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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:

1. **Comments on the Appraisal Consultation Document from Portola Pharmaceuticals**
   a. Appendices

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Anticoagulation UK
   b. British Association of Stroke Physicians
   c. British Society of Gastroenterology *(RCP endorse BSG comments)*
   d. British Society of Haematology and Royal College of Pathologists
   e. British Society of Interventional Radiology
   f. Thrombosis UK
   g. UK Clinical Pharmacy Association

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Evidence Review Group critique of company comments on the ACD**

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

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Andexanet alfa for reversing anticoagulation [ID1101]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 13 May 2020 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Portola Pharmaceuticals
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

1	Portola would like to thank the committee for the opportunity to respond to Appraisal Consultation Document (ACD).
	
	There is an unmet need for a specific reversal agent
	
	We welcome the recognition that direct oral anticoagulants (DOACs) are associated with a serious risk of major bleeding and that there is a clinical need for effective anticoagulation reversal agents.
	
	• Patients receiving a DOAC who present as an acute emergency with life-threatening or uncontrolled bleeds are currently treated in a variety of ways because there is no “standard of care” or approved medicines available to reverse bleeding.
	
	• The EMA stated that andexanet alfa was one of the most important advances in public health in 2019[1], and this significant advance is further reflected in at least 11 international guidelines positively recommending the use of andexanet alfa in treating life-threatening or uncontrolled bleeds associated with apixaban or rivaroxaban (Appendix A).
	
	• Patients with intracranial haemorrhage may have either a spontaneous bleed or a traumatic bleed.
	
	  • Spontaneous bleeds include intracerebral bleeding (bleeding into brain substance) - which is a form of stroke. These patients will typically be taken urgently to an acute or hyper-acute stroke unit where they will have an urgent CT scan to confirm the diagnosis and extent of bleed.
	
	  • Traumatic bleeds occur in situations where the skull receives an external trauma, for example in car accidents. These patients will usually be managed through a trauma unit or A&E and would have CT scan of head performed urgently to determine bleed location and size and the need for surgery.
	
	• The patients in ANNEXA-4 with life-threatening or uncontrolled GI bleeds presented with low haemoglobin (average about 5g/dl) and low systolic blood pressure (average 107mm Hg) putting them at risk of renal failure, sequential major organ failure and death. These patients will be typically seen in the A&E or acute medical assessment unit where they will be resuscitated by having their blood volume restored before the need for further intervention, such as endoscopy or surgery, is considered. It is also worth noting that despite their low Hb the patients in ANNEXA-4 had high measured levels of Anti-FXa activity contradicting the opinion expressed by the GI expert during the committee meeting that these patients will have "bled out" all of their active drug and consequently will not require a specific reversal agent.
	
	• Andexanet alfa would fit into current clinical pathways in the UK for patients with life threatening or uncontrolled bleeding who require immediate resuscitation, including intracerebral haemorrhage protocols and acute gastrointestinal bleed (GI)

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protocols.

- Whilst patients receiving dabigatran have a reimbursed specific antidote (idarucizumab, Praxbind®) to reverse its effects in the UK, approximately 600,000 patients receiving rivaroxaban and apixaban do not. Without access to andexanet alfa, patients who present with a bleed into the brain or have substantial haemorrhagic complications from a GI bleed would be denied an effective and approved reversal agent.

There is no convincing evidence to suggest life-threatening or uncontrolled bleeds are well-managed with currently available treatment options

Due to the lack of reversal agents for Factor Xa inhibitors, clinicians revert to use of off-label treatments, such as Prothrombin Complex Concentrate (PCC – a mixture of the clotting Factors II, VII, IX and X). Despite their clinical use, PCCs do not reverse the effects of FXa inhibitors. Whilst PCCs may provide an increase in thrombin generation, this cannot occur at the therapeutic levels of rivaroxaban or apixaban[2], and importantly, due to biases in their study designs, PCCs have not consistently demonstrated any clinical benefit in the treatment of the patient population expected to be eligible for andexanet alfa[3]. The lack of evidence for PCCs in anti-FXa inhibitor reversal is reflected across international guidelines that support the use of a specific reversal agent (such as andexanet alfa) where available (Appendix A).

In Section 3.3 of the ACD, the statement that "GI bleeds can be managed in most patients using measures such as endoscopy, embolisation or surgery" contradicts the written deposition of the British Society of Gastroenterology (BSG) in the Committee papers for the first Committee meeting where the written statement to NICE from the BSG stated that "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"[4].

Current BSG guidelines for the management of lower GI bleeding, strongly recommend treatment with inhibitors such as idarucizumab or andexanet alfa for life-threatening haemorrhage in patients on DOACs[5]. As such, andexanet alfa's recommended use would be as part of a comprehensive resuscitation strategy in GI bleeding patients where endoscopic procedures or surgery should not be undertaken at the expense of adequate resuscitation[6].

Evidence generated to address concerns raised in the ACD

We have gathered compelling evidence to address the concerns raised in the ACD regarding the uncertainty of andexanet alfa's comparative effectiveness and cost-effectiveness. Specifically:

- UK clinical opinion has been sought on the key clinical issues raised in the ACD; conclusions of which are contrary to clinical opinion summarised in the ACD

- Real world evidence has been collected which demonstrates that the mortality outcomes from ANNEXA-4 can be generalised to the mortality outcomes expected in UK clinical practice

- Following up on a suggestion made by a Committee member at the March 24th

	Committee meeting the Rosenbaum sensitivity analysis[7] has been conducted to demonstrate that unobserved confounding variables (such as severity, bleed volume, and embolism of bleeding vessel) do not significantly impact the results • Five indirect comparison approaches have been explored through propensity score matching and inverse probability weighting, which validate the results observed in the base case propensity score matching analysis • Threshold analyses have been conducted to demonstrate that substantial reductions in observed PCC mortality, increases in andexanet alfa mortality, or reductions in andexanet alfa morbidity benefit would need to be observed for andexanet alfa not to be a cost-effective use of NHS resources [redacted]
2	**The ANNEXA-4 trial design and primary outcomes are appropriate to assess andexanet alfa's clinical benefit** In Section 3.4 of the ACD it was noted that: *"… because ANNEXA-4 was a single-arm trial there was no comparison with existing treatments such as PCC, further adding to the uncertainty about the clinical benefit of andexanet alfa in clinical practice"* • The committee raised concerns that ANNEXA-4 is a single-arm study, which thereby creates uncertainty related to andexanet alfa's clinical benefits compared to PCC, in the absence of a randomised controlled trial (RCT). • In the ANNEXA-4 study, a single-arm design was chosen because when the trial was set up, clinical investigators and regulatory authorities agreed that it was not ethical for a trial to offer some patients a specific reversal agent whilst others received usual care which may, or may not include non-approved, non-specific treatments. • At that time, and to this day, PCCs were not considered as standard of care for reversal of DOAC bleeds given the paucity of clinical evidence. The limited evidence for PCCs as reversal agents for DOACs was and still is reflected in clinical guidance for the development of reversal agents for anticoagulants[8]. • It is important to note that the ANNEXA-4 trial design and outcomes were agreed with regulators in the US and Europe and are consistent with other reversal agent registration studies (idarucizumab)[9]. Furthermore, in Section 3.4 of the ACD, it was noted that: *"In their response to technical engagement, the clinical experts questioned the definitions of haemostatic efficacy in relation to intracerebral haemorrhage. They considered that haemostatic efficacy as defined in the trial could not be considered predictive of clinical outcomes."* • Faced with catastrophic bleeding, the first goal of therapy is to arrest bleeding. The ANNEXA-4 trial was designed to assess the ability of a specific reversal agent to

rapidly reverse the anticoagulant effect of the DOACs and thereby arrest potentially fatal bleeding.

- This approach is consistent with recommendations from the International Society of Thrombosis and Haemostasis (ISTH): clinical outcome, in the form of haemostatic efficacy, i.e. the ability to stop bleeding, is the most important parameter for evaluating therapies for major bleeding events[10,11].

- The co-primary objectives of ANNEXA-4 were: to demonstrate a decrease in anti-FXa activity following andexanet treatment and to evaluate the haemostatic efficacy of andexanet in patients receiving an FXa inhibitor who have acute life-threatening or uncontrolled major bleeding.

- ANNEXA-4 was designed to demonstrate bleeding cessation across a range of different bleeding presentations in an objective and consistent way. In addition to bringing together objective assessments of a spectrum of different bleeding presentations, the Sarode criteria for haemostatic efficacy used in ANNEXA-4 incorporated objective assessment of intracranial bleeding (ICH) including haematoma expansion via central read of CT/MRI[12].

- Contrary to clinical opinion received as part of the technical engagement, there is clear evidence that haemostatic efficacy, as measured by haematoma expansion, is associated with improvements in key clinical outcomes.

    - Minimisation of haematoma expansion is a well-recognised outcome measure for assessment of intracerebral haemorrhage therapies and is a powerful predictor of death and disability[13]
    - For each 10% increase in haematoma growth, there is a 5% increased hazard of death, a 16% greater likelihood of worsening by 1 point on the modified Rankin Scale (mRS), and 18% greater likelihood of moving from independence to assisted independence or from assisted independence to poor outcome on the Barthel Index[14].
    - In a study of 200 patients with intracerebral haemorrhage[15], those with haematoma expansion (defined as expansion of >33%) had an in-hospital mortality rate of 68%, while those without expansion had an in-hospital mortality of 20%. The study also reported a difference in length of intensive care unit stay with and without haematoma expansion[15].

- ANNEXA-4 clearly demonstrates that haemostatic efficacy for an ICH is a relevant clinical outcome associated with mortality improvement:

    - In an intracranial haemorrhage sub-analysis, haemostatic efficacy was assessed through minimisation of haematoma expansion between baseline and 12 hours. Andexanet alfa resulted in effective haemostasis in 79% (95% CI, 69.1-86.2) of patients with spontaneous ICH and in 83% (95% CI, 72%-91%) of patients with traumatic ICH[16,17].
    - Further minimisation of haematoma expansion was observed in a proportion of patients with intracerebral haemorrhage who were at high risk of haematoma expansion, given their short median time from symptom to baseline scan of 3.1 hours (1.3-6.2 IQR) and initial baseline haematoma volumes[18].
    - The mortality benefit for andexanet alfa can be seen with increasing baseline intracerebral haemorrhage volumes in patients with spontaneous intracerebral bleeding, [redacted] (Appendix B) indicating that andexanet alfa

	improves mortality outcomes in patients with the most severe bleeding. o In contrast PCCs have not shown to be effective in minimising haematoma expansion nor have any mortality benefit[19]. • Furthermore, ANNEXA-4 demonstrates that haemostatic efficacy for a GI bleed is a relevant clinical outcome which is associated with mortality improvement: o Patients with upper GI bleeding in ANNEXA-4 had a mean Glasgow Blatchford score of [redacted] o [redacted] (Appendix C). o The 30-day mortality rate of [redacted] observed in ANNEXA-4 for upper GI patients suggests a magnitude of benefit of [redacted] which is consistent (if not slightly higher) than that predicted in the propensity score matching analysis [redacted]. • Given the haemostatic results observed for andexanet alfa in ANNEXA-4, a mortality and morbidity benefit is to be expected, and was indeed observed. This is fully supported by UK clinicians engaged during this response to the ACD (Appendix D).
3	**The ANNEXA-4 30-day mortality outcomes are generalisable to routine UK clinical practice** In Section 3.4 of the ACD it was noted that: *"the trial excluded all patients with an expected lifespan of less than 1 month. The clinical experts explained that in clinical practice all patients would be offered treatment, rather than only a selected group based on anticipated survival. Therefore, the generalisability of the 30-day mortality data from ANNEXA-4 is questionable."* Furthermore, in Section 3.5 of the ACD it was noted that: *"In ANNEXA-4, people were excluded if survival was expected to be less than 1 month, they had a Glasgow Coma Score lower than 7 or an intracerebral bleed volume of more than 60 ml. However, these criteria were not used in ORANGE. The committee noted that this could affect the comparability of results for 30-day mortality."* • We took note of the committee's concerns regarding the generalisability of the ANNEXA-4 results to routine UK clinical practice, since the trial excluded people with: survival expected to be less than 1 month, a Glasgow Coma Score lower than 7, or an intracerebral bleed volume of more than 60 ml. • While we agree that in clinical practice, all patients who could benefit from treatment, should be offered treatment, rather than only a subgroup selected based on anticipated survival or severity, we would point out that with respect to the exclusion criterion "survival expected to be less than one month", the written contribution of the Stroke expert, contained in the first Committee papers, states that *"for people with ICH this is usual clinical practice and is a usual criterion in clinical trials".* • Nonetheless, the distribution of ICH types in ANNEXA-4 suggests that a severe group of ICH patients was selected; [redacted] having an intracerebral haemorrhage, considered to be the most life-threatening and disabling. In addition, severity

	scoring of the GI bleeding patients enrolled into ANNEXA-4 predict high mortality regardless of exclusion criteria for 30-day expected survival (Appendix C). • To explore the implications of the eligibility criteria on the generalisability of the ANNEXA-4 results, evidence from a multi-centre real-world analysis of 407 patients receiving andexanet alfa within its licensed indication were assessed. • The real-world analysis did not exclude patients as per the eligibility criteria in ANNEXA-4 and in keeping with UK clinical practice, all patients within andexanet alfa's licence were offered treatment (including people with less than 1 month expected survival, a Glasgow Coma Scale score lower than 7 or an intracerebral bleed volume of more than 60 ml). • As shown in Appendix E, the baseline characteristics of the populations were similar between the ANNEXA-4 study and the real-world analysis, which supports that the eligibility criteria in the ANNEXA-4 study did not enrol an inherently different population to that which would be expected in clinical practice. • Furthermore, in-hospital mortality outcomes from the real-world analysis are consistent with those observed in the ANNEXA-4 study: o ICH mortality was [redacted] in the real-world analysis versus [redacted] in ANNEXA-4 o GI mortality was [redacted] in the real-world analysis versus [redacted] in ANNEXA-4 • Results from the real-world experience with andexanet alfa demonstrate that the mortality outcomes seen in the ANNEXA-4 study are reflective of what can be expected in UK clinical practice. • This conclusion aligns with the extremely low screen failure rate from the ANNEXA-4 eligibility criteria [redacted] and UK clinical opinion as noted in the ACD that all eligible patients meeting the licence would have indeed been screened, unless they were on a known end-of-life pathway (which constitutes a small population for which neither andexanet alfa or PCC would be offered in clinical practice). • Therefore, the 30-day mortality outcomes from ANNEXA-4 can be generalised to the mortality outcomes expected in UK clinical practice.
4	**The ANNEXA-4 and PCC-ORANGE populations are comparable** In Section 3.5 of the ACD it was noted that: *"The committee concluded that the comparability of the 2 studies and of their 30-day mortality rates are subject to great uncertainty."* Furthermore, in Section 3.6 of the ACD it was noted that: *"The company assumed that patients who had PCC in ORANGE were a good proxy for those with more severe bleeds, because PCC is used off-label and would be reserved for more severely affected patients. The committee noted that this assumption was not supported by evidence."* • Whilst we acknowledge that there are some differences between the eligibility criteria of ANNEXA-4 and ORANGE patient populations, these differences are

	minor and the resultant enrolled ANNEXA-4 and ORANGE populations are comparable for the purposes of mortality analyses (Appendix F). • As demonstrated through real world evidence and the low screen failure rate in ANNEXA-4, 30-day mortality outcomes from ANNEXA-4 can be generalised to the mortality outcomes expected in UK clinical practice. • In particular, the analysis demonstrates that the exclusion criteria observed in ANNEXA-4 (i.e. patients with survival expected to be less than 1 month, a Glasgow Coma Score lower than 7 or an intracerebral bleed volume of more than 60 ml), had minimal to no bearing on mortality outcomes, and as such should not obstruct comparability. • Furthermore, the eligibility criteria for ANNEXA-4 and the PCC-ORANGE population are highly comparable and aligned with ISTH guidelines. Both studies include major bleeds where: o Bleeding is in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial bleeding, or intramuscular bleeding with compartment syndrome o Bleeding is expected to be fatal (ANNEXA-4) or results in death (ORANGE) o There is a fall in haemoglobin concentration in the blood of more than 2g/dL. • The severity of the ANNEXA-4 bleeding population was confirmed through independent adjudication of clinical severity of all subjects' bleed presentation, such as haemodynamic instability. This is consistent with andexanet alfa's licence for life-threatening or uncontrolled bleeding. • Any patients who may have been included in ORANGE but not in ANNEXA-4 are likely to have suffered bleeds which were not non-life threatening or uncontrolled; i.e. falling outside of andexanet alfa's marketing authorisation and less severe. • By restricting propensity score matching analyses to the PCC-receiving subset of the ORANGE population, the analysis effectively selected a population of patients with severe bleeding that reflected the ANNEXA-4 study population, and andexanet alfa's indication. • Contrary to the ACD's comments, this assumption is supported by evidence in the ORANGE study. PCC ICH patients had significantly worse 30-day mortality outcomes ([redacted]) compared to non-PCC patients ([redacted])(internal analysis of ORANGE dataset[20]). Further evidence of comparability in terms of severity can be seen when observing the ICH sub-types, with a similar proportion of patients having the most severe ICH sub-type of an intracerebral bleed with ANNEXA-4 and PCC-ORANGE, as compared to non-PCC ORANGE (internal analysis of ORANGE dataset[12,20]): o Intracerebral: [redacted] (ANNEXA-4), [redacted] (PCC-ORANGE), [redacted] (non-PCC ORANGE) o Subarachnoid: [redacted] (ANNEXA-4), [redacted] (PCC-ORANGE), [redacted] (non-PCC ORANGE) o Subdural/epidural: [redacted] (ANNEXA-4), [redacted] (PCC-ORANGE), [redacted] (non-PCC ORANGE)

	• A similar observation is seen for GI bleeds. PCC GI bleed patients had significantly worse 30-day mortality outcomes ([redacted]) compared to non-PCC patients ([redacted]) (internal analysis of ORANGE dataset[20]). This aligns with the expected mortality for patients in ANNEXA-4 based on baseline mortality prognostic scoring (Appendix C). • UK clinicians confirm that 'choosing the PCC-treated subset of the DOAC bleeds in the ORANGE cohort provides a reasonable basis for evaluating the most severe bleeds which may be considered life threatening or uncontrolled in the UK' (Appendix D). • Finally, the written contribution of the Stroke expert, contained in the first Committee papers, states that the GCS and ICH bleed volume criterion used in ANNEXA-4 "*was likely to exclude people in whom a palliative care management pathway would be instituted*". Consultation with stroke experts confirmed that ICH palliative pathways do not include use of PCCs to reverse anticoagulation. Thus, by choosing to compare the ANNEXA-4 population with the PCC-treated cohort in ORANGE two comparable groups are created. • Therefore, it can be concluded that any differences in the selection criteria for ANNEXA-4 and ORANGE have either a negligible effect on mortality outcomes (in the case of ANNEXA-4 exclusion criteria) or can be appropriately restricted (in the case of PCC-ORANGE) to enable a robust comparison of 30-day mortality between andexanet alfa and PCC.
a5	**The indirect comparison to measure the comparative effectiveness of andexanet alfa versus PCC is robust and can be generalised to the benefit expected in UK clinical practice** In Section 3.6 of the ACD it was noted that: *"The clinical experts explained that severity and volume of bleeds were the primary prognostic factors for bleed-related mortality. The committee considered that without key prognostic factors accounted for, the results of the propensity score matching analysis were very uncertain. In addition, the committee noted that for GI bleed, no comparative data was available on what other treatment people had received in the two studies, particularly embolisation of a bleeding vessel."* • UK clinical opinion obtained during the response to the ACD (Appendix D) and which we agreed with, confirmed that it would be clinically implausible to assume no mortality benefit for andexanet alfa when considering: ○ Andexanet alfa's proven mechanism of action to specifically target and rapidly reverse anticoagulation in Factor Xa inhibitors ○ Haemostatic efficacy observed via haematoma expansion in ANNEXA-4 (Appendix B), which is a known predictor of mortality for ICH. ○ Substantial differences observed in mortality rates between ANNEXA-4 actual outcomes versus predicted outcomes at baseline using prognostic scoring for GI (Appendix C). ○ 30-day mortality results in ANNEXA-4 [redacted] compared to the ranges naively observed for PCC in ORANGE [redacted] • We note the point that there is potential for unobserved confounders, including prognostic factors such as severity, bleed volume, and embolism of bleeding

	vessel, to impact the results of any indirect comparison performed. • However, it is important to highlight that unobserved confounders, including severity, bleed volume, and embolism of bleeding vessel, will be correlated to covariates already included in the propensity score matching analysis presented: o Age o Bleed sites (ICH, GI, Other) and their subtypes, and o Medical history (Stroke, CAD, TIA, AF, hypertension, diabetes, renal dysfunction, cancer) • The question is of whether there is potential for unobserved confounding outside of the covariates already included in the propensity score matching analysis. • To explore the potential impact of such unobserved confounders, which may include severity, bleed volume, and embolism of bleeding vessel, a Rosenbaum sensitivity analysis was conducted. • This sensitivity analysis specifically evaluates how robust results are to confounding caused by unobserved variables, using a parameter called gamma (Γ). It does this by testing the p-value which would be obtained if we assume that one individual in a matched pair differs in propensity to the other matched partner by a factor of at most Γ on account of unobserved confounding variables – Rosenbaum recommends testing a range of Γ between 1 and 2. Full methods of the sensitivity analysis are described in Appendix G. • The results show that even if unobserved variables meant that one partner in a matched pair was [redacted] times more likely to receive andexanet alfa in reality than the other partner, we could still conclude that andexanet alfa made patients less likely to die within 30 days for the ICH+GI cohort. • The sensitivity analysis shows that even if unobserved variables had a substantial effect on propensity score, outside of the covariates already included in the analysis, the conclusions which we would draw about andexanet alfa's treatment effect for ICH+GI would not be changed in the face of a reasonable level of impact due to unobserved variables affecting both treatment assignment and 30-day mortality. • Therefore, unobserved confounders, including prognostic factors such as severity, bleed volume, and embolism of bleeding vessel, are unlikely to change the results observed in the indirect comparison. Furthermore, in Section 3.6 of the ACD it was noted that: *"The committee considered that the results of the propensity score matching analysis were too uncertain and unreliable to be used for decision making. The committee concluded that the potential benefit of andexanet alfa on mortality has not been adequately demonstrated or quantified."* • To further explore the robustness of the base case indirect comparison, five indirect comparison approaches have been explored through propensity score matching and inverse probability weighting. The methods of these are described in Appendix H. • Whilst we maintain that the base case indirect comparison using a propensity score

	matching analysis is the most appropriate methodology, in line with NICE Decision Support Unit guidelines and using methods externally ratified by a lead ERG assessor at the University of Sheffield, it is reassuring to see that other approaches provide similar results: ○ Propensity score matching with replacement (base case) found relative reductions in 30-day mortality with andexanet alfa of [redacted] for ICH+GI, ICH and GI, respectively ○ Propensity score matching without replacement (ITC scenario 1) found relative reductions in 30-day mortality with andexanet alfa of [redacted] for ICH+GI, ICH and GI, respectively ○ Propensity score matching with replacement, without subtype covariates (ITC scenario 2), found relative reductions in 30-day mortality with andexanet alfa of [redacted] for ICH+GI, ICH and GI, respectively ○ Propensity score matching without replacement, without subtype covariates (ITC scenario 3), found relative reductions in 30-day mortality with andexanet alfa of [redacted] for ICH+GI, ICH and GI, respectively ○ Inverse probability weighting found relative reductions in 30-day mortality with andexanet alfa of [redacted] for ICH+GI, ICH and GI, respectively • Therefore, the indirect comparison of andexanet alfa and PCC using propensity score matching is robust to changes in methodology, and is unlikely to be significantly impacted by unobserved confounders such as severity, bleed volume, and embolism of bleeding vessel. • As such, the mortality benefit inferred from the indirect comparison of a relative reduction in [redacted], can be generalised to the benefit expected in UK clinical practice, which is in line with UK clinical opinion obtained during the response to the ACD (Appendix D).

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	A morbidity benefit is expected for andexanet alfa based on clinical consensus in the UK In Section 3.7 of the ACD it was noted that: *… there was no direct evidence that people would have better mRS scores and less disability after andexanet alfa than PCC, and that the comparison was based on a naive comparison of data from ANNEXA-4 and Øie et al. The committee concluded that a benefit from andexanet alfa on long-term disability was not demonstrated by the evidence.* • We agree with UK clinical opinion obtained during the response to the ACD (Appendix D), that it would be clinically implausible to assume no morbidity benefit for andexanet alfa when considering: o Andexanet alfa's proven mechanism of action to specifically target and rapidly reverse anticoagulation in Factor Xa inhibitors o Haemostatic efficacy including minimisation of haematoma expansion observed in ANNEXA-4, which as discussed previously, is an important predictor of morbidity (including mRS) in persons with intracerebral bleeding o No adverse changes in ANNEXA-4 ICH patients' NIHSS and GCS score between baseline and 30 days. • There is a strong link between minimising haematoma expansion and preventing long-term morbidity. For each 10% increase in haematoma growth, there is estimated to be a 16% greater likelihood of worsening by 1 point on mRS, and 18% greater likelihood of moving from independence to assisted independence or from assisted independence to poor outcome on the Barthel Index[14]. • As mentioned previously, ANNEXA-4 demonstrated minimised haematoma expansion in spontaneous and traumatic intracranial haemorrhage as well as minimised haematoma expansion in intracerebral haemorrhage[16,17]. • We note the concerns "that the company's comparison overestimated the severity of disability and mRS scores for PCC". Whilst we recognise ICH utility with andexanet alfa might be argued to be high, EQ-5D utilities were used in the analysis, and a baseline utility of 0.61 was applied to standard of care using a utility for ICH from a previous NICE appraisal – TA341. • On the other hand, the ERG's preferred base case assumes an implausible baseline utility of 0.42 for standard of care post ICH – equivalent to lung cancer being treated with radiation therapy, whilst the ERG's alternative base case assumes a plausible baseline utility of 0.61 for standard of care, but with no benefit for andexanet alfa. • Given the uncertainty, it might make best sense to evaluate varying levels of benefit from the ERG's alternative base case (no benefit) to the manufacturer's base case (100% benefit as derived using Oie et al.).
7	**Revised cost-effectiveness results and threshold analyses (ICH + GI)** • Full details of the revised base case methods and results can be found in Appendix I. A summary of the base case changes following the ACD are as follows: o 12 months rehabilitation for patients who suffered from an ICH, in line with

	the ERG's assumption o A revised PAS, with list price discounted at [redacted] • The results of our revised base case are as follows: o ICH+GI ICER = [redacted] o ICH ICER = [redacted] o GI ICER = [redacted] • Alternative indirect comparison approaches provided extremely similar conclusions ranging from: o ICH+GI ICER = [redacted] o ICH ICER = [redacted] o GI ICER = [redacted] • In addition, threshold analyses were conducted varying the three key parameters where uncertainty has been raised in the ACD: o Andexanet alfa 30-day mortality o PCC 30-day mortality o Andexanet alfa relative benefit for morbidity • Even under the extreme clinical assumption of no morbidity benefit, which as detailed earlier is deemed clinically implausible by UK clinicians engaged during the ACD (Appendix D), for ICH+GI, ICH only and GI only: o Andexanet alfa 30-day mortality would have to increase by over [redacted] respectively, relative to the base case to achieve an ICER>£30,000 o PCC 30-day mortality would have to decrease by over [redacted], respectively relative to the base case to achieve an ICER>£30,000 • Considering that 20% is traditionally used as an appropriate level of variation to test uncertainty in sensitivity analyses, it is reassuring to see that andexanet remains cost-effective under such variation, even under extremely conservative scenarios of morbidity benefit. • Alongside the evidence aforementioned, this seeks to address the concerns the committee has expressed regarding the uncertainty associated with the evidence base. • Therefore, it can be concluded that andexanet alfa is a cost-effective use of NHS resources in ICH and GI patients, even under extreme clinical scenarios.
8	**Revised cost-effectiveness results and threshold analyses (Other bleeds)** • We acknowledge the additional uncertainty in the evidence base for other bleeds, and unfortunately do not have additional evidence to submit outside of that already presented. • Full details of the revised base case methods and results can be found in Appendix J. A summary of the base case changes following the ACD are as follows: o 12 months rehabilitation for patients who suffered from an ICH, in line with

Andexanet alfa for reversing anticoagulation [ID1101]

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	the ERG's assumption ○ A revised PAS, with list price discounted at [redacted] • The results of the revised base case are as follows: ○ Whole cohort ICER = [redacted] ○ Other bleeds ICER = [redacted] • Alternative indirect comparison approaches provided extremely similar conclusions for the Whole cohort ranging from [redacted] • As with ICH+GI, threshold analyses were conducted varying the three key parameters where uncertainty has been raised in the ACD: ○ Andexanet alfa 30-day mortality ○ PCC 30-day mortality ○ Andexanet alfa relative benefit for morbidity • Even under the extreme clinical assumption of no morbidity benefit, which as detailed earlier is deemed clinically implausible by UK clinicians engaged during the ACD (Appendix D), for the Whole cohort: ○ Andexanet alfa 30-day mortality would have to increase by over [redacted], relative to the base case to achieve an ICER>£30,000 ○ PCC 30-day mortality would have to decrease by over [redacted] relative to the base case to achieve an ICER>£30,000 • The results also found that for other bleeds even with no mortality impact, a [redacted] benefit in morbidity would still result in [redacted] • Therefore, acknowledging the limitations in the evidence base, it is still reasonable to assume that andexanet alfa is a cost-effective use of NHS resources in patients with the most severe other bleeds (pericardial, retroperitoneal, intraspinal and intraocular bleeds) and therefore, the whole cohort.

Insert extra rows as needed

Checklist for submitting comments

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Andexanet alfa for reversing anticoagulation [ID1101]

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Comments received during our consultations 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.

1. European Medicines Agency. *Human medicines highlights 2019. Available at https://www.ema.europa.eu/en/documents/report/human-medicines-highlights-2019_en.pdf.* 2019.
2. Lu G, Lin J, Bui K, Curnutte JT, Conley PB. Contribution of Coagulation Factors in Prothrombin Complex Concentrates (PCC) to TF-Initiated Thrombin Generation in Normal and FXa Inhibitor-Anticoagulated Plasma: The Relationship between Inhibitor Concentration and PCC-Mediated Thrombin Generation. Data presented at the 27th Congress of the International Society on Thrombosis and Haemostasis (ISTH) Melbourne, Australia, July 6-10. 2019.
3. Piran S, Khatib R, Schulman S, et al. Management of direct factor Xa inhibitor-related major bleeding with prothrombin complex concentrate: a meta-analysis. *Blood Adv.* 2019;3(2):158-167.
4. National Institue for Health and Care Excellence. *Single Technology Appraisal. Andexanet alfa for reversing anticoagulation [ID1101]. Committee Papers. Available at: https://www.nice.org.uk/guidance/gid-ta10440/documents/committee-papers.* 2020.
5. Oakland K, Chadwick G, East JE, et al. Diagnosis and management of acute lower gastrointestinal bleeding: guidelines from the British Society of Gastroenterology. *Gut.* 2019;68(5):776-789.
6. Cipolletta L, Cipolletta F, Granata A, et al. What Is the Best Endoscopic Strategy in Acute Non-variceal Gastrointestinal Bleeding? *Curr Treat Options Gastroenterol.* 2018;16(4):363-375.
7. Keele L. An overview of rbounds: An R package for Rosenbaum bounds sensitivity analysis with matched data. 2009.
8. Sarich TC, Seltzer JH, Berkowitz SD, et al. Novel oral anticoagulants and reversal agents: Considerations for clinical development. *Am Heart J.* 2015;169(6):751-757.
9. Pollack CV, Jr., Reilly PA, van Ryn J, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. *N Engl J Med.* 2017;377(5):431-441.
10. Khorsand N, Majeed A, Sarode R, Beyer-Westendorf J, Schulman S, Meijer K. Assessment of effectiveness of major bleeding management: proposed definitions for effective hemostasis: communication from the SSC of the ISTH. *J Thromb Haemost.* 2016;14(1):211-214.
11. Abdoellakhan RA, Beyer-Westendorf J, Schulman S, Sarode R, Meijer K, Khorsand N. Method agreement analysis and interobserver reliability of the ISTH proposed definitions for effective hemostasis in management of major bleeding. *J Thromb Haemost.* 2019;17(3):499-506.

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12. Connolly SJ, Crowther M, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *N Engl J Med.* 2019;380(14):1326-1335.
13. Hemorrhagic Stroke Academia Industry (HEADS) Roundtable Participants. Recommendations for Clinical Trials in ICH: The Second Hemorrhagic Stroke Academia Industry Roundtable. *Stroke.* 2020;51(4).
14. Davis SM, Broderick J, Hennerici M, et al. Hematoma Growth Is a Determinant of Mortality and Poor Outcome After Intracerebral Hemorrhage. *Neurology.* 2006;66(8).
15. Yaghi S, Dibu J, Achi E, Patel A, Samant R, Hinduja. Hematoma Expansion in Spontaneous Intracerebral Hemorrhage: Predictors and Outcome. *The International journal of neuroscience.* 2014;124(12).
16. Goldstein J, Demchuk A, Zotova E, et al. Hemostatic Efficacy and Anti-fXa Reversal With Andexanet Alfa in Spontaneous Intracranial Hemorrhage. Poster Presented at NCS 2019; Vancouver, British Columbia; October 15-18, 2019.; 2019.
17. Milling T, Yue P, Zotova E, et al. Efficacy and Safety Outcomes in FXa-Associated Bleeding Following Trauma: An ANNEXA-4 Sub-study. Poster Presented at NCS 2019; Vancouver, British Columbia; October 15-18, 2019.; 2019.
18. Concha M, Yue P, Curnutte J, et al. Clinical Factors Associated With the Achievement of Hemostatic Efficacy in Patients With Intracranial Hemorrhage: An ANNEXA-4 Sub-study. Poster Presented at NCS 2019; Vancouver, British Columbia; October 15-18, 2019.; 2019.
19. Gerner ST, Kuramatsu JB, Sembill JA, et al. Association of prothrombin complex concentrate administration and hematoma enlargement in non-vitamin K antagonist oral anticoagulant-related intracerebral hemorrhage. *Annals of neurology.* 2018;83(1):186-196.
20. Green L, Tan J, Morris JK, 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;103(4):738-745.

Appendix A. International Guidelines with Recommendations for Andexanet

Table 1. EU Guidelines and Practical Recommendations

Guideline Publication	Main Conclusions (Adapted from publication)	Citation
ESO Guide line on Reversal of Oral Anticoagulants in Acute Intracerebral Haemorrhage	We recommend using andexanet alfa if available – in adult patients with ICH occurring during use of rivaroxaban or apixaban.	Christensen H, et al. Eur Stroke J. 0(0) 1 – 13; doi org/10.1177/2396987319849763
Task Force for Advanced Bleeding Care in Trauma: The European Guideline on Management of Major Bleeding and Coagulopathy Following Trauma	If bleeding is life-threatening, we suggest administration of TXA 15 mg/kg (or 1 g) intravenously and that the use of PCC (25–50 U/kg) be considered until specific antidotes are available. (Grade 2C)	Spahn DR, et al. Crit Care. 2019;23(1):98
EHRA: Practical Guide on the Use of NOACs in Patients with Atrial Fibrillation	Based on the ongoing ANNEXA-4 study (which, in contrast to REVERSE-AD only includes patients with major/life-threatening bleeding), andexanet alfa may become the first choice of therapy in life-threatening bleeding under FXa-inhibitor therapy (pending its regulatory approval and availability).	Steffel J, et al. Eur Heart J. 2018; 39(16):1330-1393
ESC: Guidelines for the Management of Atrial Fibrillation	Immediate reversal of the antithrombotic effect is indicated in severe or life-threatening bleeding events […] Andexanet alfa, a modified recombinant human factor Xa that lacks enzymatic activity, reverses the anti-coagulant activity of factor Xa antagonists in healthy subjects within minutes after administration and for the duration of infusion, with a transient increase in markers of coagulation activity of uncertain clinical relevance.	Kirchoff P, et al. Eur J Cardio thorac Surg. 2016;50(5):e1-e88

BSG: UK national guideline on acute lower gastro intestinal bleeding	We recommend considering treatment with inhibitors such as idarucizumab or andexanet for life-threatening hemorrhage on direct oral anticoagulants.	Oakland K, et al. Gut. 2019;68:776–789. doi:10.1136/gutjnl-2018-317807

Table 2. US Guidelines

Guideline Publication	**Main Conclusions (Adapted from publication)**	**Citation**
Anticoagulation (AC) Forum Guidance: Reversal of Direct Oral Anticoagulants	In patients with rivaroxaban-associated or apixaban-associated major bleeding in whom a reversal agent is warranted, we suggest treatment with andexanet alfa dosed according to the US FDA label.	Cuker A, et al. Am J Hematol. 2019; doi: 10.1002/ajh.25475
NCCN: Cancer-Associated Venous Thromboembolic Disease Guidelines	Beneficial effects have been ascribed to the following: - Consider oral charcoal if dose within 2 hours of ingestion and repeat within 6 hours - Administer: • Andexanet alfa (consider for patient with intracranial hemorrhage) • Alternative options may include: aPCC; 4-factor PCC; rhFVIIa; If 4-factor PCC is unavailable or patient is allergic to heparin and/previous history of HIT in the last 12 months then administer 3-factor PCC	Streiff M, et al. NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease. NCCN Guidelines & Clinical Resources. February 28, 2019. Available at: www.nccn.org/professionals/physician_gls/pdf/vte.pdf, Accessed June 4, 2019
AHA/ACC/HRS: Focused Update of the 2014 Guideline for the Management of Patients With Atrial Fibrillation	Andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding.	January CT, et al. Circulation. 2019;pii: S0735-1097(19)30209-8
American College of Chest Physicians (ACCP): CHEST Guideline – Antithrombotic Therapy for Atrial Fibrillation	In a patient with serious bleeding, a specific reversal agent (where available) should be used instead. General haemostatic agents as nonspecific agents are less effective in reversing coagulation abnormalities and have not been shown to improve outcomes, and are potentially prothrombotic.	Lip G, et al. Chest. 2018;154:1121-1201
American Society of Hematology (ASH):	For patients with life-threatening bleeding during oral direct Xa	Witt D, et al. Blood Adv. 2018;22:32173291

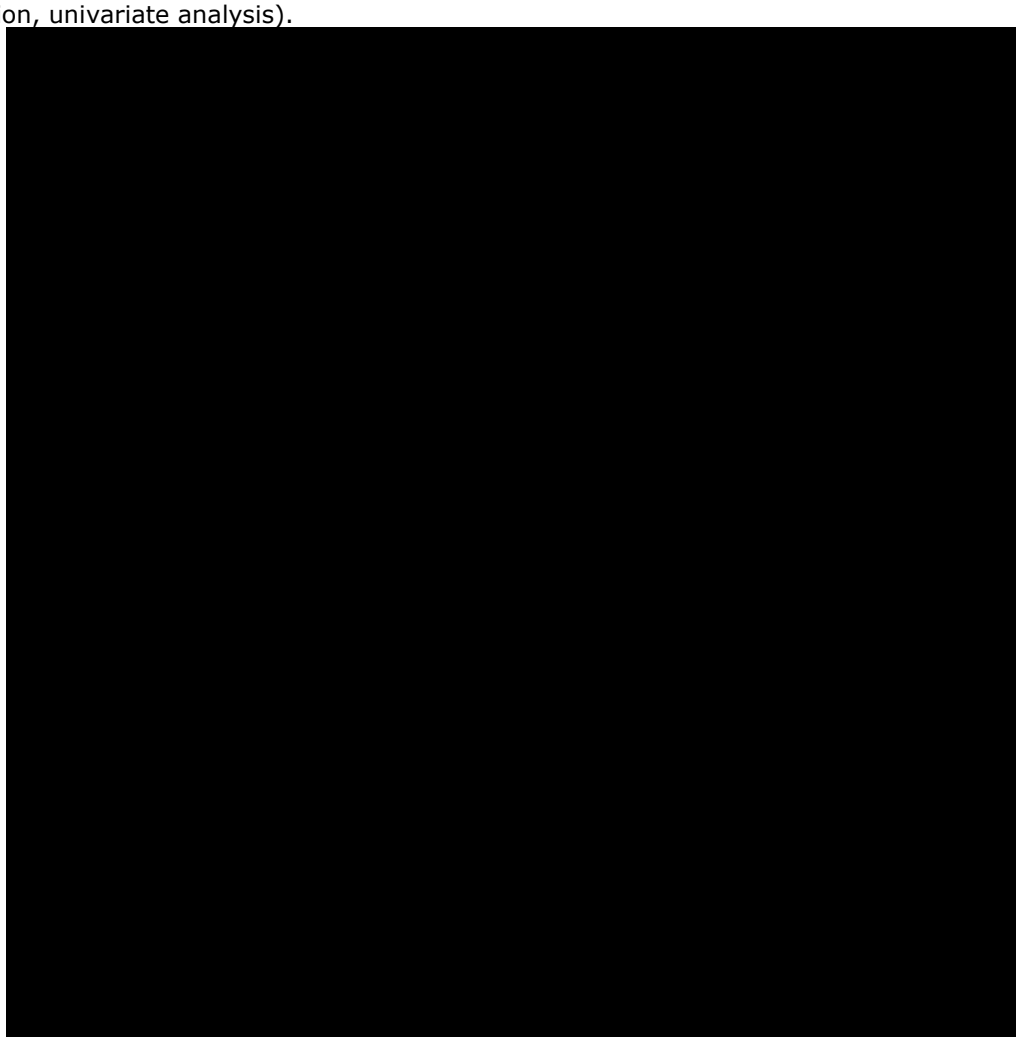
Guidelines for Management of Venous Thromboembolism	inhibitor treatment of VTE, the ASH guideline panel suggests using coagulation factor Xa (recombinant), inactivated-zhzo in addition to cessation of oral direct Xa inhibitor rather than no coagulation factor Xa (recombinant), inactivated-zhzo (conditional recommendation based on very low certainty in the evidence about effects). Remark: This recommendation does not apply to non-life-threatening bleeding. No data are available comparing the efficacy of 4-factor PCC and coagulation factor Xa (recombinant), inactivated-zhzo. The guideline panel offers no recommendation for 1 approach over the other.	
Anticoagulant Reversal Strategies in the Emergency Department Settings: Recommendations of a Multidisciplinary Expert Panel	Therefore, we suggest prothrombin complex concentrate for direct oral anticoagulant treatment only if first line reversal agents (e.g. Idarucizumab, andexanet alfa) are unavailable.	Baugh CW, et al. Annals of Emergency Medicine. Nov 2019. DOI: https://doi.org/10.1016/j.annemergmed.2019.09.001

Appendix B. ANNEXA-4 analysis of mortality by haematoma expansion

[redacted]

Figure 1. [redacted]

Patients surviving 30 days are indicated by the blue bars; patients dying within 30 days are indicated by the red bars. P for effect of baseline hematoma volume on death = 0.293 (logistic regression, univariate analysis).



Quartile	Volumes (cc)	N	Died (%)
1	0-3.85	[redacted]	[redacted]
2	3.85-9.46	[redacted]	[redacted]
3	9.46-21.29	[redacted]	[redacted]
4	21.29-58.25	[redacted]	[redacted]
All	0-58.25	[redacted]	[redacted]

Appendix C. ANNEXA-4 GI bleeding population

Analysis of the baseline characteristics of patients in ANNEXA-4 with GI bleeding indicates a population at high risk of death.

In ANNEXA-4, there were [redacted] subjects with GI bleeding of which [redacted] subjects had upper GI bleeding, [redacted] subjects had lower GI bleeding and [redacted] subjects with GI bleeding of an unknown location. [redacted] subjects with upper GI bleed and all [redacted] subjects with lower GI bleeding were taking either apixaban or rivaroxaban.

All subjects in ANNEXA-4 were reviewed by an independent external adjudication committee (EAC) comprised of three clinicians to ensure subjects met eligibility criteria and to validate haemostatic efficacy as per Sarode criteria.[1] Furthermore, where there was uncertainty regarding the severity of the bleed including assessment of haemodynamic instability, the EAC reviewed submitted patient records and raised queries to investigators.

For subjects with upper GI bleeding, mean age was [redacted] years with [redacted] of subjects whom were male. The median lowest documented baseline systolic blood pressure pre-andexanet administration was [redacted] mmHg with corresponding median heart rate of [redacted] bpm. The median lowest baseline documented haemoglobin pre-andexanet administration was [redacted] mg/dL. [redacted] of subjects with upper GI bleed had shock index of ≥1 (Table 3 and Table 5).

For subjects with lower GI bleeding, mean age was [redacted] years with [redacted] and [redacted] of subjects whom were male and female respectively. The median lowest baseline systolic blood pressure documented pre-andexanet administration was [redacted] mmHg with corresponding median and mean heart rate of [redacted] bpm. The median lowest baseline documented haemoglobin pre-andexanet administration was [redacted] mg/dL. [redacted] of subjects with shock index of ≥1 (Table 3 and Table 5).

[redacted] subjects had GI bleeding of unknown origin as determined by investigator. ANNEXA-4 did not routinely collect endoscopic data and these bleeds could have been due to clinically indeterminate location of GI bleeding and/or unidentified location of bleeding at endoscopy. However, the mean age of these subjects was [redacted] with [redacted] and [redacted] of subjects whom were male and female respectively. The median lowest baseline systolic blood pressure documented pre-andexanet administration was [redacted] mmHg with corresponding median and mean heart rate of [redacted] and [redacted] bpm. The median lowest baseline documentted haemoglobin pre-andexanet administration was [redacted] mg/dL. [redacted] of subjects with shock index of ≥1 (Table 3 and Table 5).

Table 3. Safety population (GI patients only) baseline demographics

	Upper GI (n=[redacted])	Lower GI (n=[redacted])	Unknown GI (n=[redacted])	Overall GI Safety (n=[redacted])
Age (years)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Min, Max]	[redacted]	[redacted]	[redacted]	[redacted]
Race				
ASIAN	[redacted]	[redacted]	[redacted]	[redacted]
BLACK OR AFRICAN AMERICAN	[redacted]	[redacted]	[redacted]	[redacted]
WHITE	[redacted]	[redacted]	[redacted]	[redacted]
Sex				
F	[redacted]	[redacted]	[redacted]	[redacted]
M	[redacted]	[redacted]	[redacted]	[redacted]
Region				
EU excluding UK	[redacted]	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]	[redacted]
UK	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Anti-fXa Activity (ng/mL)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Min, Max]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Systolic BP				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Min, Max]	[redacted]	[redacted]	[redacted]	[redacted]
HR corresponding to SBP				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Min, Max]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]

Table 4. Safety population (GI patients only) In-hospital and 30-Day Mortality.

	Upper GI (n=[redacted])	Lower GI (n=[redacted])	Unknown GI (n=[redacted])	Overall GI Safety (n=[redacted])
In-Hospital Mortality				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]
30-day Mortality				
N	[redacted]	[redacted]	[redacted]	[redacted]
Y	[redacted]	[redacted]	[redacted]	[redacted]

In-hospital and 30-day mortality rates in patients with Upper GI bleeding were [redacted] and [redacted] respectively. In-hospital and 30-day mortality rates in patients with lower GI bleeding were [redacted] and [redacted] respectively (Table 4).

ANNEXA-4 did not document detailed endoscopic findings. For upper GI bleeding subjects, the mean and median pre-endoscopy Rockall scores were [redacted] and [redacted], respectively. The mean and median Glasgow-Blatchford bleeding scores (GBS) were [redacted] and [redacted] respectively with no subject scoring below [redacted] points (Scores range from 0-23, with higher scores corresponding to increasing acuity and mortality). For patients with lower GI bleeding, [redacted] of subjects had a shock index of ≥1, and the mean and median Oakland scores were [redacted] and [redacted] respectively (Table 5).

Table 5. Safety population (GI patients only) Severity scoring.

	Upper GI (n=[redacted])	Lower GI (n=[redacted])	Unknown GI (n=[redacted])	Overall GI Safety (n=[redacted])
Hemoglobin				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Min, Max]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Rockall (Pre-Endoscopy)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Min, Max]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Oakland				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Min, Max]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
GBS				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Min, Max]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
GBS.Score				

	Upper GI (n=[redacted])	Lower GI (n=[redacted])	Unknown GI (n=[redacted])	Overall GI Safety (n=[redacted])
8	[redacted]	[redacted]	[redacted]	[redacted]
9	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]
11	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
13	[redacted]	[redacted]	[redacted]	[redacted]
14	[redacted]	[redacted]	[redacted]	[redacted]
15	[redacted]	[redacted]	[redacted]	[redacted]
16	[redacted]	[redacted]	[redacted]	[redacted]
17	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Shock Index (using HR corresponding to min SBP)				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median [Min, Max]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]
Shock Index (<1 or >=1)				
<0	[redacted]	[redacted]	[redacted]	[redacted]
>=1	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]

Table 6. Safety population (GI patients only) Baseline Anti-FXa activity levels.

	Apixaban /Rivaroxaban		Overall GI Safety			
	Upper GI (n=[redacted])	Lower GI (n=[redacted])	Unknown GI (n=[redacted])	Upper GI (n=[redacted])	Lower GI (n=[redacted])	Unknown GI (n=[redacted])
Baseline Anti-fXa Activity (ng/mL)						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median [Min, Max]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Conclusion on the severity of upper and lower GI bleeding subjects

The mean GBS score of [redacted] suggests that patients with upper GI bleeding were at high risk of death or requiring intervention at baseline. In the original distribution of risk scores published by Blatchford et al.[2] [redacted] of subjects in the score development cohort with a score of [redacted] required clinical intervention. No subject in our current ANNEXA-4 GI analysis scored below [redacted] points.

The clinical (pre-endoscopic) Rockall score of [redacted] in the upper GI bleeding subjects suggests a baseline mortality risk of [redacted].The observed in-hospital mortality of [redacted] and 30-day mortality rate [redacted] was observed across the ANNEXA-4 upper GI bleeding population.

The number of subjects with Upper and Lower GI bleeding with a GBS and Oakland score were too low to analyse interventions received during hospitalisation including endoscopy and transfusion requirements. Additionally, there were no documented cases of gastrointestinal haemorrhage SAEs occurring in subjects with documented upper or lower GI bleeds.

[redacted] percent of subjects with lower GI bleed had an initial shock index of ≥1 reflecting the haemodynamic instability of a quarter of subjects despite initial resuscitative measures. Mean and median Oakland scores of [redacted] and [redacted] observed in ANNEXA-4 predict only a [redacted] chance of safe-discharge.

There were [redacted] subjects where the location of GI bleeding was unknown and no conclusion can be drawn to the relevance of GI scoring across this population. Although ANNEXA-4 did not routinely collect endoscopic findings, efforts are underway to retrospectively review clinical findings from this population for future analyses.

A limitation of the above analyses is that the scoring systems were not originally developed in an anticoagulated population including patients taking FXa inhibitors. The extent to which anticoagulation including DOAC use would have affected mortality estimates is not known, and may be conservative.

It is also notable that despite initial fluid resuscitation, baseline mean and median anti-FXa levels across the upper, lower and unknown GI bleeding population receiving apixaban or rivaroxaban prior to andexanet administration were elevated. This fact attests to the severity of the GI bleeding subjects recruited into ANNEXA-4 which included FXa anticoagulated subjects who are profoundly anaemic with a median baseline haemoglobin of [redacted] [[redacted], [redacted] range] whom were hemodynamically unstable where 'watch-and-

wait and resuscitate' management cannot be undertaken with therapeutic FXa levels at time of reversal.

In summary, ANNEXA-4 enrolled a population of severe GI bleeding subjects with high predicted mortality of less than 30-days despite exclusion criteria of 30-day mortality. Many upper GI subjects would have needed interventions such as endoscopy or at risk of death. The majority of lower GI bleeding patients were unsafe for discharge. Mean and median anti-FXa inhibitor activity were within clinically therapeutic levels despite bleeding and initial resuscitation management. It is notable that the magnitude of effect when comparing the predicted upper GI mortality rates ([redacted]) and the actual mortality rates in upper GI patients ([redacted]) suggests a relative benefit of [redacted] which is consistent (if not slightly higher) with the mortality benefit as demonstrated from the propensity score matching analysis.

Appendix D. Clinical engagement

[redacted]

[redacted]

Appendix E. Andexanet alfa US real world multi-centre analysis

In May 2018, andexanet alfa was approved in US for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.[13] Following this approval, real-world evidence has been collected for patients treated with andexanet alfa in clinical practice in the US. Unlike the ANNEXA-4 study, there are no specified exclusion criteria applied when identifying patients for treatment with andexanet alfa in clinical practice. The only requirement is that patients require reversal of apixaban or rivaroxaban due to life-threatening or uncontrolled bleeding, as per the licenced indication.

The real-world evidence comprises a chart audit, which reported evidence from a multi-centre, retrospective review of electronic medical records for adult patients hospitalised for DOAC-related bleeding between May 2018 to December 2019 from 45 US-based hospitals. All data existed within the electronic medical record and was collected prior to the analysis for clinical purposes.

Details collected from the medical records included: patient age at hospitalization, sex, bleed site (gastrointestinal bleed (GI), intracranial haemorrhage (ICH) or other), anticoagulant administered prior to the bleed, and in-hospital mortality outcome. For each data category, the electronic case report form contained a list of available options.

Similar in-hospital mortality rates are observed in clinical practice compared to the ANNEXA-4 trial. Descriptive analyses of ANNEXA-4 and the US real world multi-centre analysis are presented in Table 7, Table 8 and Table 9. These analyses provide real-world data showing that andexanet alfa is associated with low mortality rates across all bleed types, as was also demonstrated in ANNEXA-4 and indirect comparisons.

Table 7. ANNEXA-4 versus US real world multi-centre analysis baseline characteristics and in-hospital mortality (Whole cohort)

	ANNEXA-4	US real world multi-centre analysis
Patients, N	[redacted]	[redacted]
Age in years (mean)	[redacted]	[redacted]
Male (%)	[redacted]	[redacted]
DOAC (%)		
Rivaroxaban	[redacted]	[redacted]
Apixaban	[redacted]	[redacted]
Bleed Type (%)		
ICH	[redacted]	[redacted]
GI	[redacted]	[redacted]
Other	[redacted]	[redacted]
In hospital mortality (%)		
ICH	[redacted]	[redacted]
GI	[redacted]	[redacted]
Other	[redacted]	[redacted]

Table 8. ANNEXA-4 versus US real world multi-centre analysis baseline characteristics and in-hospital mortality (ICH only)

	ANNEXA-4	US real world multi-centre analysis
Patients, N	[redacted]	[redacted]
Age in years (mean)	[redacted]	[redacted]
Male (%)	[redacted]	[redacted]
DOAC (%)		
Rivaroxaban	[redacted]	[redacted]
Apixaban	[redacted]	[redacted]
In hospital mortality (%)		
ICH	[redacted]	[redacted]

Table 9. ANNEXA-4 versus US real world multi-centre analysis baseline characteristics and in-hospital mortality (GI bleed only)

	ANNEXA-4	US real world multi-centre analysis
Patients, N	[redacted]	[redacted]
Age in years (mean)	[redacted]	[redacted]
Male (%)	[redacted]	[redacted]
DOAC (%)		
Rivaroxaban	[redacted]	[redacted]
Apixaban	[redacted]	[redacted]
In hospital mortality (%)		
GI	[redacted]	[redacted]

Appendix F. ANNEXA-4 and ORANGE populations

There are several similarities between the inclusion and exclusion criteria of ANNEXA-4 and ORANGE, including the fact that both incorporate some variation of the definition of life-threatening bleedings from ISTH guidelines.[14] However, we recognise that there are differences between the studies, which were addressed where possible with data manipulation and obtaining clinical opinion on the appropriateness of the comparison.

Table 10 presents the inclusion/exclusion criteria from ANNEXA-4 and ORANGE and how we addressed the differences between the two studies. All changes were ratified with UK clinical experts to ensure a fair and appropriate comparison between studies. Appendix D confirms the clinical opinion that the studies can be compared with the measures taken.

Table 10. Inclusion and exclusion criteria from ANNEXA-4 and ORANGE

	ANNEXA-4	ORANGE	Impact and how difference was addressed
Inclusion criteria			
– Bleeding in critical area or organ*	✓	✓	-
– Bleeding expected to be fatal	✓	✓	-
– A fall in haemoglobin of more than 2g/dL	✓	✓	-
– Symptoms of hemodynamic compromise	✓	NR	**Impact:** Criterion aligned with ISTH guidelines for life-threatening bleed, which may result in more severe patients entering ANNEXA-4 than ORANGE. **Steps taken to address:** using the PCC subset of ORANGE to identify the most severe bleeds.
– Major bleeding – transfusion of >=2 units – Transfusion of FFP – Administration of one of the following products: PCC, recombinant activated factor VII, FEIBA or	-	✓	**Impact:** Criteria may result in non-life threatening major bleeds entering the ORANGE study. **Steps taken to address:** using the PCC subset of ORANGE to identify the most severe bleeds.

fibrinogen concentrates			
Exclusion criteria			
– Expected survival of less than 1 month – People with ICH with any of the following: GCS<7 or estimated intracerebral haematoma volume > 60cc as assessed by the CT or MRI	✓	NR	**Impact:** Negligible as real-world evidence shows that relaxing such criteria does not impact andexanet alfa's mortality effect. **Steps taken to address:** As noted in the ACD, all eligible patients meeting the licence would have been screened, unless they were on a known end of life pathway. Analysis of pre-screen failures [redacted] confirms that these criteria did not exclude a meaningful proportion of patients who would otherwise receive andexanet alfa in clinical practice.

**Critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome*

Abbreviations: CT, Cat scan; FFP, fresh frozen plasma; GCS, Glasgow Coma Scale; MRI, Magnetic resonance imaging; NR, Not reported; PCC, prothrombin complex concentrate

Appendix G. Rosenbaum sensitivity analysis

The Rosenbaum sensitivity analysis tests how robust results are to confounding caused by unobserved variables affecting both treatment assignment and outcome ('confounding variables'), using a parameter called gamma (Γ).[15] Let $\pi_{i=j,k}$ represent the probability of receiving the treatment of interest (in the case of this analysis, andexanet alfa) for individual i, conditional on a vector of relevant variables for each individual, i, $x_{i=j,k}$. The Γ parameter defines bounds within which the ratio of the odds of receiving treatment for a treated individual, j, and control individual, k, who have identical covariate observations $x_j = x_k$, is hypothesised to sit.

Equation 1. The hypothesis tested in the Rosenbaum sensitivity analysis for a range of Γ

$$\frac{1}{\Gamma} \leq \frac{\frac{\pi_j}{1-\pi_j}}{\frac{\pi_k}{1-\pi_k}} \leq \Gamma$$

When we generate results and interpret their p values relative to a given significance level without conducting any sensitivity analysis, we assume that the condition set out in Equation 1 need only hold for $\Gamma = 1$. That is to say that we assume that there are no confounding variables so $\pi_j = \pi_k | x_j = x_k$.

In the Rosenbaum sensitivity analysis, a range of different hypotheses are tested, each of which postulates that the condition in Equation 1 holds for a different value of Γ > 1, beginning with 2 ≥ Γ ≥ 1.[15] We thereby test by what factor confounding variables would have to cause $\frac{\pi_j}{1-\pi_j}$ to differ from $\frac{\pi_k}{1-\pi_k}$ for our statistical inference to change. The results of the test indicate whether the statistical significance of our base case results would change if the assumptions we could make around the impact of unobserved covariates became incrementally weaker, given a certain significance level. Here, the significance level α used was 0.05.

For example, if we hypothesise that the condition in Equation 1 holds for Γ = 1.8 and we get a p value of 0.03 when testing this, we can assume that the condition holds true. That is to say that if unobserved variables caused $\frac{\pi_j}{1-\pi_j}$ to differ from $\frac{\pi_k}{1-\pi_k}$ by no more than a factor of 1.8 and no less than a factor of 1/1.8 = ~0.56, then our inference around the statistical significance of our base case results would not change.

The Rosenbaum sensitivity analysis was conducted in R Studio software, using the *rbounds* package and approach described by Keele 2010.[15] The *binarysens* command was used to generate p values associated with values of 2 ≥ Γ ≥ 1 for a propensity score matching analysis with a binary outcome, as recommended by Keele 2010.[15] Data outputs from the *match* command in the *MatchIt* package were manipulated into a list format, in order to be appropriate inputs for the *binarysens* command.

The results of the sensitivity analysis in Table 11 consider our base case propensity score matching analysis, with the exception that due to the nature of the sensitivity analysis, matching must be done without replacement (see **Error! Reference source not found.**, Appendix H).

The results show that for the whole, ICH + GI and ICH cohorts, even if unobserved variables meant that one partner in a matched pair was [redacted] times more likely to receive andexanet alfa in reality than the other partner, we could still conclude that andexanet alfa made patients less likely to die within 30 days. If one partner in the matched pair was [redacted] times more likely to receive andexanet alfa in reality than the other partner, base case results may cease to be statistically significant. No interpretation could be made for the GI bleed cohort, as statistical significance was not achieved in the base case due to the low number of events.

Table 11. Rosenbaum sensitivity analysis results for propensity score matching base case

Rosenbaum sensitivity analysis results	Highest value of gamma parameter (Γ) at which p-value remains significant (p-value)
Whole cohort	[redacted]
ICH + GI bleed	[redacted]
ICH	[redacted]
GI bleed	[redacted]

Appendix H. Indirect comparison approaches

Five different approaches were used to generate indirect comparative data to compare ANNEXA-4 versus ORANGE. These analyses were:

1) Base case, with covariates included following ERG request (**Error! Reference source not found.**)
   a) 1:1 nearest neighbour matching with replacement
   b) Covariates include age, bleed sites (ICH, GI, Other) and their subtypes, and medical history (Stroke, CAD, TIA, AF, hypertension, diabetes, renal dysfunction, cancer)
2) Scenario 1 (Table 13), with covariates included following ERG request
   a) 1:1 nearest neighbour matching without replacement
   b) Covariates include age, bleed sites (ICH, GI, Other) and their subtypes, and medical history (Stroke, CAD, TIA, AF, hypertension, diabetes, renal dysfunction, cancer)
3) Scenario 2 (**Error! Reference source not found.**), with covariates included for original submission
   a) 1:1 nearest neighbour matching with replacement
   b) Covariates include age, bleed sites (ICH, GI and other) and medical history (Stroke, CAD, TIA, AF, hypertension, diabetes, renal dysfunction, cancer)
4) Scenario 3 (Table 15), with covariates included for original submission
   a) 1:1 nearest neighbour matching without replacement
   b) Covariates include age, bleed sites (ICH, GI and other) and and medical history (Stroke, CAD, TIA, AF, hypertension, diabetes, renal dysfunction, cancer)
5) Scenario 4 (Table 16)
   a) Weights stabilised by multiplying the raw weight by the real probability of treatment
   b) The impact of extreme weights addressed by removing the 1% of patients with the greatest weights and the 1% of patients with the lowest weights
   c) Covariates include age, bleed sites (ICH, GI, Other) and their subtypes, and medical history (Stroke, CAD, TIA, AF, hypertension, diabetes, renal dysfunction, cancer)

All results were consistent for whole cohort, ICH+GI, ICH and GI bleed subgroups (Tables 12-16).

Propensity score matching analyses

Analyses 1-4 above adopted different variations of a propensity score matching (PSM) methodology. Section 2.9 of the NICE re-submission submitted on the 23rd of September 2019 describes:

- The methods used to select a source of comparative data (ORANGE);
- A quality assessment of the ORANGE study;
- Baseline characteristics and results in the ORANGE study;

- The feasibility assessment undertaken prior to PSM analysis;
- Potential limitations of the analysis;
- Methods of conducting the analysis, including covariates selected for the propensity score regression equation;
- Results of the original PSM analysis, and;
- Discussion of results and their applicability to the model.

In summary, a feasibility assessment preceded analyses to ensure that the 'ignorability of treatment' and 'overlap' assumptions were met,[16] and analyses consisted of specification of a propensity score regression equation using a logit model, and then 1:1 nearest neighbour PSM with replacement, between patients from ANNEXA-4 and ORANGE.

Variables were selected for inclusion in the propensity score regression model from the variables observed in ANNEXA-4 and ORANGE, if they were considered to affect both treatment assignment and 30-day mortality. UK clinical experts in haematology were involved in making the assessment of different variables' impact on 30-day mortality, while t-tests and Chi-squared tests were used to assess the effect of the variables on treatment assignment. As a result, twelve covariates were included in the propensity score regression model.

Patients from ANNEXA-4 or ORANGE were only included in the PSM analysis if they had received apixaban or rivaroxaban and had observed data for age and mortality variables. Patients from the ORANGE population were also only included if they received PCCs, as UK clinical experts in haematology indicated that these patients would have experienced bleeds of a severity comparable to that among patients in ANNEXA-4.

Original analyses were presented for the whole cohort of patients eligible for analysis, and for three subsets of patients with each of the following bleed types: ICH, GI bleeds, and other major bleeds. Results for a further subset of the whole cohort are presented in Table 12 - Table 15, to include both patients with an ICH and with a GI bleed, since this population is now presented as a cohort in the cost effectiveness model. Analyses were all conducted using the MatchIt package in R Studio software, after data cleaning.

IPTW analyses

As an alternative to PSM, inverse probability of treatment (IPTW or IPW for short) analysis takes another approach to generating adjusted comparative results using propensity score.

This was the approach adopted in Analysis 5 described above. A Coursera course by Professor Jason Roy of the University of Pennsylvania informed the approach taken to IPTW.[17] The *tableone, ipw, sandwich, dplyr* and *survey* packages were used in R Studio to conduct analyses.

After data cleaning, a logit model was specified to estimate propensity score, using the same covariates used in the PSM analysis. Raw weights for every individual were then generated, as 1 divided by propensity score for treated patients and 1 divided by one minus

propensity score for control group patients. These were then stabilised by multiplying each weight through by the actual probability of the patient receiving the treatment they did receive, unconditional on any covariates. These probabilities of treatment were equal to the proportions of patients receiving each treatment in the sample.

As IPTW is known to give unstable results if extreme weights are included,[18] the top 1% of patients with highest weight from each group. This is a standard practice recommended in literature to avoid the uncertainty of choosing what is a large weight and choosing some maximum score to impute.[19] 30-day mortality was then estimated by generating a new, weighted data set and generating summary statistics for the 30-day mortality variable.

The results of the IPW show a similar reduction in 30-day mortality rate to the results of the PSM. As discussed previously, the other major bleeds are subject to heterogeneity in terms of bleed site, so a conservative assumption around mortality is included in the model in favour of unreliable adjusted results.

Table 12. Propensity score matching results with replacement (base case)

	ORANGE, % (N) (95% CI)	ANNEXA-4, % (N) (95% CI)	Relative reduction* (%)
Whole cohort	[redacted]	[redacted]	[redacted]
ICH + GI	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]
GI bleed	[redacted]	[redacted]	[redacted]
Other bleeds	[redacted]	[redacted]	[redacted]

*Relative reduction = (ANNEXA-4 mortality rate – ORANGE mortality rate)/(ORANGE mortality rate)

Table 13. Propensity score matching results without replacement (scenario 1)

	ORANGE, % (N) (95% CI)	ANNEXA-4, % (N) (95% CI)	Relative reduction* (%)
Whole cohort	[redacted]	[redacted]	[redacted]
ICH + GI	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]
GI bleed	[redacted]	[redacted]	[redacted]
Other bleeds	[redacted]	[redacted]	[redacted]

*Relative reduction = (ANNEXA-4 mortality rate – ORANGE mortality rate)/(ORANGE mortality rate)

Table 14. Propensity score matching results with replacement, alternative covariates (scenario 2)

	ORANGE, % (N) (95% CI)	ANNEXA-4, % (N) (95% CI)	Relative reduction* (%)
Whole cohort	[redacted]	[redacted]	[redacted]
ICH + GI	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]
GI bleed	[redacted]	[redacted]	[redacted]
Other bleeds	[redacted]	[redacted]	[redacted]

*Relative reduction = (ANNEXA-4 mortality rate – ORANGE mortality rate)/(ORANGE mortality rate)

Table 15. Propensity score matching results without replacement, alternative covariates (scenario 3)

	ORANGE, % (N) (95% CI)	ANNEXA-4, % (N) (95% CI)	Relative reduction* (%)
Whole cohort	[redacted]	[redacted]	[redacted]
ICH + GI	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]
GI bleed	[redacted]	[redacted]	[redacted]
Other bleeds	[redacted]	[redacted]	[redacted]

*Relative reduction = (ANNEXA-4 mortality rate – ORANGE mortality rate)/(ORANGE mortality rate)

Table 16. Inverse probability weighting results (scenario 4)

	ORANGE, % (N) (95% CI)	ANNEXA-4, % (N) (95% CI)	Relative reduction* (%)
Whole cohort	[redacted]	[redacted]	[redacted]
ICH + GI	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]
GI bleed	[redacted]	[redacted]	[redacted]
Other bleeds	[redacted]	[redacted]	[redacted]

*Relative reduction = (ANNEXA-4 mortality rate – ORANGE mortality rate)/(ORANGE mortality rate)

Appendix I. Updated economic results for ICH and GI cohorts

Description of revised base case

We have considered recommendations from the ERG and have revised our base case in the cost-effectiveness model (CEM), to include the following assumptions:

- Rehabilitation costs for patients who have experienced and ICH have been restricted to apply only for the first 12 months after the bleed. This decision was informed by recommendations from the ERG report, which advised that a patient would be very unlikely to incur rehabilitation costs for longer than a 12 month period. Our previous company base case, at the time of submission to the ERG, included ICH rehabilitation costs which were applied over the whole time horizon.

- A [redacted] discount as part of a patient access scheme. This discount has been applied to the cost of andexanet alfa in the revised base case.

All results presented for the revised base case for each of the model cohorts below conform to these specifications.

We present results of a number of scenarios in which the assumptions around the morbidity and mortality benefits of andexanet alfa are varied.

In the model, the key mortality benefit for andexanet alfa relative to SoC is reflected by differences in 30-day mortality between the two treatment arms. Meanwhile, morbidity benefits are reflected by differences in quality of life and long-term life expectancy between andexanet alfa and SoC for patients with ICH, and intraspinal and intraocular bleeds.

For mortality benefit, thresholds of effect and alternative indirect comparison approaches are considered to test uncertainty.

For morbidity benefit in ICH patients, the level of benefit is varied between 0% (as per ERG alternative base case) and 100% (as per our revised base case) based on the absolute differences in mRS scores sourced from ANNEXA-4 and Øie et al. 2018[20] for andexanet alfa and SoC respectively. For example, at 0% the absolute difference is assumed to be zero, at 100% the absolute difference is as observed between ANNEXA-4 and Øie et al. 2018, at 50% the absolute difference represents half the absolute difference observed between ANNEXA-4 and Øie et al. 2018.[20]

For morbidity benefit in intraspinal bleeding and intraocular bleeding patients, the proportion of patients assumed to have morbidity benefit from andexanet alfa is varied between 0% and 50%, with 25% set as the base case based on UK clinical expert opinion.

The results of these scenarios are shown below under sub-headings presenting results of scenarios varying mortality and morbidity.

Results for ICH + GI

Table 17 shows the primary results of different threshold analyses and scenarios varying the mortality and morbidity benefit of andexanet alfa for the ICH + GI combined cohort. In none of the scenarios tested did the ICER exceed £30,000. Likewise, no ICER above £20,000 was generated in any scenario until the morbidity benefit was reduced to [redacted] or less than its assumed value in the revised base.

Table 17. Results of six different scenarios combined with different assumptions between 0 and 100% around the relative benefit of andexanet alfa relative to SoC, for the ICH + GI cohort

Andexanet alfa vs. SoC relative morbidity benefit (%)	Revised base case	*Threshold Analysis 1*	*Threshold Analysis 2*	*ITC Scenario 1*	*ITC Scenario 2*	*ITC Scenario 3*	*ITC Scenario 4*
		Andexanet alfa 30-day mortality increased by [redacted]	*SoC 30-day mortality decreased by* [redacted]	*Base case PSM, except matching without replacement*	*Base case PSM, except covariates not dissagregated by subtype*	*Base case PSM, except matching without replacement and covariates not dissagregated by subtype*	*IPW*
100	[redacted]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: IPW, inverse probability weighting; ITC, Inverse treatment comparison; PSM, propensity score matching; SoC, standard of care
**Manufacturer's revised base case, **ERG alternative base case*

Results of revised base case

Table 18 shows the results of our revised base case for the ICH + GI bleed cohort. For the group including both ICH and GI bleeds, andexanet alfa was associated with [redacted] additional QALYs relative to PCCs, at an additional cost of [redacted], to give an ICER of [redacted] per QALY.

Table 18. Cost effectiveness results for revised base case

Cohort	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
ICH + GI bleed								
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: QALY, quality-adjusted life-year; LY, life-year: ICER, Incremental cost-effectiveness ratio								

Results of probabilistic and one-way sensitivity analysis

Table 19 shows the mean results, including the mean ICER, across 10,000 iterations of probabilistic sensitivity analysis for the ICH + GI bleed cohort. The results are similar to the revised model base case for the ICH + GI population.

The incremental cost effectiveness plane for the ICH + GI cohort is presented in

Figure 2. This shows that for the ICH + GI bleed all iterations of the probabilistic sensitivity analysis yielded results falling in the upper right quadrant of the incremental cost effectiveness plane, indicating that andexanet alfa was associated with a higher QALY gain than SoC and some additional cost in almost all cases.

Figure 3 shows the cost effectiveness acceptability frontier for the ICH + GI bleed cohort, while

Figure 4. [redacted]

shows the cost effectiveness acceptability curve for this population. These show that at a willingness to pay under £20,000, andexanet alfa becomes more cost effective than SoC.

Finally, **Error! Reference source not found.** shows a tornado diagrams, which presents the upper and lower bound ICERs associated with upward and downward variation in key parameters in order of the magnitude of their impact on the ICER, for the ICH + GI cohort. The ICERs associated with the upper and lower bounds between which the key parameters are varied are presented in Table 20 for the 20 key parameters with the greatest impact on the model ICERs for the ICH + GI cohort.

Table 19. ICH + GI cohort - mean results of probabilistic sensitivity analysis over 10,000 iterations

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Cost per QALY (£)
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: QALY, quality-adjusted life-year					

Figure 2. [redacted]

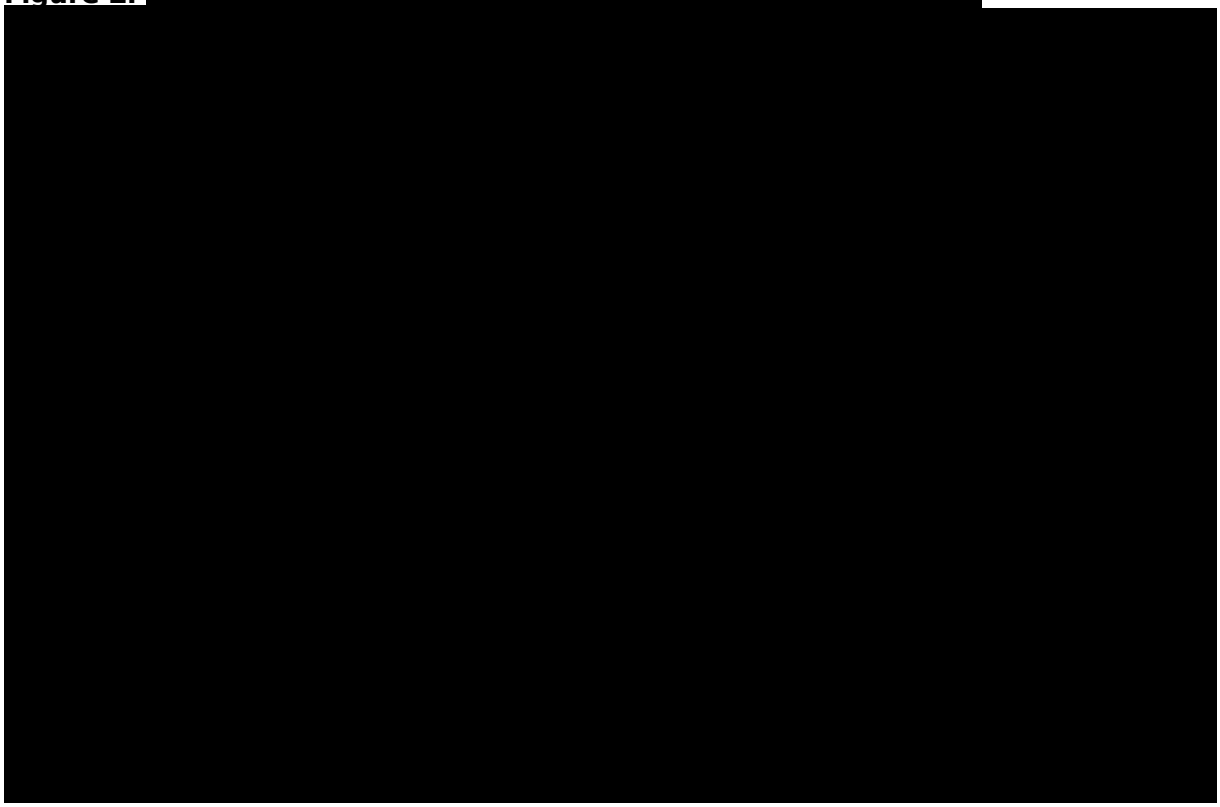


Figure 3. [redacted]

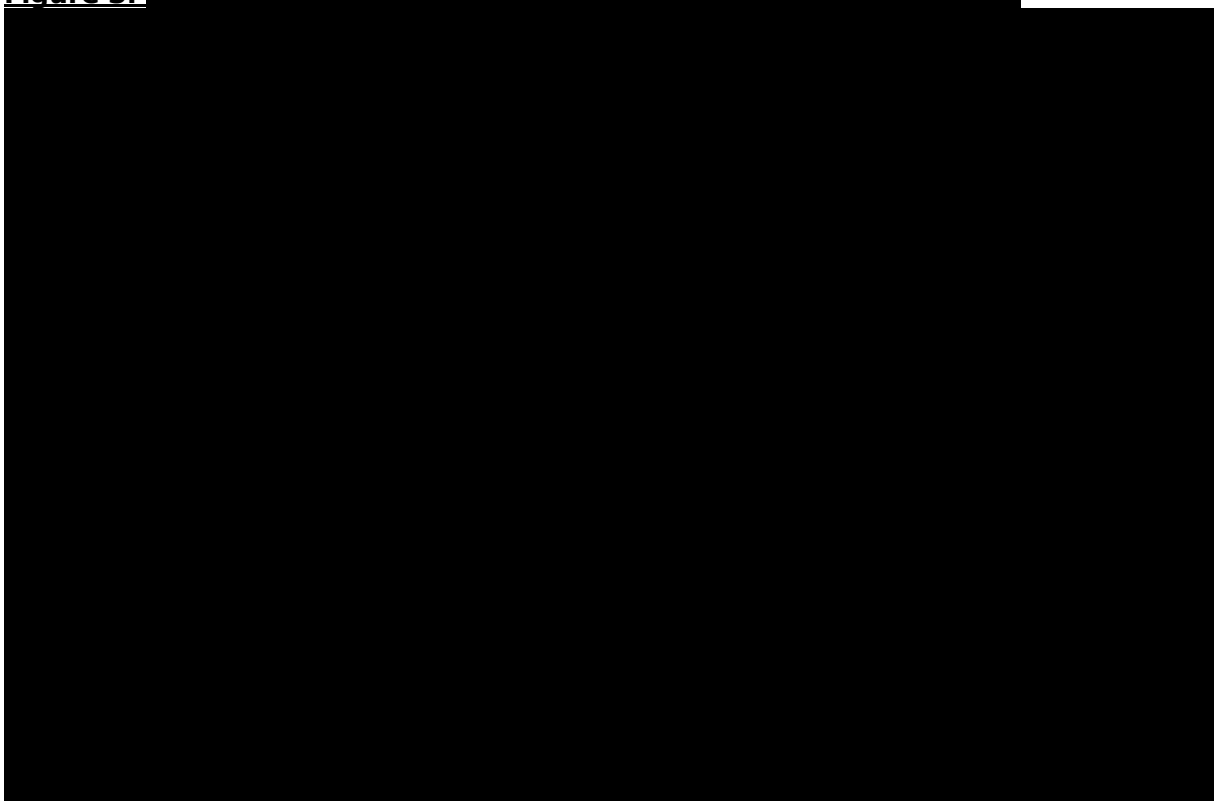


Figure 4. [redacted]

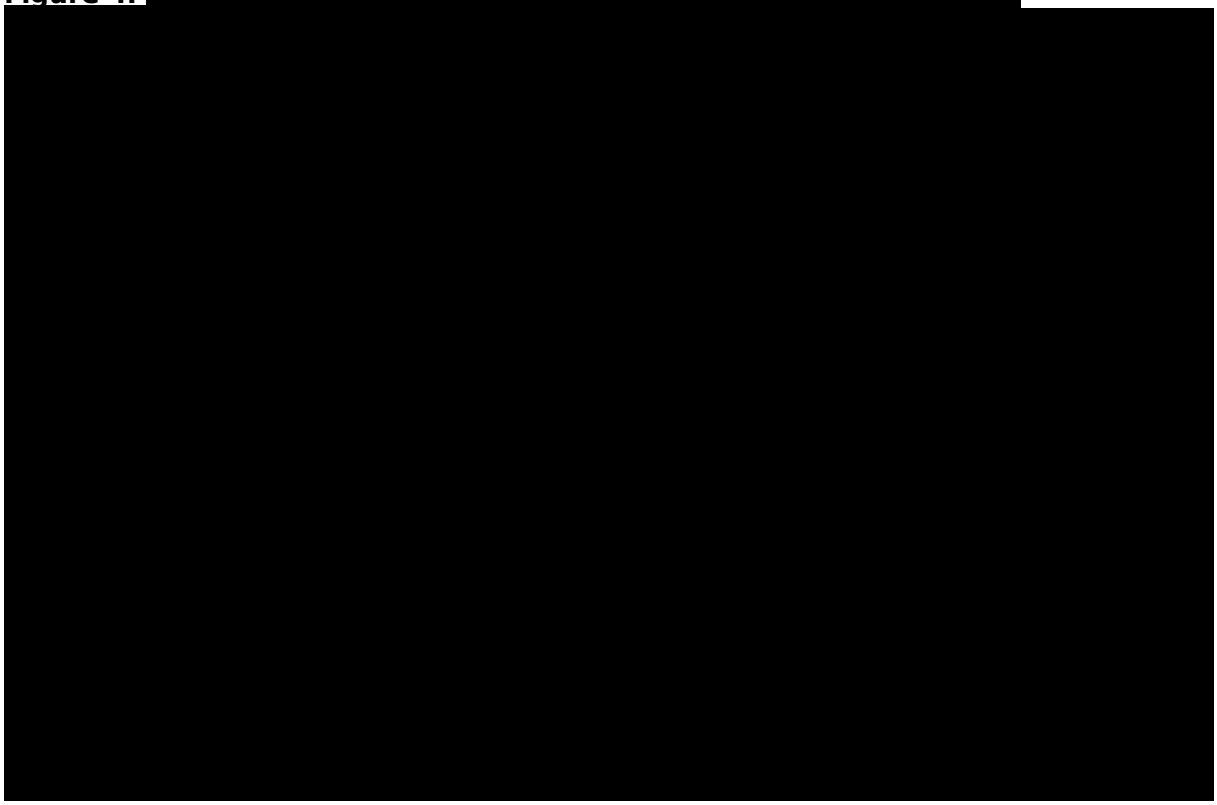


Figure 5. [redacted]

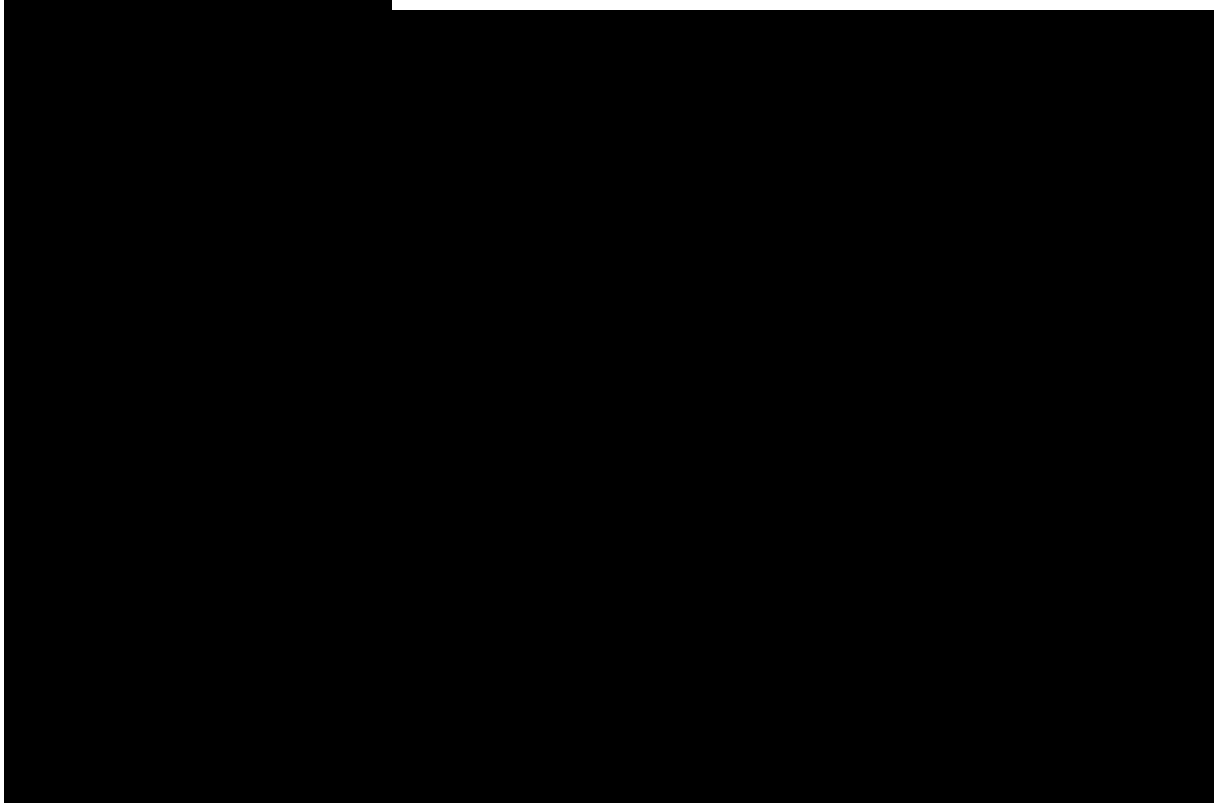


Table 20. ICH + GI cohort – one way sensitivity analysis results showing lower and upper bound ICERs resulting from variation in key parameters

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Andexanet alfa ICH bleed long-term care cost (£)	[redacted]	[redacted]	[redacted]
Utility: ICH follow-up care	[redacted]	[redacted]	[redacted]
Standard of Care ICH bleed long-term care cost (£)	[redacted]	[redacted]	[redacted]
30-day mortality - Severe GI - Standard of Care	[redacted]	[redacted]	[redacted]
30-day mortality - ICH - Standard of Care	[redacted]	[redacted]	[redacted]
Standard of Care ICH bleed acute care cost (£)	[redacted]	[redacted]	[redacted]
Andexanet alfa ICH bleed acute care cost (£)	[redacted]	[redacted]	[redacted]
Utility: Severe GI Bleed follow-up care	[redacted]	[redacted]	[redacted]
30-day mortality - Severe GI - Andexanet alfa	[redacted]	[redacted]	[redacted]
30-day mortality - ICH - Andexanet alfa	[redacted]	[redacted]	[redacted]
Standard of Care decision tree distribution of bleed types	[redacted]	[redacted]	[redacted]
Standard of Care Severe GI bleed acute care cost (£)	[redacted]	[redacted]	[redacted]
Andexanet alfa Severe GI bleed acute care cost (£)	[redacted]	[redacted]	[redacted]
Andexanet alfa Severe GI bleed long-term care cost (£)	[redacted]	[redacted]	[redacted]
Standard of Care Severe GI bleed long-term care cost (£)	[redacted]	[redacted]	[redacted]
Administration cost per cycle with Andexanet alfa (£):	[redacted]	[redacted]	[redacted]
Utility: ICH acute care	[redacted]	[redacted]	[redacted]
Administration cost per cycle with Standard of Care (£):	[redacted]	[redacted]	[redacted]
Utility: Severe GI Bleed acute care	[redacted]	[redacted]	[redacted]
Andexanet alfa decision tree distribution of bleed types	[redacted]	[redacted]	[redacted]

Abbreviations: ICH, intracranial haemorrhage; ICER, Incremental cost-effectiveness ratio; GI, Gastrointensital

Results for ICH only

Table 21 shows the primary results of different threshold analyses and scenarios varying the mortality and morbidity benefit of andexanet alfa for the ICH only cohort. In none of the scenarios tested did the ICER exceed £30,000. Likewise, no ICER above £20,000 was generated in any scenario until the morbidity benefit was reduced to [redacted] or less than its assumed value in the revised base.

Table 21. Results of six different scenarios combined with different assumptions between 0 and 100% around the relative benefit of andexanet alfa relative to SoC, for an ICH only cohort

Andexanet alfa vs. SoC relative morbidity benefit (%)	Revised base case	*Threshold Analysis 1*	*Threshold Analysis 2*	*ITC Scenario 1*	*ITC Scenario 2*	*ITC Scenario 3*	*ITC Scenario 4*
		Andexanet alfa 30-day mortality increased by [redacted]	*SoC 30-day mortality decreased by* [redacted]	*Base case PSM, except matching without replacement*	*Base case PSM, except covariates not dissagregated by subtype*	*Base case PSM, except matching without replacement and covariates not dissagregated by subtype*	*IPW*
100	[redacted]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SoC, standard of care, IPW, inverse probability weighting: PSM, propensity score matching
**Manufacturer's revised base case, **ERG alternative base case*

Results of revised base case

Table 18 shows the results of our revised base case for the ICH only cohort. For the ICH only group, andexanet alfa was associated with [redacted] more QALYs overall than PCCs, at an additional cost of [redacted], to give an ICER of [redacted] per QALY.

Table 22. Cost effectiveness results for revised base case

Cohort	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
ICH only								
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: QALY, quality-adjusted life-year; LY, life-year: ICER, Incremental cost-effectiveness ratio								

Results of probabilistic and one-way sensitivity analysis

Table 23 shows the mean results, including the mean ICER, across 10,000 iterations of probabilistic sensitivity analysis for the ICH only cohort. The results are similar to the revised model base case for the ICH only population.

The incremental cost effectiveness plane for the ICH only cohort is presented in

Abbreviations: QALY, quality-adjusted life-year

Figure 6. [redacted]

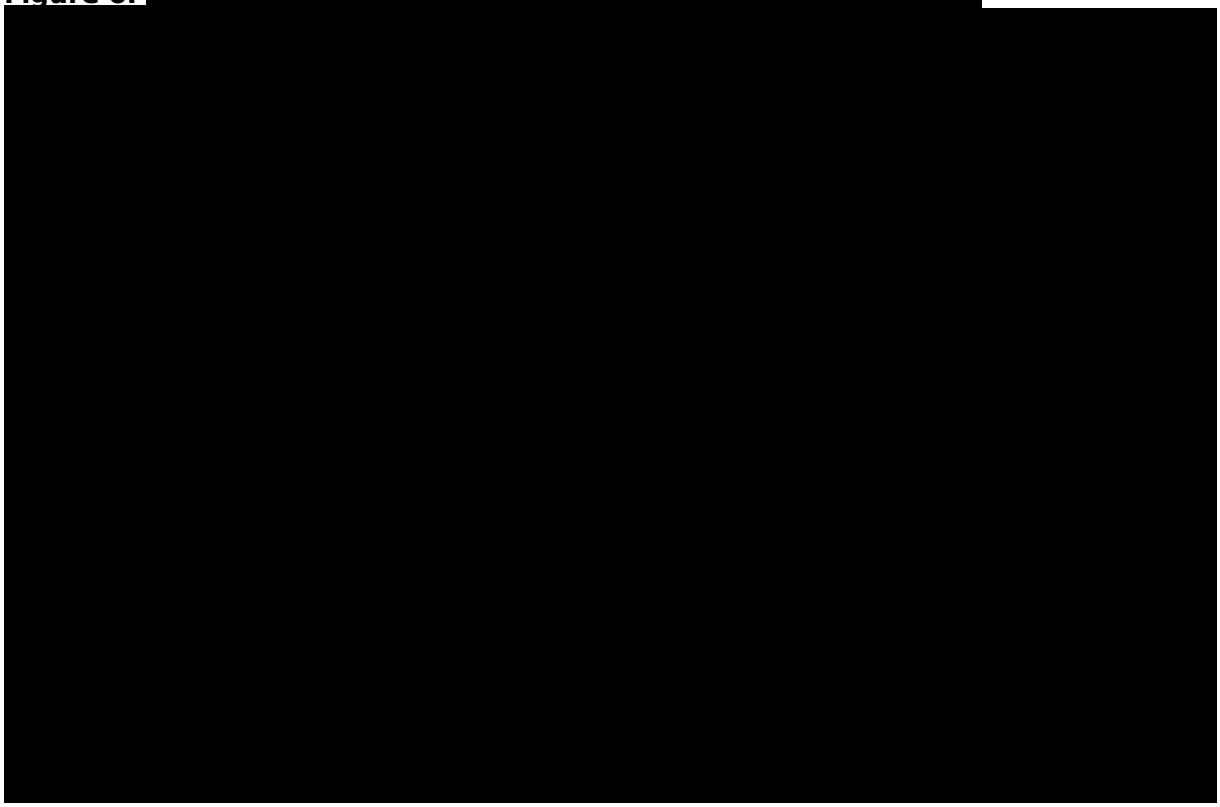


Figure 7. [redacted]

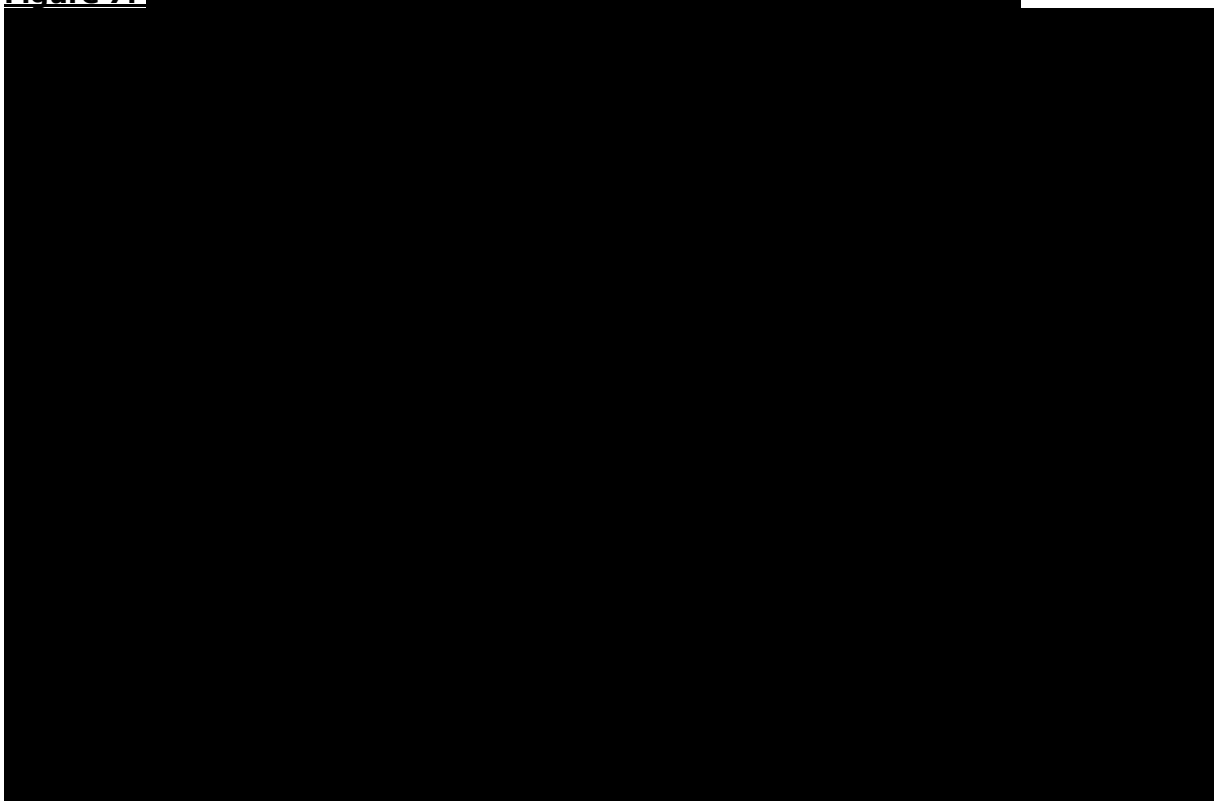


Figure 8. [redacted]

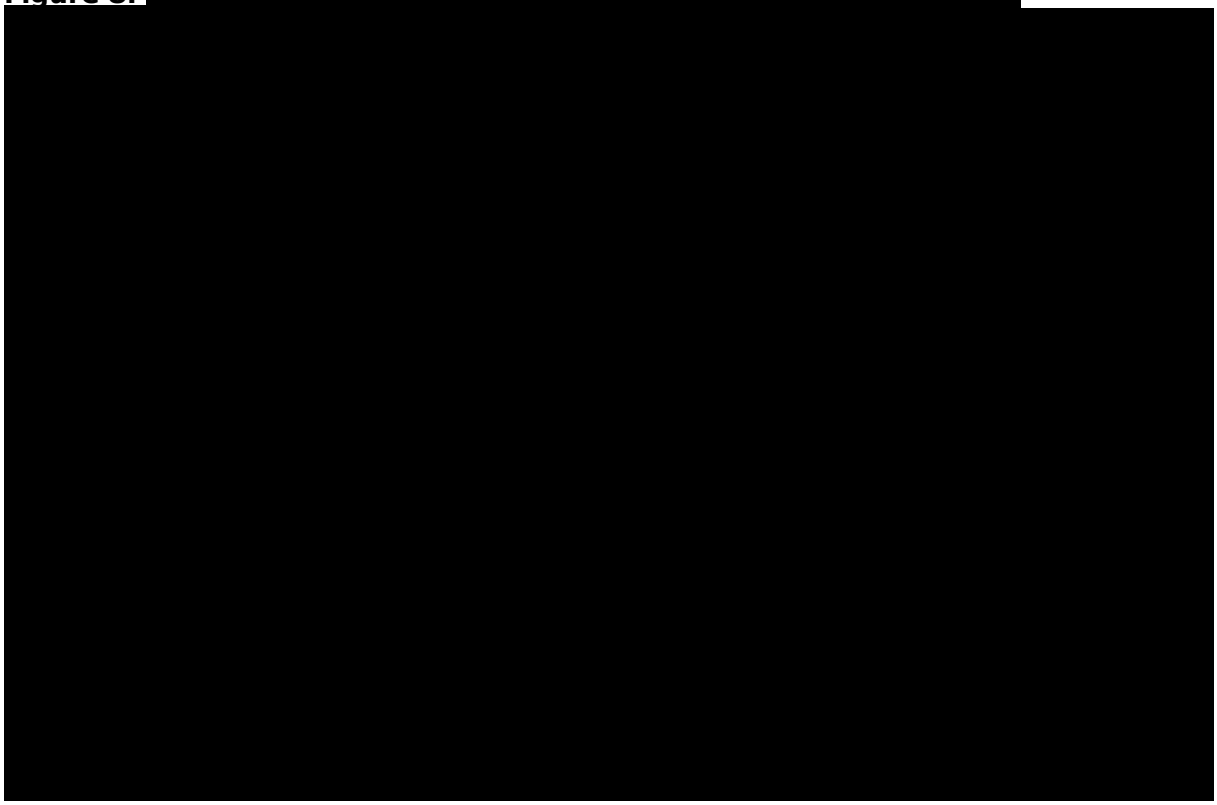
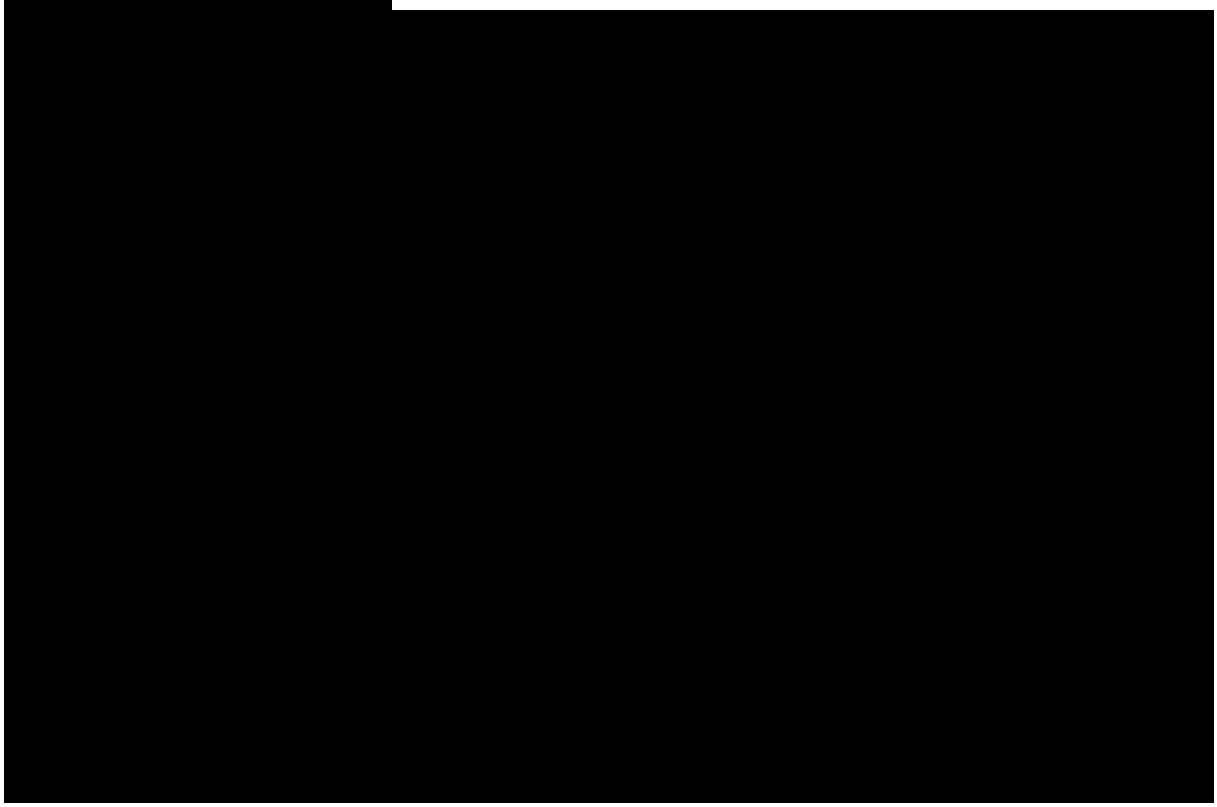


Figure 9. [redacted]



. This shows that for the ICH only cohort all iterations of the probabilistic sensitivity analysis yielded results falling in the upper right quadrant of the incremental cost effectiveness plane, indicating that andexanet alfa was associated with a higher QALY gain than SoC and some additional cost in almost all cases.

Error! Reference source not found. shows the cost effectiveness acceptability frontier for the ICH only cohort, while**Error! Reference source not found.** shows the cost effectiveness acceptability curve for this population. These show that at a willingness to pay under £20,000, andexanet alfa becomes more cost effective than SoC.

Finally, **Error! Reference source not found.** shows a tornado diagram, which presents the upper and lower bound ICERs associated with upward and downward variation in key parameters in order of the magnitude of their impact on the ICER, for the ICH only cohort. The ICERs associated with the upper and lower bounds between which the key parameters are varied are presented in Table 24 for the 10 key parameters with the greatest impact on the model ICERs for the ICH only cohort.

Table 23. ICH only cohort - mean results of probabilistic sensitivity analysis over 10,000 iterations

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Cost per QALY (£)
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: QALY, quality-adjusted life-year					

Figure 6. [redacted]

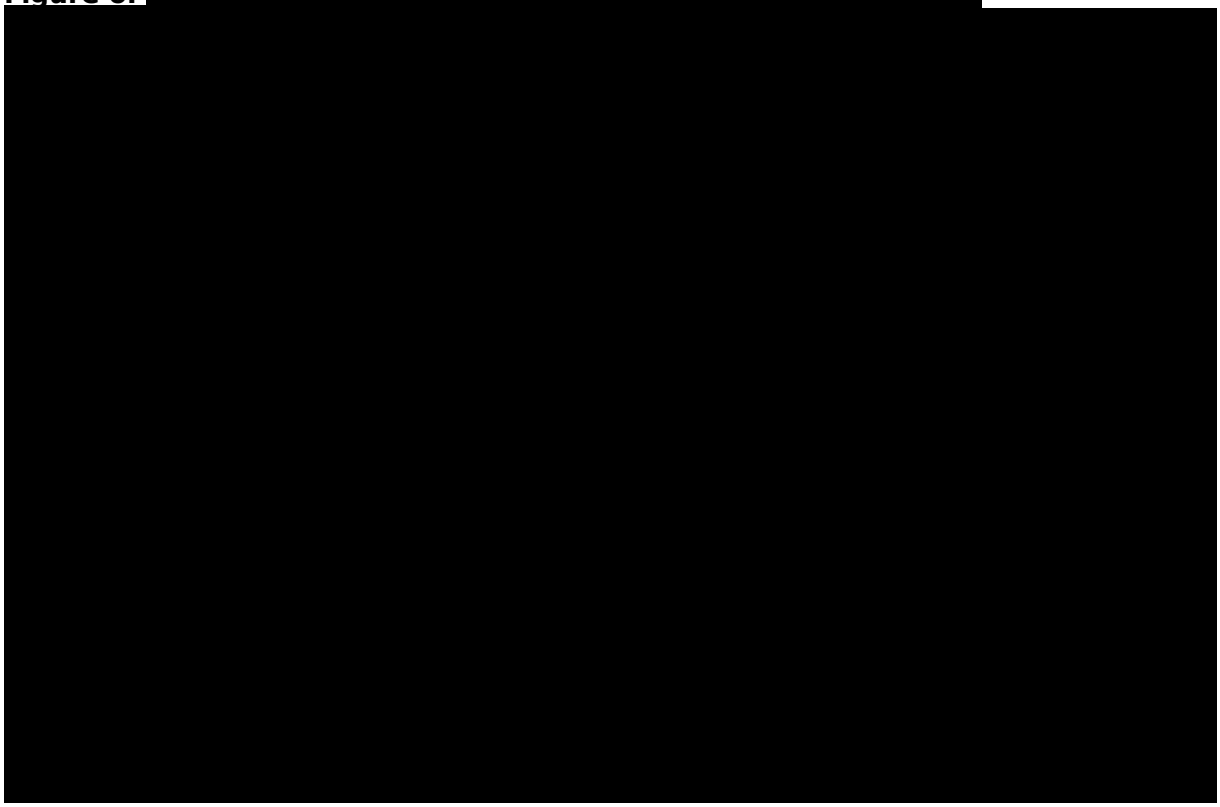


Figure 7. [redacted]

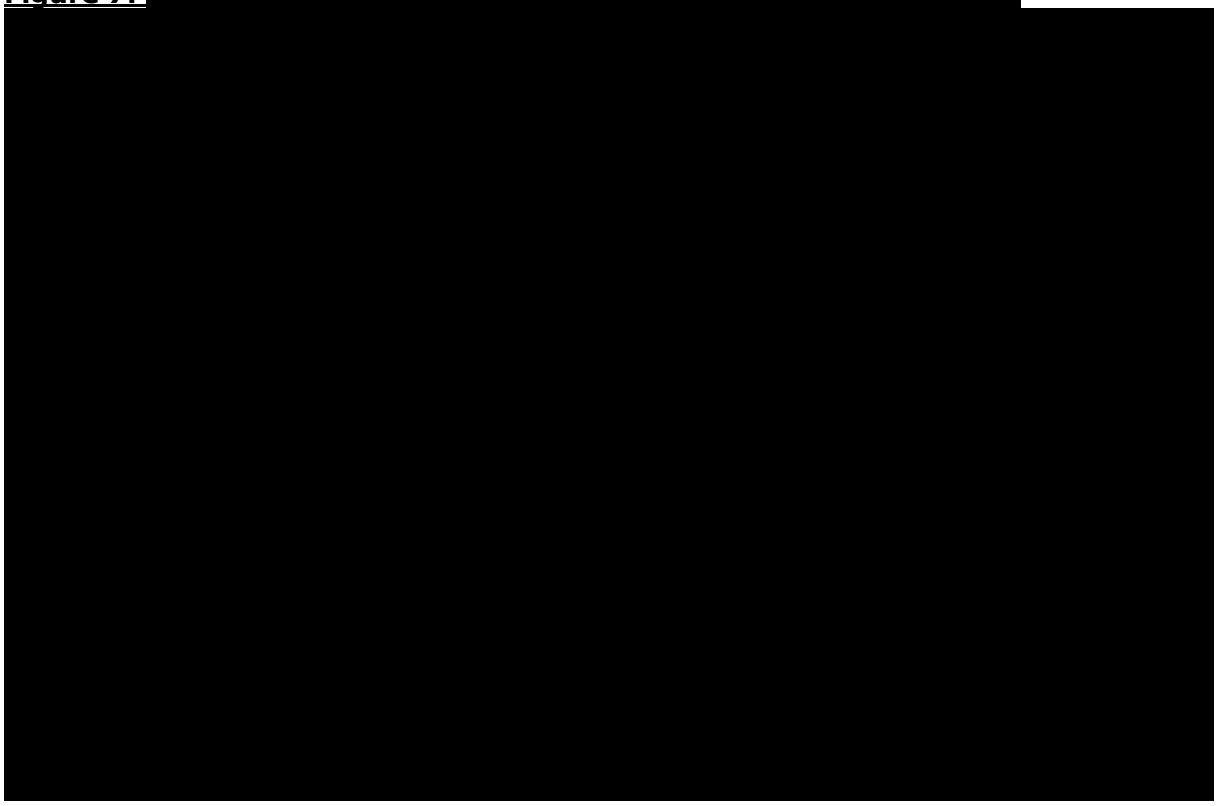


Figure 8. [redacted]

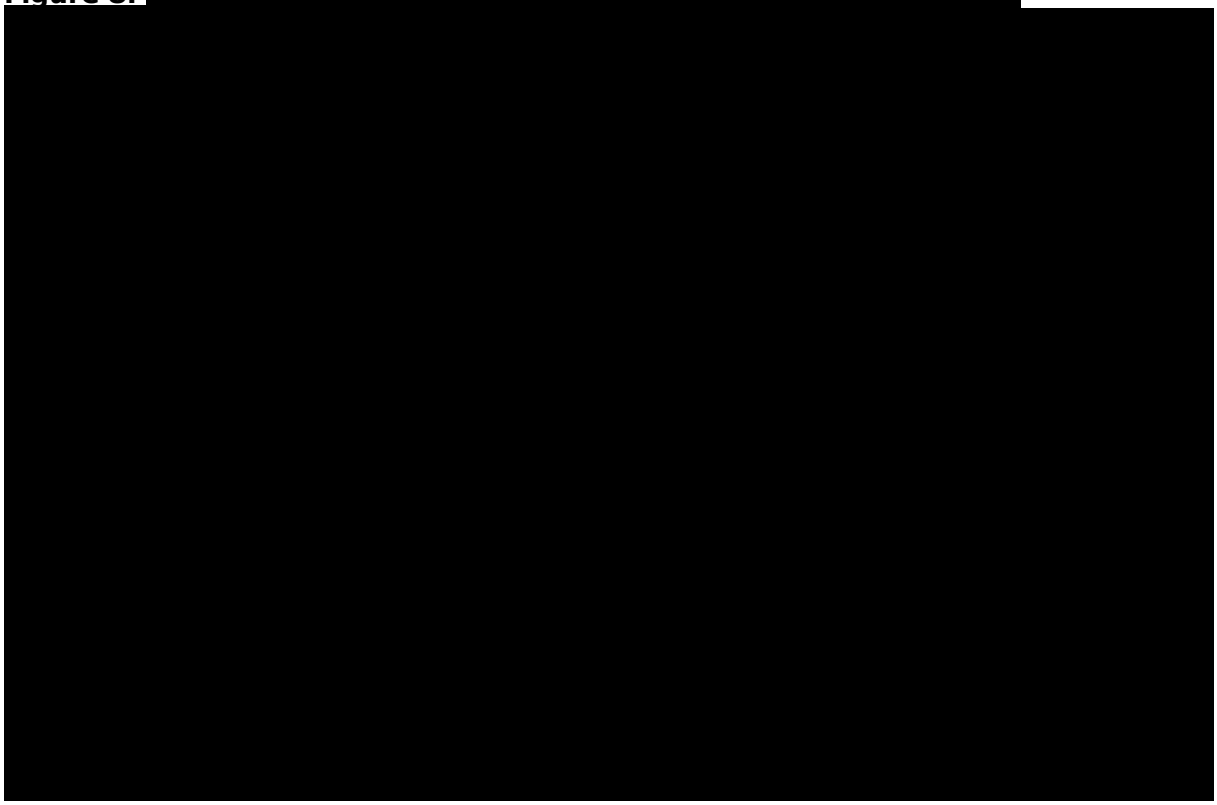


Figure 9. [redacted]

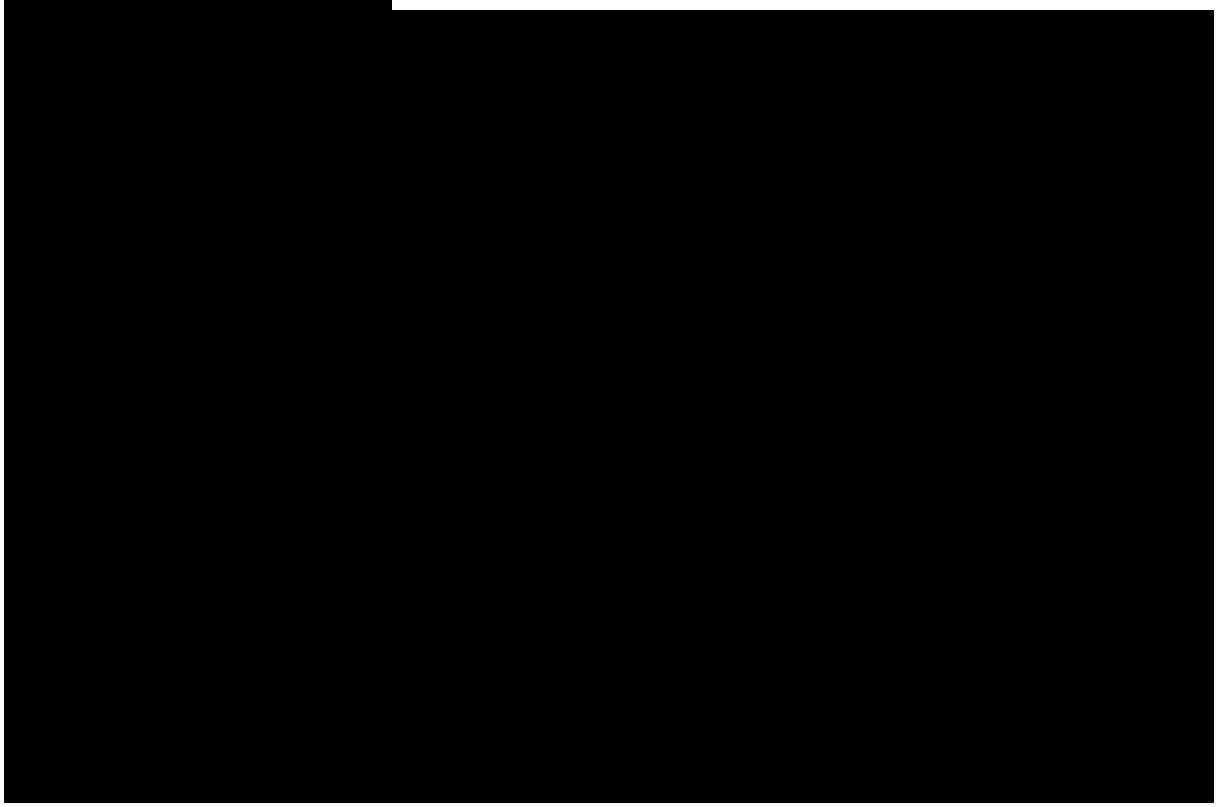


Table 24. ICH only cohort – one way sensitivity analysis results showing lower and upper bound ICERs resulting from variation in key parameters

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Andexanet alfa ICH bleed long-term care cost (£)	[redacted]	[redacted]	[redacted]
Utility: ICH follow-up care	[redacted]	[redacted]	[redacted]
Standard of Care ICH bleed long-term care cost (£)	[redacted]	[redacted]	[redacted]
Standard of Care ICH bleed acute care cost (£)	[redacted]	[redacted]	[redacted]
Andexanet alfa ICH bleed acute care cost (£)	[redacted]	[redacted]	[redacted]
30-day mortality - ICH - Standard of Care	[redacted]	[redacted]	[redacted]
30-day mortality - ICH - Andexanet alfa	[redacted]	[redacted]	[redacted]
Standard of Care decision tree distribution of bleed types	[redacted]	[redacted]	[redacted]
Utility: ICH acute care	[redacted]	[redacted]	[redacted]
Administration cost per cycle with Andexanet alfa (£):	[redacted]	[redacted]	[redacted]
Administration cost per cycle with Standard of Care (£):	[redacted]	[redacted]	[redacted]
Abbreviations: ICH, intracranial haemorrhage; ICER, Incremental cost-effectiveness ratio			

Results for GI only

Table 25 shows the primary results of different threshold analyses and scenarios varying the mortality benefit of andexanet alfa for the GI only cohort. In none of the scenarios tested did the ICER exceed £30,000.

Table 25. Results of six different scenarios combined with different assumptions between 0 and 100% around the relative benefit of andexanet alfa relative to SoC, for a GI bleeds only cohort

	Our revised base case (equivalent to ERG base case)	*Threshold Analysis 1*	*Threshold Analysis 2*	*ITC Scenario 1*	*ITC Scenario 2*	*ITC Scenario 3*	*ITC Scenario 4*
		Andexanet alfa 30-day mortality increased by 53%	*SoC 30-day mortality decreased by 25%*	*Base case PSM, except matching without replacement*	*Base case PSM, except covariates not dissagregated by subtype*	*Base case PSM, except matching without replacement and covariates not dissagregated by subtype*	*IPW*
	[redacted]*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: SoC, standard of care, IPW, inverse probability weighting: PSM, propensity score matching							

Results of revised base case

Table 26 shows the results of our revised base case for the GI bleed only cohort. For the GI bleed only group, andexanet alfa was associated with [redacted] more QALYs overall than PCCs, at an additional cost of [redacted], to give an ICER of [redacted] per QALY.

Table 26. Cost effectiveness results for revised base case for GI bleed only cohort

Cohort	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
GI bleed only								
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: QALY, quality-adjusted life-year; LY, life-year: ICER, Incremental cost-effectiveness ratio								

Results of probabilistic and one-way sensitivity analysis

Table 27 shows the mean results, including the mean ICER, across 10,000 iterations of probabilistic sensitivity analysis for the GI only cohort. The results are similar to the revised model base case for the GI only population.

The incremental cost effectiveness plane for the GI only cohort is presented in

Abbreviations: QALY, quality-adjusted life-year

Figure 10. [redacted]

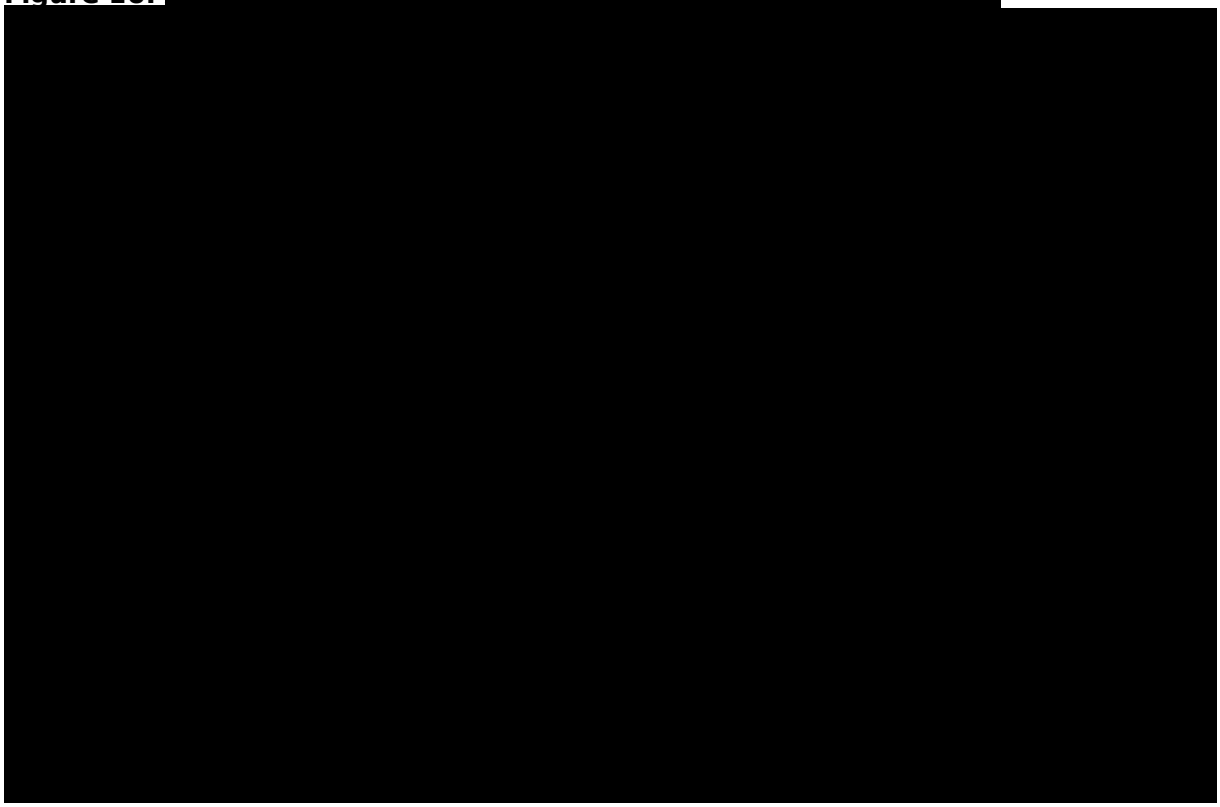


Figure 11. [redacted]

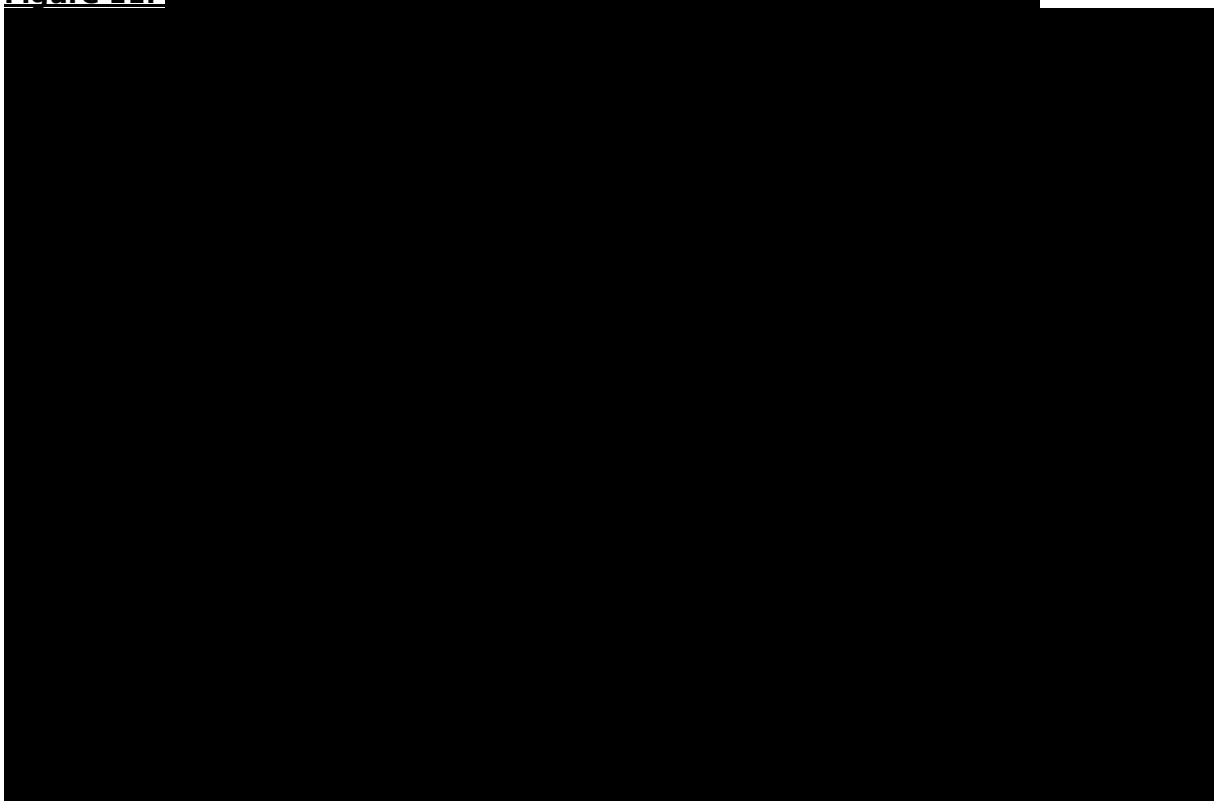


Figure 12. [redacted]

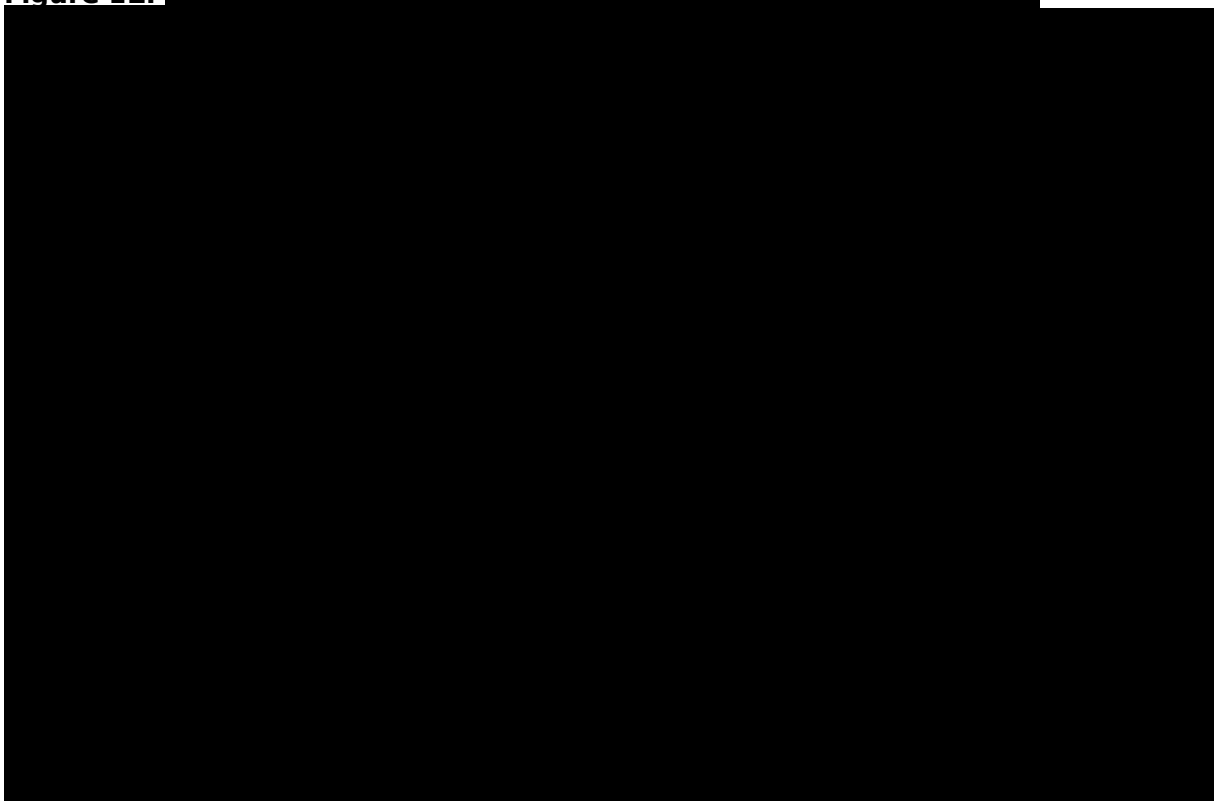


Figure 13. [redacted]

. This shows that for the GI only cohort the majority of iterations of the probabilistic sensitivity analysis yielded results falling in the upper right quadrant of the incremental cost effectiveness plane, indicating that andexanet alfa was associated with a higher QALY gain than SoC and some additional cost in almost all cases.

Error! Reference source not found. shows the cost effectiveness acceptability frontier for the GI only cohort, while **Error! Reference source not found.** shows the cost effectiveness acceptability curve for this population. These show that at a willingness to pay under £20,000, andexanet alfa becomes more cost effective than SoC.

Finally, **Error! Reference source not found.** shows a tornado diagram, which presents the upper and lower bound ICERs associated with upward and downward variation in key parameters in order of the magnitude of their impact on the ICER, for the GI only cohort. The ICERs associated with the upper and lower bounds between which the key parameters are varied are presented in Table 28 for the 10 key parameters with the greatest impact on the model ICERs for the GI only cohort.

Table 27. GI bleed only cohort - mean results of probabilistic sensitivity analysis over 10,000 iterations

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Cost per QALY (£)
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: QALY, quality-adjusted life-year					

Figure 10. [redacted]

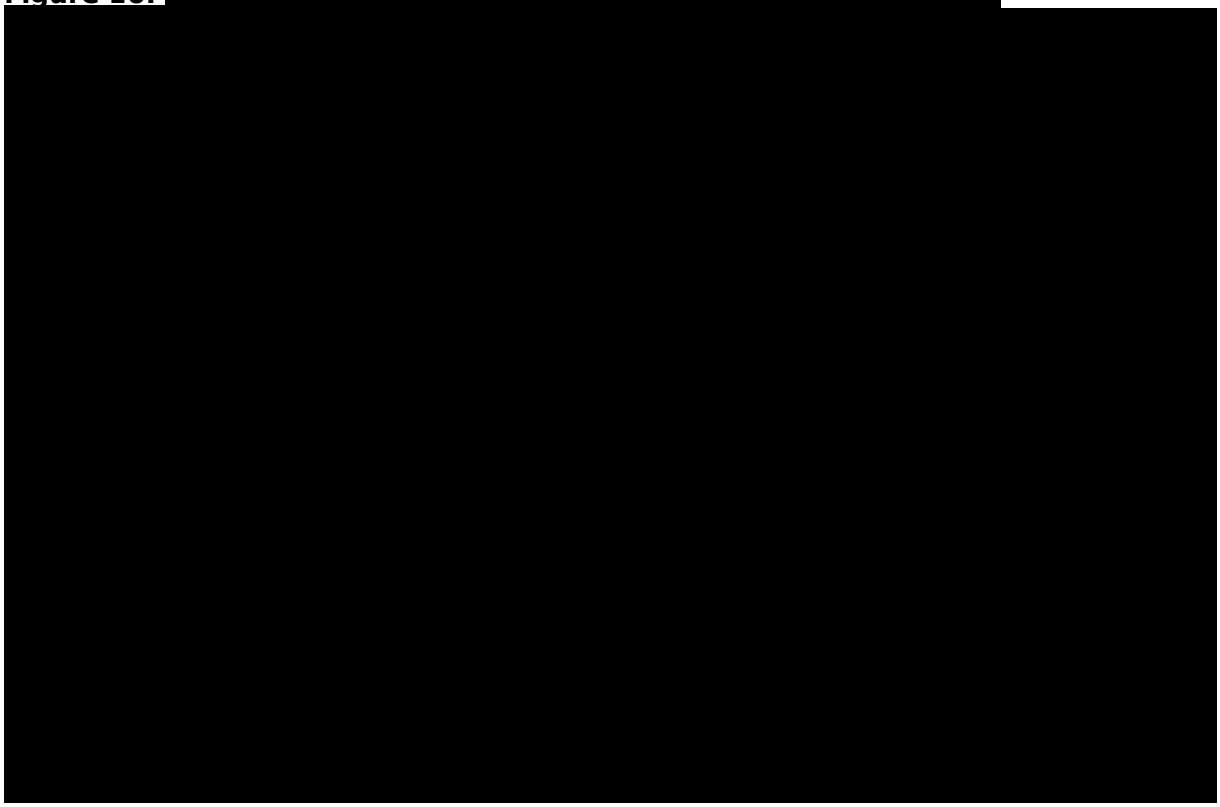


Figure 11. [redacted]

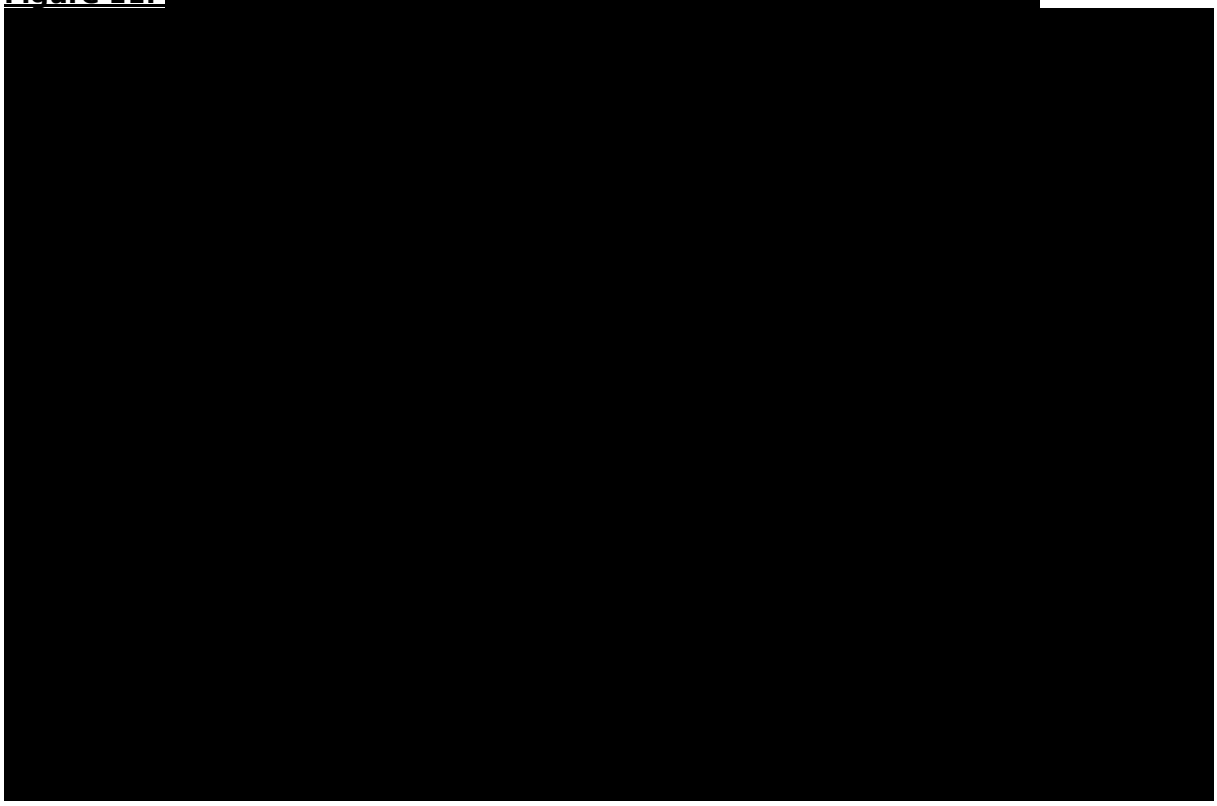


Figure 12. [redacted]

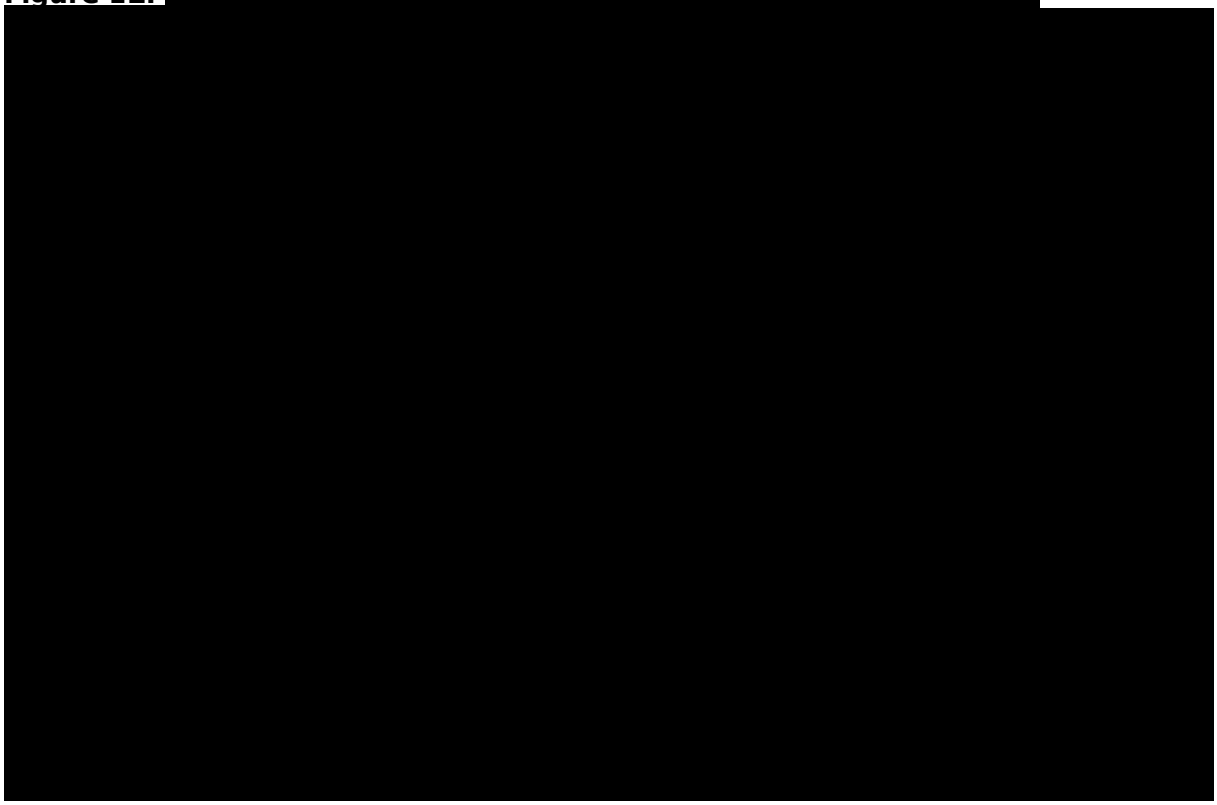


Figure 13. [redacted]

Table 28. GI only cohort – one way sensitivity analysis results showing lower and upper bound ICERs resulting from variation in key parameters

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
30-day mortality - Severe GI - Standard of Care	[redacted]	[redacted]	[redacted]
Utility: Severe GI Bleed follow-up care	[redacted]	[redacted]	[redacted]
30-day mortality - Severe GI - Andexanet alfa	[redacted]	[redacted]	[redacted]
Andexanet alfa Severe GI bleed long-term care cost (£)	[redacted]	[redacted]	[redacted]
Standard of Care Severe GI bleed acute care cost (£)	[redacted]	[redacted]	[redacted]
Andexanet alfa Severe GI bleed acute care cost (£)	[redacted]	[redacted]	[redacted]
Standard of Care Severe GI bleed long-term care cost (£)	[redacted]	[redacted]	[redacted]
Standard of Care decision tree distribution of bleed types	[redacted]	[redacted]	[redacted]
Administration cost per cycle with Andexanet alfa (£):	[redacted]	[redacted]	[redacted]
Administration cost per cycle with Standard of Care (£):	[redacted]	[redacted]	[redacted]
Utility: Severe GI Bleed acute care	[redacted]	[redacted]	[redacted]
Abbreviations: GI, Gastrointestinal; ICER, incremental cost effectiveness ratio			

Appendix J. Updated economic results for whole cohort and other major bleeds

Results for whole cohort

Table 29 shows the primary results of different threshold analyses and scenarios varying the mortality and morbidity benefit of andexanet alfa for the Whole cohort. In none of the scenarios tested did the ICER exceed £30,000. Likewise, no ICER above £20,000 was generated in any scenario until the morbidity benefit was reduced to [redacted] or less than its assumed value in the revised base.

Table 29. Results of six different scenarios combined with different assumptions between 0 and 100% around the relative benefit of andexanet alfa relative to SoC, for the whole cohort

Andexanet alfa vs. SoC relative morbidity benefit (%)	Revised base case	*Threshold Analysis 1*	*Threshold Analysis 2*	*ITC Scenario 1*	*ITC Scenario 2*	*ITC Scenario 3*	*ITC Scenario 4*
		Andexanet alfa 30-day mortality increased by [redacted]	*SoC 30-day mortality decreased by* [redacted]	*Base case PSM, except matching without replacement*	*Base case PSM, except covariates not dissagregated by subtype*	*Base case PSM, except matching without replacement and covariates not dissagregated by subtype*	*IPW*
100	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
80	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SoC, standard of care, IPW, inverse probability weighting: PSM, propensity score matching

Results of revised base case

Table 30 presents the results of the revised base case for the whole cohort. For the whole cohort, andexanet alfa was associated with [redacted] more QALYs overall than PCCs, at an additional cost of [redacted], to give an ICER of [redacted] per QALY.

Table 30. Results of the revised base case for the whole cohort

Cohort	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Whole cohort								
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: QALY, quality-adjusted life-year; LY, life-year: ICER, Incremental cost-effectiveness ratio								

Results of probabilistic and one-way sensitivity analysis

Table 31 shows the mean results, including the mean ICER, across 10,000 iterations of probabilistic sensitivity analysis for the whole cohort. The results are similar to the revised model base case for the whole cohort.

The incremental cost effectiveness plane for the whole cohort is presented in

Abbreviations: QALY, quality-adjusted life-year

Figure 14. [redacted]

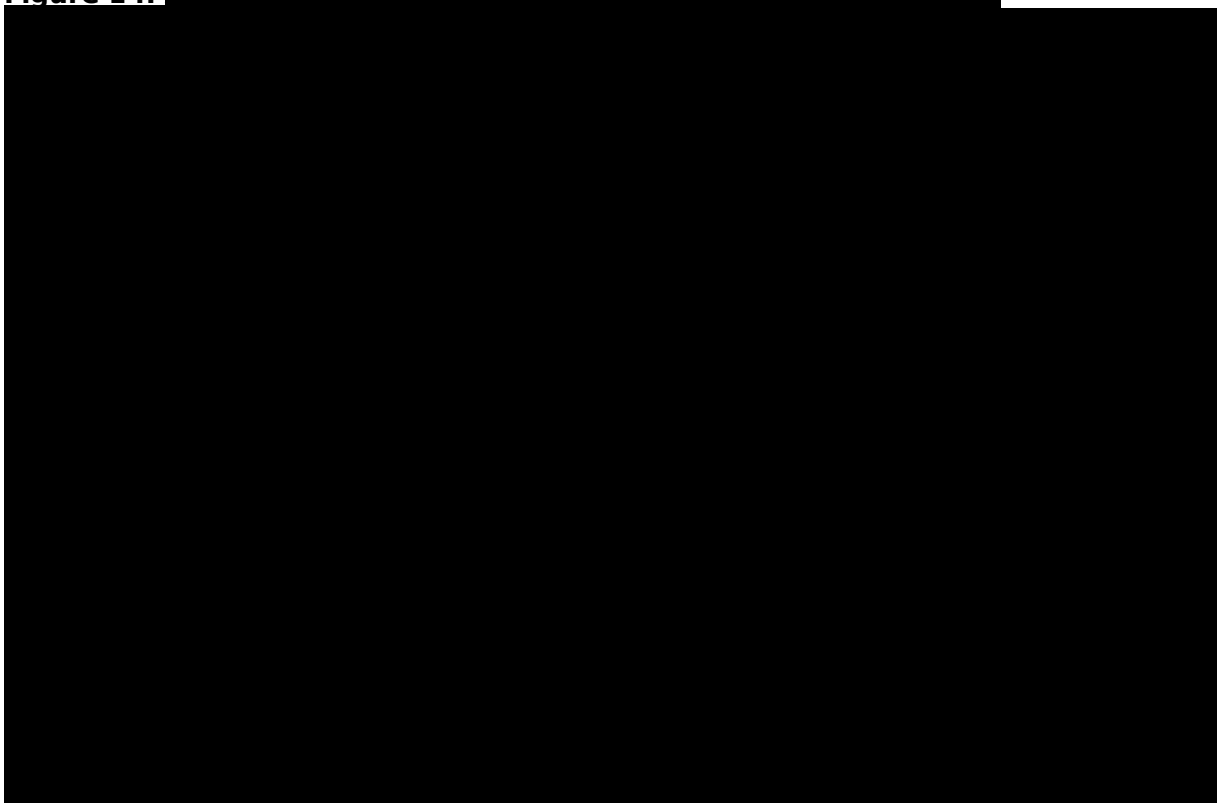


Figure 15. [redacted]

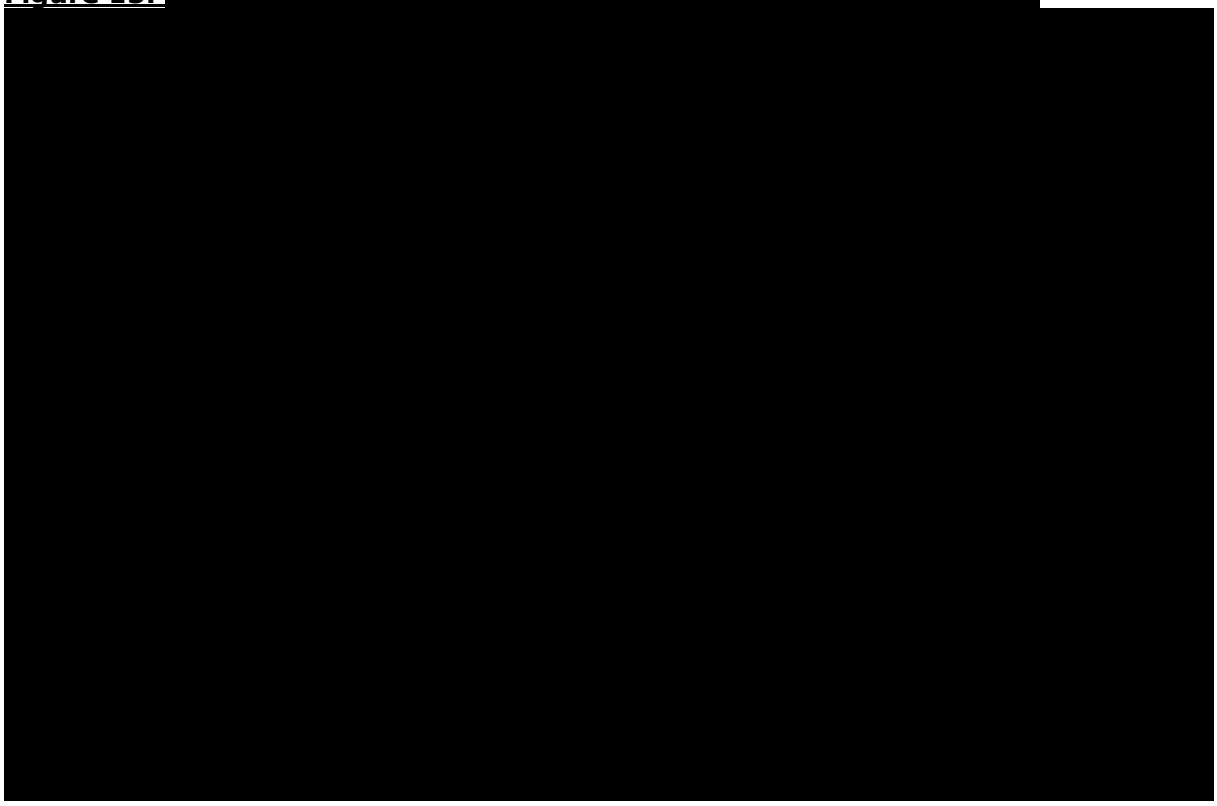


Figure 16. [redacted]

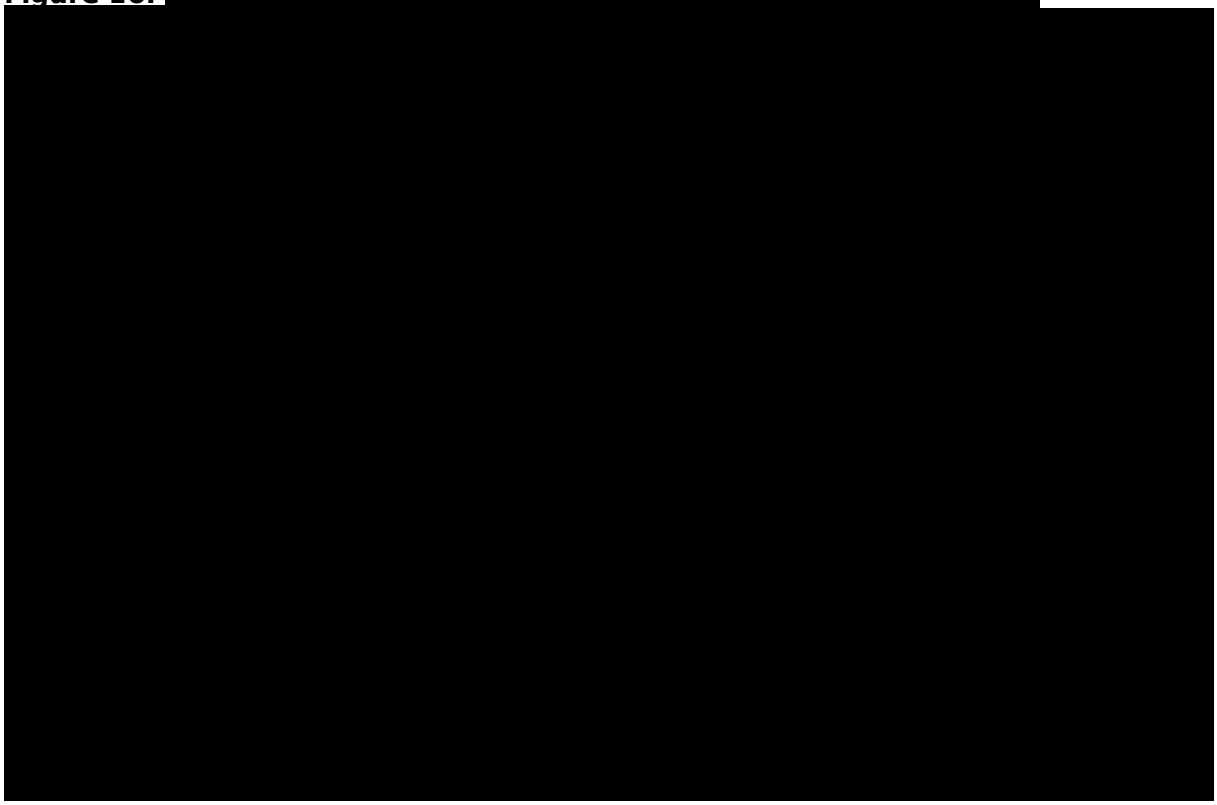


Figure 17. [redacted]

. For the whole cohort, the incremental cost effectiveness plane shows that results are spread across the upper and lower right quadrants of the cost effectiveness plane. This

indicates that while andexanet alfa is consistently associated with a greater gain in QALYs than SoC, in a number of sensitivity analysis iterations it was associated with a cost saving.

Error! Reference source not found. shows the cost effectiveness acceptability frontier for the whole cohort, while**Error! Reference source not found.** shows the cost effectiveness acceptability curve for this population. These show that andexanet alfa becomes cost effective relative to SoC at a willingness to pay well below £20,000.

Finally, **Error! Reference source not found.** shows a tornado diagram, which presents the upper and lower bound ICERs associated with upward and downward variation in key parameters in order of the magnitude of their impact on the ICER, for the whole cohort. The ICERs associated with the upper and lower bounds between which the key parameters are varied are presented in Table 32 for the 20 key parameters with the greatest impact on the model ICERs for the ICH only cohort.

Table 31. Whole cohort - mean results of probabilistic sensitivity analysis over 10,000 iterations

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Cost per QALY (£)
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: QALY, quality-adjusted life-year					

Figure 14. [redacted]

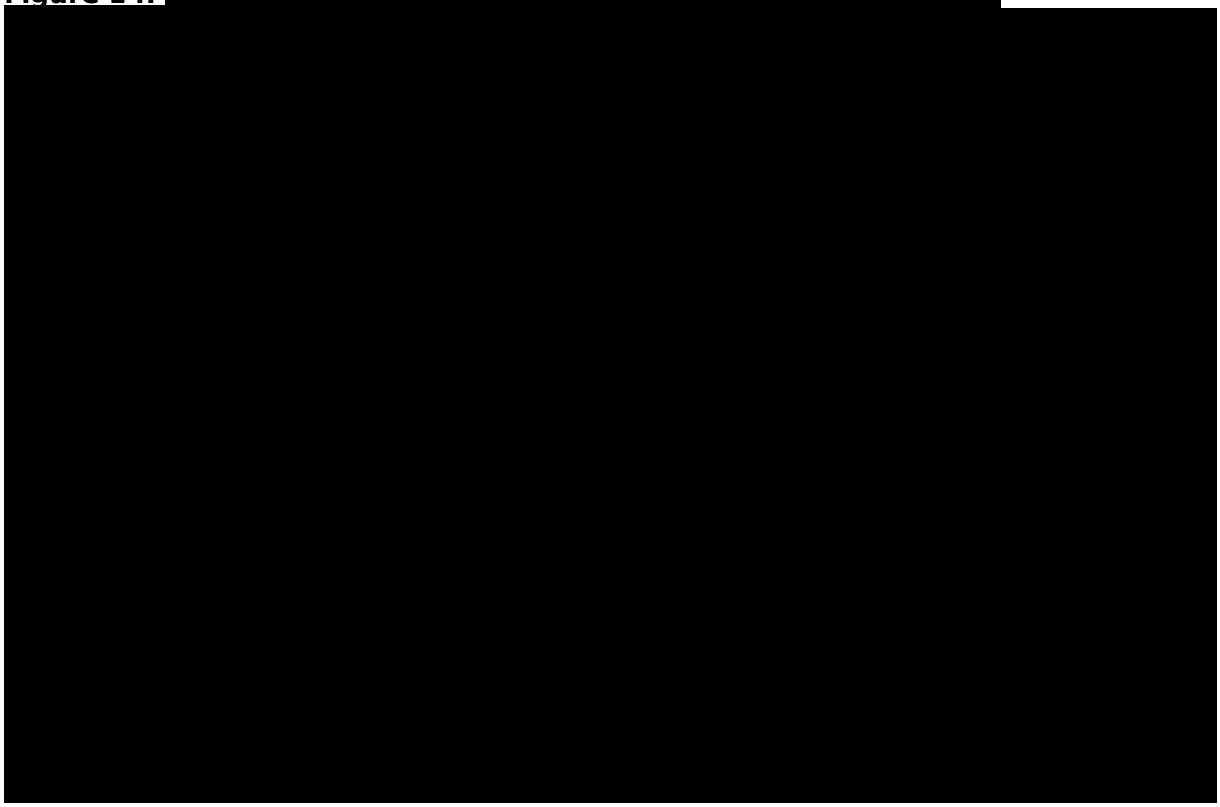


Figure 15. [redacted]

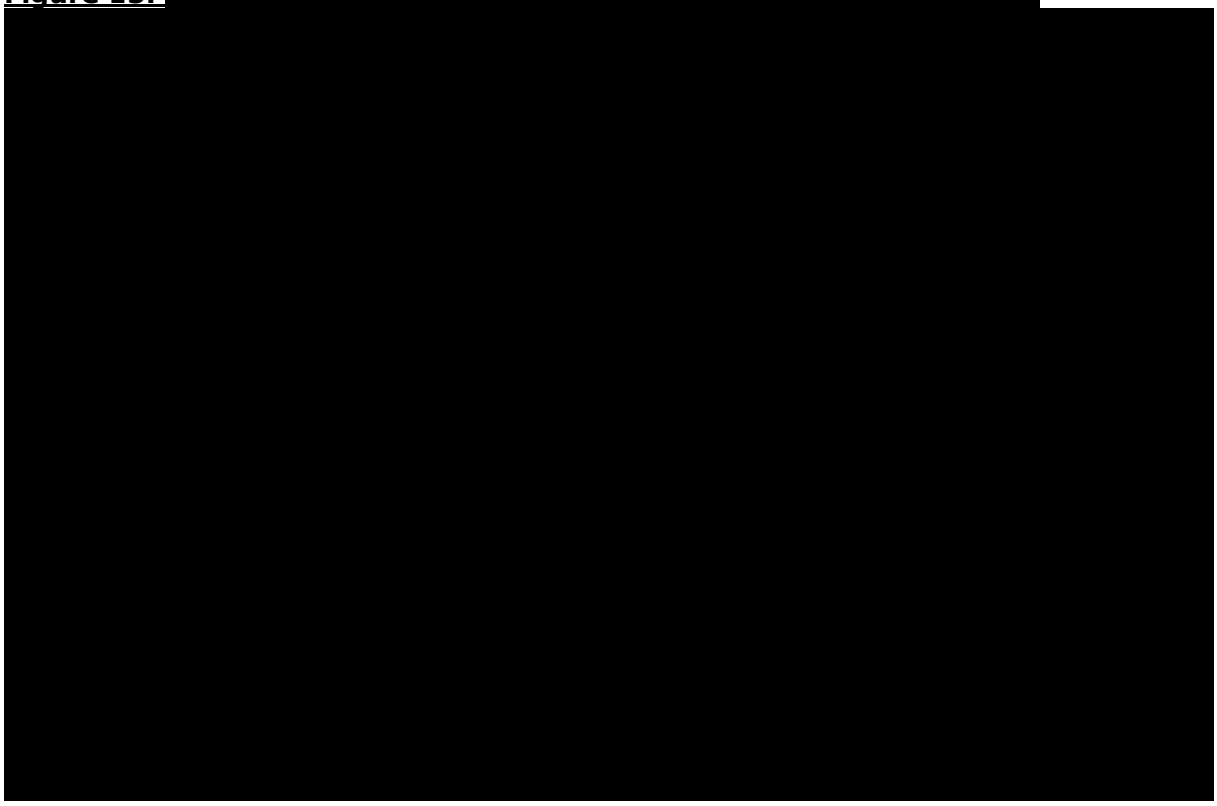


Figure 16. [redacted]

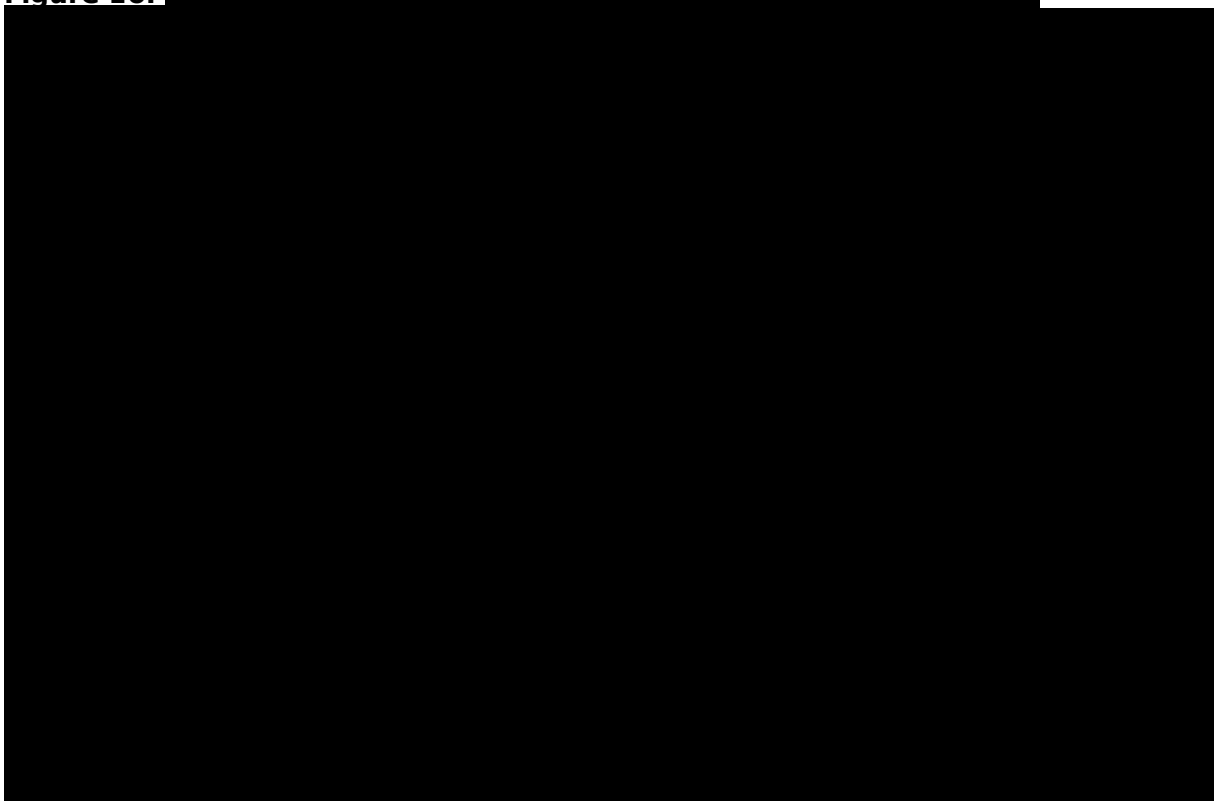


Figure 17. [redacted]

Table 32. Whole cohort – one way sensitivity analysis results showing lower and upper bound ICERs resulting from variation in key parameters

Parameter	Lower bound (£) ICER	Upper bound (£) ICER	Difference (£) ICER
Andexanet alfa Intraspinal long-term care cost (£) - Year 2	[redacted]	[redacted]	[redacted]
Andexanet alfa relative improvement of intraspinal bleed Survivor long-term utility	[redacted]	[redacted]	[redacted]
Andexanet alfa ICH bleed long-term care cost (£)	[redacted]	[redacted]	[redacted]
Standard of Care decision tree distribution of bleed types	[redacted]	[redacted]	[redacted]
Standard of Care ICH bleed long-term care cost (£)	[redacted]	[redacted]	[redacted]
Utility: ICH follow-up care	[redacted]	[redacted]	[redacted]
Standard of Care ICH bleed acute care cost (£)	[redacted]	[redacted]	[redacted]
Andexanet alfa ICH bleed acute care cost (£)	[redacted]	[redacted]	[redacted]
30-day mortality - Severe GI - Standard of Care	[redacted]	[redacted]	[redacted]
Utility: Severe GI Bleed follow-up care	[redacted]	[redacted]	[redacted]
30-day mortality - ICH - Standard of Care	[redacted]	[redacted]	[redacted]
30-day mortality - Severe GI - Andexanet alfa	[redacted]	[redacted]	[redacted]
Standard of Care Severe GI bleed acute care cost (£)	[redacted]	[redacted]	[redacted]
Andexanet alfa Severe GI bleed acute care cost (£)	[redacted]	[redacted]	[redacted]
Andexanet alfa Severe GI bleed long-term care cost (£)	[redacted]	[redacted]	[redacted]
Utility: Intraocular follow-up care	[redacted]	[redacted]	[redacted]
Standard of Care Severe GI bleed long-term care cost (£)	[redacted]	[redacted]	[redacted]
Utility: Intraspinal follow-up care	[redacted]	[redacted]	[redacted]
Administration cost per cycle with Andexanet alfa (£):	[redacted]	[redacted]	[redacted]
Standard of Care Intraspinal long-term care cost (£) - Year 1	[redacted]	[redacted]	[redacted]
Abbreviations: ICH, intracranial haemorrhage; ICER, Incremental cost-effectiveness ratio			

Results for other major bleeds

Table 33 presents the results of applying a range of relative reductions in each 30-day mortality and morbidity, in the other major bleeds group. Provided a small improvement in morbidity of [redacted] is observed, [redacted].

Table 33. Scenario analyses testing the relative reduction in 30-day mortality and long term morbidity for the other major bleeds cohort

Andexanet alfa relative reduction in morbidity vs. standard of care	Andexanet alfa relative reduction in 30-day mortality vs. standard of care										
	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
0%	[redacted]										
5%	[redacted]										
10%	[redacted]										
15%	[redacted]										
20%	[redacted]										
25%	[redacted]										
30%	[redacted]										
35%	[redacted]										
40%	[redacted]										
45%	[redacted]										
50%	[redacted]										

Results of revised base case

Table 34 presents the results of the revised base case for the other major bleeds cohort. For the other major bleeds group, andexanet alfa was associated with [redacted] more QALYs overall than PCCs, at a saving of [redacted], given which andexanet alfa is considered the dominant treatment in the other major bleeds group.

Table 34. Results of the revised base case for the other major bleeds cohort

Cohort	Total Costs (£)	Total LYs	Total QALYs	Incremental Costs (£)	Incremental LYs	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) versus incremental (QALYs)
Other bleeds								
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: QALY, quality-adjusted life-year; LY, life-year: ICER, Incremental cost-effectiveness ratio								

Results of probabilistic and one-way sensitivity analysis

Table 35 shows the mean results, including the mean ICER, across 10,000 iterations of probabilistic sensitivity analysis for the other major bleeds cohort. The results are similar to the revised model base case for the other major bleeds population, with andexanet alfa being a dominating treatment strategy in this group.

The incremental cost effectiveness plane for the other major bleeds cohort is presented in

Figure 18. [redacted]

Figure 19. [redacted]

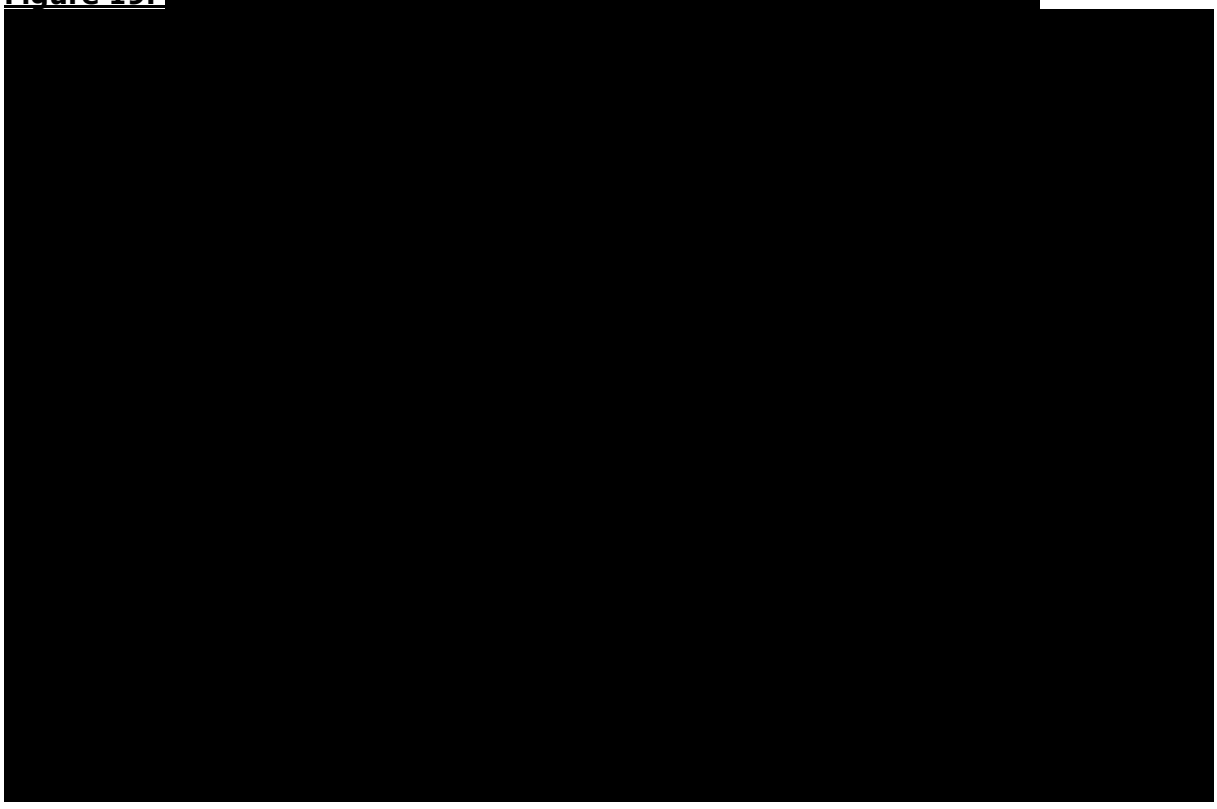


Figure 20. [redacted]

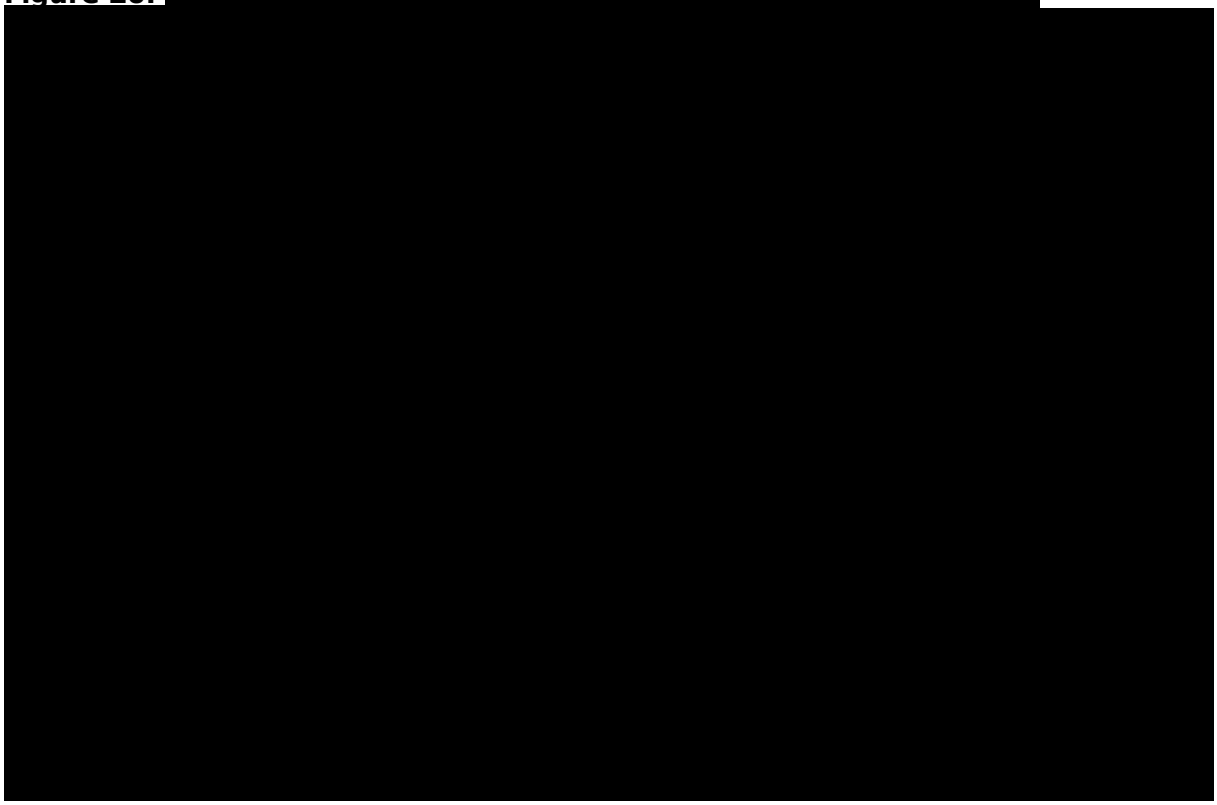


Figure 21. [redacted]

. For the other major bleeds cohort, the incremental cost effectiveness plane shows that results are spread across all four quadrants. This reflects the uncertainty known to be

associated with this model cohort, and shows that the base case results are not stable to variation in key parameters.

Error! Reference source not found. shows the cost effectiveness acceptability frontier for the other major bleeds cohort, while **Error! Reference source not found.** shows the cost effectiveness acceptability curve for this population. For the other major bleeds cohort, andexanet alfa is consistently the dominant treatment strategy, though results maintain some level of uncertainty on account of their instability at all willingness to pay thresholds.

Finally, **Error! Reference source not found.** shows a tornado diagram, which presents the upper and lower bound ICERs associated with upward and downward variation in key parameters in order of the magnitude of their impact on the ICER, for the ICH only cohort. The ICERs associated with the upper and lower bounds between which the key parameters are varied are presented in Table 36 for the 20 key parameters with the greatest impact on the model ICERs for the ICH only cohort.

Table 35. Other major bleeds cohort - mean results of probabilistic sensitivity analysis over 10,000 iterations

	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Cost per QALY (£)
Standard of Care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: QALY, quality-adjusted life-year					

Figure 18. [redacted]

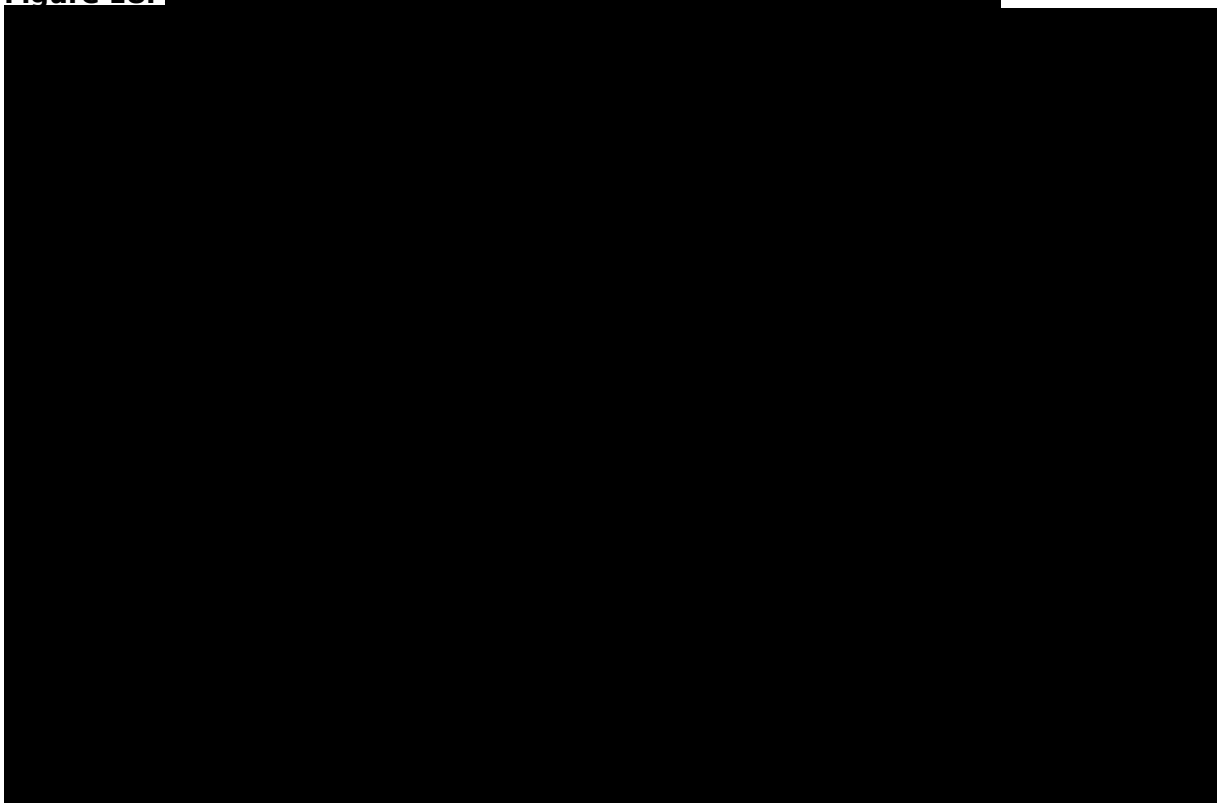


Figure 19. [redacted]

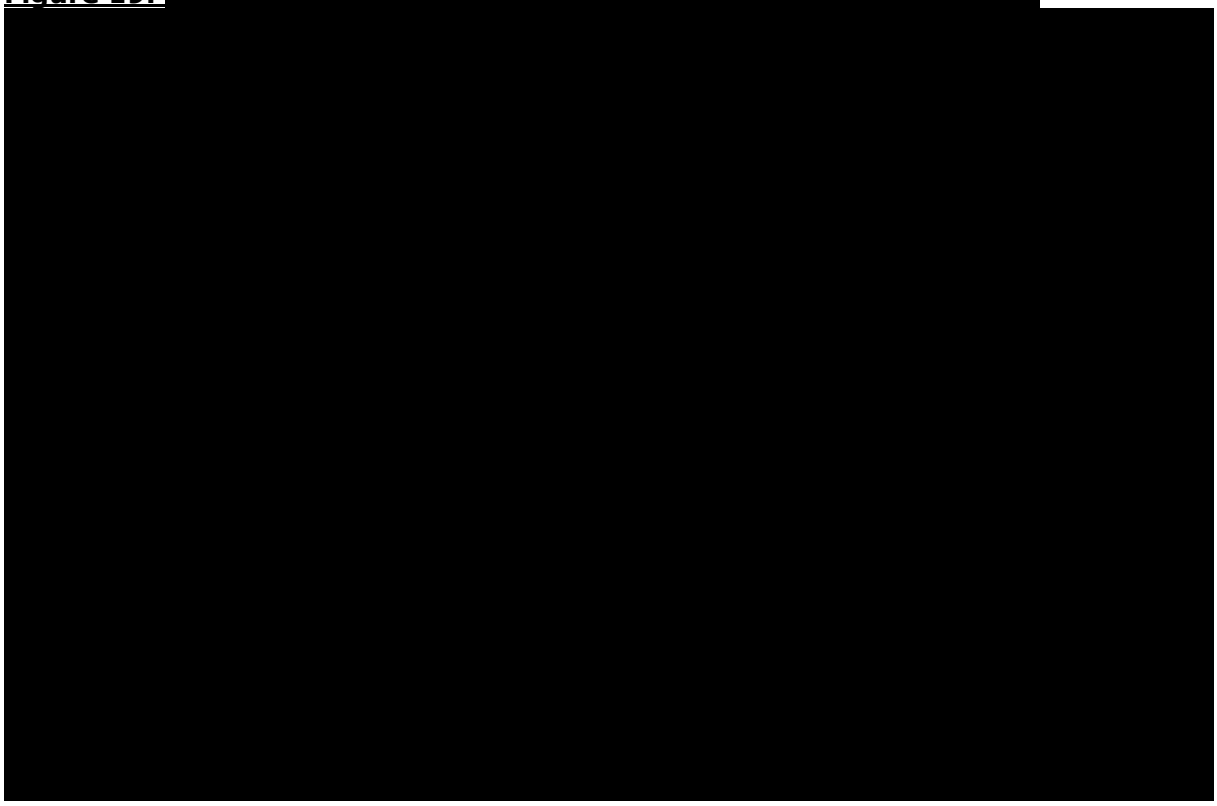


Figure 20. [redacted]

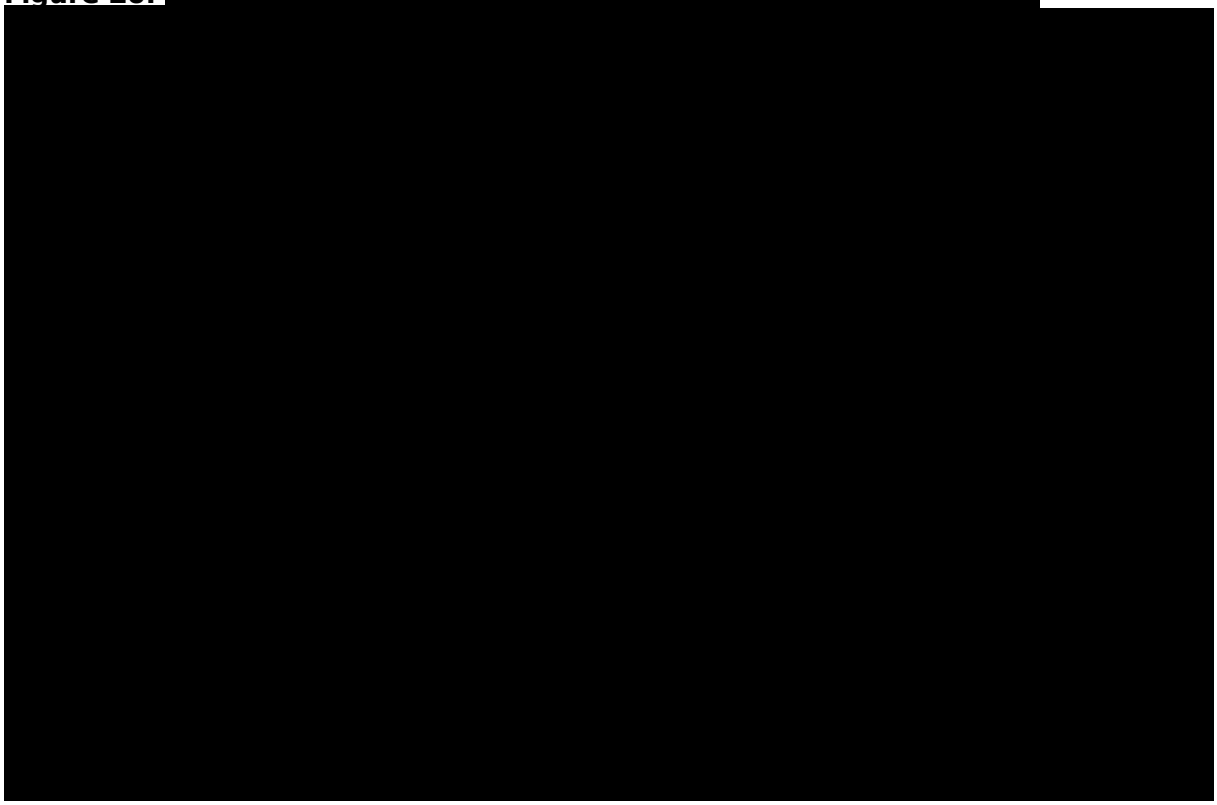


Figure 21. [redacted]

Table 36. Other major bleeds cohort – one way sensitivity analysis results showing lower and upper bound NMB resulting from variation in key parameters

Parameter	Lower bound (£) NMB	Upper bound (£) NMB	Difference (£) NMB
Standard of Care Intraspinal long-term care cost (£) - Year 2	[redacted]	[redacted]	[redacted]
Andexanet alfa Intraspinal long-term care cost (£) - Year 2	[redacted]	[redacted]	[redacted]
Andexanet alfa relative improvement of intraspinal bleed Survivor long-term utility	[redacted]	[redacted]	[redacted]
Utility: Intraocular follow-up care	[redacted]	[redacted]	[redacted]
Utility: Intraspinal follow-up care	[redacted]	[redacted]	[redacted]
30-day mortality - Retroperitoneal - Andexanet alfa	[redacted]	[redacted]	[redacted]
30-day mortality - Pericardial - Andexanet alfa	[redacted]	[redacted]	[redacted]
Standard of Care Intraocular long-term care cost (£)	[redacted]	[redacted]	[redacted]
Andexanet alfa Intraocular long-term care cost (£)	[redacted]	[redacted]	[redacted]
Standard of Care Intraspinal long-term care cost (£) - Year 1	[redacted]	[redacted]	[redacted]
Andexanet alfa Intraspinal long-term care cost (£) - Year 1	[redacted]	[redacted]	[redacted]
Andexanet alfa relative improvement of intraocular bleed Survivor long-term utility	[redacted]	[redacted]	[redacted]
Standard of Care decision tree distribution of bleed types	[redacted]	[redacted]	[redacted]
30-day mortality - Retroperitoneal - Standard of Care	[redacted]	[redacted]	[redacted]
30-day mortality - Pericardial - Standard of Care	[redacted]	[redacted]	[redacted]
Utility: Retroperitoneal Bleed follow-up care	[redacted]	[redacted]	[redacted]
Utility: Pericardial Bleed follow-up care	[redacted]	[redacted]	[redacted]
Andexanet alfa Retroperitoneal long-term care cost (£)	[redacted]	[redacted]	[redacted]
Andexanet alfa Pericardial long-term care cost (£)	[redacted]	[redacted]	[redacted]
Standard of Care Retroperitoneal long-term care cost (£)	[redacted]	[redacted]	[redacted]
Abbreviations: NMB, Net monetary benefit			

References for appendices

1. Sarode R, Milling TJ, Refaai MA, *et al.* Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation* 2013. 128: 1234–1243.
2. Blatchford O, Murray WR & Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. *Lancet* 2000. 356: 1318–1321.
3. Hankey GJ, Stevens SR, Piccini JP, *et al.* Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban: the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation. *Stroke* 2014. 45: 1304–1312.
4. Held C, Hylek EM, Alexander JH, *et al.* Clinical outcomes and management associated with major bleeding in patients with atrial fibrillation treated with apixaban or warfarin: insights from the ARISTOTLE trial. *Eur Heart J* 2015. 36: 1264–1272.
5. Kaide CG & Gulseth MP. Current Strategies for the Management of Bleeding Associated with Direct Oral Anticoagulants and a Review of Investigational Reversal Agents. *J Emerg Med* 2020. 58: 217–233.
6. Milling TJ, Clark CL, Feronti C, *et al.* Management of Factor Xa inhibitor-associated life-threatening major hemorrhage: A retrospective multi-center analysis. *Am J Emerg Med* 2018. 36: 396–402.
7. Green L, Tan J, Antoniou S, *et al.* Haematological management of major bleeding associated with direct oral anticoagulants – UK experience. *British Journal of Haematology* 2019. 185: 514–522.

8. Green L, Tan J, Morris JK, *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. 103: 738–745.
9. Connolly SJ, Crowther M, Eikelboom JW, *et al.* Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *New England Journal of Medicine* 2019. 380: 1326–1335.
10. Siegal DM, Curnutte JT, Connolly SJ, *et al.* Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity. *New England Journal of Medicine* 2015. 373: 2413–2424.
11. Christensen H, Cordonnier C, Kõrv J, *et al.* European Stroke Organisation Guideline on Reversal of Oral Anticoagulants in Acute Intracerebral Haemorrhage. *European Stroke Journal* 2019. 4: 294–306.
12. Oakland K, Chadwick G, East JE, *et al.* Diagnosis and management of acute lower gastrointestinal bleeding: guidelines from the British Society of Gastroenterology. *Gut* 2019. 68: 776.
13. Research C for BE and. ANDEXXA (coagulation factor Xa (recombinant), inactivated-zhzo). *FDA* 2019. at <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/andexxa-coagulation-factor-xa-recombinant-inactivated-zhzo>
14. Schulman S & Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *Journal of Thrombosis and Haemostasis* 2005. 3: 692–694.
15. Keele L. An overview of rbounds: An R package for Rosenbaum bounds sensitivity analysis with matched data. 15.
16. Caliendo M & Kopeinig S. SOME PRACTICAL GUIDANCE FOR THE IMPLEMENTATION OF PROPENSITY SCORE MATCHING. *Journal of Economic Surveys* 2008. 22: 31–72.

17. A Crash Course in Causality: Inferring Causal Effects from Observational Data. *Coursera* at <https://www.coursera.org/learn/crash-course-in-causality#instructors>

18. Phillippo D. NICE DSU Technical Support Document 18. 82.

19. Elze MC, Gregson J, Baber U, *et al.* Comparison of Propensity Score Methods and Covariate Adjustment: Evaluation in 4 Cardiovascular Studies. *Journal of the American College of Cardiology* 2017. 69: 345–357.

20. Øie LR, Madsbu MA, Solheim O, *et al.* Functional outcome and survival following spontaneous intracerebral hemorrhage: A retrospective population-based study. *Brain and Behavior* 2018. 8: e01113.

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Andexanet alfa for reversing anticoagulation [ID1101]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 13 May 2020 **email:** NICE DOCS

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Anticoagulation UK
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nothing to declare
Name of commentator person completing form:	[redacted]

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Andexanet alfa for reversing anticoagulation [ID1101]

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1	ACUK was invited to attend both the technical engagement meeting and Technology advisory Committee meeting. Following the TA meeting on 24th March 2020, ACUK submitted written feedback to NICE primarily relating to points of concern relating to limitations of patient input around impact of the technology for patients and lack of clinical experts across Trauma, Emergency Dept and Neurology being available to answer questions on the practise and outcomes for patients presenting with ICH bleeds on Doacs. The Public Involvement team at NICE acknowledged points made within the feedback. The following comments are in response to the current decision outcomes and our considerations in light of our involvement in the TA meeting.
2	The Committee has acknowledged that DOACS are associated with a risk of major bleeding events and the availability of an effective reversal agent would be greatly valued by patients and healthcare professionals. Andexanet alfa is approved by the FDA and EMA and the recently published NG158 guidelines on VTE thromboembolic diseases recommends Apixaban and Rivaroxaban as first line treatments for VTE. Doacs are used extensively for Atrial Fibrillation and for clot prevention in hip and knee surgery.
3	The initial barriers to uptake of DOACS raised significant concerns both from clinicians and patients due to lack of a reversal agent being available in the event of a major bleed. Whilst warfarin and INR monitoring may be demanding on the patient and service provision, patients switching to DOACS or having to anticoagulate after a recurrence of a VTE look for reassurance that if a bleed occurs, it can be controlled to avoid deterioration or compounding health issues per se.
4	People who are on the Doac Dabigatran now have this reassurance as NICE has approved Idarucizumab as a reversal agent. The projected upsurge in patients being treated with Apixaban and Rivaroxaban for VTE and AF will prompt patients concerns around bleed risk and understandably, the shared decision making process to involve patient choice may be compromised without a reversal agent being available.
5	With the COVID 19 pandemic, the National Clinical Advisor for AHSNs has developed guidance which is now in place for switching patients from warfarin to Doacs, ACUK was asked to review **https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Coronavirus/FINAL%20Guidance%20on%20safe%20switching%20of%20warfarin%20to%20DOAC%20COVID-19%20Mar%202020.pdf?ver=2020-03-26-180945-627** Within this document it states ' Major bleeds managed/reversed by supportive measures, Prothrombin Complex Concentrate (PCC), and availability of antidote' The technology has been approved and licenced for use in the USA and Europe. With COVID 19 being a global pandemic, we raise the question that patients in the UK may be disadvantaged as a comparison to patients being able to access a reversal agent provided in Europe and USA.
6	Evidence is forthcoming that COVID 19 patients may be experiencing higher risk of clotting and we understand that this cohort of patients will now be given DOACs post discharge. Existing health anxiety will be high post COVID and could be severely elevated with the knowledge that taking an anticoagulant which could cause a potential bleed(and potentially be life threatening) without a specific reversal agent being available.
7	The treatment pathway for major bleeding in patients on DOACS clearly illustrates the outcomes of risk across specific bleed sites and whilst most patients on anticoagulation will be content in the

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	knowledge that they are reducing their risk of clots, they may not be fully aware of the implications of having a ICH, GI or Retroperitoneal bleed which could be fatal or leave them with severe disabilities, or in the case of an intraocular bleed, cause blindness. The responsibility to ensure these patients are given every chance to survive the trauma of a major bleed lies with the managing clinician who may be frustrated if they cannot provide the optimum treatment which they know may help the patient.
8	During the shared decision process of initiating or switching patients to Doacs, patients will need adequate information around bleed risk and how this will be managed effectively and safely. The availability of a reversal agent for Apixaban and Rivaroxaban along with sound clinical pathways on managing bleeds will bring reassurance to patients and provide options to clinicians when managing these clinically vulnerable patients.
9	ACUK is unable to comment on the design, recruitment or costing model for the trial but note the following as summarised within the NICE consultation documentation. In ANNEXA –4, the ICH bleed cohort reported 80% rate of excellent or good haemostatic efficacy with the GI bleed rate assessed at 85%.Clinical experts commented that 'any patient with major bleed could benefit from andexanet alfa but the ICH group seem to benefit the most' but GI bleeds may be more common.
10	In response to patient concerns around COVID 19 and anticoagulation management, ACUK has consulted with clinicians and produced information for warfarin patients wishing to self – test. Prior to publication, ACUK was invited to review and comment on the NHSEI Clinical guide for the management of anticoagulant services during the coronavirus pandemic 31 March 2020 Version **https://www.anticoagulationuk.org/downloads/NHS%20clinical%20guide%20for%20management%20of%20anticoagulation.pdf**
11	Key factors we wish the committee to consider: • The TA committee meeting was held virtually due to the current landscape. Whilst there were several clinicians in attendance, the opportunity to hear from specialists working in trauma, ED and neurology would of enriched the understanding and knowledge around current reversal methodologies and potential utilisation of a reversal agent in the real work setting. • More opportunities to present patient perspective of being on a DOAC and highlighting concerns of the anticoagulation population, the carers and family involved in supporting these patients. • The rapid response to change in managing anticoagulation patients to optimise individual and population risk of VTE and blood clots necessitating in new clinical guidelines. • The stated unmet need for an increasing population of people who need to be protected from blood clots whilst balancing bleed risk and potential outcomes of an event, fatality or severe disability. • The limitations imposed restrict a potential clinical treatment being made available and this could have significant positive outcomes for a patient.

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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BASP response andexanet alfa

1. Andexanet alfa is an expensive drug designed (~£15,000/patient) for the reversal of apixaban or rivaroxaban anticoagulation.

2. It appears to be effective at reversing the anticoagulant effect of these factor Xa inhibitors in both the ANNEXA studies. The ANNEXA-4 publication, a single armed study with no control group, did not report the survival or disability of enrolled participants with moderate ICH (GCS >7), but on average 10% of enrolled patients had an MI, ischaemic stroke, TIA, DVT or PE by 30 days (most common was ischaemic stroke). ANNEXA-4 also included a mixture of different forms of intracranial bleeding (with different prognoses) and used unvalidated measures of haemostatic efficacy. The section of the committee papers with information on disability on patients with ICH (p54 , p55 of 163) is redacted.

3. Does reversal of anticoagulation improve outcomes in warfarin associated ICH? There is one small RCT of FFP versus PCC in patients with vitamin K antagonist associated ICH which demonstrated that PCC reversed INR more quickly than FFP, and seemed to reduce haematoma expansion. There was no evidence of an effect on clinical outcomes, but the trial was very small and stopped early. Therefore, it is likely that reversal improves clinical outcomes, but whether this is largely improving very disabled survival in people who would otherwise die, or is improving the number of people with an excellent recovery is unclear (and very relevant to this application).

4. Early and rapid reversal of anticoagulation in patients with anticoagulant related ICH is strongly recommended in a European Stroke Organisation guideline, but for this medication indicates:

5. *"We recommend using andexanet alfa if available – in adult patients with ICH occurring during use of rivaroxaban or apixaban. We also recommend randomising into trials as based on the low quality of evidence, there is significant uncertainty whether desirable outweigh undesirable effects."*

6. A randomised study of andexanet alfa is ongoing in patients with ICH, but has yet to report (https://clinicaltrials.gov/ct2/show/NCT03661528)

7. Therefore, it is difficult to estimate any effect of this treatment on quality of life or recovery, as the size of any beneficial treatment effect is unclear, and the target patient population undefined.

8. However, in the absence of further evidence, andexanet alfa would: almost certainly reverse the anticoagulant effect of factor Xa inhibitors in patients with ICH; would probably reduce the rate of haematoma growth; and may reduce the number of patients who die with anticoagulant related ICH. Whether it would increase the number who survive less disabled or survive with no disability and whether it is cost-effective – or more cost-effective than PCC – in doing this is unclear.

9. Relatively small differences in these estimates (guesses) would may make relatively large differences to the estimates of cost-effectiveness, because of the cost of long-term care in survivors.

10. Therefore BASP has no objection to the NICE interim guidance.

[redacted]
Scientific Committee Chair

NICE National Institute for Health and Care Excellence

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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 disclose**]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We agree that there is an unmet need for a reversal agent for factor Xa inhibitors, but agree with the conclusions of the committee that the available data fails to find convincing evidence of clinical efficacy or cost effectiveness for Andexanet alpha. We are not aware of any data that was not considered in the technology appraisal
2	Page 8 line 7: we suggest this should read “particularly endoscopic therapy”, rather than “particularly embolisation of a bleeding vessel”
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Society for Haematology and Royal College of Pathologsts
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Received sponsorship to attend international scientific meeting from Bayer
Name of commentator person completing form:	[redacted]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	we have no concerns about this recommendation but thrombosis as a complication following the use of andexanet alfa to treat acute bleed has not been mentioned
2	
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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[BSIR]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Reversal of DOACs is an essential issue. I personally have had 3 cases in the last 6 months of IR oncall, of life threatening bleeding requiring IR angio +/- embolization and then suture mediated closure device to prevent a second bleed from the groin puncture site.
2	The concern is that the recommendation may imply that in the situation of retroperitoneal bleeding, from for example, the kidney, does not require reversal/intervention. This is not my experience.
3	
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

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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.	**None**
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	When Direct Oral Anticoagulants (DOACs) first came to market, they offered a novel, safe and effective alternative for many patients requiring anticoagulation therapy who previously had only one oral therapy option – warfarin, which was challenging to maintain therapeutic levels, interacted with a great number of drug, food and drink items and as a result made anticoagulation therapy impactful on continuing 'normal' life, work, travel and routine social activities from coffee or lunch with friends to occasional alcohol and change in diet. As a consequence, despite best efforts, often many patients taking anticoagulation struggled maintaining a stable International Normalised Ratio (INR) and so the risk of stroke or dangerous bleed, remained. In the advent of new 'DOAC' therapies the benefits of a more predictable, stable and at least as effective therapy option were welcomed. However, a continued barrier for patients and prescribers has been the issue that the DOAC therapies had no specific reversal agent should an emergency require this. We are concerned that the current decision by the Committee to not approve Andexanet alfa, has failed to consider the lack of reversal therapy options for patients taking a DOAC and who suffer a severe and life-threatening bleed, and who have recently received a factor Xa direct oral anticoagulant. Not least for those with an intracranial bleed, where there is currently no alternative effective therapy option.
2	Andexanet alfa is the first novel reversal agent for DOAC therapies which has been shown to be effective in reversing life-threatening and emergency bleeds on patients taking apixaban or rivaroxaban. Whilst we appreciate trials to date have not included a randomised control trial (RCT) has limitations, the ANNEXA4 Trial did evidence good reversal action that also benefit outcome and quality of life. This evidence, while noted as with limitations, has allowed Andexanet alfa to be given a conditional marketing authorisation license by the European Medicine Agency (EMA) because: "*This was granted in the interest of public health because the medicine addresses an unmet medical need and the benefit of immediate availability outweighs the risk from less comprehensive data than normally required"* We believe in the UK there is a cohort of patients prescribed apixaban or rivaroxaban who have an unmet need and who could – in an emergency, could be clinically identified as likely to benefit from being treated with Andexanet alfa when there is no other suitable or available standard therapy option. We urge the committee to reconsider their recommendation and consider the unmet need especially for certain patient groups.
3	Intracranial haemorrhage is one of the most life-threatening / life limiting acute medical events. Unsurprisingly, an intracranial bleed is therefore feared by many patients requiring anticoagulation therapy. Currently there is no affective reversal therapy for a life-threatening intracranial bleed for patients taking a DOAC, including apixaban or rivaroxaban. In the ANNEXA4 Trial, 80% of patients who had suffered an intracranial bleed and were then treated with Andexanet alfa had regained good haemostatic efficacy within 12 hours post initiation of therapy. We strongly feel that the committee should review this cohort of patients and consider the potential improved outcomes for patients, (both in lifesaving and in preserving function and quality of life) who have taken apixaban or rivaroxaban and subsequently urgently need reversal therapy due to suffering an intercranial bleed.
4	The impact of an intracranial bleed on the individual, their health needs, disabilities and burden of care and costs often faced by family cannot be underestimated.

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	Currently there is no proven treatment option for reversal of apixaban or rivaroxaban in this cohort of patients. Approximately only 50% of patients who suffer an intracranial bleed, survive, and those who do often suffer permanent brain damage, paralysis or significant disability including loss of sight. Only a minority of people regain complete or near-complete functioning. Recovery to an 'improved' level most usually takes many months and requires extensive rehabilitation including physical, occupational, and speech therapy. The impact of an intracranial bleed on the individual, their family and the NHS services may be difficult to cost but must be considered. For the individual, there are considerable life-style changes, loss in independence and need for support – often 24 hour, adaptation in the home or need for a care setting, loss in opportunity to work which brings ongoing financial changes and challenges. For a family member, the burden of care, costs, possible loss in income(s), 24/7 requirement of help or to be the career, change in lifestyle, social interaction, increased need for medical appointments including regular rehabilitation, – are all immense, costly and impactful changes that will affect health-related quality of life as well. This negative impact on carers' quality of life would need to be taken into account. While for the NHS there is extensive hospitalisation and care for the immediate recovery period, considerable rehabilitation and on-going medical management for the majority of survivors. Critical to improving survival and reduced brain damage leading to long-term disability including loss of sight, is the reversal of the bleed as quickly as possible. Currently in patients who suffer an intracranial bleed and need factor Xa anticoagulation (specifically apixaban or rivaroxaban) reversal, there is no treatment option and hence rehabilitation is the mainstay of treatment to reduce impairment, improve independence in activities, and return the individual to meaningful quality of life. The impact on cost and human burden is immense. There is a clear unmet need and no availability of an alternative proven treatment therapy for this group of patients. We believe the unmet need and cost burden in this cohort of patients should be part of the cost consideration by the Committee.
5	Last-minute change is unavoidable; however, we strongly urge the NICE Committee to do their utmost to ensure a specialist in intracranial bleeds is available to attend and present at the next NICE Andexanet alfa committee meeting. In the ANNEXA4 trial, of the patients followed, major bleeding that was treated with Andexanet alfa was predominantly intracranial (64%). As a result of the absence of a specialist able to attend in the first meeting, it resulted in their experience of the current challenges, barriers, options and possible clinical benefits for this therapy to be unable to be properly explained or understood, thus leaving a serious information gap. Without a specialist available, the impact many patients suffer of long-term disability after an intracranial bleed was not shared in detail for the Committee to be fully informed.
6	Understanding of the pathway: A life-threatening bleed is a medical emergency, and rapid response, along with access to effective therapy is critical not only to save life, but also to preserve quality of life that may be enjoyed if the person survives. In an emergency situation, patients with life threatening bleeds would most commonly be seen and managed by emergency care, which may not always be in a specialist centre.

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	Current management of patients entering Emergency Care with a bleed, was not able to be fully considered as there was no representation from Emergency Care included in the Committee and we would suggest that to understand the full challenges and care pathway for these dangerously ill patients, a representative from Emergency Care should be invited to the next Committee meeting.
7	In reaction to the COVID-19 pandemic in March 2020 NHS England issued updated guidelines on anticoagulation services during COVID-19. Ref: https://thrombosisuk.org/downloads/C0077-Specialty-guide_Anticoagulant-services-and-coronavirus-v1-31-March.pdf Page 2: An important inclusion was the management of patients requiring anticoagulation: *"Patients requiring initiation of oral anticoagulation* *DOACs should be initiated, if possible, instead of warfarin to minimise the monitoring burden and need for regular INR (International Normalised Ratio) monitoring."* Similarly, in March 2020, *"Guidance for the safe switching of warfarin to direct oral anticoagulants (DOACs) for patients with non-valvular AF and venous thromboembolism (DVT / PE) during the coronavirus pandemic"* (Ref at bottom of document) Endorsed by professional bodies and Royal College Which advised that in light of the Covid-19 pandemic, *"Switching appropriate patients from warfarin to a DOAC may be considered to avoid regular blood tests for INR monitoring."* These guidelines have been published since the first Committee meeting, but the implications arising from these need to be considered. It is very unlikely that a further 'switch' would be made once a patient was initiated or switched to a DOAC unless there was a medical indications, as a result, it is likely that a far greater number of anticoagulated patients are now prescribed a DOAC than pre-March 2020. Thrombosis UK has received many enquiries and comments from patients who are extremely anxious at the thought of 'switching' to a DOAC, and one of the primary reasons given is their concern about no 'reversal agent being available'. In some areas of England, prescribing of DOAC therapy has been relatively low despite a person being medically suited for consideration of a DOAC agent. Cost may have been a factor in this, but the reason many patients are repeatedly told is that there is 'no reversal agent for a DOAC'. An example of a recent comment received by Thrombosis UK: "*Had my app with haematology my bloods are good... I'm on apixaban now for 6 months till August and she said it's not reversible but trying to explain that to hubby I'm getting tongue tied what is a simple explanation if anyone can help at all?"* The change in practice is also resulting in many patients and their families being extremely anxious, worrying for their outcome should they need emergency reversal treatment in the event of a bleed while on a DOAC. Thrombosis UK is aware of individuals refusing to switch fearing the outcome of a serious bleed more than the risks associated with less frequent INR testing or attending INR testing stations during the pandemic. We believe the Committee was unaware of this new factor at the time of the last Committee meeting, but that this should be consideration given the: - NHS lead change in advice - Increased numbers prescribed apixaban and rivaroxaban - The understandable concerns and anxieties of patients Some patients being left at increased risk of thrombotic and bleed events if INR monitoring is reduced.

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8	In the March 2020 published guidance documents, low molecular weight heparin (LMWH) has also been listed as an alternative option to warfarin therapy for patients during Covid-19. While for certain patients, this is the most appropriate and safest anticoagulation therapy option, globally there is a shortage of LMWH and as such, it is not a viable therapy option for patients who medically, are appropriate for DOAC therapy. The guidance also includes reference to this: (Pg 2 NHS Guidance for Anticoagulation Services, ref: https://thrombosisuk.org/downloads/C0077-Specialty-guide_Anticoagulant-services-and-coronavirus-v1-31-March.pdf): *"In view of recognised supply issues with LMWH, these should only be used if there are no other appropriate options."*
9	In the first Committee meeting (March 12th) we believe an important national guideline update was unavailable as it was pending publication: NG158 – NICE Guidelines for Venous thromboembolic diseases: diagnosis management and thrombophilia testing [March 2020] Ref: https://thrombosisuk.org/downloads/NICE-ng158-venous-thromboembolic-diseases.pdf NG158 guideline recommends: 1. (Ref 1.3.8) Rivaroxaban and apixaban as the preferred options for interim and continuing anticoagulation. In light of this change and new recommendation to use apixaban or rivaroxaban, we would urge the Committee to reconsider its current recommendation. With updated NICE and NHS England guidance now published many more patients are and will be being initiated or switched to a DOAC, and the DOAC of first choice, as guided by NICE will be either apixaban or rivaroxaban. Yet in England, neither have a recognised licensed reversal agent. 2. NG158 (Ref 1.3.3) also recommended using a DOAC (preferred apixaban or rivaroxaban) as interim anticoagulation therapy pending diagnosis. This change means that if suspected of a deep vein thrombosis or pulmonary embolism, and pending diagnosis, if appropriate, a patient can be initiated on a DOAC (apixaban or rivaroxaban the preferred choice). As a result there is likely to be considerable increase in prescribing levels of apixaban and rivaroxaban, and as such, a greater number of individuals at risk should they suffer a severe and dangerous bleed. 3. NG158 has also given support to prescribe DOAC therapy as first line therapy in cancer associated thrombosis (CAT) if clinically appropriate. Whilst different cancers and different cancer treatments affect risk factors, 1 in 4 patients with a diagnosis of active cancer develop blood clots – either deep vein thrombosis (DVT), pulmonary embolism (PE) or both. These particular patients are often complex to manage and can also be at increased risk of bleeds. In light of this high-risk group, we urge the Committee to reconsider the clinical benefits of a DOAC (apixaban and rivaroxaban) reversal agent. Whilst evidence was presented that certain types of severe bleeds can often be effectively managed with other therapy options such as blood products and prothrombin complex concentrate (PCC), this is not effective for all bleeds nor for all patients. For patients who do not respond, or for whom other options are not clinically appropriate/effective, Andexanet alfa could be an effective alternative that has been shown to save lives and reduce long term harm from a dangerous bleed. We urge the Committee to consider the speed with which an intracranial bleed is stopped is critical in reducing long-term harm as well as saving life. In the ANNEXA4 Trial, 80% of patients who had suffered an intracranial bleed and were then treated with Andexanet alfa had regained good haemostatic efficacy within 12 hours post initiation of therapy.
10	During the first Committee meeting, the patient view and experience of managing bleeding risk and experience of bleed reversal, was only touched upon in the Lay Committee presentation about thrombosis.

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	As was the procedure after the clinical summary was presented, the Committee would have gained much more insight into the patient experience, considerations and viewpoint if the patient group representatives had been questioned or invited to comment further. In the same way questions are addressed to the clinical specialists, eg "If approved, do you think this therapy would make a difference to practice?" Questions such as: "What difference do you think it would make to patients if a DOAC reversal agent was made available based on the submitted trial evidence?" Would provide the Committee with a balance of clinical and patient perspectives on perceived risk, benefit and value. In the absence of a specialist and further questions to the patient representatives invited to the Committee, the impact of surviving a severe and life-threatening bleed was not discussed, in particular the long term disability, cost, health and social needs for patients who had survived an intracranial bleed but who as a consequence, suffered severe long-term disabilities.
11	Due to the Covid-19 pandemic, the planned Committee meeting had to be held remotely, and this was a learning experience for all participants and organisers. However, given these were 'unchartered waters', without opportunity for further questioning during Part 1 of the Committee review, it was extremely difficult for the invited patient representatives on the panel to express views and stress how important this technology will be for the growing number of patients prescribed apixaban or rivaroxaban. Perhaps particularly so for those requiring long term DOAC anticoagulation therapy. With a lack of opportunity to respond to questions or voice comment, we believe the Committee was not made aware of the concerns nor that as a result some patients would rather choose a less safe option or an option that required daily self-injecting, than a therapy that did not have a reversal agent and that this was often based on information they had been told from their healthcare professionals previous to the Covid-19 pandemic on risks and benefits in their anticoagulation options. Many patients and prescribers at present are of a view that there is no specific reversal agent for the factor DOAC anticoagulants approved by NICE and pre-Covid-19, this has been a recognised ongoing barrier to their general adoption by some patients and some prescribers despite their other advantages. It should not be underestimated that the availability of a specific antidote for reversal of a DOAC (apixaban, rivaroxaban) will provide reassurance and this may benefit certain populations.

Insert extra rows as needed

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https://www.rpharms.com/Portals/0/RPS%20document%20library/Open%20access/Coronavirus/FINAL%20Guidance%20on%20safe%20switching%20of%20warfarin%20to%20DOAC%20COVID-19%20Mar%202020.pdf?ver=2020-03-26-180945-627

NICE National Institute for Health and Care Excellence

Professional organisation submission

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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

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- 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	**UK Clinical Pharmacy Association – Cardiovascular Committee**

3. Job title or position	**Lead Cardiac Pharmacist**
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).	**Non profit membership association representing clinical pharmacists.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**

General Comments

Pg 3
Section 1.1 Recommendations
'The clinical evidence is very limited. There is no direct evidence that andexanet alfa is better than an existing treatment, prothrombin complex concentrate, at helping people survive a major bleed'
Of note there are no therapies licensed for reversal of major bleeding due to FXa inhibitors including PCC. So whilst the clinical evidence is very limited, current management plans is off label and risk promoting off label use at the expense of a licensed product. Incidentally evidence suggest PCC for this indication may be thrombotic without the optimal dose evaluated (as observed in the ORANGE registry).

Pg 5, section 3.1 – Direct anticoagulants are associate with a serious risk of major bleeding.
UKCPA agrees, there is a need of a reversal agent for severe/life threatening bleeding on DOACs noting that the use of DOACs as an percentage of oral anticoagulants has surpassed warfarin.
Pg 5, section 3.3
We agree the highest risk group are ICH, for which options are very limited.

Pg 7
Section 3.5 Comparability of ANNEXa-4 and the ORANGE study is uncertain
Whilst the comparison against the two studies can be debated, it is worth noting that PCC is not licensed for the management of bleeds associated with factor Xa inhibitors. The difference in mortality for ICH should not simply be ignored. Whilst we welcome Portola undertaking a propensity score matching to be able to compare, there are significant limitations with the inclusion criteria that make this difficult. Noting the delay in outcomes for a direct comparison, we urge NICE/NHSE and Portola to consider a patient access scheme that would warrant andexanet cost effective (noting the absence of a direct comparison against an off label indication) to enable the NHS to have andexanet as option for managing the reversal of severe life threatening bleeding in particular ICH.

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

To NICE Committee A members,

We, the undersigned, are extremely disappointed with the provisional decision of NICE not to recommend andexanet alfa in its licensed indications. We believe that this decision denies clinicians access to an approved medicine for the treatment of high-mortality medical emergencies and will, in our view, lead to potentially avoidable loss of life.

Clinicians in England and Wales who deal with life-threatening or uncontrolled bleeding urgently require an effective option to reverse the effect of the most commonly used direct oral anticoagulants (DOACs) in patients.

In the DOAC registration studies 30-day mortality rates for the most severe DOAC-related bleeds were substantial, particularly for patients with intracranial haemorrhage, where mortality rates up to 48%1-3 were observed, and in patients with gastrointestinal bleeding4. These rates are consistent with outcomes observed for patients in the ORANGE study treated with four-factor prothrombin complex concentrates (PCCs)5,6 and our experience in UK clinical practice.

There is currently no specific antidote available in the UK to reverse the anticoagulation effects of DOACs. Consequently, unproven strategies have been used in an attempt to manage bleeding, including off-label use of PCCs. These concentrates include various mixtures of four clotting factors - II, VII, IX and X - which were developed to replace clotting factors when deficiencies occur, such as during vitamin K antagonist therapy. Although many case series describing the use of PCCs for managing DOAC-related bleeding have been published, the presence of common methodological flaws in both objective assessments of outcome and series analyses necessitates caution in their interpretation. Therefore, PCCs should not be considered standard of care and this view is reflected across many international guidelines, from different medical specialities, which recommend a preference for the use of specific reversal agents where these are available.

Andexanet alfa has been developed to act as a specific decoy protein to inhibit FXa inhibitors. Andexanet alfa's mechanism and speed of action has been demonstrated through a reduction of FXa activity in healthy anticoagulated elderly subjects.

We appreciate the certainty of results afforded by a randomised controlled trial (RCT) and a RCT is currently being undertaken with Andexanet alfa as a condition of the EU and FDA licence. However, at the time of starting the Annexa-4 trial there was no comparable or licensed reversal agent to which andexanet alfa could

be compared and a randomised controlled trial against usual care was considered unethical. In this context, the clinical evidence for andexanet alfa might be seen as analogous to the evidence for the use of an antidote to a poison.

The ANNEXA-4 study was therefore appropriately set up as a single arm trial and demonstrated, using standardised clinical trial criteria, that rapid reversal of FXa inhibition led to objective demonstration of haemostatic efficacy in acutely bleeding patients7,8. In other words, andexanet alfa rapidly and effectively stops bleeding in life-threatening situations.

We understand the limitations of the single arm trial of andexanet alfa in guiding NICE to an estimate of the survival benefit in life-threatening or uncontrolled bleeding associated with apixaban or rivaroxaban therapy. However, it would be clinically implausible to hypothesise that a specific, fast-acting reversal agent will have no benefit on mortality in life-threatening or uncontrollable bleeds.

In our clinical experience, choosing the PCC-treated subset of the DOAC bleeds in the ORANGE cohort provides a reasonable basis for evaluating the most severe bleeds which may be considered life threatening or uncontrolled in the UK.

Whilst we understand the limitations of indirect comparisons, the observed relative reductions in mortality for ICH (69%) and GI (51%) seem clinically plausible. This is something we might expect given the mortality results observed for andexanet alfa in ANNEXA-4 (15% in ICH and 12% GI) compared to those observed with PCC-treated patients in ORANGE, various case series of PCC use and our own clinical experience with PCC.

Furthermore, given andexanet alfa's mechanism of action, and its ability to limit haematoma expansion we would expect to see an impact on quality of life in ICH patients – andexanet alfa's encouraging effects have been published demonstrating that 80% of patients had a volume expansion ≤ 35% from baseline at 1 hour. As such, assuming no effect on the quality of life of ICH patients would be overly conservative and not in keeping with clinical expectations in the UK.

Finally, we draw NICE's attention to the fact that over 15 International guidelines positively recommend the use of andexanet alfa in treating life-threatening or uncontrolled bleeds associated with apixaban or rivaroxaban including those from the European Stroke Organisation and the British Society of Gastroenterology9,10.

We urge NICE to work with Portola to ensure that patients in England and Wales with the highest risk of death or severe life-long disability have access to this medicine. Specifically, this includes patients with intracranial haemorrhage, particularly haemorrhagic stroke; patients with gastrointestinal bleeding who are haemodynamically unstable and patients with bleeds in other sites that threaten life, limb, vision or paralysis.

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References

1. Hankey GJ, Stevens SR, Piccini JP, et al. Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban: the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation. Stroke. 2014;45(5):1304-1312.
2. Held C, Hylek EM, Alexander JH, et al. Clinical outcomes and management associated with major bleeding in patients with atrial fibrillation treated with apixaban or warfarin: insights from the ARISTOTLE trial. Eur Heart J. 2015;36(20):1264-1272.
3. Kaide C, Gulseth M. Current Strategies for the Management of Bleeding Associated With Direct Oral Anticoagulants and a Review of Investigational Reversal Agents. The Journal of emergency medicine. 2019.
4. Milling TJ, Jr., Clark CL, Feronti C, et al. Management of Factor Xa inhibitor-associated life-threatening major hemorrhage: A retrospective multi-center analysis. Am J Emerg Med. 2018;36(3):396-402.
5. Green L, Tan J, Antoniou S, et al. Haematological management of major bleeding associated with direct oral anticoagulants - UK experience. Br J Haematol. 2019;185(3):514-522.
6. Green L, Tan J, Morris JK, 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;103(4):738-745.
7. Connolly SJ, Crowther M, Eikelboom JW, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2019;380(14):1326-1335.
8. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373(25):2413-2424.
9. Christensen H, Cordonnier C, Kõrv J, et al. European Stroke Organisation Guideline on Reversal of Oral Anticoagulants in Acute Intracerebral Haemorrhage. European Stroke Journal. 2019;doi.org/10.1177/2396987319849763.
10. Oakland K, Chadwick G, East JE, et al. Diagnosis and management of acute lower gastrointestinal bleeding: guidelines from the British Society of Gastroenterology. Gut. 2019;68(5):776-789.

Name	[redacted]
Role	
Other role	
Organisation	Pumping marvellous Foundation
Location	
Conflict	
Notes	

Comments on the ACD:

The committee concluded that a benefit from andexanet alfa on long-term disability was not demonstrated by the evidence.
People take DOACS to significantly reduce the risk of thromboembolisms. Patients fear not only the risk of out of control bleeds but also the downstream impact of not being able to stop the bleeds. I have taken apixaban since 2013 . I have lived with apixaban, positives as well as negatives, for nearly 7 years. It is a testament to the medicine, however it does take a heavy burden on my quality of life to the point that I am forever cautious of the risks. It's burden presents itself in a number of decisions of how I live my life. I have been waiting for an antidote to a situation which may present due to taking a DOAC.

Are the recommendations sound and a suitable basis for guidance to the NHS?

I really don't think that the recommendation is suitable or favourable for patients because it doesn't seem that the QOL of life, downstream impact of a major bleed has been assessed other than the mortality benefit to satisfy the calculation. When you are offered a DOAC there is high anxiety around safety from a patients position. Not having an "antidote" to a medicine that acutely raises the risk of bleeding is a significant leap of faith for the patient, irrespective of the clinical benefit. From a patients position, moving from warfarin, for example, to a DOAC is based on a QOL decision, not a clinical benefit. Therefore QOL of life is paramount for patients and therefore, the general availability of a technology like Adexanet alfa is important to patients and their families.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

No

The clinical evidence is very limited. There is no direct evidence that andexanet alfa is better than an existing treatment, prothrombin complex concentrate, at helping people survive a major bleed. Also, there is not enough evidence to know whether andexanet alfa reduces long-term disability in people who have had an intracranial haemorrhage (bleeding inside the skull), paralysis in people who had an intraspinal bleed and monocular blindness in people who had an intraocular bleed.

This statement concerns me that it seems the whole purpose of the technology is based on survivability (mortality) - surely the purpose is stop the bleed as soon as it is discovered. I believe that the technology does this, therefore the impact of

being able to switch off the bleed is important for the individuals quality of life. The quicker you stop the bleeding the better the quality of life.

Also, because ANNEXA-4 was a single-arm trial there was no comparison with existing treatments such as prothrombin complex concentrate (PCC), further adding to the uncertainty about the clinical benefit of andexanet alfa in clinical practice.
Isn't the single armed trial the most ethical way of conducting a trial where the technology has such a profound benefit to the patient in such a short amount of time when clinical judgement is paramount to patient safety. Also have PCC been through the NICE authorisation process if using as a comparator?

I don't think the committee needed to be persuaded around the unmet need; however to prevent progression of this technology due to perceived lack of cost effectiveness and lack of insight into the potential impact on QOL to patients living downstream after an ICH for example, I vehemently challenge.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Has all of the relevant evidence been taken into account?

We are aware of the limitations of the ANNEXA-4 study, however this trial demonstrated a marked reduction of anti-Xa activity after andexanet and 82%of patients had excellent or good haemostatic efficacy after 12 hours. Within all the limitations of this study, there is evidence for effectiveness.

Are the summaries of clinical and resource savings reasonable interpretations of the evidence?
No comment

Are the recommendations sound and a suitable basis for guidance to the NHS?

There is not evidence for the clinical effectiveness (only case series) for prothrombin complex concentrate, which is used in our hospital protocol (Addenbrooke's), to reverse bleeding in the context of rivaroxaban and apixaban. We would draw your attention to the GMC guidance (Good practice in prescribing and managing medicines and devices) which states 'Prescribing unlicensed medicines may be necessary where: There is no suitably licensed medicine that will meet the patient's need (https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines, last accessed 1st May 2020)'. If andexanet is not licenced then there will be a position where alternatively prothrombin complex concentrate will be used off licence without evidence for its efficacy, when a licenced medication is available. It is desirable to prescribe a licenced drug where it is available. In this regard the NICE TA means that ongoing prescription of a medication which is neither licenced or known to be effective will continue if andexanet is not available.

Hospitals will be forced to individually decide on whether to purchase andexanet (if there is a negative TA) placing a large burden of time on hard pressed resources to decide on this for each Trust. Criteria for the drugs will differ locally and some Trusts may or may not stock the drug locally creating inequality of services. In addition, deciding on which cases would deserve doses purchased by Trusts would create ethical dilemmas of which patients to treat.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Some patients for whom blood products are not acceptable would not have the option of andexanet and would also be unable to accept prothrombin complex concentrate. In this regard the NICE TA creates a degree of inequality.

Name	[redacted]
Role	
Other role	
Organisation	CSL Behring
Location	
Conflict	
Notes	
Comments on the ACD:	
Andexanet alfa has not been shown to be cost effective compared with PCC We note that maximum list prices have been used to calculate the acquisition costs of PCCs. PCCs are available through a pricing framework (CM/PHS/15/5499) at considerable discounts to these list prices. We propose that the framework prices should be used to calculate any ICER estimate.	

Andexanet alfa for reversing anticoagulation [ID1101]

ERG review of company's response to the ACD

May 2020

This report was commissioned by the NIHR HTA Programme as project number 16/168/04T

BMJ Technology Assessment Group

1 SUMMARY

According to the appraisal consultation document (ACD) produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of andexanet alfa for reversing anticoagulation [ID1101], the lack of evidence makes the cost-effectiveness estimates for andexanet alfa very uncertain. Therefore, it cannot be recommended.

This document provides:

1. The company's updated base case analyses (comments 7 and 8 from the company) (Section 2);

2. The Evidence Review Group's (ERG's) response to comments 2, 3, 4, 5 and 6 from the company which concern the ANNEXA-4 trial design and primary outcomes, the ANNEXA-4 30-day mortality outcomes, the comparability of the ANNEXA-4 and PCC-ORANGE populations, the indirect comparison to measure the comparative effectiveness of andexanet alfa versus PCC and the morbidity benefit expected for andexanet alfa (Section 3);

3. The ERG's updated base case analyses (Section 4).

2 UPDATED COMPANY BASE CASE ANALYSES

In response to the ACD, the company presented updated base case analyses for the following cohorts:

1. Whole cohort (Table 1)
2. Intracranial (ICH) plus GI (gastrointestinal) cohort and (Table 2);
3. ICH cohort (Table 3);
4. GI cohort (Table 4);
5. Other major bleed cohort (Table 5).

The changes that have been made to the company's base case analyses following the ACD include a revised patient access scheme (PAS), with list price discounted at [redacted], and 12 months' rehabilitation for patients who suffered from an ICH (previously lifetime rehabilitation), in line with the ERG's preferred assumption. The company also presented probabilistic results and the ERG considers these to be comparable to the deterministic results.

Table 1. Deterministic results of company's updated base case analysis – Whole cohort

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

Table 2. Deterministic results of company's updated base case analysis – ICH plus GI cohort

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: GI, gastrointestinal; ICER, incremental cost effectiveness ratio; ICH, intracranial haemorrhage; LY, life year; QALY, quality-adjusted life year.

Table 3. Deterministic results of company's updated base case analysis – ICH cohort

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; ICH, intracranial haemorrhage; LY, life year; QALY, quality-adjusted life year.

Table 4. Deterministic results of company's updated base case analysis – GI cohort

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental Lys	Incremental QALYs	ICER (£/QALY)
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: GI, gastrointestinal; ICER, incremental cost effectiveness ratio; LY, life year; QALY, quality-adjusted life year.							

Table 5. Deterministic results of company's updated base case analysis – other major bleed cohort

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental Lys	Incremental QALYs	ICER (£/QALY)
Standard care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Andexanet alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost effectiveness ratio; LY, life year; QALY, quality-adjusted life year.							

According to the company's one-way sensitivity analysis, the top two key drivers in the whole cohort and other major bleed cohort include the long-term cost of intraspinal care and long-term utility associated with intraspinal survivors. Thus, the ERG reiterates the importance of the company's assumption that andexanet alfa results in a relative reduction of 25% for paralysis in intraspinal bleed survivors compared to standard care. The ERG maintains that in the absence of any evidence to substantiate a relative reduction of 25%, no reduction is more appropriate, if, conservative. All of the ERG's preferred assumptions are described further in Section 4.

3 ERG REVIEW OF COMMENTS

3.1 Comment 2: The ANNEXA-4 trial design and primary outcomes are appropriate to assess andexanet alfa's clinical benefit

The ERG notes that the committee raised concerns in the ACD that ANNEXA-4[1] is a single-arm study and therefore the comparison of andexanet alfa with standard care (defined as PCC in the company submission) is uncertain. The ERG notes that no new data, for example, from a randomised controlled trial (RCT) have been provided by the company and therefore the ERG considers the issues around the use of single-arm data remain.

The company cited three references for papers which they consider provide evidence that haemostatic efficacy is predictive of clinical outcomes in ICH patients; however due to time constraints the ERG has not been able to fully review these studies.[2-4] The ERG does, however, note that the three papers all report on a link between haematoma expansion in ICH patients being associated with increased mortality but the ERG is unsure how these papers were identified and how representative they are of the evidence base on this subject . The ERG also notes that the company presents further data from ANNEXA-4 ICH patients on mortality in relation to baseline intracerebral haemorrhage volumes in patients with spontaneous intracerebral bleeding (Table 6). The ERG considers the ANNEXA-4 data suggest a trend towards [redacted] mortality rates with the [redacted] volume bleeds but does not consider these data suitable for drawing conclusions about any potential mortality benefit with andexanet alfa in relation to PCC. The ERG also notes that the data are restricted to patients with non-traumatic spontaneous intracerebral haemorrhage although it is unclear how many, if any, traumatic intracerebral haemorrhage patients were enrolled in ANNEXA-4 or if their results differ from the spontaneous intracerebral haemorrhage patients.

Table 6. ANNEXA-4 mortality rates for subgroups of baseline intracerebral haemorrhage volume in patients with spontaneous intracerebral bleeding (Reproduced from company additional evidence, appendix B, Table 1).

Quartile	Volumes (cc)	N	Died (%)
1	0-3.85	[redacted]	[redacted]
2	3.85-9.46	[redacted]	[redacted]
3	9.46-21.29	[redacted]	[redacted]
4	21.29-58.25	[redacted]	[redacted]
All	0-58.25	[redacted]	[redacted]
Abbreviations: cc, cubic centimetres, N, number or patients.			

The company also provided additional baseline characteristic data in their additional evidence for the GI bleed subgroup of ANNEXA-4. The baseline characteristic data included the pre-endoscopy Rockall scores and Glasgow-Blatchford bleeding scores (GBS) based on bleed location (upper or lower GI). The company cited the results of the scores in relation to the expected mortality and morbidity predicted

by the scoring tools and reported that the rates of mortality observed in ANNEXA-4 for upper GI bleed patients (30-day mortality [redacted]) were lower than the mortality predicted by the pre-endoscopy Rockall score ([redacted]). However, the ERG does not consider this to be a reasonable comparison as the ANNEXA-4 population were selected based on expected survival of at least 1 month and as such the ERG considers the mortality in ANNEXA-4 maybe skewed in favour of andexanet alfa. In addition, as highlighted by the company, the ERG notes that the Rockall score was not originally developed in an anticoagulated population such as in patients taking FXa inhibitors. The ERG therefore considers the extent to which anticoagulation affects the mortality estimates generated by the Rockall score to be unknown.

In summary, the ERG does not consider the additional data presented for the ICH or GI subgroups of ANNEXA-4 to provide suitable evidence to draw conclusions regarding the relationship between haemostatic efficacy and clinical outcomes. The ERG notes that the company's clinical engagement findings suggest that it is reasonable to expect a mortality benefit with andexanet alfa in comparison with PCC and the ERG considers this hypothesis should be formally tested in an appropriately powered RCT in order to confirm the existence of any mortality benefit. The ERG considers it important to highlight that the results of the propensity score matching (PSM) are used to inform the company's base case and [redacted].

3.2 Comment 3: The ANNEXA-4 30-day mortality outcomes are generalisable to routine UK clinical practice

ANNEXA-4 excluded people with survival expected to be less than 1 month, a Glasgow Coma Score lower than 7, or an intracerebral bleed volume of more than 60 ml and the ERG notes that the committee was concerned that these patients would potentially be eligible for andexanet alfa in clinical practice. The company's additional evidence includes real world evidence from a United States of America (USA) retrospective study of [redacted] patients who have received andexanet alfa within its marketing authorisation across 45 USA-based hospitals to provide justification that the mortality outcomes seen in ANNEXA-4 are generalisable to routine UK clinical practice. The ERG notes that there are [redacted] in the baseline characteristics of patients in ANNEXA-4 compared with the real world evidence study, for example in ANNEXA-4 the mean age and proportion of use of apixaban are [redacted] (Table 7). The ERG also notes that baseline characteristic data on bleed severity, volume of bleed and the specific site of the bleeds were not reported for the real-world evidence study and these were deemed by the ERG's clinical experts to be important covariates in the PSM analyses. The ERG therefore recommends caution in drawing any conclusions from the real word evidence study as there may be important differences between it and ANNEXA-4 that could impact on the comparability of the mortality data between the two studies. The ERG does, however, note that the real world evidence study suggests [redacted] in hospital mortality rates for the ICH subgroup compared to ANNEXA-4 and a [redacted]

[redacted] in hospital mortality rate for the GI bleed subgroup (Table 7). The ERG notes that only in hospital mortality rates are presented rather than 30-day mortality, the outcome of relevance for the PSM analysis and economic analysis, which further limits the suitability of the real world evidence in terms of suggesting the results of ANNEXA-4 are generalisable to UK clinical practice. In addition, there may be other issues with the use of the in hospital mortality outcome such as differences in outcome definition, assessment, and analysis between ANNEXA-4 and the real-world evidence study as no further information was provided (e.g. any differences in censoring criteria could have considerable impact on the results).

Table 7. ANNEXA-4 (whole cohort) versus USA real world multi-centre analysis baseline characteristics and in-hospital mortality (Reproduced from company addiitonal evidence, appendix E, Table 7)

	ANNEXA-4	**USA real world multi-centre analysis**
Patients, N	[redacted]	[redacted]
Age in years (mean)	[redacted]	[redacted]
Male (%)	[redacted]	[redacted]
DOAC (%)		
Rivaroxaban	[redacted]	[redacted]
Apixaban	[redacted]	[redacted]
Bleed Type (%)		
ICH	[redacted]	[redacted]
GI	[redacted]	[redacted]
Other	[redacted]	[redacted]
In hospital mortality (%)		
ICH	[redacted]	[redacted]
GI	[redacted]	[redacted]
Other	[redacted]	[redacted]
Abbreviations: DOAC, direct oral anticoagulant; GI, gastrointestinal; ICH, intracranial; N, number of patients; USA, United States of America.		

As noted in the ERG report, 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 less than 1 month expected survival exclusion criteria appropriate because it is likely patients wouldn't have entered screening if clinicians did not consider them likely to meet the study inclusion criteria.

To explore this uncertainty, the ERG has provided the cost-effectiveness results for a scenario where the 30-day mortality for andexanet alfa is assumed to be the same as 4F-PCC (from the ORANGE study) for all bleeds. This scenario increased the company's base case incremental cost effectiveness ratio (ICER) in each cohort as follows:

- Whole cohort from [redacted] to [redacted];

- ICH plus GI cohort from [redacted] to [redacted];
- ICH cohort from [redacted] to [redacted];
- GI cohort from [redacted] to [redacted];
- Other major bleed cohort from [redacted] to [redacted].

3.3 Comment 4: The ANNEXA-4 and PCC-ORANGE populations are comparable

The ERG and its clinical experts agree with the company that the use of the PCC subgroup from ORANGE[5] is the most appropriate comparator dataset currently available to reflect standard care for patients likely to be eligible for andexanet alfa in UK clinical practice. The ERG notes that the company cites data comparing the non-PCC subgroup with the PCC subgroup of ORANGE and ANNEXA-4 in their response to the ACD although the ERG does not consider the ACD to be questioning the suitability of the PCC subgroup of ORANGE. The ERG therefore does not consider it necessary to critique these data but nevertheless agrees with the company that they add support to the argument that the PCC subgroup of ORANGE is the most suitable population for the comparison with ANNEXA-4.

The ERG notes that the company has supplied data from a real world evidence study to attempt to overcome the uncertainty relating to the impact of the expected survival of less than 1 month exclusion criterion applied in ANNEXA-4 (please see Section 3.2 for further details). However, as discussed in Section 3.2, the ERG has concerns relating to the use of the real world study to draw conclusions relating to mortality and therefore the ERG considers the impact of this exclusion criterion on the results of ANNEXA-4 remains unknown.

3.4 Comment 5: The indirect comparison to measure the comparative effectiveness of andexanet alfa versus PCC is robust and can be generalised to the benefit expected in UK clinical practice

The ERG notes that the company conducted Rosenbaum[6] sensitivity analysis tests in an attempt to assess how robust the results of the PSM analysis used in their economic base case are to confounding caused by unobserved variables affecting both treatment assignment and outcome ('confounding variables'). However, the ERG notes that the company reports a limitation of the Rosenbaum sensitivity analysis is that matching must be done without replacement, whereas the ERG notes that in the company's PSM analysis that is used in the company's base case a matching with replacement method was used. The ERG thus considers the results of the Rosenbaum sensitivity analysis of limited value in relation to assessing the robustness of the PSM analysis that underpins the company's base case. The

ERG notes that the company does, however, also conduct a scenario analysis that utilises the PSM analysis data from the matching without replacement analysis used in their Rosenbaum sensitivity analysis (Scenario 1, detailed below).

The results of the Rosenbaum sensitivity analysis show that even if unobserved variables meant that one partner in a matched pair was [redacted] times more likely to receive andexanet alfa in reality than the other partner, it could still be concluded that andexanet alfa made patients less likely to die within 30 days for the whole cohort, ICH+GI cohort and ICH cohort. However, if one partner in the matched pair was [redacted] times more likely to receive andexanet alfa in reality than the other partner, then the propensity score matched analysis results may cease to be statistically significant. Rosenbaum sensitivity analysis couldn't be conducted for the GI bleed cohort because statistical significance was not achieved; the ERG notes that this may be related to the low number of mortality events in the analysis.

In addition to the Rosenbaum sensitivity analysis, the company reported that they have conducted indirect comparisons using five different methods: four different PSM analyses which comprise of using two different sets of covariates and matching with and without replacement methodologies as well as a fifth analysis using inverse probability of treatment weighting (IPTW) methodology. The analyses and their results are summarised in the company's additional evidence Appendix H. The ERG notes that three of the analyses are new and these comprise the two analyses that use matching without replacement (Scenario 1 and Scenario 3) and the IPTW analysis (Scenario 4). As discussed in the ERG report, the ERG prefers the more extensive covariates used in the analysis informing the company base case (Base case) compared to the more limited range of covariates implemented in the PSM in the original company submission. The ERG therefore does not discuss the results of scenario 2 and 3 further as these used the limited range of covariates for matching with (Scenario 2) and without (Scenario 3) replacement.

The ERG provides a summary of the percentage relative reduction in 30-day mortality with andexanet alfa for the analyses used to inform the base case and scenarios 1 and 4 in Table 8; full results are presented in the company's additional evidence, Appendix H, Tables 11 to 15. The ERG considers the indirect comparison results are [redacted] the three analyses (Base case, Scenario 1 and Scenario 4) for the whole cohort, ICH + GI subgroup and ICH subgroup. In terms of GI bleed, [redacted]

In terms of other major bleeds, as discussed in the ERG report, the ERG does not consider the data on other major bleeds to be suitable for PSM analysis or any other analysis given the [redacted]

[redacted]. The ERG, therefore, recommends caution when interpreting the results for the other bleeds population in the PSM and IPTW analyses.

Table 8. Propensity score matching (PSM) results for 30-day mortality in relation to the data used in the company's economic model.

Cohort	Relative reduction* (%)		
	Base case (matching with replacement)	Scenario 1 (matching without replacement)	Scenario 4 (IPTW)
Whole cohort	[redacted]	[redacted]	[redacted]
ICH + GI	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]
GI bleed	[redacted]	[redacted]	[redacted]
Other bleeds	[redacted]	[redacted]	[redacted]

*Relative reduction = (ANNEXA-4 mortality rate – ORANGE mortality rate)/(ORANGE mortality rate)
Abbreviations: GI, gastrointestinal; ICH, intracranial haemorrhage; IPTW, inverse probability of treatment weighting.

Alternative indirect comparison approaches provided similar ICERs in the whole cohort, ICH+GI cohort and ICH cohort. However, the ICERs in the GI cohort were much more sensitive to the indirect comparison approach (Table 9).

Table 9. Results (ICERs) of alternative indirect comparison approaches

Cohort	Company's revised base case (matching with replacement)	Scenario 1 (matching without replacement)	Scenario 4 (IPTW)
Whole	[redacted]	[redacted]	[redacted]
ICH+GI	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]
GI	[redacted]	[redacted]	[redacted]

Abbreviations: GI, gastrointestinal; ICER, incremental cost effectiveness ratio; ICH, intracranial; IPTW, inverse probability treatment weighting: ITC, indirect treatment comparison; PSM, propensity score matching
Note: 30-day mortality in other major bleeds informed by clinical expert opinion in the absence of a robust PSM analysis

3.5 Comment 6: A morbidity benefit is expected for andexanet alfa based on clinical consensus in the UK

The ERG agrees with the company that UK clinical opinion obtained during the response to the ACD suggests that function and quality of life could be preserved in ICH survivors following treatment with andexanet alfa. As noted in the ERG report, clinical expert opinion sought by the ERG also considered that andexanet alfa may have the largest effect on intracerebral bleeds as it could prevent haematoma expansion. However, given that the company is unable to provide any comparative data to support their assumption that andexanet alfa leads to better mRS and less disability than PCC, the ERG maintains that applying the same mRS distributions in both treatment arms is more appropriate, if, conservative.

Nonetheless, in order to account for the uncertainty as to what the morbidity benefit for andexanet alfa could be in ICH survivors, the company presented varying levels of benefit from the ERG's base case (no benefit) to the company's base case (100% benefit derived from Øie *et al.* 2018[7]). The company

also noted that, "*at 50% the absolute difference represents half the absolute difference observed between ANNEXA-4 and Øie et al. 2018"*. The ERG has provided the mRS distributions for this example in Table 10. Following this, the ERG identified an error in the company's absolute difference calculation for mRS 2. As such, the ERG updated the company's threshold analyses in the ICH cohort and provides these results in Table 11.

The ERG considers the company's approach to account for this uncertainty to be simplistic. The ERG considers that it would be more useful for a 50% relative morbidity benefit to represent half of the andexanet alfa benefits in the PCC arm (i.e. removing Øie *et al.* 2018 from the analysis) given that the mRS distributions recorded in Øie *et al.* 2018 are not representative of all ICH subtypes. Unfortunately, the ERG is unable to explore such a scenario due to time constraints.

Table 10. mRS distributions and absolute differences

mRS	Oie *et al.* 2018[7] (PCC)	Andexanet alfa	Absolute difference in mRS
Base case			
0	1.6%	[redacted]	[redacted]
1	8.2%	[redacted]	[redacted]
2	14.8%	[redacted]	[redacted]
3	19.7%	[redacted]	[redacted]
4	36.1%	[redacted]	[redacted]
5	19.7%	[redacted]	[redacted]
Half the absolute difference observed between ANNEXA-4 and Øie *et al.* 2018			
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: mRS, modified rankin score; PCC, prothrombin complex concentrate
The following estimates were corrected by the ERG from:
a - [redacted]
b [redacted]
c [redacted]

Table 11. Threshold analysis on morbidity benefits in an ICH only cohort

Andexanet alfa vs. standard care relative morbidity benefit (%)*	Revised base case ICER, company	Revised base case ICER, corrected by the ERG
100	[redacted]	[redacted]
90	[redacted]	[redacted]
80	[redacted]	[redacted]
70	[redacted]	[redacted]
60	[redacted]	[redacted]
50	[redacted]	[redacted]
40	[redacted]	[redacted]
30	[redacted]	[redacted]
20	[redacted]	[redacted]

10	[redacted]	[redacted]
0	[redacted]	[redacted]

*based on the absolute differences in mRS distributions sourced from ANNEXA-4 and Øie *et al.* 2018 for andexanet alfa and standard care respectively.
Abbreviations: ICER, incremental cost effectiveness ratio; mRS, modified rankin sore

Finally, in Appendix I and J of the company's ACD response, the company presented results varying morbidity benefits in intraspinal bleeding and intraocular bleeding patients. However, no evidence or clinical rationale was provided to justify these variations in morbidity benefits. Thus, the ERG does not consider it useful to include these results in its response.

4 UPDATED ERG BASE CASE ANALYSES

The ERG considers that ICH bleeds, GI bleeds and other major bleeds (including intraocular bleeds, intraspinal bleeds, pericardial bleeds and retroperitoneal bleeds) are easily identifiable as clinically distinct subgroups and should be considered separately because their treatment and outcomes vary. Additionally, the impact of alternative modelling assumptions for other major bleeds in the whole cohort is minimised by the large proportion of ICH and GI bleeds [redacted] which may lead to inappropriate recommendations for treating patients with other major bleeds. For these reasons, the ERG presents its base results in a ICH cohort, GI cohort and other major bleed cohort.

Furthermore, in the ERG's preferred base case results, it is assumed that the comparison between ANNEXA-4 and ORANGE is not fundamentally flawed. In consequence, the ERG recommends caution in interpreting its results because the patient populations might not be comparable.

To align with UK clinical opinion obtained during the response to the ACD, the ERG has removed its scenario related to the use of mRS scores from Øie *et al.* 2018[7] only in people who had an intracerebral haemorrhage in ANNEXA-4 as this led to patients having better morbidity benefits (in terms of mRS) on 4F-PCC than andexanet alfa, which may be clinically implausible. As such, the ERG has employed the ANNEXA-4 mRS distributions in both treatment arms (assuming no benefit in mRS) in its base case analysis. Following this, the utility of an ICH survivor is 0.53 in both treatment arms. 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 base case analyses.

The ERG's preferred base case analyses in the ICH cohort and other major bleed cohort are given in Table 12 and Table 13, respectively. As for the GI cohort, the company's base case is reflective of the ERG's preferred base case.

The ERG acknowledges the NICE final scope[8] is for the full population covered by the marketing authorisation (i.e. the whole cohort) and so has provided an ICER in the whole cohort using its preferred assumptions (Table 14) despite considering this to be a potentially misleading ICER.

Table 12. ERG's preferred model assumptions, cumulative results – ICH cohort

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY
Company's updated base case	NA	[redacted]	[redacted]	[redacted]
Weighted utility values by mRS	5.3.9.3	[redacted]	[redacted]	[redacted]
mRS distributions from ANNEXA-4 applied to both treatment arms	5.3.5.3	[redacted]	[redacted]	[redacted]

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.

Table 13. ERG's preferred model assumptions, cumulative results – other major bleed cohort

Preferred assumption	Section in ERG report	Incremental costs	Incremental QALYs	Cumulative ICER £/QALY
Company's updated base case	NA	[redacted]	[redacted]	[redacted]
0% relative reduction in 30-day mortality for 'other major bleeds' for andexanet alfa compared to standard care	5.3.5.3	[redacted]	[redacted]	[redacted]
0% relative reduction of paralysis and blindness for andexanet alfa compared to standard care	5.3.5.3	[redacted]	[redacted]	[redacted]
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.				

Table 14. 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	NA	[redacted]	[redacted]	[redacted]
0% relative reduction in 30-day mortality for 'other major bleeds' for andexanet alfa compared to standard care	5.3.5.3	[redacted]	[redacted]	[redacted]
0% relative reduction of paralysis and blindness for andexanet alfa compared to standard care	5.3.5.3	[redacted]	[redacted]	[redacted]
Weighted utility values by mRS	5.3.9.3	[redacted]	[redacted]	[redacted]
mRS distributions from ANNEXA-4 applied to both treatment arms	5.3.5.3	[redacted]	[redacted]	[redacted]
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.				

To account for the uncertainty as to what the morbidity benefit for andexanet alfa could be in ICH survivors (see comment 6), the ERG has presented varying levels of benefit from the ERG's base case (no benefit) to the company's base case (100% benefit derived from Øie *et al.* 2018[7]) including the ERG's other preferred assumption in the ICH cohort (weighted utility values by mRS). These results are given in Table 15 for the ICH cohort.

Table 15. ERG's preferred model assumptions with a threshold analysis on morbidity benefits - ICH cohort

Andexanet alfa vs. standard care relative morbidity benefit (%)*	ICER
100	[redacted]
90	[redacted]
80	[redacted]
70	[redacted]
60	[redacted]
50	[redacted]
40	[redacted]
30	[redacted]
20	[redacted]

10	[redacted]
0	[redacted]
*based on the absolute differences in mRS distributions sourced from ANNEXA-4 and Øie *et al.* 2018 for andexanet alfa and standard care respectively. Abbreviations: ICER, incremental cost effectiveness ratio; mRS, modified Rankin scale	

Finally, to address committee concerns that the ANNEXA-4 30-day mortality outcomes may not be generalisable to routine UK clinical practice (see comment 3), the ERG has provided a scenario on top of its preferred base case assumptions where the 30-day mortality for andexanet alfa is assumed to be the same as PCC for all bleeds. These results are given in Table 16.

Table 16. ERG's preferred model assumptions plus no 30-day mortality benefit

Cohort	Incremental costs	Incremental QALYs	ICER £/QALY
Whole cohort	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]
GI	[redacted]	[redacted]	[redacted]
Other major bleeds	[redacted]	[redacted]	[redacted]
Abbreviations: ERG, evidence review group; GI, gastrointestinal; ICH, intracranial haemorrhage; ICER, incremental cost effectiveness ratio; mRS, modified Rankin scale; QALYs, quality adjusted life years.			

5 REFERENCES

1. Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. *N Engl J Med* 2019; **380**: 1326-35.

2. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology* 2006; **66**: 1175-81.

3. Hemorrhagic Stroke Academia Industry Roundtable P, Second HRP. Recommendations for Clinical Trials in ICH: The Second Hemorrhagic Stroke Academia Industry Roundtable. *Stroke* 2020; **51**: 1333-8.

4. Yaghi S, Dibu J, Achi E, Patel A, Samant R, Hinduja A. Hematoma expansion in spontaneous intracerebral hemorrhage: predictors and outcome. *The International journal of neuroscience* 2014; **124**: 890-3.

5. Green L, Tan J, Morris JK, Alikhan R, Curry N, Everington T, 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; **103**: 738-45.

6. Keele L. An overview of rbounds: An R package for Rosenbaum bounds sensitivity analysis with matched data. 2009.

7. Øie LR, Madsbu MA, Solheim O, Jakola AS, Giannadakis C, Vorhaug A, et al. Functional outcome and survival following spontaneous intracerebral hemorrhage: A retrospective population-based study. *Brain Behav* 2018; **8**: e01113.

8. National Institute for Health and Care Excellence. Single Technology Appraisal: Andexanet alfa for reversing anticoagulation [ID1101]: Final scope, 2019. Available from: https://www.nice.org.uk/guidance/gid-ta10440/documents/final-scope. Date accessed: 10 Jul 2019.