ELSEVIER

European Journal of Cancer 41 (2005) 2784–2786

European Journal of Cancer

www.ejconline.com

Editorial Comment

Why did the study fail?

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Received 4 August 2005; accepted 5 August 2005
Available online 25 October 2005

There is nothing in the world so purifying as knowledge

(ancient Sanskrit wisdom)

Designing and conducting a multicentric randomised phase III clinical trial requires considerable enthusiasm and great powers of endurance and asks for enormous investment of time, resources, and efforts. It involves scientific, linguistic, regulatory, legal, ethical, political, diplomatic, cultural, and socio-economic considerations. Trials in cancer medicine need rapid recruitment for obtaining results in a timely fashion. This allows fast publication of data that might affect treatment and outcome of patients suffering from a disease for which cure is mostly not possible and clinical research is therefore of highest priority.

In this issue of the European Journal of Cancer, Sinacki and colleagues report about the failure in reaching accrual in the EORTC 10974/22002 (LAMANOMA) study, opened in October 2001 to answer the question of whether mastectomy plus postoperative radiotherapy could be safely replaced by breast conserving treatment (radiotherapy alone or tumourectomy followed or preceded by radiotherapy) in patients with locally advanced breast cancer after induction chemotherapy.

The calculated sample size for the trial was 1210 patients, to be randomised over a period of 5 years. In reality, only 11 out of 30 institutions, initially declaring their intent to participate in this trial, accrued as few as 23 patients over a period of 21 months. The study was closed in December 2003 and a questionnaire was issued to investigate the reasons precluding centers' participation (25 replies; 83%). However, no dominant reason for the study's failure could be detected.

Lack of accrual in a phase III trial can arise from several causes:

1. The participants/investigators may overestimate the number of eligible patients in their institutions as well as awareness and enthusiasm of their colleagues for a determined trial. It must be noted that physicians sometimes have well founded or biased treatment preferences that may reduce the likelihood of offering their patients the chance of participation in a trial [1–4].
2. Many patients may not wish to participate in a clinical experiment. Communication with cancer patients about randomised clinical trials is difficult and poorly trained professionals may deter patients from entering trials [5]. In an assessment performed by Jenkins the main reasons for patient clinical trial participation were: that 'others will benefit' (23.1%); and 'trust in the doctor' (21.1%). The main reason for refusing trial entry was 'worry about randomisation' (19.6%). Trials providing active treatment in every arm had a significantly higher acceptance rate as compared with those with a no treatment option [6]. The traditional model of decision-making primacy of the individual patient–physician pair is shifted by participating in a clinical trial to a research model. In the research model all aspects of determination of patient eligibility, allowable treatment modifications, co-medication and many other areas of patient care are pre-specified in the clinical protocol and do not allow for much individual freedom [7].
3. The hospitals frequently lack an appreciation for clinical research and have inadequate infrastructures to support participation in trials. A survey, conducted

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doi:10.1016/j.ejca.2005.08.024

in Britain among oncologists, identified constraints imposed by the healthcare system as significant impediments for trial participation (lack of time and support, and conflicts between the role of clinician and scientist) [8]. Also American oncologists, interviewed by Somkin [9], complained about internal health plan resources and identified a critical need for infrastructures to support trials, especially additional support staff and research nurses.

4. Regulatory authorities (Regulatory Authorities, Ethical Committees, Institutional Review Boards) can be unnecessarily bureaucratic leading to further delays in trial initiation.
5. The pharmaceutical companies involved may have to follow cumbersome internal rules issuing from over-interpretation of regulatory requirements or may fail in delivering enough study drug in a timely fashion.
6. The research funding entities with their frequently long review processes and complex decision pathways may hold trial start.
7. Finally, the trial itself may be unrealistically planned or have restrictive eligibility criteria. This could then cause a major hindrance in patient accrual, increase trial complexity and costs, and limit the generalisation of results [7,9]. Despite repeated calls in favour of large simple phase III trials [10,11], most of them are still relatively small and complex, possibly due to the inherent difficulty in investigating multimodal treatments that are applicable for several cancers (surgery, radiotherapy, chemotherapy, biological therapies, *etc*). In addition, the question asked in the trial may be of limited relevance to most of the potential participants who therefore may decide to invest their resources in other projects.

Choosing to participate in a clinical trial is an important personal decision for patients and, often, for their family. The informed consent process might be an additional source of anxiety for someone with a recent diagnosis of cancer, and implies that people without a scientific cultural background should offer judgment about study details, risks and potential benefits during very difficult medical circumstances. The possibility to withdraw from the trial at any time does not temper the anxiety related to accepting participation.

A clinical trial implies an agreement between the physician and the patient, but also between the investigator and the scientific community. The planning and conduct of large clinical trials are extremely expensive activities often funded by a variety of organisations such as medical or academic institutions, foundations, voluntary groups, and pharmaceutical companies, in addition to national and/or federal agencies. Careful planning, timely conduct and publication are therefore mandatory in order to avoid waste of public and private resources. The control of the quality and the pace of these activities can therefore probably not be left entirely to the investigators alone.

Nowadays, a plethora of Good Clinical Practice principles, directives, regulations and guidelines inform and oversee clinical research. The recent adoption of new legislations in the European Union, the guidance provided by the International Conference on Harmonization (ICH) and the latest amendment to the Declaration of Helsinki, in October 2000, have all coincided to move 'ethics' to the forefront of attention in the clinical trials community and 'ethics issues have moved from discussion to action'.

Who should then supervise the conduct of large phase III clinical trials? We wish that this task not be mandated to instances with administrative priorities that may add to the unnecessary burden of clinical research, but possibly to people with the understanding for the importance of clinical research and with high scientific, ethical and management knowledge. Ethical committees seem ''predestined'' for this task. The duty of Ethics Committees cannot be limited, as sometimes observed, to ''protect'' safety of patients included in clinical trials but must be extended to hindering the premature closure of clinical trials due to insufficient accrual, which after all makes patient efforts useless [12]. Ethics Committees should also verify that centers declaring intent to participate in a clinical trial have enough financial and human resources to conduct the study; monitor accrual and achievements; and guarantee the patients a fast disclosure of the results to the scientific community.

Conclusions

The premature closure of this trial after including 23 patients over 21 months represents a failure of several people and instances:

1. The principal investigator, who failed to motivate his colleagues to enter patients in his trial and to recognise that participation in a research project must be the treatment of choice in cancer medicine.
2. The participants and potential participants that failed to realistically evaluate the number of patients they would be able to enter, or to honestly disclose that their interest in the trial question was non-existent or weak.
3. The 23 patients who accepted to enter the trial but failed to see their effort rewarded by a publication that would help the community to choose a better treatment for locally advanced breast cancer.
4. The patients who were not entered in the trial, either due to personal or lack of choice.
5. The Ethics Committees, who failed to understand that the trial was not realistic and failed to assess feasibility before allowing investigators to engage in the trial.

6. The funding organisation that could have used the resources for completing other programs.
7. The scientific community, that due to the closure of the trial will not have insights into this clinical hypothesis.

The only "winners" in this very sad issue are the authors of this editorial: we would never have been asked to write it, if the trial had been completed on time.

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