Guide Book

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 inter-group trials, this guide book collects and organizes these. The guide book is organized into a brief introductory part and a series of appendices, the introduction covers basic definitions and summarizes the responsibilities of the different entities involved in a GCIG trial.
The appendices cover the more specific trial issues in detail including guidelines for translational research, randomization and the inter-group agreement template necessary to set up a trial.

Comment [TK1]: Delete or add appendix?

Definitions

An inter-group trial is a trial where at least 2 national or international GCIG member groups collaborate, non GCIG groups may participate but the leading group must be a GCIG member. Inter-group 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 CRFs or one eCRF which must be used by~~for~~ all participating~~collaborating~~ groups
- The data from all participating groups are collected in the ~~coordinating~~ leading group data centre for entry into the trial database or entered directly into the eCRF by the participating sites.
- Inter-group trials are not conducted by the industry

An inter-group trial consists of the following entities:

- Steering committee also known as "Trial Committee" or "Trial Steering Committee"
- ~~Coordinating~~ Leading group
- ~~Coordinating~~ Leading group data centre
- Participating groups
- Participating group data centres

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

1. Development of a new inter-group trial

A new inter-group trial can be proposed by one or several groups. If there is sufficient interest in the GCIG community for performing the trial the initiating groups must establish a steering committee. The steering committee consists of members from the interested groups and must include a data manager and a statistician from the leading group.

Comment [TK2]: And or an administrative representative

The steering committee has the following responsibilities:

- Determine which group should be the ~~coordinating~~ leading group
- Evaluating and approving the protocol, CRF~~s~~ and possible amendments
- Accept members of Data Monitoring Committee (DMC) if applicable for the trial
- Discuss and take relevant actions based on DMC recommendations
- Discuss and agree on trial conduct issues, data analysis and publications
- Ensuring that the trial is in accordance with the Declaration of Helsinki, EC Directive 2001/20/EC, Commission Directive 2005/28/EC and with the principals of ICH GCP (Harmonised Tripartite Guideline for Good Clinical Practise).

The ~~coordinating~~ leading group is responsible for the following:

- Setting up the inter-group agreement and group specific appendix
- Writing of the protocol, and obtaining the approval of the protocol by the steering committee as well as by the appropriate executive body for each of the participating groups
- Designing the CRF/eCRF~~s~~ and approval of these by the steering committee and the appropriate body for each of the participating groups
- Ensuring that all necessary legal regulatory or other approvals are in place
- Ensuring that the data bases used at the local data centres are compatible with the data base used at the coordinating data centre
- Setting up and maintain the TMF and provide relevant documents and guidelines to participating groups
- Performing the final analysis and ensuring presentation and publication of the results
- Providing the ~~coordinating~~ leading group data centre with the capacity to conduct the study
- Decide if sponsorship and financial support should be handled by the ~~coordinating~~ leading group on behalf of all groups, or separately by each participating group, and define and write the necessary agreements
- Writing amendments and obtaining approval of these by the steering committee.

Add chapter with responsibilities of participating groups

During the course of the planning phase of a trial, several meetings should be held preferably in connection to the biannual GCIG meetings or as online meetings. ~~-~~ These meetings are arranged by the leading~~coordinating~~ group and all interested groups as well as relevant industry representatives should participate. This ensures an open and effective protocol development process leading to a widely approved and correct protocol.

The conduct of the study

The conduct of the study should be in accordance with the inter-group agreement document.

Practical issues in relation to conducting of the study

- Before starting a trial everyone should describe in details how their data is recorded, for example how the personal data of their patients are recorded. The description should prevent misunderstanding.
- Randomisation procedure. The ~~coordinating~~ leading group is responsible for providing the participating groups with details about randomisation including stratification. The leading~~coordinating~~ group should ensure that the

Comment [TK3]: And/or IDMC?

Comment [TK4]: To be updated

Comment [TK5]: Still applicable?

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Comment [TK6]: To be rephrased or deleted? Not sure it makes sense anymore.

randomisation program used by the individual group offices is compatible with the data base at the coordinating groups Data Centre.

- The participating groups are responsible for informing the local investigator about the randomisation procedure.
  The randomisation could be done by phone, fax or online. It is necessary that the randomisation procedure minimises misunderstanding for groups with participants from several countries.
  A randomisation check list is filled in before the randomisation is initiated. On study form should be send to the secretariat within a fixed time.

Comment [TK7]: Delete?

Comment [TK8]: Delete? Or rephrase?

Data Managing

- The ~~coordinating~~ leading 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 by the centres in eCRF ~~on-line.~~
- It is the responsibility of the participating group ~~data secretariat~~ to ensure that the local investigator complete CRF/eCRF ~~sent in record forms~~ within fixed timelines. ~~If it is not done the groups secretariat should recall for the record forms. In case where CRFs are not sent to the group's secretariat after recalling the investigator could be prohibited to randomise before all CRFs are in place.~~
  Participating groups are responsible to assist the leading group in case of missing data and queries.

Reporting of SAE and SUSARS

SAE reporting should be described in details in the protocol and reported according to international guidelines for clinical trials. The leading group and participating group responsibilities regarding SUSAR reporting should be agreed upon.

Comment [TK9]: Add DSUR responsibilities?

Independent Data Monitoring Committee.

It should be decided for the individual protocol if there should be an independent data monitoring committee. This monitoring committee should be set up at the start of the trial and the members should be accepted by the steering committee.

Comment [TK10]: Consistency with wording . DMC/IDMC or both?

Amendment handling.

Amendment should only be done after discussion and approval by the steering committee. The leading group will make a draft amendment. After approval by the steering committee the ~~individual~~ participating groups are responsible for the approval of the amendments by the local investigators and by regulatory authorities.
~~Amendments could not be done by individual groups.~~

Insurance.

It should be ensured before starting a new trial that there is an appropriate insurance.

Communication

Before start of a protocol a plan for communication and escalation of questions should be agreed upon ~~there should be made an agreement about communication, which person should receive which information. There should also be made an agreement about responsibility for actions after information is given.~~

Comment [TK11]: Upcoming discussion in Chicago 2015

The ~~coordinating~~ leading group is responsible for providing the participating groups with information on the accrual of patients and the status of the trial including tables of patient characteristics, toxic effects, serious adverse events and other important data. This information should be sent at regular intervals. Newsletters? TC's?

Add something about monitoring, site selection, TR?

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Appendices

The appendices of the guidebook are made up of following GCIG generated documents:

1. Intergroup Agreement Template (Group Document Owner – MRC)
2. Data Monitoring Committees for GCIG Trials Document. (Group Document Owner – SGCTG)
3. Checklist for Tissue Banking Consent Form (Group Document Owner –ANZGOG)
4. Essential Documents Checklist (Group Document Owner – GINECO)
5. Randomisation procedures

Comment [TK12]: New versions of existing documents to be added – or perhaps only a link to avoid to many pages within the document.
Randomization procedure to be deleted or added if existing?
Add Group specific appendix
Any checklists to be added ? Site approval? TR?
Criteria for joining a GCIG trial?

Comment [KC13]: Page: 3
Not sure what exactly should be in this appendice, checked with Statisticians re this at GCIG meeting Florida May 2009 – Val kindly agreed he would put together a document

Guidance and Reference Documents

In addition to the appendices to the guidebook a list of useful guidance and reference documents are listed below with the current web link for each:

Comment [TK14]: All links to be checked

1. Common Data Elements (CDEs) (https://cdebrowser.nci.nih.gov/CDEBrowser/)
2. ICH Harmonised Tripartite Guidance Guideline for Good Clinical Practice (http://www.ich.org/LOB/media/MEDIA482.pdf)
3. ICH Topic E9 Statistical Principles for Clinical Trials (http://www.emea.europa.eu/pdfs/human/ich/036396en.pdf)
4. EMEA Points to Consider on the Choice of Non-Inferiority Margin (http://home.att.ne.jp/red/akihiro/emea/215899en_ptc.pdf)
5. ICH Topic E10 Choice of Control Group in Clinical Trials (http://www.emea.europa.eu/pdfs/human/ich/036496.en.pdf)
6. EMEA Points to Consider on Switching Between Superiority and Non-Inferiority (http://www.emea.europa.eu/pdfs/human/ewp/048299en.pdf)
7. GCIG CA125 Response Definition (http://gcig.igcs.org/images/jncirustin.pdf)
8. New Guidelines to Evaluate the Response to Treatment in Solid Tumours – 2000 (http://gcig.igcs.org/images/jncitherasse.pdf)
9. GCIG Progression Definition Incorporating RECIST and CA125 – 2000 (http://gcig.igcs.org/images/progdef.pdf)
10. GCIG Consensus Statements:
    Ovarian Cancer – 2004 Consensus Statement on the management of Ovarian Cancer (http://annonc.oxfordjournals.org/cgi/reprint/16/suppl_8/viii7)

Appendix 1 Guidebook: Intergroup Agreement Template

1 of 2 originals

(short name of trial here) CLINICAL TRIAL

RESEARCH AGREEMENT FOR THE PERFORMANCE OF AN INTERGROUP CLINICAL TRIAL

BETWEEN

(lead group name here, also known as Sponsor)

AND

(participating GCIG group)

CLINICAL TRIAL RESEARCH AGREEMENT

BETWEEN

(participating GCIG group), describe type of entity here, and full address, represented by and acting through the (name and address of scientific structure if applicable) (**"short name reference here")**

AND

(name of Sponsor here), (Sponsor address here) on behalf of (name of scientific structure here if applicable), jointly and severally referred to as
« short name reference here »

WHEREAS

A Members of **(scientific structure of participating group GCIG group)**, an association of practicing clinicians, has identified the need for medical research into ovarian cancer and has recommended to **(participating GCIG group)** that it pursue such research.

B **(scientific structure of participating group GCIG group)** has independently analyzed the proposal and agrees with the recommendation. In accepting this proposal **(participating GCIG group)** has not relied on any statements or assertions on the part of **(scientific structure of participating group GCIG group)** but relies on its own independent assessment.

C Both **(participating group GCIG group)** and **(name of Sponsor here)** wish to jointly undertake an intergroup clinical trial entitled:

"full title of protocol here"
EUDRACT# XXXXXXXXXX
("the Study")

which is to be conducted according to the **(name of Sponsor here)** protocol named the "short title of protocol here" protocol, hereinafter referred to as the "Protocol".

D **(name of Sponsor here)** has access to clinical centres in XX countries and possibly other countries from which to recruit study participants and **(participating GCIG group)** has access to clinical centres in XX countries from which to recruit study participants.

E **(participating GCIG group)** is represented by **(name of Sponsor here)**, and **(name of Sponsor here)** is represented by **(name of Scientific Coordinator here)**.

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NOW IT IS HEREBY AGREED AND DECLARED as follows:

2. Definitions and glossary

"Agreement" means this agreement and all Schedules, Appendices and other documents as may be incorporated by reference;
"define further the scientific structure of participating group here"
"define further the scientific structure of Sponsor here"
"Background Intellectual Property" means Intellectual Property owned by (participating group name here) at the commencement of the Agreement, which is reasonably required by (Sponsor name here) to utilise Project Intellectual Property provided that:

a) such Background Intellectual Property is not a registered or unregistered trademark;
b) such Background Intellectual Property is not the subject of an exclusive licence to a third party or parties;

"CRF" means Clinical Research Form: A printed optical or electronic document designed to record all of the protocol-required information to be reported to (Sponsor name here) on each study participant;

"DMC" means the Data Monitoring Committee**,** an independent data monitoring committee that may be established by the(Sponsor name here) to assess at intervals the progress of the Study, the safety data and the critical efficacy endpoints, and to recommend to the (Sponsor name here) whether to continue, modify or stop the Study;

"GCIG" means the Gynecologic Cancer Intergroup, An Organisation of International Cooperative Groups for Clinical Trials in Gynecologic Cancers, consisting of appointed representatives from international and national research groups, including (scientific structure of Sponsor here) and (scientific structure of participating group here), which perform clinical trials in gynaecological cancer;
"GCP" means Good Clinical Practice: A standard for the design, conduct, performance, monitoring, recording, analyses and reporting of clinical trials that provides assurance that the data and recorded results are credible and accurate and that the rights, integrity and confidentiality of trial subjects are protected;

"GST" has the same meaning as GST Law;
"GST Law" means "*A New Tax System (Goods and Services Tax)(if applicable)*";
"GST Rate" has the meaning giving in GST Law;

"Institutional Review Board" means an independent body constituted of medical, scientific and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in the Study, among other things, reviewing, approving and providing continuing review of the (short study title here) protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the study participants;

"Intellectual Property" includes all copyright and neighbouring rights, all rights in relation to inventions (including patent rights), plant varieties, registered and unregistered trademarks (including service marks), registered designs, confidential information (including trade secrets and know-how) and circuit layouts, and all other rights resulting from intellectual activity in the industrial, scientific, literary or artistic fields;

"Parties" means (Sponsor name here) and (participating group name here) and **"Party"** means either of them as the context requires;

"Project Intellectual Property" means any Intellectual Property arising from the Study;

"RCTI" means a Recipient Created Tax Invoice and has the meaning given in GST Law;

"Registrable Intellectual Property" means Intellectual Property capable of being registered according to relevant local legislation granting monopoly rights to the registrant and includes but is not limited to patents, patentable inventions, trademarks, copyrights, circuit layouts, designs and plant breeders rights.

"SAE" means Serious Adverse Event: Any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;
- requires in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect, or
- an important medical event.

"SUSAR" means Suspected Unexpected Serious Adverse Reaction;

"(participating group)Clinical Centres" means those hospital sites in (countries XX) at which (participating group) Study Participants receive treatment as part of the Study;

"TMG" means the Trial Management Group, a group that may be established by the Sponsor for reviewing the progress of the Study within all clinical centres;

By signature of the Agreement by both Parties, it is hereby agreed that:

3. Conduct of the Study

3.1. The Study is an intergroup study in which **(SPONSOR NAME HERE)** is the leading group as well as the Sponsor of the Protocol where **(SPONSOR NAME HERE)** has delegated via (PARTICIPATING GROUP NAME HERE) certain 'Sponsor responsibilities' to (participating group name here)**.** Each Party shall undertake the Study as the respective entities for their clinical centres within the Study as set down in the Protocol.

3.2. **(SPONSOR NAME HERE)** shall be responsible for compliance with clinical and/or regulatory procedures in (countries XX) and for their affiliated clinical centres where **(SPONSOR NAME HERE)** conducts the Study, and (participating group name here) shall be responsible for compliance with clinical and/or regulatory procedures in (countries YY) and for the (participating group name here) Clinical Centres. All Parties will assure that each of its clinical centres receives all necessary local and national regulatory approvals from the respective competent authority.

3.3. The Study shall be conducted by **(SPONSOR NAME HERE)** and (participating group name here) severally under the obligations imposed on each of them respectively under the Agreement:

3.3.1. In accordance with the Protocol and any amendments to the Protocol as approved by the competent (name different governing bodies here) authorities;

3.3.2. In clinical centres to be selected respectively by **(SPONSOR NAME HERE)** and (participating group name here) in each of their jurisdictions. Clinical centres in (countries YY) shall be known as (participating group name here) Clinical Centres, the suitability of such centres ultimately subject to (SPONSOR NAME HERE) agreement;

3.3.3. With study participants selected in accordance with the eligibility criteria specified in the Protocol and only after all necessary legal, regulatory or other approvals have been granted including those of the Institutional Review Board or of any ethics committee, at the clinical centres and strictly in accordance with the terms of any such approval;

3.3.4. In accordance with the Declaration of Helsinki, and with the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (Note for Guidance on GCP), and the European Directive.

3.3.5. In accordance with the requirements laid down by laws applicable in the countries where the Study is conducted.

4. Duties

4.1. **Obligations of (SPONSOR NAME HERE)**

(SPONSOR NAME HERE) agree that:

4.1.1. **(SPONSOR NAME HERE)** shall be responsible for the operational management of the Study at its participating clinical centres in (countries XX);

4.1.2. **(SPONSOR NAME HERE)** shall be responsible for the central data management of the Study, including the collection and analysis of the data and its inclusion in the study database. **(SPONSOR NAME HERE)** shall ensure the collected data are kept as required by GCP and shall create a database for the Study;

4.1.3. **(SPONSOR NAME HERE)** will be responsible for drawing up CRF completion guidelines and all other guidelines required for the proper conduct of the Study;

4.1.4. **(SPONSOR NAME HERE)** shall process the data in accordance to the law applicable with regard to data protection and shall ensure that the Patient Information Sheet and Informed Consent models found in the Protocol contain all the required information in this regard;

4.1.5. **(SPONSOR NAME HERE)** shall be responsible for documenting operating procedures for randomisations, either centrally (all done through **(SPONSOR NAME HERE)**) or by group ((**participating group NAME HERE)** randomises study participants in **(SPONSOR NAME HERE)**'s clinical centres, (participating group name here) randomises study participants in (participating group name here) Clinical Centres);

4.1.6. **(SPONSOR NAME HERE)** shall be responsible for setting up a system of pharmacovigilance within the Study (in consultation with (participating group name here) and other participating groups) including data recording, assessment, expedited and periodic reporting to regulatory authorities, relevant ethics committees and investigators;

4.1.7. **(SPONSOR NAME HERE)** shall provide (participating group name here) with information on the progress of the Study in clinical centres managed by both **(SPONSOR NAME HERE)** and (participating group name here). Such information will be provided as 6-monthly reports including study participant accrual, eligibility status, and treatment status;

4.1.8. (**SPONSOR NAME HERE)** shall provide (participating group name here) with a copy of the final study report within a year's time after completion of the Study;

4.1.9. Upon completion of the Study and after the final analysis, **(SPONSOR NAME HERE)** agrees to transfer the section of the database to (participating group name here) containing (participating group name here) Clinical Centres, investigators and study participants in the existing format;

4.1.10. **(SPONSOR NAME HERE)** agrees to form an independent DMC to regularly and confidentially review the accumulating data. (participating group name here) may have the opportunity to nominate at least one member to the DMC;

4.1.11. **(SPONSOR NAME HERE)** may form a TMG which will include trial statisticians, data management staff and chief investigators from several participating GCIG Groups. The TMG will meet regularly in person or by phone to review the progress of the Study within all clinical centres including recruitment, problems with protocol compliance, unexpected toxicities and need for protocol amendments;

4.1.12. **(SPONSOR NAME HERE)** shall ensure that clinical trial insurance to the coverage limits normally applicable to a study of this type is in place for all clinical centres participating in the Study, including (participating group name here)

Clinical Centres. Insurance shall remain in effect for the duration of the Agreement and or Study, covering any liability of **(SPONSOR NAME HERE)** and the study participants in accordance with the requirements laid down by laws applicable in the countries where the Study is conducted.

4.1.13. **(SPONSOR NAME HERE)** may form an independent Trial Steering Committee and will consult (participating group name here) and other GCIG groups on this matter as appropriate.

4.2. **Obligations of (participating group name here)**

(participating group name here) agrees that:

4.2.1. (participating group name here) shall be responsible for the operational management of the Study at its (participating group name here) Clinical Centres in (countries YY), as set down in the Roles and Responsibilities table of **Appendix 2**;

4.2.2. (participating group name here) shall be responsible for the randomisation of its study participants, collection of CRFs (if not using e-CRFs) from (participating group name here) Clinical Centres, and forwarding them to **(SPONSOR NAME HERE)**;

4.2.3. (participating group name here) will ensure that (participating group name here) Clinical Centres understand the CRF completion guidelines, both in terms of data completeness and the timescale for completing and returning completed CRFs. (participating group name here) will perform on-site monitoring of (participating group name here) Clinical Centres as described in the monitoring plan; (this paragraph to be adjusted as appropriate)

4.2.4. (participating group name here) will screen completed CRFs before forwarding them to **(SPONSOR NAME HERE)**, to ensure that forwarded CRFs are complete and accurate;

4.2.5. (participating group name here) shall inform **(SPONSOR NAME HERE)** of all protocol-defined Serious Adverse Events (SAEs and SUSARs) occurring at (participating group name here) Clinical Centres during the conduct of the Study, and shall report unexpected and related SAEs, per regulatory requirements, to the (enter name of authorities here) as appropriate;

4.2.6. No (participating group name here) Clinical Centre may participate in the Study unless appropriate clinical trial insurance is in place for the duration of the Agreement and/or Study, covering any liability of (participating group name here), (**SPONSOR NAME HERE**) and the study participants in accordance with the requirements laid down by laws applicable in the countries where the Study is conducted; and

4.2.7. (participating group name here)'s Data Centre shall require clinical investigators and (participating group name here) Clinical Centres to handle any information provided by **(SPONSOR NAME HERE)** in accordance with terms equivalent to the confidentiality provisions of clause 12 of the Agreement.

5. Protocols and Forms

5.1. **(SPONSOR NAME HERE)** will create and provide (participating group name here) with the study CRFs, whether paper-based or electronic. (participating group name here) will be responsible for distribution of the CRFs to (participating group name here) Clinical Centres as appropriate.

5.2. **(SPONSOR NAME HERE)** has ownership of the master protocol and CRFs.

5.3. Changes to the master protocol and CRFs can only be made after discussion with the Participating GCIG groups, the Trial Management Group (if applicable, including representatives from **(SPONSOR NAME HERE)** and (participating group name here))

6. Financial Support

6.1. **(SPONSOR NAME HERE)** agrees to compensate (participating group name here) for their work performed on the Study per the Table 1 below:

Table 1

Task achieved	Per study participant payment in Euros
For each study participant randomised but not treated (with the exception of non-eligibility)	€ XXXXXX
For each study participant randomised, treated, monitored and CRF completed	€ XXXXXX

6.2. **(SPONSOR NAME HERE)** agrees to compensate (participating group name here) according to the schedule of payments described in the Table 2 below:

Table 2

Milestones	Payment in Euros
Upon Intergroup Agreement finalisation and sign-off	€XXXXXX *
Upon 1st dose administered to each study participant	€ XXXXXX
Upon completion and submittal to **(SPONSOR NAME HERE)** of each complete study participant CRF	€ XXXXX

* € XXXXXXX to be deducted from the total per study participant payments

6.3. After achieving each of the milestones set out in Table 2, (participating group name here) shall notify (SPONSOR NAME HERE) and send a payment request on a quarterly basis. All payments shall be made within ninety (90) days of receipt of the payment request of (participating group name here). No additional costs will be reimbursed.

Reference for payments to (participating group name here):

Account number : XXXXXXX
Bank Name :
Account name holder :
IBAN :
Swift code :
Name of contact person at bank :

Payment requests shall be addressed to:
(SPONSOR NAME HERE)
(contact person)
(address)
Tel:
Fax:
Email :

7. GST (Goods and Services Tax)

6.1 If GST is payable on any supply by one party to the other party under the Agreement (including the supply of any goods, services, rights, benefits or other items) it will be specified on tax invoices issued or provided to (SPONSOR NAME HERE) by (participating group name here). Under current GST Law…….(specify here if GST tax to be paid or not, and by whom whenever applicable)

8. Drug Supply

8.1. **(SPONSOR NAME HERE)** agrees to arrange for (participating group name here) Clinical Centres to be provided with Study Drug for all study participants, to be randomised and distributed by (name of 3rd party whenever applicable). The Study Drug is defined here as (name of Study drug(s). (name of 3rd party) will provide (name of Study drug(s) directly to (participating group name here) Clinical Centres and will organise re-supply throughout the Study;

8.2. (name of 3rd party will be used solely for the purposes of the Study;

8.3. (participating group name here) Clinical Centres will be required to provide all other medications to study participants;

8.4. (name of 3rd party) will provide to (participating group name here) evidence of quality assurance for (name of Study drug(s);

9. Indemnity

9.1. (participating group name here) shall indemnify, release and discharge (SPONSOR NAME HERE), its agents and employees from any loss, costs, claims, demands or actions which may be made by reason of personal injury (including death) to any person, or damage to property, arising out of or in connection with liability resulting from the negligent acts or omissions of (participating group name here), its agents or employees in the performance of its obligations pursuant to the Agreement;

9.2. (SPONSOR NAME HERE) shall indemnify, release and discharge (participating group name here), its agents and employees from any loss, costs, claims, demands or actions which may be made by reason of personal injury (including death) to any person, or damage to property, arising out of or in connection with liability resulting from the negligent acts or omissions of (SPONSOR NAME HERE), its agents or employees in the performance of its obligations pursuant to the Agreement.

10. Project Intellectual Property as Study Data

10.1. The study data arising from the Study, which is related to the contribution of **(SPONSOR NAME HERE)**, shall be the property of **(SPONSOR NAME HERE);**

10.2. The study data arising from the Study, which is related to the contribution of (participating group name here), shall be the property of (participating group name here) but will be available licence-fee free to **(SPONSOR NAME HERE)** at all times for publication purposes;

10.3. In the event that **(SPONSOR NAME HERE)** wish to make available for purchase by a third party the complete database set of the Study, (participating group name here) and **(SPONSOR NAME HERE)** will agree to a fixed fee owed to (participating group name here) for the data generated from the participation of (participating group name here). Further to be agreed are the conditions of purchase, including a provision that any such purchase will not breach laws relating to personal or private information;

9.4 Any invention or discovery arising from the study data which is related to the contribution of (participating group name here), shall be the property of **(SPONSOR NAME HERE)**, provided such invention or discovery is directly related to the Study. Serendipitous discovery with applications not contemplated in the Study shall be subject to negotiation in good faith between (participating group name here) and **(SPONSOR NAME HERE)** regarding Registrable Intellectual Property; (reference: Appendix I)

11. Publication

10.1 The publication of the final report of the results of the Study shall be in accordance with the Protocol, and the GCIG publication guidelines.

10.2 **(SPONSOR NAME HERE)** may wish to publish or present scientific papers dealing with the Study in accordance with accepted scientific practice. **(SPONSOR NAME HERE)** agrees that 30 days prior to submission of publication or any other dissemination of results, **(SPONSOR NAME HERE)** shall invite (participating group name here) to comment on the content of the material to be published or presented. (participating group name here) shall have the opportunity to review and comment upon such submissions for an agreed period of time prior to submission for abstract, and for an agreed period of time prior to submission for manuscripts.

10.3 (participating group name here) may wish to publish or present scientific papers dealing with the Study in accordance with accepted scientific practice. (participating group name here) agrees that 30 days prior to submission of publication or any other dissemination of results including oral dissemination, (participating group name here) shall invite **(SPONSOR NAME HERE)** to comment on the content of the material to be published or presented. **(SPONSOR NAME HERE)** shall have the opportunity to review and comment upon such submissions for an agreed period of time prior to submission for abstract, and for an agreed period of time prior to submission for manuscripts.

10.4 (participating group name here) shall not publish any material from their component of the Study before the publication of the full study report without prior written agreement from **(SPONSOR NAME HERE)**.

10.5 Following final analysis of the mature results of the Study and submission of any abstract(s), **(SPONSOR NAME HERE)** and (participating group name here) agree to submit the final paper for publication within an agreed period of time.

12. Term and Termination of the Agreement

11.1 The Agreement shall take effect at the date of signature of the last Party thereto, and shall remain in force for the duration of the Study;

11.2 The Agreement can, only after discussing between the Parties, be terminated by written notice in case of:

- an early termination of the Study for reasons which could include study participant safety, unsatisfactory study participant enrolment or the decision of a regulatory body;
- a material and irremediable breach by one Party of the Agreement;
- any technical or methodological impossibility to pursue the Study;

11.3 In the event the Agreement or Study is terminated by (SPONSOR NAME HERE) during the recruitment period for any reason other than an irremediable material breach of the Agreement by (participating group name here), (participating group name here) is entitled to recover from (SPONSOR NAME HERE) or retain from (SPONSOR NAME HERE) funding an amount reflecting the number of study participants under recruitment at the date of termination. The Parties agree to negotiate a fair commercial settlement which takes into consideration the amounts actually or irrevocably committed by (participating group name here) in relation to the Agreement or Study at the date of termination.

13. Confidentiality

13.1. All information related to the Study shall be confidential within the participating GCIG group and none of the Parties shall disclose any information to a third party, without the prior written permission of the leading group (**(SPONSOR NAME HERE)**), other than as required to perform the Study except if required by law. This does not apply to any information which:

- is in the public domain
- is made public by a third party acting without impropriety in doing so

- is made by investigators at clinical centres in the report of his/her activities that is requested by competent authorities

14. Entire Agreement

13.1 The Agreement constitutes the entire agreement between the Parties and supersedes all prior representations, agreements, statements and understandings, whether verbal or in writing.

15. Governing Law

14.1 The Agreement is governed by the law applicable in the (generally name of country where Sponsor is located in) and the Parties unconditionally submit to the Courts exercising jurisdiction in (name of country where Sponsor is located in).

16. No Partnership

15.1 No servants or agents of either Party shall by virtue of the Agreement be deemed to be employees of the other Party, and nothing in the Agreement shall create a partnership between the Parties or give to a Party any rights of a Partner or subject such Party to any liabilities of a partner in relation to the other Party's business.

17. Counterparts

16.1 The Agreement may consist of a number of counterparts, and those counterparts taken together constitute one and the same instrument.

18. Form of written notice

Any written notice to be given under the terms of the Agreement shall be sent to:

For (SPONSOR NAME HERE):
Name & address
Tel/Fax:
Email

For (participating group name here):
Name & address
Tel/Fax:
Email

EXECUTED by the Parties as an Agreement effective at the date of the last signature hereto.

Signed for and on behalf of **(participating group name here),**
represented by and acting through (name of scientific entity behind participating group)
by its duly authorised representative:

_____
name of person, title
place of business

in the presence of:

_____
Witness, name and title

Name of city , date

Signed for and on behalf of (name of scientific entity behind for Sponsor),
by its duly authorised representative:

_____
name of person, title
place of business

in the presence of:

_____
Witness, name & title

Name of city , date

Appendix 1

COMPANY INTELLECTUAL PROPERTY ACKNOWLEDGMENT

(add intellectual property info here if applicable)

Name: (PARTICIPATING GROUP NAME HERE)

Address:

(Hereinafter referred to as "Participating Group")

Name:

(Hereinafter referred to as "Affiliate Investigator")

The Participating Group and Affiliate Investigator wish to participate in "**full name of protocol here"** (hereinafter referred to as the "Study"). The Study is to be conducted pursuant to the PROTOCOL (short tilte here) Eudract no XXXXXXXXXXX
("Protocol").

Affiliate Investigator and Participating Group acknowledge that during and for a period of ten (10) years after the termination of the Study, Affiliate Investigator and Participating Group shall retain in confidence all information obtained from Company relating to the Study Drug and any other information or material disclosed obtained from Company that is marked Confidential and Proprietary.

The sole and exclusive right to any inventions, discoveries or innovations ("Inventions"), whether patentable or not, arising directly or indirectly in the performance of the Protocol and Study under this Agreement, arising out of the use of (name of study drug) the Study Drug, shall be the property of Company. Affiliate Investigator and Participating Group will promptly notify Company in writing of any such Inventions, and at Company's request and expense Affiliate Investigator and Participating Group will cause to be assigned to Company all right, title and interest in and to any such Inventions and provide reasonable assistance to obtain patents, including causing the execution of any invention assignment or other documents.

Agreed and Accepted:

PARTICIPATING GROUP

BY: (PARTICIPATING GROUP NAME HERE)
NAME: _____
TITLE:_____
DATE: _____

I hereby acknowledge that I have read and agree with the terms of this Acknowledgment and that I will act and perform my duties in the Study in accordance therewith, including but not limited to the assignment to Company of any proprietary rights relating to the study data and/or Inventions that I may otherwise have according to law.

AFFILIATE INVESTIGATOR

BY: _____clinical investigator at each (participating group name here) Clinical Centre
NAME: _____
TITLE: _____
DATE: _____

Appendix 2

(Sponsor)/(PARTICIPATING GROUP NAME HERE) ROLES AND RESPONSIBILITIES

GCIG HARMONISATION ROLES AND RESPONSIBILITIES CHECKLIST					
		SPONSOR	(PARTICIPATING GROUP NAME HERE) Centre	(participating group name here) Clinical Centres	(3rd party)
1	PROTOCOL				
1.	Protocol preparation				
2.	Protocol review				
3.	Protocol printing				
4.	Protocol distribution to the groups				
5.	Protocol distribution to clinical centres				
6.	Preparation of country specific appendices				
2	PROTOCOL AMENDMENTS				
1.	Amendment preparation				
2.	Amendment review				
3.	Amendment printing				
4.	Amendment distribution to the groups				
5.	Amendment distribution to the clinical centres				
6.	Tracking approvals				
3	CASE REPORT FORMS (CRFs)				
1.	CRF design				
2.	CRF printing				
3.	CRF distribution to groups				
4.	CRF distribution to the centres				
4	CONSENT (IC) FORM				
1.	IC master sample preparation, review and approval				
2.	IC national sample preparation, review and approval				
3.	IC local preparation, review and approval				
4.	Local IC translation to local language				
5.	Approval of local IC (if required by lead group)				
5	HEALTH/REGULATORY AUTHORITY				
1.	Preparation of submissions				
2.	Submission				
3.	Submission of annual safety reports to authorities				
4.	Submission of annual safety report to relevant companies.				
5.	Review and assessment of SAE reports				
6.	Reporting of SAEs/SARS/SUSARS authorities				
7.	Reporting of SAEs/SARS/SUSARS to Groups				
8.	Reporting of SAEs/SARS/SUSARS to investigators				
9.	Reporting of SAEs/SARS/SUSARS to company				
10.	Reporting of SAE's/SARS/SUSARS from other trials (ISL's) to HA (pending discussion w/ EMEA)				
11.	Reporting of SAE's/SARS/SUSARS from other trials (ISL's) to Groups (same as above)				

GCIG HARMONISATION ROLES AND RESPONSIBILITIES CHECKLIST					
		SPONSOR	(PARTICIPATING GROUP NAME HERE) Centre	(participating group name here) Clinical Centres	(3rd party)
6	INVESTIGATIONAL MEDICINAL PRODUCT (IMP)				
1.	Manufacturing, packing and release				
2.	Import License				
3.	Packaging/Labelling and release				
4.	Label compliance with regulations				
5.	Shipping/Distribution to CRO (if applicable)				
6.	Shipping / Distribution to centres				
7.	Provision of shipping receipts to participating group (if applicable)				
8.	Blinding/unblinding				
9.	Randomisation				
10.	IMP Recall				
11.	Destruction				
12.	Drug Accountability				
13.	IMP reconciliation				
7	ETHICS ACTIVITIES				
1.	Reporting of SAEs/SARS/SUSARS to centres				
2.	Reporting of SAEs/SARS/SUSARS to relevant ethics				
3.	Provide Electronic IB to to groups				
4.	Forwarding updated IB's to centres				
5.	Providing updated IBs to groups				
6.	Tracking proof of submission of SL's/ISL's to ECs				
7.	Checking EC approval of protocol/amendments				
8.	EC fees if applicable				
8	SELECTION OF INVESTIGATORS				
1.	Selection of Investigators				
2.	Release of authorized centres list				
3.	Termination of centres				
4.	Assurance that sites work according to GCP				
9	AUDITING AND MONITORING				
1.	Central Monitoring				
2.	Monitoring Plan				
3.	Auditing Plan				
4.	On site monitoring				
5.	Centre Audits				
6.	Pre NDA/regulatory submission audits				
10	TRIAL/CENTRE INITIATION				
1.	Participating Centre Agreement				
2.	Additional Contract as required				
3.	Financial disclosure information / 1572 if applicable				
4.	Conduct of initiation/opening visit				
5.	Checking of documentation				
6.	Formally activating a centre				
11	INVESTIGATOR MEETINGS				
1.	International Investigator Meeting if required				
2.	National investigator meeting				
3.	Costs of investigator meetings				

GCIG HARMONISATION ROLES AND RESPONSIBILITIES CHECKLIST					
		SPONSOR	(PARTICIPATING GROUP NAME HERE) Centre	(participating group name here) Clinical Centres	(3rd party)
12	DATA MANAGEMENT				
1.	Initial patient registration				
2.	Randomisation process				
3.	Timely CRF flow from centres				
4.	Data Entry of paper CRF received from centres				
5.	Updating database, data checking				
6.	Cross checks of database				
7.	Final clinical validation of cases				
8.	Data Queries generation				
9.	Data query delivery to centres				
10.	Data query retrieval from centres				
11.	Timely Data Query resolution				
12.	All data queries from Company (including SAE queries) will be routed via Group				
13.	Coding and cleaning of concomitant medication database				
14.	Provision of complete database will be provided to participating group in specified format within a reasonable timeframe after the final analysis				
15.	Coding of adverse events				
13	TRIAL CLOSE OUT				
1.	Decision on appropriate time for closure according to number of patients required.				
2.	Informing company that trial is closed				
14	OTHER STUDY RELATED ACTIVITIES				
1.	Retention of CRFs				
2.	Scanning of CRF if required				
3.	Retention of regulatory files				
4.	Writing of Investigator Brochure/addendums				
15	SAFETY MONITORING				
1.	Safety monitoring and IC update				
2.	IC update				
3.	Investigators brochure update				
4.	Provision of unblinding information for individual patients for regulatory reporting				
5.	Forward relevant clinical and preclinical information to lead Groups				
16	COMMUNICATION				
1.	Sponsor should receive a copy of all relevant mail sent to the investigators by participating group				
2.	Sponsor to provide SAE listings 3-monthly.				
3.	Primary contact with clinical centres				
17	STATISTICAL ANALYSIS AND TRIAL REPORT				
1.	Analyses for DSMC and final analyses				
2.	Preparation of final report and all primary publications				
3.	Review of final report and publication				
4.	Preparation of the Company final study report				
18	MISCELLANEOUS				

GCIG HARMONISATION ROLES AND RESPONSIBILITIES CHECKLIST					
		SPONSOR	(PARTICIPATING GROUP NAME HERE) Centre	(participating group name here) Clinical Centres	(3rd party)
1.	Obtaining appropriate permission to use QoL instruments as well as validated translations				
2.	Pharmacokinetic analyses of Study Drug				
3.	PK report for study drug prior to final analysis				
4.	Pharmacokinetic analyses of concomitant chemotherapy				
5.	PK report prior to final analysis				
6.	Retrieval archival tissue for Tumour Bank				
7.	Coordination of sample collection and shipping				
19	CONTRACTS				
1.	Selection of Project Management CRO				
2.	Enter into contract with Project Management CRO				
3.	Approval and Provisions of Costs of PM CRO contract				
4.	Inspection and QA of PM CRO				
5.	Selection of Country CRO				
6.	Enter into contract with Country CRO's				
7.	Approval and Provision of Costs for Country CRO contract				
8.	Inspection and QA of Country CRO				
9.	Selection of Drug Warehousing CRO				
10.	Enter into contract with Drug Warehousing CRO				
11.	Approval and Provision of Costs for Drug Warehousing CRO contract				
12.	Inspection and QA for Drug Warehousing CRO				

Appendix 2 Guidebook: Data Monitoring Committees for GCIG Trials Document

This section is closely based on the work the DAMOCLES study group[1] which has conducted an extensive review of the working of Data Monitoring Committees and the policies of major organizations involved in RCTs.

A Data Monitoring Committee (DMC) is defined to be any committee set up to assess at intervals during the course of a trial, the progress of the trial, the trial safety data and the trial outcome data with a view to recommending whether the trial should continue, be modified or be terminated.

A DMC should be set up for all RCT phase III studies conducted under the auspices of the GCIG. The lead group is responsible for setting up the DMC. If no DMC is to be set up then this should be justified by the lead group and agreed by the participating GCIG groups.

The following are the minimum requirements for a DMC for a GCIG study:-

- The membership of the DMC should include at least one experienced statistician and at least one clinician experienced in clinical trials. Additional membership should reflect the specialities involved in the trial. All members of the DMC should be independent of the trial. If non-independent members are to be included this must be justified and agreed by the participating GCIG groups.

- The deliberations of the DMC when considering outcome data by treatment arm are confidential. These data are not to be shared with anyone who is not a member of the DMC, unless agreed by the DMC itself.

- The DMC acts in an advisory role and reports its recommendations in writing to the Trial Steering Committee, the sponsor's representative or some other body/individual with the authority to oversee the conduct of the study.

- A recognised formal statistical approach for the conduct of interim analyses should be employed, but in general the final recommendation from the DMC on the continuation of the study should be based on all the available evidence.

- The DMC must formally approve any public disclosure of any trial data that would take place prior to the publication of the protocol specified definitive analysis based on the primary outcome measure. This excludes the reporting of safety data to bodies who have formal responsibility for oversight of adverse event data (e.g. GOG Data Safety and Monitoring Board, the MHRA in the UK etc)

- The DMC must have defined reporting lines for urgent communications agreed by all GCIG groups participating in the study.

- A detailed DMC charter for each GCIG study must be drawn up by the lead group and agreed by the participating groups. It is recommended that this charter follows the guidelines and layout published by the DAMOCLES study group[2]. A template and worked example of a DMC charter can be found at http://www.abdn.ac.uk/hsru/hta/damocles.shtml.

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[1] Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, *et al*. **Issues in data monitoring and interim analysis of trials.** *Health Technol Assess* 2005;**9**(7).

[2] The DAMOCLES Study Group. **A proposed charter for clinical trial 2005 data monitoring committees: helping them do their job well.** Lancet 2005; 365: 711-22

Appendix 3 Guidebook – Checklist for Tissue Banking Consent Form

Checklist for Tissue Banking Consent Form

GCIG Group:_____

Protocol Title:_____

Protocol Version and Date:_____

Element	Yes	No	N/A
Introduction			
Invitation to take part in the research study.			
Brief description of and purpose of the research.			
Research to be conducted			
Details and methods of testing to be carried out (e.g. biochemical, genetic)			
Details of material to be removed / used			
a) access to tissue collected within the treatment process/already collected			
b) consent to remove additional material - blood samples (incl. volume and frequency) - additional tissue			
Details of samples to be retained for open–ended research and/or any future research including genetic research			
Consent for access to study medical records			
Disclosure of any potential commercial benefits and if the subject will receive money or other benefits.			
Specify the length of time the specimen will be stored eg your sample/tissue will be stored as long as analysis can be carried out.			
Potential risks			
Details of risks including invasive procedures, possible discomforts, psychological distress etc.			
Details of any results and by which method may be conveyed to the participant and any potential consequences clearly stated e.g. counselling for family members, health insurance etc.			
When appropriate, statement that the particular treatment or procedure may involve risks to the subject which are currently not foreseeable.			
Expected benefits			
Details of any benefits the participant may expect from taking part in the research. When there is no intended benefit, the participant should be made aware of this.			
Research which will NOT be done			
Details of research which will definitely not be conducted on samples collected eg reproductive cloning			
Subject care			
Stated that participation is voluntary, without detriment to future patient care.			
Option and mechanism by which donor may withdraw consent/samples from research. • Will patients be able to request the destruction of their biological specimen? *(not possible if the data is de-identified and unlinked).* • Who will guarantee destruction?			
The alternative procedure(s) that may be available to the participant, and their important potential benefits and risks.			
Ethical and cultural considerations			
Details of ethical review and IRB/EC requirements.			
Information is in plain language, comprehensible to the target population including any cultural considerations e.g. if interpreter			

required; cultural/community leader input required.			
That the subject or subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.			
Interstate/Overseas research			
Details of where samples will be sent and any national/international legal requirements			
Participant's responsibilities			
What will be required of the participant during the research.			
Expected duration in the study.			
Compensation/research related injury and research costs			
The compensation and/or treatment available, if any, in the event of research-related injury. The person(s) to contact in the event of research-related injury.			
The anticipated pro-rated payment, if any, for participating in the research.			
The anticipated expenses, if any, to the subject for participating in the research.			
Confidentiality, access to medical information and data protection			
That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws/regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.			
Degree of anonymisation / coded data			
That the sponsor, monitor(s), auditors, IRB/EC and the regulatory authority(ies) will be granted direct access to the subject's original study medical records for verification of research procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorising such access.			
That the GCIG group will store information on samples and subjects (if subjects can be identified this should be clearly stated) and assurances that samples will be stored carefully.			
In case of transfer to another country / continent, details of where samples will be sent and any national/international legal requirements.			
Administrative			
Footer specifying the version number and/or date, and site identifier.			
Contact details for further information regarding the research, the rights of subjects and complaints regarding the research, including principal investigator and key research staff.			
Informed Consent Form			
Statement that the subject is to receive a copy of the signed and dated Subject Information and Consent Form.			
Collection / use of samples sub-divided as a, b, etc with options provided to participate in all **or** part of the research (tick boxes options provided).			
Agreement on use of material for future ethically approved research			
Option for subject to be contacted in future about participation in more research.			

Signature and date fields for participant/legally acceptable representative) and person conducting consent process (where required witness should also be included)			

Comments (continue on separate form if required):_____
_____
_____
_____

Checklist Prepared by:_____ Date:_____
(name, position)

Checklist Approved by: _____ Date:_____
(name, position)

Appendix 4 Guidebook: Essential Documents Checklist

ESSENTIAL DOCUMENTS
BEFORE STUDY STARTS

Groups	GINECO FRANCE	EORTC	AGO AUSTRIA	NSGO	SGCTG	NCIC-CTG	AGO-OVAR	MITO	MRC	GOG	J-GOG	ANZGOG
EUDRACT registration [1]	X	X	X	X	X		X	X	X			
Insurance statement [2]	X		X	X	X		X	X	X	IND Study	IND Study	
EC Approval + CA Approval [3]	X	X	X	X	X	X	X	X	X	X	X	X
Financial Disclosure statement				X			X	X				
Contract with Hosp / Site [4]	X		X	X	X	Center Activation Letter	X	X	X		IND Study	X
Investigator's contract	X	X	X	X	X		X	X		IND Study	IND Study	
Investigator Acceptance Statement [5]	X	X	X	X	X	X	X	X	X	X	IND Study	
Investigator's CV (no more than 2 years)	X	X	X	X	X	X	X	X	X	IND Study	IND Study	X
Protocol Education [6]	X		X	X	X	X	X	X	X		X	X
Delegations of duties + Sample signature sheet	X	X	X	X	X	X	X		X	IND Study	IND Study	X
LAB ranges + Accreditation	(X)			X	X	X	X		X		IND Study	X

1 EUDRACT registration : for European countries only (New Directive)

2 Exception Canada : = insurance of the centre

3 EC approval + CA approval : Ethics Comittee (IRB) / Competent Authorities

4 Not specific for us

5 Investigator Acceptance Statement : Protocol Acceptance Form / Investigator Statement

6 Protocol Education : Can be Initiation visit, Quizz, Start-up meeting, Teleconference

In bold = Mandatory for all GCIG Studies