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Pragmatic Advice to Improve Assessment Schedule of Preference-Based Measures of Health to Estimate Utilities in Clinical Trials

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All authors are employees of F Hoffman-La Roche, Ltd. RB, SG, CSS and YMG own shares in the company.

BACKGROUND

- Preference-based measures (PBMs), such as EQ-5D, are collected in clinical trials to estimate utility values needed for deriving Quality-Adjusted Life Years (QALYs) in cost-effectiveness models (CEMs) (Brazier et al 2016).
- Utilities quantify individuals' preference for specific health states (HS), usually ranging from 0 ("dead") to 1 ("perfect health") (Berger et al 2003).
- Accurate and precise utility estimates are essential for rigorous cost-utility analyses, to calculate the incremental cost-effectiveness ratio (ICER) and directly impacting treatment reimbursement decisions.
- Relying solely on literature values for utilities can introduce bias, uncertainty, and inconsistency due to variations in study design, populations and methodologies.

OBJECTIVE and METHODS

Objective

To provide pragmatic guidance on the assessment schedule for PBMs in pivotal clinical trials, ensuring the robust estimation of utilities needed for cost-effectiveness models (CEMs).

Methods

Guidance was developed by:

1. Interviewing internal Roche experts in clinical trial design and utility analysis.
2. Collecting internal examples where suboptimal PBM timing potentially led to increased bias and/or uncertainty in utility estimates (e.g., selection bias from missing post-progression data in metastatic cancer trials; lack of suitable utility values remarked upon by NICE in technology appraisals).
3. Synthesizing information to develop pragmatic recommendations for PBM assessment frequency and timing. The guidance is meant to be applicable across disease areas and indications

Rationale for Robust Data Collection for PBM in RCTs

Collecting PBMs directly in pivotal trials is strongly recommended for several key reasons:

- **Consistency**: Using the same source for utilities and other model parameters (e.g., clinical efficacy) increases CEM consistency.
- **HTA Scrutiny**: Relying on literature values instead of patient-derived data may raise questions during Health Technology Assessment (HTA) deliberation.
- **Local requirements**: data collected using PMBs are converted into country-specific utilities by applying local value sets to meet local requirements for CEMs.
- **Treatment Effect Assessment**: Individual Patient Data (IPD) is needed to assess whether there is a treatment effect on utility values beyond the health state.

References:

1. Brazier, John, and others, Measuring and Valuing Health Benefits for Economic Evaluation, 2 ed (Oxford, 2016; online ed Oxford Academic, 1 Dec. 2016)
2. Berger, M.L., Bingefors, K., Hedblom, E.C., Pashos, C.L., & Torrance, G.W. (2003). Health Care Cost, Quality, and Outcomes. ISPOR Book of Terms.
3. Drummond, M. F., et al. (2015). Methods for the Economic Evaluation of Health Care Programmes. Oxford University Press.

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RESULTS

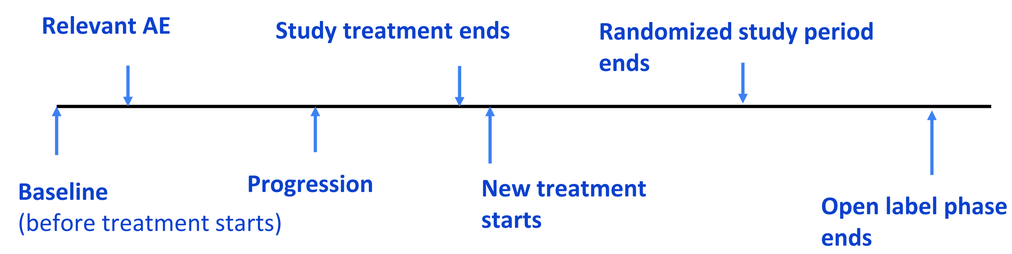
Pragmatic Recommendations for PBM Assessment Schedule

The recommendations focus on both timing (key events) and frequency. Appropriate timing to ensure coverage of all disease stages and relevant events is more important than the total number of assessments per patient.

1. Always Administer PBMs at Key Clinical Trial Event Points

Assessments should always occur at relevant study milestones:

Figure 1 Example of PBM assessment schedule timing in oncology

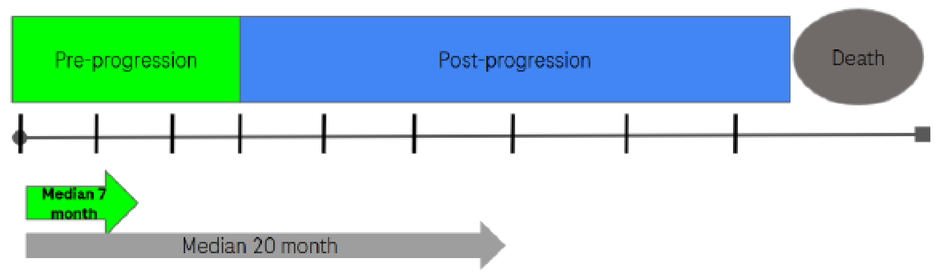


2. Ensure Sufficient Coverage of Each Disease Stage (Health State)

The assessment schedule should cover the major milestones (health states) that impact Health-Related Quality of Life (HRQoL), as defined in the CEM.

- Ideally, for each patient there should be ≥3 health PBM assessments within each disease stage, to characterize inter- and intra-patient variability, fit statistical models (e.g. linear mixed effects models), and compensate for dropouts.
- Based on estimates of time to reach each health state (e.g. progression, death), the schedule should be chosen to cover all disease stages.

Figure 2 Example of PBM assessment schedule frequency in oncology



LIMITATIONS

- Guidance has not been peer-reviewed outside Roche
- Generalizability: mostly based on internal examples in oncology setting
- Implementation not tested

CONCLUSIONS

Properly scheduled PBM assessments in pivotal clinical trials are crucial for mitigating the risks associated with relying on inconsistent or outdated utility values from the literature.

- We emphasize the need for rigorous PBM data collection throughout the clinical trial follow-up period (including open label extensions) to characterize all potential disease stages, key study events and account for dropouts.

- This approach enhances the credibility of cost-utility analyses and facilitates smoother HTA deliberations and informed reimbursement decisions.