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COMMENTARY

The need for trial identifiers

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SUMMARY

The medical literature is distorted by publication bias, duplicate publication and under-reporting of clinical trials. This can create problems in systematic reviews and meta-analysis which are increasingly used as the basis for evidence-based guidelines and therefore for treatment decisions. Various schemes for identifying trials and their associated publications are reviewed. These include trial registers and trial numbering systems. The inclusion of trial identifiers in all publications could greatly enhance the value of the medical literature and increase the robustness of systematic reviews and meta-analyses.

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Clinical trials form a vital link in the chain of medical research that starts with a promising molecule or an inspiration and ends with a medicine that can save or improve lives. Yet, as our knowledge of conditions and treatments increases, so does the volume of available information. It is impossible for most busy clinicians to keep abreast of even highly specialised fields, and generalists stand no chance of being able to assess all the new research that might be relevant to their practice.

The burgeoning medical literature is one reason for the rise of evidence-based medicine and the new discipline that has grown up around the synthesis of information. The preparation of systematic reviews has highlighted the complexity of the literature and the difficulty of identifying publications arising from the same study.

People preparing systematic reviews try to obtain all the relevant evidence. This will certainly mean trying to identify all published results, and may also involve seeking unpublished data. If studies use comparable methods, results may be pooled to produce a meta-analysis. Even if a meta-analysis is not possible, the reliability of the review may be compromised if all studies are not included, or if the results of some are included more than once. In the case of meta-analysis, Tramèr *et al*. have demonstrated the distorting effect that duplicate publication can have[1]. In a review of the effects of the antiemetic ondansetron they showed how a measure of the drug's effectiveness (expressed as the 'number-needed-to-treat' or NNT) was skewed by including duplicate publications. The NNT calculated from all 25 published papers was 4.9 (indicating that for every five patients treated, one would be completely free from vomiting for 24 h). However, six of these papers were found to be duplicates. When the duplicates were removed from the analysis, the NNT rose to 6.4 (a higher NNT means the drug is less effective and around six patients would need to be treated for one to achieve a response). The authors noted that trials reporting greater treatment effect were more likely to be duplicated – in fact the NNT calculated from the duplicated studies was just 3.9, compared with 9.5 for the non-duplicated studies. As well as distorting the measure of ondansetron's effectiveness, the duplicates may have led to 'unwarranted assumptions about safety' since, as the authors note: 'no major drug-related adverse effect seen in 11 980 patients sounds more persuasive than none in 8645 patients'.

The Tramèr study makes another important point. The researchers undertaking the systematic review were experts in their field and had considerable experience in preparing reviews, yet they initially failed to identify the duplicates. They concluded that 'covert duplicate

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reports can be very difficult to recognise'. Not only were the original findings of the meta-analysis distorted by the duplicates, but the duplicate reports were unwittingly cited in opinion leaders' articles, a widely circulated review and a standard surgical textbook. The duplicates were hard to detect because the publications often listed different authors and presented data pooled from a number of studies. In 21 of the papers there was no clear cross-referencing to other publications, and even when papers were cited there was no indication about the relations between them.

A more recent study has shown the sometimes complex ways in which studies are published[2]. Melander *et al*. compared the reports of 42 trials of five selective serotonin reuptake inhibitors (SSRIs) submitted to the Swedish regulatory authorities with publications identified from databases, reference lists and contacts with the manufacturers. They found that 21 studies contributed to at least two publications each and three studies contributed to five publications. Studies with significant findings were more likely to appear as stand-alone publications than those with non-significant results. Like Tramèr *et al*., they found that publications were rarely cross-referenced, often had different authors and presented pooled data in a confusing fashion. They concluded that 'any attempt to recommend an SSRI from the publicly available data only is likely to be based on biased evidence'.

The Melander study also showed the occurrence of publication bias. This occurs when favourable (or statistically significant) findings are more likely to be published than unfavourable (or non-significant) ones. In the case of one drug, all three studies with significant findings had been published, whereas a non-significant one had not. In the case of another, all eight studies with significant findings had contributed to at least one paper, while three trials with non-significant findings had not been published.

It is hard to estimate how common duplicate publication and selective publication is. Possibly the Tramèr and Melander studies represent extreme examples, but they do provide incontrovertible evidence that these problems exist. Multiple publication has also been documented in trials of non-steroidal anti-inflammatory drugs[3], vaccines[4] and a journal of industrial medicine[5], suggesting that the problem may be widespread.

Editors of medical journals have, for many years, discouraged redundant publication and asked authors to disclose related publications. The Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE) state that manuscripts are reviewed on the understanding that they 'have not been published, simultaneously submitted, or already accepted for publication elsewhere'[6]. Some journals ask authors to sign a statement or mention in their covering letter that their paper meets these requirements, but, judging by the evidence of duplicate publication across several different fields, this has little effect.

Another initiative, aimed at reducing selective publication, has been the creation of trial registers. These were originally proposed over a decade ago[7], but the response has been slower than hoped for[8]. One problem is that trial registers have been set up by a number of different authorities and organisations so there is no single source of information. However, many registers can be accessed via the *meta*Register of Controlled Trials which is available at www.controlled-trials.com/mrct/.

The original idea behind trial registers was to reduce, or even eliminate, selective or under-publication. However, registering a trial does not guarantee that it will be published, or even that the investigators or sponsors will make the unpublished data available. Furthermore, unless the registry number is included in all publications, registration does not solve the problem of duplicate publication.

The latest initiative to reduce distortion in the medical literature is an international system of trial identifiers. This is based on the simple concept that all randomised trials will be assigned a unique number which will then be included in all publications. Some information about the trial is entered onto a central database, but this need not be as detailed as that for a trial registry, and it is also possible for trials to be given numbers retrospectively, after they are under way.

The International Standard Randomised Controlled Trial Number (ISRCTN) scheme has recently been launched and has already assigned unique numbers to nearly 1360 trials. Each number consists of the prefix ISRCTN followed by 8 digits. Trial sponsors are being encouraged to join the scheme, and details can be found at www.controlled-trials.com/isrctn/. Several major funders such as the UK Medical Research Council (MRC), the National Health Service in England, and some leading medical charities have joined the scheme. A small administrative fee is charged for each number (currently this is €100, but this fee may be reduced for sponsors submitting large numbers of studies or for trials submitted from developing countries). Some journals have endorsed the scheme, although BioMed Central is the only publisher that requires a unique trial identifier to be included in all its publications.

Some major funding organisations such as the Veteran's Administration in the United States have their own trial databases, but these are limited to trials that they are directly funding. The National Library of Medicine (NLM) register (http://clinicaltrials.gov) assigns a unique number to all trials on their database,

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but this only includes trials conducted in the United States on serious and life-threatening diseases. Such systems do not offer the possibility for the organisers of other studies to apply for an identifying number or to be included in the database.

Trials funded by pharmaceutical companies usually have protocol numbers which often indicate the sponsoring company and the study compound. Although the ISRCTN system is preferable, since it offers a unique number and some details of the study in a searchable database, recent guidelines have suggested that one simple remedy for duplicate publication would be to include the protocol number in all publications[9]. This would not overcome the problem of selective publication, but it has the advantage of requiring no additional administration or cost. Since protocol numbers are usually lengthy alphanumeric strings, the chance of two studies in a similar therapy area being assigned the same number is low, although this is a theoretical possibility, and another advantage of the ISRCTN scheme.

Since journal editors have expressed their disapproval of redundant publication, and are usually keen to ensure that they publish only original findings, they might be expected to encourage authors to include trial identifiers in manuscripts. However, my own experience of including protocol numbers has not been uniformly successful, and I have known such numbers to be removed from papers before publication, presumably by overzealous copy editors. Frustrated by this experience, I polled editors via the World Association for Medical Editors' and the European Association of Science Editors' electronic fora in 2000, asking for their views about where trial identifiers should appear. I received replies from 15 editors. Of these, seven thought identifiers should be included in the acknowledgements or funding section, five felt they should appear on the title page, in the author by-line or as a footnote, two preferred them in the Methods and one in the Introduction sections of articles. One editor suggested the identifier might appear both in the Introduction and the Acknowledgements sections.

Another more recent survey of medical editors' views on the ISRCTN (which was not complete at the time of writing) found that three journals did not support the initiative, two supported the initiative but were undecided about where the ISRCTN should appear, one will allow the ISRCTN to appear in the abstract, one in a footnote and one in the Acknowledgements section [Anne Greenwood, personal communication, September 2003].

If journal editors want to support clear trial identification they should give potential contributors clear advice about where such information should be placed, and ensure that trial identifiers do not get removed from manuscripts. A few journals mention trial registers in their Instructions to Contributors but, so far, only two publishers have taken a positive stand on this issue. *The Lancet* has requested that all investigators who submit a protocol should register for an ISRCTN[10] and BioMed Central has recently revised its instructions to contributors requiring the inclusion of a unique study number in publications[11].

The current situation can best be described as rather woolly. Some trial registers exist, and more are being developed or expanded, but there is no universal system or guarantee of public access. Drug companies appear reluctant to register trials, although there have been one or two exceptions[12]. The Association of the British Pharmaceutical Industry (ABPI) encourages its members to register trials and has set up its own register[13]. Across the Atlantic, the influential Pharmaceutical Research & Manufacturers of America (PhRMA) has stated its opposition to registration[14]. There are plans for a European register including a unique number for all European drug trials, but this would be accessible only to the regulatory authorities[8].

At present, over 160 sponsors from 23 countries have applied for ISRCTNs. Several major research funders in the UK, Europe, Canada and Australia are taking part in the ISRCTN scheme, and it is hoped that this will grow. A handful of pharmaceutical companies have signed up to Good Publication Practice for Pharmaceutical Companies which encourages them to include some form of trial identifier, such as an ISRCTN or protocol number, in all publications[9]. Some medical journals have expressed support for trial registers and/or the ISRCTN scheme but editors are not consistent in their views about where trial identifiers should appear and only one journal publisher has made an identifier a mandatory requirement for publication.

Clear identification of trials should not be the concern of only a few, dedicated researchers, journal editors or people preparing systematic reviews. Since guidelines and treatment recommendations are increasingly based on the findings of systematic reviews and meta-analysis, it is vital that these are as robust and reliable as possible. Duplicate and selective publication can distort review findings and therefore have the potential to undermine attempts to identify the best treatments. Anybody concerned with the care of patients and improving healthcare should therefore be concerned about publication bias. Taken in the context of the huge amounts spent on medical research, the costs of eradicating publication bias are tiny, but concerted efforts to ensure that all trials are published, and that all publications include clear trial identifiers, could greatly increase the value of the medical literature.

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