Guidebook

In gynaecological cancer the relative rareness of the specific malignancies and the often small differences considered clinically relevant makes it very difficult to perform well-powered phase III studies on a national level within a sensible time frame. If allowed, under-powered trials will use up the patient population, especially for first-line treatment, and hence potentially useful new treatments may miss their window of opportunity. Thus international collaboration on phase III trials is essential. To ease the collaborative process the GCIG has set up criteria for the initiation and conduct of intergroup trials, this guide book collects and organizes these. The guide book is organized into a brief introductory part which covers basic definitions and summarizes the responsibilities of the different entities involved in a GCIG trial and a series of links to documents covering trial specific issues as Intergroup Agreement, translational research etc.

Definitions
An intergroup trial is a trial where at least two national or international GCIG member groups collaborate, non-GCIG groups may participate but the leading group must be a GCIG member.

Intergroup trials have the following characteristics:

- There can be only one official protocol which has to be used by all participating groups
- There can be only one set of Case Report Forms (CRFs or eCRFs) which must be used by all participating groups
- The data from all participating groups are collected by the Leading Group data centre for entry into the trial database or entered directly into the eCRF by the participating sites.
- Intergroup trials are not sponsored by the industry

Intergroup trials consist of the following entities:

- Steering committee also known as “Trial Management Group”
- Lead Group
- Lead Group data centre
- Participating Groups
- Participating Group data centres

Each of these entities will have specific responsibilities briefly outlined below and detailed in the intergroup agreement document. There may be additional subordinate entities, such as local investigators, CRO’s (Clinical Research Organization) or other, but only the above mentioned are directly regulated by the GCIG criteria.

Development of a New Intergroup Trial
A new intergroup trial can be proposed by one or several groups. If there is sufficient interest in the GCIG community for performing the trial then the initiating groups must establish a Trial Management Group. The Trial Management Group would consist of members from the interested groups and in addition to the clinicians, must include an administrative representative and a statistician from the Lead Group.

The Trial Management Group has the following responsibilities:

- Determine which group should be the Lead Group
- Evaluate and approve the protocol, CRF and future amendments
- Discuss and take relevant actions based on IDSMC and TSC recommendations

- Discuss and agree on trial conduct issues, data analysis and publications
- Ensure that the trial is in accordance with, but not limited to:
  - The Declaration of Helsinki
  - The principals of ICH GCP (Harmonised Tripartite Guideline for Good Clinical Practise)
  - Any regional directives/laws/statues such as FDA or Health Canada, etc
  - The terms and conditions of the ethical approval given to the trial
  - Directive 2001/20/EC, Commission Directive 2005/28/EC (when applicable to the trial) http://ec.europa.eu/health/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf)
  - EU Clinical Trials Regulation EU/536/2014 when it comes into effect (when applicable to the trial) http://ec.europa.eu/health/human-use/clinical-trials/regulation/index_en.htm

The Lead Group is responsible for the following as appropriate:

- Setting up the Intergroup Agreement, Group Specific Appendix, and Roles & Responsibilities Agreement for the trial; templates available on the GCIC website (https://gciggroup.com/content/harmonization)
- Writing the protocol, and obtaining protocol approval from the Trial Management Group & the appropriate executive body for each of the participating groups
- Designing the CRF/eCRF
- Developing a Communication Plan (or its equivalent) for the trial
- Developing a Monitoring and Audit Plan for the trial
- Developing a Data Management Plan (including a data validation plan)
- Developing a Statistical Plan
- Ensuring that all necessary legal regulatory approvals are in place
- Ensuring that the local databases (if required) are compatible with the Coordinating Centre's database.
- Setting up and maintaining the Trial Master File
- Developing an Essential Documents Checklist
- Providing relevant documents and guidelines to the participating groups
- Performing the final data analysis and ensuring presentation and publication of the results
- Decide if sponsorship and financial support should be handled by the Lead Group on behalf of all groups, or separately by each Participating Group (to be defined and necessary agreements written)

The Participating Group is responsible for the following; this can be further expanded in the Roles and Responsibilities Agreement:

- Establishing an agreement with the Lead Group
- Providing translations of protocol and patient information
- Conducting feasibility assessment and site selection for its own participating sites (checklists available on the GCIG website
- Obtaining regulatory approvals according to national guidelines
- Ensuring compliance with national safety reporting requirements
- Maintaining a Trial Master File
- Overseeing study conduct in their own participating sites in collaboration with Lead Group

During the planning phase of the trial several meetings should be held (preferably in connection to the biannual GCIG meetings, as online meetings, or as teleconferences) to ensure that the protocol development process is open and collaborative. These meetings are to be arranged by the Lead Group with all interested Participating Groups and relevant Industry Representatives (if applicable) in attendance.

Conduct of the Study

The conduct of the study should be in accordance with the Intergroup Agreement Document and Roles and Responsibilities Agreement.

- Source Documentation: Source documentation collection procedures are to be described and outlined at the onset of the trial at each Participating Group
- Randomisation Procedure: It is necessary that the randomisation procedures are clear and understandable for all participating groups around the world. Randomisation can be done by phone, fax, email, online or a combination of methods depending on the way it is setup by the Lead Group).
    - The Lead Group is responsible for providing the Participating Groups with details about randomisation including stratification.
    - The Participating Groups are responsible for informing the local investigator about the randomization procedure.

Data Management

- The Lead Group is responsible for the central data management of the study including the collection, validation and analysis of the data.
- The Participating Groups are responsible for collecting and forwarding data from their centres to the coordinating group; unless data is entered directly into the eCRFs by the centres.
- It is the responsibility of the Participating Group to ensure that the local investigator completes CRFs/eCRFs within the fixed timelines. Delays in the return of CRFs could result in the Participating Group being prohibited from randomising subsequent patients until pending CRFs are complete and received.
- Participating Groups are responsible for responding to the Lead Group in case of missing data and queries.

Reporting of Serious Adverse Events (SAEs) and SUSARS / Safety Reporting

SAE reporting should be described in detail in the protocol and reported according to international guidelines for clinical trials. The Lead and Participating Group responsibilities regarding SUSAR reporting (including EudraVigilance), preparation and submission of annual safety reports, and the development of safety update reports (DSUR) is to be agreed at the outset of trial and will be detailed in the Roles and Responsibilities Agreement included in the Intergroup Agreement for the trial.

Independent Data and Safety Monitoring Committee

For each individual protocol it should be decided if an independent Data and Safety Monitoring Committee should be established. This monitoring committee should be set up at the start of the trial and the members should be accepted by the Trial Management Group. Refer to the GCIG website for a template document.

Protocol and / or Consent Amendments

The Lead Group will be responsible for authoring the amendment after discussion and approval by the Trial Management Group. Participating Groups are responsible for obtaining approval by the local investigators and by national regulatory authorities and ethics committees.

Insurance

Appropriate insurance (as applicable) is to be in place prior to initiation of a trial.

Communication

A Communication Plan is to be developed, agreed upon, and in place prior to the initiation of a trial. It should address, at a minimum, the following points:

- The method in which questions can be raised and will be addressed

- The manner and timeframe in which the Leading Group will provide information on patient accrual, trial status, toxic effects, SAE reporting, etc.

Monitoring
The Monitoring and Audit Plan for each trial is to be developed, agreed upon, and in place prior to the initiation of a trial. Refer to the Site Specific Appendix for an outline of the monitoring and audit models that are in place for each GCIG participating member group.

Site Selection
Should be performed by the Participating Group in accordance with the agreed Roles and Responsibilities.

Guidance and Reference Documents
Useful guidance and reference documents:

- GCIC website (https://gciggroup.com/content/harmonization)
- Common Data Elements (CDEs) (https://cdebrowser.nci.nih.gov/CDEBrowser/)
- ICH Harmonised Tripartite Guidance Guideline for Good Clinical Practice (https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf)
- ICH Topic E9 Statistical Principles for Clinical Trials (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf)
- EMEA Points to Consider on the Choice of Non-Inferiority Margin (http://home.att.ne.jp/red/akihiro/emea/215899en_ptc.pdf)
- ICH Topic E10 Choice of Control Group in Clinical Trials (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002925.pdf)
- EMEA Points to Consider on Switching Between Superiority and Non-Inferiority (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003658.pdf)
- GCIG CA125 Response Definition (http://gcig.igcs.org/images/jncirustin.pdf)
- New Guidelines to Evaluate the Response to Treatment in Solid Tumours – 2000 (http://gcig.igcs.org/images/jncitherasse.pdf)
- GCIG Progression Definition Incorporating RECIST and CA125 – 2000 (http://gcig.igcs.org/images/progdef.pdf)
- GCIG Consensus Statements: Ovarian Cancer – 2004 Consensus Statement on the management of Ovarian Cancer (http://annonc.oxfordjournals.org/cgi/reprint/16/suppl_8/viii7)