THE BREAST CANCER RESEARCH SCANDAL: ADDRESSING THE ISSUES

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Abstract • Résumé

The three claims put forward by Dr. Roger Poisson to rationalize his enrolment of ineligible subjects in clinical trials do not justify research fraud. None the less, certain lessons for the conduct of clinical research can be learned from the affair: experimental therapies should be made available to technically ineligible subjects when no effective therapy exists for their disease; further research must investigate the possible benefits of clinical-trial participation; broadly based, pragmatic trials must be regarded as the ideal model; and each eligibility criterion in a clinical-trial protocol should be justified.

Les trois raisons invoquées par le Dr Roger Poisson pour rationaliser le fait qu'il a utilisé des sujets non admissibles à des essais cliniques ne justifient pas la fraude en recherche. On peut néanmoins tirer de cette affaire certaines leçons sur la conduite des recherches cliniques : il faudrait offrir des thérapies expérimentales à des sujets qui ne sont pas admissibles sur le plan technique lorsqu'il n'existe aucun traitement efficace pour leur maladie; d'autres recherches doivent porter sur les avantages possibles d'une participation à des essais cliniques; il faut considérer des essais pratiques généraux comme le modèle idéal; et chaque critère d'admissibilité à un protocole d'essai clinique doit être justifié.

In 1993 a report from the US Office for Research Integrity (ORI) concluded that Dr. Roger Poisson, of the Hôpital Saint-Luc, Montreal, had falsified data on 99 of the 1511 women he had enrolled in clinical trials of the US-based National Surgical Adjuvant Breast and Bowel Project (NSABP).[1,2] In correspondence with the ORI and the *New England Journal of Medicine*[3] and in an interview published in *CMAJ*,[4] Poisson offered several justifications for altering data pertaining to subject eligibility. He argued that patients receive better treatment in clinical trials than is available elsewhere, that eligibility criteria for trial participants are arbitrary and too restrictive and that randomization ensures that trial findings are not biased, even when ineligible subjects are enrolled. Although the events surrounding the research fraud have received extensive media coverage, a critical examination of Poisson's justifications has not been published.

Fraud is antithetical to scientific inquiry, and therefore we should not be swayed by Poisson's "justifications." We are taught, as medical scientists, to be sceptical of data and the conclusions derived therefrom; we must, however, be able to trust the scientist who has generated the data. Although they are well equipped to detect faulty methods and analysis, journal editors, peer reviewers and consumers of medical information are ill equipped to detect fraud.[2] A critical examination of Poisson's claims may none the less generate some benefit. Erroneous assertions may be challenged and corrected; true propositions, although incapable of excusing research fraud, may suggest ways to improve the conduct of clinical research.

DO PATIENTS RECEIVE BETTER TREATMENT IN CLINICAL TRIALS?

Subjects enrolled in clinical trials may receive treatment superior to that offered in nonexperimental settings in two ways. First, a given therapy that is known or believed to be superior to the standard therapy may be available only in a clinical trial. Second, the fastidious delivery of treatment and the thoroughness of follow-up in clinical trials may offer benefits over and above the specific therapy under scrutiny. If trial subjects receive superior therapies or better treatment in general, is the enrolment of ineligible subjects justified? I think not. Although enrolment of an ineligible subject may indeed benefit that person, it can only be the result of a one-sided moral calculus. By slowing or even preventing the approval and dissemination of a new medical therapy, research fraud can adversely affect the treatment of thousands of patients. The disclosure of fraud may delay the

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release of results until the legitimate data have been reanalysed. Indeed, even if the reanalysis confirms the original findings, clinicians and drug regulatory agencies may simply find the results less credible. As Vanderpool and Weiss[5] pointed out, fraudulent enrolment may do harm by "affecting the careers of researchers, consuming scarce resources, and heightening distrust in medical research." In the wake of the breast cancer research scandal, who could doubt this claim?

Are better therapies available in individual clinical trials? The glib answer is If any therapy were known to be superior, we would not be doing a clinical trial. Indeed, although enthusiasm for untried therapies may be great, randomized controlled trials (RCTs) prove the standard therapy to be superior to the experimental therapy about half the time.[6] When effective therapies are expensive or difficult to obtain, however, they may not become available until they have been proven to be cost-effective as well. Recent clinical trials of erythropoietin for the treatment of anemia in chronic renal failure,[7] and of epoprostenol for primary pulmonary hypertension, highlight the fact that the best therapy may initially be available only in a clinical trial.[8] In other cases, experimental therapies seem to offer the best hope for life-threatening conditions for which no effective standard therapy currently exists. For example, at the time of the first RCT of zidovudine for the treatment of AIDS, no effective therapy for HIV infection and AIDS existed. Patients with AIDS who were ineligible for the trial were therefore denied access to the most promising therapeutic agent available. Fortunately, fraud is not the only possible solution to dilemmas of this kind. When no effective therapy exists for a life-threatening condition, a trial should have an open treatment arm that would allow technically ineligible patients access to an experimental therapy.[9] Moreover, experimental drugs can, in defined circumstances, be released on compassionate grounds.

Does clinical-trial participation in and of itself offer benefits to subjects? Cancer patients treated in clinical trials have been reported to survive significantly longer than those treated outside of trials.[10–13] Part of this difference in outcome is, no doubt, explained by prognostic discrepancies between the two groups. The difference may also be explained in part by the fact that clinical-trial treatment usually takes place in tertiary care centres, where specialists have greater experience in the delivery of complex treatment regimens.[14] Tentative evidence suggests, however, that the fastidious treatment and follow-up regimens offered by clinical trials of cancer treatments improve survival.[15,16] Further research is needed to examine this possibility. If clinical-trial participation does prove to offer an advantage, two options, which are not mutually exclusive, exist. First, criteria for clinical-trial eligibility can be made less restrictive to allow more subjects to participate. Second, steps can to be taken by such means as clinical practice guidelines to make treatment and follow-up in clinical practice resemble more closely that provided in clinical trials.

Are eligibility criteria too restrictive?

Criteria for clinical-trial eligibility define the study population by defining the study disease, excluding subjects likely to suffer adverse effects from the experimental therapy and attempting to ensure that the outcome can be measured (e.g., by requiring that subjects have a life expectancy greater than the length of the follow-up period). Although eligibility criteria ought to be carefully scrutinized at the planning stage, once a trial is initiated they must be respected. Even if eligibility criteria are felt to be too restrictive, the enrolment of ineligible subjects interferes with the generalizability of the trial results and may diminish their impact on clinical practice.

This being said, I believe that eligibility criteria in oncologic clinical trials in North America are frequently too restrictive. Begg and Engstrom[17] found that a sample of concurrent breast cancer trials had numerous eligibility criteria, some of which seemed to be arbitrary. Another review of eligibility criteria in NSABP trials[18] found that the number of criteria per trial increased over time in a way that diminished the clinical relevance or generalizability of results from later trials. If a large proportion of candidates with the target disease is excluded from a trial, the generalizability of that trial's results must be questioned.[19] I recently performed a comprehensive review of published studies of enrolment patterns in RCTs and found that, among subjects for whom an RCT relevant to their type and stage of disease was available, 56% were excluded by eligibility criteria (unpublished data). As well as diminishing generalizability, unduly restrictive criteria can slow the rate of accrual of subjects to a clinical trial by reducing the pool of eligible subjects.[19,20] Clinical trials with such criteria may take longer to complete and thus slow the pace of medical progress. Clinical-trial designers ought, therefore, to embrace the ideal of broadly based, pragmatic trials that mirror clinical reality. Furthermore, individual eligibility criteria should be explicitly justified in the clinical-trial protocol to demonstrate their necessity to investigators and to members of research ethics boards.[21]

Does randomization prevent bias?

Randomization is the distinguishing feature of RCTs. Because people with potentially different prognoses are assigned to the two (or more) arms of a clinical trial by chance, the validity of the comparison made in the study is protected.[22] Indeed, it is this characteristic that has

made the RCT the preferred instrument of medical research. To claim that randomization protects the clinical trial from the impact of the accrual of ineligible subjects is, however, naïve. First, ineligible subjects may add statistical "noise" to a trial. Assuming a fixed sample size, this will diminish the probability that a trial will, if a given difference between treatments exists, succeed in demonstrating that difference. Second, clinicians depend on reported eligibility criteria to judge whether the results of a given trial are relevant to their practice. If ineligible subjects have been silently included it will be difficult to assess to whom the results of a given trial are applicable. Third, the disclosure of methodologic discrepancies, intentional or unintentional, will diminish the impact of a trial on clinical practice by reducing its credibility. (Had the treatments in the NSABP trials not been verified by other clinical trials[23,24] the harm done by the breast cancer research fraud would, I think, have been even worse.)

Conclusion

My purpose in discussing Poisson's justifications for falsifying research data is not to give these excuses any credence; they have none. Nor is it my purpose to portray Poisson as a visionary in the reform of clinical trials; he is not. The debate surrounding eligibility criteria and clinical trials dates back to at least 1976.[22] My purpose, rather, is twofold: first, to criticize Poisson's claims and, second, to offer some suggestions for the conduct of future clinical research. With regard to research, I have argued that experimental therapies should be made available to technically ineligible subjects when no effective therapy exists for their disease; that further research must investigate the possible benefits of clinical-trial participation; that broadly based, pragmatic trials must be regarded as the ideal model; and that individual eligibility criteria should be justified explicitly in the trial protocol to highlight their necessity.

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