Using Structured Expert Elicitation to Estimate Long-term Organ Damage Risk in an Ultra-rare Condition: A STEER Case Study

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AUTHORS:

Amie Padhiar, MSc[1]
Colin Burke, MPharm, MSc[2]
Mathilde Puls, MPH[2]
Annie Berkley, MSc[1]
Oliver Heard, MPH[1]
Harold Wolff, MSc, PhD[2]
Linda Murphy, PhD, BA, BAI[2]
Harneet Kaur, MSc[3]

Objectives

To elicit estimates from clinicians on long-term organ damage risk in patients with congenital thrombotic thrombocytopenic purpura (cTTP) who have received recombinant ADAMTS13 (rADAMTS13) prophylactically in the UK.

What is cTTP?

cTTP is an ultra-rare blood disorder caused by an inherited deficiency of the von Willebrand factor-cleaving enzyme ADAMTS13.

Persistently low ADAMTS13 activity results in the accumulation of thrombi in the microvasculature, elevating the risk of long-term organ damage (LTOD), and the overall risk of morbidity and mortality. A European/US study (N=78) found organ damage in 28% of patients with cTTP receiving regular prophylaxis, affecting neurological (n=15), renal (n=11), and cardiac (n=8) systems.[1]

Given this high risk of long-term complications, treatment strategies focus on replacing functional ADAMTS13, historically with plasma-based therapies (PBTs). However, PBT treatment is time-intensive, carries a risk of adverse reactions, and only variably restores ADAMTS13 activity. Patients receiving PBTs experience a high treatment burden and remain at risk of cTTP complications and LTOD.[2,3]

What is rADAMTS13?

rADAMTS13 is a purified recombinant form of the human ADAMTS13 enzyme. It is an enzyme replacement therapy indicated for the treatment of patients with cTTP. In a Phase 3 study (N=48), prophylactic use of rADAMTS13 provided peak ADAMTS13 activity levels of ~100%, with low levels of acute disease-related events and manifestations over 12 months.[4] Based on these data, rADAMTS13 has received regulatory approval from the FDA, EMA, PMDA and MHRA, and ISTH 2025 guidelines recommend prophylactic rADAMTS13 over PBT to prevent acute episodes for patients with cTTP.[5-9]

Why was the study conducted?

Although rADAMTS13 is expected to reduce the risk of LTOD, empirical data to quantify this are unavailable and infeasible to obtain in a timely manner due to the rarity of cTTP and the length of follow up required.

Reducing LTOD risk is expected to deliver both clinical and economic benefits.

Robust estimates are needed to demonstrate the full value of rADAMTS13 and support HTA submissions.

What is Structured Expert Elicitation (SEE)?

SEE is a formal approach of capturing judgements from experts where empirical data are not available.

SEE works by asking experts to quantify their beliefs in a structured way. It generates probability distributions to quantify uncertainty and aims to reduce known biases. As such, SEE is recommended by HTA bodies such as NICE in the absence of empirical data.

Study design

SEE was used to elicit estimates of LTOD risk to meet the objectives. The study followed the Structured Expert Elicitation Resources (STEER) methodology developed by the University of York, aligned with the Medical Research Council (MRC) protocol.[10]

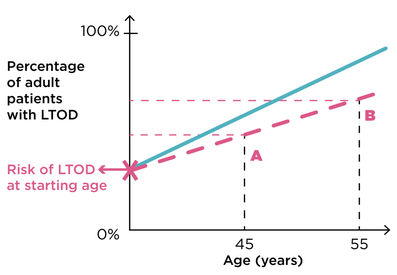
The timepoints selected as the quantities of interest were considered clinically meaningful to capture changes in organ damage risk over time, and sufficiently proximate for experts to make informed judgements

Population			Quantity of interest	Setting
Adults (≥18 yrs) and children/ adolescents (<18 yrs)* • with confirmed or newly diagnosed cTTP, • with no prior organ damage, • who are receiving rADAMTS13 prophylactically.	Adults	A	The percentage of adults with at least one LTOD at **45 years of age**	Real-world clinical practice in the UK where rADAMTS13 may be available for prophylactic treatment of cTTP patients.
		B	The percentage of adults with at least one LTOD at **55 years of age**	
	Children and adolescents	C	The percentage of children/adolescents with at least one LTOD at **15 years of age**	
		D	The percentage of children/adolescents with at least one LTOD at **20 years of age**	
		E	The percentage of children/adolescents with at least one LTOD at **25 years of age**	

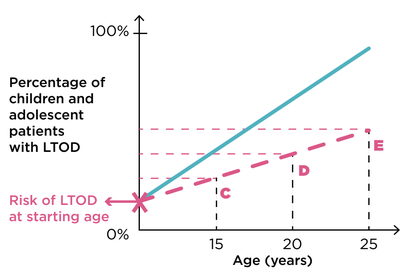
*Experts were provided with a mean age for adults of 38.3 years (standard deviation [SD]: 11.4), and a mean age for children/adolescents of 9.08 years (SD: 4.17) based on the rADAMTS13 Phase 3 trial.[4]

Experts were asked to estimate the risks for patients receiving rADAMTS13, while being presented with a corresponding set of risks for patients receiving standard treatment as a benchmark

Illustrative example of cumulative LTOD risk in adults



Illustrative example of cumulative LTOD risk in children and adolescents



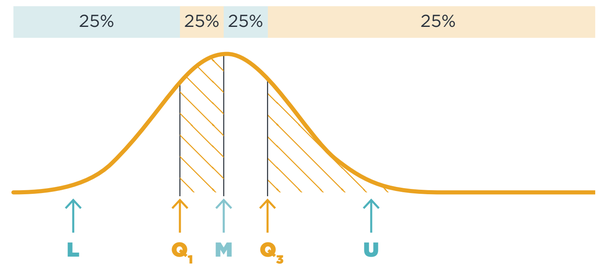
Standard treatment was defined as the treatment offered to patients with cTTP in standard UK clinical practice, at the time of this study, without the availability of rADAMTS13. For most patients, this included prophylactic PBTs, with additional on-demand treatment for those experiencing an acute or subacute cTTP event.

The main prophylactic treatment for adults is PBTs (mainly solvent/detergent-treated plasma), and BPL 8Y for children and adolescents.

Key: Patients on rADAMTS13 — Patients receiving PBT

Experts provided individual judgments using the quartile method

For each quantity of interest, each clinician was asked to estimate 5 values:



Note: Q1 and Q3 are usually much closer to M than to L or U

Key:

L Lower plausible limit (L): a value such that the clinician believes that there is a 1% probability that the true value is less than L

U Upper plausible limit (U): a value such that the clinician believes that there is a 1% probability that the true value is greater than U

M Median (M): a value such that the true value is equally likely to be less than or greater than M

Q_1 Lower quartile (Q1): a value such that the clinician judges it equally likely that the true value is below Q1 or between Q1 and M

Q_3 Upper quartile (Q3): a value such that the clinician judges it equally likely that the true value is between M and Q3 or above Q3

SEE process

Clinician engagement process

Clinician identification and recruitment ▶ **Contracting** ▶ **Evidence brief review (~2 weeks before training)** ▶ **Training and online survey session (facilitated by vendor)** ▶ **Post-survey follow-up (if needed)**

Pre-specified criteria developed to identify clinicians:
UK haematology specialist with at least 3 years' cTTP experience having at least one patient with cTTP under their care in a TTP-specific treatment centre.

Training brief (1 hour)
Researchers explained what SEE was to the clinicians, provided a practice question and briefed them on the evidence and values to elicit.

Online survey (~1 hour)
Directly after receiving the training, clinicians independently completed a survey to provide their estimates.

Evidence brief

An evidence brief was developed to provide clinicians with key clinical trial data and real-world evidence (RWE) to inform their inputs.

Key evidence included in the evidence brief:

Phase 3 trial (rADAMTS13 vs. PBT)[4] | **Phase 3b trial (rADAMTS13)[11]** | **Borogovac et al. (2022) (RWE LTOD outcomes provided as a benchmark)[12]**

A **targeted literature review** was conducted to identify relevant RWE on LTOD that could be presented to clinicians to aid their estimates of the quantities of interest.

This led to the identification of Borogovac et al. (2022), which was used to provide a **benchmark** for **real-world LTOD outcomes** for patients treated with **PBTs**.

Data collection and analysis

1. Experts' elicited values were entered into an online R Shiny Sheffield Elicitation Framework (SHELF) tool to produce probability distributions. A best-fitting distribution was selected to represent the clinicians' uncertainty per STEER guidance.
2. The identities of the responders remained 'quasi-anonymous' (known to the researchers) but responses remained anonymous outside of the research team.
3. Judgements were checked for consistency and clinicians were required to check anomalies and amend responses.
4. Individual-level distributions were mathematically aggregated using unweighted linear opinion pooling to generate one probability distribution per quantity of interest, as recommended in the MRC protocol.
5. To explore the dispersion (uncertainty) in the experts' estimates, the SD was calculated based on the 95% credible interval and the number of samples (i.e., number of experts), assuming a normal distribution for pragmatic summarisation.
6. Between-expert variability was explored via qualitative analysis of the rationales provided for each judgement.

Study outcomes

Six UK clinical experts in cTTP meeting the pre-specified criteria were recruited and completed the study.

All experts independently estimated a lower median cumulative risk of LTOD for rADAMTS13 prophylaxis versus PBT from the benchmark study across all quantities of interest, with uncertainty primarily attributed to patient age and level of treatment adherence.

Variability in risk estimates was generally higher in the adult versus the child/adolescent population, possibly due to less consistent clinical experiences and long-term disease complexities.

Qualitative rationales provided indicated that, in general, experts agreed on the lower risk of LTOD events with rADAMTS13 prophylaxis than with PBT, and this was primarily attributable to maintenance of higher ADAMTS13 levels.

Limitations

All experts were weighted equally despite variations in clinical experience, and experts were not asked about the LTOD risks associated with PBTs, which could have introduced a control.

Conclusions

Findings demonstrate a consistent expert consensus that rADAMTS13 prophylaxis reduces LTOD risk compared with PBTs.

Where empirical data were lacking and infeasible to attain in a timely manner, SEE provided estimates of LTOD risk in cTTP in line with HTA guidance.

These estimates are intended to support rADAMTS13 HTA submissions and provide a case study for using SEE in an ultra-rare disease where traditional evidence collection is infeasible.

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Key: cTTP, congenital thrombotic thrombocytopenic purpura; EMA, European Medicines Agency; FDA, Food and Drug Administration; HTA, health technology assessment; ISTH, International Society on Thrombosis and Haemostasis; LTOD, long-term organ damage; MHRA, Medicines and Healthcare Products Regulatory Agency; MRC, Medical Research Council; PBT, plasma-based therapy; PMDA, Pharmaceuticals and Medical Devices Agency; rADAMTS13, recombinant ADAMTS13; RWE, real-world evidence; SD, standard deviation; SEE, structured expert elicitation; SHELF, Sheffield Elicitation Framework; STEER, Structured Expert Elicitation Resources; TTP, thrombotic thrombocytopenic purpura.

[1]Takeda UK Ltd, London, United Kingdom; [2]Lumanity, London, United Kingdom; [3]Takeda Pharmaceuticals International AG.

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