

# Registering Clinical Trials

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**I**N 1974, SHORTLY AFTER PRESIDENT Nixon had called for a “War Against Cancer,” Mary Lasker, patroness and advocate of clinical research, at a meeting of the President’s Cancer Panel, asked the National Cancer Institute to publish a book, to be updated every 6 months, listing all ongoing cancer treatment protocols in the United States.<sup>1</sup> The idea was that physicians would be able to identify open trials in which their patients could enroll. Just a few years later, Tom Chalmers, former director of the National Institutes of Health (NIH) Clinical Center, and president and dean at Mt Sinai Medical Center, extended this concept to include registers of clinical trials in all areas.<sup>2</sup> Lasker and Chalmers had different aims. Lasker’s aim was to speed a “cure for cancer” by disseminating information to physicians and their patients, so that there would be no shortage of participants in clinical trials. Chalmers’ aim was at least as important in any such “war”; it was to reduce bias in the reporting of trials. Ultimately, both recognized an enormous gap in the dissemination of good information and both hoped to speed the delivery of the best new treatments to the patient.

Yet Manheimer and Anderson,<sup>3</sup> nearly 30 years after Lasker, could write, “No comprehensive system for tracking, organizing, and disseminating information about ongoing clinical trials currently exists.” And decades after Chalmers, different groups in differ-

ent countries, making energetic and meticulous efforts to perform systematic reviews of the evidence for different types of treatments, have each reported substantial difficulties in obtaining a good account of the existence and number of trials, the numbers of patients included, the number of reports associated with each trial, and the investigators involved.<sup>4-10</sup>

That it is not possible to find information about all initiated clinical trials is of international concern. This is a particular worry because scientists tend to publish their positive findings more often than their negative findings (publication bias). A comprehensive register of initiated clinical trials, with each trial assigned a unique identifier, would inform reviewers, physicians, and others (eg, consumers) about which trials had been started and directly address the problem of publication bias. Patients and their clinicians could also know which trials are open for enrollment, thus speeding medical advances. Individuals who participate in clinical trials typically provide consent in the belief that they are contributing to medical knowledge. But if the knowledge gained is never reported, the trust between patients and investigators and that between patients and research ethics review boards are both damaged. Ethical issues are of particular concern if industry is gaining financially from public involvement in trials, but refusing to reciprocate by making information from industry-sponsored trials generally available. All stakeholders—investigators, research organizations and institutions, journal editors, lawmakers, consumers, and others—must act now, together and in their own domains, to ensure comprehensive registration of clinical trials.

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## The Importance and Number of Randomized Clinical Trials

The study design conferring the best evidence for effects of interventions is the randomized clinical trial (RCT).<sup>11</sup> This has been borne out recently by the Heart and Estrogen/progestin Replacement Study and the Women’s Health Initiative Study, both of which are clinical trials that have overturned what had

seemed irrefutable evidence gathered from observational studies that hormone therapy was effective in preventing cardiovascular events.<sup>12-15</sup> Since the British Medical Research Council’s landmark RCT of streptomycin in pulmonary tuberculosis was reported in 1948,<sup>16</sup> perhaps as many as 1 million controlled trials have been carried out; it is estimated that only about half of which have been reported. This estimate is derived by using the current

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See also p 495.

total number of trials in the Cochrane Central Register of Controlled Trials,<sup>17</sup> the proportion of total initiated trials that are estimated to be published,<sup>17-19</sup> and the total number of biomedical journals that remain to be hand searched.<sup>17</sup> In addition, many trials are terminated early and are never published.<sup>20</sup>

Systematic reviews of randomized trials are considered the highest level of evidence, better than a single RCT. Many probably believe that all published RCTs for systematic reviews are readily available through various large bibliographic databases, notably the National Library of Medicine's MEDLINE, the Institute for Scientific Information's Science Citation Index, and Elsevier's EMBASE. But these databases capture mainly publications from the journals they index, the majority of them in the English language. MEDLINE for example contained only 229 160 citations to controlled trials at the time of writing this article (January 2003).

A more comprehensive source for published reports of controlled trials is the Cochrane Central Register of Controlled Trials,<sup>17</sup> coordinated by the US Cochrane Center, which currently contains more than 350 000 reports of trials. The Cochrane Central Register of Controlled Trials database has been developed as a result of a massive and continuing effort on the part of the Cochrane Collaboration to search by hand issues from 1948 to the present of more than 2200 journals to find relevant articles and trials otherwise lost to medicine and systematic reviews.<sup>21,22</sup> This time-consuming, inefficient, and costly effort has shown that at the very least one third of RCTs since 1966 have not been indexed in MEDLINE, and thus are effectively lost to the majority of searchers who limit their searching in this way.<sup>23,24</sup>

This article focuses on issues related to registration of controlled clinical trials designed to test the efficacy or other effects of an intervention, and not clinical trials, such as phase I studies, designed primarily to test dosage and safety.

### Unpublished Trials and Publication Bias

Even if there were a perfect system for indexing published trials, it is likely that a sizeable proportion of trials would remain unpublished.<sup>18,19</sup> Studies in numerous areas of medicine have shown that about 50% of presentations at scientific meetings never result in published articles, and these numbers include clinical trials.<sup>19</sup> Efforts to try to contact experts and authors after the fact have invariably proved inefficient.<sup>25,26</sup>

The fact that some trial results are never published would not be a problem except that there is good evidence that the results from unpublished trials are systematically different from those of published trials (publication bias). For decades, scientists have complained about the over-reporting of "positive" results (results that favor the new therapy).<sup>27</sup> Publication bias is common and is almost always because of failure of the investigators to complete, write up, and submit to journals findings from trials with negative results.<sup>18,28</sup> Ioannidis<sup>29</sup> has shown that even when all trials are published, those with positive results tend to be submitted much sooner after completion. Thus, news about new (and perhaps more expensive) treatments is disseminated faster, and these interventions may be adopted at the expense of those that are cheaper, just as effective, and safer.

### Harms Resulting From Trials Disappearing Without Trace

Patients who agree to participate in clinical research do so with the understanding that they are contributing to medical knowledge. If the knowledge gained in a trial is never communicated to others, then their contribution is unrealized and the covenant between researcher and patient, indeed between ethical review boards and patients, is broken.

A crucial question is whether the distortion of available evidence, aside from being unethical, actually harms patients. There is evidence that it does. Starting with Furberg's 1983 systematic review of 14 trials of class I antiarrhythmic drugs,<sup>30</sup> meta-analyses have failed to

detect any beneficial effect on substantive outcomes but did show an increase in sudden death for patients with ventricular arrhythmias.<sup>31</sup> Despite the fact that more than 50 trials involving more than 23 000 patients had been conducted, the effects observed were apparently not large enough to convince scientists and physicians to abandon new trials or to stop using the drugs in practice until the 1990s. One study completed in 1980 was not published until 1993.<sup>32</sup> If the existence of this study had been known earlier and its results generally available, the use of this dangerous although biologically rational drug may have been halted.<sup>33</sup> Indeed, there are estimates that 20 000 to 75 000 lives were lost each year in the 1980s in the United States alone from inappropriate administration of antiarrhythmic drugs for secondary prevention of myocardial infarction.<sup>34</sup> It is not difficult to see why the failure to publish studies has been called scientific misconduct.<sup>35</sup>

In baseball, it is easy to find out just how well Cal Ripken has hit against various pitchers in the past, at home or away games, in recent weeks or during his career.<sup>36,37</sup> Yet in medicine, there is no comprehensive source for finding out similar, accurate statistics for medical interventions. How can baseball be better organized and keep better records than medical science? The Cochrane Collaboration is now assembling regularly updated systematic reviews of the results of clinical trials of health care interventions. But nowhere is there reliable, comprehensive information on all initiated clinical trials that a systematic review would bring together to arrive at an estimate of an intervention's effectiveness and safety. Depending solely on the accessible published medical literature for assessing a treatment's efficacy is akin to using only information from Ripken's home games to calculate his batting average.

The result of not knowing who has performed what is loss and distortion of the evidence, waste and duplication of trials, inability of funding agencies to plan, and a chaotic system from which only certain sponsors might benefit, and

which is invariably against the interest of those who offered to participate in trials and of patients in general.

### Trial Registers

It has been known since the seminal work of Simes in 1986<sup>38</sup> that basing reviews on the results of trials registered in advance is likely to produce an estimate of effect free of publication bias. The idea is that even if a trial were never

reported, one would be able to examine a trials register and observe that the trial had taken place; this in turn could lead to finding out more about the trial's design and outcome.

The objective in establishing a comprehensive clinical trials register would be to make information about all trials undertaken publicly available. The ideal register would be comprehensive, accurate, and easy to access and it must

be inexpensive and simple to contribute to for those registering trials. Trial entries would need to include at least the condition under study and contact details for obtaining additional information, but trial results could be optional. The ideal register would also need to use a unique identifier for each trial conducted because trials may have more than 1 site or funder. This requirement has been recognized since the 1960s<sup>39</sup> and can be compared with use of the International Standard Book Number, the unique identification number assigned internationally to books.

Trials registers have been in existence at least since the 1960s.<sup>39</sup> A searchable computerized international register of therapeutic trials of psychopharmacological agents, first operational in 1967, was developed by the US National Institute of Mental Health. Participants in its Early Clinical Drug Evaluation Units Program recognized the problems associated with finding out about unpublished trials and obtaining an unduplicated count of trials, and the effect of publishing delays on knowledge. Since that time, much has been written about the need for coordinated comprehensive trials registers, but until now no single effort has survived in the long term (TABLE 1).

Registers have been recommended by individuals,<sup>2</sup> presidentially appointed committees,<sup>1</sup> and expert panels such as those appointed by the Institute of Medicine.<sup>45,46</sup> Biomedical journals have tried to do their part by publishing trial protocols,<sup>49,50</sup> unique trial registration numbers,<sup>51,69,70</sup> editorials about the importance of registration,<sup>40,41</sup> and regular lists of ongoing trials.<sup>48</sup> There have been country-wide registration efforts, for example, in Spain,<sup>61</sup> and laws mandating registers.<sup>66-68</sup> Some government funding agencies, such as the UK Medical Research Council, have required registration of trials they support.<sup>24</sup> In the United States, the NIH registered its trials from 1975 to 1979<sup>57</sup> but not again until it was legislatively mandated for trials of serious and life-threatening diseases in 1997.<sup>67,68</sup>

**Table 1.** Selected Events Supporting and Leading to Trials Registration\*

|   | Examples   |
|---|--|
| Publications recommending/supporting registration         |  |
| Letter to the editor                                      | Opinion leader <sup>2</sup>  |
| Editorials  | Journal editors <sup>40-42</sup>   |
| Special panels  | Society for Clinical Trials Panel on Trial Registration <sup>43</sup><br>International Collaborative Group <sup>44</sup><br>Institute of Medicine committees <sup>45,46</sup>  |
| Special columns in journal                                | <i>Controlled Clinical Trials</i> <sup>47</sup>  |
| Special columns in lay magazine                           | <i>MAMM—Women, Cancer and the Community</i> <sup>48</sup>  |
| Research articles   | Demonstration of publication bias favoring positive results among published trials compared with registered trials <sup>38</sup><br>Demonstration that even the best trials registers are incomplete <sup>3</sup>  |
| Registration efforts                                      |  |
| Registration of trial protocols                           | Major biomedical journals <sup>49,50</sup>   |
| Assignment of unique number to individual trials          | Various registers <sup>39,44,51,52</sup>   |
| Publication of unique registration number with manuscript | Major biomedical journals <sup>53,54</sup>   |
| Industry registers  | Individual registers <sup>55</sup><br>Compilation register (CenterWatch) <sup>56</sup>   |
| Government registers                                      | NIH:<br>NIMH register of therapeutic trials of pharmacologic agents (1967-1972) <sup>39</sup><br>NIH all trials (1975-1979) <sup>57</sup><br>ClinicalTrials.gov (2000 to present) <sup>52</sup><br>HIV/AIDS trials (1989 to present) <sup>58</sup><br>United Kingdom:<br>National Health Service Research Register <sup>59</sup><br>Medical Research Council Trials Register <sup>60</sup>   |
| Country-wide registers                                    | Registration in Spain through ethics committees <sup>61</sup>  |
| Collaborative efforts                                     | Comprehensive registers of published trials: Oxford Database of Perinatal Trials (1986-1993) <sup>62</sup><br>Cochrane Central Register of Controlled Trials <sup>17</sup><br>Prospective registers of initiated trials: International Committee on Thrombosis and Haemostasis <sup>63</sup><br><i>Current Controlled Trials</i> Meta-Register (a compilation of more than 20 individual registers) <sup>64</sup><br>TrialsCentral (an online register of more than 200 US-based trials registers) <sup>65</sup> |
| Legislation mandating registers                           | National Cancer Act of 1971, leading to National Cancer Institute International Cancer Research Data Bank <sup>1</sup><br>Health Omnibus Programs Extension Act of 1988, leading to establishment of HIV/AIDS trials register <sup>66</sup><br>Food and Drug Administration Modernization Act of 1997, leading to establishment of ClinicalTrials.gov <sup>67,68</sup>   |

Abbreviations: HIV, human immunodeficiency virus; NIH, National Institutes of Health; NIMH, National Institute of Mental Health.

\*The events represent a selected nonrandom sample and are not intended to be all-inclusive.

### Specialty or Regional Registers

An increasing number of small medical center registers or disease-based registers exist in many countries, but even taken together are by no means comprehensive.<sup>63,65</sup> TrialsCentral (<http://www.trialscentral.org>) attempts to bring the 200 or more US-based registers under a single umbrella<sup>65</sup> but also serves to demonstrate the underlying disorganization of the clinical trials enterprise as a whole.

Meetings about trial registration were first held in Europe in 1991,<sup>44</sup> leading 10 years later to pan-European support for trial registration. In May 2001, the European Science Foundation advised its member organizations to require registration as a condition of funding trials, contribute to the Meta-Register of controlled trials (<http://www.controlled-trials.com>), and support the use of an international standard randomized controlled trial number.<sup>71</sup> Even such broad support did not guarantee action; however, when a funding application for such a register was made last year to the European commission by scientific leaders from 11 countries, it was unexpectedly turned down on the dubious basis that legislation would first be needed to make information about trials publicly available (I. Chalmers, written communication, January 2, 2003).

The most recent development is a European Science Foundation–convened meeting in Frankfurt, Germany, in November 2002 to discuss ways to initiate the process. The European Science Foundation secretary general urged a greater sense of openness about trials and noted that a system for European registration is important for ensuring public trust in the biomedical community. Many of those attending the meeting noted that public trust cannot possibly be fostered by the existing European Clinical Trials Database for medicinals because it is confidential and access is limited to the regulatory agency and funders, and not to those physicians, patients, and others who most need access to the information.

At the Frankfurt meeting, a representative from the NIH, Dr William

Harlan, presented a history and update of the US ClinicalTrials.gov Web site, developed through the National Library of Medicine in collaboration with NIH and the Food and Drug Administration (FDA).<sup>52</sup> ClinicalTrials.gov was launched in February 2000 and currently contains more than 5000 studies sponsored by federal agencies and the pharmaceutical industry in North America and about 80 countries.

ClinicalTrials.gov was developed largely as a result of breast cancer consumer lobbying, which led to authorizing language in the FDA Modernization Act of 1997.<sup>67,68</sup> This effort was modeled on the Health Omnibus Programs Extension (HOPE) Act of 1988,<sup>66</sup> which led to a successful human immunodeficiency virus/AIDS trials register.

ClinicalTrials.gov is mandated only to include trials of serious and life-threatening diseases, but even in studies of cancer it is deficient. Manheimer and Anderson<sup>3</sup> have shown that ClinicalTrials.gov included only 17 of 32 known and ongoing prostate and colon cancer controlled trials that were funded by industry. Given that industry funds more than 60% of clinical trials,<sup>72,73</sup> the fact that the register is far from comprehensive when it comes to industry-funded trials is a serious defect.

CenterWatch, a trials register recruiting Web site for the drug industry, may well be the largest single trials register, claiming to have between 7500 and 41 000 trials listed (information on site varies).<sup>56</sup> However, much of the information (eg, funding source) about the trials listed on CenterWatch is not directly accessible by the user. In addition, there is no unique identifier to allow the user to determine, for example, whether the 12 sites listing trials of Zometa (zoledronic acid for injection) for bone metastases are 12 unique trials or a single trial with 12 recruiting sites.

### "Comprehensive" Registers

*Current Controlled Trials*, established in 1998 by the publisher Biomed Central, is a composite of 26 (as of June 26, 2003) registers from 4 continents, in-

cluding ClinicalTrials.gov.<sup>64</sup> The Meta-Register is the most comprehensive register in existence and may be the best approach if regional registers are more practical to achieve than a single international register. If this route is taken, however, there must be a way to ensure comprehensiveness of the smaller registers, as well as compliance of the registers in submitting their contents to a meta-register.

### Barriers

There are several major barriers to development of a comprehensive register of clinical trials: industry resistance, the lack of a funding appropriation for a serious and sustained effort, lack of a mechanism for enforcement of policies, and lack of awareness of the importance of the problem.

**Industry Resistance.** The Pharmaceutical Research and Manufacturers of America is explicit that it will not commit to publish or to a register of trials. The group's "Public Disclosure of Clinical Trial Results" states, "Sponsors do not commit to publish the results of every exploratory study performed, or to make the designs of clinical trial protocols available publicly at inception, as in a clinical trials registry."<sup>74</sup> Indeed, high-level industry executives rejected a proposed "Good Publication Practice: Guidelines for Pharmaceutical Companies," which provides guidelines that would reduce publication bias and define appropriate publishing relationships between industry and investigators.<sup>75</sup>

There is evidence that many industry trials are never published. For example, in a systematic review of trials of nonsteroidal anti-inflammatory drugs, MacLean et al<sup>76</sup> found that only 1 of 37 studies reported in FDA reviews had been published. Because there is commercial advantage to be gained by early publication of positive results and the suppression of negative results, industry reluctance to publish negative findings would not come as a surprise. Nor would it be a surprise if pharmaceutical and industry executives in general were opposed to the

idea of registration of trials. Reasons for avoiding registration given to each of the authors in various public and private meetings over the years include protection of information about products under development, patents, and information about good recruiting centers, and not wanting to be bothered by dealing with consumers and others who contact them for information.<sup>77</sup> In addition, companies may assess many trials as performed solely to meet regulatory requirements rather than providing information patients have a right to know about.

Given the minimal information (TABLE 2) that would be required to be publicly disclosed in any register and the easy availability of information about what is in the pipeline,<sup>3</sup> it is difficult to understand the reluctance of industry to register trials. Two companies, GlaxoWellcome and Schering Healthcare UK, agreed to register their trials in 1998,<sup>55,77</sup> but these efforts have been extremely circumscribed. More re-

cently, the Association of the British Pharmaceutical Industry has encouraged its members to register trials,<sup>78,79</sup> which undermines the arguments against registration put forward by industry leaders elsewhere.

**Lack of Funding.** In 2001, a reported \$30.3 billion was spent by the Pharmaceutical Research and Manufacturers of America—member companies on pharmaceutical research and development, and on average \$800 million was spent to develop a single drug.<sup>80</sup> Industry spends more on pharmaceutical research than was provided to NIH (about \$20 billion in 2001) for its entire operating budget.<sup>81</sup> *Current Controlled Trials* estimates that since its start in 1998 it has incurred expenses of £500 000 (approximately US \$830 000) (I. Chalmers, written communication, May 27, 2002). The savings to society effected by a comprehensive register would exceed many-fold the money that is at present wasted on inaccessible and unnecessarily duplicated knowledge.

Who should pay for comprehensive trials registration? Industry and government bear the largest responsibility for this, because they support the trials and stand to gain the most, either financially or through better science and a healthier public. Funding issues have also arisen with the implementation of new federal guidelines on ethical review of human studies, protecting research from conflicts of interest and privacy protection; however, there has been general agreement that ethical concerns outweigh those of efficiency and cost.

**Lack of Mechanisms for Enforcement.** The FDA Modernization Act of 1997<sup>67</sup> may have mandated that clinical trials conducted to test effectiveness of an investigational new drug for a serious or life-threatening disease or condition are required to be submitted to ClinicalTrials.gov for registration, but the law provided neither funding nor a mechanism of enforcement. Although industry generally wants to cooperate with the FDA because it approves new drug and device applications, industry also knows that any adverse consequences of failure to comply fully with the mandate are unlikely. ClinicalTrials.gov (accessed January 24, 2003) lists almost 2700 NIH studies, 200 other federally funded studies, more than 1800 university studies, and only 618 industry studies recruiting patients, a large proportion from biotechnology companies. Given other available data,<sup>3,80,82</sup> it seems unlikely that the trials listed are a complete count of industry trials in serious and life-threatening diseases.

A poster presented at the FDA Science Forum on April 24, 2003, confirms that compliance with the law is low, at least for cancer trials.<sup>83</sup> The authors found that 366 commercial cancer protocols were submitted to the FDA for approval between January 1, 2002, and September 30, 2002, and 187 (51%) of these met the criteria for listing in ClinicalTrials.gov. However, only 115 (61%) of 187 were submitted to the register: 61 (48%) of 127 pharmaceutical industry protocols, 52 (91%) of 57

**Table 2.** Trial Details Requested by *Current Controlled Trials* and ClinicalTrials.gov

| Details Requested  | Current<br>Controlled<br>Trials | Clinical<br>Trials.gov |
|--|---------------------------------|------------------------|
| Identifying information  |                                 |                        |
| Name of organization/individual supplying the record   | X                               |                        |
| Name of trial sponsor  | X                               | X                      |
| Protocol number given to the trial by the sponsor, if relevant   | X                               | X                      |
| Trial details  |                                 |                        |
| Trial purpose  |                                 | X                      |
| Interventions (all interventions and trial groups)   | X                               | X                      |
| Title of trial   | X                               | X                      |
| Acronym (if relevant)  | X                               |                        |
| Disease or condition   | X                               | X                      |
| Participants (eligibility criteria)  | X                               | X                      |
| Phase of trial (1, 2, 3, 4)  |                                 | X                      |
| Trial locations  |                                 | X                      |
| Recruitment status   |                                 | X                      |
| Date study started   |                                 | X                      |
| Funding  |                                 |                        |
| Sources of funding (all known funding sources and reference numbers given to the trial by each funding agency) | X                               | X                      |
| Contact  |                                 |                        |
| Lead principal investigator or person with overall responsibility  |                                 |                        |
| Name   | X                               | X                      |
| Full address   | X                               |                        |
| Telephone  | X*                              | X                      |
| Fax  | X*                              |                        |
| E-mail   | X*                              | X                      |

\*Does not have to be displayed but must be provided.

of NIH/National Cancer Institute protocols, and 2 (67%) of 3 other protocols. Industry compliance with the law was the same before and after the law went into effect (May 2, 2002). The authors concluded, "Participation by the pharmaceutical industry was less than expected one year after the availability of a final guidance document despite a federal law, a targeted educational program, and an easy-to-use web-based data entry tool." Indeed, FDA officials have indicated that in the future they could take steps to facilitate or even compel registration.<sup>84</sup>

**Lack of Awareness.** One of the biggest barriers to comprehensive trials registration is the relative obscurity of this issue in the lay and biomedical press. There are almost no articles in medical journals touting the existence of a specific trials register, even those as large as the National Health Service's National Research Register (UK), *Current Controlled Trials*' Meta-Register, Physician Data Query, or ClinicalTrials.gov. Because there is no news in reporting that trials registers exist, there is no written record of it and scientists get the message that their community does not think registers are important.

### Our Recommendations

**The NIH Should Take Responsibility for Ensuring Trial Registration in the United States.** An example of a successful registry system exists in molecular biology. GenBank is a database that has been in existence for more than 20 years and serves as the electronic repository in which investigators contribute genetic sequences for more than 100 000 different organisms.<sup>85</sup> Data are also contributed to GenBank by the US Office of Patents and Trademarks for issued patents and are exchanged internationally on a daily basis with 2 other international sites to ensure comprehensiveness. Many journals require submission of sequence information to GenBank and assignment of an accession number before publication.<sup>53</sup>

GenBank's production is supported and maintained entirely by the NIH as part of the National Library of Medi-

cine budget (D. Lipman, written communication, May 21, 2003). Its budget is approximately \$5.5 million annually, which covers biological curators who handle sequence submissions, programmers and database developers, hardware, software, and networking expenses. Data are made available free of charge to the international public by the National Library of Medicine via the Internet. Thus, NIH has coordinated a responsible effort by investigators, journals, industry, and others for creating a system that helps to ensure research data are not lost and helps to prevent unnecessary duplication of effort.

Similar strong coordination of comprehensive trials registration in the United States is also required. Providing a means whereby the public can find all clinical trials would be at least as important as GenBank is now, and its importance will increase as the products of research in molecular biology are tested in humans. The NIH is the logical place for coordination of registration, given its experience in the area over the years and the public responsibilities it has been entrusted with for research related to health. Given that an initial NIH conference on the topic of comprehensive trials registration was held almost a decade ago,<sup>86</sup> it is not clear that further workshops and discussion about "why" or "whether" are needed. In our opinion, it is long past time to make it happen.

**Those at the Highest Level at Institutions and Organizations That Conduct Research Must Require Registration of Trials for Which They Are Responsible.** Given that patients are most at risk for harm from the present chaos and bias, and also are most likely to gain from a working, comprehensive, and easily searchable register, failure to register trials should be recognized as unethical. The fact that industry could be gaining financially from the public involvement in trials yet not reciprocating by making scientific information publicly available is of particular concern.

Institutional review boards (research ethics review boards) should

make registration a condition of approval.<sup>87,88</sup> The Institute of Medicine Committee on Assessing the System for Protecting Human Research Participants has recommended that the responsibility for ensuring ethical conduct of research be taken at the highest level of the organization conducting that research.<sup>46</sup> The responsibility for registering trials also lies there. Institutions, organizations, and research ethics review boards also have responsibility for ensuring that trials registers are actually consulted to avoid unnecessary duplication of research.

**Industry Leaders Must Agree to and Insist on Comprehensive Registration.** In the United States, government-funded trials are registered through ClinicalTrials.gov. However, the largest funder of clinical trials is industry and ensuring cooperation of this group to register all trials they are supporting is essential. One approach may be for patient advocacy groups, which have more power than ever before, to demand that industry be proactive in complying with the registration effort. The individual patient should insist that a trial is registered before enrolling. Another strategy would be for clinician-scientists to require that a trial is centrally registered before enrolling patients, and research ethics review boards should insist trials are registered and that this information is in the informed consent document before trials are approved.

Leaders at the highest levels in industry<sup>55</sup> must actively support and be involved in trial registration. Those at lower levels are unlikely to have reason to advance the cause and doing so is unlikely to advance their career. Anecdotal, it is difficult to find a single person who considers himself/herself in charge. For instance, when we have asked about local trial tracking mechanisms, industry representatives claim that within a company there is usually not a centralized repository of information about which trials are ongoing. Thus, they have argued, those in charge of knowing about ongoing oncology trials are typically not aware of

ongoing allergy trials, which makes it difficult to talk to industry about agreeing to registration generally. There is no alternative but for the leadership of pharmaceutical companies to agree to comprehensive registration.

It is unlikely that registration of broad details about clinical trials will infringe on the patent rights of manufacturers. Information about ongoing trials is already readily available to that community but not to the public. In 1999, one of us wrote about commercial sponsors and registration of trials, "It is hard to think of any step a pharmaceutical company could take that would so reassure its clients as to its ethical, clinical, and scientific good intentions."<sup>8</sup> In an era when mistrust of pharmaceutical companies is increasing, that statement is even truer. It will require the efforts of the entire clinical research community for registration to become routine.

**Journal Editors Should Require Unique Registration Numbers for Trial Reports.** Some major medical journals have been actively advocating for trial registration, but efforts must be broader and stronger. At the European Science Foundation meeting in Frankfurt, Fiona Godlee, instrumental in *Current Controlled Trials'* development of the Meta-Register, outlined several specific action areas for journals related to trial registration. Journals should encourage a culture of transparency in research and reporting, publish study protocols, publish negative results, and strongly promote trial registration. Perhaps most important, journals should make provision of a unique identifier, such as the international standard randomized controlled trial number assigned by *Current Controlled Trials*, a condition of acceptance of an RCT.

**Lawmakers Must Protect the Public by Requiring Comprehensive Trial Registration Through Ethics Committees.** These actions might not be successful; therefore, the only recourse may be to change the law. The public should be firm in its insistence that the government has a moral responsibility to fund, require, and enforce public registra-

tion of all trials involving human participants, regardless of the topic or funding source. Perhaps the most direct way to comprehensively register trials is through research ethics review boards<sup>11</sup>; this approach provides a framework for ensuring comprehensiveness and compliance of those conducting trials.

Congress should start immediately to consider legislation that would implement such a process. Legislation mandating, funding, and enforcing registration of all clinical trials initiated in the United States is needed immediately. The mandate must carry with it sufficient funding for start-up and continuation, as well as assignment of the authority to monitor the process and to take action against those not complying with the law. Based on previous experience, lobbying by patients' groups, clinical researchers, and physicians to produce this type of legislation appears to be the best way forward, at least in countries where such practices are used.

### Conclusions

The public and private sectors must end the inertia and take responsibility to overcome the problem of wasted and unnecessarily duplicated research. At least initially, it will probably be necessary to approach comprehensive trial registration through the merging of several registers (eg, country-wide registers). *Current Controlled Trials'* Meta-Register is an example of the type of compilation that can work with international collaboration. The United States can start by funding its own comprehensive register of initiated trials. Investigators, research organizations and institutions, research sponsors, industry leaders, journal editors, lawmakers, and consumers—it's time for action.

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### REFERENCES

- Hubbard S, DeVita VT. PDQ: an innovation in information dissemination linking cancer research and clinical practice. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Important Advances in Oncology*. Philadelphia, Pa: JB Lippincott Co; 1987.
- Chalmers TC. Randomize the first patient! *N Engl J Med*. 1977;296:107.
- Manheimer E, Anderson D. Survey of public information about ongoing clinical trials funded by industry: evaluation of completeness and accessibility. *BMJ*. 2002;325:528-531.
- Göttsche PC. Multiple publication of reports of drug trials. *Eur J Clin Pharmacol*. 1989;36:429-432.
- Huston P, Moher D. Redundancy, disaggregation, and the integrity of medical research. *Lancet*. 1996;347:1024-1026.
- Tramèr MR, Reynolds DJM, Moore RA, McQuay HJ. Impact of covert duplicate publication on meta-analysis: a case study. *BMJ*. 1997;315:635-640.
- Johansen HK, Göttsche PC. Problems in the design and reporting of trials of antifungal agents encountered during meta-analysis. *JAMA*. 1999;282:1752-1759.
- Rennie D. Fair conduct and fair reporting of clinical trials. *JAMA*. 1999;282:1766-1768.
- Flanagin A, Fontanarosa PB, DeAngelis CD. Authorship for research groups. *JAMA*. 2002;288:3166-3168.
- Dickersin K, Scherer R, Suci E, Gil-Montero M. Problems with indexing and citation of articles with group authorship. *JAMA*. 2002;287:2772-2774.
- Chalmers I. Unbiased, relevant, and reliable assessments in health care. *BMJ*. 1998;317:1167-1168.
- Grady D, Herrington D, Bittner V, et al, for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy. *JAMA*. 2002;288:49-57.
- Hulley S, Furberg C, Barrett-Connor E, et al. Non-cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA*. 2002;288:58-66.
- Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-333.
- Petitti DB. Hormone replacement therapy for prevention: more evidence, more pessimism. *JAMA*. 2002;288:99-101.
- The Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *BMJ*. 1948;2:769-782.
- Dickersin K, Manheimer E, Wieland S, Robinson K, Lefebvre C, McDonald S. Development of the Cochrane Collaboration's CENTRAL register of controlled clinical trials. *Eval Health Prof*. 2002;25:38-64.
- Dickersin K. How important is publication bias? a synthesis of available data. *AIDS Educ Prev*. 1997;9(suppl A):15-21.
- Scherer RW, Langenberg P. Full publication of results initially presented in abstracts [Cochrane Methodology Review]. Oxford, England: Cochrane Library, Update Software; 2003; issue 1.

20. Pich J, Carne X, Arnaiz JA, Gomez B, Trilla A, Rodes J. Role of a research ethics committee in follow-up and publication of results. *Lancet*. 2003;361:1015-1016.
21. Hayward S, Brunton G, Thomas K, Ciliska D. Searching for the evidence: source, time and yield. In: Proceedings of the Second International Conference, Scientific Basis of Health Services and the 5th Annual Cochrane Colloquium; October 5-12, 1997; Amsterdam, the Netherlands.
22. Brazier H. Poorly executed and inadequately documented? an analysis of the literature searches on which systematic reviews are based. In: Proceedings of the Second Symposium on Systematic Reviews: Beyond the Basics; January 5-7, 1999; Oxford, England.
23. Hopewell S, Clarke M, Lusher A, Lefebvre C, Westby M. A comparison of handsearching versus MEDLINE searching to identify reports of randomized controlled trials. *Stat Med*. 2002;21:1625-1634.
24. Jull A, Chalmers I, Rodgers A. Clinical trials in NZ: does anybody know what's going on? *N Z Med J*. 2002;115:U269.
25. Hetherington J, Dickersin K, Chalmers I, Meinert CL. Retrospective and prospective identification of unpublished controlled trials: lessons from a survey of obstetricians and pediatricians. *Pediatrics*. 1989;84:374-380.
26. McManus RJ, Wilson S, Delaney BC, et al. Review of the usefulness of contacting other experts when conducting a literature search for systematic reviews. *BMJ*. 1998;317:1562-1563.
27. Sterling TD. Publication decisions and their possible effects on inferences drawn from tests of significance: or vice versa. *J Am Stat Assoc*. 1959;54:30-34.
28. Dickersin K, Chan S, Chalmers TC, Sacks HS, Smith HJR. Publication bias and clinical trials. *Control Clin Trials*. 1987;8:343-353.
29. Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. *JAMA*. 1998;279:281-286.
30. Furberg CD. Effect of antiarrhythmic drugs on mortality after myocardial infarction. *Am J Cardiol*. 1983;52:32C-36C.
31. Teo KK, Yusuf S, Furberg CD. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction: an overview of results from randomized controlled trials. *JAMA*. 1993;270:1589-1595.
32. Cowley AJ, Skene A, Stainer K, Hampton JR. The effect of lorainide on arrhythmias and survival in patients with acute myocardial infarction: an example of publication bias. *Int J Cardiol*. 1993;40:161-166.
33. Chalmers I. Using systematic reviews and registers of ongoing trials for scientific and ethical trials design, monitoring, and reporting. In: Egger M, Smith GD, Altman DG, eds. *Systematic Reviews in Health Care: Meta-analysis in Context*. London, England: BMJ Books; 2001:429-443.
34. Moore T. *Deadly Medicine: Why Tens of Thousands of Heart Patients Died in America's Worst Drug Disaster*. New York, NY: Simon & Schuster; 1995.
35. Chalmers I. Underreporting research is scientific misconduct. *JAMA*. 1990;263:1405-1408.
36. The Macmillan Publishing Staff. *The Baseball Encyclopedia: The Complete and Definitive Record of Major League Baseball*. 10th ed. New York, NY: MacMillan; 1996.
37. Thorn J, Palmer P, Gershman M, Silverman M, Lahman S, Spira G, eds. *Total Baseball: The Official Encyclopedia of Major League Baseball*. 7th ed. Kingston, NY: Total Sports Publishing; 2001.
38. Simes RJ. The case for an international registry of clinical trials. *J Clin Oncol*. 1986;4:1529-1541.
39. Levine J, Guy W, Cleary P. Therapeutic trials of psychopharmacologic agents: 1968-1972. In: McMahon G, ed. *Psychopharmacological Agents*. Armonk, NY: Futura Publishing Co; 1974.
40. Horton R, Smith R. Time to register randomised trials: the case is now unanswerable. *BMJ*. 1999;319:865-866.
41. Horton R, Smith R. Time to register randomised trials. *Lancet*. 1999;354:1138-1139.
42. Meinert CL. Toward prospective registration of clinical trials. *Control Clin Trials*. 1988;9:1-5.
43. Dickersin K. Report from the panel on the case for registers of clinical trials at the Eighth Annual Meeting of the Society for Clinical Trials. *Control Clin Trials*. 1988;9:76-81.
44. Ad Hoc Working Party of the International Collaborative Group on Clinical Trials Registries. Position paper and consensus recommendations on clinical trial registries. *Clin Trials Metaanal*. 1993;28:199-201.
45. Institute of Medicine Committee on Routine Patient Care Costs in Clinical Trials for Medicare Beneficiaries. *Extending Medicare Reimbursement in Clinical Trials*. Washington, DC: National Academy Press; 2000.
46. Institute of Medicine Committee on Assessing the System for Protecting Human Research Participants. *Responsible Research: A Systems Approach to Protecting Research Participants*. Washington, DC: National Academy Press; 2002.
47. Dickersin K. Why register clinical trials? revisited. *Control Clin Trials*. 1992;13:170-177.
48. Schiff H, Haran C. On the trials trail: clinical trial watch. *MAMM*. October/November. 1998:86.
49. Horton R. Pardonable revisions and protocol revisions. *Lancet*. 1997;349:6.
50. BioMed Central. Information for authors: publish your study protocols. Available at: <http://www.biomedcentral.com/info/authors/protocols>. Accessed January 24, 2003.
51. Vale CL, Stewart LA. The International Standard Controlled Trial Number (ISRCTN): what does it mean for reviewers? In: Proceedings of the 9th International Cochrane Colloquium; 2001; Lyon, France.
52. McCray AT. Better access to information about clinical trials. *Ann Intern Med*. 2001;133:609-614.
53. Information for Authors. Writing for the *Lancet*. Available at: <http://thelancet.com/authorinfo>. Accessed January 24, 2003.
54. Information for Authors. Manuscript format and style: trial registry information. *Ann Intern Med*. Available at: [http://www.annals.org/shared/manu\\_format.html](http://www.annals.org/shared/manu_format.html). Accessed January 24, 2003.
55. Sykes R. Being a modern pharmaceutical company: involves making information available on clinical trial programmes. *BMJ*. 1998;317:1172.
56. CenterWatch. Clinical Trials Listing Service. Available at: <http://www.centerwatch.com>. Accessed May 20, 2003.
57. Dickersin K, Min YI. NIH clinical trials and publication bias. *Online J Curr Clin Trials*. 1993;Doc No. 50.
58. AIDSinfo. Available at: <http://www.aidsinfo.nih.gov>. Accessed January 28, 2003.
59. The UK National Health Service National Research Register (NRR). Available at: <http://www.doh.gov.uk/research>. Accessed January 30, 2003.
60. MRC Trials Register. Available at: <http://www.controlledtrials.com>. Accessed February 5, 2003.
61. Dickersin K, Garcia-Lopez F. Regulatory process effects clinical trial registration in Spain. *Control Clin Trials*. 1992;13:507-512.
62. Chalmers I, Hetherington J, Newdick M, et al. The Oxford Database of Perinatal Trials: developing a register of published reports of controlled trials. *Control Clin Trials*. 1986;7:306-324.
63. Verstraete M. International Committee on Thrombosis and Haemostasis Basil, 8-11: September 1974 subcommittee on clinical investigations: registry of prospective clinical trials. *Thromb Diath Haemorrh*. 1975;33:655-663.
64. Chalmers I. *Current Controlled Trials*: an opportunity to help improve the quality of clinical research. *Curr Control Trials Cardiovasc Med*. 2000;1:3-8.
65. Anderson D, Costa I, Dickersin K. Building TrialsCentral, an online register of clinical trials registers. *Control Clin Trials*. 2001;22(suppl 2):405.
66. Pub L No. 100-607 (1988).
67. Pub L No. 105-115, §113 Stat 2296 (1997).
68. DeMarinis AD. Current considerations: regulatory: clinical trials databank. *Res Practitioner*. 2002;3:105-106.
69. Rowland D, Di Guiseppi C, Roberts I, et al. Prevalence of working smoke alarms in local authority inner city housing: randomized clinical trial. *BMJ*. 2002;325:998-1001.
70. Information for authors. *Ann Intern Med*. 1995;123:I-10.
71. European Science Foundation Policy Briefing No. 13, May 2001. Available at: <http://www.esf.org/publication/90/ESPB13.pdf>. Accessibility verified June 27, 2003.
72. Moses H 3rd, Martin JB. Academic relationships with industry: a new model for biomedical research. *JAMA*. 2001;285:933-935.
73. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA*. 2003;289:454-465.
74. PhRMA. Public Disclosure of Clinical Trial Results. June 24, 2002. Available at: <http://www.phrma.org/publications/policy/2002-06-24.430.pdf>. Accessed May 21, 2003.
75. Wager E, Field EA, Grossman L. Good publication practice for pharmaceutical companies. *Curr Med Res Opin*. 2003;19:149-154.
76. MacLean CH, Morton SC, Ofman JJ, et al, for the Southern California Evidence-Based Practice Center. How useful are unpublished data from the Food and Drug Administration in meta-analysis? *J Clin Epidemiol*. 2003;56:44-51.
77. Gibbs TG, Wager E. Clinical trial registration: the Glaxo Wellcome experience. *Int J Pharm Med*. 2000;14:203-205.
78. Kmietowicz Z. UK drugs industry sets up trials register. *BMJ*. 2000;321:850.
79. Tonks A. A clinical trials register for Europe. *BMJ*. 2002;325:1314-1315.
80. Pharmaceutical Research and Manufacturers of America. *2002 Industry Profile: Research and Development—The Key to Innovation*. Washington, DC: PhRMA; 2002.
81. Pharmaceutical Research and Manufacturers of America. *2003 Industry Profile: Dramatic Growth of Research and Development*. Available at: <http://www.phrma.org/publications/profile02/2003%20chapter%202.pdf>. Accessed June 4, 2003.
82. Research! America. How much is really spent on medical and health research? Available at: [http://www.researchamerica.org/members/4.6\\_cents.html](http://www.researchamerica.org/members/4.6_cents.html). Accessed October 17, 2001.
83. Derbis J, Toigo T, Woods J, Evelyn B, Banks D. FDAMA section 113: information program on clinical trials for serious and life-threatening diseases. Poster presented at: 9th Annual FDA Science Forum; April 24, 2003; Washington, DC.
84. Reynolds T. Researchers push for publication, registration of all clinical trials. *J Natl Cancer Inst*. 2003;95:772-774.
85. Benson DA, Karsch-Mizrachi I, Lipman DJ, et al. GenBank. *Nucleic Acids Res*. 2002;30:17-20.
86. Harlan WR. Creating an NIH Clinical Trials Registry: a user-friendly approach to health care. *JAMA*. 1994;271:1729.
87. Savulescu J, Chalmers I, Blunt J. Are research ethics committees behaving unethically? some suggestions for improving performance and accountability. *BMJ*. 1996;313:1390-1393.
88. Blunt J. Research ethics committees must ensure registration of research and accessibility of results. *BMJ*. 1998;316:312.