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EDITORIAL

Why should clinical trials be registered?

Elizabeth Wager and Nadia Elia

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Would you enter a clinical trial if the consent form included the statement 'Although clinical trials aim to improve medical knowledge, only about half ever get published in medical journals and, of those that are published, around half the measurements won't be reported in the article, so doctors won't have a chance to read about them'? Or, even worse: 'If this trial doesn't produce results that support the sponsor's product (or the investigator's theory) it probably won't be published'. It is hard to imagine any patient consenting to take part in a trial under these circumstances. To make matters worse, positive findings may be published more than once, and sometimes in ways that deliberately obscure the fact that they are duplicates, and this can further skew the evidence base towards the positive findings.[1] Nonpublication, selective publication and covert duplicate publication all contribute to the problem of publication bias.[2]

What is the evidence of publication bias?

Trial registers have been used to measure the problem of nonpublication. Ross *et al.*[3] found that only 46% of a sample of 677 trials (excluding phase I studies) that were registered on ClinicalTrials.gov, and had completed by 2005, were published by 2007. (If they could not find a publication on Medline, Ross's team emailed a trial official to ask whether the trial had been published; of the 117 contacted, four provided a publication, 40 confirmed that the trial had not been published, and 73 did not reply). More recently, Jones *et al.*[4] assessed 585 clinical trials that had recruited at least 500 participants, were registered on ClinicalTrials.gov and had completed by January 2009. They found that, by November 2012, 29% of these trials remained unpublished. These studies show the worrying rate of nonpublication in both registered and large trials. It is likely that the problem is even worse among nonregistered and smaller studies.

Yet, until recently, publication bias has received little attention in the medical literature. One reason for this may have been the fact that, by its very nature, nonpublication is difficult to investigate, and is hidden from journal editors. Although peer-review can be used to assess and improve reports submitted to journals, editors are powerless about research that is never written up. One factor that has raised the profile of publication bias is the growing influence of evidence-based medicine with its emphasis on systematic reviews and meta-analyses. The process of assembling and analysing all publications on a topic may uncover redundant publications and may also suggest the existence of trials that have remained unpublished.[1]

Although editors can do little or nothing about studies that are not submitted to their journals, they can help to alleviate the problems of publication bias by supporting trial registration and by making a commitment to consider reports of well designed studies regardless of the direction or statistical significance of their findings. It is, therefore, good news that the *European Journal of Anaesthesiology* will make trial registration a requirement for the publication of interventional trials. This editorial explains the policy in more detail and the reasons for its adoption.

What is trial registration?

Registration involves entering details of a trial's design on a public database. The WHO has published a 20-item minimum dataset, which has been adopted by many registers and used as a criterion for complete registration by several journals.[5,6] When a trial is accepted onto the database, it receives a registration number, which can be quoted on subsequent publications. Some databases (notably the US register, ClinicalTrials.gov) also enable a summary of trial results to be posted, but this is a separate function from the initial registration, which should, ideally, occur before patients are recruited (and therefore long before results are available).

Why register trials?

There are several reasons why trials should be registered. The first reason is that trial registration helps to alleviate

From Sideview, Princes Risborough, UK (EW), and Division of Anaesthesiology, University Hospitals of Geneva, Geneva, Switzerland (NE)

Correspondence to Dr Nadia Elia, MD, MSc, Division of Anaesthesiology, University Hospitals of Geneva, Rue Gabrielle-Perret-Gentil 4, CH-1211 Geneva, Switzerland
Tel: +41 22 382 74 41; fax: +41 22 382 75 11; e-mail: nadia.elia@hcuge.ch

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publication bias in several ways. If all studies are registered at inception, nonpublication is at least apparent rather than invisible and can be pursued with investigators or sponsors. Furthermore, if publications include a registration number, then multiple publications from a single dataset can be distinguished.[7]

The second reason is that trial registration provides a record of a trial's primary outcome as stated in the protocol at the start of the study. This should reduce the temptation of switching endpoints or introducing new ones and enables peer reviewers (and readers) to identify such selective or misleading reporting. Strong evidence of selective reporting exists. Chan *et al.*[8] compared the protocols from 102 trials approved by a Danish ethics committee with reports published in journals. This revealed that 50% of efficacy outcomes and 65% of safety outcomes mentioned in trial protocols were not reported in the journal articles. They also found that, in 62% of the trials, there was a discrepancy between the journal article and the protocol relating to at least one primary outcome (i.e. the outcome was omitted, introduced or changed). In a similar cohort of 48 trials funded by the Canadian Institutes of Health Research, Chan *et al.*[9] found that 31% of efficacy outcomes and 59% of safety outcomes were incompletely reported, showing that the problem of selective reporting is not restricted to commercially sponsored research.

A third reason is that trial registration may improve collaboration and communication among researchers. For example, by allowing researchers to be aware of ongoing trials that are similar to one they are planning to perform, and thus avoiding unnecessary (and unethical) duplication of research. In conjunction with literature searches, trial registers may also help researchers identify where research is needed.

Finally, trial registration informs the public about current research and may allow potential trial participants to be aware of recruiting trials for which they might be eligible.

When should trials be registered?

The full benefits of registration are achieved only when trials are registered at the start. The Declaration of Helsinki demands that 'Every clinical trial (..) be registered in a publicly accessible database before recruitment of the first subject'.[10] Similarly, the International Committee of Medical Journal Editors (ICMJE) requires trials to be registered before the enrolment of the first participant.[6] Under the US Food and Drug Administration Amendments Act (FDAAA) legislation, trials must be registered within 10 days of the first patient being recruited.[11] Some trial registers allow retrospective registration (i.e. after a trial has started or even after it has finished), but may highlight this fact.[12]

The UK National Health Service research ethics committees recently announced that trial registration would be a requirement for ethical approval.[13] If trials are registered before receiving ethics approval, the approval status should be updated later.

Which trials should be registered?

The ICMJE requires that 'Any research project that prospectively assigns 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' should be registered.[6] The US FDAAA legislation, largely aimed at drug companies, has slightly different requirements and uses definitions based on the phase of drug development.[11]

The WHO minimum dataset was developed primarily to capture the design of prospective, interventional studies.[5] The ethical arguments around the duty to publish research findings are strongest and clearest for research involving patients. Jones *et al.*[4] wrote that 'The lack of availability of results (..) constitutes a failure to honour the ethical contract that is the basis for exposing study participants to the risks inherent in trial participation.' However, it can also be argued that registration of all types of medical research is good practice insofar as it can prevent (or at least highlight) selective publication, nonpublication and duplicate publication. Many registers accept registration of any design of trial, although the fields are generally based on prospective, interventional trial designs. There is, as yet, no agreed minimum dataset to describe observational studies, but there is a specialised register for systematic reviews of medical interventions (http://www.crd.york.ac.uk/prospero/), which, like clinical trials, may also not be published if they reach unfavourable conclusions.

Where should trials be registered?

A number of trial registries exist, including national registers and those focusing on particular disease areas. Multiple registration is permissible (and may even be required to comply with national legislation and drug regulatory requirements), but, where possible, these should be cross-linked and include registration numbers obtained from other registers for the same trial. The ICMJE 'accepts registration in any registry that is a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) (see http://www.who.int/ictrp) or in ClinicalTrials.gov' (which supplies data to the WHO). The ICMJE has identified these registries because they are publicly searchable, open to all registrants, managed by not-for-profit organisations, have mechanisms for validating registration data and are electronically searchable.[6]

One of the most complete registers of drug trials is maintained by the European Medicines Agency (EMA). The European Clinical Trials Database, or EudraCT (https://eudract.ema.europa.eu/index.html), contains information on all trials reported by manufacturers to the EMA in support of license applications since May 2004. This

amounted to 38 503 trials in October 2013.[14] Yet, until recently, this register was not open to the public. Following a change of policy, details of trials registered on EudraCT since 20 June 2011 are publicly accessible; therefore, ICMJE now accepts such trials as registered. Another recognised register based in Europe is the International Standardized Randomized Controlled Trial Numbering (ISRCTN) scheme (http://www.isrctn.org/).

The largest trial register is ClinicalTrials.gov, which is run by the US National Library of Medicine at the National Institutes of Health. It was established with US government funding as a result of legislation passed in 1997 (the FDA Modernization Act). Registrations on ClinicalTrials.gov increased dramatically in 2005 around the deadline set by the ICMJE for registering existing trials.[15] Use of ClinicalTrials.gov was further boosted when US legislation was tightened in 2007 by FDAAA, which required companies to register phase II to IV trials as a condition for submitting licensing applications for new products.[11] As of July 2013, ClinicalTrials.gov contained over 150 000 registered trials being conducted in 185 countries.[16] WHO does not maintain a register of its own, but provides a useful portal (the ICTRP) that enables searching across multiple registers.[5]

Who should register the trial?

It is obviously important that trials are not inadvertently registered twice in the same register (as this would result in a single trial having two registration numbers). Because drug and device companies may have to comply with legislation such as the US FDAAA (which applies to new products submitted for approval in the USA), the sponsor will often take responsibility for registering the trial. In other cases, registration is usually the responsibility of the principal investigator.

How should trials be registered?

Complete registration should include all 20 items recommended in the WHO minimum dataset.[5] However, this may need to be adapted for observational studies, as the data fields were designed to capture details of randomised, controlled trials.

How much does registration cost?

Nearly all the major registers receive government funding and, therefore, do not charge registrants. The ISRCTN Scheme is independent and therefore charges a fee for registration (currently GBP £205).[17]

The *European Journal of Anaesthesiology* policy

Up to now, registration was not mandatory for trial publication in the *Journal*. After considerable discussions, and because we believe that it will further improve the quality of the articles published, the editors have decided to make prospective trial registration (i.e. before recruitment of the first patient) mandatory for the publication of interventional studies in our journal.

Therefore, the *Journal* requires authors to prospectively register the protocol of any interventional trial, which will start enrollment of patients after 1 January 2015. This will be a mandatory requirement for subsequent publication in the *Journal*. Authors of interventional trials who have started enrollment of patients before 1 January 2015, and who have not prospectively registered their protocol, may submit manuscripts to the *Journal* who will consider them for possible publication on the basis of their individual methodological quality.

Interventional studies include randomised and nonrandomised trials on humans. Researchers who are uncertain whether their trial meets the criteria for registration should err on the side of registration if they wish to seek publication in the *Journal*. We strongly encourage the registration of observational studies and of systematic reviews, although their registration will not be mandatory for publication at the moment (Table 1).

Authors may choose any registry acceptable to the ICMJE[6] to register their protocol and are required to give clear registration details (name of the registry and registration number) at the end of the abstract. The editorial team will check the validity of the registration details provided.

Recognising that journals may also contribute to publication bias if they favour positive over negative results, the editors of the *Journal* commit themselves to consider for publication trials with sound methodology that have been appropriately registered, regardless of whether the findings are positive or negative. By doing so, we hope to improve the overall quality of published anaesthesiology research.

Of note, some trial registers (notably ClinicalTrials.gov) not only permit the design of a trial to be registered (before it has begun), but also allow short summaries of numerical results to be posted after the trial has completed. Such results posting has been required under the US FDAAA since 2008 for many trials that form part of licence applications to the FDA for new products. In Europe, the European Medicines Agency has announced that it will require similar results posting in the future for

Table 1 New policy for trial registration for the *European Journal of Anaesthesiology*

Trial	Journal requirement
Interventional trial starting recruitment after 1 January 2015	Must be registered before recruitment begins
Interventional trial starting recruitment before 1 January 2015	May be submitted. *EJA* will consider publication on the basis of sound methodology
Observational trials and systematic reviews	Registration encouraged, but not mandatory for publication

licence applicants, and it launched a voluntary scheme in October 2013. The *Journal* encourages the posting of trial results on public registers (alongside the protocol details registered at the start of the study) as a useful step towards research transparency. Therefore, authors should not worry that posting summary results on a trial register will prevent subsequent publication in the *Journal*. However, unlike prospective registration of the study design, the *Journal* (like the ICMJE) does not require such posting.

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