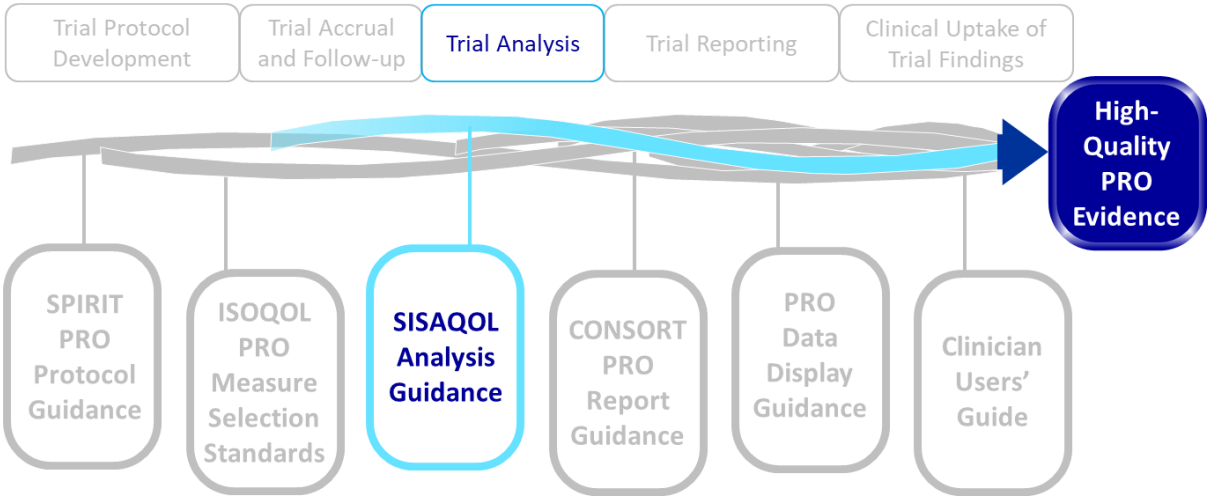
Chapter 4. Analyzing PRO Data



Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium

The European Organization for the Research and Treatment of Cancer (EORTC) formed the SISAQOL Consortium to set international standards in analyzing patient-reported outcomes and quality of life data from cancer clinical trials. SISAQOL provides a taxonomy of research objectives, outlines appropriate statistical methods for these objectives, and advises on handling missing data. Although SISAQOL focused on cancer clinical trials, many issues discussed here may also be applied to other health conditions, which warrants further scrutiny.

This chapter summarizes the preliminary SISAQOL recommendations; work is continuing via the SISAQOL-IMI initiative.

View SISAQOL Standards article

View the Checklist for the SISAQOL Analysis Guidance for Clinical Trials

References

Acknowledgements

Why is This Resource Needed?

To ensure a consistent and methodologically appropriate PRO data analysis

Recommends statistical approaches for analyzing PRO data

PRO data have unique properties compared to other clinical trial data.

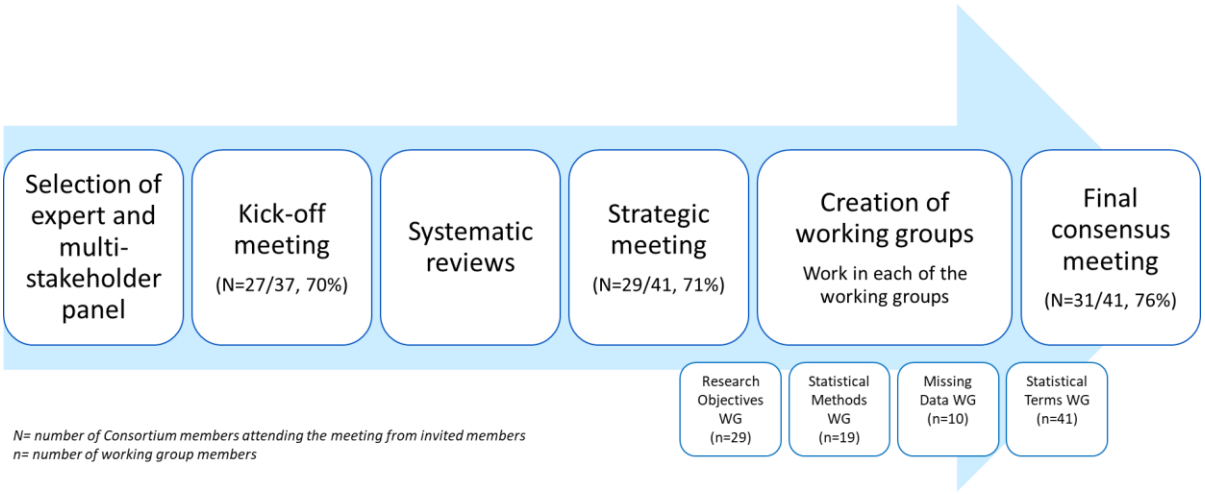
- Multidimensional – composed of different domains yielding multiple outcomes
- Longitudinal – data are collected repeatedly over time
- Missing data – occurs more frequently and have stronger clinical implications due to voluntary patient participation

Major hurdles in applying standardized statistical methods are:

- Unclear PRO objectives
- Inconsistent terminology

Methods for Resource Development

The SISAQOL Consortium was established from a group of international stake-holders experienced with PROs in cancer clinical trials to develop international consensus recommendations on the analysis of PRO data. The initial SISAQOL recommendations are based on discussions with stakeholder groups and (systematic) literature reviews of PRO analysis in cancer clinical trials. Four working groups were assembled: (1) research objectives, (2) statistical methods, (3) standardization of statistical terms, and (4) management of missing data. Final outputs from each working group were used as proposed statements for the SISAQOL recommendations. A consensus meeting was held to ratify the proposed recommendation statements, which informed the final SISAQOL recommendations.



SISAQOL Recommendations

Overview

The recommendations made by SISAQOL fall into three main categories: Taxonomy of research objectives, statistical methods, and missing data. It is important to note that the SISAQOL work is currently ongoing with SISAQOL-IMI and these recommendations will be updated in the future. The recommendations below are based on the initial SISAQOL work published in Lancet Oncology by Coens, Pe et al. (2020).

Taxonomy of Research Objectives

The first of these are recommendations regarding the **research objectives**. When developing a PRO objective, the PRO domain(s) and time frame of interest should be pre-specified. Additionally, four key attributes need to be considered when developing a PRO objective so that it can be aligned with an appropriate statistical method:

- Broad PRO research objectives: What is the overall goal of including PROs in the RCT? Is it to demonstrate *treatment efficacy/clinical benefit* (*confirmatory*)? Or is the goal to *describe patient perspective*, without drawing strong conclusions about treatment efficacy/clinical benefit (*exploratory/ descriptive*)?
- Between-arm PRO objective: For a treatment efficacy/clinical benefit (confirmatory) objective, is the goal to demonstrate that the treatment arm is *superior* to the reference arm? Or is the goal to demonstrate that the treatment arm is *equivalent* or *non-inferior* to the reference arm? Note that a non-significant superiority result should not be interpreted as evidence of equivalence or non-inferiority.
- Within-treatment group assumption: What is the assumption regarding how patients will report their experience in this trial? Will patients *improve, worsen, or remain stable* relative to their baseline (e.g., before randomization)? Or are there no assumptions (i.e., overall effect)?

- Within-patient/within-treatment PRO objective: What kind of PRO endpoint will be meaningful for this trial? Is it a *time to event*, *magnitude of change* at a specific time point, *responder* at a specific time point, or other?

For more detail, please refer to the Checklist for the SISAQOL Analysis Guidance for Clinical Trials.

Statistical Methods

The second category of SISAQOL recommendations relates to aligning the **appropriate statistical methods** with the research objective. Since there is no single analysis method that can address all clinical trial design and analytical concerns, set criteria to evaluate what *appropriate* statistical methods for a given PRO objective are needed.

Two essential statistical properties are:

- The ability to perform a comparative test (statistical significance)
- The ability to produce interpretable treatment effect estimates (clinical relevance)

Highly desirable criteria include:

- The ability to adjust for covariates, including baseline PRO score
- Handling missing data with the least restrictions
- Handling clustered data (repeated assessments)

These criteria informed the selection of specific statistical methods for each PRO objective. It should be noted that these recommendations are under further development as part of the SISAQOL-IMI initiative.

For more detail, please refer to the Checklist for the SISAQOL Analysis Guidance for Clinical Trials.

Missing Data

Finally, recommendations are provided for dealing with **missing PRO data.** To evaluate the extent of missing data, the PRO analysis population and missing data rates should be reported in a standardized way. Additionally, managing missing data, including collecting reasons for missing data, is critical to minimize the potential bias of the trial findings.

For more detail, please refer to the Checklist for the SISAQOL Analysis Guidance for Clinical Trials.

Implications of Using the SISAQOL Guidance

- Improved PRO analysis in clinical trials will enable robust evidence to inform patient choice, aid clinical decision making, and inform policy
- Clear PRO objectives should be specified at the study design phase
    - Consider design in relation to SPIRIT-PRO Initiative
- More standardized PRO analysis will lead to easier and better cross-trial comparison of PRO results, improving the value of such outcomes
    - Standardization recommendations still ongoing as part of SISAQOL-IMI
- Foster better collaboration and understanding between clinicians, patients, and methodologists on statistical analysis and interpretation
- Better PRO analysis will facilitate high-quality reporting, including clear and comprehensible description of the methods used
    - Consider reporting in relation to CONSORT-PRO

Checklist for the SISAQOL Analysis Guidance for Clinical Trials

Consideration	Recommended content	Notes/ comments
Part 1: General Considerations		

For each PRO scale or domain to be analyzed, specify *a priori* whether the research objectives are:	- **Confirmatory** *(see Part 2a below)*
	  ○ The broad goal is typically to demonstrate treatment efficacy or clinical benefit by providing formal comparative conclusions between treatment groups
	  ○ An *a priori* hypothesis is needed
	  ○ Statistical testing is required, so correction for multiple testing is needed
	  ○ Conclusions regarding comparisons between treatment arms are possible
	
	- **Exploratory/descriptive** *(see Part 2b below)*
	  ○ The broad goal is typically to describe the patient perspective or to explore the PRO data and use its findings to inform future studies. These outcomes cannot be used to draw comparative conclusions or used as support for treatment efficacy or clinical benefit
	  ○ No *a priori* hypothesis needed
	  ○ No statistical comparisons between treatment arms
	  ○ Multiple testing is not an issue
	
	- Regardless of the research objective, **missing data** needs to be addressed (*see Part 3 below)*
	
	- For all statistical models, **assumptions** should be checked and must hold *(see Coens et al, 2020)*	

If applicable, specify the within-patient/within-treatment assumption and relevant endpoint for each PRO domain or item of interest	- When within-group assumption is **improvement/worsening***:*
	  ○ Time to improvement/worsening
	  ○ Magnitude of improvement/worsening at time *t*
	  ○ Proportion of responders with improvement/worsening at time *t*
	- When within-group assumption is **time to (end of) maintenance:**
	  ○ Time to (end of) maintenance
	  ○ Proportion of responders with maintenance at time *t*
	- When within-group assumption is **overall effect**
	  ○ Overall PRO score over time
	  ○ Response patterns/profiles	

Consideration	Recommended content	Notes/ comments
Clearly differentiate the ITT population, the PRO study population, and the PRO analysis population	- **Intent-to-treat** (ITT) **population:** all patients randomized to the allocated treatment - **PRO study population:** all patients who consented and were eligible to participate in the PRO data collection (ideally but not necessarily the same as the ITT population) - **PRO analysis population:** patients included in the primary PRO analysis; should be as close as possible to the PRO study population; exists only in relation to a defined PRO analysis	
Part 2a: CONFIRMATORY Research Objectives		
Specify one of the following between-arm objectives for each PRO domain or item of interest	- **Superiority** of the experimental arm relative to the control arm - **Equivalence** of the trial arms - **Non-inferiority** of the trial arms	
Recommended statistical models	For **time-to-event** objectives: improvement, (end of) stable state, or worsening - Cox proportional hazards models are recommended For **magnitude-of-event** at time *t* objectives: improvement or worsening - If design is baseline + more than 1 follow-up: linear mixed models (time as discrete) are recommended - If design is baseline + 1 follow-up only: linear regression is recommended Note: Caution is needed because many statistical programs (e.g., SAS) use complete case analysis for linear regression and inferences are valid only when missing data are missing completely at random For **proportion of responders** at time *t* - The SISAQOL recommendations on this point are not yet finalized. This work continues in SISAQOL-IMI For **overall PRO score over time** The SISAQOL recommendations on this point are not yet finalized. This work continues in SISAQOL-IMI	

Consideration	Recommended content	Notes/ comments
Part 2b: DESCRIPTIVE/EXPLORATORY Research Objectives		
For **time-to-event** objectives: improvement, (end of) stable state, or worsening	Cox proportional hazards models are recommended Options for descriptive objectives are: - Median time to improvement / (end of) stable state / worsening - Probability of improvement / (end of) stable state / worsening at a specific time point - Hazards ratio (with CI)	
For **magnitude-of-event** at time *t* objectives: improvement or worsening	- If design is baseline + more than 1 follow-up: linear mixed models (time as discrete) are recommended - If design is baseline + 1 follow-up only: linear regression is recommended Note: Caution is needed because many statistical programs (e.g., SAS) use complete case analysis for linear regression and inferences are valid only when missing data are missing completely at random Additional options for descriptive objectives are: - Mean magnitude at baseline and time *t* (with CI): improvement / (end of) stable state / worsening - Mean magnitude of improvement / (end of) stable state / worsening at time *t* (with CI)	
For **response patterns/ profiles over time objectives**	For descriptive/exploratory objectives *only*: A linear mixed model (omnibus test; time as discrete variable; time*group interaction) is recommended Options for descriptive objectives are: - Mean magnitude at baseline and at every time point within a time frame (with CI) - Mean change at every time point within a time frame (with CI) - Mean profile over time (with CI)	
Part 3: Missing Data Considerations		
General considerations and definition of missing data	Statistical reports from clinical trials should specify the proportion of missing data, the reasons for missing data, and the analytic approaches used to address missing data Note: Missing data that are considered meaningful for analysis (would contribute to the PRO findings) can affect the interpretability of PRO findings (e.g., by reducing the sample size [non-informative missing data], distorting the treatment estimate [informative missing data], or both).	

Consideration	Recommended content	Notes/ comments
Calculate the completion rate (variable denominator rate)	**PRO completion rate** = the number of patients *on PRO assessment* submitting a valid PRO assessment at the designated time point as a proportion of the number of patients *on PRO assessment* at the designated time point - Absolute numbers for numerator and denominator should also be reported at every time point - On PRO assessment: patients still expected to provide PRO assessments at that time point - After death, patients are considered off PRO assessment and no longer included in the denominator	
Calculate the available data rate (fixed denominator rate)	**Available PRO data rate** = the number of patients *on PRO assessment* submitting a valid PRO assessment at the designated time point as a proportion of the number of patients *in the PRO study population* - Absolute numbers for numerator and denominator should also be reported at every time point	
Record the reasons for missing data	To assess the impact of missing data on PRO findings, a case report form to collect reasons for missing data in a standardized way should be included in every trial	
Handle item-level missing data according to the scoring algorithm	- Item-level missing data within a scale should be handled according to the instrument scoring algorithm (when available) - If changes in official scoring algorithms for the PRO measure occur, the resulting updated guidelines from the developers should be followed	

State methods for handling missing PRO data in statistical analysis	- The approach for handling missing data at the item- and scale- levels should be specified *a priori*
	- Depending on the reason and amount of missing data, the approach to handling missing data may include:
	  ○ Sensitivity analyses (specified *a priori*) to test the robustness of the conclusions using a different set of assumptions regarding missing data
	  ▪ At least two different approaches to handle missing data are recommended to assess the impact of missing data across various assumptions
	  ○ Methods that use all available data are recommended as they make weaker assumptions about missing data compared to complete case analysis
	  ○ Explicit simple imputation methods are not recommended unless justified within the context of the clinical trial
	  ○ Approaches that ignore missing data and only include patients with complete data in analysis are not recommended (e.g., complete case analysis)	

Abbreviations: confidence interval (CI), health-related quality of life (HRQOL), patient-reported outcomes (PRO)

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Bottomley A, Pe M, et al, Coens C; Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) consortium. Analysing data from patient-reported outcome and quality of life endpoints for cancer clinical trials: a start in setting international standards. Lancet Oncol. 2016 Nov;17(11):e510-e514. doi: 10.1016/S1470-2045(16)30510-1. Epub 2016 Oct 18. PMID: 27769798

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