SISAQOL Analysis Guidance for Randomized Controlled 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 if applicable
	  ○ 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)*	

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	

Adapted from: Coens C, Pe M, Dueck AC, et al. International Standards for the Analysis of Quality of Life and Patient Reported Outcomes Endpoints in Cancer Randomised Controlled Trials; Recommendations based on critical reviews of the literature and international multi-expert, multi-stakeholder collaborative process. *The Lancet Oncology.* 2020; 21(2):E83-E96. doi:10.1016/S1470-2045(19)30790-9; *Recommended:* EORTC SISAQOL Interactive webtool

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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	

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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 All recommendations refer to PRO data missing as a full assessment, unless otherwise stated (e.g., item-level 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).	

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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 timepoint as a proportion of the number of patients *on PRO assessment* at the designated timepoint - Absolute numbers for numerator and denominator should also be reported at every timepoint - On PRO assessment: patients still expected to provide PRO assessments at that timepoint - 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 timepoint 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 timepoint	
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)