

Intergroup trials

POL005

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(Always refer to the Intranet to check the validity of this document)

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Distribution

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1. Objectives

In Europe, many research groups conduct cancer research and therefore perform clinical trials. In this framework, it is essential to be able to rapidly accrue a very large number of patients. This can be achieved through the close collaboration between research groups within the "Intergroup" clinical trials including usually 3 to 4 groups and up to 15 different groups (national, international) collaborating together.

The aim of this document is to outline the EORTC policy on intergroup trials that facilitate this type of collaboration.

2. Definitions

Good Clinical practice (GCP): written document describing rules that are considered as good clinical practice (the EORTC refer to the ICH guidelines for GCP).

Group: national/international network of investigators and/or institutions and/or groups or structure/agency working for a group of investigators and/or institutions and/or groups.

Trial conduct: the term that covers all the procedures necessary to design, initiate and manage the trial as well as to publish its results

Coordinating group: group responsible for the scientific content of the protocol and contribute to the conduct of the trial or coordinates it.

Clinical Trial Office (CTO): administrative office responsible for the management of the trial

Data Center (DC): CTO that includes the data management and statistical office.

Coordinating DC: DC of the coordinating group or the one contracted by the coordinating group to conduct the trial.

Steering committee (SC): Committee of representatives of the collaborating groups and the representative of the coordinating DC.

Study Coordinator of the group: medical representative of the group responsible for the coordination of all issues related to the trial that are of the resort of his group

Study chairman: Chairman of the steering committee, clinical representative and Study Coordinator of the coordinating group.

The outline: the short proposal of the future trial with some rationale, design and the statistics.

3. Responsibilities

3.1. Steering committee (SC)¹

The **SC** is responsible for the scientific value of the trial and decisions on eventual future utilization of the material, data and results pertaining to the trial (within the limits defined by the Sponsor(s)).

3.2. Coordinating group¹

The coordinating group is responsible for the scientific content of the trial (including the protocol, the CRF content and the publication). The coordinating group is responsible to develop the scientific parts of the protocol and the CRFs, to monitor the status and the progress of the trial and to write the publication (in collaboration with other parties).

3.3. Coordinating data center

The responsibility of the Coordinating Data Center is to coordinate in collaboration with the Study Chairman all issues related to the conduct of the trial following the scientific protocol written by the Coordinating group and/or the Steering Committee and therefore to:

- ◇ clearly define the modalities of collaboration with all other involved parties and assure a fluent communication with them;
- ◇ coordinate the development and finalize the protocol (based on the scientific content decided by the Coordinating Group and/or the Steering Committee, adds chapters relatives to their tasks such as Data Management and logistic);
- ◇ design the CRFs (based on the content decided by the Coordinating Group and/or the Steering Committee) and the Data Base;
- ◇ establish a randomization procedure, preferably centralized;
- ◇ establish all data management procedures, including data entry and data validation;
- ◇ coordinate or perform all analyses, including status reports, interim analyses and the final analysis;
- ◇ coordinate the publication;
- ◇ some additional issues, such as monitoring, drug supply and labeling, this list is not exhaustive (can be delegated to other organizations).

3.4. Collaborating group & data center

The responsibilities of all collaborating groups are determined on a case by case basis depending on the trials and should be fixed in a written document (protocol, appendixes, agreements etc.).

¹ Some responsibilities of the SC and the Coordinating group are overlapping and their precise distribution should be defined on a trial by trial basis and usually will depend on whether the trial has been initiated by one group or by several groups closely working together from the very beginning.

4. Procedures

4.1. Main principles

The EORTC policy is based on 3 main principles:

- ◇ There can be only one official protocol which must be used by all collaborating groups.
- ◇ There can be only one set of CRFs, which must be used by all collaborating groups.
- ◇ The data from all collaborating groups are collected in one data center (called coordinating) for entry into their database, which is used to perform the analysis.

These principles imply that the coordinating data center performs all data management and analyses. This assures maximum efficiency in terms of reducing the duplication of efforts as well as a uniform quality of the data because all data are handled according to the same standard operating procedures.

Many major cooperative groups in Europe, the US and other parts of the world recognize these rules as international standards for intergroup collaboration. The EORTC Board and EORTC Chairmen Assembly accepted them in March 1996.

Therefore, it should be clear that *these commonly accepted principles are NOT to be negotiated* unless there are valid scientific reasons to do so. In the latter situation, the Director of the EORTC Data Center must approve any deviation from these basic principles.

The following sections describe a framework for developing and conducting intergroup trials according to the principles mentioned above. As opposed to the main principles, this framework should be considered as recommendations and reflects the general philosophy of the EORTC regarding Intergroup Collaboration.

The more detailed information about the EORTC support to intergroup trials can be found in the Pol 012 ("EORTC support to Intergroup Trials", ref.: POL012).

4.2. Development of a new intergroup trial

4.2.1. Set-up of the Steering Committee

4.2.1.1. Trials initiated by one group

This group will usually become Coordinating Group of the trial. As soon as at least one collaborating group become known, a steering committee (SC) has to be composed, consisting of one clinical representative of each collaborating group, a clinical representative of the Coordinating group and at least one representative of the Coordinating DC. The SC can be extended to include any other person needed for the trial (such as statistician, representative of the industry, Quality of life specialist etc...). The Study Chairman (Study Coordinator of the Coordinating group) will usually be the Chairman of the Steering Committee in this case.

4.2.1.2. Trials initiated by several groups.

The SC consisting of clinical representatives of these groups decides which group becomes the coordinating group. Together with the coordinating group, the SC agrees on the Study Chairman (usually the clinical representative of the coordinating group) and the Chairman of the Steering Committee (that can be the same or a different person).

The Study Chairman, together with the representative of the Coordinating Data Center, will implement the decisions made by the SC. In addition, the Study Chairman will write the manuscript for publication in collaboration with the members of the SC.

4.2.2. Selection of the Coordinating Data Center

The Coordinating Group should inform the SC about the Coordinating Data Center (in most of cases, the data center of the Coordinating Group). The representative of the data center of the coordinating group or of the one used by the coordinating group to conduct the trial becomes a member of the steering committee.

4.2.3. Protocol and CRF development

4.2.3.1. Trial outline

Based upon the discussions in the SC, the Coordinating Group should charge the Study Chairman and the representative of the Coordinating DC to write an outline of the trial containing the scientific idea, the trial design and the statistical considerations including the sample size. To avoid contradictory opinions, the steering committee should prospectively agree on one review body considered as central (usually the review body of the Coordinating group and/or the Coordinating Data Center) to whom the outline (and the future protocol) will be submitted.

On the decision of the Steering committee, the outline can be sent before its submission to all collaborating groups for comments/opinions from their respective review bodies/scientific committees. *However, the final comments and decisions should be taken by the selected central review body.*

4.2.3.2. Full protocol and CRF

In collaboration with the study chairman and taking into account the comments of the central review body and, as much as possible, the comments from all collaborating groups, the representative of the Coordinating DC will coordinate the finalization of the full protocol and the design the CRFs. He will assure that the CRFs meet the needs of all collaborating groups concerning the format of the content (proposed units, prohibited information), the logo, the CRF submission address and administrative fields for patient identification.

Once finalized and agreed upon by all members of the steering committee, the full protocol and the CRFs are sent to all collaborating groups for approval from their respective review bodies.

The representative of the Coordinating DC communicates with the data centers of all collaborating groups in order to agree on all the modalities of the future collaboration.

Once the protocol is finalized, only one person should be allowed to edit the protocol and the CRFs. This includes any protocol modifications and the addition of administrative information pertaining to the collaborating groups.

4.2.3.3. Communications

In order to avoid confusion and misunderstandings (e.g. circulation of old and new versions of the protocol at the same time), it is highly recommended that ALL 'official' documents are distributed by one person from the Coordinating group/DC to one representative of the collaborating groups. Conversely, all communications from the collaborating groups should be sent to one prospectively defined person at the Coordinating group/DC.

4.2.4. Trial conduct

4.2.4.1. Patient inclusion in the trial

The inclusion of patients in the trial usually requires the collection of legal-administrative information (such as date of birth, initials, the name of the investigator that includes this patient...), the verification of the eligibility criteria and, for the randomized trials, the treatment allocation (taking in account all stratification factors). The way to verify the eligibility of patients and the procedure used for the treatment allocation should be common for all collaborating groups.

To respect this rule one of the following three possibilities should be followed:

- ◇ Investigators members of the collaborating group register and/or randomize patients directly at the coordinating data center.

- ◇ Investigators members of the collaborating group register and/or randomize patients at the Coordinating Data Center, but via the Data Center of the collaborating group (this way of working allow the collaborating group to directly collect all the legal and administrative information necessary for them to comply with the laws of their country(s)).
- ◇ Investigators members of the collaborating group register and/or randomize patients at the Data Center of the collaborating group. This last option is possible only if:
 - ◇ The procedure is the same (the scientific questions asked to the investigator and the stratification factors are the same as those used by the Coordinating group);
 - ◇ The statistical method used for the treatment allocation is the same as the one used by the Coordinating group;
 - ◇ The immediate transfer of this data to the coordinating Data Center is possible without the manual handling of data at the last one.

4.2.4.2. Handling of data

4.2.4.2.1. Data management

In order to comply with the main principles for intergroup collaboration, the Collaborating Group(s) and their DCs/CTOs should guarantee that:

- ◇ There will be no corrections/modifications done to the CRFs by the Collaborating Groups
- ◇ Only the coordinating DC will enter the data in the computer and perform the quality control of data; when necessary, queries will be issued by the coordinating DC/CTO (i.e. the data center is not supposed to enter the data into the data base, nor validate the CRFs. If nevertheless they decide to do so, these databases will not be taken into account and no attempt at reconciliation will be made)
- ◇ There will be only one main analysis organized by the Coordinating group based on the data handled by the Coordinating DC

These principles are not to be negotiated!

In addition, it should be taken in consideration that the direct communication between the Coordinating DC and investigators of the Collaborating Groups can lead to an increase of work for the DM of the Coordinating DC and to the lack of information on the quality of the Collaborating Group (which is frequently the Sponsor). Therefore, there should be preferably no direct communication between the Coordinating DC and the investigators of Collaborating groups. The CRFs, queries and all correspondence will go through the DC/CTO of the Collaborating group without modification, as mentioned before. This system is called "**mail-box system**".

4.2.4.2.2. Data protection

EORTC works in compliance with the European Directive 95/46/EC on the individual data protection. Therefore, EORTC will collaborate with groups outside European Union only if their national law or a signed contract guarantees the same level of protection.

4.2.5. Analyses

The Coordinating DC will perform all analyses (status reports, interim analysis, and final analysis) on the central Data Base and distribute the results as appropriate. The contents and timing of the analyses during the trial should be agreed upon by the steering committee and described in the protocol.

In case, the Coordinating Group uses an exterior DC as Coordinating DC, but have the necessary statistical resources, the final analysis can be performed by both parties in collaboration.

4.2.6. Publication

The Study Chairman on the basis of the statistical analysis performed at the Coordinating DC will write the final publication of the trial results. Before submission for publication, a draft manuscript will be circulated to all members of the Steering Committee and any other co-author for review.

Interim publications or presentations of the study before the recruitment is discontinued may not disclose any results concerning therapeutic efficacy or any other major endpoint of the trial by treatment arm.

For all publications using the data or a part of data pertaining to the trial (during the trial or after its end), authorization from the steering committee is required, unless otherwise agreed.

4.2.7. Data ownership and availability.

The Data Base should be maintained centrally after the publication of results of the trial, preferably by the Coordinating DC. Nevertheless, all Sponsor(s) are owners of the data of the sub-set of patients under their responsibility. In case collaborating groups are not Sponsors of their members, they should have the license to use the data of the sub-set of patients randomized by their members, except otherwise agreed in writing.

The release of data of the collaborating group's sub-set of patients should be considered by the Coordinating DC after the final analysis and the publication upon request of the collaborating group, provided that is not prohibited by any previous agreement. The data will preferably be supplied in electronic format. The format of such a transfer will be agreed upon by the concerned groups.

The receiver will guarantee that the data will be used conforming to the paragraph 4.2.4.2.2 and 4.2.6.

4.2.8. Handling of data after the main analysis

The decision on the extent of the update of the Data Base after the main publication of the trial should be taken prospectively by the steering committee or at least agreed between the Coordinating Group and the Coordinating DC.

For any use of data that do not belongs to the group, the agreement of concerned groups is mandatory, unless otherwise agreed. In case of use of data for publication the SC should be consulted as described in 4.2.6.

4.3. Joining a running trial

A group joining a running trial from another group should accept the protocol and CRFs without any modifications (except the administrative section). The clinical representative from the group who started the trial becomes the Study Chairman and the data center of his group becomes the Coordinating Data Center.

The representative of the Coordinating DC should assure that each collaborating group is contracted in order to properly fix the details of their participation.

From then on, the trial is considered as an intergroup trial and follows the same guidelines as described for intergroup trials that were developed jointly.

5. List of abbreviations

Abbreviation	Full name
CRF:	Case report form
CTO:	Clinical Trial Office
DC:	Data Center
GCP:	Good Clinical Practice
SC:	Steering Committee

6. Appendices and references

Document title	Reference (file name)
EORTC support to Intergroup trials	POL012