GENE GUT

Oral delivery of encapsulated RNA nanotherapeutics for targeted treatment of ileal Crohn's disease.

EE47

Methodological challenges associated with early economic evaluation: A case of an RNA-based therapy for fistulizing Crohn's disease

Hang Su[1]; Dyfrig A. Hughes[1]

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

hns23qqx@bangor.ac.uk

Introduction

- Crohn's disease is a chronic, progressive GI inflammatory disorder marked by irreversible bowel damage accumulation, yet despite advances in biologics and small-molecule agents, up to 30% of patients fail to respond to available advanced therapies[1].
- RNA-based therapy (RNA) offer the potential for local, tissue-targeted modulation of gene expression, thereby treating inflammation at its source while avoiding systemic side effects[2].
- Early health technology assessment (eHTA), unlike traditional cost-effectiveness analysis (CEA), may be used to address the questions:
  - **What is the value-based price of a novel technology under a range of efficacy scenarios?**
  - **Which attributes of the technology contribute most to its value?**
  - **What evidence would be most valuable to inform drug development?**
- The aim was to estimate the price at which an RNA-based therapy that is in pre-clinical development for Crohn's disease, represents good value to a healthcare payer compared with upadacitinib (UPA)

Conclusions

- Based on structured expert elicitation estimates of benefit, the **RNA is predicted to be dominated at a price matching upadacitinib** (£900/month).
- Equivalence in cost-effectiveness could be achieved with a **price reduction (**to ≤ £875/month)**, or a gain in utility** potentially achieved with fewer adverse reactions or improved patient convenience.

Methods

- Markov model constructed with monthly cycles representing induction and maintenance phases, a 12-month horizon and a UK National Health Service perspective (Figure 1).
- Transition probabilities (monthly transition matrices represented as ***T***) from trials of UPA[3] (Figures 2&3), and expert elicitation survey of RNA-based therapy (**poster SA6**).
- Large-period matrices (***M***) fitted to observed states via constrained optimization (with recurrence/new-onset constraints), then matrix root extraction[6]:

  For the induction phase (week 0 to week 12, ~12 weeks): $T_1^3 = M_{12}$, thus: $T_1 = M_{12}^{1/3}$

  For the maintenance phrase (week 12 to week 52, ~40 weeks): $T_2^9 = M_{40}$, thus: $T_2 = M_{40}^{1/9}$
- Weighted least squares error function minimised:

  $$total\ error = \| P_0 M_{12}^3 - P_{12} \|^2 + (predicted\ recurrence_{12} - observed\ recurrence_{12})^2;$$

  $$total\ error = \| P_{12} M_{40}^9 - P_{52} \|^2 + (predicted\ recurrence_{52} - observed\ recurrence_{52})^2$$
- 10 random-restart solutions per arm used to avoid local optima (Figure 4), then aggregated final matrices equally and weighted by inverse of trace-fitting error.
- Cost and utility derive from published literature[4,5].
- Value-based price of RNA-based therapy determined from a threshold analysis for zero Incremental net monetary benefit (INMB) at £25,000 and £35,000 QALY gained[7]. A two-way sensitivity analysis jointly varied drug price and utility gain to pricing boundaries

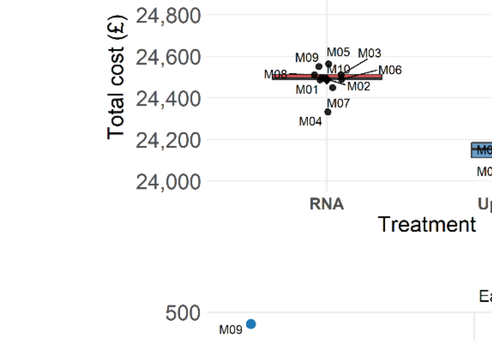

Figure 1. The *de novo* Markov model for fistulizing Crohn's disease

Results

- Across the 10 fitted transition matrix scenarios (M01-10), total costs were consistently higher for RNA-based therapy (at an assumed cost of £900/month) than for UPA. Total QALYs were lower (Figures 5, 6).
- In the base-case analysis, RNA-based therapy was dominated by UPA with higher costs (+£341, +£335) and fewer QALYs (−0.011, −0.009) (Table 1).
- The value-based price was £851-£853/month at a threshold of £25,000/QALY (Table 2).
- Sensitivity analysis indicated that at £900/month, the RNA-based therapy required a utility gain of at least +0.025 across all health states to achieve £0 NMB at £25,000/QALY (Figure 7).
- The density of points on the cost-effectiveness plane was centred in the northwest quadrant, consistent with the finding of dominance (Figure 8).

Table 1. Base-case results

	Total Cost (£)		Total QALY		ΔCost (£)	ΔQALY	INMB (£)
	RNA	UPA	RNA	UPA			
Unequal Weighted	24508	24167	0.497	0.508	341	-0.011	-615
Equal Weighted	24489	24154	0.501	0.510	335	-0.009	-566

Table 2. RNA price achieves £0 INMB

WTP £/QALY	Equal Weighted	Unequal Weighted
£25,000	£853	£851
£35,000	£845	£842

Figure 5. Distribution of total costs and QALYs across 10 fitted transition matrix scenarios

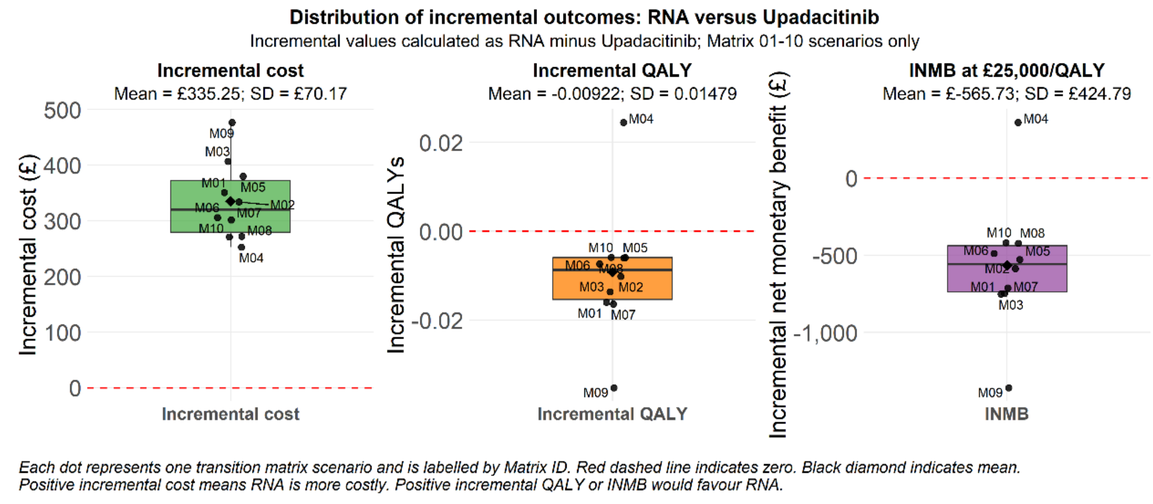

Figure 6. Distribution of incremental results across 10 fitted transition matrix scenarios

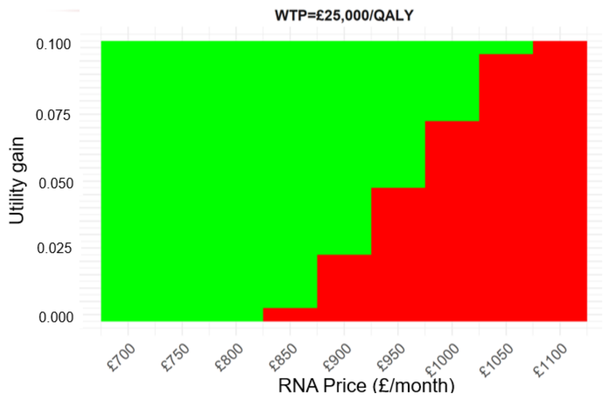

Figure 7. Cost-effectiveness zones at £25K/QALY WTP

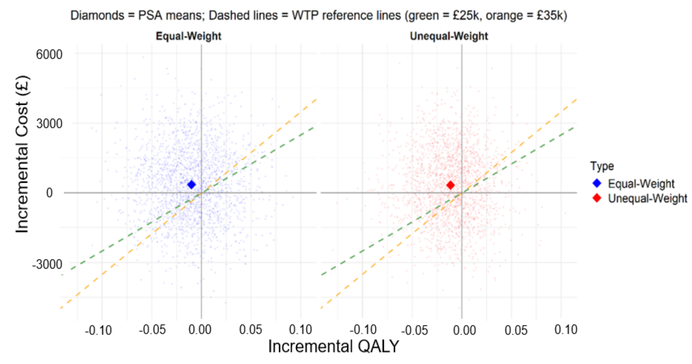

Figure 8. Cost-effectiveness plane

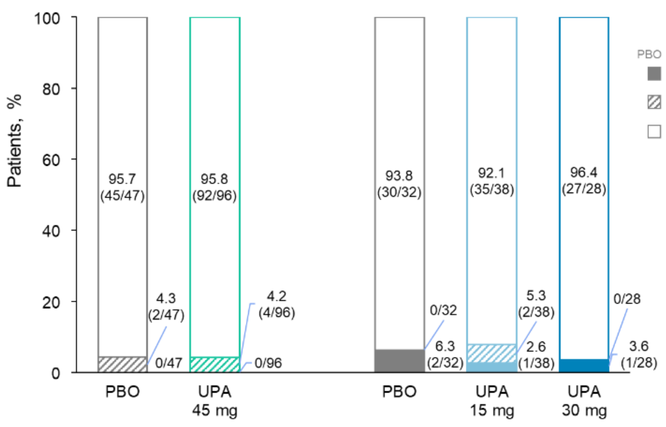

Figure 3. Proportion of patients with fistula recurrence or new onset of fistulas using UPA or PBO at week 12 (far left) and week 52 (left)

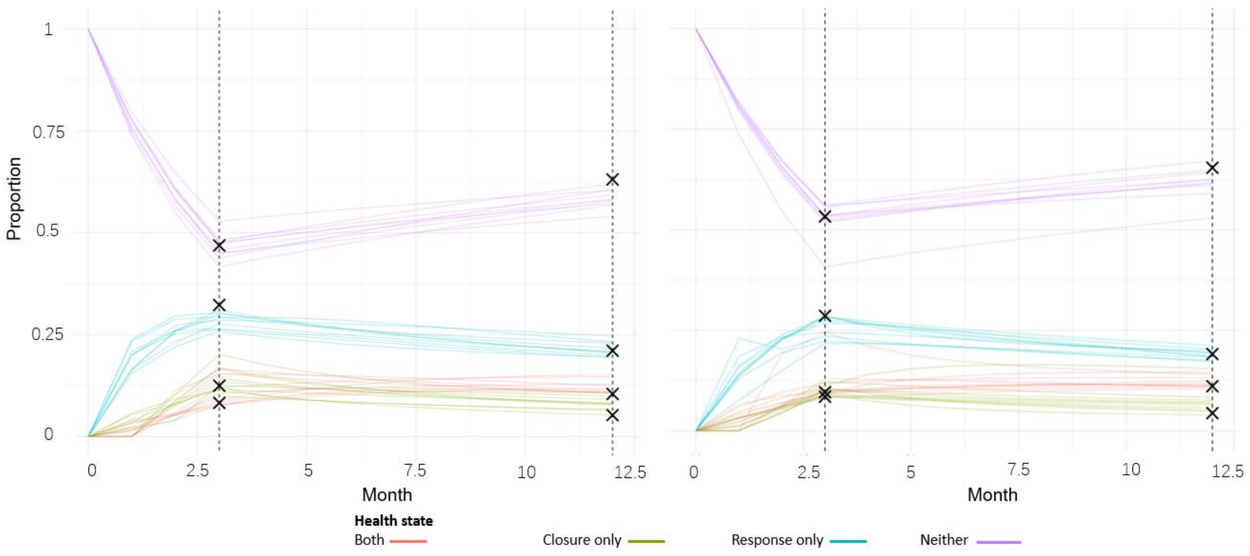

Figure 4. All 10 Markov simulated traces for UPA (left) and RNA (right)

References

1. Rieder F, Zimmermann EM, Remzi FH, Sandborn WJ. Crohn's disease complicated by strictures: A systematic review. Gut. 2013 Jul;62(7):1072–84. doi:10.1136/gutjnl-2012-304353 PubMed PMID: 23626373; PubMed Central PMCID: PMC4884453.
2. Ball RL, Bajaj P, Whitehead KA. Oral delivery of siRNA lipid nanoparticles: Fate in the GI tract. Sci Rep. 2018 Feb 1;8(1):2178. doi:10.1038/s41598-018-20632-6
3. Colombel JF, Lacerda AP, Irving PM, Panaccione R, Reinisch W, Rieder F, et al. Efficacy and Safety of Upadacitinib for Perianal Fistulizing Crohn's Disease: A Post Hoc Analysis of 3 Phase 3 Trials. Clinical Gastroenterology and Hepatology. 2024 Sep 24. doi:10.1016/j.cgh.2024.08.032.
4. Lindsay J, Punekar YS, Morris J, Chung-Faye G. Health-economic analysis: cost-effectiveness of scheduled maintenance treatment with infliximab for Crohn's disease – modelling outcomes in active luminal and fistulizing disease in adults. Alimentary Pharmacology & Therapeutics. 2008;28(1):76–87. doi:10.1111/j.1365-2036.2008.03709.x.
5. National institute for Health and Care Excellence, NICE. Darvadstrocel for treating complex perianal fistulas in Crohn's disease: Technology appraisal guidance TA556 [Internet]. NICE; 2019 Jan [cited 2025 Jun 30]. Available from: https://www.nice.org.uk/guidance/ta556/evidence.
6. Gene H. Golub, Charles F. Van Loan. Matrix Computations (Fourth Edition) [Internet]. Baltimore (MD): Johns Hopkins University Press; 2013.
7. Gidwani R, Russell LB. Estimating Transition Probabilities from Published Evidence: A Tutorial for Decision Modelers. Pharmacoeconomics. 2020;38(11):1153–64. doi:10.1007/s40273-020-00937-z PubMed PMID: 32797380; PubMed Central PMCID: PMC7426391.

Funded by the European Union (GA 101057491) and supported by the UK's innovation agency, Innovate UK. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Health and Digital Executive Agency (HADEA). Neither the European Union nor the granting authority can be held responsible for them.