EE570

DEVELOPMENT AND PILOT TESTING OF A STANDARDIZED, SIMPLIFIED MODELING TOOL FOR HEALTH TECHNOLOGY ASSESSMENT SCOPING

Moradi A[1], Richardson M[1], Campbell JD[1]

[1]Institute for Clinical and Economic Review (ICER), Boston, MA, United States

Background

- Early scoping phases in Health Technology Assessment (HTA) often comprise a literature review, stakeholder input, and PICOTS (population, intervention, comparator, outcomes, timing, setting) identification.[1]
- Consideration of cost-effectiveness modeling activities during early review scoping phases could help identify evidentiary gaps, support internal and external modeling team discussions, and help optimize workflows.

Objective

- To develop and pilot test a simplified modeling tool during early scoping phases of HTA at ICER.

Methods

- We developed a 3-state Markov model tool in Microsoft Excel (Microsoft 365) accommodating various disease process pathways: episodic disease, progressive disease, and partitioned survival (Figure 1). A fourth structure was later added reflective of treatment persistence and supportive of external risk equations.
- Key model inputs included time horizon, cycle length, baseline demographics, transition probabilities, treatment effectiveness, health state utilities, and costs. Durations over which to apply cost and effectiveness estimates were included.
- Development (N=6) included the primary domains of feasibility testing via dependent reference model replication with corresponding accuracy checks (n=2) and *de novo* model building (n=2), and performance testing via independent model replication with corresponding accuracy checks (n=2).
- Piloting encompassed collaboration during early review stages to identify raw data for early modeling exercises and to communicate critical data gaps, among other considerations, for a full review model build; open-ended qualitative feedback from pilot test collaborators was solicited and aggregated.

Results

- All models (N=6) demonstrated acceptable internal validity (*development*).
- Dependent model replication (*feasibility testing*) generated incremental cost-effectiveness (CE) ratio spreads of ≤25% versus reference models in multiple sclerosis (MS) and oncology (Figure 2). *De novo* model development (*feasibility testing*) for two case studies (potential/unannounced review topics) revealed domains where greater flexibility may be needed in a comprehensive model, namely time-varying transition probabilities exterior to a partitioned survival framework and a more flexible modeling approach reflective of treatment persistence and external risk equation modeling. Independent replication (*performance testing*) demonstrated cost-effectiveness spreads of <20% versus reference models, and suggested better reproducibility when replicating partitioned survival models (Duchenne muscular dystrophy [DMD]) (Figure 3).

Figure 1: Supported Cohort Model Structures for Simplified Early Modeling

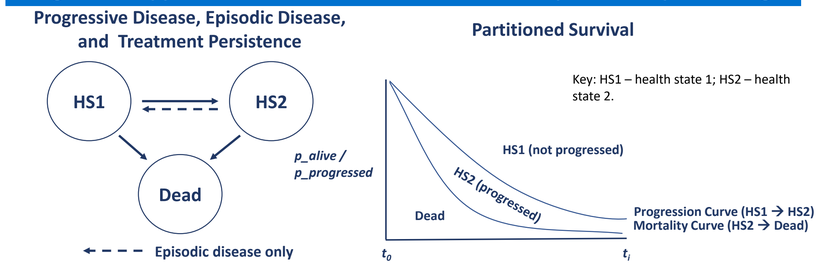

Figure 2: Feasibility Testing: Dependent Reference Modeling

*The oncology reference model did not report incremental $/LYs despite possible life extension; therefore, those values are reported for neither the reference model nor the replication model

Key: DMD – Duchenne muscular dystrophy; DMF – dimethyl fumarate; LY – life-year; MS – multiple sclerosis; QALY – quality-adjusted life-year.

Figure 3: Performance Testing: Independent Model Replication

- Open-ended qualitative feedback solicited from academic and ICER modelers reflected the following domains (ongoing ICER review): temporal considerations of early modeling exercises (e.g., pre- *vs* intra-review; precise intra-review timing); duplication of work; propensity to inform key data gaps and assumptions; data gap handling and imputation approaches; limitations of simplified modeling exercise assumptions and related shortfalls of early exercise heuristics.

Discussion

- Given the market authorization of an appreciable number of high-cost health technologies in recent years[2], there is a clear precedent to effectively manage resources allocated to HTA – streamlining review processes by conducting value-adding CE modeling activities may help achieve ongoing HTA commitments to operational excellence. Piloting of an early modeling tool facilitating these CE modeling activities during the scoping phases of a review were met with cautious optimism from academic collaborators citing concerns of duplication of workstreams; these exercises were welcomed by ICER health economists as a method to optimize model development and decision-making.
- Our developmental efforts and piloting exercises are complicated by limitations. These include the unavailability of full pilot conclusions, as the ICER assessment is still ongoing, minimal assessment piloting (1 pilot), few early modeling tool development iterations (2 to 3), and a lack of data on early modeling tool performance in the absence of state membership information (i.e., trace data).

Conclusions

- A standardized, simplified early modeling tool performed reasonably well during feasibility testing and performance testing.
- Simplified modeling exercises during early scoping phases of a review were assessed as potentially duplicative when full review model builds are conducted by well-resourced academic modeling teams. Despite this, early modeling exercises may be sufficiently resource efficient and informative regarding key evidentiary and data gaps to facilitate increased downstream operational efficiency along a longitudinal 8- to 10-month ICER review.
- Further research is warranted aimed at tailoring early modeling approaches for internal and external modeling teams, understanding impact on broader HTA teams, and revising approaches and timing in support of operational excellence.

Early Scientific Advice Exploration

- *What are health technology manufacturers' interest levels in receiving early scientific or US-specific HTA advice for development programs (i.e., in early or mid-stage clinical research: post-investigational new drug [IND] application, Phase I-II)?*
- *To what extent would manufacturers value and provide a fee for ICER-led rapid and/or simplified economic evaluation findings and corresponding knowledge sharing as part of early scientific/HTA advice consultations?*
- *How can ICER provide these services in a manner conducive to avoidance of conflicts of interest as interpreted by both ICER and manufacturer legal and regulatory teams?*

References

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Development and Pilot Testing of a Standardized, Simplified Modeling Tool for Health Technology Assessment Scoping

Moradi A[1], Richardson M[1], Campbell JD[1]

[1]Institute for Clinical and Economic Review (ICER), Boston, MA, United States

ISPOR Annual 2023, Boston, MA, United States

Poster Code: EE570
Date: Wednesday, May 10, 2023
Poster session time: 8:30 AM - 11:30 AM

Background

Early health technology assessment (HTA) has recently been defined as ‘‘all methods used to inform industry and other stakeholders about the potential value of new medical products in development, including methods to quantify and manage uncertainty’’.[1] A variety of techniques may be used to support goals of early HTA, including interviews, qualitative and quantitative survey methods, clinical trial simulation, multicriteria decision analysis, return on investment analysis, and value of information analysis, with cost-utility analysis or cost-effectiveness (CE) analysis (CEA) perhaps being the most versatile.[2]

In principle, however, early CE modeling should not be construed as a one-off activity but instead utilized iteratively as more information is released about the technology itself or the environment in which it would be used.[3] Moreover, most early HTA research focuses on value to manufacturers;[2,5,6,7] there is little evidence to suggest early HTA has been used to support broader therapeutic appraisals and peripheral activities, such as horizon scanning led by HTA bodies. However, early CE modeling may be of particular value in streamlining processes and operations within a particular HTA appraisal; such streamlining is underscored in importance as the number, range, and complexity of technologies for which HTA is necessary rises. As testament to this, there is precedent for streamlining activities supporting full economic evaluations given initiatives recently announced by the National Institute for Health and Care Excellence (NICE).[4]

At ICER, after a topic has been chosen for review, early project scoping phases comprise literature review, stakeholder input, and PICOTS (population, intervention, comparator, outcomes, timing, setting) identification.[8] We hypothesized that simplified early CE modeling activities during early review scoping phases could help identify evidentiary gaps and generally support internal and external modeling teams in a value-adding and resource efficient manner.

Objective

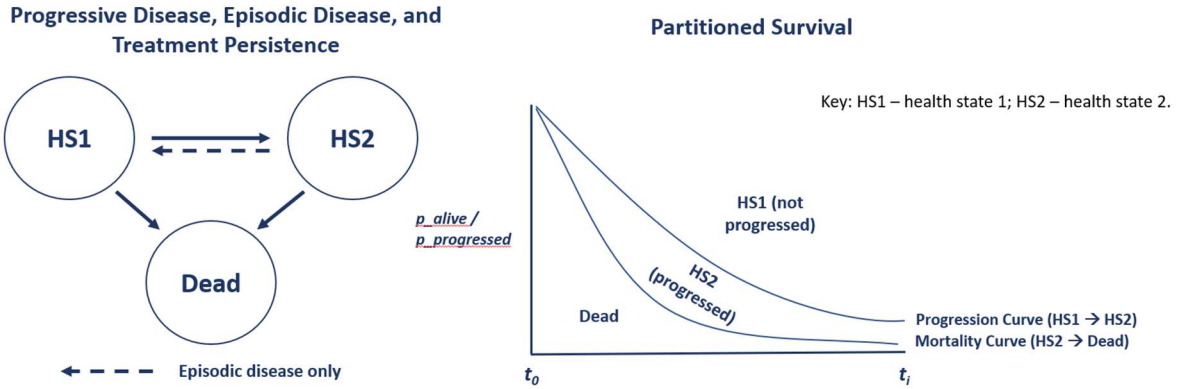
To develop and pilot a simplified modeling tool during early scoping phases of health technology assessments aimed at supporting appraisal teams and further streamlining ICER reviews

Methods

We developed a 3-state Markov model tool in Microsoft Excel (Microsoft 365) accommodating various disease process pathways: episodic disease, progressive disease, and partitioned survival (Figure 1). A more flexible structure was later added in the development phase, reflective of treatment persistence and suitable for models built using external risk equations. Key model inputs included time horizon, cycle length, baseline demographics, transition probabilities, treatment effectiveness, health state utilities, and costs. Durations over which to apply cost and effectiveness estimates were included. Key model outputs included state membership over time, health outcomes, costs, cost-effectiveness ratios, threshold prices, and quantitative net health/monetary benefit.

Development spanned internal model validation, feasibility testing via dependent reference model replication with corresponding accuracy checks plus *de novo* model building, and performance testing via independent model replication with corresponding accuracy checks. Piloting encompassed collaboration across ICER analysts, ICER health economists, and academic modelers to both identify raw data for early modeling exercises and to communicate critical data gaps, early modeling challenges, successes, and considerations for the full review model build; open-ended qualitative feedback from pilot test collaborators was solicited and aggregated concerning implications for full assessment and general utility of the early modeling exercises. Development and feasibility testing spanned 5 primary models, while early model exercise piloting spanned 1 technology assessment (N=6); models for replication and *de novo* building were chosen based on factors such as model (trace) availability, survival curve availability, and relevance of the therapeutic area to potential future ICER reviews.

Figure 1: Supported Cohort Model Structures for Simplified Early Modeling



Results

All models (N=6) demonstrated acceptable internal validity (*development*). Dependent model replication (feasibility testing) generated incremental cost-effectiveness ratio spreads of ≤25% versus reference models in multiple sclerosis (MS) and oncology (Figure 2). *De novo* model development (*feasibility testing*) for two case studies (potential/unannounced review topics) revealed domains where greater flexibility may be needed in a comprehensive model, namely time-varying transition probabilities

exterior to a partitioned survival framework and a more flexible modeling approach reflective of treatment persistence and external risk equation modeling. Independent replication (*performance testing*) demonstrated cost-effectiveness spreads of <20% versus reference models and suggested better reproducibility when replicating partitioned survival models (Duchenne muscular dystrophy [DMD]) (Figure 3).

Open-ended qualitative feedback solicited from ICER health economists, analysts, and academics modelers spanned the following domains (ongoing ICER review): temporal considerations of early modeling exercises (e.g., pre- *vs* intra-review; precise intra-review timing optimally supporting key review and development milestones); duplication of work; propensity to reduce anchoring bias; propensity to inform key data gaps and assumptions; data gap handling and imputation approaches; limitations of simplified modeling exercise assumptions and related shortfalls of early exercise rapidity; informing implications of alternative modeling approaches across different outcome measures (e.g., proportional hazards effect *vs* accelerated failure time risk modification on quality-adjusted life-years [QALYs] and equal value life-years [evLYs]).

Figure 2: Feasibility Testing: Dependent Reference Modeling

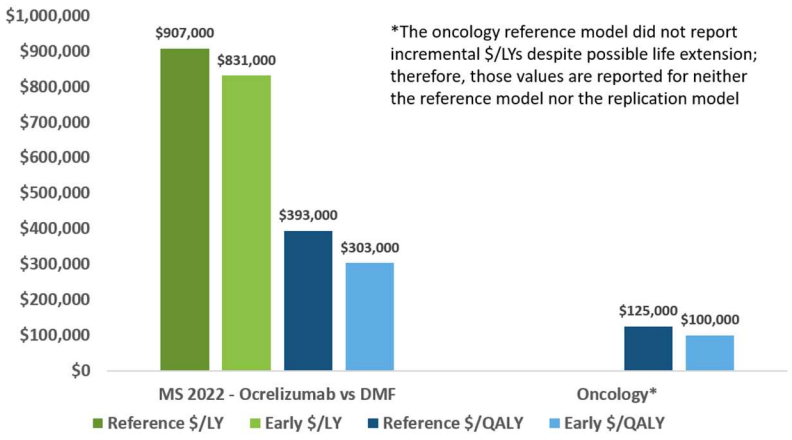


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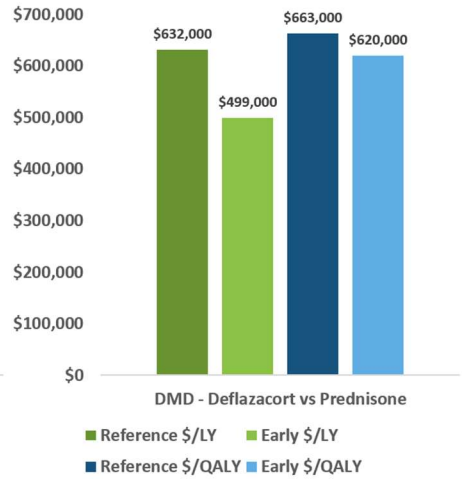
Figure 3: Performance Testing: Independent Model Replication



Discussion

Given the market authorization of an appreciable number of high cost, potentially high value health technologies in recent years and in the near future (up to 13 cell and gene therapy U.S. approvals anticipated in 2023 alone[9]) with specialty pharmacy spend expected to grow 7% year-over-year for the next 3 years,[10] there is a clear precedent to effectively manage resources allocated for HTA – streamlining review processes by conducting value adding CE modeling activities may help achieve ongoing HTA commitments to operational excellence. Piloting of an early modeling tool facilitating these CE modeling activities during the scoping phases of a review were met with cautious optimism from academic collaborators citing concerns of duplication of workstreams despite incremental value that

may be elicited regarding data gap identification, but were wholly welcomed by ICER analysts and health economists as a method to optimize decision-making surrounding key model inputs, structural approaches, and structural assumptions in early review stages. ICER health economists were generally encouraged by the results of the feasibility tests and performance tests, citing that the degree of simplified modeling exercise performance may be sufficient to inform rough notions (e.g., directional interpretations) of incremental cost-effectiveness; however, ICER staff stressed that the performance of the tool would render it insufficient in acting as a substitute for a full review model build (nor is it the intent of this research to facilitate or inform such a substitution). It is possible that utility of early modeling exercises to academic modeling collaborators may be a function of the precise timing of early modeling activities and the extent to which academic groups have already undertaken these activities. To this end of maximizing utility, early model exercise findings may be best shared with collaborators immediately upon ICER review information sharing with collaborators.

Our developmental efforts and piloting exercises are complicated by a variety of limitations. Key limitations include the right-censoring of full piloting and general review findings upon conclusion of the ongoing ICER assessment, minimal assessment piloting (1 pilot), few early modeling tool development iterations (2 to 3), and a lack of data on early modeling tool performance in the absence of critical survival curves or state membership information (i.e., trace data). We look forward to how our approaches will compare or contrast with those of NICE in its efforts to streamline activities supporting full model builds underpinning HTA and value-based pricing exercises.[4]

Conclusions

A standardized, simplified early modeling tool performed reasonably well during feasibility testing and performance testing, deeming it acceptable for HTA piloting aimed at facilitating increased review operational efficiency. The simplified early modeling tool built is insufficiently sensitive and accurate to supplant or validate full model builds. Upon pilot testing, simplified modeling exercises during early scoping phases of a review were assessed as potentially duplicative when full review model builds are conducted by well-resourced academic modeling teams. In contrast, early modeling exercises may be sufficiently resource efficient and informative regarding key evidentiary and data gaps to facilitate increased downstream operational efficiency along a longitudinal 8- to 10-month ICER review. Further research is warranted aimed at tailoring early modeling approaches for internal and external modeling teams, understanding impact on broader HTA teams (e.g., clinical researchers and project managers), and revising approaches and timing in support of operational excellence.

Early Scientific Advice Exploration

The authors of this poster presentation would like to invite poster visitors during the corresponding poster session to participate in scholarly discussion surrounding the utility of early modeling activities supporting ICER-led early scientific advice consultation with health technology manufacturers, sponsors, and other interested parties (e.g., consultants to the pharmaceutical industry). Key questions acting as a springboard for discussion may include but are not limited to:

- What are health technology manufacturers' interest levels in receiving early scientific or US-specific HTA advice (i.e., in early or mid-stage development such as during post-IND, Phase I, or Phase II)?
- To what extent would manufacturers value and provide a fee for ICER-led rapid and/or simplified economic evaluation findings and corresponding knowledge sharing as part of early scientific/HTA advice consultations?
- How can ICER provide these services in a manner conducive to avoidance of conflicts of interest as interpreted by both ICER and manufacturer legal and regulatory teams?
- How should ICER theoretically bring awareness of these services to the appropriate advice recipients (e.g., pharmaceutical or biotech manufacturers, related consultants)?

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