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

imi innovative medicines initiative

efpia

Guiding the path from Patient Reported Outcomes to treatment registration based on randomised and single arm studies: STRATOS engaged in the European IMI-SISAQOL project.

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Patients 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

- Seek 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

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- 8 workpackages
  - WP 1- Management and coordination.
  - WP 2- Methodological work for cancer RCTs.
  - **WP 3- Feasibility of developing recommendations for non-RCTs, with single-arm studies as a case study.**
  - WP 4- Communication tools for PRO findings from CCTs.
  - WP 5- Independent validation and feasibility of methodological work and communication tools.
  - WP 6- Develop recommendations for the terminology and definitions of clinically meaningful change in CCTs
  - WP 7- Develop international recommendations for analysis and interpretation of PRO results for various stakeholders.
  - WP 8- Patient engagement, dissemination strategies and educational programmes/workshops.

WP 3:Feasibility of developing recommendations for non-RCTs, with single-arm studies as a case study.

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- Lead by Saskia le Cessie & Els Goetghebeur, together with Satrajit Roychoudhury (Pfizer)
- Members of core team: Jan Choi (LUMC), Limin Lui (Ghent), Jammbe Musoro(EORTC), Cecilie Delphin Amdal (Oslo, University hospital), Willi Sauerbrei (Freiburg), Cecilie Delphin Amdal (Oslo)

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)?

- Distinction between explorative and confirmative PRO aims

PRO endpoints of interest (Coens 2020)

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Improvement

- Time to improvement
- Responder (improvement) at time t
- Magnitude of change (improvement) from baseline at time t

Worsening

- Time to worsening
- Responder (worsening) at time t
- Magnitude of change (worsening) from baseline at time t

Stable state

- Time to stable state
- Time to end of stable state
- Responder (stable state) at time t

Overall effects

- Overall mean / median over time
- Change over time
- Area under the curve over time
- Best score over time
- Worst score over time
- Response patterns / profile over time

Estimands are becoming popular in drug research

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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

Estimand (target of estimation)

- Estimands require specification of
  - Population
  - PRO endpoint of interest
  - Treatment
  - Control (in a confirmatory setting)
  - Summarizing treatment effect
    - Descriptive (in exploratory setting) vs comparison with external control (in a confirmatory setting)
  - Handling intercurrent and terminal events (death)

- We distinguished between assessing efficacy and safety

ICH-E9 addendum on estimands and sensitivity analysis

- Strategies to handle intercurrent (and terminal) events
  - Treatment policy strategy (ignore the intercurrent event, analyse PROs as measured, ITT)
  - Hypothetical strategies (what would happen to PROs if the intercurrent event did not happen?)
  - Composite variable strategies (Make intercurrent event part of the PRO outcome)
  - While on treatment strategies (Conditional on not having the event)
  - Principal stratum strategies

- We explored in a survey among SISAQOL members which strategies were considered best practices to describe PROs (and to compare PROs)
- In recommendations: we aim to connect analysis methodology to summarize the estimand

Question to you as STRATOS Members

- Have you analysed a single arm PRO studies? What are your experiences?
- What is your opinion about this estimand framework?
- What is your opinion about our approach to start with the estimand framework and link analysis methods to the estimands.

Estimands when death in follow up occurs

- Example: a single arm study on a new treatment,
- PROs measured at baseline, and 1,2, and 3 months after start treatment.
- PRO endpoint is the **Mean change from baseline to month 3.**
- Some measurements at 3 months are missing, because patients have died between month 2 and month 3.

Possible Estimands. The mean change from baseline to month 3:

- in the subgroup of patients still alive at month 3 (“while on treatment strategies”)
- for a composite outcome, where all patients who died are assigned a very low score (“composite variable strategy”)
- in the (hypothetical) situation that all patients would survive until month 3 . (“hypothetical strategy”)
- for the (latent) set of patients who would be alive under either treatment (“Principal stratum strategy”)

- …

Estimands for intercurrent event

- PROs measured at baseline, and 1,2, and 3 months after start treatment.
- Aim **Explorative**, PRO endpoint is the **Mean change from baseline to month 3**.
- Some patients experience disease progression between month 2 and month 3.

Possible Estimands.

- The mean change from baseline to month 3
  - In all patients, regardless of whether disease progression occurs (“intention to treat strategy”)
  - in the subgroup of patients without disease progression (“while on … strategy”)
  - for a composite outcome, where for patients with disease progression PRO measurements are replaced by a very low score. (“composite variable strategy”)
  - in the (hypothetical) situation that none of the patients would have disease progression. (“hypothetical strategy”)
  - …

Extra challenge: confirmatory aims

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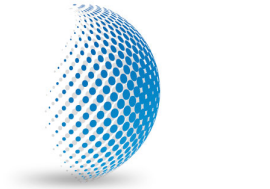
How to handle the absence of a randomized control group?

- Use a clinical important difference value from literature
- Define a clinical important difference based on expert opinion elicitation
- Indirect comparison with external control from other data sources (historic/external control data)
- Use change from baseline
- …

After identifying relevant estimands



- Define corresponding optimal analysis methods (which may depend on the outcome of interest)

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

How will we develop recommendations for single arm studies (if it seems feasible)?

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First year:

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

Use this information to develop first set of recommendations

First consensus meeting spring 2022

How will we proceed developing recommendations (2)?

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Second year:

- Identify unresolved issues in recommendations
- Work on it; improve recommendations

Second round of recommendations: identifying levels of agreement/consensus on what (not) to do

Year 3 and 4, pilot analysis based on recommendations in different pilot studies

How will we involve STRATOS?

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- Discuss findings and sollicite feedback on recommendations in year 1
- Collaborating on resolving open issues in year 2 (we plan a meeting for this summer next year)

Conclusions/discussion

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- This is important work
- It (will) benefit from the broad coverage of stakeholders
- Consensus risks weaker statements: we want an outlet for both
- What with other non-randomized studies (e,g. disease registers -> to come)

- Please let us know if you want to be involved.

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