MEASUREMENT OF HEALTH-STATE UTILITY VALUES FOR ECONOMIC MODELS IN CLINICAL STUDIES:
GOOD PRACTICE TASK FORCE
Monday, May 18, 2015

Lynda Doward, MRes
European Head, Patient-Reported Outcomes RTI Health Solutions, Manchester, United Kingdom

Andrew Briggs, DPhil, MSc
Professor of Health Economics, Institute of Health & Wellbeing, University of Glasgow, Glasgow, United Kingdom

Sorrel Wolowacz, PhD
Head, European Health Economics, RTI Health Solutions, Manchester, United Kingdom

Moderator

Speakers

Lynda Doward, MRes
European Head, Patient-Reported Outcomes RTI Health Solutions, Manchester, United Kingdom

Andrew Lloyd, DPhil,
Director, Bladon Associates Ltd, Oxford, United Kingdom
The quality of health-state utility value estimates is critical to the quality of cost-utility analyses and to the health technology assessment decision-making processes that determine whether new health interventions are made available to patients in many countries.

ISPOR’s Vision 2020 Research Committee identified “Estimating HRQL weights (health-state utilities) for cost-effectiveness analysis” as one of the top two priorities.

*Guidance is lacking and good research practices task forces should be convened.*

Good Research Practices in development:
[http://www.ispor.org/ISPOR-Good-Practices-for-Development.pdf](http://www.ispor.org/ISPOR-Good-Practices-for-Development.pdf)

---

**MEASUREMENT OF HEALTH-STATE UTILITY VALUES FOR ECONOMIC MODELS IN CLINICAL STUDIES**

**THE REPORT WILL BE ONE OF A SET COVERING HEALTH UTILITY MEASUREMENT**

- In development: Mapping to estimate health state utility values from non-preference based outcomes measures for cost per QALY economic analysis
- Other proposals being invited by ISPOR

**OUR WORK WILL BE VALUABLE FOR**

- Researchers
  - Involved in the design, implementation, and analysis of studies to estimate health-state utility values (HSUVs)
- Decision Makers
  - Responsible for receiving, reviewing, and making decisions based on these analyses

*Guidance on best practices to provide high-quality HSUVs*
MEASUREMENT OF HEALTH-STATE UTILITY VALUES FOR ECONOMIC MODELS IN CLINICAL STUDIES

GOOD PRACTICES TASK FORCE: CO-CHAIRS

Sorrel Wolowacz, PhD
Head, European Health Economics, RTI Health Solutions, Manchester, United Kingdom

Andrew Briggs, DPhil, MSc
Professor of Health Economics, Institute of Health & Wellbeing, University of Glasgow, Glasgow, United Kingdom

GOOD PRACTICES TASK FORCE: LEADERSHIP GROUP

Vasily Belozeroff, PhD, Health Economics Director, Global Health Economics, Amgen Inc., Thousand Oaks, CA, United States of America

Philip Clarke, PhD, MEc, Associate Professor of Health Economics, Centre for Health Policy, Programs and Economics, University of Melbourne, Melbourne, Australia

Lynda Doward, MRes, European Head, Patient-Reported Outcomes, RTI Health Solutions, Manchester, United Kingdom

Ron Goeree, BA, MA, Director, PATH Research Institute, St. Joseph’s Hospital; and Professor, Department CE&B, McMaster University, Hamilton, Ontario, Canada

Andrew Lloyd, DPhil, Director, Bladon Associates Ltd, Oxford, United Kingdom

Richard Norman, PhD, MSc, BA, Senior Research Fellow, School of Public Health, Curtin University, Western Australia, Australia
GOOD PRACTICES TASK FORCE: OBJECTIVES

- Identify and discuss issues inherent in the collection of HSUVs for economic models in clinical studies
- Provide researchers with an understanding of how to analyze and resolve these issues

GOOD PRACTICES TASK FORCE: OBJECTIVES

- Make recommendations for
  - Early planning of utility data collection within a product development program
  - Design of utility data collection during protocol development for a planned clinical trial
  - Design of supplementary or alternative studies, including prospective and cross-sectional observational studies
  - Analyses and reporting to make best use of the data for economic models

- Applicable for
  - Pharmaceuticals, medical devices, diagnostics, and vaccines
  - Public sector-funded and private sector-funded trials
OUTLINE

1. Background
2. Introduction
3. General Considerations for the Collection of Health-Utility Data for Economic Models
4. Early Planning of Utility Data Collection Within a Product’s Research and Development Program
5. Design of Studies to Collect HSUVs for Economic Models
   • Clinical trials
   • Prospective or cross-sectional observational studies
   • Other study types
6. Data Analysis and Reporting
7. Conclusions

WHAT THE GUIDELINE WILL NOT CONSIDER

• Empirical and theoretical merits of different methods of eliciting utilities (including time-trade off, discrete choice experiments etc.)
• In depth guidance on selection / development of utility measure(s) – we refer to existing guidance (incl. HTA)
• Relative merit of basing utilities on concepts other than HRQL (e.g. well-being)
• Measurement of health-related quality of life (HRQL) in general within clinical studies
• Utility estimates for economic analyses alongside trials
• Mapping
TIMELINE

<table>
<thead>
<tr>
<th>Activity</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposal reviewed by ISPOR Health Science Policy Council</td>
<td>May 2014</td>
</tr>
<tr>
<td>ISPOR Board of Directors approved proposal</td>
<td>June 2014</td>
</tr>
<tr>
<td>Assign sections of the manuscript to the task force members</td>
<td>July 2014</td>
</tr>
<tr>
<td>Draft manuscript sections</td>
<td>September – October 2014</td>
</tr>
<tr>
<td>Joint Forum Amsterdam</td>
<td>November 11, 2014</td>
</tr>
<tr>
<td>Revisions based on ISPOR Amsterdam meeting</td>
<td>November 2014– March 2015</td>
</tr>
<tr>
<td>Manuscript draft sent to ISPOR Primary Review Group</td>
<td>April 2015</td>
</tr>
<tr>
<td>Presentation at ISPOR Annual International Meeting, Philadelphia</td>
<td>May 18, 2015</td>
</tr>
<tr>
<td>Task Force meeting at ISPOR conference</td>
<td>May 19, 2015</td>
</tr>
<tr>
<td>Revised manuscript sent to Review Group</td>
<td>June 2015</td>
</tr>
<tr>
<td>Manuscript revised based on comments</td>
<td>July 2015</td>
</tr>
<tr>
<td>Review of manuscript by ISPOR membership</td>
<td>August 2015</td>
</tr>
<tr>
<td>Revisions to manuscript based on review</td>
<td>September 2015</td>
</tr>
<tr>
<td>Members and chair finalize and sign off on final report</td>
<td>October 2015</td>
</tr>
<tr>
<td>Manuscript submitted to Value in Health</td>
<td>November 2015</td>
</tr>
</tbody>
</table>

GENERAL CONSIDERATIONS

- HSUV estimates must fit the needs of the decision problem
  - Values for model health states or events should be captured
  - Criteria used to categorize patient assessments into health states should match model health-state definitions

- HSUV measure selection should take account of:
  - Suitability to health condition of interest
  - Any needs / preferences of the economic model’s audience

- Study participants should reflect the indication and population considered in the economic model

- Changes in health utility over time should be captured
  - Longitudinal studies – multiple assessments to capture patient progress through health states
  - Cross-sectional studies - ensure that data sample is fully representative of each health state
Valid arguments for collecting utilities in real-world clinical practice versus clinical trials
- E.g. representativeness of model population

Problems with collecting data for rare health states or events
- Are estimates important? (do they influence incremental cost-effectiveness ratio)
- Consider recruiting patients who are at increased risk
- Consider continued follow up after active treatment phase

Mode of administration
- Paper instruments / electronic data capture / mobile apps
- Can affect response rates, task comprehension, response strategies, and representativeness of the sample
- Standardization across patient sample and devices preferred

Establish and define HSUVs required for the model
- Describe HRQL impact of condition
- Assess potential HRQL benefits of intervention
- Develop an early economic model

Establish appropriate health-utility measure
- If there is any doubt, evaluate validity and responsiveness for the health condition of interest based on empirical evidence
- Identify any requirements and preferences of key model audiences (e.g., HTA authorities)

Identify data available in published literature
- Evaluate quality, relevance to the model health states and perspective / audience
- Identify need for new data
EARLY PLANNING OF UTILITY DATA COLLECTION WITHIN A PRODUCT’S RESEARCH AND DEVELOPMENT PROGRAM

- Evaluate planned research and development program for opportunities to collect HSUV data
  - Phase 2 trials: long-term longitudinal data; validation of measure to be used in phase 3 studies; potential for regulatory approval based on phase 2 data
  - Phase 3 trials
  - Prospective or cross-sectional observational studies
  - Early-access or compassionate-use–type programs
  - Phase 4 studies
  - Registries
  - Other post-licensing commitments
- Recognize benefits of collecting all key HSUVs within a single study (or using single methodology)

FORUM

EARLY PLANNING OF UTILITY DATA COLLECTION WITHIN A PRODUCT’S RESEARCH AND DEVELOPMENT PROGRAM

- Prepare an HSUV research plan, including:
  - Definition of model population
  - Description of HRQL impact of condition / potential HRQL benefits of intervention
  - Definitions of model health states / events
  - Summary of validity of utility measures for condition of interest and acceptability to economic model’s audience (if relevant)
  - Summary of HSUV estimates already available
  - Assessment of opportunities to collect HSUVs in planned research and development program; outline plan for data collection
  - Summary of data gaps and plan for additional studies
Clinical trials represent an important opportunity to measure health utility
- Provide efficient access to large patient sample
- High performance and monitoring standards maximize data quality and completeness

A number of issues can affect the value of the HSUV data collected in trials
- Trials designed primarily for regulatory approval
- May present hurdles for optimal collection of utility data

Identify issues and make plans to address them, e.g.:
- Timing of clinical assessments not optimal for utility measurement
- Not feasible to capture data for some health states / events
  - E.g. rare events, events occurring after trial follow-up
  - Make alternative plans to collect these data
- Trial population not fully representative of model population
  - E.g. due to trial exclusion criteria / geographic footprint etc.
  - Evaluate potential for bias, adjust trial selection criteria, collect data for excluded patients, adjust estimates in analyses
- Respondents unable to complete utility assessments
  - E.g. young children, cognitively impaired, severely ill
  - Examine relevant literature; if proxy respondent is best solution, examine potential for bias
Health economists who understand the needs of the economic model should be influential in the design of trials in which health-utility data are collected, and the data analyses.

Development of a utility data collection protocol is recommended (or section of trial protocol).

Design of utility data collection should be justified in terms of the needs of the economic model.

Protocol content

Objectives of health-utility measurement

- Identify and define model health states / events for which it is feasible to estimate health utility in the trial, considering:
  - The number of assessments feasible for each health state
  - Whether HSUVs for acute events are important for the economic model and feasible to estimate in the trial
- Specify whether differences between treatment groups within health states will be investigated
- Specify whether statistical comparisons between treatment groups in overall utility over time also will be performed
### Protocol content cont.

- **Choice of instrument (with rationale) and mode of administration**
- **Choice of respondents (e.g., patient or proxy)**
- **Assessment timing and frequency, and period of follow-up**
  - Optimize to capture data for model health states / events and maximize amount and quality of data
  - Optimal timing may not coincide with clinical assessments
  - Consider recall period of utility instrument
  - Consider acute events and duration of HRQL impact
  - Consider changes in HRQL over time within a single model health state (e.g., "post progression" health states in cancer)

### Design of Studies to Collect HSUVS for Economic Models: Clinical Trials

#### Protocol content cont…

- **Variables to be collected at baseline and alongside each health-utility assessment**
  - To determine health state at the time of assessment
  - To allow adjustment for covariates
- **Methods to address any heterogeneity of patient sample / generalizability of results**
- **Missing data**
  - Identify likely causes, e.g., reasons for planned or unplanned loss of follow-up, types of patients less likely to complete assessments
  - Address as far as possible by adjusting study design; make plans to adjust for missing data in analysis
Observational studies health utility studies

- Prospective and cross-sectional
- Can range in complexity from complex studies performed at clinical sites to very simple online surveys
- Many of issues and recommendations discussed previously apply to these studies and should be evaluated during the study’s design phase

CROSS-SECTIONAL SURVEYS

- Can be set up and run quite rapidly
- Can be conducted nationally or internationally
  - Patient recruitment via clinical sites, patient advocacy groups, social media, and recruitment panels
  - Confirmed diagnoses and detailed clinical, laboratory, or radiographic data will require participation of clinical sites
- Validated web/tablet-based versions of most HRQL measures are available
  - Online surveys may be better for capturing sensitive data
  - Risk of selection bias needs to be considered
- Variables for categorizing participant assessments into health states need to be captured
LONGITUDINAL STUDIES IN CLINICAL SITES

- Observe HRQL over time
  - Change between health states for individual patients
  - Reduces “noise” from individual variation among patients
- Clinical sites can ensure patient inclusion and exclusion criteria are applied and provide detailed clinical data
- More complex and time consuming than online surveys
  - Centers may prioritize other studies, e.g., trials; may affect the number and representativeness of patients recruited
  - Careful study site selection and engagement with medical specialists and advocacy groups may help
  - Recruitment through patient advocacy groups, etc. may be appropriate if detailed or confirmed clinical data are not essential

OTHER OPPORTUNITIES FOR UTILITY ASSESSMENT

- Early-access or compassionate-use–type programs, phase 4 studies, registries, and other post-licensing commitments
- Design issues and recommendations discussed previously also apply to these studies
- Can be an efficient way to capture utility data
- But may be too late in the product development program to provide HSUV estimates for HTA submissions
Valuation of health-state descriptions (vignettes) by general population
- May be an option when other methods are not possible
- Quality of the health-state descriptions is critical
- Recent guidelines recommend:
  - qualitative work with patients
  - independent psychometric validation of vignette descriptions,
  - use of quantitative HRQL data to inform vignette content
- Subject to potential bias that may limit value

Estimation of HSUVs by health care professionals should be avoided
- However, clinical expert opinion can be helpful in evaluating plausibility of alternative available estimates

Data analysis approach should reflect needs of the economic analysis
- Should not be constrained by traditional regulatory approach to analyzing data (e.g., comparison between treatment arms)

Data are constrained to < 1 and are left skewed
- Consider simple linear transformation: \( X = 1 - U \)
- Then use familiar methods for right-skewed data, e.g., generalized linear modeling or generalized estimating equations for longitudinal data, with the possibility of two-part model to handle excess zeros
**DATA ANALYSIS AND REPORTING**

**FORUM**

- Consider explicit modeling of prognostic factors
  - Has potential to increase generalizability of results by adjusting clinical trial data to characteristics of real-world populations

- Transferability in multinational studies
  - Predictable differences in the way patients map to the index score of the health-utility instrument
  - Country or region effects can be handled as a covariate in statistical modeling
  - Use value set / tariff appropriate for the economic model audience
  - Separate analyses may be needed for each country-specific model

**DATA ANALYSIS AND REPORTING**

**FORUM**

- Careful reporting can maximize value of research for future economic evaluations
  - E.g., effect of treatment, independent of health state, for use in future indirect comparisons with current drug

- Report variance and covariance estimates from statistical models as well as point estimates
  - Important for other analysts seeking to apply the results in future models, including appropriate assessment of uncertainty

- Covariance can be used to retain the integrity of the logical ordering of health-utility values under conditions of uncertainty
  - Alternatively, consider specifying a functional form that maintains the logical ordering of health-state utilities
Quality of HSUVs is critical to the decisions being made by HTA and pricing and reimbursement authorities

These decisions affect:

- Patients’ access to new treatments
- Physicians’ ability to use them
- Manufacturers’ return on investment

Health economists with an understanding of the economic model should be influential in the design of any studies in which health-utility data are collected

Methods should be optimized as far as possible to meet the needs of economic models

Careful planning is needed, beginning early in the product development process

- Define the HSUVs that will be needed for the economic model(s)
- Determine which of these may be measured in the planned trial program
- Establish the optimal design for the data collection and analyses
- Plan any appropriate additional health-utility research

Phase 2 trials may present a useful opportunity to evaluate instruments or collect HSUV estimates
CONCLUSION

- The design of health-utility studies should start with a clear statement of the objectives, framed in terms of the needs of the economic model
- The following design aspects should be carefully considered
  - Choice of instrument
  - Choice of respondents and mode of administration
  - Timing and frequency of assessments
  - Data to be collected alongside each assessment
  - Period of follow-up
  - Issues related to sample heterogeneity and generalizability of results

CONCLUSION

- Analyses should be designed to provide HSUVs for model health states / events
  - Making appropriate adjustments to generalize the results to the population of interest in the economic model and preserve valuable information available in the patient-level data
MEASUREMENT OF HEALTH-STATE UTILITY VALUES FOR ECONOMIC MODELS IN CLINICAL STUDIES

FORUM

Sign up as Review Group Member

- Business card to Theresa
- Sign-up sheet
- Website: Task Forces
- Join ISPOR Task Forces
FORUM SLIDES are AVAILABLE

Go to the ISPOR PHL MEETING home page and click on the orange Released Presentations menu

OR

via this link to ISPOR’s Released Presentations webpage:

http://www.ispor.org/Event/ReleasedPresentations/2015Philadelphia