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

Developing recommendations to handle patient reported outcome data in oncology cancer trials: SISAQOL-IMI

Saskia le Cessie, Satrajit Roychoudhury, 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

- 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

- Academia,
- Industry,
- Regulators
- 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.

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

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

Single arm studies

- 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. Way of working

- Yearly 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)
  - Results of literature review published in Liu et al, Lancet Oncology 2023
- An overview of current standards (review of guidelines, survey)
- First set of recommendations

Second year

- Advice from STRATOS members on unsolved issues (ISCB Newcastle)
- Conducted a pilot case study
- Worked on several unsolved issues
- Second set of recommendations

The literature review on single arm trials (Limin Liu et al, Lancet Oncology 2023)

- 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

Advice from STRATOS members

- Meeting with STRATOS members took place in August 2022 in Newcastle.
- Provided input on 8 topics (Core set of variables, Changes over time, Comparisons with external data, Summarizing PRO data, Handling death, Missing data, Timing of measurements, Intercurrent events)
- A summary of the meeting has been written and used as input for the second round of recommendations

The pilot case study

- **Pfizer PROFILE 1005, single arm study**
  - **Population**: patients with locally advanced or metastatic ALK-positive non-small cell lung cancer in whom systemic treatment had previously failed.
  - **Intervention**: crizotinib 250mg twice daily
  - **Comparator**: none (single arm study)
  - PROs: EORTC QLQ-C30 and QLQ-LC13, EuroQol-5D (EQ-5D), VSAQ-ALK.
- Aim: to discuss design and analysis issues and provide guidance
- Results are currently written down

Unsolved issue: handling missing data in repeated PRO data

- Modeling with standard linear mixed (or generalized mixed) models doesn't work well
  - The models assume MAR, which is not realistic.
  - The models implicitly impute missing values after death
- We considered:
  - Estimand: mean PRO while alive
  - impute missing values, only while alive
  - For imputation, use extensive models which also incorporate information about time of death and time of disease progression
- Doranne Thomassen presented this work on this conference earlier this week

Unsolved issue: Using external information to estimate effect of treatment

- Information on a RCT with similar patients (Pfizer PROFILE 1007 RCT) was available

- Els Goetghebeur will present some issues in a minute

The recommendations

- The final versions are not yet there
  - Need to be validated by independent users (a different WP takes care of this)
  - Need to be harmonised with the recommendations on PROs in cancer RCTs (WP 2)

- Therefore, I will not show current version of recommendations, but give some indication of the direction in which we are heading

- Your opinion is very welcome

1. Use the estimand framework in single arm PRO studies

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 February 2020
EMA/CHMP/ICH/436221/2017
Committee for Medicinal Products for Human Use

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

1. Use the estimand framework in single arm PRO studies

Need to define

- The target population
- The treatment(s)
- The outcome of interest
- Strategies to handle intercurrent events
- Summary measure

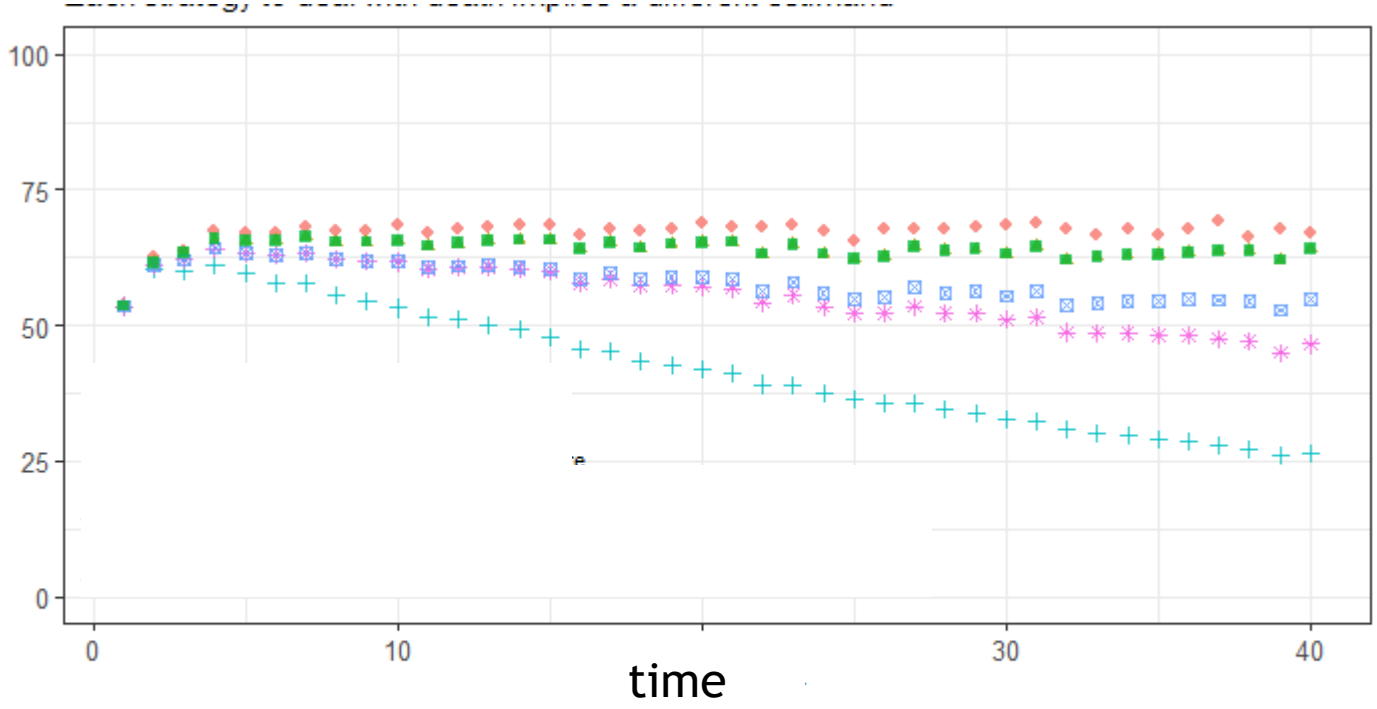
1. Strategies to handle death

PROs after death do not exist.

Ways to handle death (ICH-E9 addendum)

a. Describe PROs per time point while alive (with estimate of % 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?)

Handling death: different estimands can yield very different results



survival	1	0.88	0.8	0.72	0.64	0.58	0.51	0.47	0.43
PROs avail.	834	689	537	389	221	238	107	140	60

Observed
While alive

Hypothetical

Composite

Handling death

- PROs after death are not defined
- A while alive approach, combined with estimated % to be alive is often to be prefered
- (generalized) linear mixed models follow a hypothetical strategy, as they impute values after death
- So therefore the standard use of (generalized) linear mixed models is in general not advisable

2. Handling other intercurrent events

- 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, ignore IE
    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

- Approach 1. is often preferred. But not always feasible (no PRO data after treatment stopping) and not always a good approach (e.g., PROs measurering side effects of treatment)

3. Summarizing/describing PRO data

Many different options

- 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

….

3. Summarizing PRO data

Several recent papers have suggested that quantitative PROs should ideally be initially analysed as continuous/ordinal outcomes

- Fiero et al (Lancet Oncol 2022), Collister et al.(J Clin Epidemiol 2021), Cappelleri JC. (J Clin Epidemiol. 2021)

4. Considering changes over time

One should be extremely cautious !

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

Potential ways to handle this

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

5. Comparisons with external data

- Els will discuss some issues

6. Missing values

- Reasons for missing data should be collected
- Missing at random assumption should be justified
- Incorporating information on intercurrent events and death, may make the missing at random assumption more likely
- Sensitivity analysis to study robustness against deviations of assumptions

7. Core set of variables

We considered:

- 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 account for missing data
- To perform meta-analysis

Next steps

- Finish case-studies
- Meeting with STRATOS experts for their advice, meeting in October 2023
- Fine-tuning and harmonisation