



Oldeland J, Beuermann J, Köhnemann F

(Almost) One Million Ways to Define Change – Analyzing PROs in EU HTA Context

Background

Patient-reported outcomes (PROs) play a crucial role in assessing patient improvement or deterioration of symptoms, functions, or scores, yet their evaluation in health technology assessments (HTAs) remain highly variable. Given the multitude of analytical possibilities, a key question arises: what is the workload, i.e. computation and staff time, associated with analyzing multiple PRO endpoints considering an increasing complexity in subsequent analyses and thresholds in the EU HTA framework?

Methodology

We analyzed adagrasib (Krazati®) from “PICO exercise 3” [1] as monotherapy for adult patients with advanced NSCLC with KRAS G12C mutation and disease progression after at least one prior systemic therapy. We documented the requested PRO endpoints for each PICO and anticipated the required analyses considering questionnaire subscales, endpoint operationalization (Responder analysis, Time-to-Event analysis, Change from baseline), analysis timepoints, Minimal Important Differences (MIDs), multiple imputations, and sub-group analyses. PICO-Scoping resulted in 13 PICOs, each with five questionnaires (EQ-5D, EORTC QLQ-C30/LC-13, SF-36 PCS/MCS) composed of a different number of subscales. A set of 30 multiple imputations were assumed necessary for each analysis. We compared two scenarios with only total scores and one analysis time point (“standard”) versus all subscales and multiple timepoints (“expanded”) (Fig 1.). We assumed a calculation time of 2 seconds per analysis to be realistic. Workload was then calculated as number of analyses (N_i) x calculation time in hours and days.

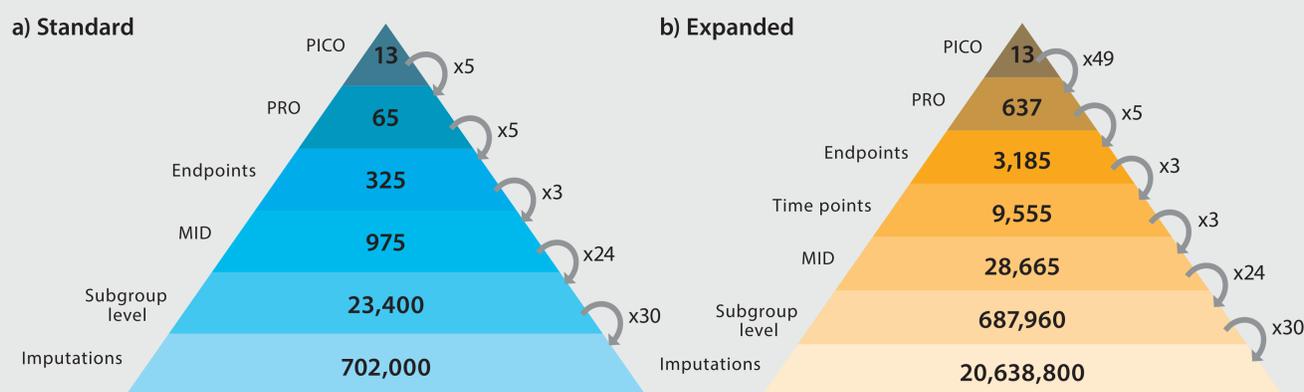


Fig.1. Display of required number of analyses for increased level of complexity in “standard” (a) and “expanded” (b) scenario.

Number of...	Standard	Expanded
Populations in PICO-Scoping	13	13
PRO instruments	5	49
Operationalizations (Number of endpoints)	5	5
Analysis time points	1	3
MIDs	3	3
Subgroup categories	12	12
N_1 (Analysis)	23,400	687,960
Time in hours (days)	13 (0.5)	382 (16)
Imputations	30	30
N_2 (Analysis)	702,000	20,638,800
Time in hours (days)	390 (16)	11,466 (478)

Tab.1. Results of workload assessment (analysis count, time in hours and days) for basic and expanded scenario. Number of time points, MIDs and subgroups were assumed while the number of PRO subscales were derived from the respective questionnaires.

Results

Analysis of “standard” versus “expanded” scenarios (Tab.1) reveals a 30-fold increase in processing time (13 vs. 382 hours). This dramatic difference results from increased complexity across multiple dimensions: First, if subscales are considered for each PRO, the number of analyses is heavily inflated requiring more than half a million analyses (N_1 , Tab. 1). The computational burden increases significantly when imputation procedures are required (N_2 , Tab.1), contrasting 478 theoretical days in the “expanded” scenario versus 16 days in the “standard” scenario. These findings highlight crucial resource implications which statistical analysis for EU HTA submission can involve, suggesting careful evaluation of the value-added by subscales and imputation analyses.

Conclusion

We found that a standard PRO analysis using total scales is feasible with imputations. However, multiple subscales can lead to an unfeasible workload, with imputations being a particular critical bottleneck. Interpretation of results is also much more complex to impossible in case of the “expanded” scenario. We recommend calculating analysis time requirements during the planning phase. Workload can be reduced by limiting analyses to relevant subscales, including subgroups only for total scales, reducing analysis time points or MIDs, and avoiding imputations in subgroup analyses where possible. Strategic planning is crucial for efficient patient-reported outcome research and successful submission for EU HTA.

References

[1] European Commission (2025). Background document, PICO Exercises, URL: https://health.ec.europa.eu/publications/pico-exercises_en (12.02.2025)