Mind the Gap: A Need for Guidance on Modelling Disease Activity Outcomes in Economic Models

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Background

- While multiple guidelines are available to describe the analysis of survival outcomes for cost-effectiveness models (CEMs) with clear algorithms, there is limited guidance on analysis and use of disease activity outcomes (DAOs) in CEMs

Objective

- To explore the issues related to the analysis and use of these outcomes and provide an initial thought for a future framework.

Methods

- An HTA review was carried out on the previous 5 years
  - Critiques of CEMs based on DAOs from three HTAs (NICE, CDA, SMC) were assessed, using rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) as examples
  - FADs from NICE, detailed advice from SMC, and the Reimbursement reports from CDA were reviewed
- RA and SLE both have:
  - A relapsing-remitting nature
  - A list of outcomes measuring disease activity
- Using these, an initial framework was outlined with potential steps for the analyses and inclusion of disease activity outcomes in CEMs.

Results

SLE

There was no data on long-term use of new treatments (belimumab, anifrolumab) due to an insufficiently long follow-up period

HTA submissions identified for SLE drugs

Drug	HTA agency	Year	Decision
Belimumab SC[1]	CDA	2020	Not recommended
Belimumab IV and SC TA752[2]	NICE	2021	Recommended
Belimumab IV[3]	SMC	2022	Recommended
Anifrolumab[4]	NICE	2022	Terminated appraisal due to non-submission
Anifrolumab IV[5]	CDA	2023	Recommended

Summary of critiques of CEMs from the identified SLE HTA submissions

Data issues
• Limited follow-up, which creates high uncertainty for long-term use, especially in relapsing-remitting diseases

• RWE data has limitations
  • Limited patient characteristics limit prognostic factors that can be used for matching with the clinical trial population
  • Non-systematic selection process

• Questions around generalisability to other countries
• Age of the data might limit generalisability to current clinical practice
• Uncertainty in linking short-term and long-term data
Outcome issues
• Outcomes used in historical data might not align with outcomes used in more recent trials (e.g. SLEDAI vs. SELENA-SLEDAI for belimumab appraisals)
• Different outcomes in different trials
• Use of AMS might smooth out flares, thereby not accurately representing the relapsing-remitting nature of the disease
Clinical plausibility
• Does not reflect the relapsing-remitting nature of the disease
• Plateau at the end of the curve might not reflect long-term disease progression
Methodological issues
• Difficulty incorporating treatment effect: assumption-based   • This brings up questions around treatment waning
• Form of regression: linear; extrapolation of other forms not presented

RA

Biologics have been available for a longer time in RA than in SLE (infliximab was approved by EMA in 1999)[6], therefore longer historic data was available

HTA submissions identified for RA drugs

Drug	HTA agency	Year	Decision
Upadacitinib[7]	CDA	2020	Recommended
Upadacitinib TA665[8]	NICE	2020	Recommended
Upadacitinib[9]	SMC	2021	Recommended
Upadacitinib TA744[10]	NICE	2021	Recommended
Upadacitinib[11]	SMC	2022	Recommended
Filgotinib[12]	CDA	2021	Withdrawn
Filgotinib[13]	SMC	2021	Recommended
Filgotinib TA676[14]	NICE	2021	Recommended
Filgotinib[15]	SMC	2022	Recommended
Adalimumab, etanercept, infliximab and abatacept (partial review) TA715[16]	NICE	2021	Recommended
Infliximab[17]	CDA	2021	Recommended

Summary of critiques of CEMs from the identified RA HTA submissions

Data issues
• Timeframe of trials may be insufficient to accurately estimate disease progression – this increases the results' uncertainty
• Lack of long-term data
• Historical progression estimates may be irrelevant due to the changing treatment landscape
Outcome issues
• Correlation between outcome measures used for modelling and ones used for determining severity levels (HAQ and DAS28) is uncertain and based on short-term trial data
• Some patients may start treatment for severe disease during a flare, which would temporarily increase their disease activity to a severe level
Clinical plausibility
• Questions around long term disease activity: would disease activity be stable over time, or would a large proportion of patients have an increased DAS28 score?
Methodological issues
• Form of regression: linear; extrapolation of other forms not presented
• Relationship between HAQ-DI and DAS28 is not linear
• Single assessment of disease activity at given timepoints could be subject to temporary fluctuation in disease activity, including flares

Predictive equations often:

- **use linear models**, focusing on long-term trends only (with annual mean scores)
- **have covariates driven by already available data**
- **are developed to understand drivers of disease activity to inform acute clinical decisions**, rather than for extrapolation, resulting in challenges in their inclusion in CEMs.
- **have limited follow-up compared to the disease duration**, and so may not fully capture the relapsing-remitting nature of the disease, resulting in questions around clinical plausibility

A future framework should focus on:

The assessment of different functional forms	Incorporation of uncertainties
Limitations and advantages of smoothing flares	Clinical/biological plausibility of extrapolations*
Formal selection of prognostic factors	Building conceptual models	Adaptability for CEMs
Considering the aim to inform health resource allocation decisions	Consistent selection of DAOs

*Clinical/biological plausibility would be essential from the discussion of prognostic factors to the assessment of extrapolation

Conclusions

- The current challenges in analysing and implementing disease activity outcomes emphasize the importance of developing detailed guidelines similarly to survival analysis.
- A framework would help to:
  - Increase transparency
  - Increase ease of use in CEMs
  - Contribute to more robust decisions
  - Understand limitations and uncertainties
  - Assess clinical plausibility.

References

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Abbreviations

AMS, Adjusted Mean Systemic Lupus Erythematosus Disease Activity Index; CDA, Canada's Drug Agency; CEM, cost-effectiveness model; DAO, disease activity outcome; DAS28, Disease Activity Score-28; EMA, European Medicines Agency; FAD, final appraisal determination; HAQ, Health Assessment Questionnaire; HAQ-DI, Health Assessment Questionnaire – Disability Index; HTA, health technology assessment; IV, intravenous; NICE, National Institute for Health and Care Excellence; RA, rheumatoid arthritis; RWE, real-world evidence; SC, subcutaneous; SELENA-SLEDAI, Safety of Estrogens in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SMC, Scottish Medicines Consortium; TA, technology assessment

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