Pergamon

*European Journal of Cancer* Vol. 31A, No. 12, pp. 1921–1923, 1995
Elsevier Science Ltd
Printed in Great Britain
0959-8049/95 $9.50+0.00

0959-8049(95)00433-5

# Point of View

# A Proposal for a New Approach to Intergroup Cancer Trials

J. L. Pater,[1] B. Zee,[1] J. Myles,[1] J.-P. Pignon,[2] C. Milan,[3] T. Sahmoud,[4] V. Torri[5] and S. Marsoni[5]

[1]NCIC Clinical Trials Group, Queen's University, 82–84 Barrie Street, Kingston, Ontario, Canada K7L 3N6; [2]Institute Gustave-Roussy, Villejuif, France; [3]Fondation Française Cancérologie Digestive, Dijon, France; [4]EORTC Data Centre, Brussels, Belgium; and [5]Institute Mario Negri, Milan, Italy

**Currently, North American intergroup trials are conducted according to the Intergroup Guidelines, which require that a lead group take responsibility for data management. Intergroup studies conducted in this manner have been very successful in rapidly accruing large numbers of patients to trials addressing significant questions, but it has been difficult for group statistical centres to cope with the resultant peaks in data flow. Our groups recently succeeded in combining the data from three independently designed and conducted trials to carry out a planned pooled analysis. This experience has led us to employ the same approach to data management in designing a forthcoming intergroup trial. We will use a common protocol and capture the same data elements on our forms, but each group will be responsible for the collection and quality control of its own data. A common data set will be created and updated periodically during the study, and will be used for the final analysis. We suggest that this model has advantages over the current approach to data management on intergroup trials, but still retains the features which distinguish an intergroup study from meta-analysis.**

**Key words: co-operative clinical trials groups, data management, intergroup studies, meta-analysis**
*Eur J Cancer*, Vol. 31A, No. 12, pp. 1921–1923, 1995

## INTRODUCTION

THE CONDUCT of clinical trials in cancer has been strongly influenced by the existence of co-operative clinical trials groups [1]. These self-standing organisations are funded to undertake an ongoing programme of studies in different disease sites. Each group has a distinctive history, organisational structure and approach to data management. For many years, groups in the same country funded by the same agency functioned in isolation, pursuing similar, but separate research agendas. However, in the 1980s, the U.S. National Cancer Institute began to encourage co-operative efforts among groups, particularly in studies addressing high priority questions [2]. This effort has been very successful and many intergroup studies have now been completed or are underway. Further, participation has extended beyond the U.S.A. in North America.

A key factor in facilitating the development of intergroup studies has been the creation of a mutually accepted approach to the development and conduct of intergroup studies—the Intergroup Guidelines [3]. These guidelines have made it possible to carry out studies expeditiously without needing to redefine the rules for each trial.

Ironically, the success of the intergroup approach in facilitating the timely accrual of large numbers of patients has created the problem which we wish to address in this article; namely, a data management overload for the group given responsibility for this aspect of the trial. Under the intergroup guidelines, a lead group must be designated and that group becomes responsible for review, computerisation and analysis of all data on the trial. The other groups involved function as central post offices for their members, simply receiving case report forms and passing them on to the lead group. While being the lead group in an intergroup study still has the appeal of primacy in authorship, the role carries with it the task of dealing expeditiously with much larger than usual amounts of data. This burden has made some data centres reluctant to provide support for intergroup trials, especially at a time when funding to co-operative groups has not been increasing relative to inflation. Further, data managers in "co-operating" groups must learn to deal with unfamiliar forms and procedures.

A recent experience retrospectively combining data from three nearly identical co-operative groups trials suggested to us a

Correspondence to J.L. Pater.
Received 12 Dec. 1994; accepted 12 Apr. 1995.

different approach to conducting intergroup studies. The concept is that each group would be responsible for its own data, thus eliminating the "peaks and valleys" of data flow created by rotating responsibility for co-ordinating such studies, and also allowing participating centres to become more familiar with the procedures. This paper will review our experience with retrospective data combination, describe a current trial for which we have adopted the method suggested and discuss advantages and disadvantages of this approach.

## INTERGROUP POOLING AFTER TRIAL COMPLETION

In October 1989, the U.S. National Cancer Institute issued a clinical alert regarding the impact of the positive results of two trials testing the effectiveness of 5-fluorouracil (5-FU) and levamisole in postsurgical adjuvant treatment of colorectal carcinoma. The alert stated that there was a clear survival benefit for patients with lymph node positive (Dukes' C) disease and that, consequently, enrolment on trials of such patients, where one of the arms did not include active postsurgical therapy, should cease. U.S. co-operative groups were obliged to follow this directive; groups in other countries responded variably. Our group, the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) decided to close prematurely the Dukes' C portion of the trial comparing 5-FU plus folinic acid (FUFA) to no further therapy. At the time, we were unaware of similar studies. However, it became evident that two other groups, Gruppo Interdisciplinare Valutazione Interventi in Oncologia (GIVIO) Italy, and Fondation Française de Cancérologie Digestive (FCCD) France, had undertaken virtually identical trials and, like us, had to terminate them prematurely for the same reason.

In October 1991, representatives of our three groups met to develop a methodology for combining and analysing our data. The approach we followed included the following elements [4, 5]: (1) a joint review of the study protocols, data collection forms and statistical centres to confirm that we had studied the same populations, used the same therapies and assessed the same primary outcomes; (2) a decision to postpone any analysis until the number of events in the overall pooled data set provided sufficient power to detect the smallest treatment effect postulated in sample size calculations of the three trials; and (3) agreement that, unless a test for intertrial heterogeneity was positive, the primary analysis would be on the pooled data, stratifying for country.

The first analysis of these pooled trials was carried out in September 1992. The endpoint considered was progression-free survival. A striking and highly significant difference favouring the use of adjuvant FUFA was found [6], a finding observed in two other studies also presented at the same meeting [7, 8]. Sufficient events to allow an analysis of overall survival occurred by November 1993 [9]. Both of these analyses were carried out well before any of our trials had reached sufficient maturity for an independent examination of the data.

## PREPLANNED POOLING

Our experience in salvaging data from prematurely terminated trials by prospectively pooling the data after the trials had closed but prior to their analyses, led us to consider using the same approach, that is, having each group collect and manage its own data in an intergroup trial. The opportunity to do so arose in the context of a trial assessing the role of FUFA chemotherapy after complete resection of metastatic colorectal cancer. Proposals for such a trial had been developed independently in Italy and Canada, and both the European Organization for Research and Treatment of Cancer (EORTC) and the NCIC CTG were considering the initiation of a trial. After discussion among principal investigators and statisticians in Italy, Canada and the EORTC, and with the approval of the appropriate protocol committees, it has been decided to conduct this study as described below.

Three independent co-operative groups (the EORTC, NCIC CTG, GIVIO) will conduct this "ENG" trial using a common, mutually developed English language protocol which specifies identical eligibility criteria, treatment, schedules of investigation and outcome assessment for all three groups. Case report forms were developed by NCIC CTG, but will be modified by the EORTC and GIVIO to fit their traditional formats. All three groups will collect the same data elements. Randomisations will be carried out by each statistical centre using the same minimisation procedure. Each group will develop and carry out data entry in its usual manner. However, SAS databases generated at the three statistical centres will be identical in structure, variable description and classification. Each group will be responsible for ensuring timely and accurate data submission from its centres employing its standard quality assurance procedures. Principal investigators from the three groups will meet on a regular basis to review problem cases and to resolve difficulties in administering or interpreting the protocol.

The co-ordinating centres will maintain regular electronic communication regarding the progress of the trial. At 6 monthly intervals, data from each of the co-ordinating centres will be electronically collected together at a designated centre, in this case the NCIC CTG. This centre will be responsible for quality control of the combined database with respect to completeness and compatibility among groups. It will also be responsible for generating reports for group meetings, for independent monitoring and for the final analysis of the trial. The analysis will be carried out, however, jointly by the principal investigators and study statisticians. As in the case already described where pooling was done after the studies were closed, the first step in this analysis will be to test for heterogeneity in the effects of a major prognostic variables and treatment among the three groups. If no heterogeneity is present, a pooled analysis, stratifying for group will be conducted.

## DISCUSSION

The need to combine the resources of groups carrying out independent clinical trials in order to achieve the sample sizes needed to assess moderate therapeutic effects is now widely appreciated. Currently, there are two approaches to realising this goal; collaborative intergroup trials and meta-analyses (or overviews). Though they have similar goals, these two techniques are functionally (and to some extent conceptually [10]) quite different. The characteristics of the three approaches mentioned are described in Table 1. In that its intention is to broaden the scope of a single trial addressing a prespecified and clinically well defined [10] question, preplanned pooling is, however, much closer in concept to the intergroup model than to traditional meta-analysis.

The advantages and disadvantages of our proposed approach relative to current intergroup procedures are listed in Table 2. The most important issue is whether the results of a study carried out in this manner will have the same credibility as one in which all aspects of the trial were under control of a single organisation. Our view is that differences in trial conduct and quality control among experienced clinical trials groups are unlikely to outweigh the impact of the therapy. Indeed, if this were the case, then the benefit of therapy is unlikely to survive

*Table 1. Features of three methods of combining trials*

| | "Classical" intergroup | "Preplanned pooling" | Meta-analysis |
|---|---|---|---|
| Prospective agreed upon study question | Yes | Yes | No |
| Common protocol, eligibility criteria and endpoints | Yes | Yes | No |
| Common data collection method | Yes | Partly | No |
| Creation of common database | Continuous | At intervals | After trial completion |
| Quality control | Defined by investigators in advance, uniform | Defined by investigators in advance, group specific | Not under control of investigators conducting analysis except to a limited extent |
| Analysis | | | |
| Scope | Prospectively limited to one trial—other groups may join | Prospectively limited | Can be broadened to include "similar" trials |
| Approach | Not stratified by participating group | Stratified by participating group | Stratified by trial |

*Table 2. Advantages and disadvantages of "preplanned pooling" relative to ordinary intergroup trials*

Advantages
- — Workload of co-ordinating centre is more predictable and budgetary planning easier
- — Co-ordinating centre conducts trial according to familiar well-established procedures
- — Institutional data managers deal with familiar forms, query procedures
- — Responsibility and credit for the conduct of the study is more evenly divided
- — Features of group's operating procedures that are uniquely appropriate to its setting are preserved

Disadvantages
- — Precision may be reduced if quality control is not uniform
- — Some effort may be duplicated, i.e. in developing forms and data entry procedures
- — There is little precedent for the approach and results may, therefore, be less easily accepted
- — Study management may be more cumbersome in the aggregate

translation into clinical practice. Further, given the growing acceptance of the results of meta-analyses as guides to therapeutic decisions [11], it is difficult to see how an approach such as ours, which controls interstudy variation to a much greater extent than a typical meta-analysis, should be viewed with suspicion. Finally, it is even possible that quality control and protocol compliance will be superior when participating centres are dealing with familiar forms and familiar query procedures, and the study is administered by a data centre that is able to deal timely with problems.

In addition, but not quite so important, is the fact that this model has not been used in the ongoing conduct of an intergroup trial, and unexpected difficulties may emerge. However, our previous experience is encouraging in this regard. Further, most of the difficulties we have had and will encounter are intrinsic to the process of intergroup (and international) collaboration, not to the process of collecting and assembling data. We, therefore, feel this model deserves consideration by other groups undertaking collaborative studies.


1. Pocock SJ. *Clinical Trials. A Practical Approach.* Toronto, Wiley, 1983.
2. Wittes RE, Friedman MA, Simon R. Some thoughts on the future of clinical trials in cancer. *Cancer Treat Rep* 1986, **70**, 241–250.
3. McFadden ET. Intergroup participation—the challenge of multi-group trials (abstract). *Controlled Clin Trials* 1991, **22**, 674–675.
4. Zee B, Pater JL, Torri V, Marsoni Pancera G, Milan C, Pignon JP. Salvaging clinical trials forced to terminate early by results of external information. *Controlled Clin Trials* 1993, **1**, 439–440
5. Pater JL. Timing the collaborative analysis of three trials comparing 5-FU plus folinic acid (FUFA) to surgery alone in the management of resected colorectal cancer: A National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) perspective. *Stat Med* 1994, **13**, 1337–1340.
6. Zaniboni A, Erlichman C, Seitz JF, *et al.* FUFA increases disease-free survival in resected B2/C colon cancer: results of a prospective pooled analysis of 3 randomized trials (abstract). *Proc Am Soc Clin Oncol* 1993, **12**, 191.
7. O'Connell MA, Mailliard J, Macdonald J, Haller D, Mayer R, Wieand H. An intergroup trial of intensive course 5FU and low dose leucovorin as surgical adjuvant therapy for high risk colon cancer. *Proc Am Soc Clin Oncol* 1993, **12**, 190.
8. Wolmark N, Rockette H, Fisher B, *et al.* The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel project protocol C-03. *J Clin Oncol* 1993, **11**, 1879–1887.
9. The IMPACT Investigators—Marsoni S, Labianca R, Torri V, *et al.* Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. *Lancet* 1995, **345**, 939–944.
10. Wittes RE. Problems in the medical interpretation of overviews. *Stat Med* 1987, **6**, 269–276.
11. Chalmers TC. Clinical trial quality needs to be improved to faciliate meta-analyses (editorial). *Online J Curr Clin Trials* (serial online) 11 September 1993 (Doc No. 89).