

Structured expert elicitation to inform clinical effectiveness of emerging pharmaceuticals in “difficult-to-treat” Crohn’s disease



hns23qqx@bangor.ac.uk

Hang Su¹; Dyfrig A. Hughes¹

¹Centre for Health Economics and Medicines Evaluation, Bangor University, Bangor, Wales

Introduction

- A novel, orally-active RNA-based therapy aimed at modulating expression of target genes associated with ileal Crohn’s disease, is expected to attenuate or prevent stricture formation, and reduce fistulas¹. However, **the treatment remains in the preclinical stage of development**.
- In this context, early value assessments undertaken to support decisions concerning the commercial viability of candidate drugs, may be shaped by experts’ beliefs regarding expected clinical efficacy in addition to evidence extrapolation and modelling.
- This study describes the use of structured expert elicitation (SEE) to gather expert judgment and related **uncertainties concerning the clinical performance of RNA-based therapy**, in the absence of any clinical data².
- The aim is to obtain and evaluate expert estimates of expected effects of the RNA-based therapy for “difficult-to-treat” Crohn’s disease (DTT-CD) in preparation for subsequent early health technology assessment (eHTA) (**poster EE47**).

Results

- Based on the SEE, the difference in mean (95% confidence interval, CI) between RNA-based therapy and upadacitinib in the percentage of patients **with both endoscopic response and fistula closure** was 1.2% (-5.8, 8.3) at 12-weeks [absolute rates of 9.6% vs. 8.3%], and 0.6% (-10.4, 11.5) at 52 weeks [11.1% vs. 10.5%].
- **For endoscopic response alone**, these were -3.7% (-17.3, 9.9) and -2.0% (-16.6, 12.7) respectively; and for **fistula closure alone**, -4.0% (-11.9, 4.0) and -0.8% (-8.9, 7.2), respectively (Figure 1, Table 1).

Conclusions

- Experts recruited to the study were cautious in predicting any therapeutic advantage of the experimental RNA-based therapy over upadacitinib in relation to outcomes in DTT-CD.
- By offering a structured framework for quantifying uncertainty explicitly, belief elicitation has an emerging role in the context of treatments at an early stage of development.
- The results of the SEE provide parameter estimates for an early HTA analysis; however, clinical studies are needed to validate this elicitation approach.

Table 1. Equally weighted potential performance of RNA-based therapy for all respondents

Timepoint	Outcome	RNA Therapy (CIs)	Upadacitinib (CIs)	Difference
12 weeks	Endoscopic response	28.6% (18.7%-38.5%)	32.3%(22.9%-41.6%)	-3.7% (-17.3%-9.9%)
12 weeks	Fistula closure	8.5% (4.1%-12.9%)	12.5%(5.9%-19.1%)	-4% (-11.9%-4%)
12 weeks	Composite endpoint	9.6%(5.2%-14%)	8.3% (2.8%-13.9%)	1.2% (-5.8%-8.3%)
52 weeks	Endoscopic response	19.1% (12.3%-25.9%)	21.1% (8.1%-34%)	-2% (-16.6%-12.7%)
52 weeks	Fistula closure	4.4% (0.7%-8.2%)	5.3% (-1.8%-12.4%)	-0.8% (-8.9%-7.2%)
52 weeks	Composite endpoint	11.1% (6.1%-16.1%)	10.5% (0.8%-20.3%)	0.6% (-10.4%-11.5%)

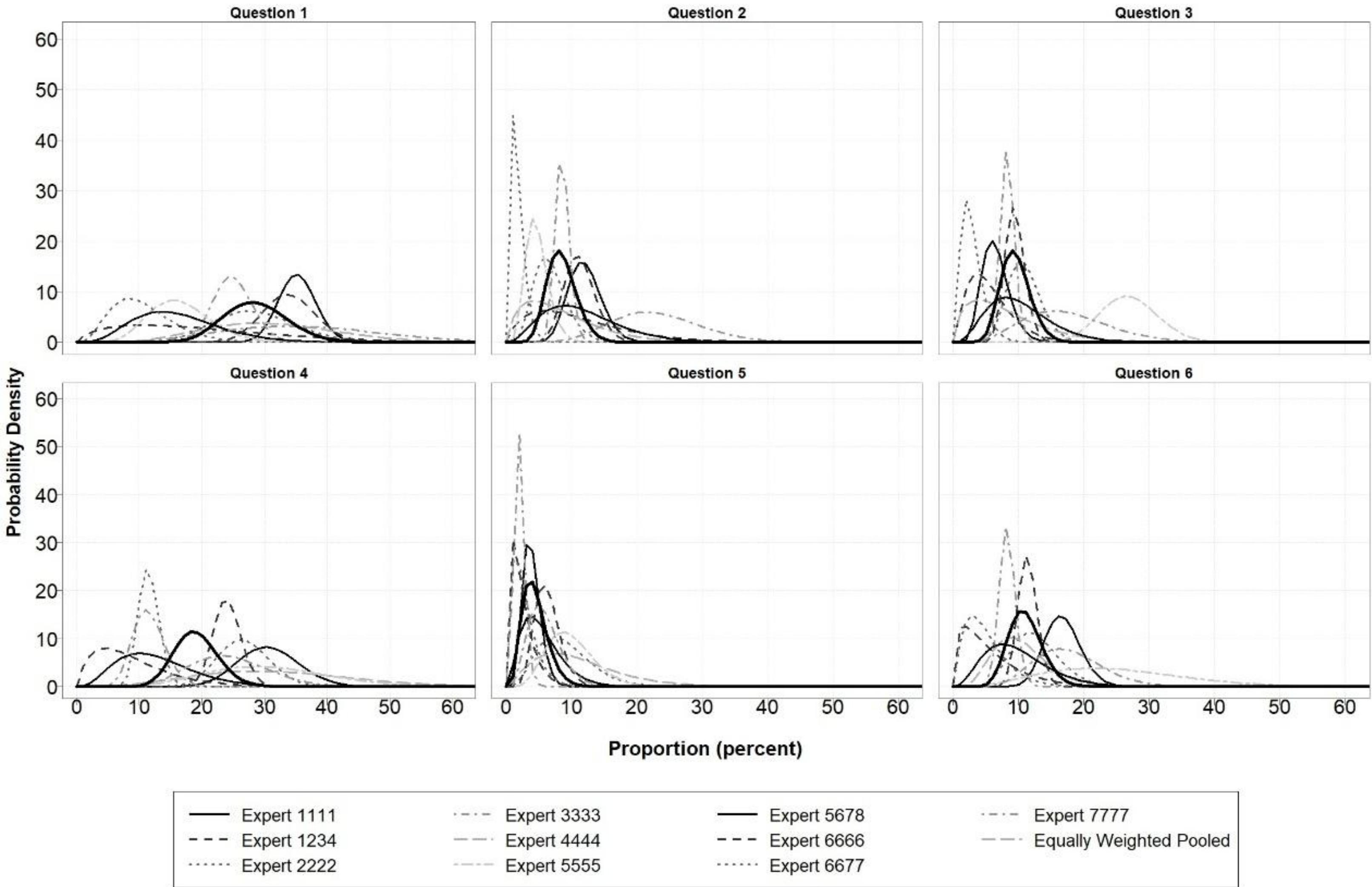


Figure 1. Probability density functions of potential performance of RNA-based therapy of 10 gastroenterologists

Methods

- We recruited **10 gastroenterologists** from the UK, Ireland, Italy and Denmark. These experts assessed the clinical endpoints of endoscopic response and closure of external fistula openings in patients with DTT-CD, and in comparison with upadacitinib at 12 and 52 weeks³.
- The questions were as follows: What percentage of patients with fistula and difficult-to-treat CD, would you expect to:
 - **Q1:** achieve **endoscopic response only** following **12 weeks** treatment with RNA-based therapy? (considering that 32% of patients achieve this with upadacitinib)
 - **Q2:** have **closure of external fistula openings only** following **12 weeks** treatment with RNA-based therapy? (considering that 13% of patients achieve this with upadacitinib)
 - **Q3:** achieve **both closure of external fistula openings and endoscopic response** following **12 weeks** treatment with RNA-based therapy? (considering that 8% of patients achieve this with upadacitinib)
 - **Q4:** achieve **endoscopic response only** following **52 weeks** treatment with RNA-based therapy? (considering that 21% of patients achieved endoscopic response only with upadacitinib)
 - **Q5:** have **closure of external fistula openings only** following **52 weeks** treatment with RNA-based therapy? (considering that 5% of patients achieve this with upadacitinib)
 - **Q6:** achieve **both closure of external fistula openings and endoscopic response** following **52 weeks** treatment with RNA-based therapy? (considering that 11% of patients achieve this with upadacitinib)

Survey data analysis:

- The elicited judgements were aggregated using linear opinion pooling, to derive the overall pooled probability density functions⁴.
- Probability distributions, $p(\theta)$, were fitted to the histogram data (Figure 2) provided by each expert⁵;
- Fitted distributions were aggregated to construct an overall pooled probability density functions: $p(\theta)=\sum_i \times p_i(\theta)$

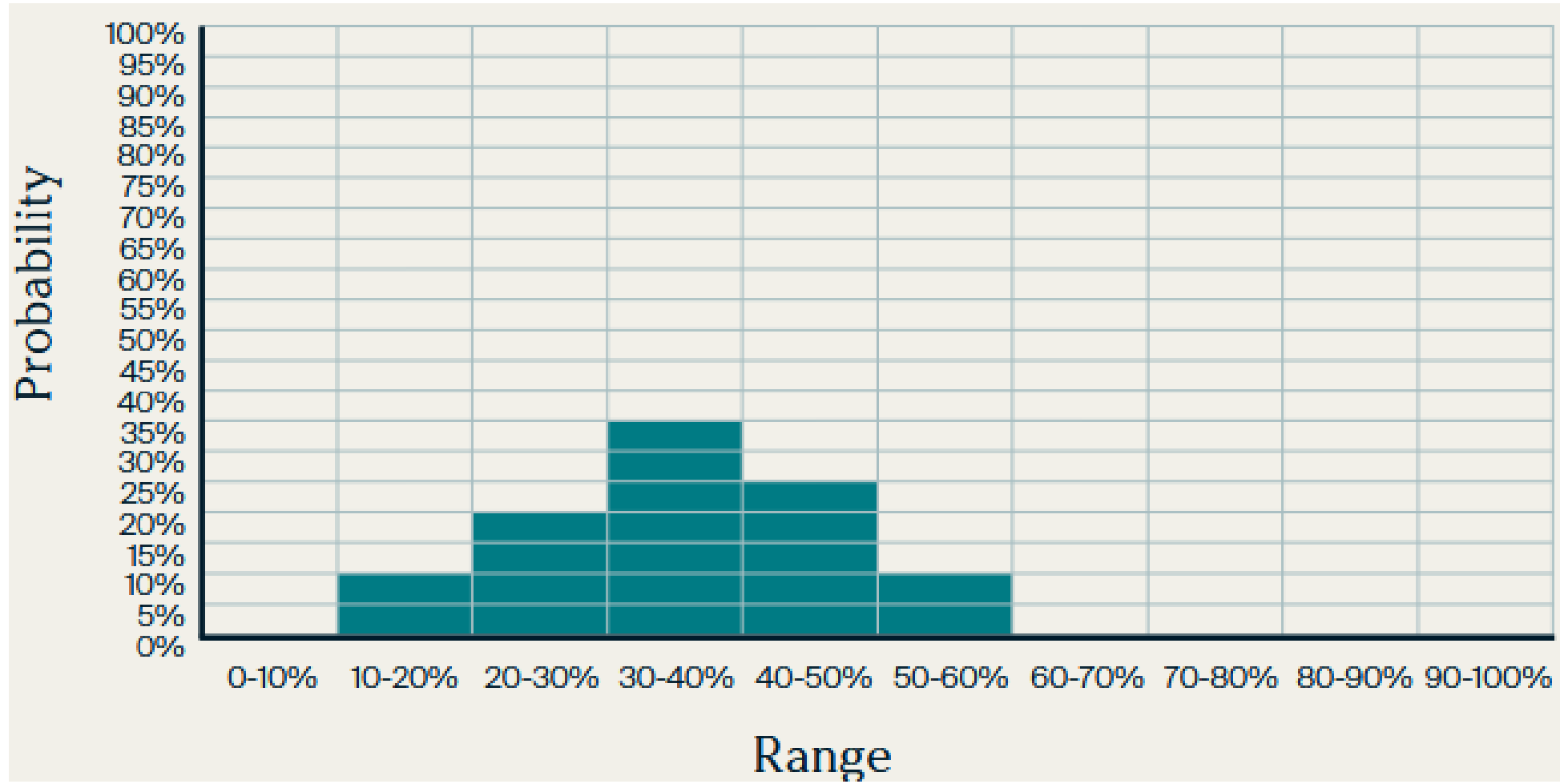


Figure 2. Example answer for question 1 displayed in Microsoft® Excel® survey

References

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