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Trial Registration: Lessons Learned from Nursing Research

Trial Registration: Lessons Learned From *Nursing Research*

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Richard John Gray (2016) makes good points about the importance of registering randomized controlled clinical trials (RCTs): registration guards against outcome switching, reduces publication bias and selective reporting, and disseminates information about trials underway to avoid duplication of effort by multiple groups of investigators. At *Nursing Research*, we have required registration since January 1, 2015. We publicized the requirement, with a detailed editorial, in the March/April 2014 issue (Chyun, 2014). When primary reports of full-scale or pilot RCTs have not been registered prior to recruitment of first participants are submitted, they

receive a “do not review” decision. RCT protocols must also be registered in order to be reviewed and considered for publication.

We have found that the registration requirement triggers many additional specific tasks as we manage manuscripts—instituting the policy change involves many actions beyond posting the registration requirement. In this article, we will discuss a few “lessons learned” that we hope will be helpful to other editors, as we all move forward achieving the standard of making sure trials are registered before publication.

WHAT IS A CLINICAL TRIAL?

Be prepared to define “clinical trial.” Published definitions vary, and author-investigators will need to know what you mean. For example, the definition from the International Council of Medical Editors (ICMJE) is broad:

> *…any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome (ICJME, 2016a).*

As defined in a National Institutes of Health (NIH) policy that will go into effect January 18, 2017, a clinical trial is:

> *…a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes (NIH, 2016).*

Importantly, the new policy dictates not only that all NIH-funded clinical trials be registered on Clinical Trials.gov within 21 days of enrollment of the first subject, but also that results be submitted within one year of the study completion date. There are certain exceptions under which results reporting may be delayed for up to two additional years.

Some issues are not clear. For example, if there is no comparison group, can you really be studying cause-and-effect? Is a comparison between existing groups defined by whether they received an intervention or not (as documented in a health record) a trial?

At *Nursing Research,* we limit the registration requirement to RCTs (intervention studies with randomization to treatment conditions), but other editors may have different criteria. Determine whether your policy about registration applies to primary reports of trial findings, and/or primary reports plus any secondary analyses based on the trial dataset, and/or pilot studies. ICMJE suggests that if the researcher is uncertain whether their study meets the definition for a clinical trial that they should err on the side of registration (ICJME, 2016b).

REGISTRATION SITES

Communicate to authors which registration sites are acceptable, and make it clear what registration is. We have had several authors who thought that approval by an Institutional Review Board (IRB) constituted RCT registration and were surprised when we pointed out the difference. A registration site should be approved by the ICJME or World Health Organization (WHO, 2016). The WHO currently lists 16 primary registration sites on the International Clinical Trials Registry Platform (ICTRP) or ClinicalTrials.gov, which is a data provider to the WHO ICTRP.

The WHO Trial Registration Data Set (Version 1.1.) includes 20 items that are considered the minimum amount of trial information that must be included in a register for it to be fully registered (WHO, 2016):

1. Primary registry and trial identifying number,
2. Date of registration in primary registry,
3. Secondary identifying numbers,
4. Sources of monetary or material support,
5. Primary sponsor,
6. Secondary sponsor,
7. Contact for public queries,
8. Contact for scientific queries,
9. Public title,
10. Scientific title,
11. Countries of recruitment,
12. Health condition(s) or problem(s) studied,
13. Interventions,
14. Key inclusion and exclusion criteria,
15. Study type,
16. Date of first enrollment,
17. Target sample size,
18. Recruitment status,
19. Primary outcome(s), and
20. Key secondary outcomes.

EDITORIAL PROCESSES

In the journal office, it is important to create a mechanism for obtaining and documenting registration numbers, registration dates, data collection dates, and links to the registration on the registration site as part of manuscript submission. At *Nursing Research*, required questions used to obtain this information are part of the Author Questionnaire embedded in the online manuscript submission process.

Be prepared to verify registration date and compare the date with the date of first participant recruitment (which also needs to be verified). These tasks are facilitated when corresponding authors provide the information during manuscript submission. If the information is not on hand, corresponding authors need to be queried, adding a step to the pre-review stage of manuscript management. At *Nursing Research*, the Managing Editor verifies the information and the Editor makes notations about RCT registration status on the manuscript record as part of decision-making documentation.

Be prepared to verify that manuscript is accurately reporting on pre-specified criteria. Descriptions of intervention and comparison conditions in the manuscript should match information provided on the trial registration site. Likewise, primary and secondary outcomes should be analyzed as planned.

Be prepared to write letters to authors stating that papers reporting clinical trials will not be reviewed when they have not been registered. The letter should refer to trial registration policy at the journal, and to published information about the rationale for trial registration (e.g., Gray, 2016; International Committee of Medical Journal Editors, 2016b). Many authors will be very surprised to hear that registration is required, or may not even be aware of clinical trial registration practices. In reply to correspondence, authors have written back to us with comments like “This isn’t required in my country,” or “Trial registration wasn’t

required at the time the study was carried out," or "My school approved the project," or "Can you make an exception to the policy?" Editors should be firm in their response about adherence to the trial registration policy, and professional in tone.

UPDATE THE INFORMATION FOR AUTHORS TO INCLUDE INFORMATION ABOUT TRIAL REGISTRATION

Place information about trial registration requirements in the Information for Authors (IFA). Adequate lead time in terms of policy initiation should be allowed so that authors have the opportunity to comply. Consider publishing an editorial, not only to alert authors on the requirement, but to underscore the need for clinical trial registration.

Trial registration information should be included in published papers. Provide the name of the registry and the trial registration number. The information may be included at the end of the Abstract or in notes at the end of the paper.

CLOSING THOUGHTS

The aim of clinical trial registration is to make study design information accessible to all. While registration of trials allows the opportunity for the researcher(s) to make complete study plans known and widely available, and supports reporting of both negative and positive trial results, registration of a trial does not mandate results reporting. Failure to report clinical trial results remains a significant problem. A new tool, TrialsTracker, demonstrated that 45.2% of trials had missing results (Powell-Smith & Goldacre, 2016). Dr. Ben Goldacre, whose site All Trials Gray (2016) highlights, has also tracked "switched" outcomes in clinical trials (Goldacre et al., 2016). Out of 67 trials published in the top five medical journals, nine trials were perfectly reported (as specified according to registry); 354 outcomes were not reported; and 357 new outcomes were silently added.

Use of Consolidated Standards of Reporting Trials (CONSORT) for RCTs and guidelines recently developed for reporting of Pragmatic Clinical Trials (PCTs), by the NIH Collaboratory (NIH Collaboratory, 2016), along with prospective registration of all clinical trials can assist in assuring that the necessary information needed for healthcare decision making is widely available. As reviewers and editors we have a responsibility to assure that clinical trial manuscripts are consistent with what has been registered. As editors we should not preferentially publish trials with positive findings at the expense of those with negative results.

Careful attention to the implementation of editorial processes needed to support the standard requiring trial registration and clear, timely communications with author-investigators are critical to advancing transparent dissemination of trial findings as the basis for clinical care. Gray (2016) noted that, as nursing editors, we have yet to speak with the same collective voice about trial registration as a requirement for publication. We believe that the time is now.

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