Development of a *De Novo* Model To Assess the Cost-Effectiveness of a New Treatment Option for Patients With Primary Immunoglobulin A Nephropathy (IgAN)

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Introduction

Immunoglobulin A nephropathy (IgAN) is a progressive, chronic disease of the kidney that occurs when IgA antibody complexes deposit in the kidney, causing inflammation and fibrosis, which can lead to kidney failure (1-3).

- IgAN is an orphan disease estimated to affect 4 people per 10,000 in the EU (4)
- A recent UK registry analysis found IgAN patients are typically younger, with an average age of 41.7 years and predominantly male (68%) (5)
- The data indicates higher proteinuria is associated with worse 10-year kidney survival; for example, patients with UPCR 0.88 to <1.76 g/g had a 40% 10-year kidney survival rate, relative to 15% in patients with ≥1.76 g/g (6)
- The first disease-specific therapy for patients with IgAN and a UPCR ≥1.5 g/g received UK marketing authorisation in 2023 and conditional EU marketing authorisation in 2022 (targeted-release formulation budesonide) (7)

Methodology

- To inform the model's structure, functionality, assumptions and data sources, 45 previous global HTA submissions were reviewed
- Health-state unit costs, resource use, adverse event costs, and health-related QoL data were identified from a targeted literature review
- Real-world evidence (RWE) of IgAN patients from RaDaR, the largest UK registry of people with IgAN (2,299 adults, 140 children) (5), was used to address key evidence gaps

Objectives

This research aimed to conceptualise a cost-effectiveness model capturing disease progression, long-term risk of end-stage renal disease (ESRD), quality of life (QoL), and the impact a new treatment may have for patients with IgAN and UPCR ≥1.5 g/g.

Results

Previous NICE submissions

No IgAN-specific UK cost-effectiveness analyses have been published to date (based on a systematic literature review [SLR] conducted in November 2022). Searches were subsequently expanded to include chronic kidney disease (CKD); a total of 45 HTA submissions were identified.
Of the seven relevant NICE submissions that informed the development of the *de novo* model, the majority utilised a cohort Markov model structure (71.4%) (8-12) and 57.14% defined health states by estimated glomerular filtration rate (eGFR) (10, 11, 13, 14).

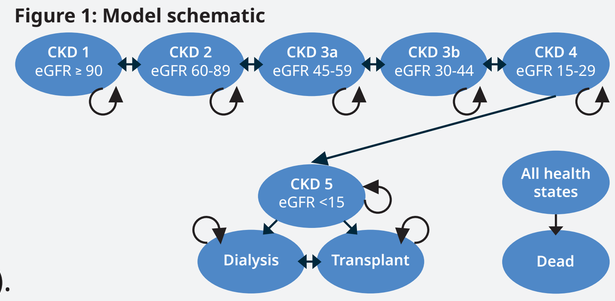
Model structure

A *de novo* Markov cohort model, including eight health states and an absorbing mortality state, was developed (Figure 1). The reduced flexibility of a cohort-level approach was considered appropriate considering its audience-friendly benefits.
The model's health states were primarily defined by CKD state (by eGFR levels) and validated during an advisory board with three UK nephrologists and two health economists.

Utility and cost data

Health state utility data were sourced from analysis in CKD by Cooper et al 2020 (15). Health state costs were identified using existing literature in CKD (16-18), BNF (19), PSSRU (20), and the NHS National Cost Collection (21).

Figure 1: Model schematic



Abbreviations: CKD, chronic kidney disease.

Transitions between CKD 1–4

Patients with more severe disease (i.e. eGFR <30 mL/min per 1.73 m^2) are typically excluded from IgAN clinical trials due to uncertain treatment benefits (22). As such, observed patient transitions between CKD health states from clinical trials may only be able to inform the transitions between less severe CKD health states within models (i.e., CKD 1-4).
By calculating the log odds of improvement and worsening using a logistic regression and individual patient level data from trials, transition probabilities between CKD stages 1–4 can be estimated. This methodology was applied in this analysis using available clinical trial data.

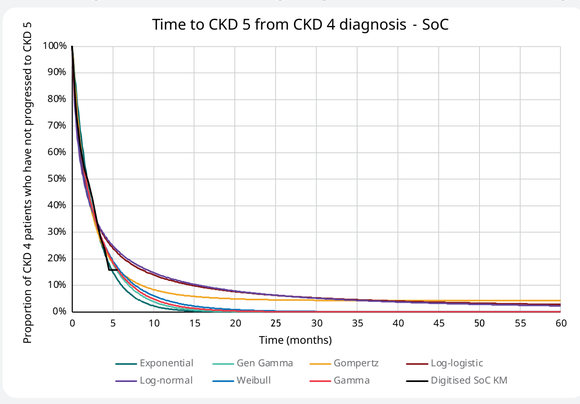
Transition probabilities from CKD 5, dialysis, and transplant

Transitions between CKD 5, dialysis, and transplant health states were sourced from a previous NICE submission in CKD. Due to limited data availability, transitions from CKD 5 were assumed equivalent across comparators (10).

Transitions from CKD 4 to CKD 5

Due to the potential lack of clinical trial data on patients with more severe disease (22), health state transitions from CKD 4 to CKD 5 need to be informed by RWE.
CKD 4 to CKD 5 lifetime transitions in the standard of care (SoC) arm of our model were derived from a Kaplan–Meier (KM) curve of UK RaDaR data, on patients with IgAN with UPCR ≥ 1.5 g/g. The KM curve was digitised and extrapolated using standard parametric modelling (5) (Figure 2).

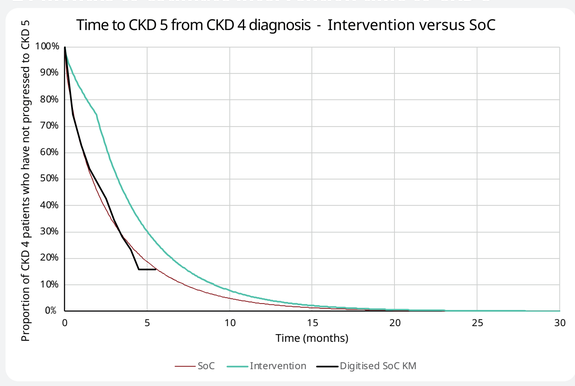
Figure 2: UK RaDaR KM data and fitted parametric extrapolations estimating time to CKD 5 in IgAN patients with UPCR ≥1.5 g/g



Abbreviations: CKD, chronic kidney disease; KM, Kaplan Meier; SoC, standard of care.

A hazard ratio (HR) applied to the intervention arm can be calculated using clinical trial data and Inker et al.'s published meta-analysis (23) which links relative changes in 2-year eGFR to long-term clinical outcomes using the following formula: $\mathbf{HR = e^{(-0.14+[-0.30 \times 2\text{-year eGFR total slope}])}}$

Figure 3: HR applied to SoC estimated time to CKD 5 up to 24-months to estimate intervention time to CKD 5



Abbreviations: CKD, chronic kidney disease; KM, Kaplan Meier; SoC, standard of care.

This HR can be subsequently applied to the first 24 months of the extrapolated SoC curve to estimate the long-term risks of transitioning from CKD 4 to CKD 5 for the intervention arm (Figure 3).
The HR presented in Figure 3 is an indicative HR of 0.38 based on 2-year eGFR analysis of the NefIgArd full trial population (24).

Mortality

10-year survival probability data in patients with IgAN from UK RaDaR was used to inform the risk of mortality (5). The standardised mortality rates (SMRs) from the UK RaDaR data were calculated using a Cox regression model with age, sex, and CKD stage as covariates. The calculated SMRs (Table 1) were then used to inform the risk of mortality from all model health states.

Table 1: SMRs calculated using UK RaDaR 10-year survival data for patients with IgAN and UPCR ≥1.5 g/g

CKD stage	SMR
CKD 1	1.00
CKD 2	1.65
CKD 3a	1.08
CKD 3b	1.03
CKD 4	2.04
CKD 5	2.58
Renal replacement therapy	4.62

Abbreviations: CKD, chronic kidney disease; SMR, standardised mortality rate.

Conclusion

- The presented IgAN economic analysis utilised a Markov model cohort structure endorsed by clinical and health economic experts who deemed it representative of IgAN disease presentation; it was informed by both clinical efficacy and safety data, and RWE from a large IgAN patient cohort
- The analysis' comprehensive approach could provide a valuable foundation for assessing future cost effectiveness of new treatments in IgAN
- The economic analysis utilised data showing reductions in eGFR, which is a well-accepted (by regulatory authorities and clinical experts) surrogate marker, to model disease progression in IgAN; the use of other endpoints to model IgAN disease progression warrants further investigation
- IgAN is a rare disease with limited published data; the representativeness of CKD data for IgAN patients is to be further explored

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Abbreviations

CKD: chronic kidney disease
eGFR: estimated glomerular filtration rate
ESRD: End-stage renal disease
HTA: Health technology appraisal
IgAN: immunoglobulin A nephropathy
NICE: National Institution for Health and Care Excellence
RaDaR: National Registry of Rare Kidney Diseases
RWE: Real-world evidence
SLR: Systematic literature review
SoC: Standard of Care
UPCR: Urine Protein Creatinine Ratio