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EDITORIALS

Health Research Authority's great leap forward on UK trial registration

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Trial registration is now required as a condition of ethical approval. The recently published report of the House of Commons Science and Technology Committee is the latest of numerous calls for the registration of clinical trials.[1] Nearly three decades ago, oncologist John Simes showed how prospective trial registration could help to detect and take account of biased under-reporting of clinical trials.[2] Other academics then showed how under-reporting of clinical research can harm patients,[3] characterising it as a form of scientific misconduct.[4]

In the mid-1990s, the publisher Current Controlled Trials offered trial registration in its international randomised controlled trial register (ISRCTN; www.controlled-trials.com). Some research funders in the United Kingdom, such as the Medical Research Council, Wellcome Trust, and NHS Research and Development Programme, required the trials that they were supporting to be registered. In the United States, the FDA (Modernization) Act 1997 required registration of clinical trials of treatments for serious or life threatening diseases, and a US national register (www.clinicaltrials.gov) was established as a result. In some other countries, Spain for example, registration of all clinical trials became required by law.

Despite these developments, trial registration remained patchy. It was not being used by most clinical trialists or required by most research funders or research ethics committees. Only a handful of journal editors, such as the editors of the *BMJ* and the *Lancet*,[5] showed any serious interest in the subject.

In the early years of this century, the World Health Organization played a key coordinating role. It convened meetings of those already involved in trial registration to seek agreement on a minimum dataset for registration,[6] and it encouraged efforts to reduce unwanted duplicate registration. It established the international clinical trials registry platform as a gateway for searching across international, regional, and national registers.[7]

It was not the research community, however, but a lawyer—Eliot Spitzer, attorney general of New York State—whose action led to biased under-reporting of research to be taken more seriously. Legal investigations confirmed allegations that, under its former chief executive Jean-Paul Garnier, GlaxoSmithKline had withheld important information about adverse, potentially lethal, effects of one of its antidepressant drugs. Spitzer secured a large out-of-court settlement from the company, and his successful exposure of this misbehaviour prompted the International Committee of Medical Journal Editors (ICMJE) to take action that it should have taken years before. The committee announced in 2005 that in future its member journals would consider publishing reports of clinical trials only if they had been registered at inception.[8] The US National Library of Medicine then opened up its national trials register (www.clinicaltrials.gov) to trials being done in other countries.

This announcement resulted in a dramatic spike in the frequency of registrations. Yet, even eight years after the ICMJE requirement was announced, Wager and Williams have shown that only a third of journals publishing clinical trials require prior trial registration.[9] Furthermore, only a minority (12%) of the editors of a sample of high quality and clinically relevant journals made clear in their websites that they welcome research reports regardless of the direction or strength of the results.[10] Many journal editors seem to be unaware that they are implicitly acquiescing in a form of scientific misconduct—biased under-reporting of research—which harms patients.[9]

Throughout the three decades since John Simes first showed how publication bias should be tackled,[2] the guardians of the one gateway that had the power to require trial registration—research ethics committees (institutional review boards)—remained largely silent. As long ago as 1996, the failure of such committees to require trial registration was one of two ways in which they were judged to be behaving unethically and so betraying their responsibilities to trial participants, patients, and the public.[11] Some of us concluded that universal trial registration would never be achieved while it remained voluntary.[12]

In the UK, universal trial registration could have been introduced years ago had the national oversight of research ethics committees been blessed with the quality of leadership that it now has. In just over a year since her installation as chief executive of the Health Research Authority, Janet Wisely has achieved the political and professional consensus to enable her to announce that, from 30 September 2013, trial registration will be required as a condition for ethical approval.[13] Without the uncertain and drawn out process of trying to introduce

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legislation to require trial registration, the authority has put in place the first step needed to monitor and deal with under-reporting of clinical research in this country.

Now that the authority has established the basis for complete registration of UK trials, it should be tasked to ensure that trialists' use of its integrated research application system (www.myresearchproject.org.uk) automatically generates a trial registration entry, and that the resulting records are used to create a UK clinical trials register. This register would not only allow UK specific monitoring of trial publication but would also meet the criteria for inclusion in the international clinical trials registry platform. Searches using this platform would then cover all UK trials and those registered in national registers in Australia, Brazil, China, Cuba, Germany, India, Iran, Japan, Korea, the Netherlands, New Zealand, and Sri Lanka, as well as those in the ISRCTN register, ClinicalTrials.gov, the European Union register, and the Pan-African registry (http://apps.who.int/trialsearch/Default.aspx).

The Health Research Authority could develop the integrated research application system to reduce the bureaucracy of trial registration for UK based trialists. The authority could also ensure that trial protocols become available routinely at the time of registration,[14] and that user friendly information about currently recruiting trials is provided for potential trial participants.[15]

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