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) or cost-utility analysis (CUA) as key cut-offs of decision-making.
• 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; there is substantial uncertainty in long-term effects, positive or negative; 4) potential 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 potential solutions specific to small clinical trials.

RESULTS
1) Assessment of clinical effectiveness and safety based on small clinical trials
• 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 the 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 outcomes from historical cohorts1

1. Stress assessment and rationale for not doing RCT (e.g. disease with high irreversible damage)
2. Preliminary data suggesting dramatic magnitude of treatment effect size versus historical data
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 and trustworthy 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 prospectively assessed

2) Valuation of health outcomes for children, who are often targeted by GRT
• The CQLY model has been widely challenged 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 CQLYs in the health economic literature, may be worth reconsidering2-3.
• First, the SAVE approach would avoid assumptions of the CQLY 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 difficulty of eliciting utilities for very young children from self-perspective.
• Cost-benefit analysis would be avoided to the concerns of the CQLY model, which would address the problems of the value of health outcomes being dependent on the duration of health states. If Willingness To Pay (WTP) was elicited over health states during a certain time period, the same life, the type of problems as with CQLYs would occur when aggregating WTPs for different health states to a health profile for eliciting WTP directly for a health profile, representing a full life, this would probably be a very difficult task for respondents.

VALUES
• The burden of caregivers, induced by both emotional distress facing suffering from a disease of a close relative as well as by the need for improvement, should be substantially considered the severity of diseases treated by GRT.
• In cases where there is evidence of an impact on the health of family caregivers, it would make legitimate to take it into consideration in the CQLYs or other valuation of health outcomes.
• This should be done irrespective of whether costs are estimated from health care payer or societal perspective.

3) Time horizon and extrapolation, as there is substantial uncertainty over long-term effects, positive or negative
• Broader elements of value could be taken into consideration in the cost/QALY evaluation framework through some modifications, such as a new guidance to HTA agencies to consider elements of value through a deliberative process, and it would be important to identify all relevant elements when presenting evaluations of GRT.

4) Possible development of new payment models specific to GRT
• With GRT, there would be potentially high upfront drug acquisition costs, and costs offset in the long term. Thus, assuming everything else equals positive results 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 maximisation of health benefits under a budget constraint, but this object may not reach the budget constraint, and the budget constraint and the budget constraint are not the same.
• New technologies and gene replacement therapies, an upfront investment analysis will be particularly important to inform health care payers making decisions regarding GRT. Approval as a treatment for a disease 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 due to clinical data and lack of experience with GRT, and likely more than in any other kind of health technology, others may be addressed by methodological research to be conducted by health economists.

REFERENCES

ISPOR 2019, Copenhagen, Europe, November 2-6 2019, PB110.