PERGAMON

European Journal of Cancer 38 (2002) S169–S172

European Journal of Cancer

www.ejconline.com

Addressing the challenge of intergroup studies in oncology: the EORTC experience

A. Zurlo*, P. Therasse on behalf of the EORTC Data Center

EORTC Data Center, Avenue E. Mounier 83, 1200 Brussels, Belgium

Abstract

Intergroup studies are conducted by more than one clinical research group. There are several difficulties that hamper in practice the possibility of conducting such trials, as all interested parties will have to address unusual and complex issues. These are mainly related to differences in size, interests, motivations and means among different research organisations. The EORTC recognises the importance to promote intergroup collaboration providing to all interested groups the necessary expertise and organisational support to conduct intergroup studies. The role of the EORTC evolved from the spontaneous organisations of intergroup trials to the definition of a basic set of principles and criteria that groups have to fulfil to participate in intergroup trials. Recently, a specific EORTC Intergroup Office started its activity devoted to solve the issues related to the intergroup co-operation. This office will have an increasing role to promote and help in conducting intergroup studies.

Keywords: Intergroup trials; International collaboration; Clinical research groups; Human research protection

1. Introduction

Intergroup studies are clinical trials conducted by more than one clinical research group. The rationale for undertaking an intergroup study often lies in the need to recruit a large number of patients for phase III studies as quickly as possible or to realise trials concerning rare or uncommon tumour types. In addition, an intergroup study may be conducted when several groups have the same research interests in order to decrease the number of competing protocols and share a common effort among the groups. In the present era of evidence-based medicine, intergroup trials allow the collection of large, homogeneous and prospective individual data, reducing the need and pitfalls of retrospective merging of databases in meta-analyses.

There are several difficulties that in practice hamper the possibility of conducting clinical trials among different research groups, often dramatically reducing the speed of aimed accrual and eventually leading to the failure of the common effort. Research groups are very different in size (with national groups overweighing in number the international organisations), interests (some groups are specialised in specific disease sites, others would cover most disciplines of oncology), motivations and means. As an example, the EORTC in its 40 years history has evolved to provide itself with the instruments to conduct trials in all European countries and has developed working procedures that integrate Good Clinical Practice (GCP) guidelines and are filed at the Food and Drug Administration (FDA). Nevertheless, the EORTC has clearly understood the necessity of promoting and conducting intergroup trials also with smaller and younger organisations that cannot have completed yet this long organisational path. Therefore, setting up an intergroup trial will require all parties addressing and solving complex and unusual issues related to:

- the differences in the organisational work and procedures among the research groups (use of different quality assurance instruments, different administrative procedures and bylaws)
- the differences in national regulations that need to be properly addressed in a case-by-case approach, even among European countries;
- the costs related to international co-operation (financial support, drug distribution...);
- the increased need for information flow that requires a specific standardisation effort;
- the loss of interest and commitment from groups and investigators, after confrontation with the

* Corresponding author. Tel.: +32-2-774-1671; fax: +32-2-771-3810.

E-mail address: azu@eortc.be (A. Zurlo).

0959-8049/02/$ - see front matter
PII: S0959-8049(01)00441-5

administrative efforts needed to implement the international co-operation;
- the issue of individual group visibility, often complicating the intergroup collaboration of small groups together with larger organisations due to the fear of losing the evidence of their contribution.

For all these reasons, despite their high potentiality, intergroup trials are still not very widespread and suffer the concurrence of smaller mono-organisational studies, eventually leading to the proliferation of small-scale trials that are usually under-powered to answer the scientific questions, but much easier to organise. These complex organisational issues also reduce the interest and collaboration with the pharmaceutical companies, together with the regulatory agencies, interested in supporting and promoting large phase III trials to validate new therapeutic approaches.

The EORTC recognised early on the need to overcome these sorts of problems and has tried to provide itself with the structure and instruments to promote collaboration between international organisations and research groups that are active in the field of cancer research, providing to all of the interested parties the necessary expertise and support to conduct large-scale international studies. The role of the EORTC evolved from the spontaneous organisation of intergroup trials based on very differentiated approaches to the creation of a basic set of rules and, finally, creating an office devoted to solving the issues related to intergroup co-operation.

2. Historical perspectives

Since their first years of activity, several EORTC clinical disease groups have conducted intergroup trials among themselves, successfully finding the instruments to address the possible differences in internal procedures and quality assurance that existed among them. From the early 1980's, intergroup trials with other national groups such as HOVON (Belgian-Dutch Haemato-Oncology Group), GIMEMA (Italian group active in the field of leukaemia), BNLI (British National Lymphoma Investigation) and MRC (Medical Research Council, collaborating with the EORTC in different solid tumour types and particularly in genito-urinary tract cancers) also flourished. The philosophy of intergroup collaboration rapidly expanded to all EORTC research groups across Europe. In the early 1990s, transatlantic collaboration was first established with the National Cancer Institute of Canada (NCIC) clinical trials groups and later on, in the mid-1990s, with several United States (US) groups such as the Eastern Cooperative Oncology Group (ECOG), the South West Oncology Group (SWOG), the Cancer and Leukemia Group B (CALGB) and the Radiation Therapy Oncology Group (RTOG). More recently, the EORTC groups started to directly put their efforts into actively setting up and participating in large intergroup structures such as the BIG (Breast International Group) [1], the PETACC (Pan-European Trials in Adjuvant Colon Cancer) [2], or the GCIG (Gynecological Cancer Intergroup) [3].

Due to the lack of common rules, each intergroup setting followed specific principles and organisational procedures, but the need for harmonisation progressively emerged with the experience of all the possible pitfalls related to this non-structured approach. As a matter of fact, the different models of intergroup activity among the EORTC groups allowed the testing and comparison of various approaches of collaboration. In the EORTC experience, the system in which all groups send the data to a central database proved much more reliable than models based on individual group databases merging performed at the end of an intergroup study. This evidence, confirmed also by similar models of data flow and collection in use among the North-American groups, eventually led to an established EORTC policy enforcing the so-called 'mailbox system' [4].

3. The EORTC Intergroup Policy

In 1996, the EORTC Board and the EORTC Chairmen Assembly approved basic principles for intergroup trials, that formed subsequently the basis of a specific Intergroup Policy in 1999 (all the EORTC policies are public documents available on the EORTC website (www.eortc.be)).

Three main principles have been identified:

- there can be only one official protocol, which must be used by all participating groups;
- there can be only one set of Case Report Forms (CRFs), which must be used by all participating groups;
- there can be only one co-ordinating data centre that keeps the central database collecting the data from all the participating groups. This implies that the co-ordinating data centre performs all data management and analyses to ensure maximum efficiency in terms of reducing the duplication of efforts, as well as a uniform quality of data management and cleaning, as all data are handled according to the same standard operating procedures.

These principles are not open to negotiation unless valid scientific reasons are provided. In this case, any deviation from these basic principles will require a beforehand approval by the Director of the Data Center and the Chairman of the EORTC group.

The Intergroup Policy also defines the minimal criteria that a non-EORTC organisation must fulfil to join an intergroup trial co-ordinated by the EORTC. This should be a multi-institutional co-operative group that can prove to have a track record of participation in clinical trials in the specific disease site, a co-ordinating office able to handle the administrative matters of the group and the study data flow, and a system to monitor the quality of its centres. EORTC groups can participate in intergroup trials organised by other organisations only if the structure of the intergroup collaboration is not in contradiction with the above mentioned rules and complying with the usual EORTC standards of quality management.

The EORTC was also the first European organisation to set up the necessary structure to participate in the Cooperative Protocol Research Program (CPRP) with American groups according to the guidelines set by the Office for Human Research Protection (OHRP) [5]. The Internal Co-operative Project Assurance (ICPA) is a document which provides assurance of compliance for the protection of human research subjects involved in CPRP trials. An ICPA committee reviews regularly the ethical part of the study protocols and the suitability of the EORTC centres that aim to participate in CPRP trials, in order to ensure the protection of the rights, safety and well being of the patients. The ICPA committee approval provides the EORTC institutions with the necessary assurance to participate in CPRP trials.

4. EORTC Intergroup Office (EIO): composition and activities

The EORTC Intergroup Office (EIO) started its activity in October 2000 as part of a project aiming to further promote intergroup studies. It aims to provide information and support to the EORTC groups and to the non-EORTC organisations willing to set up an intergroup collaboration or to join an EORTC trial.

In the beginning, the EIO staff was composed only of a project leader. In the following months, a secretarial support has been assigned to the office and more personnel with experience in the field of regulatory affairs and contracts will be added in the future. The EIO started with a survey of previous experiences and different intergroup study models employed by the various EORTC groups. On the basis of this survey, a database of all intergroup studies conducted by the EORTC was created, listing the contact persons for all the groups, the level and complexity of activities shared and the problems that were encountered in the specific studies. This instrument will be continuously updated to become in the near future a reliable, automated database of ongoing intergroup trials with all the related information on the trial and the participating groups. It will also list all of the procedures and regulatory requirements necessary to run international studies in different countries and will be linked to the EORTC Regulatory Affairs Unit and Safety Desk database. The aim is to create a reference working instrument that will also be at the disposal of non-EORTC organisations.

Another important initial activity of the EIO has been the preparation of working packages that are currently sent to non-EORTC groups wishing to join EORTC trials. They provide full information about the EORTC policy and procedures for intergroup trials with the aim to standardise the procedures and to reduce the frequent lack of information about the other groups' organisation. Groups are invited to provide some basic information about their organisation and are also requested to sign their commitment to the EORTC policy and working procedures before being able to officially join a trial co-ordinated by the EORTC. In any case, groups can ask to receive assistance to accomplish the necessary tasks and requirements. This help is felt to be particularly useful for small groups that are thus clearly informed about their obligations as they commit to enter an intergroup effort and are also assisted to develop the appropriate procedures. The information and commitments obtained through the templates and contacts allow the consideration of the feasibility of the intergroup collaboration on a case-by-case basis. Whenever major divergences from the standard requirements of the EORTC Intergroup Policy are foreseen, a visit from the Quality Assurance Unit and the EIO allows a final decision to be made.

The EIO not only supports non-EORTC groups, but also actively supports the activity of the involved EORTC groups concerning the unusual and more complex administrative procedures of intergroup trials. For this purpose, intergroup trials can be basically distinguished as EORTC co-ordinated trials and non-EORTC co-ordinated trials. A second distinction, applicable to both cases, is based on whether the intergroup study started from the beginning or subsequently became an intergroup trial. In all of these cases, some specific procedures may apply if American organisations supported by federal grant funding participate within the intergroup and thus the ICPA needs to be involved. All the issues related to these different scenarios have been discussed with the members of the specific units inside the EORTC, particularly the Protocol Review Committee, the Safety Desk and the Regulatory affair Unit, in order to prepare clear guidelines for the EORTC groups.

5. Projection over the future

In its 40 years of history, the EORTC has had a track record of collaboration with more than 30 international

research organisations. Taking advantage of this wide experience, the EIO is in the process of updating the EORTC Intergroup policy and implementing more specific and detailed procedures. In addition, the EIO will consider taking a more active role in stimulating the structural development of organisations involved in clinical research, particularly regarding quality assurance requirements. It is also developing the logistic instruments to provide a direct support to small groups that may need assistance in fulfilling the more complex regulatory requirements (such as Safety Desk organisation, serious adverse events reporting to health authorities, or adequate trial insurance) before being able to join an intergroup trial.

In the future, the EIO will hopefully have a role in promoting and conducting intergroup studies to a larger audience. In an extensive communication effort, procedures to facilitate international intergroup clinical research will be prepared and proposed to international organisations and regulatory authorities. A forum will be made available on the EORTC web pages in order to spread the information and to receive it from the other research groups that have no experience of previous collaboration with the EORTC. It will be a relevant means of exchange of information and knowledge regarding this new approach in clinical research, involving groups with different organisations, but sharing the same interest in promoting intergroup co-operation.

As contacts with other groups progress, distinguished members of other clinical research organisations sharing an interest in intergroup collaboration will be asked to participate in the development of the EIO activities. This may lead to the preparation of a Steering Committee for intergroup studies that will develop future actions to address the issues hindering widespread intergroup collaborations.

References

1. Piccart MJ, van de Velde CJ. The EORTC-Breast Cancer Cooperative Group clinical research programme in early breast cancer. EORTC-BCCG. *Recent Results Cancer Res* 1998, **152**, 447–452.
2. Wils J. The establishment of a large collaborative trial programme in the adjuvant treatment of colon cancer. *Br J Cancer* 1998, **77**(Suppl. 2), 23–28.
3. Vermorken JB. Intergroup collaboration in ovarian cancer: the Gynecologic Cancer Intergroup (GCIG). *Int J Gynecol Cancer* 2001, **11**(Suppl. 1), 73–76.
4. Therasse P. Intergroup trials involving non-EORTC group (www.eortc.be).
5. Ellis GB. Office for Protection from Research Risks (OPRR). *Politics Life Sci* 1994, **13**, 271–273.