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Challenges in health economic evaluation of gene replacement therapies: potential solutions for key methodological issues

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BACKGROUND

- Several limitations and challenges have been identified when conducting economic evaluations of gene replacement therapies (GRT) using standard approaches, such as recommended by HTA organisations using cost-effectiveness analysis (CEA) as a key driver of decisions.
- These include in particular: 1) assessment of clinical effectiveness and safety based on small clinical trials, often single-arm; 2) valuation of health outcomes for children, who are often targeted by GRT; 3) time horizon and extrapolation, as there is substantial uncertainty in long-term effects, positive or negative; 4) possible development of new payment models specific to GRT.

OBJECTIVES

- To identify potential methodological solutions for these challenges.

METHODS

- A literature review on economic evaluations of GRT was performed. A workshop was conducted with 8 European and US health economic experts with experience in evaluations of GRT.
- Targeted literature reviews were conducted to investigate further potential solutions to specific challenges.

RESULTS

1) Assessment of clinical effectiveness and safety based on small clinical trials, often single-arm

- The results from clinical trials conducted on small samples and/or performed without appropriate comparators can in some instances be compared with those obtained from previous studies conducted on cohorts similar to the population of interest.
- Historical controls may include prior patients with same disorder from an observational study (prospective natural history study, medical chart data from clinical care), or from a control group from a prior randomized investigational study.
- Experts agreed on factors to be considered to ensure historical cohorts acceptability by HTA bodies, as described in Figure 1.

Figure 1. Factors ensuring acceptability of submissions using single-arm trials with external control by HTA bodies[1]

1) Strong assessment and rationale for not doing RCT (e.g. disease with risk of irreversible damage)
2) Preliminary data suggesting dramatic magnitude of treatment effect size versus historical cohort
3) Treatment effect size objectively measured in a robust way minimizing bias
4) External cohort relatively homogeneous and very similar to the treated group, or impact of study heterogeneity in the patient population and on outcomes to be studied
5) Well-known confounding factors affecting outcomes and statistically sound matching method used to control for confounding (e.g. propensity score matching)
6) Generalizability and transferability of clinical data toward historical cohort to be proactively assessed

Single arm trials with historic control

2) Valuation of health outcomes for children, who are often targeted by GRT

→ Valuing quality of life in very young children

- The QALY model has been widely challenged[2], and appears to be problematic when it is applied for children, as the assumption of mutual independence between health-related quality of life (HRQoL) and duration of a health state does not hold.
- The Saved Young Life Equivalents (SAVE) approach, which has attracted less interest than QALYs in the health economic literature, may be worth reconsidering[2,3].
  - First, the SAVE approach would avoid assumptions of the QALY model such as independence between health state value and duration. It would thus avoid the need for stratifying valuation tasks according to “normal” stages of child development.
  - Second, SAVEs would be elicited using a Person Trade-off (PTO) approach, from a societal perspective, thus avoiding the difficulties to elicit utilities for very young children from self-perspective.
- Cost-benefit analysis would avoid the assumptions related to the QALY model, but would not solve the problems related the value of health outcomes being dependent on the duration of health states. If Willingness To Pay (WTP) was elicited over health states at different stages of life, the same type of problems as with QALYs would occur when aggregating WTPs for different stages into a value for a health profile. As for eliciting WTP directly for a health profile, representing a full life, this would probably be a very difficult task for respondents.

→ Valuing the HRQoL of families and caregivers

- The burden of caregivers, involved by both emotional distresses facing suffering from a disease of a close relative as well as by the burden of caring, will be substantial considering the severity of diseases treated by GRT.
- In cases where there is evidence of an impact of disease on the HRQoL of families and caregivers, it would seem legitimate to take it into consideration in the QALYs or other valuation of health outcomes.
- This should be done irrespective of whether costs are estimated from health care payer or societal perspective.

→ Incorporating broader elements of value

- Broader elements of value could be taken into consideration in the cost/QALY evaluation framework through some modifiers, such as the application of a factor to inflate the QALYs or a higher cost-effectiveness threshold.
- Drummond et al. highlighted the fact that in practice, HTA agencies consider those elements of value through a deliberative process, and it would be important to identify all relevant elements when presenting evaluations of GRT[4].

3) Time horizon and extrapolation, as there is substantial uncertainty long-term effects, positive or negative

→ Selection of an appropriate time horizon

- While a lifetime horizon may seem desirable for GRT, it may be misleading for decision-makers if we have no way to know whether the net benefits of treatment will be positive or negative in distant years.
- One solution to palliate long-term uncertainty would be to assess scenario analyses with different time horizons pertaining to different knowledge about treatment benefit.
- However, when different scenarios produce a wide range of ICERs, some expert guidance via the use of Delphi panels could be useful for decision-makers to weigh the different results presented to them.

→ Eliciting expert opinion

- Experts acknowledged the importance of expert opinion due to limited data available in the context of GRT.
- Several elicitation procedures are available to obtain information from experts and make a probabilistic representation of their knowledge[5].
- While methodological guidance on elicitation procedures for HTA is needed, two different approaches of elicitation are commonly used in the literature of structured elicitations for cost-effectiveness analyses: 1) the fixed interval method, in which the expert reports his/her probability of the uncertain quantity of interest θ, for example the recurrence rate, the mortality rate or the time to death, lying in specified intervals, and 2) the variable interval method, in which he/she makes quantile judgements[6].

→ Extrapolation methods

- Standard modelling techniques used in economic evaluation, such as Markov models and Discrete Event Simulation, will likely be appropriate for GRT. The challenge will be to find appropriate data, such as transition probabilities, to populate these models.
- Information from historical patients might be used to generate the input data.
- When there is uncertainty around the proportion of cured patients, then mixture cure models may be helpful to determine the probability of reaching key development endpoints[7].

4) Possible development of new payment models specific to GRT

- With GRT, there would be potentially high upfront drug acquisition costs, and cost offsets in the long term. Thus, assuming everything else equal, the budget constraint would be exceeded in the coming years where GRT therapies are launched, and costs would be below the budget constraint in distant years.
- Does it mean that GRT should be considered as an investment for the future, and payers should borrow money to pay for GRT? The application of CEA is expected to lead to a maximization of health benefits under a budget constraint, but this objective may not be achieved if the timeframes of the CEA and of the budget constraint are not the same.
- While researchers investigate these questions, budget impact analysis will be particularly important to inform health care payers making decisions regarding GRT.
- Approaches such as spreading the payment over patients’ life, e.g. make an annual payment for each year as long as patient is alive, might be relevant tactics to face affordability issues with GRT.

CONCLUSIONS

- While some of the limitations of economic evaluations of GRT are inherent to limited clinical data and lack of experience with GRT, and likely more present than in any other kind of health technology, others may be addressed by methodological research to be conducted by health economists.

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