NICE National Institute for Health and Care Excellence

Andexanet alfa for reversing anticoagulation

2nd Appraisal Committee meeting

Chair presentation

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Key issues

- Is the committee still minded to consider ICH, GI bleeds and 'other' bleeds separately?
- Does the committee consider that the 30-day mortality in ANNEXA-4 would translate to the UK general population on the basis of real world evidence in the USA, and is this an improvement on UK outcomes with PCC, as outlined in the ORANGE study?
- ANNEXA-4 used haemostatic efficacy outcomes for ICH and predicted less disability in survivors after andexanet than after PCC. What is the natural history of intracranial bleeds, do the haemostatic outcomes align with clinical expectation?
- The company considers that further analyses (Rosenbaum sensitivity analysis) validate their method of indirect comparison of 30-day mortality with ORANGE, is the committee satisfied with this evidence?
- What is the committee's view on the company's scenario analyses on morbidity and mortality?
- Does the committee consider that it has relevant evidence on 'other bleeds'?
- Equality consideration - Some patients for whom blood products are not acceptable would be unable to accept PCC

Andexanet alfa

Conditional Marketing authorisation	Indicated for adults with a direct factor Xa (FXa) inhibitor (apixaban or rivaroxaban) when reversal is needed due to life-threatening or uncontrolled bleeding
Post authorisation measures	To substantiate correlation of anti-FXa-activity with haemostatic efficacy and clarify the risk of thromboses and thromboembolic events, the company should submit results of a global **RCT** of andexanet alfa vs standard of care in patients with **ICH** (results expected 2023)
Dosage and administration	2 possible doses based on type and timing of last dose of FXa inhibitor: Low dose: 400 mg IV bolus then 4mg/min IV High dose: 800 mg IV bolus then 8mg/min
Mechanism of action	Specific reversal agent for FXa inhibitors – Predominant action is binding and sequestration of the FXa inhibitor
Average list price per course of treatment	£15,081 based on the proportion receiving each low and high dose with wastage
Patient access scheme	Confidential discount on list price

Committee considerations at ACM1 (1)

- Direct anticoagulants are associated with a serious risk of major bleeding
- There is a clinical need for effective anticoagulation reversal agents
- It is not appropriate to combine all bleed types for decision making
- There is no primary clinical outcome or direct comparative evidence for andexanet alfa
  - The 2 primary outcomes in the trial are both haematological: change in 'anti-factor Xa activity' and haemostatic efficacy
  - Clinical experts explained that haemostatic efficacy as defined in the trial could not be predictive of clinical outcomes
  - The evidence available for andexanet alfa is limited

Clinical evidence for andexanet alfa – ANNEXA-4

Study design	Single-arm, open-label, prospective, multicentre Phase IIIb/IV trial (ongoing)
Population (N=352)	People receiving apixaban, rivaroxaban, edoxaban, or enoxaparin with acute major bleeding and baseline anti-fXa activity≥75ng/mL – most received apixaban or rivaroxaban (n=322)
Exclusion criteria (not exhaustive)	• Expected survival < 30 days • People with ICH with any of the following: Glasgow coma score <7 or estimated intracerebral haematoma volume > 60cc as assessed on imaging
Intervention	Andexanet alfa - 2 possible regimens Low dose: 400 mg IV bolus then 4mg/min IV High dose: 800 mg IV bolus then 8mg/min
Outcomes	• Primary endpoints: • % change in anti-FXa activity • rate of excellent/good haemostatic efficacy 12 hours after andexanet alfa infusion • Secondary endpoint: Relationship between anti-FXa activity and haemostatic efficacy, (is anti-FXa activity predictor of haemostatic efficacy) • Safety endpoint: 30-day all-cause mortality and overall safety
Protocol amendment	Amendment 4: 1) Threshold time and dose criteria to determine a low vs high dose 2) Population enriched with ICH people. 139 people enrolled under Amendment 4 of the protocol

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2 additional RCT vs placebo in healthy volunteers (ANNEXA-A and ANNEXA-R) supported application for marketing authorisation but not used in model

Haemostasis (co-primary trial outcome): definition used in the trial for ICH bleeds

Excellent (effective)	**≤ 20% increase:** • Intracerebral haematoma: **haematoma volume** compared to baseline on repeat imaging at both the 1- and 12-hour post infusion time points • Subarachnoid bleed: **maximum thickness** on the follow-up vs baseline at both the 1- and 12-hour post infusion time points • Subdural haematoma: **maximum thickness** at both the 1- and 12-hour post infusion assessments compared to baseline.
Good (effective)	**> 20% but ≤ 35% increase:** • in haematoma volume compared to baseline on a repeat imaging at +12-hour time point for **intracerebral haematoma** • in maximum thickness using the most dense area on the follow-up at +12 hours vs baseline for **subarachnoid bleeding**. • in maximum thickness at +12 hours compared to baseline for **subdural haematoma**.
Poor (not effective)	**> 35% increase:** • in haematoma volume on a CT or MRI compared to baseline on a repeat CT or MRI scan at +12-hour time point in **intracerebral haematoma**. • in maximum thickness using the most dense area on the +12 hours vs at baseline for **subarachnoid bleeding**. • in maximum thickness at +12 hours compared to baseline for **subdural haematoma**.

Haemostasis results in the trial

- In the whole cohort of ANNEXA-4, 69% patients were adjudicated as excellent haemostatic efficacy and 33 (13%) as good
- In the ICH bleed cohort, the rate of excellent or good haemostatic efficacy was 80%
- In the GI bleed cohort, the rate of excellent or good haemostatic efficacy was 85%

Clinical experts' comments

- These criteria are not used routinely
- Most of the criteria used in the trial for haemostasis are not in line with clinical practice. There are no such data from ORANGE study

In clinical practice, what is the natural history of intracranial haemorrhage size over time?

30-day mortality rates in ANNEXA-4 trial

- Bleeds included in submission: ICH, severe GI, pericardial, peritoneal, intraocular and intraspinal – last four classified as 'other major bleeds'

Patients with apixaban or rivaroxaban in the ANNEXA-4 trial	
	Deaths within 30 days % (95%CI)
Whole cohort ([redacted])	[redacted]
Patients with ICH ([redacted])	[redacted]
Patients with GI ([redacted])	[redacted]
Patients with other major bleeds ([redacted])	[redacted]

Clinical evidence for comparator PCC – ORANGE study

Study design	Prospective cohort study multiple hospitals in UK patients admitted for major bleeding while on oral anticoagulant (2013-2016)
Population (N=2,192)	→ 372 people developed a bleed on apixaban or rivaroxaban. Of these 372 people, **149 received PCC**
Exclusion criteria	None related to expected survival, haematoma volume or GCS score
Intervention	Normal course of treatment (included PCC, tranexamic acid, vitamin K and FEIBA [Anti-inhibitor coagulant complex]) Only people who received PCC are included in the analysis
Outcomes	• Clinical outcomes at 30 days, death or discharge • Comorbidities, bleeding sites, haematological laboratory results, management of bleeding and first outcome up to 30 days

Committee considerations at ACM1 (2)

- The comparability of ANNEXA-4 and the ORANGE study is uncertain
  - The ANNEXA-4 trial and ORANGE study did not use the same inclusion criteria – one exclusion criterion in ANNEXA-4 was expected survival less than 30 days
  - The comparability of 30-day mortality rates is subject to great uncertainty
  - Key prognostic factors such as volume and severity of bleed could not be included in analysis
- The indirect treatment comparison for 30-day mortality is too unreliable for decision making
  - In absence of a randomised controlled trial, difficult to reach any conclusion on the clinical benefit of andexanet alfa compared with PCC

Indirect treatment comparison results on matched 30-day mortality

- Andexanet alfa (ANNEXA-4) vs PCC (ORANGE)
- Studies compared using propensity score matching analysis, to replicate randomisation by identifying and comparing patients with similar characteristics: age, site of bleed, history of coronary artery disease, stroke, transient ischaemic attack, atrial fibrillation, hypertension, diabetes, renal dysfunction, cancer
- Prognostic factors such as volume and severity of bleed were not reported in ORANGE and could not be included as covariates
- 30-day mortality rates are key drivers of the model – In its response to ACD, company submitted additional scenarios on the ITC

Population	Number of matches	Matched 30-day mortality (%) (95% CI)	
		PCC	Andexanet alfa
Whole population	[redacted]	[redacted]	[redacted]
ICH subgroup	[redacted]	[redacted]	[redacted]
GI subgroup	[redacted]	[redacted]	[redacted]
Other major bleeds (non-ICH/GI)	[redacted]	[redacted]	[redacted]

Source: ERG report, table 45

Effect of andexanet alfa in the company's model

Effect in the model	Source
Reduces 30-day mortality due to ICH and GI bleeds.	Propensity score matching ANNEXA-4 vs ORANGE.
Reduces 30-day mortality due to retroperitoneal bleeds and pericardial bleeds.	Assumption based on clinical expert input.
Reduces severity of ICH as measured by mRS scores ↳ Reduces long-term mortality risk. ↳ Reduces long-term NHS costs. ↳ Improves long-term utilities.	Naïve comparison of ANNEXA-4 vs Øie et al.
Reduces paralysis and monocular blindness for intraspinal and intraocular bleeds. ↳ Reduces long-term management costs. ↳ Improves long-term utilities.	Assumption based on clinical expert input.

Committee considerations at ACM1 (3)

- A benefit from andexanet alfa on long-term disability after an ICH is not supported by evidence
  - Company assumed andexanet alfa would reduce severity of long-term disability in people who had had an ICH
  - There was no evidence that people would have better mRS scores and less disability after andexanet alfa
- The company's assumptions about 'other major bleeds' on blindness and paralysis are not sufficiently justified
- The long-term outcomes and utilities for people who had an ICH are highly uncertain
- The magnitude of clinical benefit of andexanet alfa was very uncertain, as a result the most plausible ICERs were very uncertain
  - Therefore not recommended for use in the NHS

ACD: preliminary considerations

1.1 Andexanet alfa is not recommended, within its marketing authorisation, for reversing anticoagulation with apixaban or rivaroxaban in adults with uncontrolled or life-threatening bleeding.

ACD consultation responses

Professional organisations	• British Association of Stroke Physicians • British Society of Gastroenterology • British Society of Haematology • British Society of Interventional Radiology • Royal College of Pathologists • Royal College of Physicians • UK Clinical Pharmacy Association
Patient organisations	• Thrombosis UK • Anticoagulation UK (ACUK)
Company	• Portola
Public (web) comments	• NHS clinicians 1 • NHS clinicians 2 • Patient organisation • Comparator company

Comments from British Society of Gastroenterology and Royal college of Physicians

- Agree that there is an unmet need for a reversal agent for factor Xa inhibitors
- Agree with the conclusions of the committee that the available data fails to find convincing evidence of clinical efficacy or cost effectiveness for andexanet alfa
- Not aware of any data that was not considered in the technology appraisal

Comments from British Society of Haematology and Royal College of Pathologists

- No concerns about this recommendation but thrombosis as a complication following the use of andexanet alfa to treat acute bleed has not been mentioned

Note: In ANNEXA-4 trial, about [redacted] of patients had a thrombotic event

Comments from British Association of Stroke Physicians

- Andexanet alfa appears to be effective at reversing anticoagulation, however ANNEXA-4 trial used unvalidated measures of haemostatic efficacy
- Likely that anticoagulation reversal improves clinical outcomes, but unclear whether this is improving very disabled survival in people who would otherwise die, or number of people with excellent recovery
- European Stroke Organisation guideline for ICH recommend early reversal: "*using andexanet alfa if available […] also recommend randomising into trials as based on the low quality of evidence, there is significant uncertainty whether desirable outweigh undesirable effects*"
- Difficult to estimate any effect of andexanet alfa on quality of life or recovery, as size of any beneficial treatment effect is unclear, and target population undefined – Ongoing RCT in ICH
- However, andexanet alfa would almost certainly reverse anticoagulation in ICH patients; probably reduce rate of haematoma growth; and may reduce number of patients who die with anticoagulant related ICH
- Therefore BASP has no objection to NICE interim guidance

Comments from British Society of Interventional Radiology (BSIR)

- Reversal of DOACs is an essential issue
- Concern 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.

Comments from UK Clinical pharmacy association

- No therapies licensed for reversal of major bleeding due to FXa inhibitors including PCC
- So whilst the evidence is very limited for andexanet alfa, current management plans is off label and risk promoting off label use at the expense of a licensed product
- Incidentally evidence suggests PCC for this indication may be thrombotic without the optimal dose evaluated (as observed in ORANGE)
- Agree there is a need for a reversal agent and the highest risk group are ICH, for which options are very limited
- The mortality for ICH should not be simply ignored
- 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 NHS to have andexanet as option for managing the reversal of severe life threatening bleeding in particular ICH

Comments from Thrombosis UK

- Concerned Committee decision has failed to consider the lack of reversal therapy options for patients on DOACs – Urge Committee to reconsider recommendation especially for certain patient groups
- Intracranial haemorrhage is one of the most life-threatening/life limiting acute medical events – urge Committee to consider the speed with which an intracranial bleed is stopped is critical in reducing long-term harm as well as saving life.
- Impact on ICH survivors and their family considerable and cannot be underestimated - unmet need and cost burden in this cohort of patients should be part of Committee consideration
- NICE guidelines for venous thromboembolic disease (NG158) recommends apixaban or rivaroxaban as preferred options for interim and continuing anticoagulation (published just after 1st committee meeting in March)
- With published guidelines, many more patients are and will be initiated/switched to a DOAC (first choice either apixaban or rivaroxaban)
- NG158 also recommended first line DOAC therapy in cancer associated thrombosis - 1 in 4 patients with active cancer develop blood clots. 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 clinical benefits of a DOAC reversal agent

Comments from Anticoagulation UK

- Concerns relating to limitations of patient input around impact of the technology for patients
- Lack of neurology, emergency dept and trauma experts being available to answer questions - should be included in discussions
- Limitations imposed restrict a potential treatment being available which could have significant positive outcomes for patients – Clinicians may not be able to provide optimum treatment
- Acknowledge RCT not available, however andexanet alfa has been shown to be effective; 80% of patients with ICH had regained good haemostatic efficacy and 85% in the GI cohort
- Recently published guidelines NG158 on VTE thromboembolic diseases recommends apixaban or rivaroxaban as first line treatment

Considerations in light of COVID-19 pandemic (Thrombosis UK and anticoagulation UK)

- NHS England updated guidelines on anticoagulation services during the pandemic, to avoid need for regular INR and minimise monitoring burden:
  - At initiation of oral anticoagulation, DOACs should be initiated instead of warfarin
  - Switching appropriate patients from warfarin to a DOAC may be considered
- Implications arising are that there will be more patients on DOACs where there is currently no reversal agent – the clinical need will increase
- Thrombosis UK received many comments from patients who are extremely anxious at the thought of 'switching' to a DOAC - 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 test stations during pandemic
- Evidence forthcoming that COVID-19 patients may be experiencing higher risk of clotting and this cohort of patients will be given DOACs post discharge – health anxiety will be high post COVID and could be severely elevated without a reversal agent being available

Web comments – NHS professional 1

- There is evidence for effectiveness of andexanet alfa with a marked reduction of anti-Xa factor activity. There is no evidence for clinical effectiveness of PCC, which is used in our hospital protocol.
- GMC guidance (Good practice in prescribing and managing medicines and devices): “Prescribing unlicensed medicines may be necessary where there is not suitably licensed medicine that will meet the patient’s need”
- If andexanet alfa not recommended, then PCC will be used off licence without evidence for its efficacy, when a licensed medication is available.
- Hospitals will be forced to individually decide on whether to purchase andexanet - large burden of time on hard pressed resources to decide on this for each Trust.
- Criteria will differ locally and some Trusts may not stock the drug creating inequality of services. In addition, would create ethical dilemmas of which patients to treat
- Some patients for whom blood products are not acceptable would be unable to accept PCC and would not have the option of andexanet – creates a degree of inequality

Web comments – NHS professional 2 (also included in company's response to ACD)

- Believe 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
- Off-label use PCC should not be considered standard of care - reflected across many international guidelines, use of specific reversal agents where available
- At the time of ANNEXA-4, there was no comparable or licensed agent and a RCT against usual care was considered unethical – RCT currently undertaken with andexanet alfa as a condition of EU and FDA licence
- Understand limitations of the single arm trial. However, it would be clinically implausible to hypothesis 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 DOACs bleeds in ORANGE provides a reasonable basis for evaluating the most severe bleeds
- We urge NICE to work with Portola to ensure that patients with the highest risk of deaths or severe life-long disability have access to this medicine (patients with intracranial bleeds, particularly haemorrhagic stroke, patients with GI bleedings who are haemodynamically unstable and patients with bleeds in other sites that threaten life, limb, vision or paralysis)

Web comments – Patient

- I have taken apixaban since 2013 - positives as well as negatives, it takes a heavy burden on my quality of life - I am forever cautious of the risks, burden presents itself in a number of decisions of how I live my life.
- I really don't think that the recommendation is suitable or favourable for patients because it doesn't seem that the quality of life, downstream impact of a major bleed has been assessed other than the mortality benefit to satisfy the calculation.
- High anxiety around safety of DOACs from a patient's 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 patient's position, moving from warfarin, for example, to a DOAC is based on a quality of life decision, not a clinical benefit. Therefore quality of life is paramount for patients and therefore, the general availability of a technology like andexanet alfa is important to patients
- Vehemently challenge the committee's decision 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

Web comments – PCC company

- 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.

Corresponding ICERs will be discussed in Part 2

Company Response – summary

To further support the initial submission, additional evidence was submitted:

- Analysis of ANNEXA-4 mortality by haematoma expansion and of GI bleeding population
- Real-world evidence of andexanet alfa from a multi-centre study in the US to compare baseline characteristics and mortality results
- Rosenbaum sensitivity analysis to explore the robustness and potential impact of unobserved confounders such as severity and volume of bleed on the results of the ITC
- Revised base case results including patient access scheme (PAS)
- Scenario analyses on morbidity and mortality benefit

Company comments: ANNEXA-4 trial primary outcomes are appropriate to assess andexanet alfa's benefit (1)

Committee conclusion at CM1: Concerns that the definition of haemostatic efficacy as defined in trial could not be considered predictive of clinical outcomes

- For **ICH**, company believe ANNEXA-4 demonstrates that haemostatic efficacy is a relevant clinical outcome associated with mortality improvement
- Company submitted subgroup analysis of **mortality in relation to baseline intracerebral haemorrhage volumes** - believe it shows that mortality benefit for andexanet alfa can be seen with increasing baseline intracerebral haemorrhage volumes

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]

Source: Company response to ACD (May 2020), Appendix B

ERG response

- Data suggest a trend towards [redacted] mortality rates with [redacted] volume bleeds
- But consider **data not suitable** for drawing **conclusions** about any potential mortality benefit with andexanet alfa
- ERG notes that data are restricted to patients with non-traumatic spontaneous intracerebral haemorrhage – **impact on results unknown**

Company comments: ANNEXA-4 trial primary outcomes are appropriate to assess andexanet alfa's benefit (2)

- For **GI bleeding**, company submitted additional baseline characteristics
- Patients with upper GI bleeding in ANNEXA-4 had a mean Glasgow Blatchford score of [redacted]
- For upper GI bleeding mortality prognostic scores, the clinical pre-endoscopic Rockall score predicted a [redacted] mortality rate
- The 30-day mortality rate observed in ANNEXA-4 for upper GI patients is [redacted] which is lower than the mortality rate predicted by the Rockall score
- Suggests a magnitude of benefit of [redacted] which is consistent (if not slightly higher) than that predicted in the propensity score matching analysis [redacted]

ERG response

- ERG does **not** consider this to be **a reasonable comparison** as the trial population was selected based on expected survival <1 month – mortality maybe skewed in favour of andexanet alfa
- ERG notes that the Rockall score was **not originally developed in an anticoagulated population** – therefore the extent to which anticoagulation affects the mortality estimates generated by the Rockall score is **unknown**
- ERG **does not consider** additional data submitted for ICH and GI subgroups to **provide suitable evidence** to draw conclusions on the relationship between haemostatic efficacy and mortality

Glasgow Blatchford and Rockall scores

- **Scoring systems commonly used to categorise patients into low-risk or high-risk subgroups**

Glasgow Blatchford score

- Stratifies upper GI bleeding patients who are “low-risk” and candidate for outpatient management vs admission– does not rely on endoscopic findings
- Score based on: haemoglobin, sex, heart rate, blood pressure, melena presence, recent syncope, hepatic disease history, cardiac failure presence
- Score **range from 0 to 23 –** score 0 identifies low-risk patients

Rockall score:

- Determines severity of upper GI bleeding and predicts mortality – based on clinical bleeding and endoscopy results
- Score is based on: age, shock (tachycardia, hypotension), comorbidities, diagnosis (presence of malignancy of GI tract or other condition), major stigmata of recent haemorrhage (blood in GI tract, adherent clot, visible or spurting vessel)
- Score **range from 0 to >8**

Company comments: 30-day mortality results generalisable to UK clinical practice

Committee conclusion at CM1: The committee noted that ANNEXA-4 exclusion criteria (survival expected <1 month, GSC score <7 or intracerebral bleed volume>60ml) could affect 30-day mortality results

- US Multi-centre real-world analysis of patients having andexanet alfa within its licensed indication – **Did not exclude patients** as per the eligibility criteria in ANNEXA-4
- Company believe **baseline characteristics** were similar between ANNEXA-4 and real-world analysis
- Supports that population in trial not inherently different to that expected in clinical practice
- **In-hospital mortality outcomes** from real-world analysis consistent with those observed in ANNEXA-4
- **In-hospital mortality is a different outcome than 30-day mortality**

	ANNEXA-4	US RWE
Patients, N	[redacted]	[redacted]
Age (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]

Source: Company response to ACD (May 2020), table 7, Appendix E

ERG response – Real world evidence study

- **Only in hospital mortality presented rather than 30-day mortality**, which is the outcome of relevance for propensity score matching analysis and economic analysis – Limits the suitability of the real world evidence study
- **Differences in baseline characteristics** of patients in ANNEXA-4 compared with the real world evidence study, for example, mean age and proportion of use of apixaban
- Data on bleed severity, volume of bleed and specific site of bleeds not reported - **caution in drawing any conclusions,** there may be **important differences** between studies that could **impact the comparability of mortality** data
- Real world evidence study suggest [redacted] in-hospital mortality rate for the ICH subgroup and [redacted] rate for GI bleed subgroup when patients are given andexanet alfa
- **Other issues** with use of in hospital mortality outcome: may be **differences in outcome** definition, assessment and analysis between studies as **no information provided** (e.g. difference in censoring criteria could considerably impact results)
- To explore uncertainty, **ERG conducted scenario** where 30-day mortality assumed to be the same for andexanet alfa and PCC – increased ICER in each cohort

Company comments: The ITC with ORANGE study is robust

Committee conclusion at CM1: Without prognostic factors such as severity and volume of bleed accounted for, the results of the propensity score matching analysis are very uncertain

- Company conducted **Rosenbaum sensitivity analysis** to evaluate how robust results are to confounding caused by unobserved variables
- Results showed 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.
- If one partner in the matched pair was [redacted] times more likely to receive andexanet alfa, base case results may cease to be statistically significant
- Company states that it shows that even if unobserved variables had a substantial effect on propensity score, the conclusions would not be changed

ERG response

- **Limitation** of the Rosenbaum analysis is that matching is made **without replacement** whereas in the company's propensity score matching (PSM) analysis used in base case, matching with replacement method was used
- However, **company also conducted** a scenario that uses the PSM analysis data from the matching **without replacement** used in the Rosenbaum sensitivity analysis (next slide)

Company comments: The ITC with ORANGE study is robust

Cohort	Relative reduction in mortality rate* (%)				
	Base case (matching with replacement)	**Scenario 1** (matching without replacement)	**Scenario 2** (with replacement, alternative covariates)	**Scenario 3** (without replacement, alternative covariates)	**Scenario 4** (IPTW)
Whole cohort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICH+GI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GI bleed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other bleeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Relative reduction = (ANNEXA-4 mortality rate – ORANGE mortality rate)/(ORANGE mortality rate)
IPTW: inverse probability of treatment weighting.

- Company explored 5 ICT approaches to test the robustness of the base case indirect comparison
- ITC is robust to change according to company

ERG response – Scenarios on ITC

- **ERG only considers base case, scenario 1 and scenario 4** as ERG prefers the more extensive covariates used in analysis informing the base case
- The ITC results are [redacted] across the 3 analyses, for the whole cohort, ICH+GI and ICH subgroups.
- Results using the PSM methodology [redacted] are more favourable for andexanet alfa
- In terms of **other major bleeds**, as discussed in the ERG report, the ERG does not consider the data to be suitable for PSM analysis or any other analysis given the [redacted].
- **ERG recommends caution** when interpreting the results for the other bleeds population in the PSM and IPTW analyses.

Company comments: Morbidity benefit is expected for andexanet alfa based on clinical consensus in the UK

- UK clinical opinion obtained during response to the ACD suggest that **function and quality of life could be preserved in ICH survivors** following andexanet alfa
- Company submitted **scenario analyses** where **morbidity levels are varied**
- Level of benefit is based on the **differences in mRS scores** and varied between 0% (as per ERG alternative base case) and 100% (as per company's revised base case, absolute differences between the scores)
- At 50% the absolute difference represent half the absolute difference observed between ANNEXA-4 and Oie 2018

ERG response

- Clinical expert opinion sought by ERG also considered that andexanet alfa **may have the largest effect on intracerebral bleeds** as it could prevent haematoma expansion
- However, given the **lack of comparative data** to support the assumption that andexanet alfa lead to better mRS and less disability, ERG maintains that **applying the same mRS distribution in both arm is more appropriate**
- ERG considers **the company's scenario approach to be simplistic** – would be more useful that 50% relative morbidity benefit represent half of the andexanet alfa benefit in the PCC arm (i.e remove Oie 2018 from analysis)
- ERG corrected one company's absolute difference calculation for mRS 2

Company's updated base case

- Summary of changes to company's base case:
  - Include rehabilitation costs for ICH survivors applied to 12 months only (ERG recommendation)
  - Include revised PAS

Population	deterministic	probabilistic
Whole cohort	[redacted]	[redacted]
ICH plus GI cohort	[redacted]	[redacted]
ICH cohort	[redacted]	[redacted]
GI cohort	[redacted]	[redacted]
Other major bleeds	[redacted]	[redacted]

Company's scenario analyses

- Scenarios on **morbidity benefit**
  - in ICH, the level of benefit is based on the differences in mRS scores and varied between 0% (as per ERG alternative base case) and 100% (as per company's revised base case, absolute differences between the scores)
  - in intraspinal and intraocular bleeding, the proportion of patients assumed to have morbidity benefit from andexanet alfa is varied between 0% (as per ERG base case) and 25% (as per company's revised base case)
    - At a 50% threshold, the morbidity benefit from andexanet alfa is reduced from 25% to 12.5%
- Scenarios on **mortality**
  - Threshold of effect: estimate the increase in andexanet alfa mortality or reduction in PCC mortality that would need to be observed to achieve an ICER> £30,000
  - Alternative ITC approaches – results consistent

Company's scenario analyses – ICH cohort

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

* Company's revised base case

Threshold analyses on mortality:

- Analysis 1: Under clinical assumption of no morbidity benefit, andexanet alfa 30-day mortality would have to increase by over [redacted]% relative to the base case to achieve an ICER>£30,000
- Analysis 2: Under clinical assumption of no morbidity benefit, PCC 30-day mortality would have to decrease by over [redacted]% to achieve an ICER>£30,000

Company's scenario analyses – GI and other major bleeds cohort

GI cohort - Threshold analyses on mortality:

- Analysis 1: Andexanet alfa 30-day mortality would have to increase by over [redacted]% relative to the base case to achieve an ICER>£30,000
- Analysis 2: PCC 30-day mortality would have to decrease by over [redacted]% to achieve an ICER>£30,000

- **Other major bleeds cohort - Analyses on morbidity**

Andexanet vs. SoC relative morbidity benefit (%)	Revised base case
25%	[redacted]
0%	[redacted]

* Company's revised base case

ERG's updated base case

- Summary of changes to ERG's base case
  - Removed scenario where mRS score from Oie 2018 is applied to people who had an intracerebral haemorrhage in ANNEXA-4 as this led to patients having better morbidity on PCC (clinically implausible)
  - **Same mRS distribution** from ANNEXA-4 in both treatments arms is the **preferred assumption** (ERG's alternative base case at ACM1)
- ERG considers ICH bleeds, GI bleeds and other major bleeds are identifiable as clinically distinct groups and should be considered separately because treatment and outcomes vary
- ERG base case results are in a **ICH cohort, GI cohort and other major bleed cohort**
- ERG also presented preferred assumption for the **whole cohort** as per NICE final scope but consider this to be a **potentially misleading ICER**

Population	deterministic
Whole cohort	[redacted]
ICH cohort	[redacted]
GI cohort	[redacted]
Other major bleeds	[redacted]

ERG's scenarios analyses

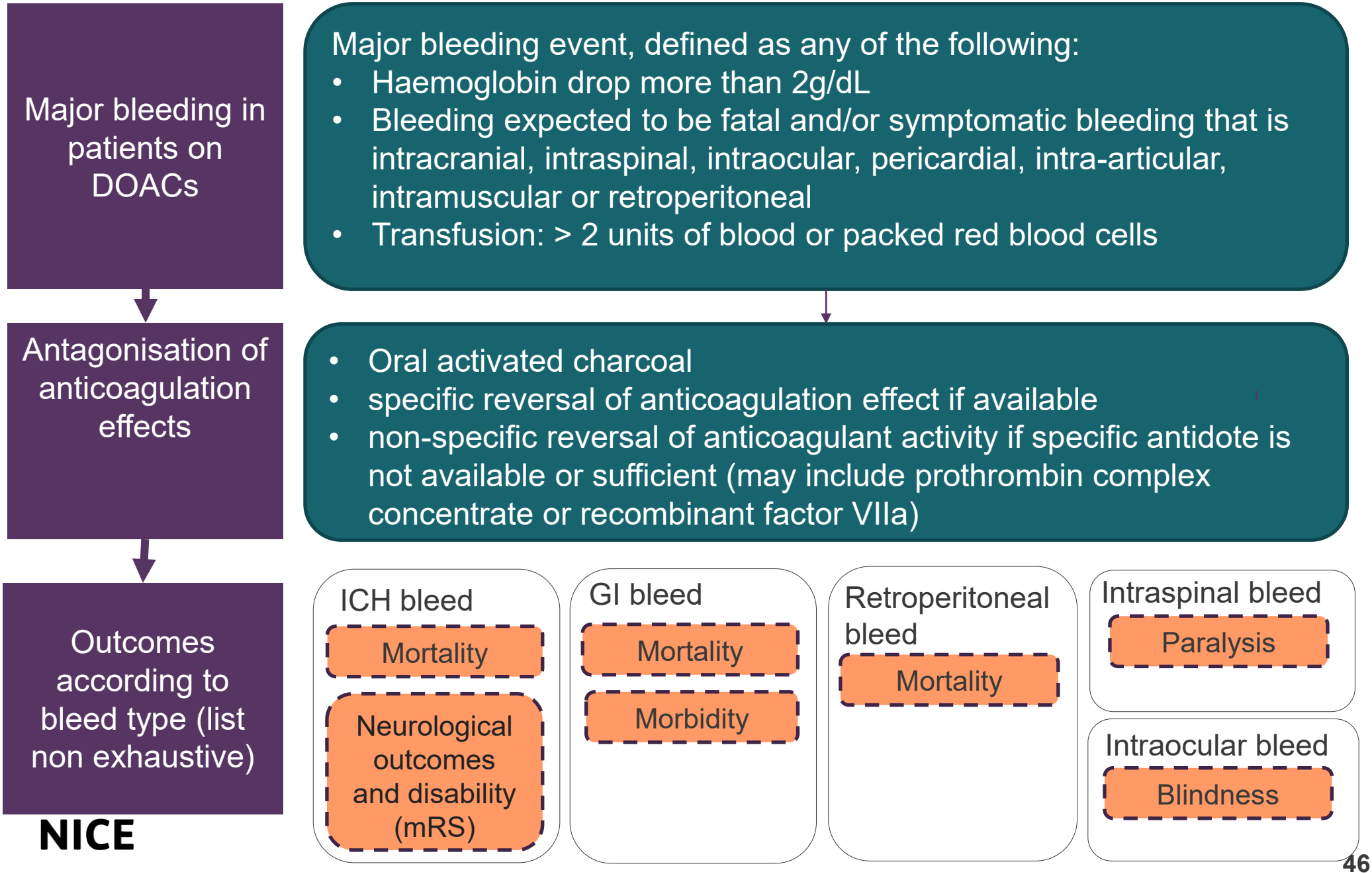
- Scenario analyses on varying levels of morbidity benefit for andexanet alfa for ICH, including the ERG's other preferred assumption of weighted utility values by mRS
  - ICERs range from [redacted] (100% benefit, company's assumption) to [redacted] (no benefit, ERG's assumption)
- Scenario analysis where 30-day mortality for andexanet alfa is assumed to be the same as PCC (on top of ERG's base case assumptions)
  - Andexanet alfa is dominated by standard care in the whole cohort, ICH cohort, GI cohort and other major bleeds cohort

Key issues

- Is the committee still minded to consider ICH, GI bleeds and 'other' bleeds separately?
- Does the committee consider that the 30 day mortality in ANNEXA-4 would translate to the UK general population on the basis of real world evidence in the USA, and is this an improvement on UK outcomes with PCC, as outlined in the ORANGE study?
- ANNEXA-4 used haemostatic efficacy outcomes for ICH and predicted less disability in survivors after andexanet than after PCC. What is the natural history of intracranial bleeds, do the haemostatic outcomes align with clinical expectation?
- The company considers that further analyses (Rosenbaum sensitivity analysis) validates their method of indirect comparison of 30 day mortality with ORANGE, is the committee satisfied with this evidence?
- What is the committee's view on the company's scenario analyses on morbidity and mortality?
- Does the committee consider that it has relevant evidence on 'other bleeds'?
- Equality consideration - Some patients for whom blood products are not acceptable would be unable to accept PCC

Back up slides

Treatment pathway



NICE

Decision problem

	Final scope issued by NICE	Company submission
Population	Adults requiring urgent reversal of anticoagulation in case of uncontrolled or life-threatening bleeding, after treatment with a factor Xa-inhibiting direct oral anticoagulant (DOAC)	As per scope
Intervention	Andexanet alfa	As per scope
Comparators	Established clinical management of uncontrolled or life-threatening bleeding without andexanet alfa (including prothrombin complex concentrate with or without tranexamic acid)	Prothrombin complex concentrate (PCC)
Outcomes	The outcome measures to be considered include: • Requirement for blood products • Control of bleeding • Need for surgical control of bleeding or interventional radiology embolisation of bleeding vessel • Neurological outcomes (in people with ICH) • Hospital stay • Mortality • Adverse effects of treatment (including thrombotic events) • Health-related quality of life	The following outcome for ANNEXA-4 was not pre-specified and analyses are not yet available: • Need for surgical control of bleeding or interventional radiology embolisation of bleeding vessel The following pharmacodynamic outcomes are key in demonstrating the reversal of anticoagulation: • Anti-fXa activity, unbound anticoagulant plasma levels and thrombin generation

Clinical evidence – definition of excellent haemostasis in the trial

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

Clinical evidence – definition of good haemostasis in the trial

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

Clinical evidence – definition of poor haemostasis in the trial

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

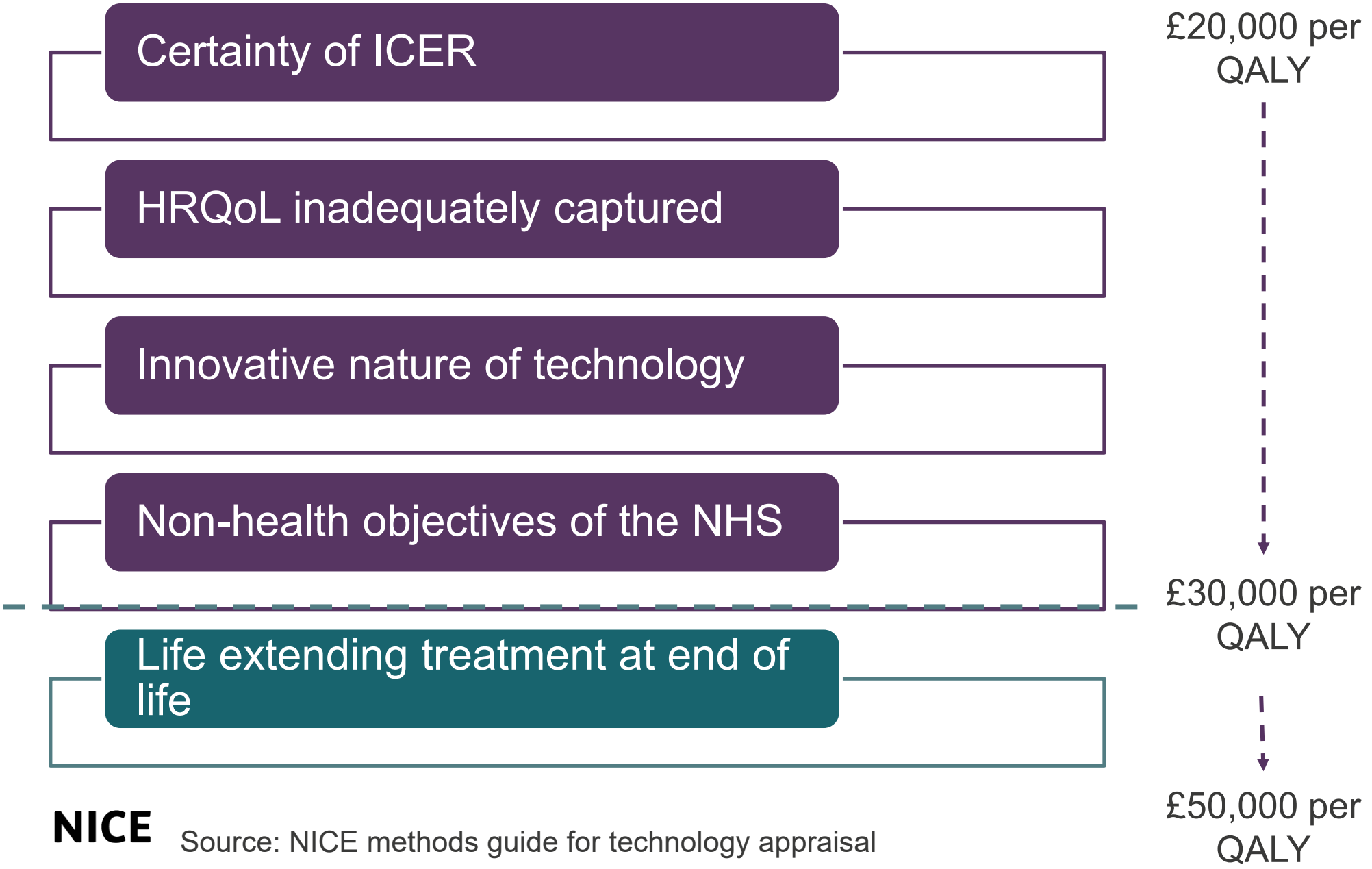
Company comments: The ITC with ORANGE study is robust

- Company explored 5 ICT approaches to test the robustness of the base case indirect comparison
- ITC is robust to change according to company
- For ICH, relative reduction in 30-day mortality ranged between [redacted] and [redacted]
- For GI, relative reduction in 30-day mortality ranged between [redacted] and [redacted]

	ORANGE	ANNEXA-4
	Mortality rate (Number of patients matched) (95%CI)	
Base case (with replacement)		
ICH	[redacted]	[redacted]
GI	[redacted]	[redacted]
Scenario 1 (without replacement)		
ICH	[redacted]	[redacted]
GI	[redacted]	[redacted]
Scenario 2 (with replacement, alternative covariates)		
ICH	[redacted]	[redacted]
GI	[redacted]	[redacted]
Scenario 3 (without replacement, alternative covariates)		
ICH	[redacted]	[redacted]
GI	[redacted]	[redacted]
Scenario 4 (inverse probability weighting)		
ICH	[redacted]	[redacted]
GI	[redacted]	[redacted]

Source: Company response to ACD (May 2020), Appendix H

Decision-making



Source: NICE methods guide for technology appraisal

Key issues

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