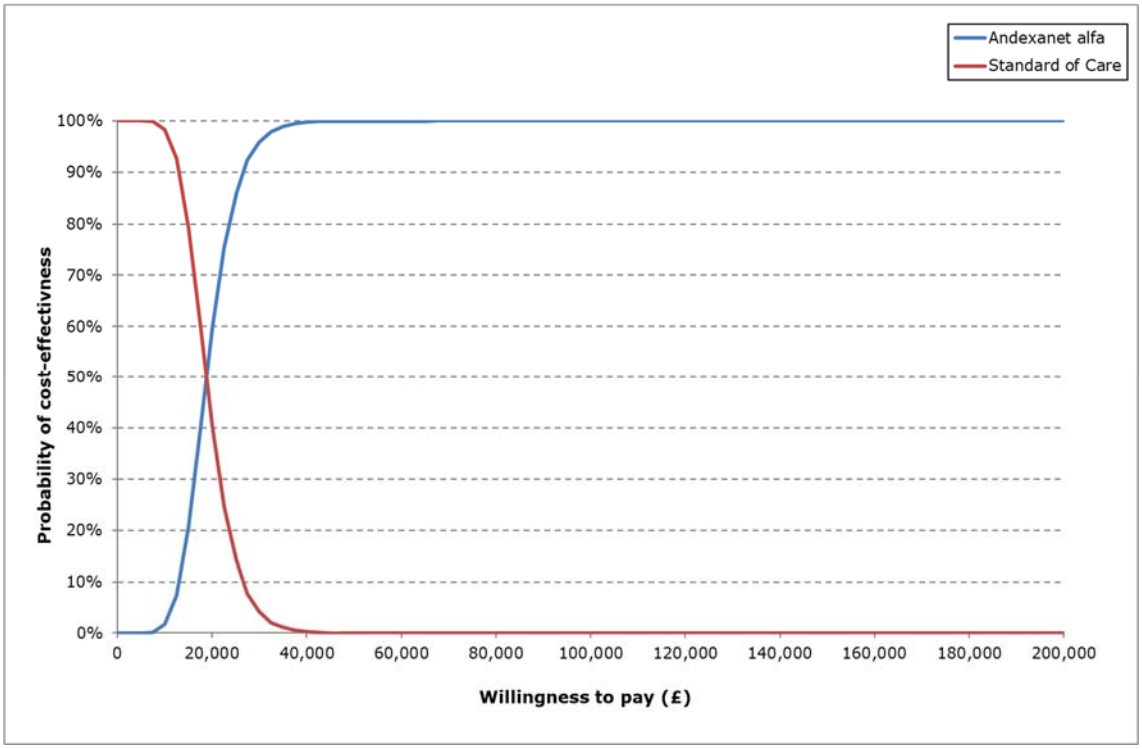


Figure 18. Cost-effectiveness curve for andexanet alfa versus standard care for the ICH and GI cohort (Figure 7 of the company's clarification response)



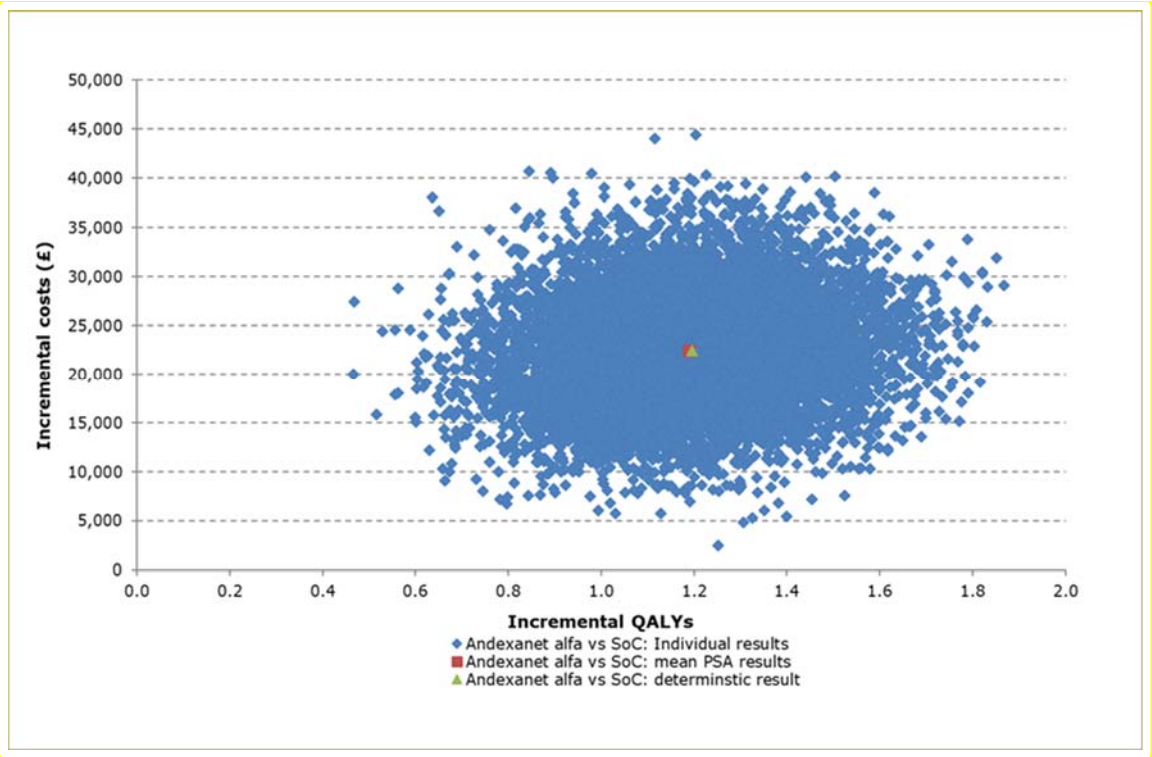
ICH cohort

The mean probabilistic ICER for the ICH cohort is presented in Table 74. The PSA results produced a mean ICER of £18,881 per QALY gained for andexanet alfa compared to standard care which the ERG considers to be comparable to the deterministic base case results. The scatterplots, CEAF and CEAC are presented in Figure 19, Figure 20 and Figure 21, respectively.

Table 74. Company's probabilistic base case results – ICH cohort (reproduced from Table 58 of the company's clarification response)

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Standard care	£18,820	0.939	-	-	-
Andexanet alfa	£41,291	2.129	£22,471	1.1902	£18,881
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.					

Figure 19. Incremental cost-effectiveness plane of andexanet alfa versus standard care for the ICH cohort (Figure 9 of the company's clarification response)



Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; PSA, probabilistic sensitivity analysis; QALYS, quality-adjusted life years; SoC, standard of care

Figure 20. Cost-effectiveness frontier for andexanet alfa versus standard care for the ICH cohort (Figure 10 of the company's clarification response)

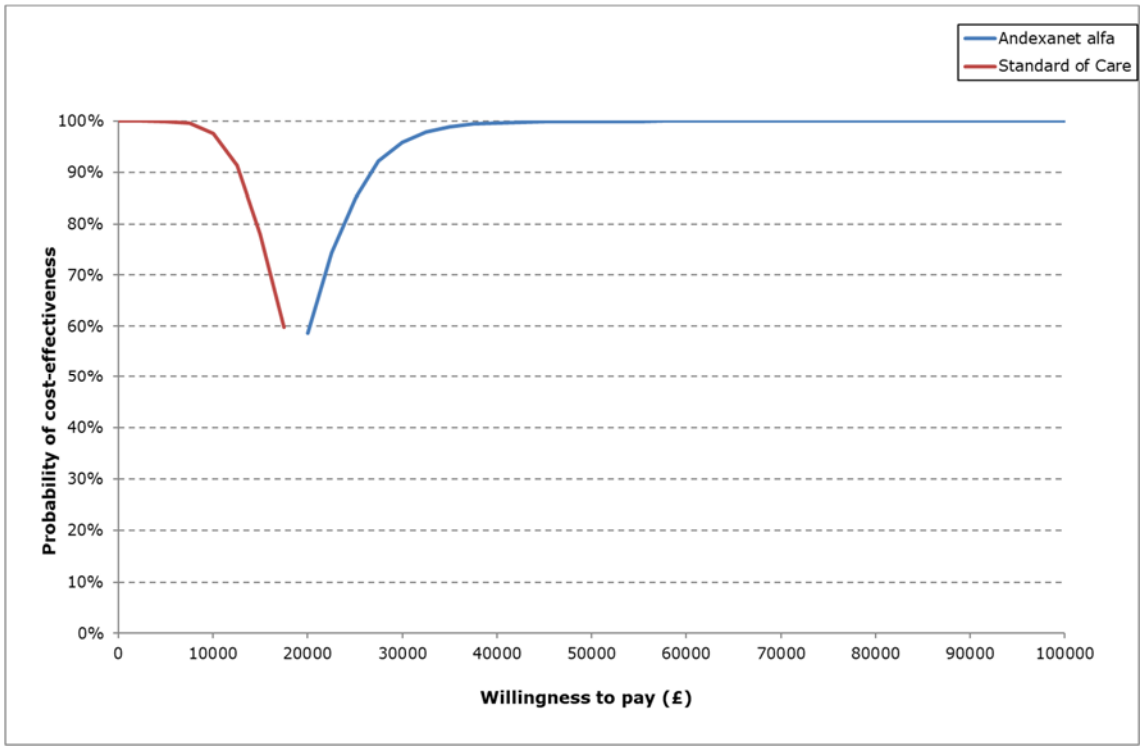
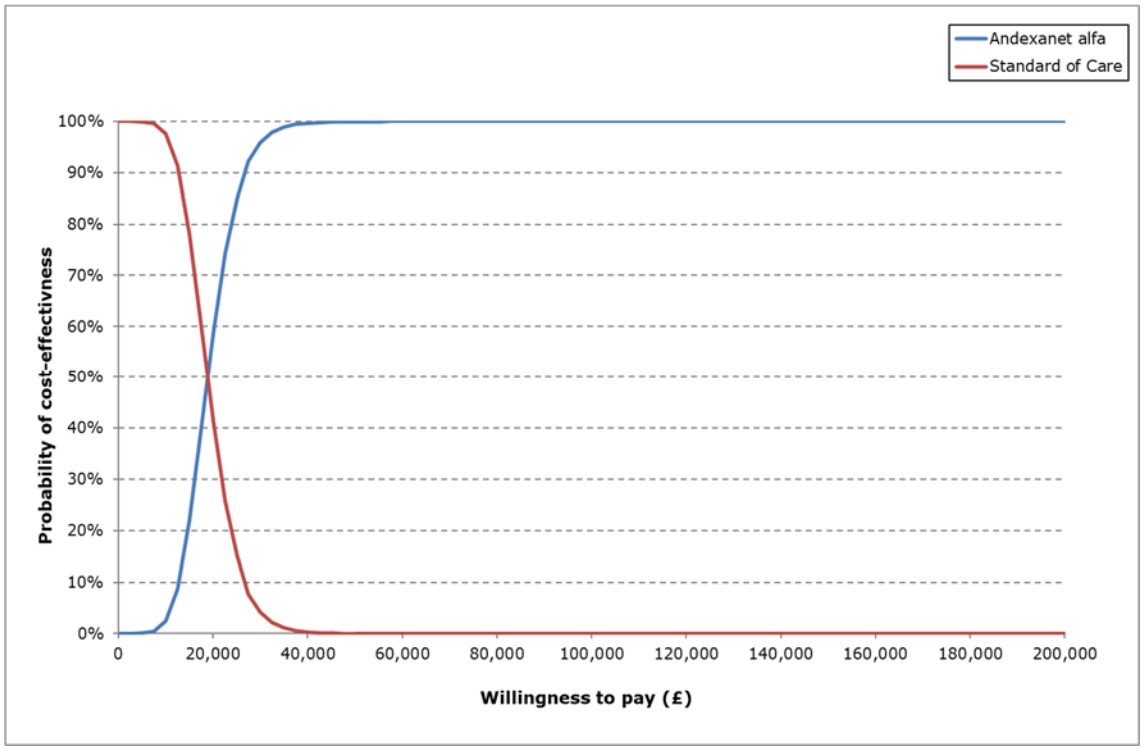


Figure 21. Cost-effectiveness curve for andexanet alfa versus standard care for the ICH cohort (Figure 11 of the company's clarification response)



5.4.4 Model validation

The model was developed for Portola Pharmaceuticals by FIECON and the CS states it was quality assured by two independent health economists. A senior research fellow from the University of Sheffield also provided advice on the methods and code used in R software to conduct the propensity score matching analysis which underpins the clinical trial data in the decision tree section of the economic model. Furthermore, the company state that UK clinical experts were consulted about key aspects of the model design, data sources and assumptions.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

The Evidence Review Group (ERG) described two implementation errors in this report, one related to the calculation of long-term mortality (Section 5.3.8.3) and a second related to the cost of intraspinal care (Section 5.3.10.5). These are summarised here, together with the combined impact of the corrections on the final incremental cost-effectiveness ratio (ICER):

(1) In the company's formula that estimated the mortality probability of survivors of an intracranial haemorrhage (ICH) in the standard care arm, the company applied a cumulative probability in place of a monthly probability and did not hold a cell reference ($). The ERG corrected this in the model by taking the monthly probability and ensuring the cell reference was held throughout all relevant cells.

(2) The company used an annual cost for the first-year cost of paralysis, but applied this as a per cycle cost. The ERG corrected this is the model by taking the annual cost and dividing it by 12, ensuring that the cost is correctly linked to the first 12 cycles of the long-term Markov model.

Deterministic results are provided in Table 75, Table 76 and Table 77 for the company's corrected base case, in the whole cohort, ICH plus gastrointestinal (GI) cohort and ICH cohort, respectively.

Table 75. Deterministic results of company's base case analysis – Whole cohort (corrected by the ERG)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Standard care	£44,370	3.210	2.153	-	-	-	-
Andexanet alfa	£57,842	4.564	3.232	£13,472	1.355	1.079	£12,489
Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.							

Table 76. Deterministic results of company's base case analysis – ICH plus GI cohort (corrected by the ERG)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Standard care	£16,435	2.681	1.788	-	-	-	-
Andexanet alfa	£37,427	4.105	2.913	£20,992	1.424	1.125	£18,663
Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.							

Table 77. Deterministic results of company's base case analysis – ICH cohort (corrected by the ERG)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Standard care	£18,365	1.539	0.905	-	-	-	-
Andexanet alfa	£41,199	3.068	2.130	£22,834	1.529	1.225	£18,640

Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

6.2 ERG scenario analysis

Throughout Section 5, the ERG has described several scenarios that warrant further exploration in addition to the company's supplied scenario and sensitivity analyses to ascertain the impact of these changes on the ICER. The scenarios that the ERG has produced are applied to the corrected company base case and are as follows:

1. Resolving the issues relating to the use of modified Rankin Scores (mRS) by applying intracerebral-specific mRS results to [redacted] of ICH patients thus feeding into long-term mortality, health-related quality of life (HRQoL) and cost calculations (Section 5.3.5.3). This scenario also involves the direct use of the weighted mRS results to calculate utility values (Section 5.3.9.3);

2. Replacing the Weibull distribution with the Exponential distribution for mRS 4 to estimate the long-term mortality of ICH survivors (Section 5.3.8.3);

3. Vial wastage for andexanet alfa (Section 5.3.10.5);

4. Reducing the duration of rehabilitation for ICH survivors from lifetime to 6 months (Section 5.3.10.5);

5. Reducing the duration of rehabilitation for ICH survivors from lifetime to 12 months (Section 5.3.10.5).

Table 78, Table 79 and Table 80 present the results of the scenarios for the whole cohort, ICH plus GI cohort and ICH cohort, respectively.

Table 78. Results of the ERG's scenario analysis – whole cohort

	Results per patient	Andexanet alfa	Standard care	Incremental value
0	**Base case corrected by the ERG**			
	Total Costs (£)	£57,842	£44,370	£13,472
	QALYs	3.232	2.153	1.079
	ICER	-	-	£12,489
1	**Resolving the issues related to the use of mRS including intracerebral-specific mRS results to [redacted]% of ICH patients**			
	Total Costs (£)	£58,441	£44,256	£14,186
	QALYs	2.685	2.041	0.644
	ICER	-	-	£22,039
2	**Exponential distribution for mRS 4**			
	Total Costs (£)	£57,864	£44,410	£13,454
	QALYs	3.234	2.156	1.078

	ICER	-	-	£12,479
3	**Vial wastage for andexanet alfa**			
	Total Costs (£)	£59,411	£44,370	£15,040
	QALYs	3.232	2.153	1.079
	ICER	-	-	£13,943
4	**ICH rehabilitation 6 months**			
	Total Costs (£)	£53,062	£40,973	£12,089
	QALYs	3.232	2.153	1.079
	ICER	-	-	£11,207
5	**ICH rehabilitation 12 months**			
	Total Costs (£)	£53,611	£41,425	£12,185
	QALYs	3.232	2.153	1.079
	ICER	-	-	£11,296
Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin score; QALYs, quality adjusted life years.				

Table 79. Results of the ERG's scenario analysis – ICH plus GI cohort

	Results per patient	**Andexanet alfa**	**Standard care**	**Incremental value**
0	**Base case corrected by the ERG**			
	Total Costs (£)	£37,427	£16,435	£20,992
	QALYs	2.913	1.788	1.125
	ICER	-	-	£18,663
1	**Resolving the issues related to the use of mRS including intracerebral-specific mRS results to [redacted]% of ICH patients**			
	Total Costs (£)	£37,975	£16,323	£21,652
	QALYs	2.330	1.671	0.659
	ICER	-	-	£32,837
2	**Exponential distribution for mRS 4**			
	Total Costs (£)	£37,461	£16,490	£20,971
	QALYs	2.916	1.792	1.124
	ICER	-	-	£18,651
3	**Vial wastage for andexanet alfa**			
	Total Costs (£)	£38,905	£16,435	£22,470
	QALYs	2.913	1.788	1.125
	ICER	-	-	£19,978
4	**ICH rehabilitation 6 months**			
	Total Costs (£)	£32,398	£12,874	£19,524
	QALYs	2.913	1.788	1.125
	ICER	-	-	£17,358
5	**ICH rehabilitation 12 months**			
	Total Costs (£)	£33,000	£13,369	£19,630
	QALYs	2.913	1.788	1.125
	ICER	-	-	£17,453
Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin score; QALYs, quality adjusted life years.				

Table 80. Results of the ERG's scenario analysis – ICH cohort

	Results per patient	Andexanet alfa	Standard care	Incremental value
0	**Base case corrected by the ERG**			
	Total Costs (£)	£41,199	£18,365	£22,834
	QALYs	2.130	0.905	1.225
	ICER	-	-	£18,640
1	**Resolving the issues related to the use of mRS including intracerebral-specific mRS results to [redacted]% of ICH patients**			
	Total Costs (£)	£41,753	£18,235	£23,518
	QALYs	1.362	0.754	0.608
	ICER	-	-	£38,654
2	**Exponential distribution for mRS 4**			
	Total Costs (£)	£41,267	£18,462	£22,805
	QALYs	2.136	0.911	1.225
	ICER	-	-	£18,615
3	**Vial wastage for andexanet alfa**			
	Total Costs (£)	£42,646	£18,365	£24,282
	QALYs	2.130	0.905	1.225
	ICER	-	-	£19,821
4	**ICH rehabilitation 6 months**			
	Total Costs (£)	£34,692	£13,781	£20,911
	QALYs	2.130	0.905	1.225
	ICER	-	-	£17,070
5	**ICH rehabilitation 12 months**			
	Total Costs (£)	£35,517	£14,459	£21,059
	QALYs	2.130	0.905	1.225
	ICER	-	-	£17,190

Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin score; QALYs, quality adjusted life years.

6.3 ERG base case ICER

In this section of the report the ERG presents its preferred base case ICER for each cohort. The ERG also presents an alternative base case ICER which reflects a different scenario in terms of mRS. The ERG caveats the analyses on mRS with the fact that there are no study data for standard care in patients with all subtypes of ICH. The standard care arm was informed by a study in patients with intracerebral haemorrhages, which as evidence suggests, is a severe subtype of ICH. Therefore, the ERG considers that the results from Øie *et al*. 2018 should only inform mRS in patients with intracerebral haemorrhages.[16] As for the other subtypes, there are no relevant mRS data to inform standard care. If the patients in Øie *et al.* 2018 are not considered comparable to the patients with intracerebral haemorrhages in ANNEXA-4, an alternative ICER assuming no treatment benefit in mRS is provided. The key changes and assumptions made to the company's updated base case ICER are:

- Treatment with andexanet alfa results in a relative reduction in 30-day mortality for other major bleed patients of 0% compared to standard care. The ERG considers that in the absence of any evidence to substantiate the company's base case assumption (a relative reduction of 25%), no relative reduction is more appropriate. The ERG's assumption also lies in-between the results obtained from propensity score matching and the company's base case assumption.

- Treatment with andexanet alfa results in a relative reduction for paralysis in intraspinal bleeds and blindness in intraocular bleeds of 0% compared to standard care The ERG considers that in the absence of any evidence to substantiate a relative reduction of 25%, no relative reduction is more appropriate, if, conservative.

- An alternative and more accurate approach to calculate vial wastage for andexanet alfa. The ERG considers the company's approach underestimates the cost of treatment.

- Reducing the duration of rehabilitation for ICH survivors from lifetime to 12 months. The ERG verified whether ICH patients would receive rehabilitation in the NHS for a lifetime with its clinical experts. The ERG's clinical experts stated that lifetime rehabilitation provided by the NHS would, at most, be given for a matter of months rather than years.

- Applying the weighted utility values by mRS directly, instead of applying the utility increment to the TA341 baseline.[79] This eliminates the introduction of another utility from a different source, resulting in an unnecessary calculation step.

- Applying alternative mRS distributions. The ERG's base case employs intracerebral-specific mRS results to [redacted] of patients thus feeding into long-term mortality, HRQoL and cost calculations, while the ERG's alternative base case employs mRS distributions from ANNEXA-4 to patients receiving andexanet alfa and patients receiving standard care.

Incorporating the assumptions above, the ERG produced six different base case ICERs for the three cohorts, ranging from £27,834 to £37,311. These include one preferred base case ICER and one alternative base case ICER for each cohort. The highest ICER corresponds to the ICH cohort where intracerebral-specific mRS results are applied to [redacted] of ICH patients. Conversely, the lowest ICER corresponds to the ICH plus GI cohort where mRS distributions from ANNEXA-4 are applied to both treatment arms.

All six ICERs produced by the ERG are above NICE's lower threshold of £20,000 which may be a cause for concern given the uncertainty in the underlying comparison of treatment effectiveness. Moreover, all results using the ERG's preferred base case assumption (intracerebral-specific mRS)

result in ICERs above NICE's upper threshold of £30,000 which highlights the importance of using different mRS assumptions on the results.

Table 81 presents a summary of the ERG preferred base case ICERs in each cohort, while Table 82 presents the ERG's alternative base case ICERs. The detailed changes made to the company base case and corresponding deterministic ICERs that form the ERG preferred ICERs are reported in Table 83, Table 84 and Table 85 for the whole cohort, ICH plus GI cohort and ICH cohort, respectively.

Table 81. Summary of ERG ICERs by population, ERG base case

Population	Company's corrected base case ICER, deterministic	ERG ICER, deterministic	ERG ICER, probabilistic (10,000 simulations)
Whole cohort	£12,489	£33,541	£33,735
ICH plus GI cohort	£18,663	£32,352	£32,217
ICH cohort	£18,640	£37,311	£37,216
Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin score; QALYs, quality adjusted life years.			

Table 82. Summary of ERG ICERs by population, ERG alternative base case

Population	Company's corrected base case ICER, deterministic	ERG ICER, deterministic	ERG ICER, probabilistic (10,000 simulations)
Whole cohort	£12,489	£28,997	£29,297
ICH plus GI cohort	£18,663	£27,834	£27,754
ICH cohort	£18,640	£30,193	£30,037
Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin score; QALYs, quality adjusted life years.			

Table 83. ERG base case ICER – whole cohort

Results per patient*	Andexanet alfa	Standard care	Incremental value
Company's corrected base case			
Total costs (£)	£57,842	£44,370	£13,472
QALYs	3.232	2.153	1.079
ICER	-		**£12,489**
0% relative reduction in 30-day mortality for 'other major bleeds'			
Total costs (£)	£57,835	£44,370	£13,464
QALYs	3.224	2.153	1.071
ICER (compared with base case)	-		£12,577
ICER with all changes incorporated	-		**£12,577**
0% relative reduction of paralysis and blindness for andexanet alfa			
Total costs (£)	£64,901	£44,370	£20,531
QALYs	3.224	2.153	1.071
ICER (compared with base case)	-		£19,166
ICER with all changes incorporated	-		**£19,306**
Vial wastage for andexanet alfa			

Total costs (£)	£59,411	£44,370	£15,040
QALYs	3.232	2.153	1.079
ICER (compared with base case)	-		£13,943
ICER with all changes incorporated	-		**£20,781**
ICH rehabilitation 12 months			
Total costs (£)	£53,611	£41,425	£12,185
QALYs	3.232	2.153	1.079
ICER (compared with base case)	-		£11,296
ICER with all changes incorporated	-		**£19,571**
Weighted utility values by mRS			
Total costs (£)	£57,842	£44,370	£13,472
QALYs	2.837	1.956	0.881
ICER (compared with base case)	-		£15,294
ICER with all changes incorporated	-		**£24,046**
Alternative mRS distributions			
Intracerebral-specific mRS results to [redacted] of ICH patients (ERG base case)			
Total costs (£)	£58,441	£44,256	£14,186
QALYs	2.685	2.041	0.644
ICER (compared with base case)	-		£22,039
ICER with all changes incorporated	-		**£33,541**
mRS distributions from ANNEXA-4 applied to both treatment arms (alternative ERG base case)			
Total costs (£)	£57,842	£43,969	£13,873
QALYs	3.001	2.270	0.732
ICER (compared with base case)	-		£18,964
ICER with all changes incorporated	-		**£28,997**

Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin score; QALYs, quality adjusted life years.

*total costs and QALYs relate to individual scenarios and not cumulative scenarios

Table 84. ERG base case ICER – ICH plus GI cohort

Results per patient*	Andexanet alfa	Standard care	Incremental value
Company's corrected base case			
Total costs (£)	£37,427	£16,435	£20,992
QALYs	2.913	1.788	1.125
ICER	-		£18,663
Vial wastage for andexanet alfa			
Total costs (£)	£38,905	£16,435	£22,470
QALYs	2.913	1.788	1.125
ICER (compared with base case)	-		£19,978
ICER with all changes incorporated	-		**£19,978**
ICH rehabilitation 12 months			
Total costs (£)	£33,000	£13,369	£19,630
QALYs	2.913	1.788	1.125
ICER (compared with base case)	-		£17,453
ICER with all changes incorporated	-		**£18,767**
Weighted utility values by mRS			

Total costs (£)	£37,427	£16,435	£20,992
QALYs	2.496	1.581	0.915
ICER (compared with base case)	-		£22,932
ICER with all changes incorporated	-		**£23,060**
Alternative mRS distributions			
Intracerebral-specific mRS results to [redacted] of ICH patients (ERG base case)			
Total costs (£)	£37,975	£16,323	£21,652
QALYs	2.330	1.671	0.659
ICER (compared with base case)	-		£32,837
ICER with all changes incorporated	-		**£32,352**
mRS distributions from ANNEXA-4 applied to both treatment arms (alternative ERG base case)			
Total costs (£)	£37,427	£16,036	£21,391
QALYs	2.669	1.913	0.756
ICER (compared with base case)	-		£28,277
ICER with all changes incorporated	-		**£27,834**
Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin score; QALYs, quality adjusted life years. *total costs and QALYs relate to individual scenarios and not cumulative scenarios			

Table 85. ERG base case ICER – ICH cohort

Results per patient*	**Andexanet alfa**	**Standard care**	**Incremental value**
Company's corrected base case			
Total costs (£)	£41,199	£18,365	£22,834
QALYs	2.130	0.905	1.225
ICER	-		**£18,640**
Vial wastage for andexanet alfa			
Total costs (£)	£42,646	£18,365	£24,282
QALYs	2.130	0.905	1.225
ICER (compared with base case)	-		£19,821
ICER with all changes incorporated	-		**£19,821**
ICH rehabilitation 12 months			
Total costs (£)	£35,517	£14,459	£21,059
QALYs	2.130	0.905	1.225
ICER (compared with base case)	-		£17,190
ICER with all changes incorporated	-		**£18,372**
Weighted utility values by mRS			
Total costs (£)	£41,199	£18,365	£22,834
QALYs	1.588	0.637	0.952
ICER (compared with base case)	-		£23,990
ICER with all changes incorporated	-		**£23,644**
Alternative mRS distributions			
Intracerebral-specific mRS results to [redacted] of ICH patients (ERG base case)			
Total costs (£)	£41,753	£18,235	£23,518
QALYs	1.362	0.754	0.608
ICER (compared with base case)	-		£38,654
ICER with all changes incorporated	-		**£37,311**

mRS distributions from ANNEXA-4 applied to both treatment arms (alternative ERG base case)			
Total costs (£)	£41,199	£17,890	£23,309
QALYs	1.814	1.071	0.743
ICER (compared with base case)	-		£31,377
ICER with all changes incorporated	-		**£30,193**
Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin score; QALYs, quality adjusted life years. *total costs and QALYs relate to individual scenarios and not cumulative scenarios			

The ERG acknowledges that the ICER which applies mRS distributions from ANNEXA-4 to both treatment arms (i.e. no treatment benefit) is lower than the ICER which applies intracerebral-specific mRS results to [redacted] of ICH patients. This is primarily because intracerebral-specific mRS results from ANNEXA-4 have the largest proportion of patients with an mRS of 5 (the most severe mRS associated with the largest impact on utility, costs and mortality). In addition, because it is assumed patients with non-intracerebral subtypes of ICH in the standard care arm have mRS results equal to the ANNEXA-4, instead of Øie *et al*. 2018, the proportion of higher mRS categories decreases in the standard care arm. However, the ERG considers it important to add that the mRS results from ANNEXA-4 applied to non-intracerebral ICH survivors encompass all subtypes of ICH. In spite of this, these scores are applied to both treatment arms, thereby reducing the impact of this inaccuracy on the ICER.

Overall, the scenario that applies intracerebral-specific mRS results to [redacted] of ICH patients favours standard care. Nonetheless, the ERG considers this to be a key scenario that accurately attributes intracerebral-specific mRS results to patients with intracerebral haemorrhages. Table 86 summarises the difference in survival, HRQoL and costs between the scenarios that implement alternative mRS results. A narrative explanation is also given below.

Table 86. Disaggregated scenarios influenced by mRS

Scenario	Standard care	Andexanet alfa	Increment (andexanet alfa – standard care)
mRS 5 (hospital costs, totally-disabling strokes)			
Base case	19.7%	[redacted]	[redacted]
Intracerebral-specific mRS results to [redacted] of ICH patients	19.3%	[redacted]	[redacted]
mRS distributions from ANNEXA-4 applied to both treatment arms	[redacted]	[redacted]	NA
% dependent (rehabilitation costs)			
Base case	75.4%	[redacted]	[redacted]
Intracerebral-specific mRS results to [redacted] of ICH patients	65.7%	[redacted]	[redacted]
mRS distributions from ANNEXA-4 applied to both treatment arms	[redacted]	[redacted]	NA
ICH health state costs (hospital costs and rehabilitation costs)			
Base case	£677.83	[redacted]	[redacted]

Intracerebral-specific mRS results to [redacted] of ICH patients	£620.86	[redacted]	[redacted]
mRS distributions from ANNEXA-4 applied to both treatment arms	[redacted]	[redacted]	NA
ICH long-term utility			
Base case	0.61	0.72	0.11
Weighted utility values directly	0.42	0.53	0.11
Intracerebral-specific mRS results to [redacted] of ICH patients	0.47	0.49	0.02
mRS distributions from ANNEXA-4 applied to both treatment arms	0.61	0.61	NA
Mean survival			
Base case	3.75	4.51	0.76
Intracerebral-specific mRS results to [redacted] of ICH patients	4.06	4.24	0.18
mRS distributions from ANNEXA-4 applied to both treatment arms	4.51	4.51	NA
Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin score; QALYs, quality adjusted life years.			

Compared to the base case, using intracerebral-specific mRS results leads to a reduction in the ICH health state costs for standard care and an increase in costs for andexanet alfa. This is due to the smaller proportions of totally-disabling and dependent ICH survivors in the standard care arm and larger proportions in the andexanet alfa arm. Subsequently, the ICH health state costs are closer together, resulting in a smaller incremental cost. Nonetheless, when the total costs are considered, the difference is minimal. As such, it is the difference in QALYs that causes the increase in the ICER from the company's base case to the ERG's base case using intracerebral-specific mRS results.

In terms of LYs, using intracerebral-specific mRS results leads to an increase in mean survival for standard care and a decrease for andexanet alfa, resulting in smaller incremental LYs, compared to the base case. As for QALYs, the ERG made two adjustments to how HRQoL was implemented in the model. The first adjustment applies weighted mRS results directly to calculate utility values for ICH survivors (described in Section 5.3.9.3), and compared with the base case, this adjustment decreases the utility in both treatment arms and results in smaller incremental QALYs. Then, when intracerebral-specific mRS results are applied (also using weighted utility values directly), the ICH utility increases for standard care and decreases for andexanet alfa, thereby bringing the utility values closer together, reducing incremental QALYs even further.

7 END OF LIFE

The ERG agrees with the company’s decision that andexanet alfa does not meet the criteria outlined by NICE for ‘life-extending treatment at the end of life'.

8 OVERALL CONCLUSIONS

The key clinical safety and efficacy data for andexanet alfa of relevance to the NICE final scope are those derived from ANNEXA-4, an ongoing phase 3b/4, prospective, open-label, single-arm study. ANNEXA-4 was designed to evaluate the efficacy and safety of andexanet alfa in patients receiving a FXa inhibitor (apixaban, rivaroxaban, edoxaban, or enoxaparin) who present with acute major bleeding. The ERG considers the key comparator for andexanet alfa to be 4-factor pro-thrombin complex concentrates (4F-PCCs) and notes that the key study providing data on 4F-PCC in the CS is the ORANGE study. However, the ERG has some concerns about the transparency of study inclusion and the identification of the ORANGE study for the propensity score matching. In addition to ANNEXA-4 and ORANGE, the company included, and data extracted 17 studies on PCC in their systematic literature review but these studies were only reported in an appendix of the company submission (CS). The ERG is therefore uncertain whether ORANGE is the only appropriate study to inform the analysis of the clinical efficacy of andexanet alfa compared with 4F-PCC, especially as propensity score matching with ORANGE could only be done for two of the key outcomes, but the ERG acknowledges that ORANGE is the largest study with UK-based data and had IPD available.

Despite the NICE final scope specifying the relevant population to be adults requiring urgent reversal of anticoagulation in case of uncontrolled or life-threatening bleeding after treatment with a factor Xa-inhibiting direct oral anticoagulant, only the FXa inhibitors apixaban and rivaroxaban are of relevance given the European Marketing authorisation for andexanet alfa. The ERG notes that this population represents a *post hoc* subgroup in both the ANNEXA-4 (n = 322) and ORANGE (n = 149) studies.

Population matching methods were used to generate statistically adjusted estimates of effect to enable a comparison of the single-arm ANNEXA-4 and ORANGE studies. However, data suitable for analysis between andexanet alfa and 4F-PCC were restricted to the outcomes of 30-day mortality and length of hospital stay. The ERG has several concerns with the propensity score matching analyses and therefore recommends the results are interpreted with caution for the reasons detailed below:

- The ERG considers length of hospital stay is likely to be intrinsically linked with mortality as the longer hospital stay a patient has, the lower their risk of dying within 30 days is likely to be (assuming similar risk of death between both ANNEXA-4 and ORANGE).

- Length of hospital stay may be impacted by differences in study location between ANNEXA-4 ([redacted] UK) and ORANGE (100% UK). In addition, the ERG notes that the data used from ORANGE for the propensity score matching analysis of length of hospital stay were censored at 30-days but ANNEXA-4 had longer follow-up and was not censored to match the data from ORANGE despite the company having access to the IPD for both studies.

- Severity of bleed (e.g. as assessed by mRS) and volume of bleed were not included as covariates in the propensity score matching analysis as these data weren't collected in the ORANGE study. However, the ERG considers bleed severity in particular to be of particular importance as clinical experts reported it was likely to be a prognostic indicator and the use of the mRS in the economic model is a key driver in the cost-effectiveness analysis (see below).

- [redacted]. In addition, due to the matching with replacement method used, [redacted]. The ERG also considers that unobserved confounders are likely to be present due to the non-randomised study design of ANNEXA-4 and ORANGE, and so the results of the propensity score matching analyses are subject to inherent bias.

Nevertheless, the results of the propensity score matching analyses suggest [redacted]

An area of concern with the cost-effectiveness analysis includes the modelling of 'other major bleeds' as it is primarily driven by assumptions based on the company's clinical expert opinion in the absence of outcomes data. The company assumed that treatment with andexanet alfa would reduce the risk of 30-day mortality by 25% for pericardial and retroperitoneal bleeds and reduce the instances of paralysis in intraspinal survivors and monocular blindness in intraocular survivors by 25% compared with standard care. The ERG considers that in the absence of any evidence to substantiate the 25% reductions associated with andexanet alfa, a scenario of no relative reduction is a more appropriate, if, conservative scenario. However, the ERG considers the most robust estimates of cost-effectiveness are for the ICH and GI plus ICH cohorts as it removes the uncertainty of assumptions needed to model 'other major bleeds'.

In addition, the use of the mRS for estimating the impact of andexanet alfa on ICH survivors has been a central issue for the cost-effectiveness analysis as it affects the estimation of costs, quality of life and mortality. In short, the ERG is concerned that the study used to inform the severity of ICH survivors in the standard care arm (Øie *et al.* 2018) represents patients with one of the most severe subtypes of ICH and therefore overestimates the severity of the mRS in the standard care arm. Therefore, to account for the proportion of patients that would experience one of the most severe subtypes of ICH (intracerebral haemorrhage), the ERG asked the company to explore a scenario where intracerebral-specific mRS results (recorded in Øie *et al.* 2018 for standard care) are applied to the proportion of patients that experienced an intracerebral haemorrhage in ANNEXA-4, and the remaining proportion of patients in both treatment arms have mRS results equal to ANNEXA-4. However, the ICER which applies mRS

distributions from ANNEXA-4 to both treatment arms (i.e. no treatment benefit) is lower than the ICER which applies intracerebral-specific mRS results to [redacted] of ICH patients. This either suggests that Øie *et al*. 2018 is not a representative population for standard care, or that the treatment benefit in terms of the prognosis for survivors of intracerebral haemorrhages is negligible. However, the ERG acknowledges that in the absence of head-to-head trial data, *Øie et al.* 2018 represents the best available evidence on mRS in people with intracerebral haemorrhage receiving standard care. To remove all uncertainty associated with mRS, the ERG also presented an alternative base case ICER where mRS values recorded in ANNEXA-4 are used in both treatment arms.

Aside from these key areas of concern, the ERG identified several issues with how costs and resources were implemented in the model, but these had negligible effects on the ICER.

Overall, using the ERG's preferred assumptions, the benefits of andexanet alfa are derived from reductions in 30-day mortality compared to standard care for ICH and GI bleeds.

8.1 Implications for research

There were no RCT data identified for the comparison of andexanet alfa with 4F-PCC and data were restricted to single-arm cohort studies. In addition, the outcome data suitable for propensity score matching analysis from the included ANNEXA-4 and ORANGE studies were limited to two outcomes of clinical relevance (length of hospital stay and 30-day mortality). The ERG notes from ClinicalTrials.gov that there is currently an ongoing RCT of andexanet alfa compared to usual care.[102] However, the ERG also notes that the RCT is restricted to ICH patients and is not expected to reach completion until 2023. The ERG therefore considers that there is still a need for RCT data on patients who would be eligible for andexanet alfa with non-ICH bleeds, and in particular GI bleeds given they are a common bleed with DOAC's.

Further UK specific data on andexanet alfa and for the clinical outcomes listed in the NICE final scope for 4F-PCC would also be beneficial to enable more robust comparisons of the interventions.

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10 APPENDICES

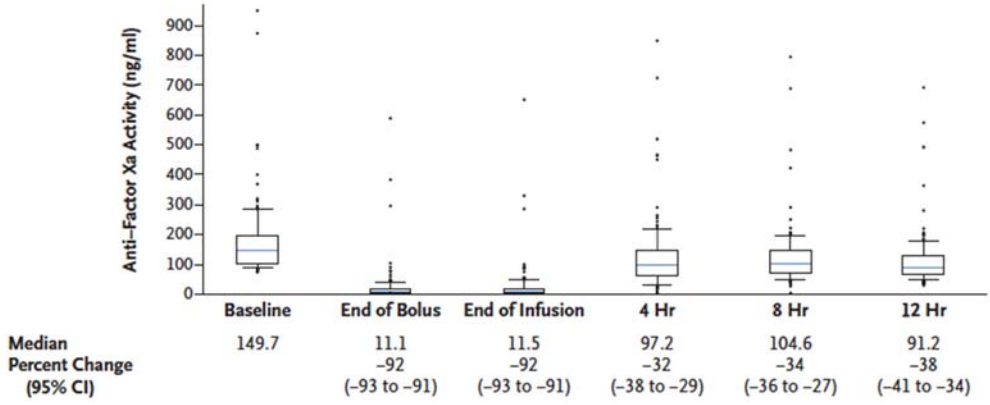
10.1 Additional efficacy outcomes from ANNEXA-4

10.1.1 Anti-fXa Activity

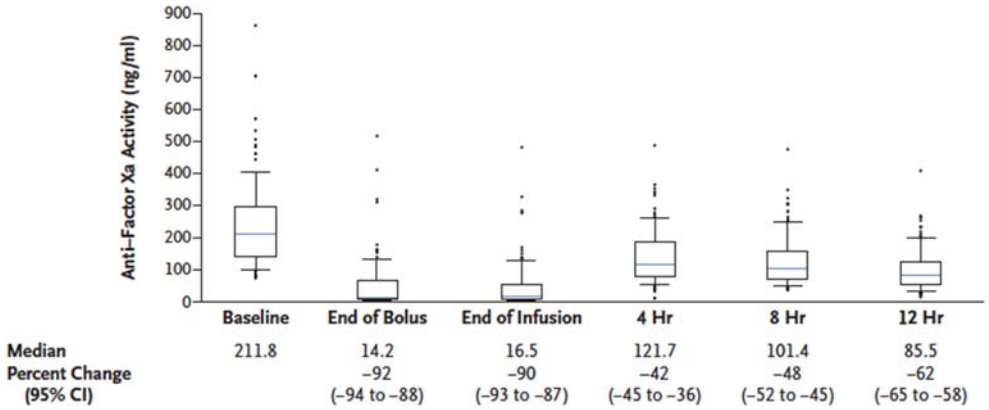
The ERG considers it important to highlight that the data discussed here relate to the efficacy population of ANNEXA-4 and therefore only includes patients who have baseline anti-FXa activity of at least 75 ng per millilitre (or ≥0.25 IU per millilitre for patients receiving enoxaparin) and confirmed major bleeding at presentation. The median anti-fXa activity (Figure 22 and Table 87) decreased by 92% (95% CI, 91–93) from baseline after administration of the bolus dose of andexanet alfa among patients receiving apixaban (n = 134) and also by 92% (95% CI, 88–94) among patients receiving rivaroxaban (n = 100) . There was a less marked decrease at 4, 8 and 12 hours after the end of the andexanet infusion dose compared to baseline, with a relative decrease from baseline of 32%, 34%, and 38% for apixaban and 42%, 48%, and 62% for rivaroxaban, respectively (Figure 22 and Table 87).

Figure 22. Anti-fXa Activity by FXa Inhibitor for the efficacy population (Reproduced from CS, Figure 11)

A. Patients Who Received Apixaban



B Patients Who Received Rivaroxaban



CI – confidence interval; Hr – hours
The median for each level of anti–FXa activity at each time point is marked as a horizontal line within the box. The top and bottom of the box denote the 75th and 25th percentiles, respectively, and the whiskers indicate the 90th and 10th percentiles. Outliers are shown as dots.

Source: Connolly et a, 2019[47]

Table 87. Summary for anti-FXa activity by FXa Inhibitor (apixaban & rivaroxaban) and bleed type (Safety Population) (adapted from company response to clarification question A9, Table 21)

Assessment Time	Statistic	Apixaban (ng/mL)				Rivaroxaban (ng/mL)			
		GI	ICH	Other	All Patients	GI	ICH	Other	All Patients
Baseline	Patients (N)	[redacted]							
	Mean (SD)	[redacted]							
	Median	[redacted]							
	Min, Max	[redacted]							
	Median 95% CI	[redacted]							
	25th, 75th Percentile	[redacted]							
End of bolus	Patients (N)	[redacted]							
	Mean (SD)	[redacted]							
	Median	[redacted]							
	Min, Max	[redacted]							
	Median 95% CI	[redacted]							
	25th, 75th Percentile	[redacted]							
End of infusion	Patients (N)	[redacted]							
	Mean (SD)	[redacted]							
	Median	[redacted]							
	Min, Max	[redacted]							
	Median 95% CI	[redacted]							
	25th, 75th Percentile	[redacted]							

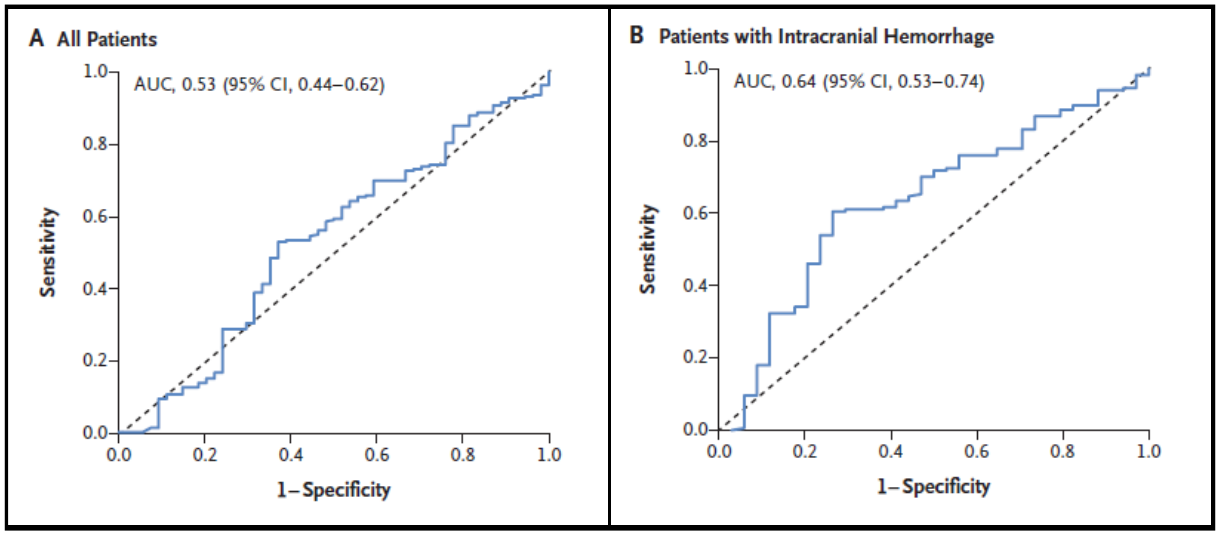
4 Hours	Patients (N)	[redacted]							
	Mean (SD)	[redacted]							
	Median	[redacted]							
	Min, Max	[redacted]							
	Median 95% CI	[redacted]							
	25th, 75th Percentile	[redacted]							
8 Hours	Patients (N)	[redacted]							
	Mean (SD)	[redacted]							
	Median	[redacted]							
	Min, Max	[redacted]							
	Median 95% CI	[redacted]							
	25th, 75th Percentile	[redacted]							
12 Hours	Patients (N)	[redacted]							
	Mean (SD)	[redacted]							
	Median	[redacted]							
	Min, Max	[redacted]							
	Median 95% CI	[redacted]							
	25th, 75th Percentile	[redacted]							

Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SD, standard deviation.
Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet alfa. Bleed type was adjudicated by the Endpoint Adjudication Committee.
Values >950 ng/mL were replaced with 950 ng/mL (the upper limit of quantitation). Values <4 ng/mL (or <0.10 IU/mL for enoxaparin) were replaced with 4 ng/mL (or 0.10 IU/mL) (the lower limit of quantitation), respectively.
The 95% CI for the median is based on distribution free method.
Patient 204002 was in the apixaban group, but was reported as the rivaroxaban group in the laboratory results. The patient is summarized in the apixaban group.

10.1.2 Relationship of Haemostatic Efficacy and Anti-fXa Activity

The relationship of haemostatic efficacy and anti-FXa activity following andexanet alfa was explored by the company and suggested no relationship for the whole ANNEXA-4 efficacy cohort (Figure 23). In contract, the magnitude of the reduction in anti-fXa activity was a predictor of haemostatic efficacy in the ICH subgroup (area under the ROC curve, 0.64; 95% CI, 0.53−0.74 [Figure 23]). The ERG considers it unclear when the anti-FXa levels were taken for these analyses and if they were consistent in all patients, therefore the ERG recommends caution when interpreting these results.

Figure 23. Receiver-Operating-Characteristic (ROC) curves for haemostatic efficacy in ANNEXA-4 (Reproduced from CS Document B, Figure 12)



AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic
Patients are included in the analysis if assessment of haemostatic efficacy was available and if the level of anti-fXa activity was available at baseline and during andexanet alfa treatment (at the end of administration of either the bolus or the infusion). The dashed line is a reference line indicating chance prediction. AUC denotes area under the curve.
Source: Connolly 2019[47]

The company reported that "*in both nonclinical and clinical studies, increases in anti-fXa activity correlate with decreases in thrombin generation*" and provided results in the CS for thrombin generation in rivaroxaban. However, the ERG also notes that thrombin generation was elevated in the majority of patients in the efficacy population at baseline even though all patients were taking FXa inhibitors. The company suggests that this may be a result of the general activation of the coagulation system in the setting of acute bleeding. [redacted]

Figure 24. Time course of thrombin generation in the efficacy population (Reproduced from CS Document B, Figure 13)

A. Rivaroxaban patients

B. Apixaban patients

Database lock date: 28Nov2018. The Efficacy Population includes all patients who received any amount of andexanet alfa, met clinical bleeding criteria, and had an anti-fXa level of ≥75 ng/mL (0.25 IU/mL for patients receiving enoxaparin).
Time course of ETP is shown as [median, 25th, 75th percentiles] at each time. -1 hour indicates the screening timepoint.
Endogenous Thrombin Potential values identified by the lab as "BMC (below measurement capacity)" were replaced with zeros.
The horizontal dashed line indicates the lower bound of the normal value for ETP of 1269 nM*min minus the SD of 230 as presented in the New England Journal of Medicine (2016), 375:1131-41.
Source ANNEXA-4 CSR[69]

10.2 ERG critique of included studies in company's SLR

Table 88. Overview of studies in individuals receiving a Factor Xa inhibitor requiring rapid reversal of anticoagulation.

	Study design	**N patients**	**Prior anticoagulant**	**intervention**	**outcomes**	**Assessment of potential comparability to ANNEXA-4/ relevance for this submission (YES/NO, reasons)**
ORANGE	Prospective cohort study, multi centre	372	76% Rivaroxaban 24% Apixaban	37% PCC 51% PCC	30-day mortality, hospital stay, thrombotic events	IPD data available – propensity score matching possible for

						mortality and hospital stay
Allison et al, 2016, Allison et al, 2018	Retrospective chart review, single centre	33	82% Rivaroxaban 18% Apixaban	4F- PCC	Hospital stay, mortality, blood products, haemostatic efficacy	Possibility of comparison of haemostatic efficacy and use of blood products.
Berger et al, 2016	Retrospective chart review, single centre	13	69% Rivaroxaban 31% Apixaban	4F- PCC	In hospital mortality, haemostatic efficacy	NO – abstract only, limited information and comparability of clinical outcomes, small sample size
Beyer-Westendorf et al, 2014	Prospective review of registry data, multicentre	59	100% Rivaroxaban	10.2% PCC	Thrombotic events, 30-day mortality	NO – small relevant patient population (6 patients with major bleed treated with PCC)
Grandhi et al, 2015	Retrospective chart review, single centre	18	89% Rivaroxaban 11% Apixaban	4F- PCC	Hospital stay, in hospital mortality, mRS	NO - small sample size, no outcomes comparable with ANNEXA-4 although 90-day mRS was reported.
Mao et al, 2016, Mao et al, 2017	Retrospective chart review, single centre	11	73% Rivaroxaban 27% Apixaban	FEIBA		NO – all patients received FEIBA
Stratman et al, 2015	Retrospective chart review, single centre	47	77% Rivaroxaban 27% Apixaban	4F- PCC	Hospital stay, mortality, thrombotic events, haematoma expansion	NO - Abstract only, limited information
Arachchillage et al, 2018	Retrospective cohort, single centre	40 40 264	12% Rivaroxaban 12% Apixaban 77% Warfarin	PCC	Major bleeds, 30-day mortality, re-bleeds, thromboembolic events, blood products	Possibility of comparison of re-bleeds, surgical control and use of blood products.
Barzilai et al, 2017	Retrospective cohort, single centre	53	9% Dabigatran 55% Rivaroxaban 36% Apixaban	PCC	Thrombotic events, 30-day mortality	NO - Abstract only, limited information
Dobesh et al, 2017	Retrospective cohort, single centre	23	48% Rivaroxaban 52% Apixaban	4F- PCC	Thrombotic events, 30-day mortality, blood products,	NO - Small sample size, no outcomes comparable

					haemostatic efficacy	with ANNEXA-4
Dybdahl et al, 2019	Retrospective cohort, two centres	62	50% Rivaroxaban 50% Apixaban	56% given PCC	Mortality, blood products, hospital stay, thrombotic events for subgroup given PCC	NO - no additional outcomes compared with ORANGE
Gerner et al, 2018	Retrospective cohort, multi centre	146	10% Dabigatran 75% Rivaroxaban 14% Apixaban	77 % given PCC	Haematoma expansion, mRS, blood products, 90-day mortality for subgroup given PCC	Possibility of comparison of haematoma expansion, no other outcomes comparable with ANNEXA-4
Kaplan et al, 2018	Retrospective cohort, single centre	22	36% Rivaroxaban 64% Apixaban	4F- PCC	In hospital mortality, thrombotic events, haemostatic efficacy	NO - Abstract only, limited information and small sample size
Majeed et al, 2017	Prospective cohort, multi centre	84	54% Rivaroxaban 46% Apixaban	PCC	Thrombotic events, 30-day mortality, haemostatic efficacy, blood products	Possibility of comparison of haemostatic efficacy
Schenk et al, 2018	Prospective cohort, single centre	13	100% Rivaroxaban	4F- PCC	Mortality, SAEs, re-bleeding	NO - small sample size
Schulman et al, 2018	Prospective cohort, multi centre	66	56% Rivaroxaban 44% Apixaban	4F- PCC	30-day mortality, haemostatic efficacy, hospital stay, thrombotic events	Possibility of comparison of haemostatic efficacy
Tao et al, 2018	Retrospective cohort, single centre	43	49% Rivaroxaban 51% Apixaban	4F- PCC	Thrombotic events, haemostatic efficacy, blood products	NO – no comparable clinical outcomes
Yoshimura et al, 2017	Prospective case series, multi centre	10	10% Dabigatran 70% Rivaroxaban 20% Apixaban	PCC	haematoma expansion, mortality, mRS	NO - small sample size
Abbreviations: PCC, prothrombin complex concentrate.						

10.3 Quality assessment of ANNEXA-4 and ORANGE

Table 89: Quality assessment of ANNEXA-4 (Adapted from CS Appendix D, Table 19)

ANNEXA-4				
	Company		**ERG**	
Section 1: Population	**Response**	**Comments**	**Response**	**Comments**

1.1 Is the source population or source area well described?	++	Patients from 63 centres in the US, Canada, Belgium, The Netherlands and the UK were recruited over the same time period (April 2015 through May 2018. From July 2016 through August 2017 only patients with intracranial haemorrhage were enrolled to enrich the study with these patients. After August 2017, patients with all types of bleeding except visible, musculoskeletal, or intraarticular bleeding were enrolled.)	++	
1.2 Is the eligible population or area representative of the source population or area?	+	Recruitment of individuals was briefly described in the published paper (i.e. patients presenting with acute major bleeding who had received apixaban, rivaroxaban, edoxaban, or enoxaparin within 18 hours), although the screening process was reported in the protocol. Due to the enrichment of patients with ICH following protocol amendment 4, however, the study included a higher proportion of patients with ICH (64%) than might be expected in the source population (i.e. a usual hospital setting). The sample size was large (n=352).	+	
1.3 Do the selected participants or areas represent the eligible population or area?	++	In this prospective study, 375 patients were screened of which 352 were enrolled, and are likely representative of the eligible population. Inclusion and exclusion criteria were defined.	++	
Section 2: Method of allocation to intervention (or comparison)				
2.1 Allocation to intervention (or comparison). How was selection bias minimised?	NA	Single arm study - all patients received andexanet alfa	NA	
2.2 Were interventions (and comparisons) well described and appropriate?	++	A clear description of the intervention is provided, with doses received reported. There was no comparator group.	++	
2.3 Was the allocation concealed?	NA	Single arm study - all patients received andexanet alfa	NA	
2.4 Were participants or investigators blind to exposure and comparison?	NA	Single arm study - all patients received andexanet alfa	NA	

2.5 Was the exposure to the intervention and comparison adequate?	++	All eligible (enrolled) patients were exposed to the intervention.	++	
2.6 Was contamination acceptably low?	NA		NA	
2.7 Were other interventions similar in both groups?	NA		NA	
2.8 Were there other confounding factors?	+	The authors did not address any potential confounding factors in their analyses.	+	At the clarification stage the company provided results based on location of bleed, ICH or GI, which will address one likely confounding factor. No other potential confounding factors were discussed or adjusted for.
2.9 Were all participants accounted for at study conclusion?	++	All the patients received andexanet alfa and were followed for at least 30 days or until death. The efficacy analysis population (n=254) included only patients who retrospectively met both of two criteria: baseline anti–factor Xa activity of at least 75 ng per milliliter (or ≥0.25 IU per milliliter for patients receiving enoxaparin) and confirmed major bleeding at presentation, as determined by the adjudication committee.	++	
2.10 Did the setting reflect usual UK practice?	++	This study was carried out in hospitals (but not further defined - although likely trauma centres), which would be a similar setting for this treatment in the UK.	+	The study is international with the possibility of differences in the setting between different countries compared with the UK although clinical experts reported it was generally comparable.
2.11 Did the intervention or control comparison reflect usual UK practice?	NA	At the time of the study the intervention was investigational and therefore not used in UK clinical practice.	NA	
Section 3: Outcomes				
3.1 Were outcome measures reliable?	++	Objective outcome measures were reported (including mortality, length of hospital stay). Anti–factor Xa activity was measured by means of a validated assay of factor Xa enzymatic activity. An independent adjudication committee reviewed each case to determine haemostatic	++	

		efficacy on the basis of predetermined criteria.		
3.2 Were all outcome measurements complete?	++	It appears that outcome measures were available for all patients.	++	
3.3 Were all important outcomes assessed?	++		++	
3.4 Were outcomes relevant?	++	Outcomes were relevant. The surrogate efficacy outcome reflects a direct measure of the treatment effect (reversal of anti-factor Xa activity).	++	The ERG considers one of the co-primary outcomes, change in anti–factor Xa activity not to be of direct clinical relevance, but other outcomes such as mortality and safety were also reported
3.5 Were there similar follow-up times in exposure and comparison groups?	NA		NA	
3.6 Was follow-up time meaningful?	++	Follow-up was 45 days	++	
Section 4: Analyses				
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?	NA	Single arm study	NA	
4.2 Was intention to treat (ITT) analysis conducted?	+	All 352 patients were included in the safety analysis, and 252 were included in the efficacy population (n=249 were included in the analysis of hemostatic efficacy).	-	The results for the efficacy population is of limited relevance to clinical practice as, although anti–factor Xa activity may be assessed in clinical practice, the results are unlikely to inform the treatment choice due to the time it takes to get the results and the urgency of intervention. However, the company provided outcome data for the safety population at the clarification stage.
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?	++	In the study protocol, the authors reported that a sample size of 162 efficacy evaluable patients will provide 80% power for a two sided 95% CI that is completely above 50% for the primary efficacy variable of effective haemostasis, demonstrating a response rate above 50% for that variable. It was estimated that ~30% of the safety population will have	++	

		anti-fXa activity <75 ng/mL and therefore not be included in the Efficacy Analysis Population. Additionally, it was estimated that up to 5% of patients will be inevaluable for reasons unrelated to andexanet alfa. Therefore, it was anticipated that up to 250 patients may have to be treated to achieve the requisite number of efficacy evaluable patients (this was achieved). The sample was adjusted to 350 patients in protocol amendment 4 (January 2017) to meet new regulatory requirements for sufficient numbers of patients for each factor Xa inhibitor and to have at least 120 patients with intracranial haemorrhage in the efficacy analysis population.		
4.4 Were the estimates of effect size given or calculable?	++	An effect size was presented for all outcomes.	++	
4.5 Were the analytical methods appropriate?	++	Data were reported as means (±SD) or medians and interquartile ranges for continuous variables and frequencies for categorical variables. The authors stated that they computed the percent change from baseline with a two-sided nonparametric confidence interval for the median. The rate of effective haemostasis was presented with an exact 95% confidence interval, as calculated with the use of the binomial test.	++	
4.6 Was the precision of intervention effects given or calculable? Were they meaningful?	++	Confidence intervals were provided. The effects were clinically meaningful.	++	
Section 5: Summary				
5.1 Are the study results internally valid (i.e. unbiased)?	+	The study is a single-arm study therefore it is impossible to determine effectiveness in the absence of a comparator.	+	Potential confounding has not been addressed in the study though the risk of attrition bias, detection bias, performance bias and reporting bias is deemed relatively low
5.2 Are the findings generalisable to the source population (i.e. externally valid)?	++	The population and study setting is reflective of that expected in UK clinical practice.	++	As the study population has been enriched in the proportion of ICH bleeds compared to the proportion expected in clinical practice, the results of the subgroups based on bleed location

				are reflective of the equivalent groups in UK clinical practice but the full trial population is less so.

Abbreviations: CI, confidence interval; ERG, evidence review group; GI, gastrointestinal; ICH, intracranial haemorrhage; SD, standard deviation.
Notes:
++ indicates that for that particular aspect of study design, the study has been designed or conducted in such a way as to minimise the risk of bias.
+ indicates that either the answer to the checklist question is not clear from the way the study is reported, or that the study may not have addressed all potential sources of bias for that particular aspect of study design.
− indicates those aspects of the study design in which significant sources of bias may persist.

Table 90: Quality assessment of ORANGE (Adapted from CS Appendix D, Table 20)

	ORANGE study			
	Company		**ERG**	
Section 1: Population	**Response**	**Comments**	**Response**	**Comments**
1.1 Is the source population or source area well described?	++	Patients were enrolled from 32 UK hospitals (across England, Scotland, Wales and Northern Ireland) over the same time period (October 1, 2013 and August 31, 2016).	++	
1.2 Is the eligible population or area representative of the source population or area?	++	Cases were reported consecutively and identified by clinical and research staff in participating hospitals from the emergency department, transfusion laboratory, pharmacy (if they stored haemostatic agents) and haematology doctors who were called to give medical advice on the management of these patients. This study was restricted to a sample of patients with prescribing data over two years ((July 2014 to June 2016).	++	
1.3 Do the selected participants or areas represent the eligible population or area?	++	In this prospective study, eligible patients over a defined period were selected for inclusion (within a larger study), but they are likely to represent the eligible population. Inclusion criteria were specified.	++	
Section 2: Method of allocation to intervention (or comparison)				
2.1 Allocation to intervention (or comparison). How was selection bias minimised?	NA	Observational study of results of different interventions for bleeding, including PCC – (and with data reported separately for those who received rivaroxaban and apixaban).	NA	

2.2 Were interventions (and comparisons) well described and appropriate?	++	Information on transfusion of any blood components (i.e. RBC, FFP, platelets and cryoprecipitate) for the management of bleeding was collected for up to 1 day after admission for bleeding. PCC administration was analysed based on the patient's weight and was categorised into None, Low (≤25IU/kg), Medium (26- 49IU/kg) and High (≥50IU/kg). Administration of other haemostatic agents, including rFVIIa, FEIBA, fibrinogen concentrate (FgC), tranexamic acid and vitamin K, was also recorded.	++	
2.3 Was the allocation concealed?	NA	Observational study - with some comparisons between treatment types	NA	
2.4 Were participants or investigators blind to exposure and comparison?	NA	Observational study	NA	
2.5 Was the exposure to the intervention and comparison adequate?	++	All eligible patients were exposed to an intervention - although not all patients received PCC (only 162/421 (38%))	++	
2.6 Was contamination acceptably low?	NA		NA	
2.7 Were other interventions similar in both groups?	NA		NA	
2.8 Were there other confounding factors?	+	The authors stated that patients underwent the normal course of treatment as directed by their clinicians and hospital protocols; at no point was their care altered for the purpose of this study.	+	The authors did adjust for bleeding site, bleeding severity and other potential confounders, but recognise that there remains scope for residual confounding.
2.9 Were all participants accounted for at study conclusion?	++	Outcomes up to 30 days were reported for 2,132 (97%) patients in overall population and 413 (98%) of those on a DOAC	++	
2.10 Did the setting reflect usual UK practice?	++	The study was carried out in UK hospitals.	++	
2.11 Did the intervention or control comparison reflect usual UK practice?	++	Patients underwent the normal course of treatment as directed by their clinicians and hospital protocols; at no point was their care altered for the purpose of this study.	++	
Section 3: Outcomes				

3.1 Were outcome measures reliable?	++	Objective outcome measures were reported (including mortality).	++	
3.2 Were all outcome measurements complete?	+	Unclear if all outcome measures were available for all patients.	+	
3.3 Were all important outcomes assessed?	+	Reversal of DOAC activity and haemostatic efficacy were not reported.	+	
3.4 Were outcomes relevant?	++	Outcomes reported were relevant	++	
3.5 Were there similar follow-up times in exposure and comparison groups?	NA		NA	
3.6 Was follow-up time meaningful?	++	Follow-up was 30 days	++	
Section 4: Analyses				
4.1 Were exposure and comparison groups similar at baseline? If not, were these adjusted?	NA		NA	
4.2 Was intention to treat (ITT) analysis conducted?	+	The authors stated that 413 (98%) patients were followed-up until discharge.	++	It is unclear why the company downgraded the rating for this item, 98% seems reasonable.
4.3 Was the study sufficiently powered to detect an intervention effect (if one exists)?	NA		NA	
4.4 Were the estimates of effect size given or calculable?	+	Hazard ratios (with 95% CIs) for time to death were presented for different interventions, including PCC.	++	It is unclear why the company downgraded the rating for this item.
4.5 Were the analytical methods appropriate?	++	Variables were summarised with frequencies/proportions, means/standard deviations or median/ interquartile ranges, as appropriate. Multivariable analysis was conducted for time to death, with different treatments as variables.	++	

4.6 Was the precision of intervention effects given or calculable? Were they meaningful?	+	Confidence intervals were provided. Use of interventions in the study may have been determined by the severity or type of bleed, therefore comparison of outcomes may not be meaningful. Interventions received were not significantly predictive of the cumulative risk of death "however there is arguably borderline evidence of the low dose regimen being associated with better outcomes"	++	Confidence intervals were provided. Comparisons between different interventions within the study are not of interest.
Section 5: Summary				
5.1 Are the study results internally valid (i.e. unbiased)?	+	The authors stated that "due to drug-specific assays not being performed to estimate the amount of DOAC onboard at the time of PCC administration and weight not necessarily being up to date, there remains scope for residual confounding." They also caveated "that cases who received PCC but did not have weight recorded were excluded from the analysis, but the findings were nonetheless based on 87% of the sample and therefore likely to be relatively robust."	+	Although regression analyses were performed to investigate several potential confounding factors, as the authors state, there is still scope for residual confounding.
5.2 Are the findings generalisable to the source population (i.e. externally valid)?	++	The study was carried out in a real-world clinical setting in the UK.	++	

Abbreviations: DOAC, direct oral anticoagulant; ERG, evidence review group.
Notes:
++ indicates that for that particular aspect of study design, the study has been designed or conducted in such a way as to minimise the risk of bias.
+ indicates that either the answer to the checklist question is not clear from the way the study is reported, or that the study may not have addressed all potential sources of bias for that particular aspect of study design.
− indicates those aspects of the study design in which significant sources of bias may persist.

10.4 Criteria for haemostatic efficacy in ANNEXA-4

Table 91. Rating system for effective haemostasis in ANNEXA-4 (adapted from CS document B, Table 11)

Rating	Description

Excellent (effective)	• Visible: Cessation of bleeding ≤ 1 hour after end of infusion and no plasma, coagulation factor or blood products (excludes pRBCs)
	• Muscular/skeletal: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤1 hour after the end of infusion; and the condition has not deteriorated during the 12-hour period
	• ICH:
	  • Intracerebral haemorrhage: ≤ 20% increase in haematoma volume compared to baseline on a repeat CT or MRI scan performed at both the 1- and 12-hour post infusion time points.
	  • Subarachnoid bleeding: ≤ 20% increase in maximum thickness using the most dense area on the follow-up vs baseline at both the 1- and 12-hour post infusion time points.
	  • Subdural haematoma: ≤ 20% increase in maximum thickness at both the 1- and 12-hour post infusion assessments compared to baseline.
	• Pericardial bleed. No increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion.
	• Intra-spinal bleed. No increase in haematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion.
	• Other (e.g., gastrointestinal bleeding, genitourinary bleeding): ≤ 10% decrease in both corrected haemoglobin/haematocrit at 12 hours compared to baseline.

Good (effective)	• Visible: Cessation of bleeding between > 1 and ≤ 4 hours after end of infusion and ≤ 2 units plasma, coagulation factor or blood products (excludes pRBCs).
	• Muscular/skeletal: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding >1 and ≤4 hours after end of infusion; and the condition has not deteriorated during the 12-hour period
	• ICH:
	  • Intracerebral haematoma: > 20% but ≤ 35% increase in haematoma volume compared to baseline on a repeat CT or MRI scan at +12-hour time point.
	  • Subarachnoid bleeding: > 20% but < 35% increase in maximum thickness using the most dense area on the follow-up at +12 hours vs baseline.
	  • Subdural haematoma: > 20% but < 35% increase in maximum thickness at +12 hours compared to baseline.
	• Pericardial bleed. < 10% increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion.
	• Intra-spinal bleed. < 10% increase in haematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion.
	• Other: > 10% to ≤ 20% decrease in both corrected haemoglobin/haematocrit at 12 hours compared to baseline.

Poor/None (not effective)	• Visible: Cessation of bleeding > 4 hours after end of the infusion and /or >2 units plasma, coagulation factor or blood products (excludes pRBCs)
	• Muscular/skeletal: No improvement by 4 hours after end of infusion and/or condition has deteriorated during the 12-hour period
	• ICH:
	  • Intracerebral haematoma: > 35% increase in haematoma volume on a CT or MRI compared to baseline on a repeat CT or MRI scan at +12-hour time point.
	  • Subarachnoid bleeding: > 35% increase in maximum thickness using the most dense area on the +12 hours vs at baseline.
	  • Subdural haematoma: > 35% increase in maximum thickness at +12 hours compared to baseline.
	• Pericardial bleed. 10% or more increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion.
	• Intra-spinal bleed. 10% or more increase in haematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion.
	• Other: > 20% decrease in both corrected haemoglobin/haematocrit.

Criteria based on 14-405 Protocol Amendment 2 Abbreviations: CT, computed tomography; GI, gastrointestinal; ICH, intracranial haemorrhage; MRI, magnetic resonance imaging, pRBCs, packed red blood cells. Source: Connolly 2019[47]	

10.5 ANNEXA-4 baseline characteristics

Table 92. Baseline characteristics of patients treated with apixaban or rivaroxaban in the ANNEXA-4 study (overall and for those with ICH or GI bleeds, Safety population) (adapted from CS document B, Table 14)

	All Patients (N=322)	**Patients with ICH (N=209)**	**Patients with GI (N=82)**
Age Distribution (years)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
$CHA_2DS_2VAS_C$ Score			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Time from Hospitalisation to Treatment (hr)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Medical History			
Atrial Fibrillation	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]
Hyperlipidaemia	[redacted]	[redacted]	[redacted]
Diabetes	[redacted]	[redacted]	[redacted]
Cancer	[redacted]	[redacted]	[redacted]
Evidence of Coronary Disease (CD)	[redacted]	[redacted]	[redacted]
Renal Dysfunction	[redacted]	[redacted]	[redacted]
Venous Thromboembolism[1]	[redacted]	[redacted]	[redacted]
Deep Vein Thrombosis	[redacted]	[redacted]	[redacted]
Pulmonary Embolism	[redacted]	[redacted]	[redacted]
Congestive Heart Failure	[redacted]	[redacted]	[redacted]
Stroke	[redacted]	[redacted]	[redacted]
Chronic Anaemia	[redacted]	[redacted]	[redacted]
Myocardial Infarction	[redacted]	[redacted]	[redacted]
Bleeding	[redacted]	[redacted]	[redacted]
Transient Ischemic Attack	[redacted]	[redacted]	[redacted]
Diverticulitis	[redacted]	[redacted]	[redacted]
Severe Peripheral Vascular Disease	[redacted]	[redacted]	[redacted]
Peptic Ulcer	[redacted]	[redacted]	[redacted]

Helicobacter Pylori	[redacted]	[redacted]	[redacted]
Inflammatory Bowel Disease	[redacted]	[redacted]	[redacted]
GI Angiodysplasia	[redacted]	[redacted]	[redacted]
Disseminated Intravascular Coagulation	[redacted]	[redacted]	[redacted]
Region			
North America	[redacted]	[redacted]	[redacted]
EU	[redacted]	[redacted]	[redacted]
United Kingdom	[redacted]	[redacted]	[redacted]
Dose of Andexanet Alfa			
Low (400 mg bolus + 480 mg IV)	[redacted]	[redacted]	[redacted]
High (800 mg bolus + 960 mg IV)	[redacted]	[redacted]	[redacted]
Baseline Daily Dose (mg) of Apixaban or Rivaroxaban			
Apixaban (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Rivaroxaban (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Time from Last AC to Treatment (hr)			
Apixaban or Rivaroxaban (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Apixaban (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Rivaroxaban (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Baseline Anti-fXa Activity (ng/mL)			
Apixaban (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Rivaroxaban (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]

Database lock date: 28Nov2018. The Safety Population included patients treated with any amount of andexanet alfa.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
[1]Patients with deep vein thrombosis or pulmonary embolism are counted.
Source: Portola data on file[48]
Abbreviations: CHA2DS2VASC, Congestive heart failure, hypertension, age ≥75, diabetes, stroke, vascular disease, age between 65-74, and female sex category; GI, gastrointestinal; ICH, intracranial haemorrhage; SD, standard deviation.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Andexanet alfa for reversing anticoagulation [ID1101]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Friday 6 December 2019** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Missing author in ERG reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 2. Missing author in 'This report should be referenced as follows: Edwards SJ, Wakefield V, Marceniuk G, Jhita T. Andexanet alfa for reversing anticoagulation: A Single Technology Appraisal. BMJ Technology Assessment Group, 2019.'	Believe it should read: Edwards SJ, Wakefield V, Marceniuk G, Jhita T, Karner, C. Andexanet alfa for reversing anticoagulation: A Single Technology Appraisal. BMJ Technology Assessment Group, 2019.	Minor amendment for ERG to confirm	We have made the suggested amendment.

Issue 2 Grammar - missing full stops

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 3. No full stops at the end of contributions of authors Gemma Marceniuk and Tracey Jhita	Believe it should read: Gemma Marceniuk: Economic lead. Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections.	Minor amendment for consistency	We have made the suggested amendment.

	Tracey Jhita	Economic support. Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections.		

Issue 3 Table of Abbreviations

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Page 12. A capital letter missing when providing HTA in full

Page 13. No abbreviation provided for IPD (Individual patient-level data)</td>
<td>Believe it should read:
<table>
<tr><th>Abbreviation</th><th>In full</th></tr>
<tr><td>HTA</td><td>Health technology assessment</td></tr>
</table>
Believe it should read:
<table>
<tr><th>Abbreviation</th><th>In full</th></tr>
<tr><td>IPD</td><td>Individual patient-level data</td></tr>
</table>
</td>
<td>Minor amendment for consistency

Minor amendment for clarity</td>
<td>We have made the suggested amendments.</td>
</tr>
</table>

Issue 4 ICH abbreviation used to refer to both intercranial haemorrhage and intracerebral haemorrhage

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 13. ICH given in full in the Table of Abbreviations as	Suggested amendment: To refer to intracranial haemorrhage as ICH	Major amendment for consistency and clarity	Thank you for highlighting this inconsistency. ICH for

Intracranial haemorrhage, but throughout the report ICH is defined as both intracranial haemorrhage and intracerebral haemorrhage Page 29. 'Intracerebral haemorrhages (ICHs)' Page 66. 'The ICH and IVH bleeds were associated with slightly fewer patients achieving excellent or good haemostatic efficacy (79.2%) compared to patients with a subdural haemorrhage (SDH) or subarachnoid haemorrhage (SAH; 89.5% and 90.9%, respectively).' Page 70. 'The ERG notes from data provided by the company in their clarification response that 74.3% of the deaths in the ICH subgroup were in patients with ICH or IVH, 20.0% in those with subdural bleeds and 5.7% in those with subarachnoid haemorrhage.' Page 108. Therefore, to account for the proportion of patients that would experience one of the most severe subtypes of ICH (intracerebral haemorrhage),	and intracerebral haemorrhage as intracerebral consistently throughout the report		intracranial haemorrhage in the abbreviations table is correct. We have amended the text on pages 29, 66 and 70.

Issue 5 Wording - role of andexanet alfa

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15. Wording of the sentence describing the role of andexanet alfa is unclear. Factor Xa-inhibiting direct oral anticoagulant should be referred to as an 'a' rather than 'the' and brackets used to explain rivaroxaban or apixaban types of DOACs referred to.	Suggested amendment: The company (Portola Pharmaceuticals) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the safety and effectiveness of andexanet alfa (Ondexxya®) for adults requiring urgent reversal of anticoagulation in case of uncontrolled or life-threatening bleeding, after treatment with a factor Xa-inhibiting direct oral anticoagulant (DOAC) (apixaban or rivaroxaban).	Minor amendment for clarity	Not a factual inaccuracy.

Issue 6 Grammar - Practice versus practise

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 17, 53, 55 and 57. The verb 'practise' is used as a noun which should be 'practice'.	Suggested amendment: Practise to be changed to practice on given pages	Minor amendment for consistency	We have made the suggested amendments.

Issue 7 Wording – thrombotic event rate

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18 and page 90: In the following text it should be noted	Suggested amendment:	Minor amendment for clarity	The text on page 18 and page 90 have been amended for

that the figures refers to the group of patients treated with apixaban or rivaroxaban (not the whole safety population as inferred. In terms of thrombotic events, [redacted] patients had a first thrombotic event by 30 days [redacted] [redacted]. The data on the restart of anticoagulation after andexanet alfa in ANNEXA-4 showed that [redacted] of patients restarted oral anticoagulation, [redacted]	In terms of thrombotic events, data for the population receiving apixaban or rivaroxaban were also presented. [redacted] patients had a first thrombotic event by 30 days [redacted]. The data on the restart of anticoagulation after andexanet alfa in ANNEXA-4 showed that [redacted] of patients restarted oral anticoagulation, [redacted]		clarity.

Issue 8 Grammar - missing space

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 20. Missing space between 200 and mg	Believe it should read: The list price of a 200 mg vial of andexanet alfa is £2,775 and the company have not proposed a patient access scheme (PAS) discount.	Minor amendment for consistency	We have made the suggested amendment on page 20. We have also made a similar amendment on page 118.

Issue 9 Wording - site of bleed in other bleeds subgroup

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 22. The wording is unclear it states site of bleed wasn't included as a covariate in the 'other bleeds' subgroup analysis. Site of bleed was stated and included as 'other bleed' but not as a more granular covariate.	Suggested amendment: However, the ERG notes that a more granular site of bleed than 'other bleeds' wasn't included as a covariate in the 'other bleeds' subgroup analysis as there was already a small sample size and the variety of other bleeds.	Minor amendment for clarity	Not a factual inaccuracy.

Issue 10 Wording - 'Other major bleeds' selection

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23. The statement 'Moreover, the NICE final scope does not limit 'other major bleeds' to the four types included in the company's economic analysis, and the ERG would emphasise that the results of the company's model only relate to intraocular, intraspinal, pericardial and retroperitoneal bleeds as opposed to the wider range of 'other major bleeds' seen in ANNEXA-4.'	Suggested amendment: Moreover, the NICE final scope does not limit 'other major bleeds' to the four types included in the company's economic analysis, and the ERG would emphasise that the results of the company's model only relate to intraocular, intraspinal, pericardial and retroperitoneal bleeds in an attempt to capture the wider range of 'other major bleeds' seen in ANNEXA-4.'	Following consultation with clinical experts and health economic experts.	Not a factual inaccuracy.

Issue 11 Wording - referring to ICH plus GI cohort

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23. ICH plus GI cohort is referred to ICH and GI this can be unclear when listing ICH and GI and ICH only cohorts	Suggested amendment: As such, the ERG considers the most robust estimates for cost-effectiveness are for the ICH plus GI and ICH only cohorts as it removes the uncertainty of assumptions needed to model 'other major bleeds'	Minor amendment for clarity	We have made the suggested amendment.

Issue 12 Wording - use of 'preferred population'

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23 and 99. The use of 'preferred population' can be confused with the 'preferred base case'.	Suggested amendment: However, the ERG acknowledges the NICE final scope is for the full population covered by the marketing authorisation and therefore consider all life-threatening or uncontrolled bleed events and critique the assumptions related to 'other major bleeds.	The term 'preferred' is also used to describe the ERGs base case. It implies the preferred base case does not include 'other bleeds'	Not a factual inaccuracy. There is no mention of the base case in either instance.

Issue 13 Wording - intracerebral haemorrhage scenario

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 24. This sentence 'To account for the proportion of patients that would experience one of the most severe subtypes of ICH (intracerebral haemorrhage) in the economic	Suggested amendment: "To account for the proportion of patients that would experience one of the most severe subtypes of ICH (intracerebral haemorrhage) in the economic analysis, the ERG asked the	Minor amendment for clarity	Not a factual inaccuracy.

analysis, the ERG asked the company to explore a scenario where intracerebral-specific mRS results (recorded in Øie et al. 2018 for standard care and ANNEXA-4 for andexanet alfa) are applied to the proportion of patients that experienced an intracerebral haemorrhage in ANNEXA-4, and the remaining proportion of patients in both treatment arms have mRS results equal to ANNEXA-4.' is very long and unclear.	company to explore a scenario where intracerebral-specific mRS results are weighted. That is applying the mRS results (recorded in Øie et al. 2018 for standard care and ANNEXA-4 for andexanet alfa) to the proportion of patients that experienced an intracerebral haemorrhage in ANNEXA-4, and the remaining proportion of patients in both treatment arms have mRS results equal to ANNEXA-4."		

Issue 14 Wording - relative reduction for paralysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 26. The use of the statement 'no reduction is more appropriate, if, conservative.'	Suggested amendment: Treatment with andexanet alfa results in a relative reduction for paralysis in intraspinal bleeds and blindness in intraocular bleeds of 0% compared to standard care. The ERG considers that in the absence of any evidence to substantiate a relative reduction of 25%, no reduction is conservative.	Minor amendment for clarity	Not a factual inaccuracy.

Issue 15 Wording - ERG preferred base case and alternative base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27. Referring to the statement 'In addition, using either the ERG's preferred or alternative base case assumptions (applying alternative mRS distributions)' it is unclear which the base case is being referred to.	Suggested amendment: In addition, using either the ERG's preferred (using intracerebral-specific mRS distributions) or alternative base case assumptions (assuming no treatment benefit in mRS), the benefits of andexanet alfa are derived from reductions in 30-day mortality compared to standard care for ICH and GI bleeds.	Minor amendment for clarity	We have made the suggested amendment for clarity.

Issue 16 Grammar - addition full stop

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42. Additional full stop	Suggested amendment: In addition, the ERG notes the company's concerns regarding differences in study location between ANNEXA-4 and ORANGE that may have impacted on the length of hospital stay of patients as 60% of ANNEXA-4 patients were located in North America and only 7% in the UK whereas ORANGE was a UK based study.	Minor amendment for consistency	We have made the suggested amendment.

Issue 17 Grammar - missing spacing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 49. Repetition there is no need to include 'given with andexanet alfa' and hyphens	Suggested amendment: In ANNEXA-A only low dose andexanet alfa	Minor amendment for consistency and clarity	We have made the suggested amendments.

when referring to dosage is inconsistent (400-g) with all other sections in the report.	was administered as a 400 mg intravenous bolus (30 mg per minute) in part 1 and as a 400 mg intravenous bolus followed by a continuous infusion of 4 mg per minute for 120 minutes (480 mg in total) in part 2. In ANNEXA-R only high dose andexanet alfa was administered, with part 1 comprising only an 800 mg intravenous bolus (30 mg per minute) and part 2 comprised an 800-mg intravenous bolus followed by a continuous infusion of 8 mg per minute for 120 minutes (960 mg in total).		

Issue 18 Link between hospital stay and mortality

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21, 84, 88 and 90. The statement 'length of hospital stay is likely to be intrinsically linked with mortality' is used throughout the report.	Suggested amendment: …there could be a relationship between length of stay and mortality.	No evidence provided to support previous statement.	Not a factual inaccuracy.

Issue 19 Incorrect cross-reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 53: there is an incorrect cross reference in the following statement: Baseline characteristics of the apixaban and rivaroxaban safety population, and the subgroups of patients with ICH or GI bleeds are	Believe it should read: Baseline characteristics of the apixaban and rivaroxaban safety population, and the subgroups of patients with ICH or GI bleeds are shown in Appendix 10.5, Table 92.	Minor amendment for clarity	We have made the suggested amendment.

shown in Appendix 0, Table 92.			

Issue 20 Description of power calculation in ANNEXA-4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 53. The incorrect population is applied to the required sample size for the power calculation. The actual number which provides 80% power is 162, which is what we were expecting would have been the number of efficacy evaluable patients. Accounting for 30% attrition due to anti-fXa threshold and 5% due to other factors, that gets us to ~250. So 230 efficacy evaluable patients is overpowered.	We would suggest removing the following sentences; The ERG notes that the apixaban and rivaroxaban combined subgroup (n = 230) falls just below the 250 required sample size to provide 80% power for the haemostatic efficacy primary outcome. The ERG notes that the power provided by a sample of 230 patients isn't reported in the CS but considers it important to highlight that underpowered studies that have statistically significant results may be biased.	This is factually incorrect	Thank you for this additional information. We have made the suggested amendment.

Issue 21 Interpretation of the haematoma expansion data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59. The following statement is a misinterpretation of the data: Only 119 patients had data at both 1 hour and 12 hours and of these, 74.82% had no additional haematoma expansion at 12 hours (haematoma volume remained ≤35% vs baseline).	We would suggest replacing the text with the following sentence; [redacted] who were stable at 1 hour [redacted], supporting durability of effect.	This is a misrepresentation of the data.	Thank you for highlighting this error. The text has been amended to reflect the data reported in Table 11 of the ERG report.

In fact, 89 of 93 patients (95.7%) who were stable at 1 hour continued to be stable at 12 hours, supporting durability of effect.			

Issue 22 Clarification of PCC administration timing

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 61. The ERG notes that [redacted] patients received 4F-PCC, [redacted] We would like to clarify that administration of PPC was after andexanet alfa.	The ERG notes that [redacted] patients received 4F-PCC, [redacted]	Clarification	Thank you for this additional information. We have made the suggested amendment.

Issue 23 Incorrect cross-reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 75. The cross reference in the table header is incorrect: Table 32. Summary of products received by the 145 PCC patients in the full before matching population in ORANGE (adapted from CS Document B, Table 28)	Believe it should read: Table 32. Summary of products received by the 145 PCC patients in the full before matching population in ORANGE (adapted from company response to clarification question A7, Table 18)	Minor amendment for clarity	We have made the suggested amendment.

Issue 24 Incorrect cross-reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 79. The cross reference in the table header is incorrect: Table 35. Mean and differences between relevant variables for patients receiving apixaban and rivaroxaban FXa inhibitors, in the whole cohort (adapted from company response to clarification question A23, Table 5)	Believe it should read: Table 35. Mean and differences between relevant variables for patients receiving apixaban and rivaroxaban FXa inhibitors, in the whole cohort (adapted from company response to clarification question A3, Table 5)	Minor amendment for clarity	We have made the suggested amendment.

Issue 25 Incorrect reference to ANNEXA-4

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 105. It is incorrectly stated 'For 'other major bleeds' the number of matches using propensity score matching was low (* patients in ANNEXA-4)'. There were 8 matches from ORANGE and 31 matches for ANNEXA-4.	Suggested amendment: For 'other major bleeds' the number of matches using propensity score matching was low (8 patients in ORANGE) and the company considered the results to be counterintuitive (adjusted 30-day mortality rate of 12.50% for standard care versus 16.13% for andexanet alfa) and therefore did not use it to inform the economic analysis.	Minor amendment for clarity	We have made the suggested amendment.

Issue 26 Incorrect cross-reference

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 99. there is an incorrect cross reference in the following statement: Furthermore, intraocular bleeds and intraspinal bleeds are associated with complications (blindness and paralysis, respectively) in the economic analysis and these complications incur larger long-term cost and quality of life decrements in patients who receive standard care compared to patients who receive andexanet alfa (see Sections 5.3.9.2 and 0).	Suggested amendment: Furthermore, intraocular bleeds and intraspinal bleeds are associated with complications (blindness and paralysis, respectively) in the economic analysis and these complications incur larger long-term cost and quality of life decrements in patients who receive standard care compared to patients who receive andexanet alfa (see Sections 5.3.9.2 and 5.3.10.3).	Minor amendment for clarity	We have made the suggested amendment.

Issue 27 Grammar

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 99. There is a ‘to’ missing before reiterate	Believe it should read: As such, the ERG considers it important to reiterate that the NICE final scope does not limit ‘other major bleeds’ to the four types included in the company’s economic analysis, and would emphasise that the results of the company’s model only relate to intraocular, intraspinal, pericardial and retroperitoneal bleeds as opposed to the wider range of ‘other major	Minor amendment for clarity	We have made the suggested amendment.

	bleeds' seen in ANNEXA-4.		

Issue 28 'Other major bleeds'

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 104. Use of the statement 'However, given that clinical experts consulted by the ERG do not consider patients with 'other major bleeds' to be eligible for andexanet alfa, the ERG does not see the value in exploring this scenario.'	Suggested amendment: 'However, given that clinical experts consulted by the ERG do not consider patients, not all UK clinical experts, with 'other major bleeds' to be eligible for andexanet alfa, the ERG does not see the value in exploring this scenario.'	Clinicians consulted by the company considered patients with 'other major bleeds' to be eligible for andexanet alfa.	This is not a factual inaccuracy as we refer to our experts and not the company's.

Issue 29 ERG critique of included studies in company's SLR

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 168. The ERG has stated there is possibility of comparing haemostatic efficacy in ANNEXA-4 with the studies by Schulman et al (2018) and Majeed et al. (2017. However, we would like to highlight that this would not be possible because follow up brain imaging not available.	Please can this be removed or changed to: NO - haemostatic efficacy was available but comparison with ANNEXA-4 would not be possible because follow up brain imaging not available.	Amendment for clarity	This is not a factual inaccuracy. Brain imaging is not the only marker of haemostatic efficacy.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft technical report

Andexanet alfa for reversing anticoagulation

This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1. Topic background

1.1 Disease background

- Anticoagulant therapy is used for preventing and treating thromboembolism across various clinical indications including treatment and secondary prevention of deep vein thrombosis (DVT), pulmonary embolism (PE), after orthopaedic surgery as well as prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation.
- Direct oral anticoagulant (DOACs) specifically inhibits components of the coagulation cascade such as factor Xa (apixaban, rivaroxaban, edoxaban) or thrombin (dabigatran).
- Major bleeding events are a serious risk associated with anticoagulants and antidotes are needed to reverse anticoagulation in the case of life-threatening bleeding.
- Major bleeding can occur spontaneously or as a result of trauma, complications of invasive procedures or other conditions.

1.2 Risk and burden of major bleeding events

- The International Society on Thrombosis and Haemostasis (ISTH) published a definition of major bleeding in non-surgical studies. A major bleed is defined as any of the following:
  - Haemoglobin drop higher than 2g/dL
  - Bleeding that is expected to be fatal and/or symptomatic bleeding that is intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular or retroperitoneal
  - Transfusion: More than 2 units of blood or packed red blood cells

- People who experience a major bleeding event are at an increased risk of or developing subsequent thrombotic events or death.
- The risk of death is especially high in people with intracranial haemorrhage (ICH) where 30-day mortality rates after major bleeding are reported to be up to 45%.

- ICH may also result in disability, which can be assessed by the modified Rankin scale (mRS).
- Gastrointestinal bleeding is also associated with increased mortality and morbidity.

1.3 The technology

- Andexanet alfa has a marketing authorisation for 'adult patients treated with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding'. It received a conditional marketing authorisation by the European Medicine Agency (EMA) which was granted in the interest of public health because the medicine addresses an unmet medical need.
- There is no reversal agent other than andexanet alfa approved to reverse the anticoagulant effects of direct FXa inhibitors.

1.4 Treatment pathway

- Treatment recommendations for urgent reversal of DOACs include general supportive measures (discontinue DOAC, mechanical compression, maintain diuresis) followed by antagonisation of anticoagulant effects with:
  - oral activated charcoal
  - specific reversal of anticoagulation effect (if available)
  - non-specific reversal of anticoagulant activity if specific antidote is not available or sufficient (may include prothrombin complex concentrate or recombinant factor VIIa)
- Lack of specific antidote for FXa inhibitors led to the off-label use of prothrombin complex concentrate (PCC) as a pro-haemostatic agent. PCCs include products that are approved for reversing the effects of warfarin.
- PCCs not specifically approved for use in FXa inhibitor related bleeding and they are associated with a potential risk of pro-thrombotic effects. There is a lack of robust evidence on the efficacy of PCCs to reverse effects of FXa inhibitors

although they are considered a treatment option in the absence of a specific reversal agent.

1.5 Decision problem

Table 1 Decision problem

	Final scope issued by NICE	Company submission
Population	Adults requiring urgent reversal of anticoagulation in case of uncontrolled or life-threatening bleeding, after treatment with a factor Xa-inhibiting direct oral anticoagulant (DOAC)	As per scope
Intervention	Andexanet alfa	As per scope
Comparators	Established clinical management of uncontrolled or life-threatening bleeding without andexanet alfa (including prothrombin complex concentrate with or without tranexamic acid)	Prothrombin complex concentrate (PCC)
Outcomes	The outcome measures to be considered include: • Requirement for blood products • Control of bleeding • Need for surgical control of bleeding or interventional radiology embolisation of bleeding vessel • Neurological outcomes (in people with intracranial bleeding) • Hospital stay • Mortality • Adverse effects of treatment (including thrombotic events) • Health-related quality of life	The following outcome for ANNEXA-4 was not pre-specified and analyses are not yet available: • Need for surgical control of bleeding or interventional radiology embolisation of bleeding vessel The following pharmacodynamic outcomes are key in demonstrating the reversal of anticoagulation: • Anti-fXa activity, unbound anticoagulant plasma levels and thrombin generation

1.6 Clinical evidence

Table 2 Andexanet alfa evidence - ANNEXA-4 trial

<table>
<tr><th colspan="5">ANNEXA-4 Trial</th></tr>
<tr><td>Study design</td><td colspan="4">Single-arm, open-label, prospective, multicentre Phase IIIb/IV trial (ongoing)</td></tr>
<tr><td>Population (n=352)</td><td colspan="4">People receiving a FXa inhibitor (apixaban, rivaroxaban, edoxaban, or enoxaparin) and presenting with acute major bleeding– 322 people received apixaban or rivaroxaban</td></tr>
<tr><td>Exclusion criteria (list not exhaustive)</td><td colspan="4">• Expected survival of less than 1 month
• People with ICH with any of the following: Glasgow coma score<7 or estimated intracerebral haematoma volume > 60cc as assessed by the CT (computerised tomography) or MRI (magnetic resonance imaging)</td></tr>
<tr><td>Intervention</td><td colspan="4">Andexanet alfa</td></tr>
<tr><td rowspan="6">Doses</td><td colspan="4">2 possible regimens of andexanet based on type and timing of last dose of FXa inhibitor received
<u>Low dose</u>: 400 mg initial IV bolus (30mg/min), then 4mg/min continuous IV infusion (120 minutes, 480 mg)
<u>High dose</u>: 800 mg initial IV bolus (30mg/min), then 8mg/min continuous IV infusion (120 minutes, 960 mg)</td></tr>
<tr><td rowspan="2">FXa Inhibitor</td><td rowspan="2">FXa Inhibitor Last Dose</td><td colspan="2">Timing of FXa Inhibitor Last Dose Before Andexanet alfa Initiation</td></tr>
<tr><td>< 8 Hours or Unknown</td><td>≥ 8 Hours</td></tr>
<tr><td rowspan="2">Rivaroxaban</td><td>≤ 10 mg</td><td>Low dose</td><td rowspan="4">Low dose</td></tr>
<tr><td>> 10 mg/ unknown</td><td>High dose</td></tr>
<tr><td rowspan="2">Apixaban</td><td>≤ 5 mg</td><td>Low dose</td></tr>
<tr><td>> 5 mg/ unknown</td><td>High dose</td></tr>
</table>

Outcomes	• Primary endpoint: Percent change in the anti-FXa activity and the rate of excellent or good haemostatic efficacy 12 hours after the andexanet alfa infusion (see table 4 below for definition of haemostatic efficacy) • Secondary endpoint: Assess relationship between primary endpoints, anti-FXa activity and haemostatic efficacy, to establish change in anti-FXa activity as a predictor of achievement of haemostatic efficacy • Exploratory endpoints included: Occurrence of re-bleeding on the same site within 24 hours of initial treatment, requirement for blood products (red blood cell transfusions, non-study prescribed blood products and haemostatic agents), neurological outcomes (Glasgow Coma Scale [GCS], modified Rankin score [mRS] and National Institute of Health Stroke Scale [NIHSS] in people with ICH. • Safety endpoint: 30-day all-cause mortality and overall safety
Protocol amendment	Protocol amendment 4: 1. Threshold time to determine a low vs high dose was changed (7 to 8 hours) 2. Specific doses of the last FXa inhibitor were added to determine a low vs high dose of andexanet alfa. 139 people were enrolled under Amendment 4 of the protocol.

Table 3 Criteria to define haemostatic efficacy in ANNEXA-4 (CS table 11 p.38)

Excellent (effective)	• Visible: Cessation of bleeding ≤ 1 hour after end of infusion and no plasma, coagulation factor or blood products (excludes pRBCs)
	• Muscular/skeletal: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤1 hour after the end of infusion; and the condition has not deteriorated during the 12-hour period
	• ICH:
	  • Intracerebral haemorrhage: ≤ 20% increase in haematoma volume compared to baseline on a repeat CT or MRI scan performed at both the 1- and 12-hour post infusion time points.
	  • Subarachnoid bleeding: ≤ 20% increase in maximum thickness using the most dense area on the follow-up vs baseline at both the 1- and 12-hour post infusion time points.
	  • Subdural haematoma: ≤ 20% increase in maximum thickness at both the 1- and 12-hour post infusion assessments compared to baseline.
	• Pericardial bleed. No increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion.
	• Intra-spinal bleed. No increase in haematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion.
	Other (e.g., gastrointestinal bleeding, genitourinary bleeding): ≤ 10% decrease in both corrected haemoglobin/haematocrit at 12 hours compared to baseline.

Good (effective)	• Visible: Cessation of bleeding between > 1 and ≤ 4 hours after end of infusion and ≤ 2 units plasma, coagulation factor or blood products (excludes pRBCs).
	• Muscular/skeletal: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding >1 and ≤4 hours after end of infusion; and the condition has not deteriorated during the 12-hour period
	• ICH:
	  • Intracerebral haematoma: > 20% but ≤ 35% increase in haematoma volume compared to baseline on a repeat CT or MRI scan at +12-hour time point.
	  • Subarachnoid bleeding: > 20% but < 35% increase in maximum thickness using the most dense area on the follow-up at +12 hours vs baseline.
	  • Subdural haematoma: > 20% but < 35% increase in maximum thickness at +12 hours compared to baseline.
	• Pericardial bleed. < 10% increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion.
	• Intra-spinal bleed. < 10% increase in haematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion.
	Other: > 10% to ≤ 20% decrease in both corrected haemoglobin/haematocrit at 12 hours compared to baseline.

Poor/non (not effective)	• Visible: Cessation of bleeding > 4 hours after end of the infusion and /or >2 units plasma, coagulation factor or blood products (excludes pRBCs)
	• Muscular/skeletal: No improvement by 4 hours after end of infusion and/or condition has deteriorated during the 12-hour period
	• ICH:
	  • Intracerebral haematoma: > 35% increase in haematoma volume on a CT or MRI compared to baseline on a repeat CT or MRI scan at +12-hour time point.
	  • Subarachnoid bleeding: > 35% increase in maximum thickness using the most dense area on the +12 hours vs at baseline.
	  • Subdural haematoma: > 35% increase in maximum thickness at +12 hours compared to baseline.
	• Pericardial bleed. 10% or more increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion.
	• Intra-spinal bleed. 10% or more increase in haematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion.
	Other: > 20% decrease in both corrected haemoglobin/haematocrit.

- 2 randomised controlled trials, ANNEXA-A and ANNEXA-R comparing andexanet alfa to placebo were conducted in healthy volunteers
- These studies showed a rapid reduction in anti-FXa activity and unbound inhibitor concentration within 2 to 5 minutes after bolus administration and in thrombin generation
- ANNEXA-A and ANNEXA-R supported the application for marketing authorisation but were not used in the economic model as it was conducted in healthy volunteers
- In absence of direct comparative evidence, an indirect treatment comparison was conducted to compare andexanet alfa (ANNEXA-4 trial) with 4F-PCC (ORANGE study).
- The ORANGE study was a UK-based, 3-year prospective cohort study that collected data from multiple hospitals on the presentation and clinical outcomes of patients admitted for a major bleeding event while on oral anticoagulant.

- Details of the ORANGE study are presented in the table below

Table 4 PCC evidence- ORANGE study

ORANGE study	
Study design	Prospective cohort study across multiple hospitals in UK (2013-2016)
Population (N=2,192)	Patient aged 18 years or over on oral anticoagulation therapy at the time when they developed major bleeding were eligible → 372 people developed a bleed on apixaban or rivaroxaban. Of these 372 people, 149 received PCC
Intervention	Normal course of treatment as directed by clinicians and hospital protocols (included PCC, tranexamic acid, vitamin K and FEIBA [Anti-inhibitor coagulant complex]) – Only results for PCC are used in the analysis
Outcomes	Clinical outcomes at 30 days, death or discharge Comorbidities, bleeding sites, haematological laboratory results, management of bleeding and first outcome up to 30 days

1.7 Key trial results

The ANNEXA-4 trial results included haemostatic efficacy, re-bleeding, requirement for blood products, neurological outcomes, hospital stay duration and need for surgical control of bleeding. These data were not included in the economic model and are reported in Appendix 1.

The safety objectives included the evaluation of the 30-day all-cause mortality. Deaths that occurred during the 30-day safety follow-up period were adjudicated by the Endpoint adjudication committee (EAC). The 30-day mortality observed in ANNEXA-4 are reported in the table below.

Table 5 ANNEXA-4 trial - Adjudicated reason for deaths at 30 days (Adapted from company submission Document B table 38)

		Patients with Apixaban or Rivaroxaban		
	[redacted]	[redacted]	[redacted]	[redacted]
Deaths [1], N	[redacted]	[redacted]	[redacted]	[redacted]
Reasons for death, N (%)				
Cardiovascular: Not Related to Bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Patients had TEs	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular: Related to Bleeding	[redacted]	[redacted]	[redacted]	[redacted]
Patients had TEs	[redacted]	[redacted]	[redacted]	[redacted]
Non-Cardiovascular	[redacted]	[redacted]	[redacted]	[redacted]
Patients had TEs	[redacted]	[redacted]	[redacted]	[redacted]
Uncertain	[redacted]	[redacted]	[redacted]	[redacted]
Unknown[2]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths within 30 days (%)	[redacted]	[redacted]	[redacted]	[redacted]

TE= Thrombotic events, [1] [redacted]

[2] Deaths of two patients were not adjudicated (as they occurred after the Day 30/45 visit)

Mortality at 30 days was also collected in the ORANGE study. The results for people who received apixaban and rivaroxaban and who were treated with PCC in the ORANGE study are reported in the table below.

Table 6 ORANGE study - mortality rates at 30 days

Patients with Apixaban or Rivaroxaban and treated with PCC	
	Deaths within 30 days (%)
Whole cohort ([redacted])	[redacted]
Patients with ICH ([redacted])	[redacted]
Patients with GI ([redacted])	[redacted]
Patients with other major bleeds ([redacted])	[redacted]

In absence of direct comparative evidence, an indirect treatment comparison was conducted to assess the comparative efficacy of andexanet alfa (ANNEXA-4 study) and 4F-PCC (ORANGE study) for the 30-day mortality and duration of hospital stay outcomes. Only 30-day mortality was used in the economic model.

The single-arm ANNEXA-4 study and the ORANGE study were compared using a propensity score matching analysis, to produce adjusted estimates of treatment effect and to replicate randomisation by identifying and comparing patients who had similar characteristics. Only patients receiving PCC in the ORANGE study were considered.

The covariates used for adjustment were selected based on clinical opinion about their effect on 30-day mortality: age, site of bleed (intracerebral, subarachnoid, subdural/epidural, GI-lower, GI-upper, GI-unknown or other), medical history of coronary artery disease, history of stroke, transient ischemic attack, atrial fibrillation, hypertension, diabetes, renal dysfunction, cancer.

Severity of bleed or volume of bleed could not be included as covariates because these were not collected in the ORANGE study.

The results of the propensity score matching analysis for 30-day mortality are reported in the table below.

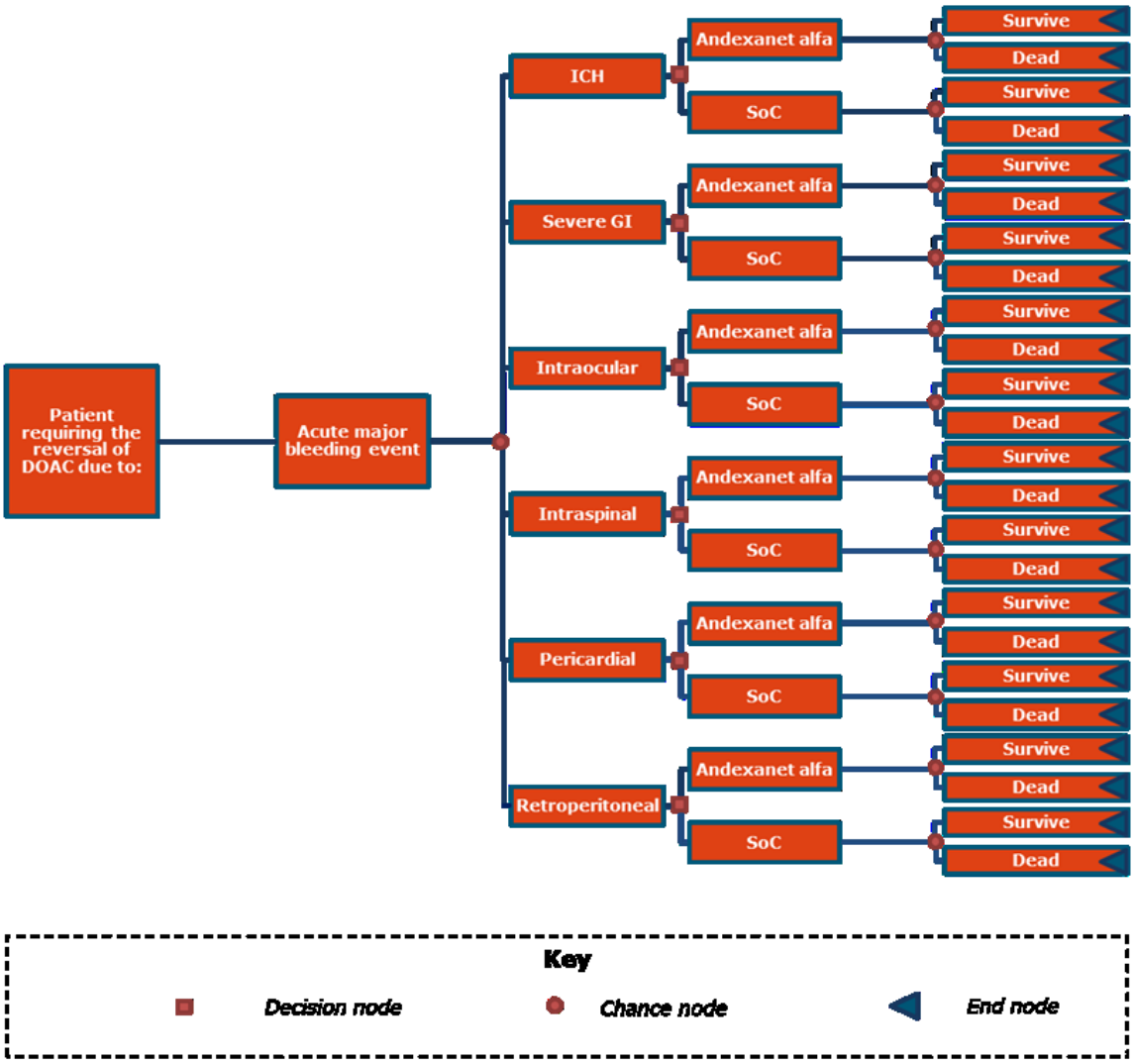
Table 7 Propensity score matching results for each cohort for 30-day mortality (based on ERG report, table 45)

Population	Number of matches	Adjusted 30-day mortality for PCC (%)	Adjusted 30-day mortality for andexanet alfa (%)
Whole population	[redacted]	[redacted]	[redacted]
ICH subgroup	[redacted]	[redacted]	[redacted]
GI subgroup	[redacted]	[redacted]	[redacted]
Other major bleeds (non-ICH/GI)	[redacted]	[redacted]	[redacted]

1.8 Model structure

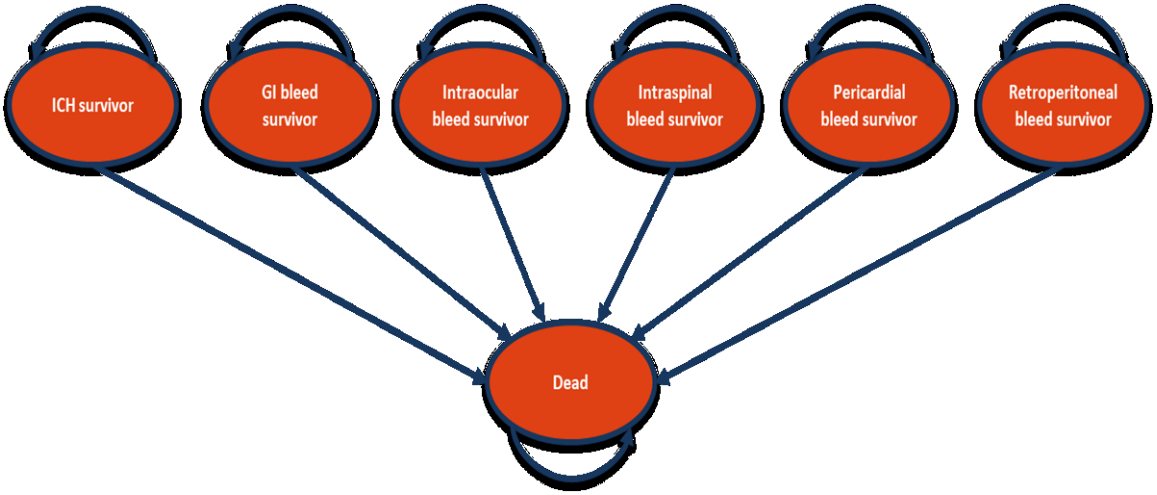
- Decision tree in the short-term to reflect the first 30 days of bleed management
- Patients entering the decision tree are assigned to health states based on bleed types (based on ANNEXA-4 baseline characteristics)
- Following intervention, patients are assigned to survivor or 'dead' state (based on indirect treatment comparison of ANNEXA-4 and ORANGE study)
- Patients surviving from the decision tree enter the Markov model in the long-term (after 30-day acute phase) in their respective survivor health states.
- Long-term mortality assumed to be worse than general population – modelled based on all-cause mortality adjusted with data from literature on people with ICH bleed for ICH survivors and atrial fibrillation for other bleed types survivors.

Decision tree



Source: Company submission, document B figure 14

Markov model

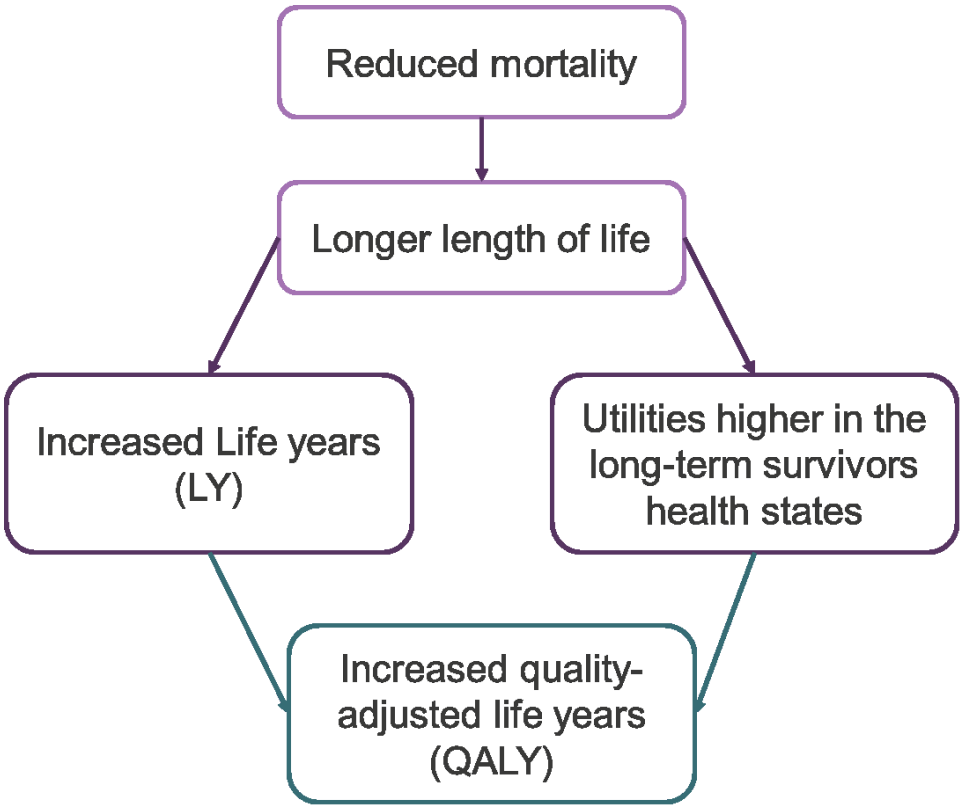


Source: Company submission, document B figure 15

1.9 Key model assumptions

Intervention	Andexanet alfa
Comparators	PCC
Mortality modelling	• Decision tree: Indirect treatment comparison between ANNEXA-4 and ORANGE study • Markov model: All-cause mortality adjusted with data from literature
Health-related quality-of-life	• Utility values based on literature – Clinical trial did not collect HRQoL data
Costs and resource use	• Wastage costs are applied • ICH rehabilitation duration and corresponding costs are assumed to be lifetime

1.10 **Overview of how quality-adjusted life years accrue in the model**



2. Summary of the draft technical report

2.1 In summary, the technical team considered the following:

Issue 1 **Who would be eligible for andexanet alfa in clinical practice?**

The company submitted results for patients in the whole cohort, patients with intracranial haemorrhage (ICH) and gastrointestinal (GI) bleedings and patients with ICH only. The intraspinal, intraocular, pericardial and retroperitoneal bleeds were classified as 'other major bleeds' in the submission. The ERG's preferred population for the estimation of clinical and cost effectiveness are the ICH and GI cohorts because of the lack of evidence and uncertainty for the effectiveness of andexanet in the types of bleeding classified under 'other major bleeds'. The technical team

welcome clinical opinion on which group would receive andexanet in clinical practice and whether the evidence in each cohort is sufficient to estimate the relative treatment effect for andexanet alfa.

Issue 2 **Generalisability and comparability of ANNEXA-4 and ORANGE studies**

ANNEXA-4 and ORANGE studies are used in an indirect treatment comparison. In ANNEXA-4, people were excluded if their survival was expected to be less than one month or if they had a GCS (Glasgow coma score) lower than 7, but it was not the case in the ORANGE study. The ANNEXA-4 trial was enriched with people with ICH. The comparability of the two studies is therefore questionable as people in ANNEXA-4 were selected using inclusion and exclusion criteria while ORANGE study included any people on oral anticoagulant with a major bleeding. Clinical opinion is sought on the generalisability and comparability of the studies.

Issue 3 **Uncertainty around the relative treatment effect of andexanet alfa compared to PCC**

ANNEXA-4 is a single-arm trial and ORANGE study is an observational study. This means that any comparison between them was 'unanchored' that is, there is no common comparator, and no randomisation to control for any bias. The studies were compared using a propensity score matching analysis, to produce adjusted estimates of treatment effect. The covariates used for adjustment were selected based on clinical opinion about their effect on 30-day mortality and whether they were statistically associated with treatment assignment. It was not possible to include severity of bleed or volume of bleed as covariates in the analysis as these were not collected in the ORANGE study. The ERG considers that it is a key limitation of the propensity score matching analysis as they may be important prognostic indicators and that there is inherent bias in the propensity score matching analysis. The ERG highlighted that the methods used to match patients from ORANGE to ANNEXA-4 leads to

the 30-day mortality with PCC possibly being underestimated because patients matched more than once had lower mortality rates. However, the technical team believes this is conservative as it is favourable for PCC against andexanet alfa. The technical team seeks clinical opinion about the plausibility of the results obtained through the propensity score matching analysis.

Issue 4 **Plausibility of the assumptions for modelling 30-day mortality, paralysis and blindness in people with 'other bleeds' in the whole cohort**

For other major bleeds, very limited evidence was available as a very small number of people experienced these bleeds in the trial. As a result, the clinical effectiveness and the modelling for these bleed types are based on strong assumptions. The company assumed a reduction of 25% in 30-day mortality between andexanet alfa and PCC for pericardial and retroperitoneal bleeds and a 25% reduction in paralysis and blindness for intraspinal bleed and intraocular bleed. However, these assumptions are not supported by evidence. The ERG believes that in the absence of evidence, a reduction of 0% should be assumed. The technical team welcome clinical opinion on the plausible mortality rate reduction between andexanet alfa and PCC in people with pericardial and retroperitoneal bleeds and the plausible reduction rate in paralysis and blindness following intraspinal and intraocular bleeds.

Issue 5 **Implementation of one-month modified Rankin scale (mRS) scores for long-term mortality, utilities and costs calculations for ICH survivors.**

Long-term mortality, long-term utilities and long-term costs for ICH survivors were calculated according to mRS scores at 30 days. The one-month mRS scores were based on ANNEXA-4 for andexanet alfa and on Øie et al. 2018 for PCC. In Øie et al. 2018, the proportion of people with mRS scores of 2 to 5 (moderate to severe disability and symptoms) was

higher than in ANNEXA-4. The ERG considers that there is no evidence to justify that ICH bleed survivors would have better mRS score when receiving andexanet alfa compared with PCC. Additionally, the ERG is concerned that the Øie et al. 2018 study represents patients with intracerebral haemorrhage only, which is the most severe type of ICH and therefore overestimates the severity of mRS in the standard care arm. The ERG's preferred scenario is that the mRS scores from Øie et al. 2018 are only applied to the proportion of patients who experience an intracerebral haemorrhage in ANNEXA-4 ([redacted]% of the ICH group) and the remaining proportion of patients in both arms have mRS scores from the ICH group of the ANNEXA-4 trial. The ERG included an alternative preferred scenario where the mRS scores are the same for andexanet alfa and standard care. The technical team seeks clinical opinion on whether mRS scores are expected to be different between intracerebral haemorrhage bleeds and other ICH types and in people treated with andexanet alfa and PCC.

Issue 6 Utilities calculations in ICH bleed survivors

Long-term health-related quality of life (HRQoL) for people who survived ICH bleed is calculated in the submission using the study from Fletcher et al. 2015 which quantifies the relationship between mRS scores and utility. The distribution of mRS scores from ANNEXA-4 and Øie et al. 2018 are used to calculate a weighted average utility score for each treatment arm for ICH survivors. The weighted mean scores were 0.53 for andexanet alfa and 0.42 for standard care, resulting in an increase of 0.11 for andexanet alfa. This increase is then applied to a 3-month post-acute care utility value of 0.61 obtained from NICE TA341 to calculate the andexanet alfa utility score of 0.72. The utility values used in the model for andexanet alfa and standard care are 0.72 and 0.61 respectively. The ERG considers that the weighted average utilities based on mRS scores (0.53 and 0.42) should be used as the source utilities for long-term ICH

survivors and believes that that the calculated utility value of 0.72 leading to a 0.01 difference between ICH survivors and general population is not plausible. The technical team agrees with the ERG regarding the fact that using the weighted utilities by mRS scores would be more consistent with the other inputs of the model.

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The ANNEXA-4 trial is a single arm trial of andexanet alfa with no comparator. The comparative effectiveness of andexanet alfa with other treatment is therefore uncertain.
- Protocol amendment 4 in ANNEXA-4: In the trial, the criteria for determining the dose of andexanet alfa was changed midway; under Amendment 4, the threshold time to determining low vs high dose andexanet was changed from 7 to 8 hours and the specific doses of the last FXa inhibitor were added to determine a low vs high dose. There were 139 patients enrolled under Amendment 4 of the study protocol. The impact of the resulting bias is unclear.

2.3 Taking these aspects into account, the range of the incremental cost-effectiveness ratio (ICER) for each cohort are reported in the tables below (ERG's base case and alternative base case).

Table 8 ICERs by population, ERG base case (based on ERG report, table 81)

Population	Company's corrected base case ICER, deterministic	ERG ICER, deterministic	ERG ICER, probabilistic (10,000 simulations)
Whole cohort	£12,489	£33,541	£33,735
ICH plus GI cohort	£18,663	£32,352	£32,217
ICH cohort	£18,640	£37,311	£37,216
Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin score; QALYs, quality adjusted life years.			

Table 9 ICERs by population, ERG alternative base case (based on ERG report, table 82)

Population	Company's corrected base case ICER, deterministic	ERG ICER, deterministic	ERG ICER, probabilistic (10,000 simulations)
Whole cohort	£12,489	£28,997	£29,297
ICH plus GI cohort	£18,663	£27,834	£27,754
ICH cohort	£18,640	£30,193	£30,037
Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin score; QALYs, quality adjusted life years.			

2.4 The committee will assess if the technology is considered innovative. It is the only agent licensed for the reversal of apixaban and rivaroxaban in case of life-threatening bleeding events. Andexanet received conditional marketing authorisation by the EMA as it addresses an unmet need and the benefit of immediate availability outweighs the risk from less comprehensive data than normally required.

2.5 No equality issues were identified.

3. Key issues for consideration

Issue 1 – Who would be eligible for andexanet alfa in clinical practice?

Background/description of issue	• The ANNEXA-4 trial was conducted in people receiving a FXa inhibitor (rivaroxaban, apixaban, edoxaban, or enoxaparin) and presenting with acute major bleeding. • The marketing authorisation for andaxanet alfa is only for bleeding related to apixaban or rivaroxaban. The submission was primarily based on the subgroup of people who had received apixaban or rivaroxaban in the ANNEXA-4 trial as this was considered to be the most relevant population to the marketing authorisation and NICE final scope. **Populations for cost-effectiveness modelling** • The company calculated incremental cost-effectiveness ratios (ICERs) for 3 cohorts 1. patients who had had any of the following types of acute major bleed (described as the whole cohort): intracranial haemorrhage (ICH), severe gastrointestinal (GI) bleed, intraspinal bleed, intraocular bleed, pericardial bleed and retroperitoneal bleeds. The last four in this list were classified as 'other major bleeds'. 2. an ICH and severe GI bleed cohort: patients with either ICH or severe GI bleed 3. an ICH cohort: patients with ICH only • The ERG highlighted that the NICE final scope does not limit major bleeds to the types included in the company's economic analysis. **Other major bleeds within the whole cohort** • To inform the proportion of people who experienced 'other major bleeds', the company used the safety population of the ORANGE study. The company assumed that intraspinal, intraocular, retroperitoneal and pericardial bleeds were all within the 'other major bleeds' of the ORANGE study and in equal quantity. • The ERG is concerned regarding the number of intraocular and intraspinal bleeds included in the economic model (based on ORANGE study and assumptions) compared with the

	number recorded in ANNEXA-4 trial. In ANNEXA-4, intraocular bleeds and intraspinal bleeds represented 0% and 6% of 'other major bleeds' while in the economic model, they represented 25% of 'other major bleeds'. • These bleeds are associated with long-term complications such as paralysis and blindness, incurring higher long-term costs and quality of life decrement for people receiving standard of care, and subsequently favouring andexanet alfa. • The ERG's preferred population is ICH and GI cohort because of the lack of evidence and uncertainty for the 'other major bleeds' (See also Issue 3 and 4). **Proportion of ICH bleeds included in the trial** • In the apixaban and rivaroxaban subgroup of ANNEXA-4 (N=322), the site of bleed was intracranial haemorrhage (ICH) for [redacted] patients ([redacted]%), gastrointestinal (GI) for [redacted] patients ([redacted]%), [redacted] for [redacted] patients and other sites for the remaining [redacted] patients. • The trial population was enriched with people with intracranial haemorrhage (ICH) under Amendment 4 because ICH bleed is associated with high mortality. The population of ANNEXA-4 is presented as a high-risk population by the company given that there is an artificially high proportion of patients with ICH.
Why this issue is important	The type of bleed is expected to impact the mortality and costs, and cost-effectiveness results vary between the cohorts. The population of interest is crucial for decision-making.
Questions for engagement	1. In clinical practice, who would be eligible for andexanet alfa (any major bleed, ICH and GI bleeds, ICH only)? Would types of acute bleed other than those included in the company's analysis be important in considering the role of anticoagulant reversal. 2. Is the evidence submitted in each cohort sufficient to estimate the relative treatment effect of andexanet alfa (whole cohort, ICH and GI, ICH only)? 3. Is it appropriate to amalgamate different types of bleed into a single 'whole cohort' for the purposes of estimating the clinical and cost effectiveness of andexanet alfa? If so: a. Is it plausible to assume that 'other major bleeds' are mainly composed of intraspinal, intraocular, pericardial and retroperitoneal bleeds?

	b. Is the company's assumption of equal proportion of intraspinal, intraocular, pericardial and retroperitoneal bleeds within 'other major bleeds' appropriate? c. Are the proportions of bleed types in ANNEXA-4 (■% of ICH, ■ % of GI and ■ % of other major bleeds) representative of clinical practice? 4. Is it appropriate to combine ICH and GI bleeds in a single subgroup? Should the ICER for GI bleeds be calculated separately?
Technical team preliminary judgement and rationale	The technical team consider that ICH is likely to be an important indication for andexanet alfa, but people with other types of life-threatening bleed may also benefit from this reversal agent. It would welcome clinical opinion on who would be eligible to andexanet alfa in clinical practice and how the clinical and cost-effectiveness might be estimated given the limitations in the evidence. The technical team would like to see some exploration of the potential benefits of andexanet alfa in different kinds of bleed, particularly in GI bleeds.

Issue 2 – Generalisability and comparability of ANNEXA-4 trial and ORANGE study

Background/description of issue	• The ANNEXA-4 study is a single-arm trial and the ORANGE study is an observational study. The ORANGE study is used in the company's submission to compare the treatment effect of andexanet alfa to PCC. • In the ANNEXA-4 trial, people were excluded if their survival was expected to be less than one month or if they had low GSC score (<7) while these criteria were not used in the ORANGE study. Therefore, the comparability of the two studies and more specifically the comparison of the 30-day mortality results is questionable. • The ANNEXA-4 trial was enriched with people with ICH bleed under Amendment 4. • In the ORANGE study, severity of bleed or volume of bleed at baseline was not reported.
Why this issue is important	The indirect treatment comparison is based on the ANNEXA-4 and ORANGE studies. The comparability of the two studies is questionable as people in ANNEXA-4 were selected using

	inclusion and exclusion criteria while ORANGE study included any people on oral anticoagulant with a major bleeding
Questions for engagement	1. In ANNEXA-4, how was the exclusion criterion 'survival expected to be less than 1 month' defined? Is this in line with clinical practice? 2. What impact do the exclusion criteria in ANNEXA-4 have on the reliability of the propensity score matching analysis (see issue 3)? 3. How were the criteria used to assess haemostasis in the trial developed (see Table 3 of this technical report)? Are these criteria in line with clinical practice?
Technical team preliminary judgement and rationale	There is uncertainty around the survival benefits associated with andexanet alfa in the absence of direct comparative evidence. The ANNEXA-4 trial and ORANGE study may not be directly comparable.

Issue 3 – Uncertainty around the relative treatment effect of andexanet alfa compared to PCC

Background/description of issue	• A propensity score matching analysis was deemed feasible and patients from ORANGE study were matched to ANNEXA-4 to estimate adjusted 30-day mortality for each treatment.
	• The covariates used for adjustment were selected based on clinical opinion about their effect on 30-day mortality:
	  ○ age
	  ○ site of bleed (intracerebral, subarachnoid, subdural/epidural, GI-lower, GI-upper, GI-unknown or other)
	  ○ medical history of coronary artery disease
	  ○ history of stroke,
	  ○ transient ischemic attack,
	  ○ atrial fibrillation,

	○ hypertension, ○ diabetes, ○ renal dysfunction, ○ cancer • Severity of bleed and volume of bleed could not be included as covariates because these were not collected in the ORANGE study. The ERG considers that it is a key limitation as they may be important prognostic indicators. • Two potential sources of bias were identified when comparing ANNEXA-4 and ORANGE studies: ○ differences in population's characteristics due to inclusion/exclusion criteria which could not be adjusted for as they were not reported in both studies ○ omission of reported data on covariates in one study • Patients from the ORANGE study were matched to the ANNEXA-4 patients, but no restriction was applied on the maximum number of times an individual could be matched. . [redacted]The ERG considers that it is a limitation and may have a big impact on the results for the 30-day mortality, [redacted] • Severity and volume of bleed could not be included in the analysis because it was not reported in the ORANGE study. • The ERG noted that there were differences remaining between andexanet alfa and PCC after propensity score matching for several characteristics (for example, higher proportion of people with subarachnoid ICH with PCC compared with andexanet alfa after matching). It is rarely possible to account for all possible effect-modifiers and prognostic factors and therefore this type of analysis is subject to inherent bias.

	• The results of the analysis suggest that 30-day mortality rates are lower with andexanet alfa compared with PCC in the whole cohort, the ICH and GI cohort and ICH cohort (see Table 7, page 9 of this report). [redacted] • A scenario was tested where the 30-day mortality with andexanet alfa was assumed to be the same as for PCC for all bleeds. This increased this ICER for all cohorts: £26,499/QALY for the whole cohort, £52,281/QALY for the ICH and GI cohort and £39,697/QALY for the ICH only cohort.
Why this issue is important	The comparative effectiveness of andexanet alfa and PCC is based on this analysis and used in the base-case analysis to inform the cost-effectiveness of andexanet alfa. The main driver of the model is the 30-day mortality.
Questions for engagement	1. Are the results of the propensity score matching analysis for 30-day mortality (lower with andexanet alfa than PCC, see Table 7) plausible and representative of what would be expected in clinical practice? 2. Given the exclusion of known prognostic factors such as severity and volume of bleed as covariates for adjustment, how suitable are the results of the propensity score matching for decision making?
Technical team preliminary judgement and rationale	The propensity score matching analysis is associated with inherent bias due to data availability and differences between studies, especially in that it was unable to include the severity and volume of bleed as covariates. The ERG highlighted that the methods used to match patients from ORANGE to ANNEXA-4 leads to the 30-day mortality with PCC being probably underestimated because patients matched more than once had lower mortality rates in GI cohort and other major bleeds. However, the technical team believes this is conservative as it favours PCC against andexanet alfa.

Issue 4 - Plausibility of the assumptions for modelling 30-day mortality, paralysis and blindness in people with 'other major bleeds' in the whole cohort

Background/description of issue	Assumption of 25% reduction in 30-day mortality in people with 'other major bleeds'
	• The propensity score matching analysis results were used to inform the 30-day mortality rate for ICH and GI bleeds but for 'other major bleeds', the company did not use it as the number of matches using this analysis was low ([redacted] patients for PCC) and considered that the results were counterintuitive (mortality rate was [redacted] with andexanet alfa than with PCC). • To inform the 30-day mortality for other major bleeds, the company set the mortality to zero in both treatment arms for intraocular and intraspinal bleeds, based on clinical opinion. For pericardial and retroperitoneal bleeds, the company assumed that andexanet alfa would provide a 25% reduction in the risk of death observed in ORANGE. • The ERG is concerned that the modelling of 30-day mortality is based on assumptions without a clear clinical rationale. The company stated that this assumption was a conservative estimate compared to the relative reductions observed in the propensity score matching analysis [redacted] and that the relative reduction of 25% was confirmed by clinical expert and was tested in scenario analyses where relative reduction ranged from [redacted] to [redacted]. • The ERG considers that the scenario of no reduction is more appropriate and conservative as there is no evidence to justify the 25% reduction in 30-day mortality. • Additionally, the ERG highlighted that the risk of death from ORANGE was not limited to pericardial and retroperitoneal bleeds as the company used the result from the propensity score matching analysis which is based on all 'other major bleeds', adding uncertainty around 'other major bleeds'. • The ERG tested a scenario where the mortality rate was the one obtained in the propensity score matching analysis ([redacted] for PCC and [redacted] for andexanet alfa), but this had small impact on the ICER (from £11,636 to £11,817).

	Assumption of 25% reduction in paralysis and blindness in people with intraspinal and intraocular bleeds • The company also assumed that andexanet alfa would reduce the occurrence of paralysis and monocular blindness by 25%, which increases the HRQoL of people with andexanet alfa compared to standard care. This assumption is applied to intraspinal and intraocular bleeds included in 'other major bleeds'. • At clarification, the company justified this assumption by the fact that it is in line with the assumption on reduced 30-day mortality. • However, the assumption of 25% reduction in 30-day mortality is also an assumption and there is no evidence to support this statement. • The ERG considers that the assumption of 25% reduction in paralysis and monocular blindness is not supported by evidence and assuming no relative reduction is a more appropriate and conservative scenario.
Why this issue is important	Estimates of mortality, incidence of paralysis and blindness in people with 'other major bleeds' are based on assumptions that are favourable to andexanet alfa but are not supported by any evidence. Changing the relative reduction in mortality from 25% to 0% increases the ICER for the whole cohort by around £1,000 and changing the reduction in paralysis and monocular blindness increases the ICER by around £7,000.
Questions for engagement	1. Is the assumption of a 25% relative reduction in mortality following pericardial and retroperitoneal bleeds between andexanet alfa and PCC plausible? 2. Is the assumption of a 25% relative reduction in paralysis and monocular blindness following intraspinal and intraocular bleeds between andexanet alfa and PCC plausible? 3. Is it reasonable to assume no relative reduction in 30-day mortality, paralysis and monocular blindness following other major bleeds between andexanet alfa and PCC? 4. Is it reasonable to set the 30-day mortality to zero in both treatment arms for intraocular and intraspinal bleeds?

	5. The “Other major bleeds” (non-ICH/GI) subgroup has a higher adjusted 30-day mortality for andexanet alfa [redacted]% compared to [redacted]% for PCC while for the other subgroups the mortality rate for andexanet alfa is lower- are these results reliable?
Technical team preliminary judgement and rationale	The company’s assumption of 25% reduction in mortality, paralysis and blindness is not based on any evidence and may be optimistic. The ERG’s assumption of 0% reduction is more conservative although it may underestimate the benefit of andexanet alfa in people experiencing other major bleeds. The technical team welcome clinical opinion on a plausible mortality rate reduction between andexanet alfa and PCC in people with in pericardial and retroperitoneal bleeds and a plausible reduction in paralysis and blindness following other major bleeds.

Issue 5 - Implementation of one-month modified Rankin scale (mRS) scores for long-term mortality, utilities and management costs calculations for ICH survivors

Background/description of issue	• The severity of ICH bleeds and neurological outcomes after ICH bleeds are reflected using the mRS scores which measure the degree of disability for daily activities or dependence of people who had a stroke or other causes of neurological disability. The scale rank from 0 (no symptoms at all) to 6 (dead). • Long-term mortality, long-term utilities and long-term management costs for ICH survivors were calculated according to mRS scores at one month, which were based on the ANNEXA-4 for andexanet alfa and on Øie et al. 2018 for PCC. **ANNEXA-4 modified Rankin scores vs intracerebral-specific modified Rankin scores from Øie et al. 2018** • The company assumed that the scores between the ANNEXA-4 study and Øie et al. 2018 (intracerebral-specific mRS scores) were comparable, because of paucity of data in people receiving PCC.

	• In Øie et al. 2018, the proportion of people with mRS scores of 2 to 5 (moderate to severe disability and symptoms) was higher than in ANNEXA-4, while proportion of people with mRS scores of 0 and 1 (no symptoms or no significant disability) was higher in ANNEXA-4 than in Øie et al. 2018. • The ERG considers that there is no evidence to justify that ICH bleed survivors would have better mRS score when receiving andexanet alfa compared with standard of care. Additionally, the ERG is concerned that the Øie et al. 2018 study represents patients with intracerebral haemorrhage only, which is the most severe type of ICH and therefore overestimates the severity of mRS in the PCC arm. The ERG noted that in the ANNEXA-4 trial, [redacted] • According to company's clinical experts, the rapid reversion of anticoagulant effects will have benefits on the hematoma expansion, prevent further irreparable damages to the brain and as a result provide improved ICH morbidity outcomes. • As Øie et al. 2018 study was conducted in patients with intracerebral haemorrhage only and no other subtypes of ICH were included, the ERG's preferred scenario is where the mRS scores from Øie et al. 2018 are only applied to the proportion of patients who experience an intracerebral haemorrhage in ANNEXA-4 (that is, [redacted]% of ICH subgroup) and the remaining proportion of patients in both arms have mRS scores from the ICH subgroup of ANNEXA-4 trial. This is fed into long-term mortality, utility and costs calculations. • The ERG acknowledges that mRS scores from ANNEXA-4 applied to non-intracerebral ICH survivors actually include all subtypes of ICH. However, the ERG considers it as key scenario to estimate the ICER and reflect accurately the mRS scores associated with intracerebral haemorrhage. • The ERG included an alternative scenario where the mRS scores were the same for andexanet alfa and PCC. This scenario also increased the ICER • The results of the 2 scenarios are reported in the table below:

<table>
<tr><td></td><td>
<table>
<tr><td></td><td>Corrected base-case</td><td>Scenario using intracerebral-specific mRS scores</td><td>Scenario using same mRS scores for andexanet and PCC</td></tr>
<tr><td>Whole cohort</td><td>£12,489/QALY</td><td>£22,039/QALY</td><td>£17,785/QALY</td></tr>
<tr><td>ICH plus GI</td><td>£18,663/QALY</td><td>£32,837/QALY</td><td>£28,277/QALY</td></tr>
<tr><td>ICH only</td><td>£18,640/QALY</td><td>£38,654/QALY</td><td>£31,377/QALY</td></tr>
</table>
</td></tr>
<tr><td>Why this issue is important</td><td>People with ICH bleed is a key subgroup of this appraisal. ICH mortality rate, long-term management costs and long-term utilities are the main drivers of the model. Estimating these inputs accurately is essential for a robust estimate of the ICER.</td></tr>
<tr><td>Questions for engagement</td><td>1. How different are the ICH subtypes in terms of morbidity and mortality? Do people surviving intracerebral haemorrhage have worse morbidity outcomes and mRS scores than people with other ICH subtypes?
2. In clinical practice, do ICH bleed survivors have better mRS scores at 30 days after the bleeding event when receiving andexanet alfa compared with PCC?
3. Is it plausible to assume that andexanet alfa will improve ICH morbidity and mortality and as a result mRS scores at 30 days after the bleeding event?</td></tr>
<tr><td>Technical team preliminary judgement and rationale</td><td>The technical team considers that in the absence of other data, the Øie et al. 2018 study is a good source for mRS scores in PCC, if it can be assumed that:
- intracerebral haemorrhage survivors have similar mRS scores to other ICH bleeds survivors.
- people with andexanet alfa will have better mRS scores than with PCC
If the ERG’s concern about Øie et al. 2018 overestimating mRS scores is confirmed, the technical team believes the ERG’s scenario where mRS scores are the same for andexanet alfa and standard care is more appropriate.</td></tr>
</table>

Issue 6 – Utilities calculations in ICH bleed survivors

Background/description of issue	• In order to calculate long-term health-related quality of life (HRQoL) for people who survived ICH bleed, the company used the study by Fletcher et al. 2015 which quantified the relationship between mRS scores and utility. The scores reported in Fletcher are presented by the company as EQ-5D scores, however the ERG underlined that the scores are obtained by time-trade off method and not EQ-5D. • The company used the distribution of mRS scores from ANNEXA-4 and Øie et al. 2018 to calculate a weighted average utility score for each treatment arm for ICH survivors. • The weighted mean scores were 0.53 after andexanet alfa and 0.42 after PCC, resulting in an increase of 0.11 for andexanet alfa. • This absolute increase was then applied to a 3-month post-acute care utility value of 0.61 obtained from NICE TA341 to calculate the post-andexanet alfa utility score of 0.72. The utility values used in the model for post-acute care following andexanet alfa and PCC are 0.72 and 0.61 respectively. • The ERG is concerned with the long-term HRQoL estimates from the company for ICH survivors, as the weighted average utilities based on mRS scores are only used to estimate the increment associated with andexanet alfa. • The final calculated utility used in the model for andexanet alfa is 0.72, which is 0.01 less than the UK general population aged 75 years and above. • Additionally, utility values according to mRS from Fletcher et al. 2015 are obtained using time trade-off and the mean age of respondent was 70 years while the utility value from NICE TA341 is based on EQ-5D and the mean age of respondents was 68 years. • The ERG considers that the weighted average utilities based on mRS scores should be used as the source utilities for long-term ICH survivors and justifies it with several arguments: the mRS scores distributions from ANNEXA-4 and Øie et al. 2018 have been used throughout the model so it is more consistent to use it for source utilities, the respondents in Fletcher et al. 2015 are closer in age to the ANNEXA-4 study and using the weighted average utilities directly would

	eliminate the use of an additional utility from a different source resulting in unnecessary calculation step. • Moreover, the ERG believes that the calculated utility value of 0.72 leading to a 0.01 difference between ICH survivors with varying degrees of severity and general population is not plausible. • The company provided alternative scenarios at clarification stage where the weighted average utilities of 0.53 and 0.42 were used, which increased the ICER for all cohorts: £14,209/QALY, £22,963/QALY and £24,053/QALY for the whole cohort, ICH plus GI cohort and ICH cohort, respectively.
Why this issue is important	People with ICH bleed is a key subgroup of this appraisal and the long-term utility following ICH is a driver of the model.
Questions for engagement	1. Is it plausible to assume that the long-term utility value for ICH survivors is 0.01 lower than UK general population aged 75 years and above? 2. Is the ERG's assumption of using the weighted utilities by mRS more appropriate?
Technical team preliminary judgement and rationale	The technical team agrees with the ERG regarding the fact that using the weighted utilities by mRS scores would be more consistent with the other inputs of the model and the respondents are closer to ANNEXA-4 respondents in terms of age. However, the utilities from NICE TA341 is derived from EQ-5D which is the NICE preferred method.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: ICERs and impact on the cost-effectiveness estimate

Alteration	ICER (deterministic)
Whole cohort	
Company's base case	**£11,636/QALY**
Company's corrected base case	**£12,489/QALY**
0% relative reduction in 30-day mortality for 'other major bleeds'	£12,577/QALY
0% relative reduction of paralysis and blindness for andexanet alfa	£19,166/QALY
Vial wastage for andexanet alfa	£13,943/QALY
ICH rehabilitation 12 months	£11,296/QALY
Weighted utility values by mRS	£15,294/QALY
Intracerebral-specific mRS results to [redacted]% of ICH patients (ERG base case)	£22,039/QALY
Cumulative impact of the ERG's preferred assumptions on the cost-effectiveness estimate	**£33,541/QALY**
mRS distributions from ANNEXA-4 applied to both treatment arms (alternative ERG base case)	£18,964/QALY
Cumulative impact of the ERG's preferred assumptions on the cost-effectiveness estimate (ERG alternative base case)	**£28,997/QALY**
Additional scenario- 0% relative reduction in 30-day mortality for all bleeds	**£26,499/QALY**
ICH and GI cohort	
Company's base case	**£18,741/QALY**
Company's corrected base case	**£18,663/QALY**
Vial wastage for andexanet alfa	£19,978/QALY

Alteration	ICER (deterministic)
ICH rehabilitation 12 months	£17,453/QALY
Weighted utility values by mRS	£22,932/QALY
Intracerebral-specific mRS results to [redacted]% of ICH patients (ERG base case)	£32,837/QALY
Cumulative impact of the ERG's preferred assumptions on the cost-effectiveness estimate	**£32,352/QALY**
mRS distributions from ANNEXA-4 applied to both treatment arms (alternative ERG base case)	£28,277/QALY
Cumulative impact of the ERG's preferred assumptions on the cost-effectiveness estimate (ERG alternative base case)	**£27,834/QALY**
Additional scenario- 0% relative reduction in 30-day mortality for all bleeds	**£52,281/QALY**
ICH only cohort	
Company's base case	**£18,738/QALY**
Company's corrected base case	**£18,640/QALY**
Vial wastage for andexanet alfa	£19,821/QALY
ICH rehabilitation 12 months	£17,190/QALY
Weighted utility values by mRS	£23,990/QALY
Intracerebral-specific mRS results to [redacted]% of ICH patients (ERG base case)	£38,654/QALY
Cumulative impact of the ERG's preferred assumptions on the cost-effectiveness estimate	**£37,311/QALY**
mRS distributions from ANNEXA-4 applied to both treatment arms (alternative ERG base case)	£31,377/QALY
Cumulative impact of the ERG's preferred assumptions on the cost-effectiveness estimate (ERG alternative base case)	**£30,193/QALY**
Additional scenario- 0% relative reduction in 30-day mortality for all bleeds	**£39,697/QALY**

The ERG's probabilistic ICERs are reported below:

Population	ERG base case ICER, (intracerebral-specific mRS scores) Probabilistic	ERG alternative base case ICER, Probabilistic
Whole cohort	£33,735/QALY	£29,297/QALY
ICH plus GI cohort	£32,217/QALY	£27,754/QALY
ICH cohort	£37,216/QALY	£30,037/QALY

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
ANNEXA-4 is a single-arm trial	The clinical trial was a single arm trial of andexanet alfa with no comparator. The comparative effectiveness of andexanet alfa with other treatment is therefore uncertain	Unknown
Protocol amendment 4 in ANNEXA-4	• In the trial, the criteria for determining the dose of andexanet alfa was changed midway; under Amendment 4, the threshold time to determining low vs high dose andexanet was changed from 7 to 8 hours and the specific doses of the last FXa inhibitor were added to determine a low vs high dose. There were 139 patients enrolled under Amendment 4 of the study protocol. • The ERG considers that some patients enrolled earlier than the amendment may not have received the licensed dose, however the impact of the resulting bias is unclear.	Unknown

Table 3: Other issues for information

Issue	Comments
ANNEXA-4 co-primary endpoints	The two primary efficacy outcomes in ANNEXA-4 (haemostatic efficacy and anti-FXa activity) were not used in the model. The ERG considers that these endpoints are intermediate endpoints of efficacy and their inclusion in the economic model is likely to have low impact on the results.
Estimation of treatment wastage costs for andexanet alfa	The ERG considers that the company's approach does not reflect correctly the wastage costs for andexanet alfa, as the weighted average number of vials should have been rounded up to 6 vials. NICE technical team considers that rounding up the weighted average number of vials to 6 as suggested by the ERG seems to result in overestimating the wastage costs because it is already factored in when rounding up vials to 5 and 9. The company's approach seems more appropriate.
ICH rehabilitation length and costs are overestimated	The company included a rehabilitation cost for the ICH survivor which was applied for a lifetime in the model. The ERG is concerned with this assumption and believes that ICH rehabilitation costs should not be applied for lifetime. According to clinical experts consulted by the ERG, rehabilitation care would be given for a few months but not years. The ERG conducted 2 scenarios where the rehabilitation costs were applied for 6 months and 12 months instead of lifetime period. This decreased the ICER slightly and the ERG's preferred assumptions is that rehabilitation costs are applied for 12 months.
Blood product use	The ERG highlighted that patients included in the data for blood product use at the different timepoints may have received blood products at more than one of the time points and it is not clear how many patients received multiple blood products over the follow-up period in ANNEXA-4.
Anti-FXa inhibitors levels	The ERG notes that both the mean and median anti-FXa inhibitor levels in the blood were lower in patients taking apixaban compared to those on rivaroxaban, although the ERG is unsure whether there is any clinical rationale for this observed difference.

Issue	Comments
Hospitalisation days between rivaroxaban and apixaban	The ERG also notes that rivaroxaban [redacted].
Length of hospital stay	The company initially included an analysis of length of hospital stay for resource use and costs in which the patients on standard care stayed longer in hospital than with andexanet alfa. The ERG requested clarification on this assumption and in the company's resubmission, length of hospital stay was excluded from the analysis. The ERG acknowledge that the differences in settings between ANNEXA-4 and ORANGE study may lead to unreliable results.
Mortality probability for ICH survivors implementation	The mortality probability for ICH survivors was incorrectly implemented in the model. The ERG corrected this to ensure the probability was appropriately applied.
Paralysis cost calculation	The company used an annual cost for the first year of paralysis but applied the yearly cost as a per cycle cost. The ERG corrected this by taking the annual cost and diving it by 12, to ensure the cost was correctly applied in the first 12 cycles of the model.

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Appendix 1 – ANNEXA-4 efficacy endpoints

Note that the results presented below relate to the safety population analysis of the apixaban and rivaroxaban subgroup of ANNEXA-4 unless reported otherwise.

4.1 Haemostatic efficacy (control of bleeding)

Table 10 Haemostatic Efficacy at 12 Hours Post Andexanet of Apixaban and Rivaroxaban (Safety Population) (Company response to clarification question A9a-c, Table 20)

Cohort	Statistic	All Patients
Overall	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
Bleed Type		
GI	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
ICH	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]
Other	Patients (N)	[redacted]
	Excellent/Good Patients (%)	[redacted]
	Exact 95% CI	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients who received any amount of andexanet.
Bleed type was adjudicated by the Endpoint Adjudication Committee.
Patients adjudicated as non-evaluable for administrative reasons were excluded.

4.2 Re-bleeding

Table 11 Analysis of Hematoma Expansion in Patients Received Apixaban or Rivaroxaban with Intracerebral Volume (Safety Population) (Company response to clarification question A9b, Table 22)

Status of Hematoma Expansion	N (%) with Intracerebral Volume > 35% Increase from Baseline to 1 hour (N=124)	Number at 1 hour Mean (SD)	N (%) with Intracerebral Volume > 35% Increase from Baseline to 1 & 12 hour (N=119)	Number at 12 hour Mean (SD)
Hematoma Expansion	[redacted]	[redacted]	[redacted]	[redacted]
No Hematoma Expansion	[redacted]	[redacted]	[redacted]	[redacted]

Database lock date: 28NOV2018. The Safety Population includes all patients treated with any amount of andexanet.
Patients who didn't have intracerebral volumes at baseline, 1 hour assessment, and/or 12 hour assessment were excluded.
Hematoma expansion defined as volume increase from baseline greater than 35%.
Study: ANNEXA4 (14-505), Program: Table A9B3.sas, Output: Table A9B3.rtf, Date: 24OCT2019

4.3 Requirement for blood products (red blood cell transfusions, non-study-prescribed blood products and haemostatic agents)

Table 12 Blood product use (mL) and non-RBC blood product use of patients with apixaban or rivaroxaban (Safety Population) (Adapted from CS Document B, Table 19)

	All Patients (N=322)	Patients with ICH (N=209)	Patients with GI (N=82)
Blood Product Use (mL)			
Before Andexanet Dosing (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
0-16 hour (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
>16 hour (N)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
IQR	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Coagulation Factor Transfusion (N)			
Before Andexanet Dosing	[redacted]	[redacted]	[redacted]
30 minutes before end of infusion	[redacted]	[redacted]	[redacted]
1 hour	[redacted]	[redacted]	[redacted]
4 hour	[redacted]	[redacted]	[redacted]
8 hour	[redacted]	[redacted]	[redacted]
12 hour	[redacted]	[redacted]	[redacted]
Haemostatic Treatments (N)		[redacted]	[redacted]
Before Andexanet Dosing	[redacted]	[redacted]	[redacted]
30 minutes before end of infusion	[redacted]	[redacted]	[redacted]
1 hour	[redacted]	[redacted]	[redacted]
4 hour	[redacted]	[redacted]	[redacted]
8 hour	[redacted]	[redacted]	[redacted]
12 hour	[redacted]	[redacted]	[redacted]
Other Blood/Coagulation (N)		[redacted]	[redacted]
Before Andexanet Dosing	[redacted]	[redacted]	[redacted]

30 minutes before end of infusion	[redacted]	[redacted]	[redacted]
1 hour	[redacted]	[redacted]	[redacted]
4 hour	[redacted]	[redacted]	[redacted]
12 hour	[redacted]	[redacted]	[redacted]

Database lock date: 28Nov2018. The Safety Population included patients treated with any amount of andexanet. Bleed type was adjudicated by the Endpoint Adjudication Committee. 16 hours is 12 hours after EOI.
Source: Portola data on file[48]

4.4 Neurological outcomes (in people with ICH)

Table 13 Modified Rankin Score (mRS) of ICH patients with Apixaban or Rivaroxaban (Safety Population) (Adapted from CS Document B, Table 21)

Timepoint	Statistic	Patients with ICH (N=209)
Screening	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	IQR	[redacted]
	Range	[redacted]
1 hour	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	IQR	[redacted]
	Range	[redacted]
12 hours	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	IQR	[redacted]
	Range	[redacted]
Day 30	N	[redacted]
	Mean (SD)	[redacted]
	Median	[redacted]
	IQR	[redacted]
	Range	[redacted]

Database lock date: 28Nov2018. The Safety Population included patients treated with any amount of andexanet. Bleed type was adjudicated by the Endpoint Adjudication Committee.
Source: Portola data on file[48]

4.5 Hospital stay duration

Table 14 Details of Hospitalisation (Days) Post Treatment in Patients Received Apixaban or Rivaroxaban by Bleed Type (Safety Populations) (Adapted from company clarification response A13, Table 27)

Bleed Type	Parameter	Apixaban (N=194)	Rivaroxaban (N=128)	All Patients (N=322)
All Patients	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
GI	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
ICH	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]
Other	Patients (N)	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]
	Median	[redacted]	[redacted]	[redacted]
	Q1, Q3	[redacted]	[redacted]	[redacted]
	Min, Max	[redacted]	[redacted]	[redacted]

Database lock date: 28NOV2018. The Safety Population included all patients who received any amount of andexanet. Bleed type was adjudicated by the Endpoint Adjudication Committee.

4.6 Need for surgical control of bleeding

Table 15 Surgical and other interventions for control of bleeding (Safety Population of apixaban and rivaroxaban subgroup) (Adapted from CS Document B, Table 24)

Bleed type & Procedure	Apixaban (n=194)	Rivaroxaban (n=128)	Overall (n=322)
ICH			
Craniotomy/craniectomy	[redacted]	[redacted]	[redacted]
Ventricular drain	[redacted]	[redacted]	[redacted]
Evacuation of haematoma	[redacted]	[redacted]	[redacted]
Burr hole	[redacted]	[redacted]	[redacted]
Unidentified procedure	[redacted]	[redacted]	[redacted]
Other procedure	[redacted]	[redacted]	[redacted]
GI			
Exploratory laparotomy	[redacted]	[redacted]	[redacted]
Intraluminal device	[redacted]	[redacted]	[redacted]

Other			
Hemiathroplasty	[redacted]	[redacted]	[redacted]
Pleural drainage	[redacted]	[redacted]	[redacted]
Vaginal packing	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

4.7 Thrombin generation

In clinical studies, increases in anti-FXa activity correlate with decreases in thrombin generation. The following figures report the time course of thrombin generation in patients taking rivaroxaban and apixaban (efficacy population).

[redacted]

[redacted]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Andexanet alfa for reversing anticoagulation [ID1101]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm, Thursday 20 February 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Company – Portola Pharmaceuticals UK Ltd**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Who would be eligible for andexanet alfa in clinical practice?	
1. In clinical practice, who would be eligible for andexanet alfa (any major bleed, ICH and GI bleeds, ICH only)? Would types of acute bleed other than those included in the company's analysis be important in considering the role of anticoagulant reversal.	It should be noted that andexanet alfa is not indicated for any major bleed, but a subset, defined as 'life-threatening or uncontrolled bleeding'. Bleeds included in the company's analysis that define life-threatening or uncontrolled, were based on the pivotal study, ANNEXA-4 which set pre-defined criteria to identify such bleeds. Alongside life-threatening or uncontrolled ICH and severe GI bleeds included in ANNEXA-4, UK clinical experts identified the following other life-threatening or uncontrolled bleeds as the most severe, which would require treatment with andexanet alfa in UK clinical practice: • Pericardial bleeds – due to a high mortality risk • Retroperitoneal bleeds - due to a high mortality risk • Intraocular bleeds – as this can result in blindness, hence a high morbidity risk • Intraspinal bleeds – as this can result in paralysis, hence a high morbidity risk Furthermore, UK clinical experts stated that other less severe life-threatening or uncontrolled bleeds included in the ANNEXA-4 study, including intra-articular and intramuscular, may not require andexanet alfa treatment in UK clinical practice. Hence, such bleeds were not included in the company's analysis.

2. Is the evidence submitted in each cohort sufficient to estimate the relative treatment effect of andexanet alfa (whole cohort, ICH and GI, ICH only)?	The three populations (whole cohort, ICH and severe GI, and ICH only) used in the analysis were selected to support NICE in their decision making since the levels of evidence for each population differs in terms of demonstrating clinical effectiveness and cost effectiveness within the licenced indication. ICH and severe GI bleeds were combined into a single subgroup as they represent the two largest subpopulations within the licenced indication. Life-threatening or uncontrolled ICH and severe GI bleeds experienced by individuals receiving rivaroxaban or apixaban accounts for [redacted] of the licenced indication (both in ANNEXA-4 and ORANGE). Furthermore, in contrast to other life-threatening or uncontrolled bleeds, sufficient numbers were available to conduct propensity score matching and evaluate a data-driven comparative effectiveness estimate. We recognise the importance the results of a severe GI bleed only cohort to inform the NICE technical team when evaluating the population for andexanet alfa. Therefore, we have provided additional analyses for a severe GI only cohort (Table 1, Table 2 and Table 3) in the Appendix.

3. Is it appropriate to amalgamate different types of bleed into a single 'whole cohort' for the purposes of estimating the clinical and cost effectiveness of andexanet alfa? If so: a. Is it plausible to assume that 'other major bleeds' are mainly composed of intraspinal, intraocular, pericardial and retroperitoneal bleeds? b. Is the company's assumption of equal proportion of intraspinal, intraocular, pericardial and retroperitoneal bleeds within 'other major bleeds' appropriate? c. Are the proportions of bleed types in ANNEXA-4 ([redacted] of ICH, [redacted] of GI and [redacted] of other major bleeds) representative of clinical practice?	Part A – Please see our response to Issue 1.1 Part B – Other bleeds split was based on the musculoskeletal and miscellaneous bleedings events recorded in the ORANGE study which gave an equal split across all bleed sites. However, there was a wide variation of bleed sites within ORANGE and limited data in published literature due to its rarity. Nevertheless, this remains to be the best available evidence to assess the proportional split. Part C – Patients in the ORANGE study which received PCC were deemed to be representative of SoC for individuals experiencing 'life-threatening or uncontrollable bleeding' while receiving DOACs in UK clinical practice. Among patients treated with PCCs whilst on rivaroxaban or apixaban in ORANGE, the majority had experienced an ICH ([redacted]). Of the remaining [redacted], [redacted] had experienced GI bleeding and [redacted] had experienced other bleeds. In ANNEXA-4, the proportion of bleeds types were similar to that of the ORANGE study with the largest proportion of patients experiencing an ICH bleed ([redacted]), followed by severe GI bleeding ([redacted]) and other bleeds ([redacted]). The difference in proportion of ICH patients between ANNEXA-4 and ORANGE was considered attributable to the purposive over-sampling of ICH patients in the response to an amendment of the ANNEXA-4 study protocol (Amendment 4) requested by the FDA to enrich for patients who were experiencing an ICH bleed. We recognise the proportion of bleed types from the ORANGE study may be a better representation of clinical practice in the UK. Therefore, we have provided an additional scenario which applies the ORANGE study bleed type proportions in our model. The results for this scenario can be found in the appendix for our base case (Table 4), ERG preferred base case (Table 5) and ERG alternative base case (Table 6). In most cases, cost-effectiveness is improved when considering the ORANGE proportional split.
4. Is it appropriate to combine ICH and GI bleeds in a single subgroup? Should the ICER for GI bleeds be calculated separately?	Please see Issue 1.2.
Issue 2: Generalisability and comparability of ANNEXA-4 trial and ORANGE study	

1. In ANNEXA-4, how was the exclusion criterion 'survival expected to be less than 1 month' defined? Is this in line with clinical practice?	The ANNEXA-4 study was designed to demonstrate the safety and efficacy of andexanet alfa in a patient population experiencing life-threatening or uncontrolled major bleeding whilst receiving a direct Factor Xa inhibitor. There was no exclusion of patients who for example had 'do not attempt resuscitation' or 'do not intubate' orders during screening nor subsequently during the 30-day observation period. The requirement for enrolled subjects to have a survival of greater than 1 month was specifically requested by the FDA. The criterion was determined by the investigator based on a 'bed-side' clinical assessment within the screening period. The rationale for criterion was to enable assessment of both safety and haemostatic efficacy during the acute clinical course (i.e. 30-day observation period). As a consequence of imposing this exclusion criterion in ANNEXA-4, some very sick subjects (e.g. those with significant / multi-organ failure, end stage-cancer, or on palliative care) may have been excluded. In UK clinical practice, some patients may not receive PCCs to reverse the bleed in these cases – although the exact proportion is unknown. Nevertheless, the ANNEXA-4 study still enrolled an older adult population with significant prior medical histories and comorbidities. The patients that were included had significant prior medical histories including a history of myocardial infarction in [redacted], stroke in [redacted], deep vein thrombosis in [redacted] and [redacted] were on anticoagulation because of a history of Atrial Fibrillation. Importantly, it should be noted that the proportion of patients that failed pre-screening due to the studies exclusion criteria was extremely low [redacted]. This statistic alone suggests that impact of including such patients would have no bearing on the overall results. Equally, it could be hypothesised that some very sick patients may not have been screened, thus the proportion of patients excluded at pre-screening may not fully reflect the proportion of patients who might be excluded in UK clinical practice. Whilst this proportion can only be hypothesised, it is not expected to substantially affect the study results – a view taken by the FDA who requested this criterion to be implemented.

2. What impact do the exclusion criteria in ANNEXA-4 have on the reliability of the propensity score matching analysis (see issue 3)?	We acknowledge the limitations of the ANNEXA-4 exclusion criterion, which although did not materially affect the enrolment of patients at pre-screening, may impact the generalisability of the results to UK clinical practice when compared to the ORANGE study which specified no exclusion criteria. Such an exclusion may have the potential to marginally over-estimate the survival expectations of patients receiving andexanet alfa when applied to UK clinical practice. However, we would also highlight that the ORANGE study did not recruit patients with life-threatening or uncontrolled bleeds. Although patients with PCCs were identified as those with a more severe bleed, without a specific inclusion criteria, milder patients outside of andexanet alfa's licence may be included in the corresponding propensity score matching analysis, which would underestimate the mortality associated with PCCs. It has also been acknowledged in the NICE technical report that patients matched more than once had lower mortality rates, resulting in conservative estimates of relative mortality benefit for andexanet, "as it is favourable for PCC against andexanet alfa". As a result, we would expect that any limitations on generalisability to UK clinical practice in the exclusion criteria for ANNEXA-4 would not affect the results of the propensity score matching analysis given the limitations in the ORANGE study in not included only patients with life-threatening or uncontrolled major bleeds and the matching of patients with low mortality. We would still anticipate the results of the propensity score matching analysis to be conservative, in favour of andexanet alfa.

3. How were the criteria used to assess haemostasis in the trial developed (see Table 4 of this technical report)? Are these criteria in line with clinical practice?	Haemostatic efficacy assessment utilised in ANNEXA-4 was the same as that utilised by Sarode et al. for a randomised phase III study of efficacy and safety of a 4-Factor Prothrombin Complex Concentrate in patients on vitamin K antagonists presenting with major bleeding.[1] The Sarode[1] haemostatic efficacy criteria relies on assessment through charter and comprises an endpoint integrating multiple types/sites of bleeding into a single parameter, and at the time of designing ANNEXA-4, was the gold-standard methodology for assessing haemostasis, previously accepted by regulatory authorities. Individual clinical assessment using the Sarode haemostatic efficacy criteria is in line with assessment in UK clinical practice.[1]
Issue 3: **Uncertainty around the relative treatment effect of andexanet alfa compared to PCC**	
1. Are the results of the propensity score matching analysis for 30-day mortality (lower with andexanet alfa than PCC, see Table 8) plausible and representative of what would be expected in clinical practice?	Our propensity score matching methodology predicts 30-day mortality rates for the SoC arm to be [redacted] for ICH patients and [redacted] for severe GI bleed patients. These results are at the top end of current literature which suggest 30-day all-cause mortality for ICH and severe GI bleed patients experiencing major bleeding to be in the range of 33-45%[2–4] and 10-20%[2,5–7], respectively. The discrepancy between our propensity score matching results and current literature can be explained by the difference between indications. Our results are predicted for 'life-threatening or uncontrollable bleeding' a more severe indication in comparison to 'major bleeding' which is commonly used in literature. As such, the 30-day mortality estimates appear to be aligned with the literature when considering life-threatening or uncontrolled bleeding. As discussed in Issue 2.2, we would anticipate the results of the propensity score matching analysis to be conservative, in favour of andexanet alfa.

2. Given the exclusion of known prognostic factors such as severity and volume of bleed as covariates for adjustment, how suitable are the results of the propensity score matching for decision making?	With the data which were included in the ORANGE study, prognostic factors such as volume of bleed and severity were not available to be included in the analysis. To account for this exclusion, 'receiving PCC' was used as proxy for severity of bleed in the ORANGE study – an approach recommended by UK clinical experts. As discussed in Issue 2.2, the exclusion of severity and volume of bleed in the propensity score matching analysis is therefore likely to result in milder patients outside of andexanet alfa's licence being included from the ORANGE study, resulting in an underestimation of mortality with PCC. Therefore, we would anticipate the results of the propensity score matching analysis to be conservative, in favour of andexanet alfa, and as such, suitable for decision making (bearing in mind that the true cost-effectiveness may be more favourable than that presented).
Issue 4: Plausibility of the assumptions for modelling 30-day mortality, paralysis and blindness in people with 'other major bleeds' in the whole cohort	
1. Is the assumption of a 25% relative reduction in mortality following pericardial and retroperitoneal bleeds between andexanet alfa and PCC plausible?	Without comparative data, the exact value for this reduction could not be estimated from data using ANNEXA-4 due to a limited number of deaths reported for pericardial and retroperitoneal bleeds. Therefore, a conservative assumption was made whereby treatment with andexanet alfa resulted in a relative reduction in mortality for pericardial and retroperitoneal bleed patients of 25% compared to SoC. This is substantially lower than the relative reduction in mortality observed in severe GI bleeds ([redacted]) and ICH ([redacted]), and was ratified with UK clinical experts – however we appreciate the uncertainty of this point estimate. To understand the impact of the varying relative reduction for other bleeds, we have included a confidence interval from 0% to 50% in scenario analyses as part of the original submission, and also within the probabilistic sensitivity analysis presented in Table 7 to 9 (this also accounts for the confidence intervals from the propensity score matching for ICH and GI bleed mortality) in the appendix.

2. Is the assumption of a 25% relative reduction in paralysis and monocular blindness following intraspinal and intraocular bleeds between andexanet alfa and PCC plausible?	Without comparative data, the exact value for this reduction could not be estimated from data using ANNEXA-4 due to no reporting of monocular blindness or paralysis in intraocular and intraspinal patients, respectively. Therefore, a conservative assumption was made whereby treatment with andexanet alfa resulted in a relative reduction in monocular blindness and paralysis of 25% compared to SoC. This is substantially lower than the relative reduction in mortality observed in severe GI bleeds ([redacted]) and ICH ([redacted]), and was ratified with UK clinical experts – however we appreciate the uncertainty of this point estimate. To understand the impact of the varying relative reduction for other bleeds, we have included a confidence interval from 0% to 50% in scenario analyses as part of the original submission, and also within the probabilistic sensitivity analysis presented in Table 7 to 9 in the appendix.
3. Is it reasonable to assume no relative reduction in 30-day mortality, paralysis and monocular blindness following other major bleeds between andexanet alfa and PCC?	Given andexanet alfa's mechanism of action is to halt life-threatening and uncontrolled bleeds, it would be clinically unrealistic that this would not result in any benefit in preventing monocular blindness. UK clinical experts suggest a 25% relative benefit is reasonable. See Issue 4.2.
4. Is it reasonable to set the 30-day mortality to zero in both treatment arms for intraocular and intraspinal bleeds?	UK clinical experts did not expect any mortality risk as a consequence of intraocular or intraspinal bleeds. Hence the 30-day mortality estimate was set to zero.
5. The "Other major bleeds" (non-ICH/GI) subgroup has a higher adjusted 30-day mortality for andexanet alfa [redacted] compared to [redacted] for PCC while for the other subgroups the mortality rate for andexanet alfa is lower- are these results reliable?	Due to the paucity of data in ANNEXA-4 for other major bleeds (N=[redacted] unadjusted, N<[redacted] adjusted), the heterogeneity of bleed types of this category, and inherent difficulty in identifying and therefore comparing life-threatening or uncontrolled bleeds from the ORANGE study using propensity score matching techniques, the results from the propensity score matching analysis cannot be considered reliable. UK clinical expert opinion suggests a 25% reduction in mortality is a more reasonable estimate. See Issue 4.1.
Issue 5: Implementation of one-month modified Rankin scale (mRS) scores for long-term mortality, utilities and management costs calculations for ICH survivors	

1. How different are the ICH subtypes in terms of morbidity and mortality? Do people surviving intracerebral haemorrhage have worse morbidity outcomes and mRS scores than people with other ICH subtypes?	Intracerebral bleed morbidity and mortality is expected to be similar to patients enrolled in ANNEXA-4 with life-threatening or uncontrolled bleeding as a consequence of ICH. As such, we believe it is suitable to compare the ANNEXA-4 outcomes with those from the Oie et al study.[8]
2. In clinical practice, do ICH bleed survivors have better mRS scores at 30 days after the bleeding event when receiving andexanet alfa compared with PCC?	Based on the comparison of ANNEXA-4 and the Oie et al.[8] study mRS scores, the answer would be yes.
3. Is it plausible to assume that andexanet alfa will improve ICH morbidity and mortality and as a result mRS scores at 30 days after the bleeding event?	It is plausible that a specific antidote which quickly reverses anti-activated FX activity and quickly returns haemostasis to normal would lead to better outcomes in general, including the mRS. When considering the propensity score matching results and comparison of ANNEXA-4 and Oie et al. mRS scores, this improvement is justified.
Issue 6: Utilities calculations in ICH bleed survivors	
1. Is it plausible to assume that the long-term utility value for ICH survivors is 0.01 lower than UK general population aged 75 years and above?	We recognise that the utilities used in our analysis appear high for the ICH population, in which ICH survivors take utilities post ICH bleeding of only 0.01 less than the general population. However, the best available data were used to calculate utilities applied in the analysis.
2. Is the ERG's assumption of using the weighted utilities by mRS more appropriate?	We respect there are many alternative methods for calculating utilities. The utilities used in our analysis from NICE TA341 were derived from EQ-5D, which is the NICE preferred method.

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Appendix- Additional scenarios

Assumption	Company base case	ERG preferred base case (excluding ERG wastage assumption)	ERG alternative base case (excluding ERG wastage assumption)
ICH mortality correction	✓	✓	✓
Intraspinal monthly cost correction	✓	✓	✓
Long-term ICH utilities	Weighted benefit for an anticoagulant population (Sourced from NICE TA341)	Intracerebral-specific mRS scores	Weighted by mRS scores
The company wastage assumption	✓	✓	✓
% Relative reduction of 30-day mortality for other bleeds	25%	0%	0%
% Relative reduction for paralysis and blindness	25%	0%	0%
Stroke rehab costs limited to the first 12 months	×	✓	✓

Table 1: Scenario for severe GI bleed only cohort

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Company base case – GI only								
SoC	9,687	6.194	4.512	-	-	-	-	-
Andexanet alfa	24,756	7.251	5.282	15,069	1.057	0.770	19,568	19,568
ERG preferred base case- GI only								
SoC	9,687	6.194	4.512	-	-	-	-	-
Andexanet alfa	24,756	7.251	5.282	15,069	1.057	0.770	19,568	19,568
ERG alternative base case – GI only								
SoC	9,687	6.194	4.512	-	-	-	-	-
Andexanet alfa	24,756	7.251	5.282	15,069	1.057	0.770	19,568	19,568
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio								

Table 2: Results of scenario analysis varying discount rate for the severe GI cohort only

Discount rate	Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
0%	SoC	10,689	7.689	5.604	-	-	-	-	-
	Andexanet alfa	25,930	9.002	6.560	15,240	1.312	0.956	15,935	15,935
3.5% (base case)	SoC	9,687	6.194	4.512	-	-	-	-	-
	Andexanet alfa	24,756	7.251	5.282	15,069	1.057	0.770	19,568	19,568
5%	SoC	9,357	5.701	4.152	-	-	-	-	-
	Andexanet alfa	24,370	6.674	4.861	15,013	0.973	0.709	21,184	21,184

Abbreviations: GI, gastrointestinal; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

Table 3: Scenario analysis without wastage for severe GI cohort only

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
SoC	9,687	6.194	4.512	-	-	-	-	-
Andexanet alfa	23,213	7.251	5.282	13,527	1.057	0.770	17,565	17,565

Abbreviations: GI, gastrointestinal; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

Table 4: Company base case – Scenario applying ORANGE study bleed type proportions

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Company base case – ANNEXA-4 bleed type proportions								
Whole Cohort								
SoC	44,370	3.210	2.153	-	-	-	-	-
Andexanet alfa	57,842	4.564	3.232	13,472	1.355	1.079	12,489	12,489
ICH and GI								
SoC	16,435	2.681	1.788	-	-	-	-	-
Andexanet alfa	37,427	4.105	2.913	20,992	1.424	1.125	18,663	18,663
Company base case – ORANGE bleed type proportions								
Whole cohort								
SoC	51,458	3.955	2.719	-	-	-	-	-
Andexanet alfa	61,754	5.220	3.719	10,296	1.265	0.999	10,303	10,303
ICH and GI								
SoC	15,278	3.349	2.305	-	-	-	-	-
Andexanet alfa	35,193	4.710	3.369	19,915	1.361	1.064	18,717	18,717
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio								

Table 5: ERG preferred base case (excluding ERG wastage assumption)– Scenario applying ORANGE study bleed type proportions

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
ERG preferred base case (excluding ERG wastage assumption)– *ANNEXA-4 bleed type proportions*								
Whole Cohort								
SoC	41,458	3.288	2.041	-	-	-	-	-
Andexanet alfa	60,956	4.415	2.669	19,498	1.127	0.628	31,044	31,044
ICH and GI								
SoC	13,405	2.764	1.671	-	-	-	-	-
Andexanet alfa	33,259	3.948	2.330	19,854	1.184	0.659	30,110	30,110
ERG preferred base case (excluding ERG wastage assumption)– ORANGE bleed type proportions								
Whole cohort								
SoC	49,111	4.017	2.629	-	-	-	-	-
Andexanet alfa	67,764	5.102	3.265	18,653	1.085	0.635	29,357	29,357
ICH and GI								
SoC	12,760	3.417	2.208	-	-	-	-	-
Andexanet alfa	31,776	4.588	2.895	19,016	1.171	0.686	27,709	27,709
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio								

Table 6: ERG alternative base case (excluding ERG wastage assumption)– Scenario applying ORANGE study bleed type proportions

Scenario	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
ERG alternative base case (excluding ERG wastage assumption)– ANNEXA-4 bleed type proportions								
Whole Cohort								
SoC	41,471	3.401	2.270	-	-	-	-	-
Andexanet alfa	60,663	4.553	2.986	19,192	1.152	0.716	26,806	26,806
ICH and GI								
SoC	13,422	2.886	1.913	-	-	-	-	-
Andexanet alfa	33,000	4.105	2.669	19,577	1.219	0.756	25,880	25,880
ERG alternative base case (excluding ERG wastage assumption)– ORANGE bleed type proportions								
Whole cohort								
SoC	49,118	4.106	2.811	-	-	-	-	-
Andexanet alfa	67,502	5.206	3.515	18,384	1.100	0.703	26,144	26,144
ICH and GI								
SoC	12,771	3.516	2.407	-	-	-	-	-
Andexanet alfa	31,530	4.710	3.170	18,759	1.194	0.763	24,582	24,582
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; SoC, standard of care; LY, life year; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio								

Table 7: PSA results for the company base case (whole cohort)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Deterministic- Company base case					
SoC	44,370	2.153	-	-	-
Andexanet alfa	57,842	3.232	13,472	1.079	12,489
PSA-company base case					
SoC	44,411	2.152	-	-	-
Andexanet alfa	57,900	3.228	13,489	1.0761	12,535
Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SoC, standard of care					

Table 8: PSA results for the company base case (GI and ICH cohort)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Deterministic- Company base case					
SoC	16,435	1.788	-	-	-
Andexanet alfa	37,427	2.913	20,992	1.125	18,663
PSA-company base case					
SoC	16,420	1.785	-	-	-
Andexanet alfa	37,366	2.909	20,946	1.1236	18,642
Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SoC, standard of care					

Table 9: PSA results for the company base case (severe GI cohort only)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Deterministic- Company base case					
SoC	9,687	4.512	-	-	-
Andexanet alfa	24,756	5.282	15,069	0.770	19,568
PSA-company base case					
SoC	9,693	4.512	-	-	-
Andexanet alfa	24,765	5.281	15,072	0.7689	19,602
Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SoC, standard of care					

Table 10: PSA results for the company base case (ICH cohort)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Deterministic- Company base case					
SoC	18,365	0.905	-	-	-
Andexanet alfa	41,199	2.130	22,834	1.225	18,640
PSA -company base case-					
SoC	18,309	0.906	-	-	-
Andexanet alfa	41,164	2.129	22,855	1.2228	18,691

Abbreviations: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; SoC, standard of care

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Technical engagement response form

Andexanet alfa for reversing anticoagulation [ID1101]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm, Thursday 20 February 2020**

Thank you for your time.

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About you

Your name	**Dr Deepa Jayakody Arachchillage**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Royal College of Pathologists/British Society for Haematology**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Who would be eligible for andexanet alfa in clinical practice?	
1. In clinical practice, who would be eligible for andexanet alfa (any major bleed, ICH and GI bleeds, ICH only)? Would types of acute bleed other than those included in the company's analysis be important in considering the role of anticoagulant reversal.	Although any patient presenting with major bleeding whilst on direct factor Xa (FXa) inhibitor (apixaban or rivaroxban) would be eligible to receive specific antidote (andexanet alfa at present), patients with ICH seem to have the most benefit from the trial data. There are no data on use of andexanet alfa in patients taking a direct acting oral Factor Xa inhibitor requiring emergency surgery. In clinical practice, patients presenting with ICH would comprise the majority of patients requiring reversal of anticoagulant effect**.** However, patients undergoing emergency surgery requiring urgent reversal of anticoagulant effect also form a major group in clinical practice (these patients receive PCC at present)
2. Is the evidence submitted in each cohort sufficient to estimate the relative treatment effect of andexanet alfa (whole cohort, ICH and GI, ICH only)?	The question here is relative to what? There are no data directly comparing andexanet to placebo or to no treatment. Nor is there such data for any other intervention, it would be regarded as unethical to perform a trial to obtain this information. Andexanet has not been studied in a trial directly comparing it to the current most frequently used intervention which is prothrombin complex concentrate (PCC). In any event, PCC has not been established to be of benefit compared to placebo or to plasma (the historical comparator). Therefore, there are no data to establish directly the relative benefit of any of the current treatment options.
3. Is it appropriate to amalgamate different types of bleed into a single 'whole cohort' for the purposes of estimating the clinical and cost effectiveness of andexanet alfa? If so:	It is not appropriate to amalgamate different types of bleed into a single 'whole cohort' Different types of bleeds will present different value. For example, the benefits of arresting an intracerebral bleed are likely to be much greater than from arresting an intraarticular bleed. Also, the time

a. Is it plausible to assume that 'other major bleeds' are mainly composed of intraspinal, intraocular, pericardial and retroperitoneal bleeds? b. Is the company's assumption of equal proportion of intraspinal, intraocular, pericardial and retroperitoneal bleeds within 'other major bleeds' appropriate? c. Are the proportions of bleed types in ANNEXA-4 ([redacted] of ICH, [redacted] of GI and [redacted] of other major bleeds) representative of clinical practice?	course over which benefit accrues will be different for different types of bleed. It is probably fairer to separate out the major groups and concentrate primarily on ICH a. The 'other major bleeds' group is small compared to GI and IC bleeding, so this is not a major problem. Musculoskeletal should also be mentioned but otherwise this seems a reasonable list of other bleeds. b. The proportions within the small numbers are not helpful but they are likely to be roughly similar although in clinical practice visceral bleeding may represent higher proportion of patients. c. The proportions of ICH and GI bleeds reflect the data in the Andexanet 4 trial, but this was deliberately biased towards ICH at the request of the FDA. It is probably not entirely representative of the types of bleeds presented in clinical practice. On the other hand, it may well represent the types of bleeds that will be treated with andexanet.
4. Is it appropriate to combine ICH and GI bleeds in a single subgroup? Should the ICER for GI bleeds be calculated separately?	No. As above they are likely to be have different behaviour and benefits and so should be considered as a separate group. Yes
Issue 2: Generalisability and comparability of ANNEXA-4 trial and ORANGE study	
1. In ANNEXA-4, how was the exclusion criterion 'survival expected to be less than 1 month' defined? Is this in line with clinical practice?	It is not clear how the trial defined this. In clinical practice, there is no such exclusion although a decision not to treat may be made following discussion with the family. In practice we would expect most patients presenting with ICH are likely to be given Andexanet if it is available.
2. What impact do the exclusion criteria in ANNEXA-4 have on the reliability of the propensity score matching analysis (see issue 3)?	The ANNEXA-4 study excluded patients expected to die within 4 weeks. Did the propensity score exclude all these? Did the propensity score exclude the expected number of patients based on this criterion? ANNEXA excluded all these: an estimated hematoma volume of more than 60 cc; expected survival of less than 1 month; the occurrence of a thrombotic event within 2 weeks before enrolment; or use of any of the following agents within the previous 7 days: vitamin K antagonist, dabigatran, prothrombin complex concentrate, recombinant factor VIIa, whole blood, or plasma. In clinical practice or the data from ORANGE study no such exclusions are made. The propensity score matching analysis is intended to correct for this but there are no details provided to allow a

	judgment of whether this has been achieved or even possible. At face value there is a favourable bias towards the ANNEXA-4 results.
3. How were the criteria used to assess haemostasis in the trial developed (see Table 4 of this technical report)? Are these criteria in line with clinical practice?	These are quite detailed as set out in the appendix to Connolly et al, 2019 and could be applied to ANNEXA-4 patients. However, most of the criteria used in the trial are not in line with clinical practice. These are no such data from ORANGE study.
Issue 3: Uncertainty around the relative treatment effect of andexanet alfa compared to PCC	
1. Are the results of the propensity score matching analysis for 30-day mortality (lower with andexanet alfa than PCC, see Table 8) plausible and representative of what would be expected in clinical practice?	This is very unlikely. It is not clear that the propensity score excludes all patients with GCS<7 and it is not possible to see whether seriously ill patients treated in ORANGE would have been excluded from ANNEXA 4 trial. OR whether very well patients not treated in ORANGE were actually treated in ANNEXA 4. The lack of detail on volume of ICH in ORANGE is a major limitation of this comparison. The use of 30cc as an exclusion prior to amendment of May 2015 may have excluded an even larger number who would have been treated in ORANGE.
2. Given the exclusion of known prognostic factors such as severity and volume of bleed as covariates for adjustment, how suitable are the results of the propensity score matching for decision making?	The propensity score is limited in its ability to match patients in the two studies. The severity and volume of ICH were not available from ORANGE study. Therefore, it is not clear how propensity score matching was done. Therefore, suitability of this for decision making is limited.
Issue 4: Plausibility of the assumptions for modelling 30-day mortality, paralysis and blindness in people with 'other major bleeds' in the whole cohort	
1. Is the assumption of a 25% relative reduction in mortality following pericardial and retroperitoneal bleeds between andexanet alfa and PCC plausible?	There is not enough evidence presented to make this assumption as the numbers are too small.
2. Is the assumption of a 25% relative reduction in paralysis and monocular blindness following intraspinal and intraocular bleeds between andexanet alfa and PCC plausible?	There is not enough evidence presented to make this assumption as the numbers are too small

3. Is it reasonable to assume no relative reduction in 30-day mortality, paralysis and monocular blindness following other major bleeds between andexanet alfa and PCC?	As a null position this is probably reasonable.
4. Is it reasonable to set the 30-day mortality to zero in both treatment arms for intraocular and intraspinal bleeds?	Yes. Mortality directly related to intraocular and intraspinal bleed is unlikely.
5. The "Other major bleeds" (non-ICH/GI) subgroup has a higher adjusted 30-day mortality for andexanet alfa [redacted] % compared to [redacted] % for PCC while for the other subgroups the mortality rate for andexanet alfa is lower- are these results reliable?	They probably reflect the uncertainty in the estimates and the number of the patients with other major bleeding represented in each study
Issue 5: Implementation of one-month modified Rankin scale (mRS) scores for long-term mortality, utilities and management costs calculations for ICH survivors	
1. How different are the ICH subtypes in terms of morbidity and mortality? Do people surviving intracerebral haemorrhage have worse morbidity outcomes and mRS scores than people with other ICH subtypes?	Although, this will be better commented by the neurologists, patients with intracerebral haemorrhage have the worse morbidity outcomes and mRS scores than people with other ICH subtypes.
2. In clinical practice, do ICH bleed survivors have better mRS scores at 30 days after the bleeding event when receiving andexanet alfa compared with PCC?	We do not have data to make a comment on this. We would have to stratify for size of bleed and type of bleed at presentation and other co-morbidities in the two studies to make this comparison.
3. Is it plausible to assume that andexanet alfa will improve ICH morbidity and mortality and as a result mRS scores at 30 days after the bleeding event?	It is plausible but without direct comparison, we cannot say with certainty.

Issue 6: Utilities calculations in ICH bleed survivors	
1. Is it plausible to assume that the long-term utility value for ICH survivors is 0.01 lower than UK general population aged 75 years and above?	This would be better commented by the neurologists
2. Is the ERG's assumption of using the weighted utilities by mRS more appropriate?	This would be better commented by the neurologists

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Andexanet alfa for reversing anticoagulation [ID1101]

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About you

Your name	**Liz Warburton**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Cambridge University Hospitals/British Association of stroke physicians (BASP)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None known**

Questions for engagement

Issue 1: Who would be eligible for andexanet alfa in clinical practice?	
1. In clinical practice, who would be eligible for andexanet alfa (any major bleed, ICH and GI bleeds, ICH only)? Would types of acute bleed other than those included in the company's analysis be important in considering the role of anticoagulant reversal.	1. Any major bleed in a person taking a relevant DOAC where clinically, mitigation of the detrimental effects of ongoing bleeding may improve eventual outcome. In addition to GI and ICH this would include rarer bleeding events in the eye, torrential epistaxis not controlled by simple measures (often a problem in the elderly), spinal hematoma where lasting disability can result, bleeding from an aneurysm (eg aortic, thoracic, vascular), trauma where bleeds into joint spaces could threaten blood supply, cardiac – pericardial where life threatening tamponade could result. Other scenarios encountered are: Severe haematuria not controlled by simple measures, severe (vaginal) P-V bleeding not controlled by simple measures. 2. A person taking a relevant DOAC requiring emergency surgery (say within 24hrs) or a life saving procedure – such as endoscopy for bleeding varices, interventional radiology for bleeding from angiodysplastic lesions (can be severe in the elderly particularly)
2. Is the evidence submitted in each cohort sufficient to estimate the relative treatment effect of andexanet alfa (whole cohort, ICH and GI, ICH only)?	The company should be congratulated on attempting to recruit a wider variety of clinical bleeding scenarios which is more representative of clinical practice than just ICH and GI bleeding as documented above. I was uncertain of the age ranges recruited but presume there was a wide range including people> 80years who are often taking DOACS for non valvular atrial fibrillation (NVAF). However the numbers in all groups are (not yet) large enough to estimate the relative treatment effect of andexanet with much certainty. (no power calculations seen).
3. Is it appropriate to amalgamate different types of bleed into a single 'whole cohort' for the purposes of estimating the clinical and cost effectiveness of andexanet alfa? If so:	a) see clinically encountered scenarios above. These will be wide across the whole of medicine and difficult to analyse as single conditions until there is more phase 1V data. Data could be

a. Is it plausible to assume that 'other major bleeds' are mainly composed of intraspinal, intraocular, pericardial and retroperitoneal bleeds? b. Is the company's assumption of equal proportion of intraspinal, intraocular, pericardial and retroperitoneal bleeds within 'other major bleeds' appropriate? c. Are the proportions of bleed types in ANNEXA-4 ([redacted] of ICH, [redacted] of GI and [redacted] of other major bleeds) representative of clinical practice?	provided as 'other major bleeds' with strong caveats on the assumptions used and limitations of the dataset up front. b) this remains an assumption. Don't think these would be given unique NHS codes? Only way I could think of to check relative incidence of each against each other. Intraspinal bleeds are rare. c) the %'s given don't reflect my reading of the relevant literature or clinical practice ?? usual expected rates are more like 40% GI 35% ICH 18% trauma 22% 'other' This corroborates with the % rates quoted in the other NICE TA (dabigatran inhibitor) Seems to be a relative excess of ICH in this cohort? I will do further research into relative rates before the meeting.
4. Is it appropriate to combine ICH and GI bleeds in a single subgroup? Should the ICER for GI bleeds be calculated separately?	Suggest calculate separately as there may be big difference in effects between GI and intracranial bleedings
Issue 2: Generalisability and comparability of ANNEXA-4 trial and ORANGE study	
1. In ANNEXA-4, how was the exclusion criterion 'survival expected to be less than 1 month' defined? Is this in line with clinical practice?	For people with ICH this is usual clinical practice. Usual exclusion criteria for people in clinical trials for example the TITCH and INTERACT 2 ICH trials. (NB: I will double check these parameters before the meeting).
2. What impact do the exclusion criteria in ANNEXA-4 have on the reliability of the propensity score matching analysis (see issue 3)?	Exclusion criteria for ICH was GCS<7 with ICH volume >60cc. This would exclude people in whom death was likely to occur rapidly and in whom a palliative care management pathway would be instituted. Hence this introduces an immediate bias in the score matching analysis as the

	ORANGE study did not specifically exclude these people. (ICH volume not measured in ORANGE).
3. How were the criteria used to assess haemostasis in the trial developed (see Table 4 of this technical report)? Are these criteria in line with clinical practice?	To my knowledge this system isn't used routinely.
Issue 3: Uncertainty around the relative treatment effect of andexanet alfa compared to PCC	
1. Are the results of the propensity score matching analysis for 30-day mortality (lower with andexanet alfa than PCC, see Table 8) plausible and representative of what would be expected in clinical practice?	Assumptions made have an intrinsic bias as documented by the interim report comments and therefore must be taken with these caveats and limitations clearly stated. Baseline inclusion between ORANGE and Andexanet studies are very different and would bias the ORANGE study to higher intrinsic mortality and morbidity rates.
2. Given the exclusion of known prognostic factors such as severity and volume of bleed as covariates for adjustment, how suitable are the results of the propensity score matching for decision making?	Haematoma volume is the major predictor of mortality and morbidity in ICH. Therefore the score as is isn't suitable
Issue 4: Plausibility of the assumptions for modelling 30-day mortality, paralysis and blindness in people with 'other major bleeds' in the whole cohort	
1. Is the assumption of a 25% relative reduction in mortality following pericardial and retroperitoneal bleeds between andexanet alfa and PCC plausible?	Not possible to say
2. Is the assumption of a 25% relative reduction in paralysis and monocular blindness following intraspinal and intraocular bleeds between andexanet alfa and PCC plausible?	
3. Is it reasonable to assume no relative reduction in 30-day mortality, paralysis and	

monocular blindness following other major bleeds between andexanet alfa and PCC?	
4. Is it reasonable to set the 30-day mortality to zero in both treatment arms for intraocular and intraspinal bleeds?	Reasonable given limitations of studies and analysis
5. The "Other major bleeds" (non-ICH/GI) subgroup has a higher adjusted 30-day mortality for andexanet alfa [redacted] % compared to [redacted] % for PCC while for the other subgroups the mortality rate for andexanet alfa is lower- are these results reliable?	Unlikely to be reliable. Very small numbers, variety of clinical scenarios as above.
Issue 5: Implementation of one-month modified Rankin scale (mRS) scores for long-term mortality, utilities and management costs calculations for ICH survivors	
1. How different are the ICH subtypes in terms of morbidity and mortality? Do people surviving intracerebral haemorrhage have worse morbidity outcomes and mRS scores than people with other ICH subtypes?	From the main published observational studies 1. ICH: - mortality around 44% by 3/12. Morbidity in survivors around 65% at mRS 3-5. Age at onset mean around 75. Main determinant of outcome is heamatoma volume and haematoma expansion (haematoma expansion occurs in around 30-40% of cases only) 2. Sub arachnoid haemorrhage (SAH) – mortatlity 16%; morbidity mRS 4-5 16%. Age at onset tends to be younger than ICH. Main determinant of outcome is clinical presentation (Hat and Hess scoring scale), rates of rebleed and vasospasm producing infarction.

	3. Subdural Haematoma (SDH): mortality 12-18%. Morbidity mRS 4-5 18-20%. Age at onset around 76. Main determinants of outcome are GCS at presentation, midline shift on CT scan, haematoma 'thickness'. Medical factors. (comorbidities, platelet count). Summary: ICH subtypes are variable in terms of mortality rates, morbidity outcomes and predictors. ICH has the highest death rate and worst morbidity of the three so any excess in ICH cases in a comparator group of 'ICH' could easily bias the death rate analysis.
2. In clinical practice, do ICH bleed survivors have better mRS scores at 30 days after the bleeding event when receiving andexanet alfa compared with PCC?	Not enough experience with andexant alfa in the UK to provide an opinion.
3. Is it plausible to assume that andexanet alfa will improve ICH morbidity and mortality and as a result mRS scores at 30 days after the bleeding event?	Difficult to assume for the following reasons: 1. To have an impact on mortality and morbidity andexanet alfa would need to reduce haematoma expansion. This occurs in 30-40% of cases of ICH only and so would require large numbers in a trial to demonstrate. The major determinant of outcome after an ICH is the volume of the bleed which occurs right at the start. By definition andexanet alfa could not affect this volume. (person would need to be pre loaded !) 2. Current observational studies published have not demonstrated any definite effect of PCC on haematoma expansion. (these are not randomised trials)

Issue 6: Utilities calculations in ICH bleed survivors	
1. Is it plausible to assume that the long-term utility value for ICH survivors is 0.01 lower than UK general population aged 75 years and above?	yes
2. Is the ERG's assumption of using the weighted utilities by mRS more appropriate?	Yes .

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Society of Gastroenterology**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None to declare**

Questions for engagement

Issue 1: Who would be eligible for andexanet alfa in clinical practice?	
1. In clinical practice, who would be eligible for andexanet alfa (any major bleed, ICH and GI bleeds, ICH only)? Would types of acute bleed other than those included in the company's analysis be important in considering the role of anticoagulant reversal.	**My expertise is in GI bleeding. Patients presenting with acute severe and life-threatening GI bleeding while on DOACs may be appropriate for andexanet . There is no mention of endoscopic intervention in this subgroup in the studies and this is a crucial intervention to assess re-bleeding risk and to apply haemostatic therapy.**
2. Is the evidence submitted in each cohort sufficient to estimate the relative treatment effect of andexanet alfa (whole cohort, ICH and GI, ICH only)?	**The lack of data on other interventions, particularly endoscopic haemostasis introduces uncertainty as to the magnitude of the effect.**
3. Is it appropriate to amalgamate different types of bleed into a single 'whole cohort' for the purposes of estimating the clinical and cost effectiveness of andexanet alfa? If so: a. Is it plausible to assume that 'other major bleeds' are mainly composed of intraspinal, intraocular, pericardial and retroperitoneal bleeds? b. Is the company's assumption of equal proportion of intraspinal, intraocular, pericardial and retroperitoneal bleeds within 'other major bleeds' appropriate?	**The mortality due to gastrointestinal bleeding is related to the haemodynamic effects of exsanguination and its sequelae.. In neurological bleeding the mortality may be related to pressure effects from a relatively small volume of bleeding.** a) and b) : I do not have sufficient knowledge of the issue to comment c) GI bleeding is very common, but I believe that ICH is much less so. This is not therefore representative of usual acute clinical practice in an unselected admission setting.

c. Are the proportions of bleed types in ANNEXA-4 ([redacted] of ICH, [redacted] of GI and [redacted] of other major bleeds) representative of clinical practice?	
4. Is it appropriate to combine ICH and GI bleeds in a single subgroup? Should the ICER for GI bleeds be calculated separately?	As discussed, ICH and GI bleeding have different pathological effects and should be considered separately
Issue 2: Generalisability and comparability of ANNEXA-4 trial and ORANGE study	
1. In ANNEXA-4, how was the exclusion criterion 'survival expected to be less than 1 month' defined? Is this in line with clinical practice?	**GI bleeding has a high mortality. Overall it is approx. 10% but this varies up to 50% depending on well-validated measures including age, co-morbidity and presence of shock. A high proportion of acute GI bleeding patients would thus be expected to have a survival of less than a month according to commonly presenting criteria.**
2. What impact do the exclusion criteria in ANNEXA-4 have on the reliability of the propensity score matching analysis (see issue 3)?	**There is uncertainty as to how these exclusion criteria were objectively assessed in a population that already has a high expected mortality.**
3. How were the criteria used to assess haemostasis in the trial developed (see Table 4 of this technical report)? Are these criteria in line with clinical practice?	**Table 4 does not include any endoscopic criteria for cessation of GI bleeding. The criteria for determining whether bleeding has ceased are not specified in the table.**
Issue 3: Uncertainty around the relative treatment effect of andexanet alfa compared to PCC	
1. Are the results of the propensity score matching analysis for 30-day mortality (lower with andexanet alfa than PCC, see Table 8) plausible and representative of what would be expected in clinical practice?	**The inclusion criteria including severe episodes of bleeding and the mortality seen with PCC would be in line with that. The comparison is between two non-randomised interventions therefore it is possible that bias may be introduced. It would be useful to see data on the matching of patients in the two groups with regard to defined prognostic indicators, as well as to age and gender. The proportion of patients in each group receiving**

	other interventions such as endoscopy within 12 hours or use of tranexamic acid will also be important.
2. Given the exclusion of known prognostic factors such as severity and volume of bleed as covariates for adjustment, how suitable are the results of the propensity score matching for decision making?	**This leads to some uncertainty**
Issue 4: Plausibility of the assumptions for modelling 30-day mortality, paralysis and blindness in people with 'other major bleeds' in the whole cohort	
1. Is the assumption of a 25% relative reduction in mortality following pericardial and retroperitoneal bleeds between andexanet alfa and PCC plausible?	This is outside my area of expertise
2. Is the assumption of a 25% relative reduction in paralysis and monocular blindness following intraspinal and intraocular bleeds between andexanet alfa and PCC plausible?	This is outside my area of expertise
3. Is it reasonable to assume no relative reduction in 30-day mortality, paralysis and monocular blindness following other major bleeds between andexanet alfa and PCC?	This is outside my area of expertise
4. Is it reasonable to set the 30-day mortality to zero in both treatment arms for intraocular and intraspinal bleeds?	This is outside my area of expertise
5. The "Other major bleeds" (non-ICH/GI) subgroup has a higher adjusted 30-day mortality for andexanet alfa [redacted]% compared to [redacted]% for PCC while for the other subgroups the mortality rate for andexanet alfa is lower- are these results reliable?	This is outside my area of expertise

Issue 5: Implementation of one-month modified Rankin scale (mRS) scores for long-term mortality, utilities and management costs calculations for ICH survivors	
1. How different are the ICH subtypes in terms of morbidity and mortality? Do people surviving intracerebral haemorrhage have worse morbidity outcomes and mRS scores than people with other ICH subtypes?	This is outside my area of expertise
2. In clinical practice, do ICH bleed survivors have better mRS scores at 30 days after the bleeding event when receiving andexanet alfa compared with PCC?	This is outside my area of expertise
3. Is it plausible to assume that andexanet alfa will improve ICH morbidity and mortality and as a result mRS scores at 30 days after the bleeding event?	This is outside my area of expertise
Issue 6: Utilities calculations in ICH bleed survivors	
1. Is it plausible to assume that the long-term utility value for ICH survivors is 0.01 lower than UK general population aged 75 years and above?	This is outside my area of expertise
2. Is the ERG's assumption of using the weighted utilities by mRS more appropriate?	This is outside my area of expertise

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As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **5pm, Thursday 20 February 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential

information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Thrombosis UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**I take no funding from pharmaceutical companies in any form**

Questions for engagement

Issue 1: Who would be eligible for andexanet alfa in clinical practice?	
1. In clinical practice, who would be eligible for andexanet alfa (any major bleed, ICH and GI bleeds, ICH only)? Would types of acute bleed other than those included in the company's analysis be important in considering the role of anticoagulant reversal.	**The use of andexanet would be limited to the indications requested by the company. In practice the need to reverse the antiXa DOAC agents with a direct reversing agent is uncommon.**
2. Is the evidence submitted in each cohort sufficient to estimate the relative treatment effect of andexanet alfa (whole cohort, ICH and GI, ICH only)?	**No. The real problem is the lack of comparative data with another agent,: -prothrombinase complex concentrate(PCC). The other issue is whether in intraocular bleeding there is a clinical need to reverse the anticoagulant. In intraocular bleeding it is important to reduce intraocular pressure but then it does not necessarily need anticoagulation reversal and in brittle thrombotic patients we often don't do this**
3. Is it appropriate to amalgamate different types of bleed into a single 'whole cohort' for the purposes of estimating the clinical and cost effectiveness of andexanet alfa? If so: a. Is it plausible to assume that 'other major bleeds' are mainly composed of intraspinal, intraocular, pericardial and retroperitoneal bleeds? b. Is the company's assumption of equal proportion of intraspinal, intraocular,	**I think that putting all the patients into one cohort is uncomfortable. The key issue is intracranial bleeding, which ideally needs a separate analysis. In our practice intraspinal and intraocular bleeds are very low frequency and that the bulk of the need for reversal is for intracranial and gastrointestinal bleeds as born out by case series in the literature. I think that section © assumption is approximately correct.**

pericardial and retroperitoneal bleeds within 'other major bleeds' appropriate? c. Are the proportions of bleed types in ANNEXA-4 ([redacted] of ICH, [redacted] of GI and [redacted] of other major bleeds) representative of clinical practice?	
4. Is it appropriate to combine ICH and GI bleeds in a single subgroup? Should the ICER for GI bleeds be calculated separately?	**I think these two groups should have separate calculations. The other issue is that CRASH-3 has shown that tranexamic acid helps improve clinical outcome in traumatic intracranial bleeds – it reduces bleeding deaths by one third. HALT-IT (tranexamic acid vs. placebo in 8,000 patients with upper GI bleeds) is about to be published and is expected to again show a positive effect. Obvious they are not directly reversing anticoagulants but they improve bleeding outcome independently.**
Issue 2: Generalisability and comparability of ANNEXA-4 trial and ORANGE study	
1. In ANNEXA-4, how was the exclusion criterion 'survival expected to be less than 1 month' defined? Is this in line with clinical practice?	**Yes**
2. What impact do the exclusion criteria in ANNEXA-4 have on the reliability of the propensity score matching analysis (see issue 3)?	**Excluding those who had less than a month's anticipated survival within the ANNEXA study makes comparison with the ORANGE study very difficult**
3. How were the criteria used to assess haemostasis in the trial developed (see Table 4 of this technical report)? Are these criteria in line with clinical practice?	**Clinical Outcome is the most important outcome to measure. Outcome at 30 days is reasonable but ideally especially where individuals have intracranial bleeds and take longer to recover, then a longer time frame such as 6 months would be preferable**
Issue 3: Uncertainty around the relative treatment effect of andexanet alfa compared to PCC	
1. Are the results of the propensity score matching analysis for 30-day mortality (lower with andexanet alfa than PCC, see Table 8) plausible and	**I think you mean table 7. There is a high death rate in those requiring anticoagulation reversal and so the figures on 30 day mortality with PCCs feel correct. However for**

representative of what would be expected in clinical practice?	**intracranial bleeding I feel we also need to know DALYS too as so many patients are left disabled. Is reducing mortality is the best outcome if it means there are many severely neurologically damage individuals with poor quality of life?**
2. Given the exclusion of known prognostic factors such as severity and volume of bleed as covariates for adjustment, how suitable are the results of the propensity score matching for decision making?	**There are too many assumptions made on too little data to feel comfortable with the propensity score matching for decision making.**
Issue 4: Plausibility of the assumptions for modelling 30-day mortality, paralysis and blindness in people with 'other major bleeds' in the whole cohort	
1. Is the assumption of a 25% relative reduction in mortality following pericardial and retroperitoneal bleeds between andexanet alfa and PCC plausible?	No. Too many assumptions to rely on this
2. Is the assumption of a 25% relative reduction in paralysis and monocular blindness following intraspinal and intraocular bleeds between andexanet alfa and PCC plausible?	No. Reversal of anticoagulation usually occurs AFTER any damage has occurred so I don't agree with a 25% reduction in paralysis and blindness. Furthermore reversal is intraocular bleeding is not the most important factor. Perhaps I can give an anecdote? A recent patient on warfarin had a major intraocular bleed. Her intraocular pressure was v high and was reduced. We did not reverse her anticoagulation but switched from warfarin to LMWH. Her sight one month later has returned with some minor peripheral loss
3. Is it reasonable to assume no relative reduction in 30-day mortality, paralysis and monocular blindness following other major bleeds between andexanet alfa and PCC?	Yes
4. Is it reasonable to set the 30-day mortality to zero in both treatment arms for intraocular and intraspinal bleeds?	Yes

5. The "Other major bleeds" (non-ICH/GI) subgroup has a higher adjusted 30-day mortality for andexanet alfa [redacted] % compared to [redacted] % for PCC while for the other subgroups the mortality rate for andexanet alfa is lower- are these results reliable?	No, there is too little data to be certain.
Issue 5: Implementation of one-month modified Rankin scale (mRS) scores for long-term mortality, utilities and management costs calculations for ICH survivors	
1. How different are the ICH subtypes in terms of morbidity and mortality? Do people surviving intracerebral haemorrhage have worse morbidity outcomes and mRS scores than people with other ICH subtypes?	Yes.
2. In clinical practice, do ICH bleed survivors have better mRS scores at 30 days after the bleeding event when receiving andexanet alfa compared with PCC?	Impossible to say as we are not using andexanet in the UK
3. Is it plausible to assume that andexanet alfa will improve ICH morbidity and mortality and as a result mRS scores at 30 days after the bleeding event?	No.
Issue 6: Utilities calculations in ICH bleed survivors	
1. Is it plausible to assume that the long-term utility value for ICH survivors is 0.01 lower than UK general population aged 75 years and above?	
2. Is the ERG's assumption of using the weighted utilities by mRS more appropriate?	

Andexanet alfa for reversing anticoagulation [ID1101]

ERG review of company's response to technical engagement report

February 2020

This report was commissioned by the NIHR HTA Programme as project number 16/168/04T

BMJ Technology Assessment Group

1 SUMMARY

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of andexanet alfa for reversing anticoagulation [ID1101]. Each of the issues outlined in the technical report are discussed in further detail in Section 3.

The company's base case analyses in response to the technical engagement report include the model corrections outlined in Section 6.1 of the main ERG report. The company also provided cost effectiveness results for a gastrointestinal (GI) only cohort. No further changes or patient access scheme (PAS) discounts have been proposed by the company in their response.

2 UPDATED COMPANY AND ALTERNATIVE ERG BASE CASE ANALYSES

In response to the technical engagement report, the company presented updated base case analyses for the whole cohort and intracranial (ICH) plus GI cohort (Table 1 and Table 2). The changes that have been made to the company's base case analyses include the model corrections suggested by the ERG. Additionally, the company provided cost effectiveness results for a GI only cohort (Table 3). The company also presented probabilistic results and the ERG considers these to be comparable to the deterministic results. The company did not provide any base case analyses for the ICH only cohort, or provide a rationale for this.

Table 1. Deterministic results of company's base case analysis – Whole cohort

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Standard care	£44,370	3.210	2.153	-	-	-	-
Andexanet alfa	£57,842	4.564	3.232	£13,472	1.355	1.079	£12,489
Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.							

Table 2. Deterministic results of company's base case analysis – ICH plus GI cohort

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Standard care	£16,435	2.681	1.788	-	-	-	-
Andexanet alfa	£37,427	4.105	2.913	£20,992	1.424	1.125	£18,663
Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.							

Table 3. Deterministic results of company's base case analysis – GI cohort

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Standard care	£9,687	6.194	4.512	-	-	-	-
Andexanet alfa	£24,756	7.251	5.282	£15,069	1.057	0.770	£19,568
Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.							

To align with assumptions accepted by the NICE technical team, the ERG has removed its scenario related to the estimation of treatment wastage costs for andexanet alfa. Except for this change, the ERG considers that the company has provided no additional evidence that require changes to any of the other assumptions made for the ERG preferred base case analyses. The ERG's preferred base case analyses in the whole cohort, ICH plus GI cohort and ICH cohort are given in Table 4 to Table 6. As for the GI cohort, the company's base case analysis is reflective of the ERG's preferred base case analysis.

Additionally, the ERG has provided its preferred base case analysis for a cohort of "other major bleeds". This is primarily because the impact of alternative modelling assumptions for "other major bleeds" is minimised by the large proportion of ICH and GI bleeds [redacted] within the whole cohort which may lead to inappropriate conclusions for "other major bleeds".

Table 4. ERG's preferred model assumptions, cumulative results – whole cohort

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY
Company's updated base case	6.1	£13,472	1.079	£12,489
0% relative reduction in 30-day mortality for 'other major bleeds' for andexanet alfa compared to standard care	5.3.5.3	£13,464	1.071	£12,577
0% relative reduction of paralysis and blindness for andexanet alfa compared to standard care	5.3.5.3	£20,524	1.063	£19,306
ICH rehabilitation for 12 months	5.3.10.5	£19,237	1.063	£18,095
Weighted utility values by mRS	5.3.9.3	£19,237	0.865	£22,233
Alternative mRS distributions				
ERG base case: intracerebral-specific mRS results to [redacted] of ICH patients	5.3.5.3	£19,498	0.628	£31,044
Alternative ERG base case: mRS distributions from ANNEXA-4 applied to both treatment arms	5.3.5.3	£19,192	0.716	£26,806
Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin scale; QALYs, quality adjusted life years.				

Table 5. ERG's preferred model assumptions, cumulative results – ICH plus GI cohort

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY
Company's updated base case	6.1	£20,992	1.125	£18,663
ICH rehabilitation for 12 months	5.3.10.5	£19,630	1.125	£17,453
Weighted utility values by mRS	5.3.9.3	£19,630	0.915	£21,445
Alternative mRS distributions				
ERG base case: intracerebral-specific mRS results to [redacted] of ICH patients	5.3.5.3	£19,854	0.659	£30,110
Alternative ERG base case: mRS distributions from ANNEXA-4 applied to both treatment arms	5.3.5.3	£19,577	0.756	£25,880
Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin scale; QALYs, quality adjusted life years.				

Table 6. ERG's preferred model assumptions, cumulative results – ICH cohort

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY
Company's corrected base case	6.1	£22,834	1.225	£18,640
ICH rehabilitation for 12 months	5.3.10.5	£21,059	1.225	£17,190
Weighted utility values by mRS	5.3.9.3	£21,059	0.952	£22,124
Alternative mRS distributions				
ERG base case: intracerebral-specific mRS results to [redacted] of ICH patients	5.3.5.3	£21,254	0.608	£34,933
Alternative ERG base case: mRS distributions from ANNEXA-4 applied to both treatment arms	5.3.5.3	£20,982	0.743	£28,244

Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin scale; QALYs, quality adjusted life years.

Table 7. ERG's preferred model assumptions, cumulative results – "other major bleed" cohort

Preferred assumption	**Section in ERG report**	**Incremental costs**	**Incremental QALYs**	**Cumulative ICER £/QALY**
Base case using the company's preferred assumptions	NA	-£58,894	0.162	Standard care dominated by andexanet alfa
0% relative reduction in 30-day mortality for 'other major bleeds' for andexanet alfa compared to standard care	5.3.5.3	-£58,971	0.078	Standard care dominated by andexanet alfa
0% relative reduction of paralysis and blindness for andexanet alfa compared to standard care	5.3.5.3	£14,356	0.000	Andexanet alfa dominated by standard care

Abbreviations: ERG, evidence review group; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin scale; NA, not applicable; QALYs, quality adjusted life years.

Note: age, gender and weight informed by the whole cohort

3 ERG REVIEW OF ISSUES

3.1 Issue 1: Who would be eligible for andexanet alfa in clinical practice?

The ERG agrees with the company that they included the most severe life-threatening or uncontrolled bleeds in the economic analysis (ICH, GI, intraocular, intraspinal, pericardial and retroperitoneal). The ERG also agrees with the company that other less severe life-threatening or uncontrolled bleeds included in the ANNEXA-4 study, including intra-articular and intramuscular, may not require andexanet alfa treatment in UK clinical practice. However, these points reinforce the ERG's view that the cost effectiveness results for the whole cohort cannot be generalisable to all life-threatening or uncontrolled bleeds. In the economic analysis, intraocular bleeds and intraspinal bleeds are associated with complications (blindness and paralysis, respectively) and in the company's analysis these complications incur larger long-term cost and quality of life decrements in patients who receive standard care compared to patients who receive andexanet alfa. For pericardial and retroperitoneal bleeds, the company also assumed treatment with andexanet alfa would lead to a 25% reduction in the risk of death compared to standard care. Therefore, if other less severe life-threatening or uncontrolled bleeds were to receive andexanet alfa treatment in UK clinical practice, the cost effectiveness of andexanet alfa compared to standard care is likely to be overestimated. This is explored further under Issue 4 (Section 3.4).

The ERG does not consider there to be sufficient data from ORANGE to inform the types or frequencies of the individual types of other major bleeds that might be suitable for treatment with andexanet alfa and therefore considers there to be uncertainty in these data. However, the ERG's clinical experts supported the company's assertion that ICH and GI bleeds are the most frequent types of bleeds in which andexanet alfa is likely to be used in clinical practice.

In response to the technical engagement report, the company presented additional cost effectiveness analyses for a GI only cohort and the ERG considers these results to be useful to determine if the combined ICH plus GI cohort is driven by benefits in the ICH cohort or GI cohort.

The company also provided a scenario which applied the ORANGE study bleed type proportions in the economic analysis (Table 8). However, the ERG considers the bleed type proportions in ANNEXA-4 to be more appropriate because patients in the ORANGE study did not receive andexanet alfa. As noted in the CS, all patients in the ORANGE study had major bleeds, but they had not necessarily suffered life-threatening or uncontrolled bleeds which is required for treatment with andexanet alfa, as such the ORANGE study may represent less severe bleed types (i.e. a larger proportion of "other major bleeds") which may not be eligible for andexanet alfa. In addition, one clinical expert response to technical engagement noted that the protocol amendment to enrich ANNEXA-4 with ICH bleeds may well

represent the distribution of bleeds that will be treated with andexanet alfa in UK clinical practice. Nonetheless, the results for this scenario can be found in the company's response to technical engagement. In most cases, the ICER decreased and the largest decrease was around £2,000.

Table 8. Proportion of bleed types in ANNEXA-4 and ORANGE

Bleeding event	ANNEXA-4	ORANGE
ICH	[redacted]	[redacted]
GI	[redacted]	[redacted]
Other major	[redacted]	[redacted]
Abbreviations: ICH, intracranial haemorrhage; GI, gastrointestinal		

3.2 Issue 2: Generalisability and comparability of ANNEXA-4 trial and ORANGE study

The ERG notes that the company report in their response to technical engagement that the requirement for enrolled subjects to have a survival of greater than 1 month was specifically requested by the FDA to enable assessment of both safety and haemostatic efficacy during the acute clinical course (i.e. 30-day observation period). The ERG notes that in the original protocol it was stipulated that patients with expected survival less than 2 months from causes other than the bleeding event would be excluded but this criterion was amended as part of protocol amendment 2 (07 May 2015) to expected survival less than 1 month, irrespective of cause.[1] The ERG also notes that this exclusion criteria of expected survival less than 1 month is an exclusion criteria in the ongoing post marketing required (PMR) randomised controlled trial (RCT) of andexanet alfa.[2] The ERG acknowledges that this exclusion criterion was not applied in ORANGE and notes it was also not applied in the RE-VERSE AD study (Reversal of Dabigatran Anticoagulant Effect With Idarucizumab),[3] a recent study of a different DOAC reversal agent.

The inclusion criteria of ORANGE required patients to have major bleeding and included patients with bleeding resulting in death. The ERG notes that 20% of patients in ORANGE had a fatal bleed (the 20% relates to the full ORANGE study cohort which includes patients on warfarin and dabigatran as well as the apixaban and rivaroxaban patients) and 21% of patients on direct oral anticoagulants (includes patients on dabigatran, apixaban and rivaroxaban) died within 30 days.[4] The ERG considers the exclusion criterion relating to expected survival in ANNEXA-4 means that deaths resulting from treatment are not obscured by expected deaths which is key given the single arm nature of the study. However, the ERG considers that 30-day mortality from ORANGE and ANNEXA-4 are not comparable and the ERG is concerned that any difference could be purely due to the expected deaths that were specifically excluded from ANNEXA-4. The ERG does not consider the use of the pre-screening failure data for ANNEXA-4 to account for the number of patients excluded based on the survival exclusion criteria appropriate because, as highlighted by the company, it is likely patients wouldn't have entered screening if clinicians did not consider them likely to meet the study inclusion

criteria. The ERG also notes that exclusion criteria for patients with ICH in ANNEXA-4 were applied that restricted the severity of ICH patients in the study: patients with ICH and Glasgow Coma Score < 7 or estimated intracerebral haematoma volume > 60 cc as assessed by the CT or MRI were excluded. Similar exclusion criteria were not applied in ORANGE.

The ERG notes that the major bleed definitions used differed slightly between ORANGE and ANNEXA-4 (Table 9) but nevertheless, as discussed above, both studies included patients with major bleeds. The ERG acknowledges that a requirement for the use of andexanet alfa is that bleeds should be life-threatening or uncontrolled and that this is a subset of major bleeds thus ORANGE may have included other less severe major bleeds. However, the ERG considers that the use of the PCC subgroup of ORANGE represents the more severe major bleeds and in addition, notes that the inclusion criteria in ORANGE included fatal bleeds. ANNEXA-4 included patients with major bleeds but as already discussed above, restricted them to having expected survival of greater than 1 month in addition to exclusion criteria for ICH severity.

Table 9. Definition of Major bleed used in ANNEXA-4 and ORANGE

ANNEXA-4	**ORANGE**
Acute major bleeding was defined by any one of the following: • Acute bleeding that is potentially life-threatening (e.g., as defined by signs of hemodynamic compromise such as poor skin perfusion, mental confusion, hypotension, low urine output); OR • Acute bleeding associated with a fall in haemoglobin level by ≥ 2g/dL, OR a Hb ≤ 8 g/dL if no baseline Hb is available OR, in the opinion of the investigator that the patient's haemoglobin will fall to ≤ 8 g/dL with resuscitation; OR • Acute symptomatic bleeding in a critical area or organ, such as, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome.	The definition of major bleeding adopted was an augmented version of the International Society on Thrombosis and Haemostasis criteria. It was defined as bleeding requiring hospitalization and at least one of the following: • resulting in death; • transfusion of ≥2 units of red blood cells or a drop in haemoglobin of ≥20 g/L; • symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intra-ocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; • transfusion of fresh-frozen plasma; • administration of prothrombin complex concentrate, recombinant activated factor VII, factor VIII inhibitor bypassing activity or fibrinogen concentrate.

Regarding the direction of bias in the results of the propensity score matching, the ERG does not consider it possible to accurately predict the direction of any resulting bias. As highlighted by the company, patients matched more than once in the PCC arm had lower mortality rates but given the lack of detail around the severity of bleeds in ORANGE and the differences in inclusion criteria between ORANGE and ANNEXA-4, the ERG considers the validity of the results of the propensity score matching to be highly uncertain.

The ERG notes that the company reports the haemostatic efficacy assessment in ANNEXA-4 used the same criteria as those developed by Sarode *et al.* for a randomised phase III study of efficacy and safety of a 4-Factor Prothrombin Complex Concentrate in patients on vitamin K antagonists presenting with major bleeding.[5] The company reported that at the time of designing ANNEXA-4, the haemostatic

efficacy scale in Sarode *et al.* was the gold-standard methodology for assessing haemostasis and it was previously accepted by regulatory authorities. The ERG notes that the Sarode *et al.* haemostatic efficacy scale was developed in discussion with the FDA and was designed to reduce potential investigator bias and to increase end point objectivity for the assessment of haemostatic efficacy. The ERG's clinical experts did not report any concerns with the haemostatic efficacy assessment in ANNEXA-4 and the ERG notes that haemostatic efficacy in ANNEXA-4 was adjudicated by an independent and blinded endpoint adjudication committee.

3.3 Issue 3: Uncertainty around the relative treatment effect of andexanet alfa compared to PCC

The ERG does not consider the data from published literature that the company uses to compare the results of their propensity score matching for 30-day mortality with standard care (prothrombin complex concentrate [PCC]) for the ICH and severe GI bleed cohorts to be appropriate. This is because the sources cited by the company include the ORANGE study, which is the study used for standard care in the propensity score matching, as well as efficacy studies of the direct oral anticoagulants (DOACs), where it is unclear what treatments were used to manage the fatal bleeds. In addition, the ERG notes that the company have included studies from DOACs other than apixaban and rivaroxaban to compare 30-day mortality with standard care to their propensity score matching results. The ERG therefore recommends caution in making naïve comparisons to validate the results of the propensity score matching analyses for 30-day mortality and considers it important to highlight that subgroup data from ORANGE were selected as the most appropriate data for the propensity score matching. The ERG's clinical experts also agreed with the company that the use of the PCC subgroup from ORANGE for the propensity score matching with ANNEXA-4 and to reflect current standard care in clinical practice is appropriate.

The ERG considers the differences in inclusion criteria between ORANGE and ANNEXA-4 discussed in Section 3.2 severely impact on the results of the 30-day mortality propensity score matching analysis. The ERG therefore maintains the view that the propensity score matching results are highly uncertain and as detailed in the ERG report, the ERG also has concerns that matching with replacement was used and in the 30-day mortality analyses [redacted] of individuals in the PCC group were matched multiple times. The ERG additionally noted in the ERG report that unobserved confounders due to the non-randomised study design are likely to be present and so the results of the propensity score matching analyses are subject to inherent bias.

3.4 Issue 4: Plausibility of the assumptions for modelling 30-day mortality, paralysis and blindness in people with 'other major bleeds' in the whole cohort

The ERG agrees with the company that the exact relative reduction in 30-day mortality, paralysis and blindness in people with "other major bleeds" between andexanet alfa and standard care cannot be estimated from the key trials due to the limited number of events recorded in those trials. However, the ERG disagrees that a relative reduction of 25% for these outcomes is a conservative assumption. Moreover, the ERG is unclear how a relative reduction of 25% was ratified with the company's clinical experts, for example, was this using a formal elicitation method or an open or closed question? The ERG considers that the company could have elicited clinical expert opinion using the SHELF methodology to aggregate judgements on relative reductions between andexanet alfa and standard care. In short, SHELF requires experts to come together to agree on plausible ranges and come to a 'consensus' judgement on the true value which reduces the impact of outliers.[6]

This issue is important because changing the relative reduction in paralysis and blindness from 25% to 0% increases the ICER for the whole cohort by around £7,000. Changing the relative reduction in 30-day mortality is minimal in the whole cohort. However, "other major bleeds" make up a small proportion [redacted] of the whole cohort, thus, changing relative reduction assumptions in a cohort made up of entirely "other major bleeds" results in a much larger impact (Table 10) and flips the ICER from "dominating" to "dominated". Overall, the ERG maintains that as there is no evidence to substantiate a relative reduction of 25%, the conservative option is to assume no difference between andexanet alfa and standard care.

Table 10. ERG scenarios on relative reductions for andexanet alfa compared to standard care in a "other major bleed" cohort

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Base case for a "other major bleed" cohort assuming a 25% relative reduction in 30-day mortality, paralysis and blindness							
Standard care	£301,436	6.966	4.763	-	-	-	-
Andexanet alfa	£242,542	7.082	4.925	-£58,894	0.116	0.162	Dominant
"other major bleed" cohort assuming no relative reduction in 30-day mortality							
Standard care	£301,436	6.966	4.763	-	-	-	-
Andexanet alfa	£242,465	6.966	4.841	-£58,971	0.000	0.078	Dominant
"other major bleed" cohort assuming no relative reduction in paralysis and blindness							
Standard care	£301,436	6.966	4.763	-	-	-	-
Andexanet alfa	£315,869	7.082	4.848	£14,433	0.116	0.084	£170,900
"other major bleed" cohort assuming no relative reduction in 30-day mortality, paralysis and blindness							
Standard care	£301,436	6.966	4.763	-	-	-	-
Andexanet alfa	£315,792	6.966	4.763	£14,356	0.000	0.000	Dominated

Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.
Note: age, gender and weight informed by the whole cohort

3.5 Issue 5: Implementation of one-month modified Rankin scale (mRS) scores for long-term mortality, utilities and management costs calculations for ICH survivors

The ERG considers that the company's justification for people with andexanet alfa to have better mRS scores than with standard care at 30 days after the bleeding event to be based on speculation. Moreover, given the clear direction from the ERG's clinical experts that people surviving intracerebral haemorrhage have worse mortality, morbidity and mRS scores than people with other ICH subtypes, the ERG considers it inappropriate to use a study conducted in patients with intracerebral haemorrhage to inform the mRS distributions of all ICH subtypes in the standard care arm (Øie *et al*. 2018)[7].

Furthermore, as explored in Section 5.3.5.3 of the main ERG report, a larger proportion of patients in ANNEXA-4 with intracerebral haemorrhage had a mRS of 5 ([redacted]) compared with Øie *et al*. 2018 ([redacted]). This finding concerns the ERG as the company and the ERG's clinical experts expected andexanet alfa to lead to greater reductions in haematoma expansion (and subsequently lower mRS results) in patients with intracerebral haemorrhage compared with standard care. However, the ERG caveats this finding with the fact that this was a naïve comparison and so no reliable conclusions can be drawn. Moreover, baseline data aren't provided for intracerebral-specific patients in ANNEXA-4 and therefore it is unclear how the distribution of patients in the different mRS categories have changed over the 30 days. Also, the Øie *et al.* 2018 population is [redacted] (74.8 years versus [redacted] years) and has a lower use of anticoagulants than ANNEXA-4 (22% versus 100%), which suggests that ANNEXA-4 could represents a more severe group of patients. Thus, either Øie *et al.* 2018 is not a representative population for standard care, or the treatment benefit in terms of the prognosis for survivors of intracerebral haemorrhages is minimal. However, the ERG acknowledges that in the absence of head-to-head trial data, Øie *et al.* 2018 is likely to represent the best available evidence on mRS distributions in people with intracerebral haemorrhage receiving standard care.

For these reasons, the ERG maintains that the company should have modelled the ICH subtypes separately or assumed the mRS distributions are the same for andexanet alfa and standard care. Further critique of this issue is outlined in Section 5.3.5.3 of the main ERG report.

3.6 Issue 6: Utilities calculations in ICH bleed survivors

The utilities used in the company's base case analysis from NICE TA341 (0.61 for ICH survivors in the standard care arm) were derived from the EQ-5D, which is the NICE preferred method.[8,9] However, the ERG maintains that the weighted average utilities based on mRS scores (0.53 and 0.42) are more appropriate to use in the model.[7,10] The ERG considers the company's calculated utility value for ICH survivors in the andexanet alfa arm (0.72), leading to a 0.01 difference between ICH survivors and general population, lacks face validity. Moreover, using the weighted utilities by mRS scores directly (0.53 and 0.42) would be more consistent with the other inputs of the model and eliminate the introduction of an additional data source (NICE TA341) and calculation step. Further critique of this issue is outlined in Section 5.3.9.3 of the main ERG report.

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