ELSEVIER

The Clinical Trial: Deceitful, Disputable, Unbelievable, Unhelpful, and Shameful—What Next?

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INTRODUCTION

If one consults a book about a disease, one aimed at patients rather than health professionals, the likelihood is that clinical trials will not figure prominently. The natural history of the condition in question will be given, together with characteristic symptoms and signs for self-diagnosis. And when it comes to treatment recommendations, clear directions are common. Patients seek certainty. Careful critiques of contrary evidence from one trial or another will confuse rather than enlighten. In sum, the contribution of clinical trials to medicine is mostly hidden from the public eye. When it comes to clinical care, we all take the importance of clinical trials for granted.

And yet we have now reached a point when the accumulated benefits of a half-century of clinical trial research are seriously threatened. Just as the positive value of trials is hidden, so the problems of trials are presently all too visible. This perverse imbalance in public perception is the principal origin of the threat to clinical trials. I wish to argue the case for five propositions about clinical trials today, all of which undermine their scientific and ethical validity. Finally, I want to offer some prospects for challenging these propositions and for creating a culture more conducive to and appreciative of trial research.

PROPOSITION 1: THAT TRIALS ARE DECEITFUL

In February 2000, *The Lancet* published the results of a randomized trial examining the efficacy of interferon in Behçet's disease [1]. Shortly afterward, a letter arrived from one of the alleged coauthors. It read:

> Sir—I do not regularly read *The Lancet* but I happened to see my name on an article supposedly by Haluk Demiroglu and colleagues. . . . I am totally unaware of the patients who were enrolled in that study and I have done nothing in the running of the study. I have signed no copyright agreement and,

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> therefore, do not share any kind of scientific or legal responsibility that may arise in the future concerning that paper.

The corresponding author could not explain the basis of this letter, or two similar letters from other "coauthors." I wrote to the dean of Hacettepe University Medical School in Turkey and he formed an "investigational committee." His inquiries revealed that signatures on the paper had been forged, that no ethics committee approval had been secured (the paper said otherwise), that no written informed consent was sought (the paper said otherwise), and that "some fabrication and falsification might have taken place." *The Lancet* retracted the paper 8 months after its original publication, a matter of great personal regret to me [2].

Similar recent cases of outright fraud have gained wide publicity [3]. A 1995 paper from Werner Bezwoda, a South African oncologist, was recently retracted after an extensive investigation [4, 5]. Patient records and diagnoses were unverifiable, and what records were verifiable were insufficient. Most patients were, in any case, ineligible for the study. A 1999 abstract presented at the American Society of Clinical Oncology was also found to be flawed for similar reasons [6].

But research misconduct is not confined to the thoroughly disreputable. The INSIGHT study was a well-conducted randomized trial [7]. But even here, the trial profile showed that 254 patients were "withdrawn for misconduct." Brown and colleagues commented that

> monitoring led to withdrawal of nine centres, in which existence of some patients could not be proved, or other serious violations of good clinical practice had occurred.

Critics of those, such as myself, who raise the issue of scientific misconduct argue that the fire of publicity surrounding rare cases deserves to be dampened down rather than fanned [8]. Certainly, a proportionate response is necessary. But there is some evidence that the community of medicine should not ignore these high-profile examples of fraud, for they may be an indicator of something far worse. A survey of 442 medical statisticians, completed in 1998, obtained a 37% response rate [9]. Despite this poor return, half of all respondents knew of at least one fraudulent project done in the previous 10 years. Forty-three (26%) statisticians reported fabrication and falsification; 32 (20%) described deceptive reporting of data; 31 (19%) knew of data suppression; and 16 (10%) were aware of instances of deceptive design and analysis. Worse still, 30% of this sample had engaged in a fraudulent project.

Susan Ellenberg, while pointing to "the embarrassingly low response rate to a survey conducted and reported by statisticians" [10], noted that "Each new instance of research fraud that makes its way into the public consciousness eats away at public confidence in the scientific enterprise."

In Europe, committees to investigate and discuss allegations of fraud have sprung up in many countries. In the United States, the Office of Research Integrity (ORI) remains preeminent in this effort. And it is now flexing its muscles. In a 2000 report focusing on editors [11], ORI invited us to take this issue more seriously: "Requiring that the data supporting all submitted manuscripts be deposited may not be feasible. However, authors could be explicitly informed that their data may be requested during the review process or if questions arise following publication."

In desperation, editors are being asked to become the science police. We editors are ill-equipped to take on this task.

PROPOSITION 2: THAT TRIALS ARE DISPUTABLE

In March 2001, the *New England Journal of Medicine* published the results of efforts to transplant human embryonic dopamine neurons into the brains of patients with Parkinson's disease [12]. The investigators conducted a randomized trial in 40 patients. Half received cultured new tissue from four embryos, while half underwent sham surgery with holes drilled into the skull only. The 1-year endpoint (a global score measuring improvement or deterioration in symptoms) was no different between the groups. Of great concern, however, was the finding that in five transplant patients there was late-onset and debilitating dystonia and dyskinesia. The authors were thus cautious in their conclusions: "the surgical technique may need further refinement," they wrote. In an accompanying editorial, Gerald Fischbach and Guy McKhann, both from the National Institute of Neurological Disorders and Stroke, drew attention not only to these disappointing findings but also to the "spirited debate" surrounding sham surgery [13].

This study was reported in the media as a severe setback in Parkinson's disease research. In one typical example, the headline of a press report read "Trial and Error" [14]. The opening paragraph ran: "Medical research needs human guinea pigs. But the news this week of patients irreversibly damaged by a new treatment for Parkinson's disease has highlighted the risks. When is it worth it?" Throughout the piece, the writer's emphasis was on concepts such as risk, guinea pigs, experiments, chance, and error. Although the value of clinical trials was discussed, the overwhelming impression left by this report was that "clinical trials remain highly risky, and public concern is understandable."

Organized research, such as that exemplified by the clinical trial, is easily open to skepticism and scare. The results of a trial are likely to have a high degree of internal validity, and so they can be trusted by journalists. When a trial reveals harm from a potentially new treatment, that result is more reliable and compelling than, say, a problem identified in an individual case report. The journalist will feel on safe ground reporting the harmful effects of a treatment studied in a trial. Yet success stories reported in the press tend to focus on the anecdote. This bias is also understandable. Journalists are not scientists. They need human stories that connect with their readers. The story of a single person's victory over a terminal disease (e.g., on receipt of a new mechanical heart pump [15]) is far easier to convey than the complexities, methodological as well as interpretive, of a clinical trial. This challenge of understanding is damaging the public's perception of the trial process.

Furthermore, when results of trials are reported, they are frequently misleading. Ray Moynihan and colleagues studied coverage in U.S. news media of the effects of three medications, pravastatin, alendronate, and aspirin [16]. They found that news reports in print and on television tended to emphasize relative over absolute benefits. Fewer than half of all reports mentioned adverse effects of drug treatment, and less than a third discussed cost. They concluded that most news reports do "not tell the full story." Although they wisely declined to set rules for media reporting of clinical (trial) research, they

did suggest that "An effective educational program or resource kit for journalists and editors, focusing on the reporting and interpretation of clinical findings, might be timely." In addition to instances of fraud, here is another example of why the public cannot trust what they read about randomized trials.

PROPOSITION 3: THAT TRIALS ARE UNBELIEVABLE

The peer review system is sacrosanct in medicine. Yet if we summarize all we know about peer review we can hardly avoid the conclusion that the present system for verifying scientific information is unjust, ignorant, inexact, unreliable, biased, and, oftentimes, just plain wrong. Editors and clinical trialists know this to be true in their hearts even if they hardly dare say it. But the enthusiasm with which the Consolidated Standards of Reporting Trials (CONSORT) guidelines were developed, embraced, and revised shows that peer review had failed to ensure the adequate reporting of a clinical trial [17, 18].

Even as the revised CONSORT statement was published, so new issues were pressing for further consideration. Subgroup analyses, cost-utility analyses, quality-of-life data, and the role of the sponsor all deserve attention [19–21]. And additional guidance on reporting meta-analyses and diagnostic studies is also being debated [22]. Only in the past few years have readers of clinical trials been reassured that what they are reading is a complete and accurate report of what took place. There is further room for improvement.

There is another reason why users of clinical trial data might have reason to pause. The influence of industry in trial research is not new. But the debate about potential and real malign influences of the sponsor has now reached such a pitch that the fragile foundation of integrity supporting the research enterprise could easily crack.

Thomas Bodenheimer recently summed up the difficulties of this "uneasy alliance" [23]. He drew attention to the way in which commercial networks (contract-research organizations and site-management organizations) were taking over clinical trial research. The academic medical center was now adopting a secondary role in the research process. Investigators seemed willing to promulgate opinions based on who was paying for their hospitality. Sponsored studies and industry-supported symposia appeared to be more favorable to the company than nonsponsored trials or events. And pharmacoeconomic analyses were often little more than marketing tools. Bodenheimer highlighted the influence of industry in trial design, data analysis, and publication. He concluded that there were serious and substantial conflicts in academic-industry partnerships, which produced "potential public and physician skepticism about the results of clinical drug trials." Marcia Angell, a former editor of the *New England Journal of Medicine*, urged that "Academic institutions and their clinical faculty members must take care not to be open to the charge that they are for sale" [24].

PROPOSITION 4: THAT TRIALS ARE UNHELPFUL

Assuming that we can trust what a clinical trial report says, what do its results actually mean? This question was tackled by Michael Clarke and Iain Chalmers in a survey of the discussion sections of 26 randomized trial reports

published in leading medical journals during May 1997 [25]. They found that only two articles included an updated systematic review of earlier trials. In four papers, references to systematic reviews were given but no formal integration of new with old data took place. Clarke and Chalmers concluded that

> The public is often confused by the conflicting messages it receives as a result of piecemeal reporting of research. To deserve the public's continued support and trust, researchers and journals need to ensure that reports of research end with scientifically defensible answers to Bradford Hill's question, "What does it mean, anyway?"

The public is also confused by the way in which trial data are presented to them. And this confusion is likely to have important clinical consequences. When risk information is presented according to relative risk reduction, absolute risk reduction, number needed to treat, or personal probability of benefit, patient decision-making changes accordingly [26]. When data from the 1985 Medical Research Council Mild Hypertension Trial were presented in these different ways to patients with hypertension and to nonhypertensives (n = 309), 92% of individuals said they would accept treatment based on the relative risks. But only 44% would accept treatment based on the personal probability model. The frame of reference strongly influenced how a patient perceived potential benefits of drug treatment. Moreover, as Misselbrook and Armstrong concluded, "given that the form of the explanation has a strong influence on the patient's decision, it is not clear how decision-making can be fully shared nor what should constitute informed consent to treatment."

There is a further issue, one based on the interpretive boundaries placed on readers by the text or by the readers themselves. Unless we investigate these interpretive processes in medicine, processes that intercept at the biologically unfamiliar crossroads between a philosophy of knowledge and cognitive science, we will misunderstand how and why doctors interpret clinical trial data in the way they do. We need to know the how and why of interpretation if we are to get some sense of the impact of trials on medicine. I call this "interpretive medicine," partly in homage to the anthropological work of Clifford Geertz and partly against overly literal versions of evidence-based medicine [27, 28].

The premise of this interpretive approach is that the research paper is, first and foremost, a document produced by a group of authors presenting an argument to the reader [29]. The task for the reader is to judge the validity of that argument [29]. In medicine, and for clinical trials in particular, editors, clinical trialists, and biostatisticians have set rules for controlling the interpretive range of a text [30]. The research paper has a formal structure (introduction, methods, results, and discussion). A structured abstract directs the reader to the key facts about the research report. Adherence to the CONSORT guidelines relieves the risk of biased reporting. The insistence on framing a result in several ways prevents the reader from taking an overly optimistic (or pessimistic) view of the treatment being tested. Hierarchies of evidence tell readers to pay more attention to particular study types. And the notion of structured discussions may assist more accurate appraisal of research data [31].

An additional way to set boundaries on interpretations is to invoke rules of reading [32]. These rules can be divided into two categories, those relating to the text and those relating to the reader.

Textual rules derive from the idea that meaning rests in words and numbers, tables and figures. The capacity to understand texts (research papers) can be acquired through training in clinical epidemiology and biostatistics. The assumption here is that the text has an objectively attainable meaning, available to readers if they have the right skills. An alternative view is that readers make meaning, not texts. To understand how the reader ascribes meaning to a clinical trial result, we need to know something about the cognitive processes of the reader. In other words, we need to appreciate the subjectivity of interpretation. For example, what are the roles of opinion leaders, authors, institutional affiliations, study design, the journal's reputation, the nature of the sponsor, views of colleagues, and the particularities of one's patients in shaping the response to a clinical trial result? Presently, we have intuitions but no answers to these questions. If we are interested in putting the results of clinical trials to good use, this project seems to warrant further study.

PROPOSITION 5: THAT TRIALS ARE SHAMEFUL

In November 2000, David Rothman, a respected medical ethicist, wrote an article in the *New York Review of Books* entitled "The Shame of Medical Research" [33]. In this polemical essay, he drew on evidence of clinical trials conducted in resource-poor countries to charge that trialists were exploiting the vulnerable, seeking participation by coercion and not consent, failing in their obligations to offer the highest standard of care to individuals in control groups, failing to offer decent posttrial care, and taking advantage of weak institutional review boards. He argued that research "practice has overwhelmed ethics."

Rothman's claims have resonance in the North as well as the South. September 17, 1999 was a turning point for medical research in the United States. On that day, Jesse Gelsinger died. He was an 18-year-old volunteer in a gene therapy trial taking place at the University of Pennsylvania in Philadelphia. Further trials were quickly suspended. Subsequent scientific soul-searching was matched only by the intrusive zeal of Federal officials [34]. In direct response to the death of Gelsinger, Donna Shalala, the Secretary of the United States Department of Health and Human Services, wrote about four "disturbing" trends in clinical research [35].

First, "researchers may not be doing enough to ensure that subjects fully understand all the potential risks and benefits of a clinical trial." Second, "too many researchers are not adhering to standards of good clinical practice." Third, institutional review boards (IRBs) "are under increasing strain" and oversight is often "inadequate." Finally, the integrity of clinical trials is now being compromised by the force of commerce. These trends had "seriously shaken" public confidence, she argued. This was an "appalling state of affairs."

Shalala offered six prescriptions: improved education and training for investigators; clearer guidance on informed consent; a requirement for more detailed monitoring of clinical trials; stricter regulations about conflicts of interest; financial penalties for violations of these codes; and an expanded role for the Office of Human Research Protections. She also asked the Institute of Medicine to review the structure and function of human research participant protection programs.

The subsequent report, Preserving Public Trust, was published in 2001 [36]. The Institute of Medicine proposed the creation of Human Research Participant Protection Programs (HRPPPs), together with a new independent accreditation body that would set standards for these programs. Research participants and representatives of other organizations would be included in these standard-setting exercises. The first step should be to pilot test an HRPPP. Here are the beginnings of regulatory hypertrophy. Indeed, the tone of this response is persecutory rather than merely proscriptive. The summary of the report circulated to news organizations began by referring to "crimes committed by Nazi scientists during World War II." On the same page, the fate of Jesse Gelsinger was reported as the principal motivation for the inquiry: "As the circumstances and events leading up to his death emerged, it became apparent that the system intended to protect him from unacceptable research risks instead failed him." The reader cannot fail to see the report's wish to equate a war crime with a present-day "science crime." It is an insulting exaggeration.

In addition to the Institute of Medicine report, the United States Presidential Bioethics Commission recently issued its report into clinical trial research in developing countries [37]. And Greg Koski, Director of the Office for Human Research Protections, has set out his agenda for further revisions to the Declaration of Helsinki.

We live in a time of enormous regulatory activity predicated on a few tragic errors and a great deal of misunderstanding. But the backlash is coming. In a recent critique of Federal crackdowns on IRBs, William Burman and colleagues discussed how a culture of obsessive oversight ("rigid enforcement of outmoded regulations that do not contribute to patient safety") was causing a crisis in clinical trials [38]. It seems that in the rush to add layers of administrative checks and balances, the whole purpose of the clinical trial, to benefit patients by providing reliable information for their care, has been forgotten.

WHAT NEXT?

The evidence supporting these propositions indicates that the clinical trial process is approaching a critical moment. Indeed, public skepticism is already producing problems in patient recruitment. A March 2001 article on BBC Online was entitled "Medical advances 'in jeopardy.'" The piece began, "A desperate lack of patients for clinical trials of new drugs for cancer may be costing lives, say experts." Part of the reason is because "patients in general do not want to become 'guinea pigs' for medicines."

Is there a way forward? Four possible lines of action deserve wide debate within the clinical trial community.

First, all those who take part in clinical trials must become far more powerful advocates for those trials. The hidden benefits of clinical trials must be hidden no longer. Iain Chalmers has written that "We should make a more concerted effort to help the public understand how biases and the play of chance can lead to dangerously incorrect conclusions about the effects of healthcare interventions" [39].

Such public outreach needs to involve governments, science policy agencies (e.g., the National Institutes of Health), schools, and patient organizations. The media might be one further avenue to pursue. However, as any self-respecting

journalist will admit, the reporter is there to report the news and not to be an instrument of public education. Nevertheless, trialists could do more to help journalists report trials more accurately [16].

Second, trialists must show far deeper concern for the threatened integrity of the clinical trial process. A part of this anxiety naturally centers on the issue of research misconduct. Limited oversight of research is valuable and reporting instances of proven misconduct as soon as they come to light is part of the scientist's responsibility to patients. If this practice becomes the norm, calls for more bureaucracy in trial organization, such as more vigilant editors, will become redundant.

There is a far more important aspect of research integrity, and that concerns the role of the sponsor in clinical trials. There are many facets to consider: the choice of research question, the contract between sponsor and investigator, the role of the sponsor in protocol development, access to data held by the sponsor, control over analysis and interpretation of the data, ghost writing, influence over publication, and investigator conflicts of interest [40]. The latter remains a key issue, despite years of attention and discussion. Recent evidence suggests that authors comply poorly with journal requests for disclosure of conflicts of interest [41]. From the public's perspective, this is now an important matter in judging the integrity of the medical research enterprise, and journalists judge those failures by editors and scientists harshly [42].

Perhaps worse still, clinical trials are now simply another weapon in a pharmaceutical company's public-relations armamentarium. Toine Pieters has shown how clinical trials legitimized and widened the therapeutic profile of interferon despite a weak evidence base [43]. He concluded that

> The interferon case provides a warning example to those who uncritically promote randomized controlled trials as the badge of rational medicine. In achieving a key position in the distribution of research resources and materials needed to set up such trials, the pharmaceutical industry increasingly dictated development and clinical use of interferon . . . [R]andomized controlled trials proved effective not only in evaluating the safety and benefit of interferon as a therapeutic drug but also in the marketing of the commercially interesting multitreatment concept that turned the interferons from unwanted drugs into top selling pharmaceuticals.

The only practicable response to this commercial pressure is, as Bodenheimer argued, to strengthen the independence of investigators [23]. Academic medical centers, trial steering and data and safety monitoring committees, and medical statisticians could all help in this process.

Third, researchers need to think more critically about the practical methodology of the studies they undertake. While the large, simple, randomized trial has huge and obvious merits, there are clearly problems in this dominant means of organizing a trial [44]. In a qualitative study of cancer trials, for example, Carole Langley and colleagues found that clinicians who were low recruiters felt that they were being asked to enroll patients "at a very vulnerable stage" in their care [45]. The notion of randomization (deciding treatment "out of an envelope") was anathema, and "eligibility is one thing, suitability is something different." In addition, patients were often surprised by the degree of uncertainty displayed by their clinicians. Langley and colleagues concluded

that "Action is needed to promote awareness of randomized trials under way, to ensure that trials address issues of importance, are acceptable to patients and clinicians, and that practical support is provided for participating centres."

Perhaps an emphasis on the better care a patient receives in a clinical trial would be one way ahead [46]. Research into written trial information for patients is an urgent need [47]. Indeed, preliminary work indicates that "written information to trial subjects should be detailed, as a majority of both potential and actual research participants prefer this" [48]. Alternative study designs intended to encourage patient participation might also be considered, although different approaches (e.g., comprehensive cohort studies or randomized consent designs) do have disadvantages as well as advantages [49].

One of the most challenging problems facing trialists remains informed consent. In a single study of attitudes to trials, Italian investigators invited four family physicians to ask 289 patients to complete a questionnaire about their views of the trial process [50]. Knowledge about informed consent was poor (only 58%) and depended on the educational level of the patient. Over 80% of patients were not interested in taking part in "a controlled scientific study involving the administration of a new drug potentially useful to you but not yet evaluated in human beings for its usefulness and its adverse effects." More attention to these practical issues is rarely mentioned by advocates of trials [44]. Yet unless these rather mundane matters are taken up, and they are only very rarely [51], the problems of clinical trials will not be addressed and public skepticism will only increase further.

Finally, editors could do more. In our journals we might be better advocates for clinical trials. We could be more helpful in our guidance to authors when publishing trial reports (e.g., by allowing full publication of all participating centers and clinicians). And we might also consider our place in protecting authors from unwelcome commercial pressures. In a *Lancet* editorial [40], we wrote that

> It is the editorially independent peer-reviewed medical journal that remains a final common path by which investigators obtain justified credit for their work. Journal editors can do much to reinforce the integrity of the science they publish. For clinical trials, one important next step is to strengthen the latest revision of the CONSORT statement to make explicit the role of the sponsor in data collection, analysis, and publication.

In sum, all health-care professionals directly or peripherally involved in clinical trials need to recommit themselves to explaining, proselytizing, promoting, understanding, encouraging, studying, protecting, strengthening, and reflecting on the clinical trial process.

And finally, a gentle warning. In all the necessary effort to uncover the benefits of clinical trials for a wider public, we also need to pay attention to the consequences of those same trials. This necessary follow-through is presently neglected. No disease has been the recipient of more clinical trial interest than coronary artery disease. But in a survey of coronary risk factors across European countries in 1995–1996 and 1999–2000, the success of risk-factor modification was only patchily apparent; the authors of EUORASPIRE called their results a "collective failure of medical practice" [52]. Smoking prevalence increased from 19.4% to 20.8%, obesity from 25.3% to 32.8%, and diabetes mellitus from 18% to 21.9%. Hypertension fell only slightly from 55.4% to 53.9%.

High serum cholesterol was the only example of a risk factor that had diminished substantially between the two periods (86.2% to 58.8%).

There is little point in devoting time, financial resources, and vast human effort to clinical trials unless we all heed their results. Here is perhaps the single most important challenge for present and future trialists.

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