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Underreporting Research Is Scientific Misconduct

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Substantial numbers of clinical trials are never reported in print, and among those that are, many are not reported in sufficient detail to enable judgments to be made about the validity of their results. Failure to publish an adequate account of a well-designed clinical trial is a form of scientific misconduct that can lead those caring for patients to make inappropriate treatment decisions. Investigators, research ethics committees, funding bodies, and scientific editors all have responsibilities to reduce underreporting of clinical trials. An extended use of prospective registration of trials at inception, as well as benefiting clinical research in other ways, could help people to play their respective roles in reducing underreporting of clinical trials.

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SCIENTIFIC misconduct is commonly conceptualized as deliberate falsification of data—a sin of commission—but sins of omission may be even more important. Other articles in this issue of THE JOURNAL have shown that a tendency exists among investigators, peer reviewers, and journal editors to allow the direction and statistical significance of research findings to influence their decisions regarding submission and publication,[1] and that about one in two trials initially reported in summary form is never reported in sufficient detail to permit an informed judgment about the validity of its results.[2] Both of these phenomena should be regarded as forms of scientific misconduct.[3]

Selective underreporting of research is almost certainly more widespread and more likely to have adverse consequences for patients than the publication of deliberately falsified data. At least there is an accepted mechanism—attempted replication of reported investigations—for reducing the likelihood of being misled by false inferences based on contrived but fully published reports. No such protective mechanism currently exists with respect to the apparently systematic tendency to underreport certain kinds of valid research findings.

Adequate reporting of clinical trials is required for both scientific and ethical reasons. Failure to publish "disappointing" or "uninteresting" research results, or failure to report results in suffi-

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cient detail, may either lead patients to receive ineffective or dangerous forms of care or result in a delay in recognizing that other forms of care are beneficial. Neither of these consequences is in the interests of patients. In addition, failure to provide adequate, publicly available reports of the results of clinical trials does an injustice to the patients who have participated in them, as well as to others who have collaborated with the investigators and those who have provided funds or other resources.

EXAMPLES OF THE CONSEQUENCES OF UNDER-REPORTING CLINICAL TRIALS

The potential consequences of underreporting the results of clinical research have been illustrated by Simes.[4,5] An analysis based on the results of published trials suggested that combination chemotherapy should be preferred to use of a single alkylating agent in the treatment of advanced ovarian cancer. A second analysis, based on data derived from trials that had been registered prior to their results being known, failed to provide support for this preference.

Two additional examples from the perinatal field illustrate further how selective reporting and underreporting of clinical research may have an adverse influence on clinical policy decisions.

Debate has existed for many years about whether routine hospitalization of women with uncomplicated twin pregnancies for bed rest reduces the risk of preterm delivery. The results of two relatively recent surveys of practice in the United Kingdom, for example, suggest that British obstetricians are more or less equally divided on the matter.[6] The issue is not trivial: if a policy of routine hospitalization does indeed decrease the risk of preterm delivery in a group of women at higher than average risk of this outcome, it would obviously be important to know this; on the other hand, if controlled trials could rule out any material advantage of such a policy, then abandoning the policy would avoid disrupting the lives of women who would rather not be admitted to a hospital, as well as allowing redistribution of health service resources.

The first randomized evaluation of hospitalization for bed rest in uncomplicated twin pregnancy was conducted in Harare, Zimbabwe, in 1977. The trial was mounted because pressure on antenatal hospital beds had become so acute that some rationalization of their use had become essential. A preliminary analysis of the trial suggested that, far from reducing the risk of preterm delivery, routine hospitalization was actually associated with an increased rate of this unwanted outcome. The trial fulfilled its immediate purpose—to provide information on which a rational policy decision could be made in Harare—and the policy of routine hospitalization for uncomplicated twin pregnancy was abandoned.

Unfortunately, the investigators did not perceive it as their duty to make the results of their study more generally available for guiding clinical practice and research elsewhere. The results of the trial would have remained unreported had it not been for the fact that, 7 years later, two visitors to Harare "discovered" these unpublished data and helped the investigators to analyze and report their unreported trial. A full account of the trial was subsequently published in *The Lancet*.[7]

The results of this trial, taken together with comparable findings in a similar trial conducted in Finland reported at about the same time,[8] provoked reevaluation of an obstetric policy that has been widely accepted for four decades and led clinical investigators to organize further controlled trials.[6] These responses were postponed unnecessarily by the initial failure to report the results of the Harare trial. At the very least, this delay led to continued inappropriate deployment of limited resources; at worst, it may have resulted in the continued use of a harmful policy.

The second example from the perinatal field concerns the unresolved question as to whether routine (as opposed to selective) ultrasonography is justified in every pregnancy.[9] Controlled comparisons of routine and selective ultrasonography have shown that routine ultrasonography is associated with a lower incidence of induction of labor in pregnancies deemed to be "postterm," but the published trials have not been large enough to assess whether this effect is associated with any reduction in the frequency of substantive adverse outcomes of pregnancy.

The confusion in this field is compounded by the fact that one large trial of routine ultrasonography, conducted nearly 10 years ago, remains unpublished.[10] If the results of this trial show beneficial effects of routine ultrasonography, this would be important evidence on which to base current policy; if no benefits are demonstrated, this might reflect either technical inadequacies of the ultrasound equipment (or its application) during the era in which the trial was conducted, or the fact that routine ultrasonography has nothing important to offer over selective use of the technology. Either way, a full report of the results of the trial has current relevance.

Assessment of the effects of routine ultrasonography in pregnancy is also bedeviled by inadequate published reports of relevant trials. The only randomized trial to suggest that routine ultrasonography has any beneficial effects on substantive outcomes of pregnancy is that conducted in Ålesund, Norway, by Eik-Nes and colleagues in 1979 and 1980. This potentially important trial has never been fully reported in a scientific journal. The reports that are available are contradictory in a very important respect. The only readily available account of the trial, published as a letter to the editor in *The Lancet*,[11] states that women allocated to routine ultrasonography were compared with controls who "were not examined routinely but could be referred for ultrasound examination on a clinical indication." This description is at odds with an account of the trial presented to and published by the National Institutes of Health some months earlier. In that report Eik-Nes and Okland[12] state that, "The pregnant population was randomized either to have routine ultrasound examination twice in pregnancy or *not to have ultrasound at all* [my emphasis]. . . . The control group with no ultrasound went through routine pregnancy care as had been done before ultrasound was introduced at the hospital. All the problems in connection with the pregnancy were solved without the use of ultrasound."

This inconsistency between the only two reports of this trial is clearly of great importance in any attempt to answer the still inadequately addressed question of whether routine ultrasonography is preferable to selective ultrasonography (as opposed to withholding ultrasonography completely). Again, substantial health service resources are involved, and, furthermore, there is no basis for assuming that routine ultrasonography is innocuous.

DIFFICULTIES IN CORRECTING THE PROBLEM OF UNDER-REPORTING AFTER THE EVENT

The two perinatal examples cited above were selected to illustrate how inadequate reporting of clinical research can jeopardize the formulation of well-founded clinical policies. Because of this effect, underreporting operates against the interests of patients, not to mention those who fund health services, including the public. In collaboration with many colleagues, I have been involved in a systematic attempt to evaluate the effects of the various elements of care offered to women during pregnan-

cy and childbirth. Using a variety of methods that have been reported in detail elsewhere,[13] we have tried to reduce the problems that can result from the kind of inadequate reporting of clinical research illustrated above.

In an attempt to identify unpublished randomized trials, we conducted a survey of over 40 000 obstetricians and pediatricians in the 18 countries in which the vast majority of published perinatal trials had been conducted.[14] However, we were notified of only 18 unpublished trials completed between 1940 and the end of 1984, a period during which at least 2300 reports of perinatal trials had been published, a ratio of unpublished to published trials of 1:128. Ratios of unpublished to published trials derived from smaller, more focused surveys of clinical research have been of the order of 1:5.[1] This suggests that we failed to identify substantial numbers of unpublished trials, and we are certainly aware of several unpublished trials that were not reported to us.

Because trials with results that are regarded as "positive" are more likely to be published in the more widely read and cited journals,[5] and because we wished (when possible) to increase the statistical precision of our estimates of the differential effects of alternative forms of care by synthesizing evidence from similar trials in overviews (meta-analyses), we conducted a systematic manual search of about 60 core journals, back to the issues published in 1950.[15] These manual searches yielded about twice the number of trials that could be retrieved through MEDLINE using methodological descriptors.[13,16]

In addition, we were concerned to reduce the biases that result from selective underreporting of results within studies. This form of underreporting may occur either when the analysis presented has not been based on all the people entered into the trial or when the investigators have selected data for presentation on the basis of the pattern of results observed—for example, because the differences observed were statistically significant. So we contacted investigators, when this was possible, and asked them to provide the missing information.

The results of this work have been published in book form[17] and as a continuously updated electronic publication, the *Oxford Database of Perinatal Trials*.[10] Although we have made considerable efforts to offset the adverse consequences of underreporting of clinical research in our review of evidence about the effects of care during pregnancy and childbirth, we can never know the extent to which implementation of these precautions succeeded in producing unbiased estimates of the effects of care.

HOW MIGHT THE PROBLEM BE REDUCED?

Many people could help to ensure that the likelihood of underreporting clinical trials is reduced.

The main change in behavior is required among clinical investigators,[18] and it is the named principal investigators who have primary responsibility for ensuring that the study is reported in full. Because short-term employment contracts may sometimes compromise the ability of principal investigators to see a project through to completion in the form of a published report, ultimate responsibility for ensuring that a full report is submitted for publication would seem to rest with the heads of the departments with which the principal investigators are, or were, affiliated.

It is surprising that so many research-funding organizations do not make an award of funds to researchers conditional on a full report being prepared and published. Similarly, it is surprising that investigators continue to collaborate in commercially organized research without ensuring that the results of the research will be analyzed and reported by people who have no commercial vested interest in selective underreporting. Matters might improve if the reasonable expectations of all parties were more frequently made explicit in the documents exchanged at the outset of the research. In addition, the parties to these implicit or explicit contracts might make better decisions if they had access to systematically collected information about the track records of specific investigators and commercial research organizations in pursuing their research through to publication.

Research ethics committees, too, have a potentially important role to play. They are only doing half their job if they approve clinical research projects but then fail to assess whether the work was conducted as agreed and then reported appropriately. Ethics committees could help to reduce underreporting of clinical research by exerting pressure on investigators in at least two ways. First, they could identify, in regularly published reports, studies that had received committee endorsement. Second, research ethics committees could help to establish mechanisms for monitoring and recording investigators' compliance with the duty to provide adequate accounts of their research.

Finally, journal editors also have duties in this field. They should ensure that they purge from their practices any tendency to dichotomize reports submitted to them into those that have "positive" and those that have "negative" results.[19,20] Studies should be accepted or rejected on the basis of whether they have been well conceptualized and competently executed, not on the basis of the direction or magnitude of any differences observed between comparison groups. The editor of at least one medical journal (*Pediatrics*) has acknowledged the need for a new approach[21]: he has indicated his willingness to arrange for trial protocols to be reviewed with a view to giving provisional acceptance of a report of the planned study on its successful completion.

In addition, journal editors should acknowledge that shortage of space in printed journals can no longer be invoked as a reason for acquiescing in underreporting of research. Medical scientific publishing must exploit the potential represented by electronic publishing. For example, structured abstracts might be published on paper, and the corresponding full reports published electronically.

THE POTENTIAL ROLE OF PROSPECTIVE REGISTRATION OF TRIALS

Wider adoption of prospective registration of trials at inception could help these various parties to play their respective roles in reducing the prevalence of some of the problems alluded to earlier. Existing registers of controlled trials have been established with a view to improving decision making, not only among investigators and potential participants in collaborative trials, but also by funding organizations, research ethics committees, and journal editors. In line with a tradition going back to the beginning of scientific publishing, such registers could also be used as a basis for assessing who deserves credit for precedence in putting forward a new idea.[22]

As Simes[4,5] and Dickersin[1] have already demonstrated, however, prospective registration of trials also makes it possible to seek and detect selective underreporting: inferences based on the data available from trials registered prior to their results being known can be compared with inferences based on available data from all trials (registered and unregistered). If the conclusions of these two analyses are in conflict, selective underreporting can be suspected, and inferences based on the results of trials registered at inception (assuming the latter were of acceptable methodological quality) preferred as being less likely to reflect biased reporting.

Trial protocols could be made publicly available,[23-25] in either printed or electronic form, as a part of any prospective registration procedure for controlled trials. This would have at least two important advantages. First, the validity of brief reports of trials could be assessed with greater confidence because some details of the research methods would be publicly available. Second, any suspicion that there may have been selective reporting of certain outcomes and not others could be addressed by consulting the protocol to find out which data items were recorded and which outcomes had been specified in prior hypotheses, a matter about which the International Committee of Medical Journal Editors has recently expressed concern.[26]

Several registers of clinical trials already exist. The National Cancer Institute,[27,28] the National Institute of Allergy and Infectious Diseases,[29] and the National Institute of Dental Research[30] have already established registers of trials in collaboration with the National Library of Medicine. Other registers have been established by the British Medical Research Council,[31] the European Organization for the Research and Treatment of Cancer,[32] the International Committee on the Study of Thrombosis and Haemostasis,[33,34] and (as noted earlier) the *Oxford Database of Perinatal Trials*.[10] A variety of avenues for identifying planned and ongoing trials are being used, and these involve contacts with investigators and heads of departments, research ethics committees, funding bodies, and journal editors.

If this activity is to be extended and strengthened to meet the various objectives outlined above,[35-38] it would seem to be appropriate to look to the national and international bodies that fund clinical research for leadership, organization, and funding, and to the National Library of Medicine to coordinate this activity. But investigators and research ethics committees must obviously play their respective roles. Journal editors can encourage these developments by indicating that registration of controlled trials at inception by investigators will be regarded as evidence of scientific good conduct.

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