



Trial registration: What do writers need to know?

by Elizabeth Wager

Trial registration: the current situation

The International Committee of Medical Journal Editors (ICMJE), which comprises the editors of some of the world's most influential medical journals, have added an extra hurdle for publication. Since September 2005, they have refused to publish trials in their journals unless they have registered. This policy was announced in late 2004 together with criteria for suitable registers [1]. Up to mid-2005 there was a grace period during which trials could be registered retrospectively, i.e. after they had started. But trials that started recruiting patients since mid-2005 must now be registered prospectively, i.e. before recruitment begins, to meet the editors' criteria.

The World Health Organization (WHO) has brought together editors and registration experts to agree a minimum data set required for registration [2, 3]. However, pharmaceutical companies have raised objections about certain items they consider sensitive and would prefer not to release at trial initiation. It would have been tidier if the editors had agreed on what information they required before making registration compulsory — but, for the moment, companies must do their best and hope that their registrations will be deemed adequate if they choose to submit results to the ICMJE member journals.

How did we get here?

The idea of trial registration was proposed around 20 years ago [4]. The main proponents were people compiling systematic reviews who were concerned that these would be biased if some trials remained unpublished. It was even suggested that underpublication of results constituted research misconduct [5]. In the 1990s one or two pharmaceutical companies and other organizations established voluntary trial registers [6], but few others followed their example and, up to the early 2000s, the US industry association, PhRMA, opposed registration despite US legislation calling for registration of trials in serious and life-threatening conditions. However, growing public concern about systematic nonpublication of unfavourable findings and legal action against Glaxo SmithKline focusing on nonpublication of safety data about its antidepressant Seroxat (which was settled out of court), increased the stakes. The demands of the ICMJE editors were the first to be accompanied by a sanction companies really feared, namely exclusion from the world's most respected medical journals.

What register should I use?

At present, two registers meet the editors' criteria: ClinicalTrials.gov and the ISRCTN (International Standardized Randomized Clinical Trial Numbering) scheme. Clinicaltrials.gov is run by the US National Library of Medicine. It was initially established in response to legislation requiring the registration of US trials into serious and life-threatening conditions. When the editors' first announcement appeared, there was some consternation that ClinicalTrials.gov would accept only trials of products being considered by the FDA. Companies that had not applied for a US licence, or investigators studying other kinds of interventions, could not register their trials. ClinicalTrials.gov quickly relaxed its entry criteria, but this has not entirely allayed concerns that it is funded by the US government and there is no guarantee over its future policies or funding.

The ISRCTN system also caused debate when the editors first published their criteria, since these stated that acceptable registers could not be run by commercial companies. The BMJ was concerned that this requirement ruled out the ISRCTN since it was then owned by the Current Science group (a commercial publishing company). The BMJ therefore issued a slightly different statement from the rest of the ICMJE [7]. However, since then, the ISRCTN has been transferred to a not-for-profit organization. Since ISRCTN is independent and self-financing, it charges a fee for registration, but this may be waived in cases of hardship and for trials from resource-poor areas. An attempt was made to secure EU funding for the ISRCTN system, but it failed.

The European Medicines Evaluation Agency (EMA) registers all trials submitted as part of licensing applications, but these data are kept confidential so the so-called EuDRACT database does not meet the editors' requirements [8].

Which journals are affected?

Initially, the requirement applied only to the journals edited by the ICMJE committee members (not to all journals that endorse the ICMJE Uniform Requirements). However, other journals are now following suit [9]. Anybody involved with publication strategies should keep a watchful eye on journals in their area.

Trial registration

Why do we need trial registration?

The main aim of registering trials is to ensure they are published responsibly. Findings that are statistically significant or that favour the sponsor's product are more likely to be published than negative ones, and such publication bias can skew the results of meta-analyses as can undetected redundant publication [10]. Unambiguous study identification should reduce these effects and make it easier to call companies to account for unpublished studies. Another possible benefit of public trial registers is that they can help patients identify studies for which they might be eligible and thus help recruitment. WHO is also encouraging national trial registers as a means for countries to develop local health research infrastructure. Public access to details of trial design such as primary endpoints should also raise reporting standards and prevent selective or biased reporting. The EMWA guidelines already suggest that writers should have access to the protocol when preparing reports [11], and trial registration should make such key information readily available to journal reviewers and interested readers.

Another argument in favour of registers is that they will allow researchers to see what other trials are underway and therefore avoid duplication. However, others argue that knowledge of development plans and full details of trial designs could reduce competitive advantage. Commercial companies and academic institutions may therefore be reluctant to make full details available at an early stage. This had led to discussions about a lock-box system under which sensitive details of trial design are entered at the start of the study but only made public later. This proposal seems unlikely to find favour from the journal editors and WHO, but it may be a useful compromise if companies refuse to release full details.

What about trial results?

Trial registration should not be confused with posting results on websites, although these are often discussed together. To achieve its goal of preventing under-publication, registration must be accompanied by a commitment to publish results of all trials [12]. Some companies, and the US industry association PhRMA, have already established websites for this. However, it is not yet clear whether journals will regard such postings as prior publication — so this route may be reserved for studies that are not being submitted to peer-reviewed journals. It seems likely that the ICMJE will agree that posting a summary (e.g. using the ICH E3 summary format from clinical trial reports) is analogous to conference abstracts and therefore will not affect full publication in their journals. However, companies do need to be cautious until the editors issue a definitive statement. On a brighter note, preparing the website summaries has created opportunities for writers in at least one company which decided not to use summaries from existing reports.

Conclusions

Trial registration is now a fact of life for anyone hoping to publish a clinical trial in one of the major medical journals.

It is likely to spread to other journals. To achieve its aims, trial registration needs to be linked to a commitment to publish results. Registration may raise the standard of reporting clinical trials and might even create a few extra jobs for medical writers!

Affiliations / Competing interests

Liz Wager is a member of the WHO Scientific Advisory Group on trial registration. She has also served on an advisory board for ISRCTN. She used to work for Glaxo Wellcome, which was the first company to establish its own trial register. She has also advised various companies about trial registration strategies.

Elizabeth Wager

Publications Consultant, Sideview, Princes Risborough, UK
liz@sideview.demon.co.uk

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What are your FOMs?

A FOM is a frequently used word that we always misspell (FOM = frequent occurrence misspelling). Most of us will have five to seven of these and according to Richard Bell they will account for 60% of our spelling mistakes (*Writing Magazine* Christmas 1993). What about a spellchecker? You say. Richard Bell is not very enthusiastic about spellcheckers partly because throughout a travel article he had written his checker endeavoured to persuade him to change Eiffel Tower to offal Tower. A solution recommended by some American researchers is to carry around a prompt list but Bell thinks you might feel rather foolish flourishing your list in front of colleagues. One alternative he suggests is to memorise a phrase like "accidents occur on occasions" to help you spell each of these words with a double c. Another is to read more so that you visualise the words on a page and recognise the word's odd shape when it is misspelled.