Modelling What Matters: The Real-World Burden of Pregnancy-Related Complications in cTTP

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Objectives

1. **Review how PRCs are incorporated in the National Institute of Health and Care Excellence (NICE) HTAs/guidelines (NGs).**
2. **Quantify the potential QALY impact of PRCs in cTTP using precedent methodologies and published chart review data.**

Introduction

- Congenital thrombotic thrombocytopenic purpura (cTTP) is an ultra-rare disease caused by homozygous or compound heterozygous mutations in ADAMTS13 gene.[1] Pregnant women with cTTP have a high risk of serious maternal and perinatal complications despite plasma-based therapy.[2.] In an international chart review, 57.8% of women experienced ≥1 pregnancy-related complication (PRC) and 35.6% had foetal death or pregnancy loss.[3]
- Conventional cost-effectiveness models often overlook PRC-related quality-adjusted life years (QALY) losses and maternal outcomes.
- Understanding the real-world burden of PRCs in cTTP is vital to inform health technology assessments (HTAs) and value-based decision-making.

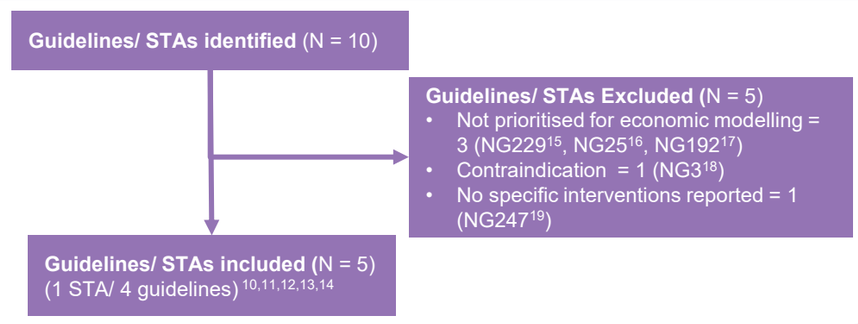
Objective 1

Understanding NICE methodologies for incorporating PRCs in economic models

Methods

- To identify methodologies previously used to incorporate PRCs in economic models, a targeted literature review (TLR) of NGs and technology appraisals (TAs) published between 2005 and 2025 related to pregnancy was conducted.
- The review included guidelines directly addressing pregnancy, as well as conditions potentially associated with an increased risk of PRCs, such as spinal muscular atrophy[4], cardiovascular disease[5], chronic kidney disease[6], diabetes[7], sickle cell[8], and rheumatoid arthritis[9].
- One reviewer screened the publications and extracted the data on 16 July 2025.

Figure 1: PRIMSA diagram for review of NICE guidelines and STAs



ABBREVIATIONS: PRIMSA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; STAs: Single technology assessments; NG: NICE guidelines; N; number

Results

Pregnancy-focused NICE guidelines and appraisals

- Among 10 pregnancy-focused NICE publications, four guidelines and one single technology appraisal (STA) incorporated PRCs in economic models (Figure 1 and Table 1).
- The NICE guidelines and STA that modelled PRCs were NG137[10], NG126[11], NG133[12], NG121[15], and TA156[14] (Table 1).
- Of these, three included a QALY loss for child loss, based on discounted lifetime QALYs had the child survived. [10,12,13]
- One applied a 10-QALY decrement for foetal death, based on previous assumptions, while another applied a QALY decrement only to the mother following neonatal death, as part of a scenario analysis.[14]
- All included publications accounted for the costs associated with PRCs.[10,11,12,13,14]

Table 1: Targeted literature review results

NICE TA/ Guideline	Title	Outcomes included	Methodology used
NG137[10]	Twin and triplet pregnancy	Costs and QALYs associated with PRCs, including neonatal death	Disutility and cost for PRCs, discounted lifetime QALYs of the child
NG126[11]	Ectopic pregnancy and miscarriage: diagnosis and initial management	Costs and QALYs associated with miscarriage	A disutility of 0.1 was applied to the mother as part of sensitivity analysis.
NG133[12]	Hypertension in pregnancy: diagnosis and management	Costs and QALYs associated with PRCs, including neonatal death/pregnancy loss	Disutility and cost for PRCs, discounted lifetime QALYs of the child
NG121[13]	Intrapartum care for women with existing medical conditions or obstetric complications and their babies		
TA156[14]	Routine antenatal anti-D prophylaxis for women who are rhesus D negative		Disutility and cost for PRCs, loss of 10 QALYs associated with foetal death

ABBREVIATIONS: TA: Technology assessment; PRCs: pregnancy-related complications; QALY: quality-adjusted life-year

Other conditions potentially linked to PRCs

- In contrast to economic models used by NICE for pregnancy-focused guidelines and appraisals, PRCs were not captured in economic models of non-pregnancy conditions.
- Of 50 NICE submissions/appraisals reviewed in these areas; 2% could not be accessed, 50% did not consider PRCs at all, 20% excluded pregnant women from the clinical trials, and 22% assessed treatments where pregnancy was contraindicated.
- Only 6% of these appraisals mentioned PRCs, and this was solely in a narrative form (e.g., concerns about reduced fertility or potential effects of the disease/medication on pregnancy), without quantitative modelling.

Objective 2

Quantifying the burden of PRCs in cTTP versus the general population

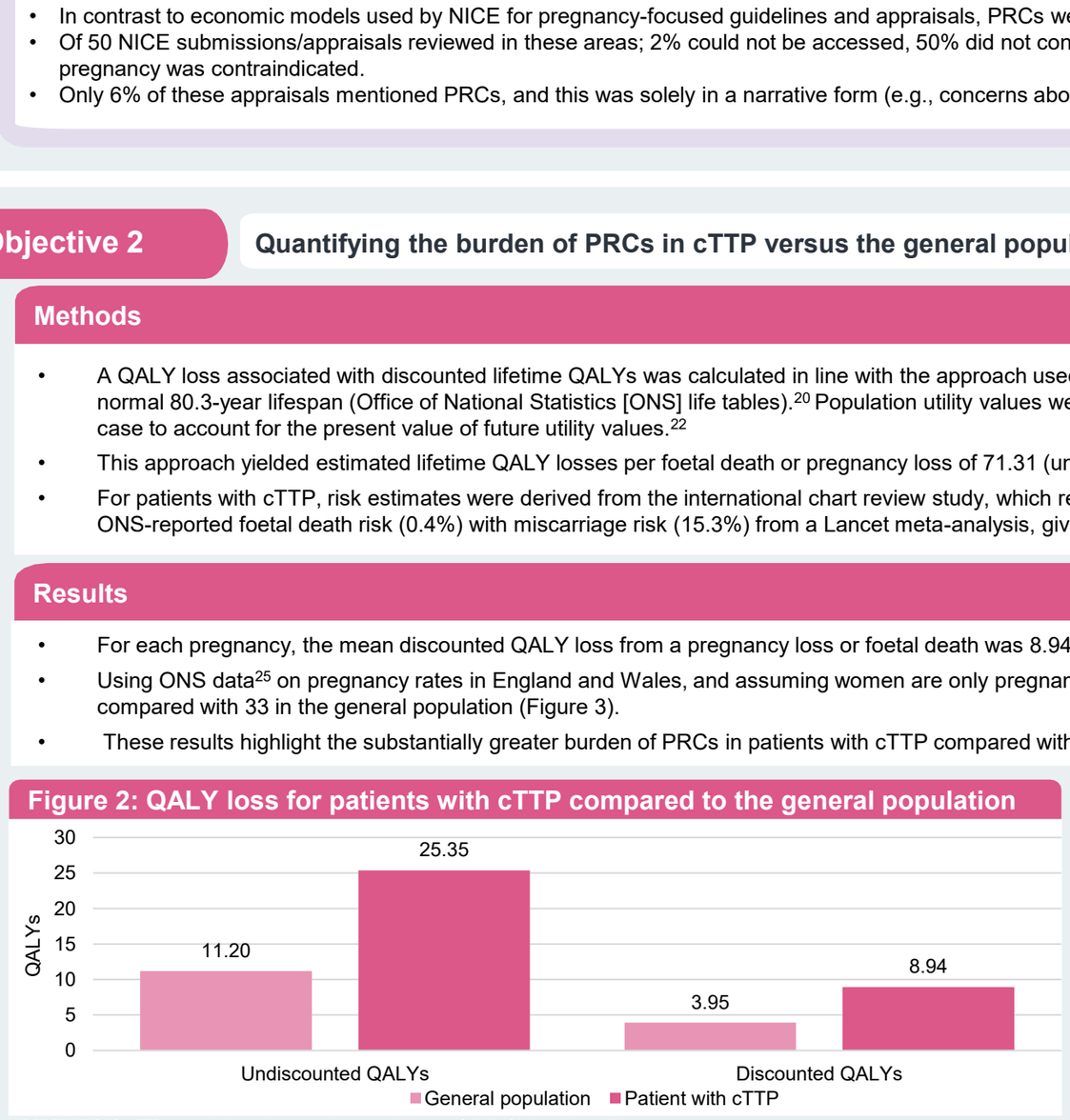
Methods

- A QALY loss associated with discounted lifetime QALYs was calculated in line with the approach used in NICE guidelines. Each averted pregnancy loss or foetal death was assumed to correspond to the loss of a normal 80.3-year lifespan (Office of National Statistics [ONS] life tables).[20] Population utility values were sourced from Hernández Alava et al (2022)[21], with a 3.5% annual discount rate applied per the NICE reference case to account for the present value of future utility values.[22]
- This approach yielded estimated lifetime QALY losses per foetal death or pregnancy loss of 71.31 (undiscounted) and 25.15 (discounted).
- For patients with cTTP, risk estimates were derived from the international chart review study, which reported a 35.6%[3] risk of foetal death or pregnancy loss. The general population risk was estimated by combining ONS-reported foetal death risk (0.4%) with miscarriage risk (15.3%) from a Lancet meta-analysis, giving a total risk of 15.7%.[23,24]

Results

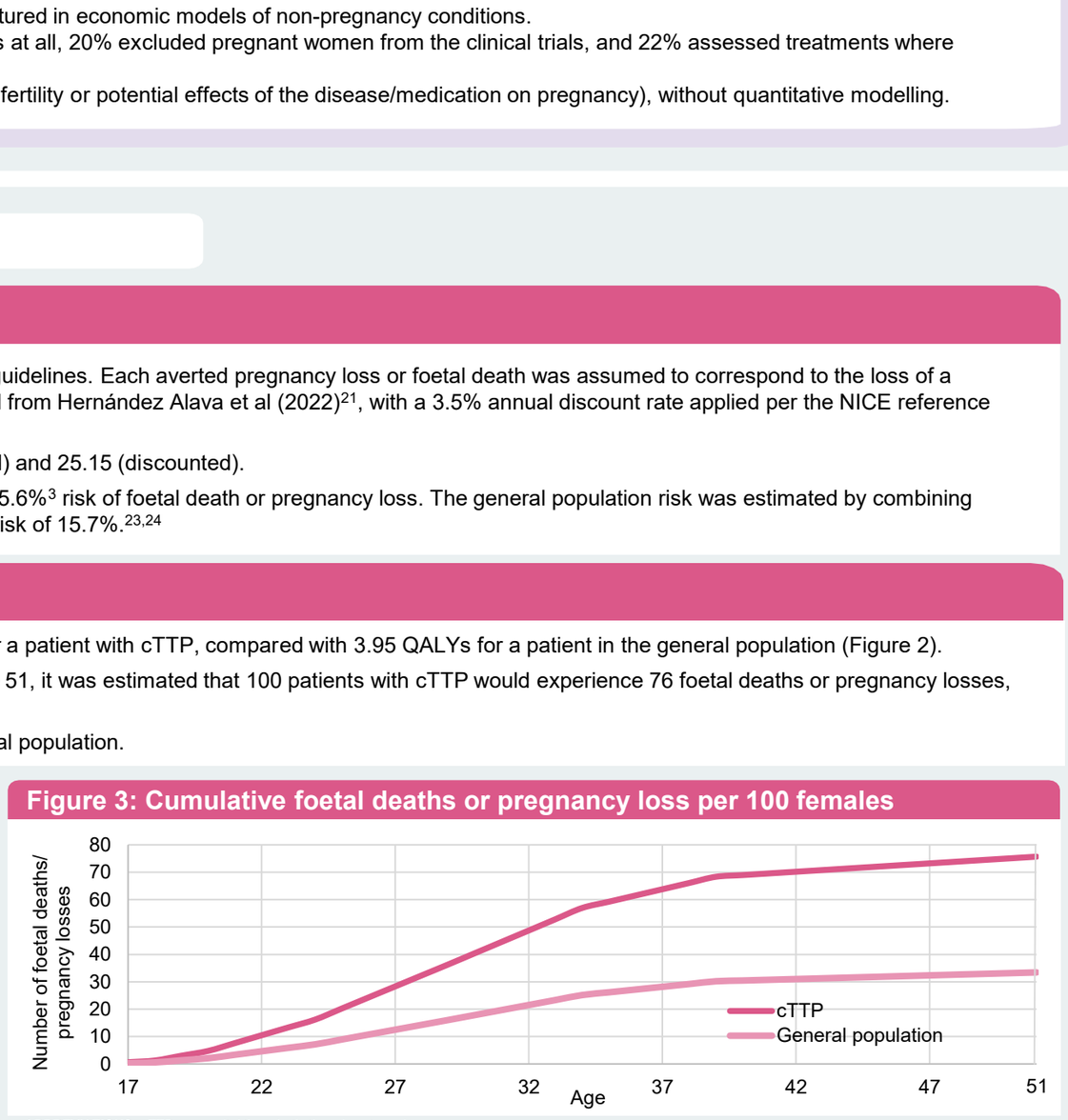
- For each pregnancy, the mean discounted QALY loss from a pregnancy loss or foetal death was 8.94 QALYs for a patient with cTTP, compared with 3.95 QALYs for a patient in the general population (Figure 2).
- Using ONS data[25] on pregnancy rates in England and Wales, and assuming women are only pregnant up to age 51, it was estimated that 100 patients with cTTP would experience 76 foetal deaths or pregnancy losses, compared with 33 in the general population (Figure 3).
- These results highlight the substantially greater burden of PRCs in patients with cTTP compared with the general population.

Figure 2: QALY loss for patients with cTTP compared to the general population



ABBREVIATIONS: cTTP: congenital thrombotic thrombocytopenic purpura; QALYs: Quality-adjusted life years

Figure 3: Cumulative foetal deaths or pregnancy loss per 100 females



ABBREVIATIONS: cTTP: congenital thrombotic thrombocytopenic purpura

Conclusions

These findings underscore the need for methodological alignment to ensure broader outcomes, such as PRCs, are incorporated into rare disease evaluations, and highlight the importance of effective treatments to reduce their impact in this vulnerable population.

1. Economic models used in HTA submissions rarely capture PRCs directly, despite the availability of established methods.
2. In ultra-rare diseases such as cTTP, accurate value assessment requires models that capture the broader disease impact, including maternal and perinatal outcomes and, not only patient outcomes.
3. In cTTP, the risk and loss of QALYs associated with foetal death or pregnancy loss including early or late miscarriage, stillbirth, and intrauterine foetal death is more than twice that observed in the general population.

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