PharmacoEconomics (2025) 43:499–508
https://doi.org/10.1007/s40273-025-01472-5

REVIEW ARTICLE

Examining Consistency Across NICE Single Technology Appraisals: A Review of Appraisals for Paroxysmal Nocturnal Haemoglobinuria

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Accepted: 19 January 2025 / Published online: 12 February 2025

Abstract
In 2024, the National Institute for Health and Care Excellence (NICE) recommended two new health technologies for paroxysmal nocturnal haemoglobinuria. This review systematically compares the clinical and cost-effectiveness evidence considered within the NICE single technology appraisals of iptacopan, danicopan and pegcetacoplan, examines the consistency of the clinical evidence and economic modelling, and considers whether single technology appraisals are a suitable apparatus for consistent decision making. The studies used different follow-up lengths and used different definitions for reporting breakthrough haemolysis (BTH), but otherwise reported similar outcomes and found a significant benefit for their interventions. A lack of direct evidence and unreliable indirect comparisons meant that naïve comparisons across trials were carried into the economic modelling despite differences in their control arms. Approaches to modelling BTH and associated dose escalation differed across appraisals, despite information for pegcetacoplan coming from the same source in each appraisal, which had a large impact on the economic results. This review raises the question of whether NICE should implement multiple technology appraisals more frequently to reduce these inconsistences. Additionally, we recommend the development of a framework for revisiting positive recommendations when the implementation of health technologies deviates from assumptions made in the economic modelling to ensure cost-effective healthcare is preserved.

1 Introduction

In 2024, two new treatments were recommended by the National Institute for Health and Care Excellence (NICE) for paroxysmal nocturnal haemoglobinuria (PNH) [1, 2]. PNH is a rare, acquired, chronic blood disorder caused by dysregulation of the complement pathway and characterised by intravascular haemolysis (IVH), thrombosis (blood clot formation) and bone marrow failure (BMF) [3, 4]. The complement pathway is a part of the body's innate immune system responsible for recognition and destruction of red blood cells (RBCs) infected with intracellular pathogens. Activation of this pathway results in the formation of a pore (membrane attack complex [MAC]), which disrupts the cell membrane and causes lysis (breakdown of the cell) [5, 6]. Healthy cells are protected from being destroyed via the same process by the presence of inhibitory proteins on the cell surface. In PNH, due to a mutation of the *PIGA* gene, RBCs become deficient in surface proteins CD55 and CD59, allowing unregulated MAC formation and destruction of healthy RBCs. This process usually takes place inside blood vessels, hence termed 'intravascular' haemolysis. IVH can result in anaemia, and patients often present with symptoms such as fatigue and shortness of breath, resulting in a reduced quality of life. IVH also leads to a change in the patency of blood vessels which increases the risk of thrombosis, which is the leading cause of mortality in this population [7].

PNH currently affects an estimated 2400 people in the UK [8]. Although the severity of symptoms is variable, patients generally report lower quality of life compared with the general population, with fatigue being the most common symptom [9]. The only definitive cure is bone

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Key Points

NICE single technology appraisals have potential for inconsistency, even those occurring in similar timelines for the same disease.

A framework for reviewing the cost effectiveness of positively recommended health technologies is recommended to ensure public healthcare receives value for money.

Inconsistency could be reduced through better consideration of health technology assessment by companies when designing and reporting clinical trials and encouraged by NICE through use of multiple technology appraisals and wider use of managed access recommendations conditional on additional data collection.

marrow transplantation (BMT) [10, 11], but for the majority of patients, the benefits of BMT are not considered to outweigh the risks unless used to treat a more acute disease associated with PNH, such as aplastic anaemia [12]. Over the last two decades, new drug therapies, including the C5 inhibitor (C5i) monoclonal therapies ravulizumab and eculizumab, have revolutionised PNH treatment for many patients; these inhibit a protein in the complement cascade, C5, thereby reducing IVH, and are associated with a reduction in thrombosis. Maintenance dosing of ravulizumab and eculizumab require infusions to be administered in an outpatient or home setting, usually every 8 and 2 weeks, respectively, with ravulizumab used more commonly.

Despite adequate C5i treatment, two thirds of people still experience some degree of anaemia, a proportion of whom require regular RBC transfusions to address symptoms [13]. This is because in addition to IVH, patients can also experience extra-vascular haemolysis (EVH) as a consequence of C5i treatment, which is the destruction of red blood cells outside blood vessels, commonly in the spleen and liver [14]. Although EVH-related anaemia may not be life-threatening, transfusions still carry intrinsic risk (organ toxicity due to transfusion-related iron overload, risk of antibody formation) and are associated with a significant degree of treatment burden for the individual. Effective management of EVH constitutes an unmet need for patients with PNH whose symptoms are not sufficiently controlled with C5is [15, 16].

One of NICE's roles is to evaluate the clinical and cost effectiveness of new health technologies seeking reimbursement on the national healthcare system (NHS) of England and Wales. NICE uses external assessment groups (EAGs, previously known as ERGs) who provide independent critique of company submissions and may generate their own set of preferred assumptions to inform the economic modelling. Reports from the company and EAG are presented to a NICE committee, which decides whether the health technology is likely to be a cost-effective use of NHS resources and should be reimbursed. This decision is usually based on whether the expected incremental cost-effectiveness ratio (ICER) is below the threshold deemed most appropriate by the committee (usually £20,000–30,000/quality-adjusted life-year) [17].

In March 2022, pegcetacoplan received a positive recommendation from NICE for people with PNH who have anaemia after 3 months of c5i treatment [18]. Pegcetacoplan targets protein C3, inhibiting the complement cascade system upstream (proximal) from C5. Inhibition of the complement system at the C3 level reduces the redirection to EVH, thus targeting both intra- and extravascular haemolysis and mitigating anaemia and thrombosis risk [19]. Pegcetacoplan is self-administered twice a week via subcutaneous infusion, meaning its administration is potentially more convenient than intravenously infused C5i, but has an increased risk of infection and injection-site reaction. Furthermore, pegcetacoplan is associated with an increased severity of breakthrough haemolysis, resulting in complications and potential discontinuation of pegcetacoplan [16].

In 2024, iptacopan and danicopan were considered for approval by NICE, with iptacopan positively recommended as an orally administered monotherapy in September 2024 [1, 2]. Iptacopan inhibits factor B to prevent formation of C3 convertase (which is involved in the action of C3), preventing excessive complement activation and addressing both IVH and EVH [20]. Despite being licensed for first- and second-line PNH therapy, we disregarded information specific to first-line PNH treatment in this review as the other therapies were not licensed for this population. Danicopan, an oral treatment used in combination with previous C5is (ravulizumab or eculizumab), was recommended by NICE in October 2024. Danicopan inhibits factor D, an enzyme also required for the formation of C3 convertase, therefore targeting both IVH and EVH. Danicopan is approved for populations who continue to experience clinically significant EVH while on treatment with a C5i [2, 21].

This paper reviews the NICE appraisal documentation and key clinical trial publications for the three treatments (pegcetacoplan, iptacopan and danicopan) to identify the key issues raised and to examine their consistency [1, 2, 18]. The aim of this review is to systematically review three technology appraisals and conduct a narrative synthesis to assess their consistency of the key issues across the clinical effectiveness evidence and economic modelling. We further

consider whether the single technology appraisal (STA) process is a suitable apparatus for consistent decision making.

2 Methods

We extracted information from the key trial publications and NICE appraisal documents for each PNH treatment, which were identified through examination of the information provided on the NICE website for each appraisal [1, 2, 18, 19, 21, 22]. Information on trial design, outcomes and results were recorded, alongside the outcomes from a risk-of-bias assessment.

For each NICE appraisal, the full set of committee papers and final appraisal documents (FAD) were reviewed. First, we extracted the key issues raised by each ERG/EAG. Second, we cross-examined the key issues across the appraisals to verify whether each EAG identified similar key issues. Finally, we extracted information on the modelling assumptions and sources of underlying evidence relating to the key issues, where this information was publicly available, and presented the findings through a narrative synthesis.

Each extraction was performed by a primary reviewer and verified for accuracy by a second reviewer. Data extraction forms were used to ensure consistency of information extracted, and these were expanded once the key issues of each appraisal were identified to ensure the relevant information from each appraisal was captured.

3 Results

Across the three appraisals, there were a total of three pivotal clinical trials and four sets of committee papers, given that the appraisal of danicopan had two committee meetings. The relevant trials for pegcetacoplan, danicopan and iptacopan were PEGASUS [19], ALPHA [21] and APPLY-PNH [22], respectively. An overview of the trials is provided in Table 1. Each trial used different cut-offs for baseline Hb eligibility and had a different length of primary follow-up, but all found a significant difference between their intervention and C5i arms. The PEGASUS trial contained only people with prior eculizumab use, and also had the worst-performing control arm compared with the other trials considered with a much lower proportion of people being transfusion-free (15% vs 38–40%). The age and sex breakdown of each population were broadly similar, accounting for the small sample size of each trial. Similar differences were also seen in the people experiencing breakthrough haemolysis (BTH) events across the studies with the control arms ranging from 0% to 23% and intervention arms from 3% to 10%. However, the definition of BTH events varied, with ALPHA reporting treated BTH events, APPLY-PNH reporting "clinical BTH" events and PEGASUS reporting all BTH events. The EAGs rated APPLY-PNH as having low risk of bias, and ALPHA as "some concerns" of bias due to missing data when the trials were assessed using the Cochrane RoB 2.0. The risk of bias for PEGASUS was not assessed during its NICE appraisal but was an open-label design and so at higher risk of bias.

An overview of the economic modelling assumptions is provided in Table 2. Each model used the same structure consisting of four similar health states: moderate Hb, low Hb, requiring transfusion and death. All appraisals used PEGASUS to inform the efficacy of pegcetacoplan despite considerable concerns around the suitability of a naïve unadjusted comparison across the danicopan and iptacopan appraisals, which both relied on published transition probabilities for pegcetacoplan [23].

Each appraisal's cost-effectiveness analyses are now presented in turn.

3.1 Pegcetacoplan

The pegcetacoplan economic model was largely populated using information from the PEGASUS trial [19]. The key issues raised by the ERG were the lack of direct comparison to ravulizumab, lack of definition for uncontrolled anaemia, small trial size with short follow-up and concerns around the matching adjusted indirect comparison (MAIC).

A comparison was made to ravulizumab based on the assumption of equal efficacy between eculizumab and ravulizumab which was justified by Study 301 and 302, which compared the two C5is [24, 25]. Although the company did perform an anchored MAIC to try and adjust for differences in baseline characteristics of PEGASUS and Study 302, this was not carried forward into the economic modelling given that the analysis could not account for some of the differences. BTH events were not explicitly captured but were considered represented by the underlying health states.

No dose escalation of pegcetacoplan was modelled, nor was the full impact of BTH events. However, this appraisal did cover the widest range of adverse events out of the appraisals reviewed, despite their likely minimal impact on the economic outcomes.

3.2 Danicopan

The danicopan appraisal was informed most heavily by the ALPHA trial [21]. The key issues raised by the EAG were the lack of a clearly defined population, small trial design with limited follow-up and lack of meaningful comparison with pegcetacoplan, subsequent therapies received, discontinuation, BTH rates, dose escalation and treatment-related disutilities.

Although an indirect comparison was reportedly performed by the company comparing the ALPHA population

Table 1 Overview of clinical trials: design and population characteristics

	PEGASUS [19]		ALPHA [21]		APPLY-PNH [22]	
Trial design	Phase III, randomised, open-label, placebo-controlled trial following a 4-week run-in period		Phase III, randomised, double-blind, placebo-controlled trial		Phase III, randomised, open-label controlled trial	
Initial trial length	16 weeks		12 weeks		24 weeks	
Population description	Adults with PNH with Hb < 10.5 g/dL whilst treated with eculizumab		Adults with PNH who have Hb < 9.5 g/dL and ARC ≥120×10^9 cells/μL whilst treated with C5i		Adults with PNH with Hb < 10 g/dL whilst treated with C5i	
Primary outcomes (key secondary outcomes)	Change in Hb (transfusion avoidance, change in FACIT-Fatigue)		Change in Hb (proportion of patients with Hb increases of ≥ 2 g/dL, transfusion avoidance, change in FACIT-Fatigue scores)		Proportion of patients with Hb increases of ≥ 2 g/dL, proportion of patients with Hb ≥12 g/dL (change in Hb, transfusion avoidance, change in FACIT-Fatigue)	
Risk of bias summary	Concerns over open-label nature and effects of run-in period		Some concerns over missing data for 27% of randomised participants		Concerns over open-label nature	
Technology	C5i	Pegcetacoplan	Placebo+C5i	Danicopan+C5i	C5i	Iptacopan
Sample size	39	41	24	49	35	62
% Eculizumab	100%	100%	46%	35%	66%	65%
% Female	56%	56%	38%	43%	69%	69%
Mean age (years)	47.3	50.2	53.1	55.0	49.8	51.7
Mean BMI (kg/m^2)	25.9	26.7	NR	NR	26.9	24.9
Mean change in Hb at primary endpoint (SE or 95% CI) (g/dL)	− 1.5 (0.7)	+2.4 (0.4) $p < 0.001$	+0.50 (− 0.13, 1.12)	+2.94 (2.52, 3.36) $p < 0.0001$	− 0.06 (− 0.5, 0.3)	+3.6 (3.3, 3.9) $p < 0.0001$
Proportion of patients with increase Hb ≥ 2g/dL without transfusion	Not reported	Not reported	0%	60% $p < 0.0001$	0%	85% $p < 0.001$
Proportion of patients avoiding transfusion	15%	85%	38%	83% $p = 0.0004$	40%	95% $p < 0.001$
Change in FACIT-Fatigue score (SE or 95% CI)	− 2.7 (2.8)	9.2 (1.6)	+1.9 (−1.3, 5.0)	+6.1 (2.3, 9.9) $p = 0.0021$	+0.3 (− 2.2, 2.8)	+8.6 (6.7, 10.5)
People with BTH events	9/39 (23%)	4/41 (10%)	0/24 (0%)	2/49 (4%)	6/35 (17%)	2/62 (3%)
Reported BTH description	Any BTH event: at least one new or worsening symptom or sign of intravascular haemolysis (fatigue; haemoglobinuria; abdominal pain; shortness of breath [dyspnea]; anaemia [Hb < 10 g/dL]; major adverse vascular events, including thrombosis; dysphagia; or erectile dysfunction) in the presence of elevated LDH [≥2 times the upper limit of the normal range after prior LDH reduction to < 1.5 times the upper limit of the normal range on therapy]		Treated BTH events: Elevated LDH level [> 1.2 times the upper limit of the normal range]		Clinical BTH events: a decrease in haemoglobin level ≥2 g/dL or PNH symptoms of gross haemoglobinuria, haemolytic crisis, dysphagia, or any other clinically significant sign or symptom associated with PNH in addition to elevated LDH level (>1.5 times the upper limit of the normal range)	

ARC absolute reticulocyte count, *BMI* body mass index, *BTH* breakthrough haemolysis, *C5i* C5 inhibitor, *CI* confidence interval, *FACIT* Functional Assessment of Chronic Illness Therapy, *Hb* haemoglobin, *LDH* lactate dehydrogenase, *PNH* paroxysmal nocturnal haemoglobinuria, *SE* standard error

Where reported, *p*-values are for the difference between trial arms within the relevant trial

Table 2 Overview of cost-effectiveness modelling and influential factors

	Pegcetacoplan TA778 [18]	Danicopan TA1010 [2]	Iptacopan TA1000 [1]
Model structure	Four health states	Four health states	Four health states
	Hb ≥ 10.5 g/dL	Hb ≥ 9.5 g/dL	Hb ≥ 10.5 g/dL
	Hb < 10.5 g/dL	Hb < 9.5 g/dL	Hb < 10.5 g/dL
	Transfusion	Transfusion	Transfusion
	Death	Death	Death
		For some parameters, the model was divided into short- and long-term periods for danicopan (24 weeks) and pegcetacoplan (16 weeks), based on reported follow-up	
Cycle length	4 weeks	4 weeks	4 weeks
Comparators	Eculizumab	Pegcetacoplan	Eculizumab
	Ravulizumab	C5i was also modelled but as subsequent therapy. The EAG argued it should be a comparator for the small number of people who do not get along with pegcetacoplan, but this was not accepted by the committee	Ravulizumab
	The same efficacy data were used for both C5i but they were modelled as separate comparators		Pegcetacoplan
			Efficacy of C5i was pooled but modelled as separate comparators
Population characteristics			
Age	Age: 48.8 years	Age: 54.30 years	Age: 51.0 years
Sex	Sex: 38.7% male	Sex: 41.27% male	Sex: 30.9% male
	Age and sex data were taken from PEGASUS [19]	Age and sex data were taken from ALPHA	Age and sex data were taken from APPLY-PNH
Source of transition probabilities	Pegcetacoplan—PEGASUS [19]	Danicopan—ALPHA [21]	Iptacopan—APPLY-PNH [22]
	Eculizumab—PEGASUS	Pegcetacoplan—PEGASUS [19]	Pegcetacoplan—PEGASUS [19]
	Ravulizumab—PEGASUS	C5i—ALPHA	C5i—APPLY-PNH
Health state utility values	Redacted values were estimated from PEGASUS trial [19]	Moderate Hb: 0.8644	Moderate Hb: 0.879
		Low Hb: 0.8181	Low Hb: 0.819
		Transfusion: 0.7018	Transfusion: 0.800
		Estimated from ALPHA trial [21]	Moderate Hb C5i: 0.775
			Low Hb C5i: 0.743
			Transfusion C5i: 0.695
			Estimated from APPLY PNH and APPOINT PNH trials [22] Committee and EAG preferred treatment-independent utility values

Table 2 (continued)

	Pegcetacoplan TA778 [18]	Danicopan TA1010 [2]	Iptacopan TA1000 [1]
Treatment disutility	A disutility of 0.025 per administration was applied for eculizumab	A disutility of 0.025 per administration was applied for eculizumab and pegcetacoplan The EAG and committee preferred to remove the disutility for pegcetacoplan	No disutilities were used since the C5i used independent utility values. Pegcetacoplan utility values were assumed equal to iptacopan
Discontinuation	A small proportion of people discontinued pegcetacoplan at week 16. No further discontinuation was modelled	Company modelled short-term discontinuation from danicopan and pegcetacoplan to C5i, matching ALPHA and PEGASUS data [19, 21] No discontinuation occurred beyond year 1	Company modelled continuous discontinuation for pegcetacoplan and iptacopan from PEGASUS [19] and APPLY [22], giving annual discontinuation rates of 3.43% and 16.13%, respectively No discontinuation of C5i was modelled
		Committee and EAG preferred to model that most people discontinuing danicopan would receive pegcetacoplan, and that some discontinuation would occur beyond 1 year for both arms	EAG and committee preferred a 10% discontinuation for pegcetacoplan
C5i assumptions	Equivalence of ravulizumab and eculizumab was assumed based on results from Study 301 and 302 [24, 25]	Ravulizumab and eculizumab were pooled on 85%/15% ratio based on the ALPHA trial, which was also the source for the dosing distributions [21]	Ravulizumab and eculizumab were pooled in 65%–35% based on using APPLY-PNH, which was also the source the dosing distributions [22]
Dose escalation	Dose escalation of pegcetacoplan was not modelled due to expectation of BTH events resulting in management with eculizumab or discontinuation instead of dose escalation	The company modelled some short-term dose escalation of danicopan based on ALPHA trial For pegcetacoplan, dose escalation was directly linked to BTH, with every BTH event resulting in dose escalation from twice weekly, to every 3 days and onto thrice weekly The committee and EAG preference was to reduce the rate of permanent dose escalation of pegcetacoplan	No dose escalation was captured within the economic model
Adverse events	Transfusion-related iron overload: costs and disutility were applied for C5i The following AEs were also modelled based on PEGASUS [19] with minor costs and disutilities: Bacterial infection Gastroenteritis Atrial fibrillation Hyperthermia Facial paralysis Dyspnoea Abdominal pain Biliary colic Hepatocellular injury HyperbilirubinemiaJaundice	Information on the below events was sourced from the ALPHA [21] and PEGASUS studies: Alanine aminotransferase increased: costs and a disutility of − 0.05 were applied for short term events on danicopan Breakthrough haemolysis: costs and a disutility of − 0.4 were applied across full model time horizon—see below for more detail Transfusion-related iron overload: costs and a disutility of −0.03 were applied for chelation therapy of all cases that were applied once within the model	Breakthrough haemolysis: Costs and a disutility of − 0.11 were applied

Table 2 (continued)

	Pegcetacoplan TA778 [18]	Danicopan TA1010 [2]	Iptacopan TA1000 [1]
Breakthrough haemolysis	Not modelled explicitly as the company considers it captured within the health states	For pegcetacoplan, the company used the short-term and long-term BTH rates from PEGASUS [19] and applied the latter for the full duration of the model (2.67%). They initially assumed all BTH events resulted in dose escalation of pegcetacoplan	Annualised BTH rates were obtained from PEGASUS [19] and APPLY [22] studies: C5i – 0.67 Pegcetacoplan – 0.13 Iptacopan – 0.07
	BTH events were partially modelled for pegcetacoplan in that the costs of accelerated dosing of eculizumab were applied	Committee and EAG preference was to model a lower long-term rate of BTH for pegcetacoplan that was consistent with some dose escalation For danicopan and C5i, ALPHA [21] data were used which had no short term BTH events and applied the long-term BTH rate for the full model duration (0.24%). One-off accelerated doses of C5i were applied for all events	A one-off dose of eculizumab was applied for 10% of all BTH events, representing severe events

AE adverse event, *BTH* breakthrough haemolysis, *C5i* C5 inhibitor, *CI* confidence interval, *Hb* haemoglobin, *LDH* lactate dehydrogenase, *PNH* paroxysmal nocturnal haemoglobinuria, *SE* standard error

to PEGASUS, the company did not provide any output due to issues of small effective sample size after weighting adjustments were applied and heterogeneity that could not be adjusted for. The EAG considered only comparisons with C5is were appropriate for decision making due to the evidence available, with the committee and company preferring to focus on the naïve comparison to pegcetacoplan despite the uncertainty. In the economic model, the company assumed that all patients discontinuing danicopan would switch to C5i. However, the committee and EAG assumed that most patients would receive pegcetacoplan. For pegcetacoplan, the company modelled that 2.67% per cycle would experience a BTH event, incurring management and dose-escalation costs, which had a large impact on economic results. The committee and EAG preferred lower estimates for these parameters, but this parameter remained an important source of uncertainty. While the company applied the same treatment-related disutility for eculizumab and pegcetacoplan (0.025 annually), the EAG and committee chose not to apply it for pegcetacoplan, making the modelling more consistent with the other appraisals.

3.3 Iptacopan

The appraisal of iptacopan relating to the people who had previously received C5i was informed by the APPLY-PNH trial [22]. The key issues raised by the EAG were the uncertainty in relative efficacy with pegcetacoplan, concerns around capture of rare events and long-term effects of iptacopan, reliance on a naïve comparison, treatment discontinuation rates and utility values.

The company performed anchored and unanchored MAIC analyses, weighting data from APPLY-PNH to match the PEGASUS study. However, results from these analyses were not used in the economic model. The company modelled substantially different discontinuation rates for pegcetacoplan compared with iptacopan, which the EAG and committee considered implausible, and preferred a lower magnitude of difference. The company also modelled treatment-specific utility values, suggesting a large benefit of quality of life for pegcetacoplan and iptacopan over C5i, which was not accepted by the committee or EAG. Dose escalation of pegcetacoplan was estimated to affect 10–30% of patients based on the opinion of the clinical experts consulted by the company; however, this was not implemented in the economic modelling.

4 Discussion

The three trials featured in the appraisals contain important differences in design and definitions used [19, 21, 22]. Despite clear differences in the standard-of-care arms of

each trial, naïve comparisons were carried forward into the economic modelling performed as part of NICE technology appraisals for iptacopan and danicopan. Although all three appraisals used the same source of data for pegcetacoplan, the evidence was implemented using a different approach in each appraisal, which had a potentially major impact on the cost-effectiveness conclusions. For example, dose escalation and BTH for people treated with pegcetacoplan were classed as having a large influence in the appraisal of danicopan, whilst these were modelled in a different way in the pegcetacoplan and iptacopan appraisals. Each appraisal used the starting age from its pivotal trial, which ranged from 49 to 54 years, alongside varying trial- and treatment-specific utility values. Such differences are expected when trials of such small sizes are used to provide model parameters, but this difference could be non-trivial when modelling across a lifetime horizon, affecting the duration for which benefits and costs are accrued. The evidence used to inform some of the health states was generated by much smaller subsets of patients. For example, in the appraisal of iptacopan, only three people experienced transfusions, leading to very scarce evidence available to provide reliable estimates of transition probabilities or patients' quality of life.

Based on our findings, we encourage companies submitting evidence for new health technologies to improve their consideration of economic modelling through longer study follow-up, better reporting and sharing of data and standardisation of definitions. When indirect treatment comparisons are unlikely to be well suited because of small sample sizes, naïve comparisons may represent a more robust approach if differences in trial designs and reporting are minimised.

We further emphasise the need for greater transparency in company submissions by redacting less information and permitting redacted information to be used in other appraisals. A limitation of this kind of review is the inability to compare information that is redacted from publicly available documents. Companies can redact information deemed commercially sensitive meaning it cannot be used in future appraisals. This prevents cross-checking of key model parameters such as long-term survival and health-state utility values. A related problem occurs when appraisals are running in parallel, where there is no mechanism for sharing information across EAGs or committees as each appraisal is considered independently. For these reasons, it is perhaps unreasonable to expect too much consistency across different STAs.

One potential cause of the observed inconsistency is the fact that each STA submission to NICE is led by the respective company. This gives companies the freedom to tailor analyses and economic models to suit their technology, capturing favourable characteristics whilst omitting others. Although each submission is then critiqued by an EAG, they may not be able to identify and explore all areas of uncertainty given the short turnaround time for these projects, particularly if the required functionality has not already been implemented within the economic model. Whilst health technology assessment (HTA) processes in other countries may differ, it is likely that these problems of inconsistency apply whenever the onus is on the pharmaceutical companies to design and build an economic model.

Within the NICE framework, there exists another pathway that could help reduce the inconsistencies within the economic modelling when considering comparable treatments for the same disease. In this approach, which is called a multiple technology appraisal, one EAG performs an evaluation of all relevant health technologies simultaneously and they are thereafter considered by one committee. It is not clear why this approach was not used for the appraisals of iptacopan and danicopan given their overlapping timelines. In this case, fully incremental analyses could have been performed, making the consideration of cost effectiveness of C5is more relevant. Where uncertainty is unavoidable and reliance on naïve or indirect comparisons is necessary, the bar for positive recommendation could be moved higher with managed access used more widely in the interim, with additional data collection mandated for a full recommendation.

Given the lifetime nature of treatments for PNH, the cost per patient is not insignificant. PNH is not unique in that an important reference treatment, eculizumab, has not been shown to be cost effective against earlier treatments for the condition. Such expenditure fails to consider opportunity costs for the NHS. We acknowledge that the impact on the NHS of any inconsistencies is ultimately likely to be small due to the low prevalence of PNH, however, issues such as these could well extend to diseases with much higher prevalence and should not be ignored. Inconsistencies add complexity to present and future decision making, which can result in contradictory decisions across appraisals around severity modifiers and final outcomes.

A review published by Canada's Drug Agency (CDA-AMC, formerly Canadian Agency for Drugs and Technologies in Health [CADTH]) reports that from nine countries with leading HTA agencies, only one (HAS, France) regularly reassesses the implementation of publicly funded health technologies [26]. A process exists for NICE to reassess heath technologies but in practice it seems to focus on outdated and ineffective technologies rather than on the cost effectiveness of recently recommend technologies. We recommend the establishment of criteria for reassessment to ensure that the NHS obtains value for money for the taxpayer. For example, in the appraisal of pegcetacoplan, the dosing of pegcetacoplan was fixed at twice per week. However, the appraisal of danicopan accepted some increase in pegcetacoplan dosing, with company-preferred modelling suggesting almost all patients would end up on three doses per week. If this was true, it would reflect a considerable increase in the costs of pegcetacoplan, which would likely

affect the cost-effectiveness conclusions. Changes to treatment dosing, administration, adverse event management and even pricing of comparator treatments are just some potential criteria that could trigger a reassessment.

Where the implementation or costs of a health technology are known to be inconsistent with assumptions made in the NICE appraisal, it seems reasonable for resources to be invested to review these decisions to ensure cost effectiveness is maintained, particularly if the possibility of such use was not at all considered by the NICE committee. This is important because these therapies go on to be the reference therapies for future appraisals, but also for balance. Technologies without positive recommendations are regularly reviewed in the short term through companies submitting additional evidence either for subsequent NICE committee meetings or following emergence from a period of managed access. Companies are also able to appeal decisions made that they consider unfair. But there are no equivalent mechanisms on the side of the tax payer for situations where new evidence may have a negative impact on the cost effectiveness of health technologies. This asymmetry has been noted by Buxton [27], whilst Lee et al. express concerns with NICE's "once cost effective, always cost effective" approach written in the context of trialling a NICE Pathways appraisal which sought to reduce heterogeneity across appraisals but has since been paused [28].

More generally, the removal of health technologies that have been previously available on the NHS is already met with strong challenge from companies and patient groups, as demonstrated through reviews of technologies emerging from periods of managed access [29, 30]. It is likely that withdrawing fully recommended technologies would generate equal or stronger backlash, however it is important to remember the other aspects of our healthcare system that would otherwise be negatively affected by sustained access to non-cost-effective treatments. We consider it vital that a mechanism exists for re-evaluating the cost effectiveness of health technologies, with outcomes including a new patient access scheme discount being applied, or withdrawal from our NHS. It's important to note that such reassessment could result in prices increasing when evidence shows a greater benefit than originally estimated.

5 Conclusion

This review has compared the appraisals of pegcetacoplan, iptacopan and danicopan and found important areas of inconsistency. Improved consideration of HTA in trial design and transparency in reporting would improve consistency. Decision risk could be reduced through greater implementation of simultaneous appraisal of similar health technologies and review of previously approved health technologies when new evidence becomes available.

Declarations

Funding MY and AR were supported by INSPIRE funding provided by the Academy of Medical Sciences. No other funding was received for this work.

Conflicts of Interest DG was a member of the EAG for the appraisal of danicopan, and NK was a member of the EAG for the appraisal of iptacopan. RT has received honoraria from Alexion, Swedish Orphan Biovitrum, and Novartis.

Authors' Contributions DG generated the research idea and led the production of the manuscript. MY, AR and JD systematically reviewed and extracted the relevant trial and appraisal documents. SV, RT and NK contributed to the development of the final manuscript.

Availability of data and materials and Code availability Not applicable.

Ethical Approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

References

1. NICE. Iptacopan for treating paroxysmal nocturnal haemoglobinuria: a single technology appraisal (TA1000); https://www.nice.org.uk/guidance/ta1000/history. Accessed 15 Oct 2024.
2. NICE. Danicopan as an add-on treatment to a C5 inhibitor for treating extravascular haemolysis in adults with paroxysmal nocturnal haemoglobinuria: a single technology appraisal (TA1010); https://www.nice.org.uk/guidance/ta1010/history. Accessed 15 Oct 2024.
3. Risitano AM, PeffaultLatour R. How we('ll) treat paroxysmal nocturnal haemoglobinuria: diving into the future. Br J Haematol. 2022;196(2):288–303.
4. Hill A, DeZern AE, Kinoshita T, et al. Paroxysmal nocturnal haemoglobinuria. Nat Rev Dis Primers. 2017;3:17028.
5. Shah, N, Bhatt, H. Paroxysmal nocturnal hemoglobinuria. In: StatPearls [Internet]. StatPearls Publishing, 2023.
6. Janeway C, Travers P, Walport M, et al. Immunobiology: the immune system in health and disease. New York: Garland Pub; 2001.

7. Hill A, Kelly RJ, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood. 2013;121(25):4985–96.
8. Richards SJ, Painter D, Dickinson AJ, et al. The incidence and prevalence of patients with paroxysmal nocturnal haemoglobinuria and aplastic anaemia PNH syndrome: A retrospective analysis of the UK's population-based haematological malignancy research network 2004–2018. Eur J Haematol. 2021;107(2):211–8.
9. Panse J, Sicre de Fontbrune F, Burmester P, et al. The burden of illness of patients with paroxysmal nocturnal haemoglobinuria receiving C5 inhibitors in France, Germany and the United Kingdom: Patient-reported insights on symptoms and quality of life. Eur J Haematol. 2022;109(4):351–63.
10. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014;124(18):2804–11.
11. Brodsky RA. Stem cell transplantation for paroxysmal nocturnal hemoglobinuria. Haematologica. 2010;95(6):855–6.
12. Brodsky RA. How I treat paroxysmal nocturnal hemoglobinuria. Blood. 2021;137(10):1304–9.
13. Risitano AM, Marotta S, Ricci P, et al. Anti-complement treatment for paroxysmal nocturnal hemoglobinuria: time for proximal complement inhibition? A position paper from the SAAWP of the EBMT. Front Immunol. 2019;10:1157.
14. Kulasekararaj AG, Lazana I. Paroxysmal nocturnal hemoglobinuria: where are we going. Am J Hematol. 2023;98(S4):S33–43.
15 Bektas M, Copley-Merriman C, Khan S, et al. Paroxysmal nocturnal hemoglobinuria: patient journey and burden of disease. J Manag Care Spec Pharm. 2020;26(12-b Suppl):S8-s14.
16. Gerber GF, Brodsky RA. Pegcetacoplan for paroxysmal nocturnal hemoglobinuria. Blood. 2022;139(23):3361–5.
17. NICE. NICE health technology evaluations: the manual. 2022.
18. NICE. Pegcetacoplan for treating paroxysmal nocturnal haemoglobinuria: a single technology appraisal (TA778); https://www.nice.org.uk/guidance/ta778/history. Accessed 15 Oct 2024.
19. Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2021;384(11):1028–37.
20. Jang JH, Wong L, Ko BS, et al. Iptacopan monotherapy in patients with paroxysmal nocturnal hemoglobinuria: a 2-cohort open-label proof-of-concept study. Blood Adv. 2022;6(15):4450–60.
21. Lee JW, Griffin M, Kim JS, et al. Addition of danicopan to ravulizumab or eculizumab in patients with paroxysmal nocturnal haemoglobinuria and clinically significant extravascular haemolysis (ALPHA): a double-blind, randomised, phase 3 trial. The Lancet Haematology. 2023;10(12):e955–65.
22 Latour R, Röth A, Kulasekararaj AG, et al. Oral iptacopan monotherapy in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2024;390(11):994–1008.
23. Hakimi Z, Wilson K, McAughey E, et al. The cost-effectiveness, of pegcetacoplan compared with ravulizumab for the treatment of paroxysmal nocturnal hemoglobinuria, in a UK setting. J Comp Eff Res. 2022;11(13):969–85.
24. Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, et al. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood. 2019;133(6):530–9.
25. Kulasekararaj AG, Hill A, Rottinghaus ST, et al. Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study. Blood. 2019;133(6):540–9.
26. SCAN, E. Health technology reassessment: An overview of Canadian and international processes. 2019.
27. Buxton M. Implications of the appraisal function of the National Institute for Clinical Excellence (NICE). Value Health. 2001;4(3):212–6.
28. Lee D, Burns D, Wilson E. NICE's pathways pilot: pursuing good decision making in difficult circumstances. PharmacoEconomics - Open. 2024;8(5):645–9.
29. Taylor, P. Sanofi wins appeal in spat with NICE over Sarclisa. *Pharmaphorum*; 2024. https://pharmaphorum.com/news/sanofi-wins-appeal-spat-nice-over-sarclisa. Accessed 4 Feb 2025.
30. NICE. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy: Appeal Documents; 2020. https://www.nice.org.uk/guidance/ta692/history. Accessed 2 Feb 2025.