Improving standards of health-related quality of life and patient reported outcomes analysis: a SISAQOL initiative

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Funded by the Patient-Centered Outcomes Research Institute and Genentech

PROTEUS
Patient-Reported Outcomes Tools: Engaging Users and Stakeholders

The PROTEUS Consortium

Patient-Reported Outcome Tools: Engaging Users & Stakeholders

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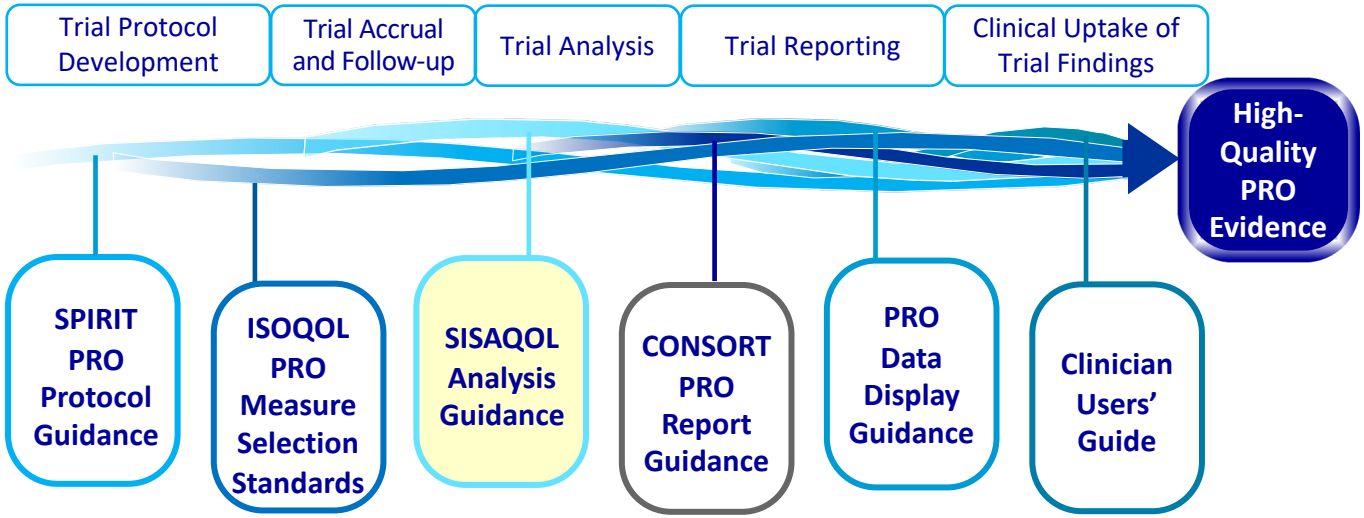
Overview of Presentations

Introduction to PROs and PROTEUS

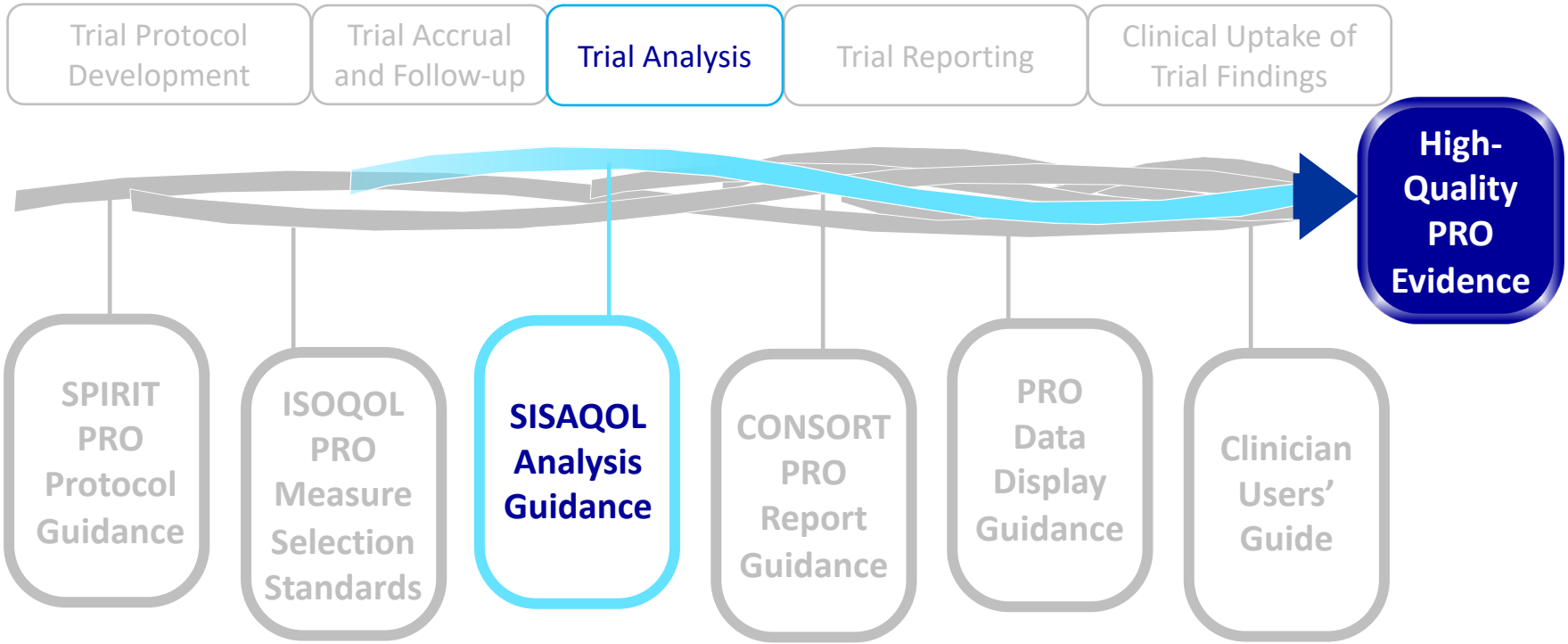
Introduction to the PROTEUS Tools



Overview of Tool Recommendations

How to Apply the Tools

Analyzing PRO Data Properly



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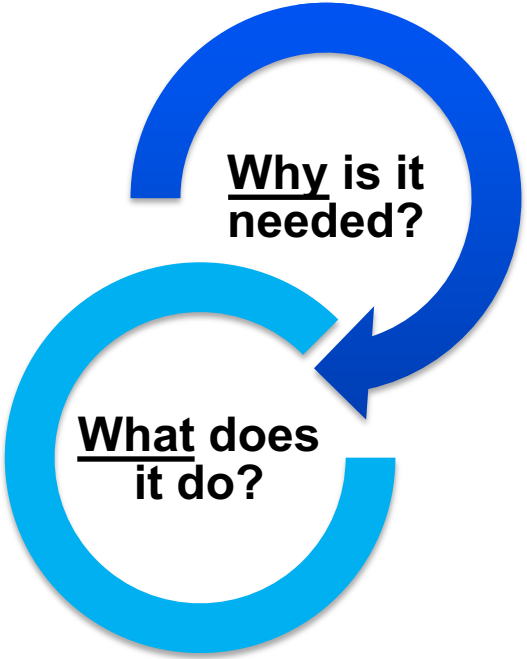
What is SISAQOL?

- **S**etting **I**nternational **S**tandards in **A**nalyzing Patient-Reported Outcomes and **Q**uality **o**f **L**ife Endpoints Data
- International multi-stakeholder consortium with shared interest in improving the standards for the **statistical analysis** of Patient-Reported Outcomes (PROs)
- Current Focus: randomized clinical trials (RCT) in oncology

Analyzing PRO Data Properly



To ensure a consistent and methodologically appropriate PRO data analysis

Recommends statistical approaches for analyzing PRO data

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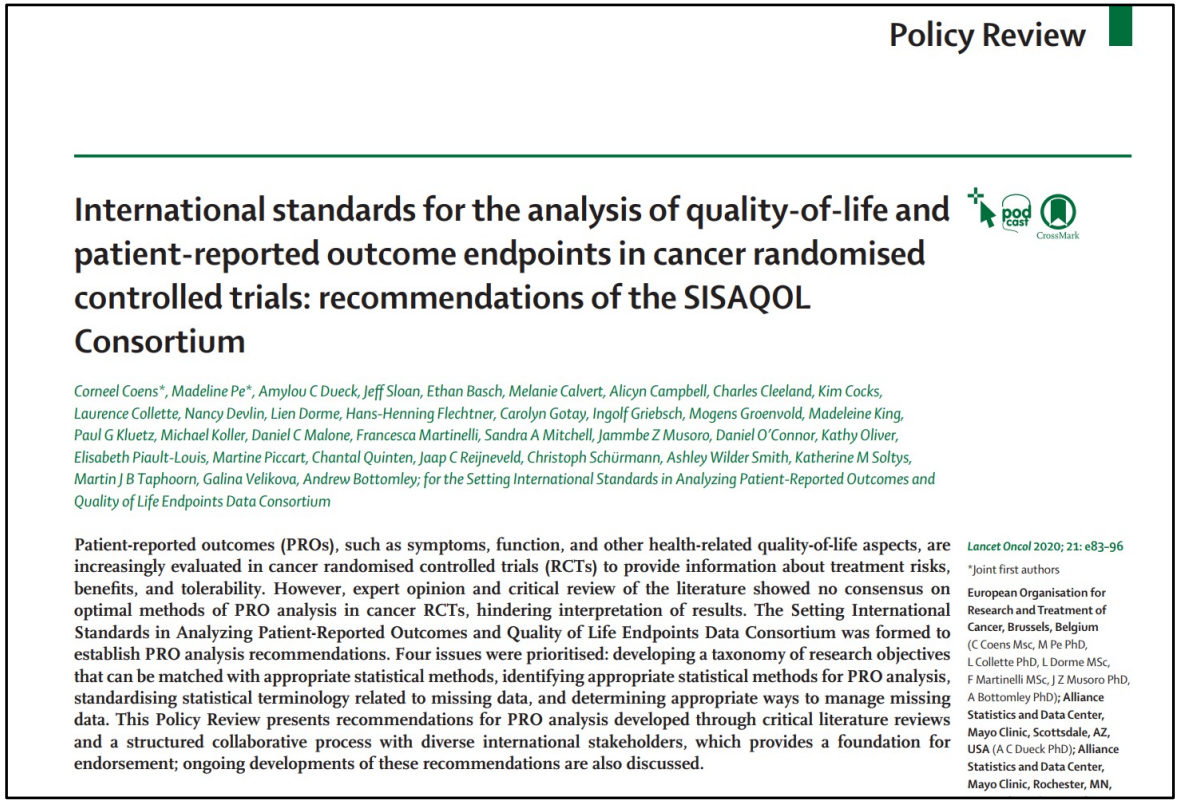
Analyzing PRO Data Properly



Policy Review

International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium

Corneel Coens, Madeline Pe*, Amylou C Dueck, Jeff Sloan, Ethan Basch, Melanie Calvert, Alicyn Campbell, Charles Cleeland, Kim Cocks, Laurence Collette, Nancy Devlin, Lien Dorme, Hans-Henning Flechtner, Carolyn Gotay, Ingolf Griebsch, Mogens Groenvold, Madeleine King, Paul G Kluetz, Michael Koller, Daniel C Malone, Francesca Martinelli, Sandra A Mitchell, Jammbe Z Musoro, Daniel O'Connor, Kathy Oliver, Elisabeth Piault-Louis, Martine Piccart, Chantal Quinten, Jaap C Reijneveld, Christoph Schürmann, Ashley Wilder Smith, Katherine M Soltys, Martin J B Taphoorn, Galina Velikova, Andrew Bottomley; for the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium*

Patient-reported outcomes (PROs), such as symptoms, function, and other health-related quality-of-life aspects, are increasingly evaluated in cancer randomised controlled trials (RCTs) to provide information about treatment risks, benefits, and tolerability. However, expert opinion and critical review of the literature showed no consensus on optimal methods of PRO analysis in cancer RCTs, hindering interpretation of results. The Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium was formed to establish PRO analysis recommendations. Four issues were prioritised: developing a taxonomy of research objectives that can be matched with appropriate statistical methods, identifying appropriate statistical methods for PRO analysis, standardising statistical terminology related to missing data, and determining appropriate ways to manage missing data. This Policy Review presents recommendations for PRO analysis developed through critical literature reviews and a structured collaborative process with diverse international stakeholders, which provides a foundation for endorsement; ongoing developments of these recommendations are also discussed.

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Coens et al, Lancet Oncol 2020, 21(2), E83-E96

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Boehringer Ingelheim

Genentech

EORTC Cancer Research Fund

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What is the Problem?

- PRO data in oncology trials have specific characteristics:
  - Multidimensional
  - Longitudinal
  - Missing data

- Major hurdles are:
  - Unclear PRO objectives
  - Terminology not consistent

Methods for recommendation

Criteria for selection of appropriate methodology:

- Essential:
  - Perform a statistical test between two samples
  - Be clinically relevant (treatment effect can be expressed in the PRO scale unit)
- Highly desirable:
  - Adjust for covariates, including baseline PRO score
  - Handle missing data with least restrictions
  - Ability to handle clustered data (repeated assessments)

SISAQOL Recommendations

- Taxonomy of research objectives
- Statistical methods:
  - Time to event
  - Intensity of event at time *t*
  - Proportion of patients with event at time *t*
  - Overall PRO score over time
- Terminology
- Missing data

Taxonomy of Research Objectives

- Between trial arms:
  - Confirmatory ↔ exploratory/descriptive
  - Superiority ↔ equivalence ↔ non-inferiority

- Within-individual / within-treatment objective
  - Improvement ↔ worsening ↔ maintenance
  - Overall effect (exploratory/descriptive)

Recommendation: state the research objective(s) for each PRO domain of interest

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Taxonomy of Research Objectives

- **Treatment efficacy / clinical benefit:** confirmatory objective
  therefore conclusions regarding comparisons between treatment arms can be drawn
  - *A priori* hypothesis needed
  - Statistical test - correction for multiple testing needed
  - Conclusions regarding comparisons between treatment arms

Taxonomy of Research Objectives

- **Describe patient experience:** Exploratory/descriptive objective therefore only presentation of findings but no comparative conclusions between treatment arms can be drawn
  - No *a priori* hypothesis needed
  - Descriptive / exploratory - multiple testing is not an issue
  - No comparisons between treatment arms

Taxonomy of Research Objectives

Recommendation: Pre-specify for each PRO domain/item of interest whether the results will be used to prove:

- **Superiority** or
- **Equivalence** or
- **Non-inferiority**

A non-significant superiority result ≠ evidence of equivalence or non-inferiority

→ pre-specify the magnitude for a clinically relevant treatment effect is needed

Taxonomy of Research Objectives

Recommendation: Valid PRO objectives at the within-individual /within-treatment level:

Improvement

- Time to improvement
- Proportion of patients improved at time *t*
- Intensity of improvement at time *t*

Worsening

- Time to worsening
- Proportion of patients worsened at time *t*
- Intensity of worsening at time *t*

(End of) Maintenance

- Time to (end) of maintenance
- Proportion of patients with maintenance at time *t*

Overall effect

- Overall PRO score over time (e.g., assessed by overall means, area under the curve, best /worst response)
- Response patterns / profiles

Time to Event

Recommendation: For evaluating time to event outcomes, it is recommended to use **Cox Proportional Hazards**

The Cox PH outperformed the log-rank test for these two criteria:

- Clinical relevance of results
- Adjustment for covariates, including baseline

Time to Event

Recommendation: For evaluating time to event outcomes, it is recommended to use **Cox Proportional Hazards**

Cautionary note:

- When using Cox PH test, the proportional hazards assumption should be checked. If this assumption is not met, we recommend employing the log-rank test, but taking note that this statistical test does not address clinical relevance
- General assumptions of time-to-event analysis must hold. Most notable: event time and censoring time should be independent

Intensity of Event at Time *t*

Recommendation: For evaluating intensity of event at time t, it is recommended to use **linear mixed models (time as discrete)**

The linear mixed model (time as discrete) has the advantage in:

- Adjustment for covariates, including baseline
- Handling of missing data
- Takes into account repeated data

while requiring fewer assumptions to be made *a priori* (e.g., regarding the relationship between time & outcome variable) than more complex mixed models extensions

Intensity of Event at Time *t*

Recommendation: For evaluating intensity of event at time *t*, it is recommended to use **linear mixed models (time as discrete)**

Cautionary note:

- Analysis strategy: fit an LMM to the data THEN obtain test estimate for specific time *t*
  - General recommendations for fitting LMMs to be provided
- Suitable if a study has a limited number of follow-up assessments
- Suitable if the general assumption of linear mixed models hold

Proportion of Patients with Event at Time *t*

No Recommendation

Based on the evaluation criteria, **logistic mixed model** could be recommended for this research objective

- Adjustment for covariates, including baseline
- Handling of missing data
- Takes into account repeated data
- Extension of the linear mixed model to address binary data at time t

However, the consortium felt that there was uncertainty about the practical application of these models. Recommendations for fitting LogMMs to be provided

Proportion of Patients with Event at Time *t*

No Recommendation

For cross-sectional outcomes: (Cochran) Mantel-Haenszel test outperformed other tests for these two criteria:

- Clinical relevance of results
- Adjustment for covariates, including baseline (stratification is possible)

Cautionary note:

- (Cochran) Mantel-Haenszel test is sensitive to missing data and will only provide valid inference when missing data are MCAR (missing completely at random)
- It is also a statistical technique that was designed for independent observations and does not take into account the repeated assessments of the PRO data

Overall PRO Score over Time

Under Discussion

Two-step analysis:

- Summarize a PRO domain into a single score over a given time period
- Comparative test on that summary score between the two arms

Recommendations for summary measures are difficult as there are few standardized summary measures available and their interpretation is debatable

Overall PRO Score over Time

Under Discussion

Two-step analysis remains sensitive to missing data and will only provide valid inference when missing data are MCAR

- Minimum or maximum: especially sensitive to missing data
- Missing data can be handled on summary or on analysis level

Note: Clinically relevant thresholds (Minimal Important Differences) need to be derived on the between-patient level (not on the within-patient level) to be applicable

Standardizing Terminology

Recommendation: PRO data is missing if data would be meaningful for the analysis of a given research objective but were not available for any reason

Consequence:

- Not all unobserved assessments are considered as missing data
- Missingness depends on the objective, ie. within a trial several missing data rates are possible
- Data is meaningful for analysis if it reduces the sample size (non-informative missing data), distorts the treatment estimate (informative missing data) or both

Standardizing Terminology

Recommendation: PRO data is missing if data would be meaningful for the analysis of a given research objective but were not available for any reason

Therefore: PRO study population ≠ PRO analysis population.

- PRO study population: all patients who consented to and were eligible to participate in the PRO data collection
  (ITC: intention-to collect population)
- PRO analysis population: all patients that will be included in the primary PRO analysis

Standardizing Terminology

Missing data rates:

The available data rate (a fixed denominator rate):

$$\frac{Nbr\ of\ patients\ submitting\ valid\ PRO\ assessment\ at\ time\ t}{Number\ of\ patients\ in\ PRO\ study\ population}$$

The completion rate (a variable denominator rate):

$$\frac{Nbr\ of\ patients\ submitting\ valid\ PRO\ assessment\ at\ time\ t}{Nbr\ of\ patients\ on\ PRO\ assessment\ at\ time\ t}$$

Note: the denominator of the completion rate depends on the research question

Missing Data

Under Discussion: Preliminary conclusions:

- **Missing data should be minimized prospectively**

- Capturing the **reasons** for missing PRO assessments is important
  - Impact of missing data depends on the reasons/mechanism for missing data
  - Justifying strategies for intercurrent events
    - Intercurrent event: either obscures or distorts the outcome value
    - Specific events can be anticipated with corresponding strategy
  - Standardizing reasons

Missing Data

Under Discussion: Preliminary conclusions:

Primary statistical analysis approach:

- Critical assessment of missing data rates and reasons (by arm and time point)
- Use all available data
- Simple imputation is not recommended unless justified within the context of the clinical trial

Missing Data

Under Discussion: Preliminary conclusions:

Primary statistical analysis approach:

- Sensitivity analysis should be specified *a priori* within the protocol/statistical analysis plan. At least two different approaches to handle missing data are recommended to assess the impact of missing data across various assumptions
  - If the results are consistent with the primary analysis, this provides some assurance that the missing data did not have an important effect on the study conclusions
  - If they produce inconsistent results, their implications for the conclusions of the trial must be discussed

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 health policy.
- More standardized PRO analysis will lead to easier and better cross-trial comparison of PRO results improving the value of such outcomes.
- Necessity of clear prespecified PRO objectives requires implementation at study design stage.
  Consider design in relation to Spirit Initiative (https://www.spirit-statement.org/)
- Foster better collaboration and understanding between clinicians, patients and methodologists on statistical analysis and the interpretation.
- Better PRO analysis will facilitate high-quality reporting, including clear and comprehensible description of the methods used.
  Consider reporting in relation to CONSORT (http://www.consort-statement.org)

Recap

- SISAQOL guidance aims to improve the standards for the **statistical analysis** of Patient-Reported Outcomes (PROs)
  - A taxonomy of research objectives is proposed to ensure the PRO objective is well defined.
  - Statistical methods recommendation are proposed for time to event, intensity of event at time t, proportion of patients with event at time t, and overall PRO score over time.
- A standardized definition for available data rate and completion rate is given.
- Missing data is acknowledged as problematic and should be prevented. Reasons for missing data need to be collected to better understand the underlying mechanism.

Further Reading

Coens C, Pe M, et al, Bottomley A; Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. *Lancet Oncol*. 2020 Feb;21(2):e83-e96. doi: 10.1016/S1470-2045(19)30790-9. PMID: 32007209.

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.