STRengthening Analytical Thinking for Observational Studies (STRATOS): Cooperation in the Setting International Standards in Analyzing Patient Reported Outcomes and Quality of Life Endpoints (SISAQOL-IMI) project

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In 2019, the STRATOS initiative, recognized in its mission to develop guidance for the design and analysis of observational studies, was approached by the SISAQOL consortium to join a European Innovative Medicines Initiative application. SISAQOL is short for Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints. The SISAQOL consortium was formed in 2016, aiming to establish recommendations for patient reported outcome (PRO) analysis (1, 2).

PROs are direct reports from patients about their health condition and treatment effects, without interpretation by clinicians, commonly collected via questionnaires. PROs are becoming increasingly important in medical research and clinical care and they are increasingly collected in both settings. Although PROs are considered important endpoints in the benefit/risk assessment of new cancer therapies, no agreed international standards exist on the design, analysis, presentation, or interpretation of these data.

STRATOS accepted the invitation, the grant application was successful, and the SISAQOL-IMI consortium started in 2021 (3). The international, multidisciplinary consortium is led by the European Organization for Research and Treatment of Cancer (EORTC) and the pharmaceutical company Boehringer Ingelheim. This four-year project aims to establish international standards in the analysis of patient reported outcomes and health-related quality of life data in cancer clinical trials. This is to be done by seeking consensus across stakeholders, which include industry, academics, clinicians, trial organizations, regulators, and patients. SISAQOL-IMI is organized in different work packages such as methodology for cancer randomized controlled trials (RCTs), the feasibility of recommendations for single-arm trials (SATs), guidance for clinically meaningful change in cancer trials, and communication tools for PRO findings in cancer trials. The work in the different working packages leads to the formulation of recommendation statements, which are subsequently discussed in yearly consensus rounds.

STRATOS is particularly involved in work package 3 (WP3), which focuses on SATs and other non-randomized studies. This work package is led by Saskia le Cessie (STRATOS member) and Satrajit Roychoudhury (Pfizer). STRATOS members Els Goetghebeur and Willi Sauerbrei actively participate in this work package while junior researchers Doranne Thomassen and Dries Reynders are carrying out some of the statistical projects, described below, with us.

The goal of WP3 is to investigate the feasibility of and to develop recommendations for the use of PROs for non-randomized cancer studies with a specific focus on SATs. In the first year of the project, an overview was made of current best practices by reviewing guidelines related to the design and analysis of PRO endpoints in SATs, and by conducting surveys among SISAQOL-IMI members involved in WP3. WP3 contributors were asked to indicate the appropriate study population, methods to handle terminal events (death) and other intercurrent events, appropriate analysis methods, methods to handle the absence of a comparator group, use of minimal clinically important differences for PROs, and appropriate visualization of PRO results for a SAT. Since many of these issues are also relevant to WP2, which focuses on randomized trials, harmonization meetings between WP2 and WP3 were planned to align recommendations wherever possible.

To obtain an overview of current practices, we performed a literature review of 60 recent single-arm cancer studies incorporating PROs. The review revealed that only 13 of these studies used PROs as a primary or co-primary endpoint, and that predefined research hypotheses regarding PROs were rare. Methods for handling missing PRO data were often unreported or unjustified, and PROs were rarely collected after the end of treatment. Remarkably, in the majority of the studies, the PRO analysis supported the investigated treatments; only one study advised against a treatment based on PRO data. This result points to a publication bias. The handling of intercurrent events, such as death or treatment discontinuation, was generally not discussed. Furthermore, only one study made a formal comparison of PROs with historical controls. The disappointing but expected results of this review are published in Lancet Oncology (4).

Based on the responses of the stakeholder surveys and the literature review, a first list of recommendation statements was formulated and discussed. The recommendations consid-

ered the aims of PROs in SATs, formulation of research questions in the context of the ICH E9(R1) estimand framework (5), choosing appropriate outcome measures, addressing the absence of a randomized control group, and handling intercurrent events and missing data. One particular issue is addressing death in the research question of a PRO study. PROs after death are not defined and therefore the estimand of interest in SAT is often a summary of PROs in those who are still alive at a specific time (6). The common practice of standard linear mixed models is not appropriate, as these models implicitly impute missing PROs after death.

The second and subsequent years of the work of WP3 were dedicated to further research on the methodology for SATs with PROs and to the extension of the list of recommendation statements. At the ISCB conference in Newcastle in 2022, a STRATOS meeting was organized to ask for STRATOS members' advice regarding PRO analyses in SATs. A second meeting was organized in the fall of 2023 in Ghent with a focus on causal inference and missing data in our setting. This greatly helped us to refine and update the recommendations.

We also performed three subprojects related to statistical issues in WP3. The first one was a case study where the set of suggested recommendations for PROs in single-arm oncology studies were piloted. This resulted in a guidance paper for designing and analyzing PRO single-arm studies which is submitted for publication (7). In the second subproject, we considered methods to deal with missing data in PRO measurements in single arm clinical cancer trials. Handling missing PRO data can be complicated because intercurrent events (e.g., death, disease progression) may be related to the occurrence of missing PRO measurements. We explored several methods to account for missing PRO data, which address the occurrence of intercurrent events, account for a longitudinal data structure, and do not impute after death, as PROs after death are undefined. A paper on this topic is currently under review by the consortium and will be submitted for publication soon.

The third subproject focused on the comparison of PRO data in SATs with external control data. This imposed several challenges as many factors can confound such a comparison. To mention some possible issues, depending on the design: different populations with different distributions of baseline covariates and treatment protocols, the use of different PRO measures or questionnaires, different timing of measurements, and different drop-out patterns. RCTs in late-stage oncology are also non-trivial in this regard since one typically allows for switching to the experimental treatment in an effort to encourage accrual. A paper that considers methods to account for baseline differences, and discusses various estimands to handle death, is currently being written. Estimators that handle differential death and censoring are further proposed and compared, focusing on the two-dimensional estimand of PROs while alive and survival. Results of the three projects have been presented at several STRATOS symposia and ISCB meetings. Slides of all talks are available on the STRATOS website (https://www.stratos-initiative.org/en/news).

In order to allow a meaningful comparison between or a feasible meta-analysis of several studies, relevant variables need to be collected using similar (ideally the same) measurement techniques across all studies. In this context, a broad agreement of clinicians and researchers on a relevant set of core variables for a disease of interest would be important. Starting such projects would be most relevant to rethinking the data elements collected and would increase the potential for multipurpose data reusability. Increased harmonization is necessary and would improve the data infrastructure for clinical research (8).

Being involved in this international SISAQOL-IMI consortium is a unique experience. The collaboration of many different disciplines has led to a set of well-thought out and well-formulated recommendation statements with broad acceptance for PROs in cancer studies. The project is in its final stages and the final recommendations will be presented soon. In 2024, the SISAQOL-IMI received the SPAIG Award from the American Statistical Association for its successful collaboration across academia, industry, and government. This recognition reflects its efforts to advance the patient-reported outcomes field by harmonizing guidance to serve diverse stakeholders.
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