Strengthening Analytical Thinking for Observational Studies (STRATOS): UPDATES FROM TOPIC GROUP ON STUDY DESIGN (TG5)

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The STRengthening Analytical Thinking for Observational Studies (STRATOS) initiative has published a series of Bulletin articles focused on individual topic groups (TGs) and collaborative activities. The second issue of the thirty-sixth volume (2019) of the Bulletin introduced TG5 on study design, which aims to provide accessible and accurate guidance for the planning and design of observational studies to mitigate avoidable flaws that persist in the literature. Here, we provide an update on TG5's membership and activities.

Since its inception, Mitchell Gail has served as chair, joined by Suzanne Cadarette as co-chair in 2016. TG5's membership has since evolved and expanded to ten members. In addition to the two co-chairs, regular members include Gary Collins, Susan Halabi, Rima Izem, Thomas Lumley, Paola Rebora, Peggy Sekula, and Neus Valveny. Nicholas Bakewell became the first member of the "Early Career Adjunct Members" category in January 2025, and has been actively participating and helping coordinate virtual TG5 meetings since early 2023, when he first started engaging with TG5 as a guest. This diverse membership brings together early-career and well-established researchers from academia, government and industry; collectively offering many years of experience on the application and development of observational study designs.

Regarding research outputs, TG5 has been involved in the development of guidance for several observational study designs. Specifically, TG5 members have published papers in BMJ Open providing guidance on how to select an appropriate observational study design for detecting an association between an exposure and disease incidence, [1] and guidance on design issues related to prognostic factor studies. [2] The first paper supports analytical thinking in the design of cohort studies and sub-samples from cohorts (case-cohort and case-control). We note that study design is the foundation of a scientifically valid study and that serious mistakes in design cannot be corrected by statistical analysis. Here we provide examples, summarize design strengths and weaknesses, and emphasize the importance of defining clear study aims as the first step to select a design to meet those aims within practical constraints. [1] The second paper provides guidance for designing prognostic studies and distinguishes between 4 types of prognostic research with examples: descriptive, single factor, prognostic models and stratified medicine.

We encourage readers to refer to our list of general aspects to consider when designing a prognostic study that is included in our guidance paper. [2] TG5 members have also contributed to an

International Society for Pharmacoepidemiology endorsed guidance document published in Pharmacoepidemiology and Drug Safety, which provides a detailed overview of self-controlled study designs to permit a foundational understanding for both novice and experienced researcher. [3]

Furthermore, TG5 has two papers close to submission. The first is a guidance paper on study design for estimating the real-world safety of long-term drug exposures that includes a case example on antidiabetic medications and hip fracture. This paper strategically provides specific guidance on four key elements: 1) etiology and validity of the outcome, 2) pathophysiology and progression of the health condition being treated, 3) clinical pharmacology of drug exposure(s), and 4) population and patient level time trends. The paper emphasizes the importance of causal thinking and transparent reporting early in the planning and design of a study. The second paper offers guidance on calculating sample size for observational studies, including examples and discussions around the impact of confounding.

Among the papers in early stages of development, one aims to provide an overview of frameworks that may be used to inform the definition of an estimand (i.e., the target quantity of interest). These frameworks include the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E9 (R1) addendum, [4] which was developed for and has primarily been applied to randomized controlled trials; and the Target Trial Emulation framework, [5] which has been rapidly adopted for the design of observational studies. This collaborative overview paper of frameworks was discussed and outlined in-person at the STRATOS 2024 Lorentz Workshop and involves STRATOS members across several TGs. The discussions from the Workshop were summarized in the fourth issue of the forty-first volume (2024) of the Bulletin. [6]

Ongoing efforts have been presented by TG5 members at several recent conferences attended by applied and methodological researchers. Here, TG5 presented an early iteration of the guidance paper on study design for estimating the real-world safety of long-term drug exposures at the 2024 annual meeting of the International Society for Pharmacoepidemiology, [7] the STRATOS 2024 Lorentz Workshop, and updated guidance at a STRATOS-led invited session at the 2025 Joint Statistical Meetings. [8] Additionally, TG5 presented preliminary ideas related to a paper specifying estimands in post-market drug safety studies that aim to quantify long-term risks and benefits of novel therapies at the 2025 Conference of the International Society for Clinical Biostatistics. [9] This paper covers alternative approaches to specify estimands for long-term drug outcome studies and focuses on cumulative exposure questions at fixed follow-up periods, informed by drug utilization patterns in real-world settings, rather than typical point exposure questions that primarily relate to treatment initiation. These alternative approaches are critical to better address the complexities of real-world drug use that often involves informative non-outcome post-treatment initiation events (e.g., dose escalation, treatment switching, add-on therapy and gaps in treatment) that can complicate causal inference.

Building on this active period of research and dissemination, TG5 will remain highly active alongside the rapid developments of methods aimed at drawing causal inferences from observational data. While these methodological advancements are welcomed and have helped to improve the quality of science generated by studies using observational data, they may at times overshadow the fundamentals of study design, as evidenced by persistent flaws in study design.

Consequently, there will be continued need for guidance on study design. Check out TG5's website for past and up-to-date news on publications and presentations.

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