RECOMMENDED APPROACHES FOR ANALYZING CLINICAL OUTCOMES ASSESSMENT DATA FROM ONCOLOGY TRIALS FOR DIFFERENT STAKEHOLDERS

Donald E. Stull[1], Pip Griffiths[2], Matthew Reaney[3], Gisoo Barnes[4]

[1]IQVIA, New York, NY, USA; [2]IQVIA, Courbevoie, France; [3]IQVIA, Reading, UK; [4]BeiGene, Ltd., Jenkintown, PA, USA

BACKGROUND

- Clinical outcome assessment (COA) data can be considered direct evidence of treatment effectiveness in oncology when it is collected using a well-defined, reliable, and valid measure and when the data are interpretable in the context of clinical use
  - The US Food and Drug Administration (FDA), European Medicines Agency (EMA), and some health technology assessment (HTA) agencies request the collection of patient-reported outcome (PRO) data to supplement core clinical outcomes
- Scientific guidance is available to help in the selection and implementation of well-defined, reliable, and valid PRO measures. However, no harmonized approach is available to guide analyses to support these endpoints with consideration of confounding intercurrent events, missing data, or the evidence needed by different stakeholders

OBJECTIVE

- To provide an overview of the required evidence and recommended content of statistical analyses of PRO data in oncology clinical trials for:
  - Regulatory evaluation and approval
  - Evaluations of comparative effectiveness by HTA agencies
  - Medical journal editors and reviewers

METHODS

- A literature review was undertaken from September 2020 to July 2021 to identify recommended analytic strategies for PROs
- The review included guidance documents and response letters from FDA, EMA, and HTA agencies, top-tier peer-reviewed oncology journal guidelines, and experts' opinions, as well as a targeted literature review
- Strategies were compared between stakeholders to provide an easy reference guide for the comprehensive analysis of COA data in oncology clinical trials
- A summary of the evidence and analytic methods by each stakeholder was provided

RESULTS

- Three important considerations in the selection, application, and analysis of COAs were identified in the guidance documents

Consideration #1: "Fit-for-Purpose" COA Instruments

- FDA, EMA, and some payers emphasize that COAs must be fit-for-purpose to ensure that patient experience data is valid and reliable
- COA instruments may not be considered as generating evidence that can be used to understand treatment effects if they are not fit-for-purpose, even if all outcome analytic recommendations are followed
- Qualitative data must be generated to support the content validity of the COA instrument, that is, that the instrument is measuring something important in a way that is easy to understand and on a scale that is easy to complete:
  - Sign, symptom, and impact concepts defining disease severity and treatment success systematically identified and well understood
  - The relationship between disease- and treatment-related signs, symptom, and impact concepts are outlined in a conceptual model
  - COA instruments are selected/developed to measure concepts of interest from the conceptual model
  - Evidence is generated to ensure that the COA instruments are well understood and easy to complete by the target population in the specific context of the forthcoming program of research
- Measurement properties of each COA must be established using psychometric analysis (**Figure 1**)

Figure 1. Psychometric Evidence Needed to Support the COA as Fit-for-Purpose Within the Context of Use

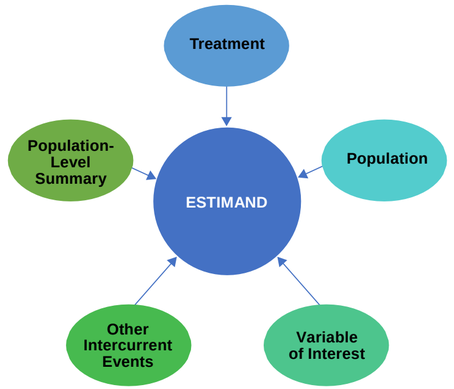
1	Item characteristics	An item is likely to be more sensitive when it shows no floor or ceiling effects and has good spread of values in the target population • Floor and ceiling • Summary statistics
2	Factor structure	Cohesiveness of instruments • What are the underlying constructs? • Do the items and constructs converge in an expected or novel way? • Can be exploratory or confirmatory
3	Reliability	Instrument consistently measures concepts; eg, same results are obtained over time, if the patient's condition does not change • Internal consistency • Test-retest reliability
4	Construct validity	Association with other instruments assessing similar concepts • Convergent and discriminant validity • Known group validity
5	Ability to detect change	Instrument changes when patients are known to be changing (and thus can potentially detect treatment changes) • Sensitivity to change
6	Meaningful change	The level of change deemed to be meaningful (beyond statistical significance) • Anchor-based approach • Distribution-based approach

Abbreviation: COA, clinical outcome assessment.

Consideration #2: The Estimand Framework

- COA instrument application and analysis should be considered in the context of the estimand framework
- An estimand is the target of estimation to address the scientific question of interest posed by the trial objective and is a way of translating the trial objective into a precise definition of the treatment effect that is to be estimated
- As shown in **Figure 2**, an estimand has five attributes[1,2]

Figure 2. Five Attributes of an Estimand for Study Design, Protocols, Endpoints, and Analysis[3]



Documenting Estimands for Regulators

- Trial protocols should define and specify a primary estimand that corresponds to the primary trial objective; in oncology trials, these will likely be survival or time-to-event outcomes, but may include other COAs
- Trial protocols and analysis plans should prespecify the main estimator that is aligned with the primary estimand and leads to the primary analysis, together with suitable sensitivity analyses to explore the robustness under deviations from its assumptions used in the statistical model of the main estimator
- Estimands for secondary trial objectives (ie, related to secondary variables) that are likely to support regulatory decisions should also be defined and specified explicitly, each with a corresponding main estimator and appropriate sensitivity analyses
  - Additional exploratory trial objectives may be considered for exploratory purposes, leading to additional estimands
  - Each estimand leads to a specific testable hypothesis and each may have several sensitivity analyses for missing data
- Intercurrent events (ICE) (ie, events occurring after treatment initiation that affect either the interpretation or the existence of the measurements) have the potential to impact on interpretability of COA data. They must be anticipated in the analysis plan

Consideration #3: Study Analysis Plans Should Consider COA Data as Central to Determining Efficacy and/or Safety of Treatments

- The COA efficacy analysis under the hypotheses derived using the estimand framework could take place over several statistical analysis plans (SAPs, **Tables 1-2**):
- **(A) Clinical SAP** includes all analyses to be performed to evaluate efficacy and safety endpoints, including COA endpoints if they are listed as part of the statistical hierarchy
  - COA endpoint analysis may be included if in the alpha-controlled endpoint hierarchy
  - Typically, only the primary estimand for the COA endpoint and the associated sensitivity analyses are included in the clinical SAP, with supplementary analyses (or secondary estimands) included in a standalone SAP, the COA/PRO
  - Alternatively, all COA analyses could be in the COA/PRO SAP, referenced in the Clinical SAP, and reported in the clinical study report (CSR)
- **(B) COA/PRO SAP:** An optional COA specific SAP can relieve the burden on the clinical SAP by either:
  - Including *all* COA analyses, or
  - Including non-alpha-controlled COA endpoints not in the clinical SAP
  - Can also include additional secondary estimands, sensitivity analyses of COA endpoints, key subgroup analyses, and meaningful change derivation
  - Results should still be included in the CSR (even if they form a separate report)
- **(C) Exploratory SAP** includes *post-hoc* analyses, subgroup analyses, or analyses not related to study endpoints as defined in the clinical study protocol, but also still making use of the clinical trial data
- **(D) Psychometric SAP** specifies the COA measurement properties analysis
- **(E) Payer SAP** can include analyses specific to individual payer requests (e.g., IQWiG) or more general HTA-related analyses

IMPORTANT NOTES

- COA-based endpoints will not be used to inform regulator and payer decision-making without pre-specification, alpha control, and appropriate positioning (ie, endpoint hierarchy)
- Clinical SAP and COA/PRO SAP must be locked before the database in order to clearly claim to have prespecified the analyses of interest
  - The exploratory and payer SAPs can be iterative and finalized *post hoc*
  - The Psychometric SAP can be completed (and analyses conducted) in advance of database lock on a blinded data snapshot
- The FDA will request that COA results are supplemented by descriptive statistics for the COAs at the item and scale/domain level
  - This can be included in the clinical SAP or COA/PRO SAP or provided as part of an information request
- FDA and EMA will not accept last observation carried forward (LOCF) as the only method of addressing missing data. Sensitivity analyses using estimators such as pattern mixture models and tipping point analyses should be considered

Core Analysis by Stakeholder Requirements

- An easy reference guide has been developed that includes evidence required by regulators, payers, and others, such as journal editors, clinicians, or patients. This can help structure analysis plans and analytical methods for COAs to help meet the needs of multiple stakeholders
- There is often overlap in the recommended best statistical practices and evidence requirements for regulatory and HTA bodies/payers; there are some notable differences
  - The evidence for publications and guidance versus HTA submissions is often quite different, in content and extent
- **Tables 1-2** include "core analyses" that should always be performed to provide a core understanding of the measurement and distributional properties of each COA and the data resulting from their use
  - Any additional analyses that are routinely required or requested by different stakeholders are also noted

Table 1. Recommended COA Descriptive Analyses by Stakeholder Group

Specific Analysis	FDA	EMA[a]	HTA/ Payers	Publications/ Other Dissemination
Patient disposition & reasons for missingness	A/B	A/B	A/B/C/E	C
Completion rate	A/B	A/B	A/B/C/E	-
Item-level descriptive statistics by treatment arm	A/B[b]	-	B/C	C
Total score and domain-level descriptive PRO statistics	A/B	A/B	A/B/C	C

A=Clinical SAP; B=COA/PRO SAP; C=Exploratory SAP; D=Psychometric SAP (for consistency with text); E=Payer SAP
[a] Most analyses for EMA can be covered by SAP inclusions for FDA. However, if labeling goals for EMA are different than goals for the FDA, both sets of analyses may need to be included in the clinical SAP (A) or may be appropriate to only include in the prespecified PRO SAP (B).
[b] The item-level data could be provided as part of an information request.
Abbreviations: COA, clinical outcome assessment; CSR, clinical study report; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HTA, health technology assessment; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care); PRO, patient-reported outcome; SAP, statistical analysis plan.

Table 2. Recommended COA Efficacy Analyses by Stakeholder Group

Specific Analysis	FDA	EMA[a]	HTA/ Payers	Publications/ Other Dissemination
Group-level treatment analysis: Between-groups mean change from baseline[e]	A/B[c]	A/B[c]	A/B/E	C
Group-level treatment analysis: Standardized mean difference[g]	B	B	B/E	-
Group-level treatment analysis: Sensitivity for evaluating assumptions of missing data	A[c]	A[c]	A	E
Group-level treatment analysis: Additional missing data sensitivity analysis (worst case)	C	C	C/E	-
Individual-level treatment response: Time-to-event analyses (e.g., Kaplan-Meier analysis; Cox proportional hazards model)[e]	A/B[f]	A	-	-
Individual-level treatment response: Responder analysis	A/B[f]	A/B[f]	A/B/E	E
Overall treatment response: CDF curves by group	A/B	A/B	A/B	E

A=Clinical SAP; B=COA/PRO SAP; C=Exploratory SAP; D=Psychometric SAP (for consistency with text); E=Payer SAP
[a] Most analyses for EMA can be covered by SAP inclusions for FDA. However, if labeling goals for EMA are different than goals for the FDA, both sets of analyses may need to be included in the clinical SAP (A) or may be appropriate to only include in the prespecified PRO SAP (B).
[c] If there is no Psychometric analysis plan, meaningful change thresholds can be derived in the COA/PRO SAP (B).
[e] This can be in A if group-level assessment is your alpha-controlled endpoint otherwise can be in B.
[g] Hedges g should be calculated as this is simple to output, easy to interpret, and will be required by Germany. Calculating this statistic as part of the general analyses will save time in the long run.
[f] The time to event analyses for PRO work uses an individual-level responder definition to define when patients reach the required improvement or deterioration
[f] If your alpha-controlled endpoint is individual-level (e.g., responder analysis or time to event), then the individual-level analysis could appear in the clinical SAP (A) and the group-level analyses will be supportive in the prespecified PRO SAP (B).
Abbreviations: CDF, cumulative distribution function; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HTA, health technology assessment; PRO, patient-reported outcome; SAP, statistical analysis plan.

Table 2 (cont.) Recommended COA Efficacy Analyses by Stakeholder Group

Specific Analysis	FDA	EMA[a]	HTA/ Payers	Publications/ Other Dissemination
Additional secondary estimands or supplementary estimands	B	B	B/E	-
Sensitivity analysis for evaluating the effects of missing data	B/C	B/C	B/C/E	B/C

A=Clinical SAP; B=COA/PRO SAP; C=Exploratory SAP; D=Psychometric SAP (for consistency with text); E=Payer SAP
[a] Most analyses for EMA can be covered by SAP inclusions for FDA. However, if labeling goals for EMA are different than goals for the FDA, both sets of analyses may need to be included in the clinical SAP (A) or may be appropriate to only include in the prespecified PRO SAP (B).
Abbreviations: COA, clinical outcome assessment; CSR, clinical study report; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HTA, health technology assessment; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care); PRO, patient-reported outcome; SAP, statistical analysis plan.

CONCLUSIONS

- This presentation provides an easy reference guide and a basic framework for structuring analysis plans (bearing in mind the estimand framework), ensuring all key analytic methods are included, and a basic checklist to determine what key information is needed for main stakeholders and decision makers
- By specifying different analytic approaches for various stakeholders, a strong reference guide can supplement current recommendations, such as those from the Setting International Standards of Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials (SISAQOL) Consortium[6,7]

REFERENCES

1. US Food & Drug Administration. E9(R1) statistical principles for clinical trials: addendum: estimands and sensitivity analysis in clinical trials: guidance for industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical. Accessed September 11, 2021.
2. Lawrance R, Degtyarev E, Griffiths P, et al. What is an estimand & how does it relate to quantifying the effect of treatment on patient-reported quality of life outcomes in clinical trials? *J Patient Rep Outcomes*. 2020;4(1):68.
3. European Medicines Agency. E9(R1) Step 5 Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-sensitivity-analysis-clinical-trials-guideline-statistical-principles_en.pdf. Accessed October 10, 2021.
4. National Research Council; Division of Behavioral and Social Sciences and Education; Committee on National Statistics; Panel on Handling Missing Data in Clinical Trials. *The Prevention and Treatment of Missing Data in Clinical Trials*. Washington, DC: The National Academies Press; 2010.
5. European Medicines Agency. 2010. Guideline on Missing Data in Confirmatory Clinical Trials. EMA/CPMP/EWP/1776/99 Rev. 1.
6. Coens C, Pe M, Dueck AC, et al. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomized controlled trials: recommendations of the SISAQOL Consortium. *Lancet Oncol*. 2020;21(2)e83-e96.
7. Bottomley A, Pe M, Sloan J, et al. Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards. *Lancet Oncol*. 2016;17(11):e510-e514.

CORRESPONDENCE

Email: gisoo.barnes@beigene.com

DISCLOSURES

GB: Employment, Stock, or Other Ownership at BeiGene.
DES, PG, and **MR** are salaried employees of IQVIA. They receive no payment or honoraria directly from BeiGene for services rendered.

ACKNOWLEDGMENTS

The authors wish to thank Jen Cline of IQVIA and Jason Allaire, PhD, of Generativity for assistance with the development of this poster.