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Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints

Developing international standards in the analysis of patient reported outcomes in cancer clinical trials: methodological issues and STRATOS engagement in the European IMI-SISAQOL project

Saskia le Cessie, Limin Liu, Doranne Thomassen and Els Goetghebeur on behalf of work package 3 of SISAQOL-IMI

S.le_Cessie@lumc.nl

Patient reported outcomes (PRO)

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- Important endpoints in the benefit/risk assessment of new cancer therapies
- PROs are becoming/should be more important in cancer research
- There is increased collection of PRO data in cancer clinical trials

- However: no agreed international standards exist on the design, analysis, presentation or interpretation of these data

In 2021 SISAQOL-IMI started

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- IMI (innovative medicines initiative) funded project
- Lead-by EORTC and Boehringer Ingelheim (BI)
- https://www.imi.europa.eu/projects-results/project-factsheets/sisaqol-imi
- https://event.eortc.org/sisaqol/

- **Aim:** Establishing **international standards** in the analysis of patient reported outcomes and health-related quality of life data in cancer clinical trials
- **By** seeking **consensus** internationally and across stakeholders (industry, academics, patients, trial organizations, regulators)

Stakeholders involved in SISAQOL-IMI

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- Academia,
- Industry,
- Regulators (including EMA and FDA `representatives')
- Health technology assessment bodies,
- Clinicians,
- Methodological and applied statisticians,
- PRO experts,
- Patient representatives

- And STRATOS

WP 3: Recommendations for non-RCTs, with single-arm studies as a case study.

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- Led by Saskia le Cessie & Els Goetghebeur, together with Satrajit Roychoudhury (Pfizer)

- Members of core team: Limin Liu (Ghent), Doranne Thomassen (LUMC), Jammbe Musoro (EORTC), Cecilie Delphin Amdal (Oslo, University hospital), Willi Sauerbrei (Freiburg)

Single arm studies

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- Studies without a randomized control group
- Becoming more popular in the (provisional) drug approval process
- Especially for rare diseases, end-stage diseases and innovative drugs

- How can PRO be used (especially in the drug approval process)?

SISAQOL-IMI project General way of working

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- Rounds of formulating recommendations
- Consensus rounds balancing needs and requirements of different stakeholders
- Piloting suggested recommendations for designing and analysis of PRO data (RCTs and single arm studies)
- After 4 years: final recommendations

What have we done so far?

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First year:

- An overview of current practice (literature review/ survey)
- An overview of current standards (review of guidelines, survey)

Used this information to develop first set of recommendations

First set of recommendations

- Focus: research question and corresponding target estimand.
- Next step: link estimands to corresponding optimal analysis methods

The literature review on single arm trials (Limin Liu et al)

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- 60 single arm cancer studies with PRO measurements
- 13 studies had PRO as (co)primary endpoint
- Predefined research hypotheses regarding PROs were rare.
- Often no method for missing data, and if so, without justification for method
- PRO data were almost never collected after stopping treatment.
- Majority of studies: PROs supported treatment. Only one study advised against treatment based on PRO data.
- Handling of intercurrent events (death, stopping treatment) not discussed

Tasks for second year

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1. Collect reactions of STRATOS members on initial SISAQOL-IMI WP 3 report

2. Address unresolved issues and derive detailed recommendations for statistical methods

3. Implementation of recommendations for single-arm studies on a pilot case study

→ I will discuss 7 unsolved issues in single arm studies

1. Core set of variables

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Our ideal:

- All studies (single-arm or RCT) in a disease domain should measure the same core set of baseline variables

Why?

- To facilitate comparisons of PRO results of single arm studies to other data sources
- To perform meta-analysis

2. Changes over time

Common outcome: change from baseline in PROs

- Problem: other reasons for change in PRO: natural course of disease, regression to the mean, response shift, lack of blinding, etc.

How to handle this?

- Benchmark against results for standard-of-care therapy
- Perform a quantitative bias analysis
- Compare with external data directly (historical control data)

3. Comparisons with external data

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- Issues when using external historical data
  - Study populations
  - Type of PROs
  - Measurement timing and frequency
  - Within and between patient PRO variation
  - Follow-up time
  - Intercurrent events/death
  - Whether the setting is blinded or un-blinded
  - …

4. Summarizing PRO data

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How to summarize PROs over time?

- Means/medians at specific time point(s)
- Magnitude of change at specific time point(s)
- Responder (high PRO)/non responder (low PRO) at specific time point(s)
- Time until PRO event (e.g., improvement in PRO, worsening of PRO)
- Area under the curve over a specified timeframe
- Response patterns/profiles over a specified time frame

….

5. Handling death

PROs after death do not exist.

Ways to handle death (ICH-E9 addendum)

a. Describe PROs while alive (with % alive)
b. Incorporate death in PRO outcome (composite outcome
   - high PRO value versus low/death
   - assign particular value to death (e.g., 0 for QOL after death).
c. Extrapolate values after death (linear mixed models, imputation
   - Hypothetical strategy (what if death did not occur?)

What is an appropriate strategy, in which circumstances?

6. Intercurrent events

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- Intercurrent events: affect PRO values and/or the collection of PROs.
- ICH-E9 addendum discussed five different strategies to handle intercurrent events
  1. Treatment policy strategy. Use PROs after IE in the analysis
  2. Hypothetical strategies . What would happen if the intercurrent event did not occur?
  3. Composite variable strategy. Make intercurrent event part of outcome
  4. While on treatment strategies. Consider PROs only while patients are on treatment
  5. Principal stratum

- Which strategy to use ? (What if no data after treatment stop is available?)

7. Missing values

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- Missing values in PROs are often informative
- Deviations from scheduled measurements may be informative

- How to handle missing PRO data?

Next steps

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- We asked STRATOS members whether they could send us their experience and opinion on these issues.
- Will have a STRATOS meeting this afternoon (1-3 pm), where these issues will be discussed: **Room 1.18**
- Will use this to formulate recommendations