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# Peer review before trial conduct could increase research value and reduce waste

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## **Conflicts of Interest**

The authors declare that they have no competing interests.

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**Abstract**

Traditional peer-review of clinical trials happens too late, after the trials are already done. However, lack of methodological rigor and presence of many biases can be detected and remedied in advance. Here, we examine several options for review and improvement of trials before their conduct: protocol review by peers, sponsors, regulatory authorities, and institutional ethical committees; registration in registry sites; deposition of protocol and/or the statistical analysis plan in a public repository; peer-review and publication of the protocol and/or the statistical analysis plan in a journal; and Registered Reports. Some practices are considered standard (e.g. registration in trial registry), while others are still uncommon but are becoming more frequent (e.g. publication of full trial protocols and statistical analysis plans). Ongoing challenges hinder a large-scale implementation of some promising practices such as Registered Reports. Innovative ideas are necessary to advance peer-review efficiency and rigor in clinical trials but also to lower the cumulative burden for peer-reviewers. We make several suggestions to enhance pre-conduct peer-review. Making all steps of research process public and open may reverse siloed environments. Pre-conduct peer-review may be improved by making routinely publicly available all protocols that have gone through review by institutional review boards and regulatory agencies.

Key words: Clinical trials, Peer-review, preregistration, registered reports, protocol, methodology

Running title: Peer review before trial conduct

## Improving trials before or after they are done?

Clinical trials have been at the forefront of debates and initiatives toward improving rigor and transparency (e.g. data sharing and registration). However, many problems still plague clinical trials. Selective reporting biases, sloppy methods, p-hacking and other pitfalls remain prevalent despite efforts from funders, researchers, journals and patient organizations (1).

According to Chalmers and Glasziou, approximately 85%, of medical research goes to waste, because of asking the wrong questions or poor design (2). The United Nations resolutions from the 75th World Health Assembly (May 2022) stress the need for more transparency, quality and safety in clinical trials (3).

Efforts to improve clinical trials may target any step in the chain leading from idea generation to design, conduct, analysis, reporting, interpretation, and dissemination. A central idea is to improve the review process. Many ongoing efforts like specialized peer-review including statisticians or patients or reporting guidelines, have been developed over the years, based on this principle. However, these interventions may have marginal gains because they occur too late, after trials have been completed. A problematic trial is very difficult to salvage at that point. At best, one can hope that its reporting, interpretation, and dissemination may be accurate so that its problems are visible. However, these problems remain even if visible. Moreover, unless there are safeguards in place, there is no guarantee that the problems will even become declared and properly acknowledged. Therefore, a stronger focus should be put on the earlier steps and the research community should have the possibility to review and improve trials before they are conducted. Here, we discuss the who, when, and how options for such early review.

## Options for pre-conduct review and improvements of trials

**Table 1** details current options for doing pre-conduct review and improvements before trials are launched. Currently, some review is happening by peers, sponsors/funding agencies, and institutional review boards (IRBs) but is mostly not publicly visible. Typically, rigor of those reviews is not guaranteed. Trialists may or may not share their ideas with peers for consultation, and the input received may vary. Some sponsors may have better review processes than others and many sponsors, in particular private ones, may even have incentives for biasing trials rather than making them unbiased. IRBs typically lack the expertise, resources, and time to look at trials at any depth in any matter beyond strict elements of ethical conduct. For the FDA it is common practice to review the study protocol before the trials can start by the manufacturer, while for the EMA, one can obtain prior scientific advice from the agency if they wish. Such consultative processes between sponsor and regulator are often not fit-for-purpose, as pharmaceutical companies later bend those rules once the trial is conducted (4).

Trial registration has become far more frequent, desirable, and even mandatory for a large share of the clinical trial agenda (5). However, typically there is no review process involved in registering information in the devoted sites, e.g., [clinicaltrials.gov](http://clinicaltrials.gov). The availability of structure/templates for the reported items in such sites may offer some guidance to investigators on what elements are essential to think about regarding their trial. However, it is very unlikely that trialists will improve their trials instigated by these templates. In fact, often non-research staff may enter the information in the registration sites. Guidelines like SPIRIT were invented to help improve reporting and completeness of protocols. However, uptake of

SPIRIT by trialists has been limited. Moreover, a recent randomized controlled trial (RCT) has shown that adherence to those guidelines is not effective (6).

Placing protocols and statistical analysis plans (SAPs) (“documents that contain a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data” (7)) in public view has become increasingly common for certain trialist groups that have routine, dedicated sites for placing that information. Moreover, the practice of publishing peer-reviewed protocols before doing the trial is becoming popular. A meta-research study identified only 596 published protocols for RCTs in PubMed (8) for the years 2001-2011. The number of RCT publications indexed in PubMed (“randomized controlled trial [pt]”) during the same time span was 179 924, i.e. 300-times larger than the number of published protocols. The publication of protocols has accelerated a lot since then. A search in PubMed with protocol [ti] AND (randomised [ti] OR randomized [ti]) identifies 16885 items as of October 19, 2022; based on random sampling 75% of them seem to be indeed trial protocols. While many more trial protocols are published currently, probably the vast majority (>90%) of trials still do not publish their protocols in journals.

Protocol publication may be even more frequent for the most influential trials that end up being published in major journals and have greater impact on both science and practice.

However, we have no information if those protocols were peer-reviewed after the beginning of the trials and how meticulous and helpful these peer-reviews were. Another meta-research study found that protocols were available for 82% of RCTs published in 2016 in high impact medical journals, a priori versions were available for 44% of RCTs and the earliest available protocols were dated around 2 years after the start of the trial for the remaining RCTs (9).

Importantly, even though protocol availability is expected to hinder selection bias and reporting bias, discrepancies between protocols and published articles happen very often. Studies showed discrepancies up to 62% between the primary outcomes specified in protocols and those defined in published articles (10)(11). More recently, findings from Goldacre et al. suggest that the prevalence of deviations (e.g. outcome switching, adding outcomes) is high in trials published in major journals (12).

While sharing the SAP allows readers to distinguish between planned and unplanned analyses (13), SAP availability has been low, ranging from 1-5% in selected past samples (14)6/5/2023 4:23:00 PM(16), except in some major medical journals in which SAPs were available for 50% (ranging from <10% for Annals of Internal Medicine, BMJ, and Lancet to 92% for NEJM) (9). SAPs published in journals remain distinctively uncommon. When searching in PubMed as October 21, 2022, for the string “statistical analysis plan [ti] AND (randomised [ti] OR randomized [ti])”, out of 160 only 155 were identified (5 were not eligible being a correction, erratum, or meta-analysis of RCTs). This output highlights the scarceness of SAPs and shows how these crucial documents are often not peer-reviewed externally.

Amendments to the protocols and SAPs can easily be placed online in public view along with justifications for why they had to happen and a statement on when they happened. However, this is done currently only in a minority of trials.

**Registered reports for clinical trials may complement existing initiatives**

Registered Report represent a publication format that values the importance of the research question and design and includes peer-review of the protocol before data collection (17). The implementation comprises two stages. At the first stage, the research protocol is sent for peer-review by the journal. The peer-review occurs before data collection and evaluates both the relevance of the research question and the appropriateness of methods. If passed, an in-principle acceptance is granted and data collection can start. In contrast to peer-reviewed publications of protocols and SAPs, registered reports wait until the study is completed for a paper to be published. In principle, the journal will accept to publish the submitted paper whatever the final results are. Stage 2 occurs for the finalized article presenting the study results and conclusions. Stage 2 peer-review intends to check that results are aligned with the accepted protocol (18). Introduced in 2012 in psychological/cognitive science disciplines (19), to date more than 300 journals offer the registered report format; most stem from the field of psychology (20). There is some evidence of their effectiveness to reduce selective reporting. Registered reports were associated with a decrease in prevalence of “positive” results when compared with classic journal articles in psychological research (44% versus 96%) (21). How much those results would translate in the field of clinical trials where registration is the norm is however unknown. Some evidence suggests that effect sizes observed in registered reports were similar to those observed in studies with pre-registration alone, both being lower than standard reports (22).

Few medical journals have adopted registered reports. BMC Medicine was the first generalist medical journal that adopted Registered Reports, in 2017 (23), but has published only 3 registered reports, none being a clinical trial (24–26). Others journals include the British Journal of General Practice, PLOS ONE (27), and journals affiliated with the Journal of Medical Internet Research (JMIR) (28). For PLOS One over 20 Registered Report Protocols



were found on their website, but no clinical trials are included (29). Almost 100 reports of clinical trials identified by an International Registered Report Identifier (IRRID) were published by the JMIR journals, but none of those papers were really registered reports. They were rather clinical trials with a published protocol. Protocols were often published after inclusion of the first patient and final reports often deviated from initial protocols (30).

Therefore, implementation of registered reports for clinical trials is almost nonexistent currently. Ironically, the field of clinical trials led these efforts 25 years ago. In the 1990s - many years before Registered Reports made their formal appearance - the Lancet offered a pathway through which important clinical trials could be submitted for peer-review and provisional commitment to publish before their conduct, based on their protocol. The program ran from 1997 to 2015. A 2008 interim analysis of the initiative reported 358 trial protocols submitted and reviewed, of which 85 received acceptance to be published in summary form on the website and 34 were eventually published after the study was completed and again peer-reviewed. In 2015 the program closed after 153 accepted protocols (31). Beyond the difficulty to identify peer-reviewers for protocols, implementation faced several challenges. Trials often deviated from the protocol (e.g. studies were only partly completed, funding run out, etc.) and sometimes the research took so long that science/evidence had moved on (32).

Such an example illustrates the implementation challenge registered reports may face regarding the publication of clinical trials, especially in an environment of journals such as Lancet that are extremely competitive in terms of impact and novelty. However, for most journals this should not be an issue: a good RCT that has been properly reviewed as a protocol and has been reasonably well conducted should find a place in their pages.

## Ways of moving forward

Any prospective initiative to improve early review of trials should be aligned with current practices. Clinical trials usually undergo various steps of siloed, disconnected, and rather not transparent peer-review by funders, IRBs, and regulatory authorities, and then before publication. While current peer-review does not achieve much that is desired, reviewers (at all steps and cumulatively) are overburdened.

Therefore, one could take advantage of all these already existing steps, by making them more transparent and sharable. This could simplify the process, hence reducing the total burden (**Table 2**). Technological innovation (e.g. AI checking of protocols) may help in some of these processes, but human review will probably remain important.

To enhance pre-conduct peer-review, relevant stakeholders, from funders, to journals should become better connected. As one example, BMJ Open is publishing protocols without further review on the condition that they have received IRB approval and independent peer-review from funders (33).

Others have proposed publishing separately online research problems, hypotheses, protocols, data, analyses, interpretations or real-world implications/translations(34). It is unclear though whether this process may increase peer-review load and whether it will result in better evidence eventually or more fragmentation.

Another step forward to relieve review burden would be to make peer-reviewed protocols from the regulatory side and comments from the sponsors available for the public. This would also enhance public trust and would spot deviations more easily. The mandatory registration of clinical trials by the International Committee of Medical Journal Editors (ICMJE) in 2005, and the subsequent requirement for a data sharing statement 13 years later, have demonstrated the potential for making research practices widely adopted when multiple journals work together towards a common goal (35)(36). A concerted effort by many stakeholders may also be needed to make improved pre-conduct review practices widely adopted – otherwise many trialists may still just seek outlets with more relaxed requirements. Also enhancing the use of Registered Reports in clinical trials may need to involve journals, funders, researchers and even health authorities to be successful (37). Since 2022 Cancer Research UK partners with 13 journals to pilot a Registered Reports consortium and researchers may opt-in for this review format in two sub-programs of their funding schemes. Part of this young initiative may involve clinical trials (38).

Finally, pre-conduct peer-review may need to be bolder in shaping the overall clinical trial agendas. Many clinical trials are too small, redundant, futile from their very inception, or overtly biased. Making their plans transparent at the earliest stages may help reduce some waste and improve trials that have the potential to offer valuable evidence.

### **Contributors and sources**

The analysis arose out of discussions on the role of how Registered Report project could be integrated into clinical research. After further input from JPAI this extended to how early interventions could improve the quality of clinical trials. MS wrote the first draft. MS, FN,

JPAI revised the manuscript critically for intellectual content, and approved the final version.

MS is the guarantor.

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### **Patient involvement**

No patients were involved when writing this manuscript.

### **Conflicts of Interest**

The authors declare that they have no competing interests.

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Journal Pre-proof

Table 1. Options for review and improvement of trials before they are launched.

<b>Options for pre-conduct review and improvement</b>	<b>Publicly visible</b>	<b>Expertise and rigor of review</b>	<b>Frequency</b>	<b>Incentives for review</b>	<b>Disincentives/problems</b>
Protocol review by peers	No	Variable	Unknown	Gain in quality	Fear of scooping
Protocol review by sponsors	No	Variable, pays attention to issues that are related to regulatory requirements and the optimal placement of the research towards successful applications for licensing	Funded trials	Quality of funded project	Conflicts of interest from other grantees may interfere
Protocol review by regulatory authorities (FDA-EMA)	Mostly no	High, but may be uneven (regulatory agencies are understaffed when compared with the volume of submissions) and bias cannot be excluded, interactions of regulators and industry may not be	Variable	Trust and confidence by public	Conflicts of interest from pharmaceutical companies may interfere



		ideal and conflict can creep in			
Protocol review by Institutional Ethical Committees / Review Boards	No	Typically review does not address design, subject matter, relevance and methodology unless considered to touch on ethical issues	Routine	Ethical and methodological concerns are addressed before conduct	Lack of standardization across Boards/Limited subject-matter and methodological expertise among Board members
Registration in registry sites, e.g. clinicaltrials.gov	Yes	None (other than guidance on structure of what is recommended to be reported)	Desired, but often missed	Traceability of changes	Registered information is often rudimentary
Protocol deposited in public repository	Yes	Usually none	Minority, but growing	Increased transparency	No structured approach/ Fear of scooping
Protocol reviewed and published	Yes	Variable, depends on journal and case-by-case circumstances	Minority, but rapidly growing	Gain in quality	Often after study starts
Statistical analysis plan deposited in public repository	Yes	Usually none	Rare, but growing	Gain in transparency	Limits flexibility of analysis
Statistical analysis plan reviewed and published	Yes	Variable, depends on journal and case-by-case circumstances	Very rare, but growing	Gain in quality	More lengthy process/Review may not be necessarily robust (few journals have strong statistical expertise)

Registered reports	Possible	Variable, depends on journal and case-by-case circumstances	Very rare	Gain in quality/ feedback from a broader range of individuals encompassing diverse perspectives and backgrounds/ publishing guaranteed even if results are negative	Limits flexibility of analysis, cumbersome process
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Table 2. Potential actions for enhanced pre-conduct peer-review that may ameliorate siloed processes

<b>Stakeholder</b>	<b>Action</b>	<b>Goals/ aims</b>	<b>Disincentives/ hurdles</b>
All stakeholders reviewing the trial at early stages	Including AI in the peer-review process to check for registration of protocols and statistical methods	Reduces possible oversights by reviewers/ Avoiding double checks	Manual checks may still be necessary if AI accuracy is imperfect/ Smaller journals might not have resources
	Providing structured guidelines for peer review	Reduces burden for researchers Identification of methodological and ethical issues easier	Expertise still needed/ Standardization of peer review might not solve issues that are topic-specific
	Making all steps of research process public and open for peer-review	Likely more efficient review and publication process avoiding redundancy and aiming for reducing total effort	Lacking digital infrastructures supporting transparency efforts
Journals	Publishing protocols that have gone through independent peer-review	Making more protocols routinely available before the conduct of the respective trials	Many protocols may be trivial/ Journals might lose in impact factor
	Offering Registered Reports as article format	Possible quality improvement and diminished selective reporting biases / Upscaling of Transparency and Openness Promotion (TOP) factor (39)	Burden of peer-review for articles that might not be completed
Institutional Review Boards	Publishing protocols that have gone through independent review by IRBs	Making more protocols routinely available before the conduct of the respective trials	Infrastructure in IRB not available/ Grantees may not agree with publishing research protocol

	Checking trial registration as condition of approval	Protecting rights of participants that trial will not disappear unnoticed	Deviations from registration still occur often without any explanation and registration of information is not detailed enough
Regulatory agencies	Making protocols from peer-review from Regulatory Agencies routinely available for the public, including regulatory comments and replies from trialists/sponsors	Making influential trials' protocols and their regulatory vetting routinely available may enhance public trust; it may be complemented with more routine opening for public comments	Conflicts of interest may interfere/ Pharmaceutical companies might lobby against such approach or twist it to their benefit
Funders/ Investigators	Running more Registered Reports in clinical trials	Possible quality improvement and diminished selective reporting biases	Difficulty of realizing such endeavor/ Infrastructure not available/ Most biomedical journals are not cooperative

## Highlights

- Traditional peer-review of clinical trials happens after the trials are already done
- In this piece we examine several options for review and improvement of trials before they are conducted
- Innovative ideas are necessary to advance quality in clinical trials and lower the cumulative burden for peer-reviewers

Journal Pre-proof

### **Conflicts of Interest**

The authors declare that they have no competing interests.

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**Author statement**

The analysis arose out of discussions on the role of how Registered Report project could be integrated into clinical research. After further input from JPAI this extended to how early interventions could improve the quality of clinical trials. MS wrote the first draft. MS, FN, JPAI revised the manuscript critically for intellectual content, and approved the final version. MS is the guarantor.

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