Short communication

Who should participate in clinical trials and who not? Can clinical trials be made more efficient and effective?

Kathleen I Pritchard

Sunnybrook Odette Cancer Centre, Sunnybrook Health Sciences Centre and University of Toronto, Bayview Avenue, Toronto, Ontario M4N 3M5, Canada

Corresponding author: Kathleen I Pritchard, kathy.pritchard@sunnybrook.ca

Published: 18 December 2008
This article is online at http://breast-cancer-research.com/content/10/S4/S23

Breast Cancer Research 2008, **10(Suppl 4):**S23 (doi:10.1186/bcr2183)

Clinical trials objectives

Although it may seem self-evident, it is important when establishing a clinical trial that there is an important question to be answered. Once such a question has been posed and an appropriate design established to answer that question, all efforts should be made to enrol as many patients into the trial as expeditiously as possible. The design of the trial should support that aim.

Eligibility criteria

Eligibility criteria should not be too elaborate or complex. For example, in an adjuvant breast cancer trial, specific details of the exact handling of tumour margins, exact doses of radiation therapy or number of nodes dissected may not be particularly important in comparison with entering a wide variety of patients from the adjuvant setting. Broader entry criteria will make trial results more generalizable and will result in more rapid trial accrual. It is important, however, that eligibility criteria ensure that the patients entered will be receiving therapy that is safe for them, and that the stated end-point(s) of the study can be obtained in all patients.

Data collection

Ideally, patients should be enrolled into large simple trials with simple outcomes such as recurrence of cancer and death. Such trials could be conducted relatively economically. In turn, however, we must balance simplicity against the need to collect important data. For example, if we compare two treatment regimens in a trial of adjuvant therapy for breast cancer, then we would want to collect toxicity data carefully. We may also be required by agencies such as the US Food and Drug Administration and the European Medicines Agency to collect certain data in order to meet registration requirements. In terms of outcome, one may not want to collect only the first site of recurrence, but patterns of recurrence; for example, does the patient initially or later develop a brain mestastasis or a bone metastasis. Furthermore, once a trial is completed, useful information can be obtained by studying concurrent medications if they are recorded. For example, it is believed that providing local vaginal oestrogen therapy may obviate the systemic adjuvant effect of the aromatase inhibitors, because there may be systemic absorption of such oestrogen. However, in a large trial of aromatase inhibitor versus placebo (MA.17) [1], although vaginal oestrogens were allowed, there was no systematic recording of their use and so a study of this interesting question in the setting of this randomized clinical trial may be difficult. Overall, one must strike a balance between collecting data that will never be used and not collecting data that one may later wish to have had.

Clinical trial hurdles

To create a clinical trial, it is still important to generate the question, write a protocol and seek funding for the trial. Regulatory approval will be involved. Most institutions have protocol review committees, which judge the science of the study and its impact on clinical practice in the institution. Separate committees (research ethics boards [REBs]) exist to judge ethical suitability and to review the process for informed consent. Contracts between the hospital and the sponsor of the trial are complex and often take considerable time to negotiate. Standard operating procedures for clinical trials must be adhered to and systematic reporting of adverse events, and particularly serious adverse events (SAEs), is required. These are just some of the many critical but time consuming issues that are involved in launching and conducting a study. As the bureaucracy and paperwork required increases and costs escalate, more trials may be run by industry and fewer by academic investigators.

The best trials are designed by investigators with burning questions to answer! However, a shortage of oncologists and

REB = research ethics board; SAE = serious adverse event.

clinical service demands are a threat to the development of young clinical investigators. It will be important over future years to protect the time of these young investigators and to help them to pose important questions, put together well designed protocols and learn to seek the funding to carry them out.

There are also important issues surrounding the issue of who should hold datasets. There are felt to be conflicts of interest when industry holds data and manages analyses, but they may be best equipped to do so because they have greater economical and data management resources, and employ many statistical experts. Running trials at academic institutions has become increasingly difficult, particularly because many peer-reviewed funding agencies often systematically under-fund clinical trials in the peer review grant process.

Within institutions, financial cutbacks have led to a tendency by hospitals to bill for every incremental procedure, test or activity that is required as part of a clinical trial. Some institutions would like to charge for every activity for a patient as long as they are in a study, even though the patient might undergo many of those same procedures in routine care.

Because breast cancer has such a long natural history, ongoing follow-up is important. Often there is not sufficient funding to carry out this activity, however. There have been proposals to match patients on long-term follow up in the adjuvant setting to cancer registries in order to record accurately adverse events, recurrence, death and cause of death. For example, many of the data on long-term side effects of tamoxifen were first clearly described in the Scandinavian countries, in which cancer registries are very accurate, by matching up patients in large randomized clinical trials with those included in registries (for instance, tamoxifen's association with endometrial cancer [2] and the reduction in cardiac disease shown with tamoxifen [3]).

Regulatory approval has become increasingly difficult in countries such as Canada. Clinical trials approval is now required even for drugs that have been commercially available for a long time but are being tested at a slightly different dosage or combination. This has added to the administrative burden of trial conduct. Protocol submissions and reviews have become more complex. Every trial, as it should, requires yearly approval and re-REB consideration. And then there are amendments! Recent regulations suggest that when substantial amendments to a trial are ongoing and have not been passed through the local REB, accrual to the trial must be suspended. This results in frequent interruptions to trial accrual. Auditing, although clearly necessary to ensure that source documentation for study-collected information is available and accurate, consumes the time of both the auditors and the trials personnel in the centres.

Studies are often designed with a lot of scientific thought, and then re-reviewed by several layers of review committees, including ethics boards, whose members may want to revise the science. Consent forms are becoming increasingly complex and, unfortunately, are directed more at legal protection of institutions, physicians and other health professionals than at explaining the study to the patient. Many consent forms in North America are now 10 to 12 pages long. It is unlikely that patients actually absorb and understand all of this material. A simpler approach would probably be more effective. Contracts have also become complex, in part because of the many legal issues surrounding confidentiality and indemnification.

The trial investigators *Good Clinical Practice* handbook, while setting a clear standard for the conduct of trials, can be interpreted in many different ways [4]. These different interpretations often present difficulties.

Solutions

Trialists are moving forward to deal with many of these issues in a more efficient way. Making entry criteria to studies very broad allows greater generalizability. In addition, trialists have developed mechanisms for advertising studies and for screening broad populations for their availability to enter. Websites such as Patient Data Query [5] list available studies, whereas others such as the Ontario Institute for Cancer Research website [6] show not only what trials may be available for patients with a particular stage or phase of breast cancer or other diseases, but also what institutions are conducting these studies.

The current systems for reporting SAEs result in multiple reports of the same events to the same investigators and lead to a large burden of paperwork that often obscures the few important SAEs that may be reported. Organizations such as the National Cancer Institute of Canada Clinical Trials Group now screen and streamline such SAEs before sending them out to individual centres so that fewer, more relevant SAEs can be considered in more detail.

The use of centralized REBs may also reduce repetitive work within each centre. For example, the Ontario Cancer Research Ethics Board has been developed to streamline ethics approval and appears to be filling this role [7].

Conclusion

A plethora of regulatory and ethics requirements around clinical trials has made them slower to initiate and more difficult and expensive to conduct. Although many of the issues that this bureaucracy is designed to regulate are important ones, it is to be hoped that in the future clinical trials can be streamlined so that they may be started faster, conducted more cheaply and efficiently, and enter more patients more quickly and with more generalizable results. This would make the conduct of clinical trials more appealing to investigators and patients, and their results more quickly relevant and useful. It is important for investigators, regulatory

agencies, ethics bodies and funding agencies to keep these issues in mind as they move forward in designing the clinical trials of the future.

Competing interests

The author declares that they have no competing interests.

Acknowledgement

This article has been published as part of *Breast Cancer Research* Volume 10 Supplement 4, 2008: Controversies in Breast Cancer 2008. The full contents of the supplement are available online at http://breast-cancer-research.com/supplements/10/S4

References

1. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, Castiglione M, Tu D, Shepherd LE, Pritchard KI, Livingston RB, Davidson NE, Norton L, Perez EA, Abrams JS, Therasse P, Palmer MJ, Pater JL: **A randomized trial of letrozole in post-menopausal women after five years of tamoxifen therapy for early-stage breast cancer.** *N Eng J Med* 2003, **349:**1793-1802.
2. Fornander T, Rutqvist L: **Adjuvant tamoxifen and second cancers.** *Lancet* 1989, **333:**616.
3. Nordenskjöld B, Rosell J, Rutqvist LE, Malmström PO, Bergh J, Bengtsson NO, Hatschek T, Wallgren A, Carstensen J: **Coronary heart disease mortality after 5 years of adjuvant tamoxifen therapy: results from a randomized trial.** *J Natl Cancer Inst* 2005, **7:**1609-1610.
4. *Good Clinical Practice Handbook: Guidance for Implementation.* World Health Organization [www.nccn.org/professionals/physician_gls/PDF/breast.pdf]
5. **PDQ®** [http://www.cancer.gov/cancertopics/pdq]
6. **Ontario Institute for Cancer Research** [http://www.oicr.on.ca/]
7. **Ontario Cancer Research Ethics Board** [www.oicr.on.ca/ocreb/about.htm]