Ensuring transparency and quality of clinical trial reporting in clinical pharmacology & therapeutics: prospective trial registration and compliance with reporting guidelines are required for all clinical trials

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Ensuring Transparency and Quality of Clinical Trial Reporting in *Clinical Pharmacology & Therapeutics*: Prospective Trial Registration and Compliance with Reporting Guidelines Are Required for all Clinical Trials

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As the premier publication in the field of clinical pharmacology, *Clinical Pharmacology & Therapeutics* (*CPT*) strives to be at the forefront of development and implementation of best practices for clinical trial reporting. The *CPT* editorial team has updated and introduced several guidelines in recent years for clinical trial registration and reporting guidelines describing the key elements that must be included in a publication (see https://ascpt.onlinelibrary.wiley.com/hub/journal/15326535/editorialpolicies). Compliance with these requirements provides transparency of what the investigators planned to do and how they planned to do it and ensures that the publication correctly describes all the defined outcomes with a clear distinction from any additional unplanned analyses and results **Figure 1**.

Pre-specifying the population, intervention, comparator, and outcome (PICO) is a well-established principle in both designing and analyzing the reports of clinical trials. Kahan and Jairath[1] highlighted this with an example of re-analysis of TRIGGER, a cluster randomized trial of transfusion to treat gastrointestinal bleeding. By changing the bleeding definition (the "O" in PICO), the authors showed how the trial could be interpreted as either strongly supportive of the intervention or having no effect at all. Making clear unambiguous decisions on PICO items before seeing the data is therefore a key protection against bias resulting from seeing the data.

In 2005, the International Committee of Medical Journal Editors (ICMJE) established a policy promoting clinical trial registration

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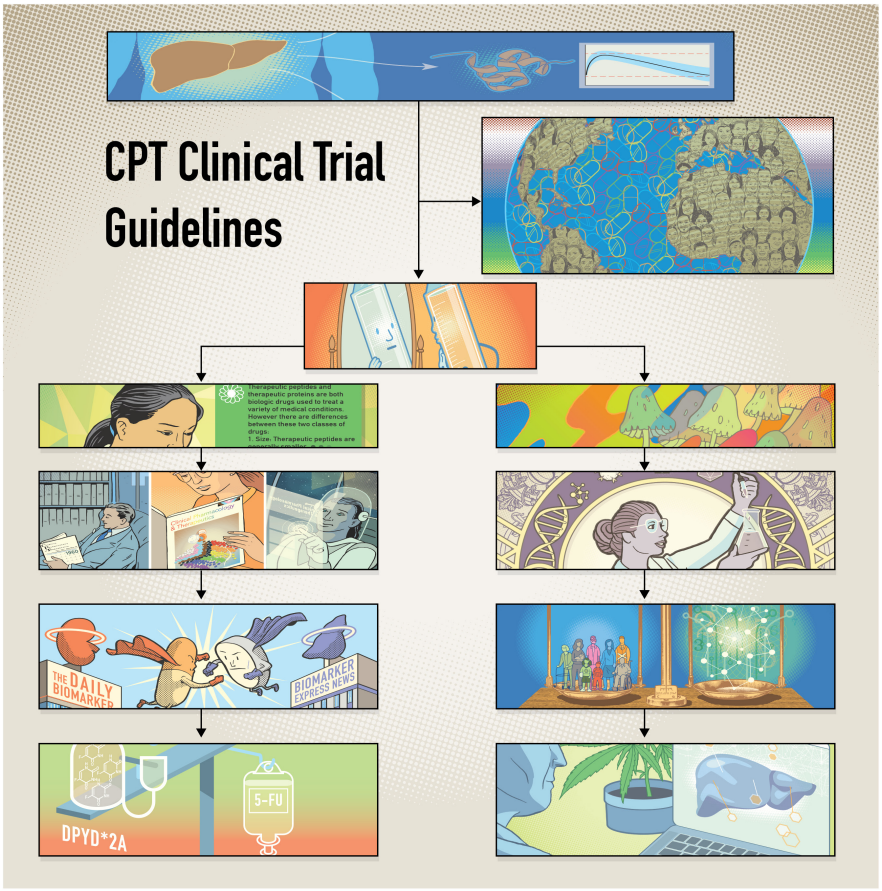

Figure 1 December cover image.

as a prerequisite of consideration for publication.[2] This policy was implemented to reduce the risk of selective reporting of trials with a significant effect of a new therapy (positive trials) or equivalence of two therapies (noninferiority trials) and to help ensure that the primary analyses and outcome measures were defined prior to the start of the trial. The intent was to address this problem of selective awareness, enable stakeholders to be aware of trials relevant to them by ensuring public documentation exists for every trial, and reduce bias in published results.

CPT adheres to ICMJE's Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.[3] Thus, registration of a clinical trial in an appropriate online public trial registry is required for publication in *CPT*. *CPT* and the ICMJE utilize the World Health Organization (WHO) definition of a clinical trial as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes."[3,4] Health-related interventions are further defined as "those used to modify a biomedical or health-related outcome; examples include drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes." Last, the ICMJE defines health outcomes as "any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events."

For trials that meet the above criteria, ICMJE (and therefore *CPT*) requires registration in a publicly accessible primary registry that is listed on the WHO International Clinical Trial Registry Platform or in ClinicalTrials.gov.[5] Primary registries include but are not limited to the EU Clinical Trials Register (EU-CTR), the Japan Primary Registries Network (JPRN), the Brazilian Clinical Trials Registry (ReBec), and the Australian New Zealand Clinical Trials Registry (ANZCTR). Suitable registries are managed by a not-for-profit organization, electronically searchable, and include a

minimum 24-item trial registration dataset.[6] Clinical trial registration must occur at or before the onset of patient enrollment.

However, a recent survey of submissions to *CPT* showed that many submissions did in fact not comply with the requirement for trial registration prior to first patient enrollment. During a 6-month period in 2021 only 50 (62%) of 81 trials fulfilled these criteria, whereas 27 (33%) were not registered appropriately and 4 (5%) required further clarification from authors. Of the 27 submitted manuscripts that were not registered appropriately, the most common reason was that the trial appeared to be unregistered or was unable to be found based on the information provided by the authors ($n = 16$, 59%). Other reasons included: trial registration after beginning of enrollment ($n = 6$, 22%), multiple issues ($n = 2$, 7%), a phase I study that was not publicly available ($n = 2$, 7%), and use of registry not recognized by ICMJE ($n = 1$, 4%; Table 1).

The CONsolidated Standards Of Reporting Trials (CONSORT) 2010 statement for completed randomized trials is widely accepted as a gold standard for publication of clinical trial results.[7] It comprises a 25-item checklist for manuscripts and sets out a framework by which editors, reviewers, and ultimately readers can assess the quality of a reported trial. *CPT* requires authors of manuscripts including clinical trials to explain how they have complied with the CONSORT 2010 guideline.

However, the existing guideline was developed principally to enable robust reporting of trials of efficacy and safety in large populations typical of those performed in phase III and IV and it is not ideal for reporting many early phase trials. Several studies have shown poor reporting quality for early phase clinical trials in oncology[8-10] and a recent study showed poor compliance with key CONSORT requirements for early phase dose-finding trials in all therapeutic areas.[11] Similarly, a study of the quality of publication of protocols for dose escalation trial protocols showed that they too are often poorly compliant with SPIRIT, the equivalent of CONSORT for publication of protocols.[12] A contributing factor to poor reporting quality could be that CONSORT 2010 was not designed for early phase dose-finding trials with some important elements being either difficult to comply with or missing from the existing guidance. It was recognized that a modified guideline was required to improve reporting of phase I/II trials, especially dose (de)-escalation trials.[13,14] This has now been addressed with the development and publication of the CONSORT – DosE FIndiNg Extension (CONSORT-DEFINE) reporting guideline.[15] A similar, new guideline (SPIRIT-DEFINE) has also been developed for the publication of trial protocols.[16]

Table 1 Reasons for non-compliance with requirement to register clinical trials reported in manuscripts submitted to *Clinical Pharmacology & Therapeutics* during 2021

Reason	*n*
Not registered[a]	16 (59%)
Registered after enrollment began	6 (22%)
Multiple issues	2 (7%)
Phase I study	2 (7%)
Registry not recognized by ICMJE	1 (4%)

ICMJE, International Committee of Medical Journal Editors.
[a]Or unable to be found based on information authors provided.

CONSORT-DEFINE was developed using a modified Delphi process involving clinical investigators, trial methodologists, clinical pharmacologists, and patient representatives from academia, the pharmaceutical industry, medical charities, and regulatory authorities in North America, Europe, Asia, and Australasia. Forty items were identified for inclusion in the final checklist, 19 of which were modifications of existing CONSORT items with the rest being new items. The new items covered subject areas critical to early phase trials, such as flexible trial designs, the use of model-assisted study designs and design adaptations, justification of the starting dose and other proposed doses, recruitment and dosing process, definition of dose-limiting toxicities (including length of assessment window), decision making for dose (de)-escalation, recommended dose(s) selection criteria, and reporting of key outcomes by dose.

CONSORT-DEFINE is intended to ensure high quality reporting of all dose (de)-escalation studies. This encompasses first administration to humans through studies including cohort expansions to phase II type studies that include multiple doses, especially if there is a(n) (de-)escalation component. It is relevant for both randomized and non-randomized trials, studies in healthy volunteers, patients, elderly, children, special populations, and for all therapeutic modalities. However, it is also

relevant to other phase I/II studies including those in new subject groups, studies to explore drug interaction risks or the impact of organ failure or other diseases and studies to establish bioequivalence. Such studies often provide key dosing information and it is very important that any and all studies on which dosing is based are published to the highest quality. For reports of pharmacokinetic/pharmacodynamic modeling, best practice in terms of prespecifying numbers of patients and timing of sampling should be followed in study design.[17]

Apart from randomized controlled and dose-finding trials, clear, unambiguous prespecification and reporting principles are equally important for limiting bias in other clinical data analysis settings. Further reporting guidelines have been established for specific study types and design (https://www.equator-network.org/reporting-guidelines), in particular Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[18] guidelines for the analysis of pooled trial results, and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[19] guidelines for reporting observational studies. Reporting guidelines were recently extended to the evolving field of real-world evidence (RWE) studies of the safety and effectiveness of treatments (STaRT-RWE: structured template for planning and reporting on the implementation of RWE studies).[20] Guidelines for reporting pharmacogenetics studies have also been developed (STROPS).[21]

We remind authors considering submitting their work to *CPT* that all clinical trials must have been registered in an appropriate trial registry prior to enrollment of the first patient. Requirement of registration includes trials irrespective of their stage, whether early (e.g., phase I) or late phase. We also strongly encourage the registration of all observational studies. Authors are reminded to disclose the clinical trial registration number together with the name of the registry in the manuscript. Numbers of ethical approvals or other study-related identifiers cannot replace the trial registration information. Of note, all manuscripts reporting results of clinical trials, including those presenting secondary or *post hoc* analyses of trial outcomes, need to present details on trial registration. Importantly, publications of secondary or *post hoc* analyses of clinical trial data should transparently and explicitly indicate the secondary nature of the analyses and results as well as citation(s) of any primary publication(s). Outcome parameters of secondary studies should be defined already in the original registration.

CPT will continue to require authors of manuscripts reporting new data from clinical trials to complete a checklist of CONSORT or CONSORT-DEFINE items to show where in the manuscript the required information can be found or to explain why an item in the checklist has not been complied with. The guidance for authors now includes links to a checklist for CONSORT-DEFINE as well as the already available CONSORT 2010 guidance. Authors are required to complete one of these checklists and to explain why they selected that checklist as most appropriate for the trial(s) they are reporting. Likewise, we require compliance with appropriate guidelines for observational studies and analyses of real-world data.

CPT's commitment to comply with ICMJE recommendations for clinical trial registration and with established guidelines for the quality of reporting will enable stakeholders to be aware of relevant clinical trials, reduce the risk of selective publication based on results, help to achieve the highest levels of reporting quality for important results of early phase and other clinical pharmacology studies, and underpin greater understanding of drugs, doses, and their effects.

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