

European Network of Gynaecological Oncological Trial Groups' Requirements for Trials Between Academic Groups and Industry Partners—First Update 2015

Andreas du Bois, MD, PhD, Alexander Reuss, Eric Pujade-Lauraine, MD, Sandro Pignata, MD, Jonathan Ledermann, MD, Antonio Casado, MD, Jalid Sehouli, MD, Mansoor Mirza, MD, Nicoletta Colombo, MD, Christian Marth, MD, Els Witteveen, MD, Jose Del Campo, MD, Paula Calvert, MD, Gerassimos Aravantinos, MD, Mehmet Ali Vardar, MD, Ate G.J. van der Zee, MD, Jacob Korach, MD, Cagatay Taskiran, MD, Mathias Fehr, MD, Ros Glasspool, MD, Jacobus Pfisterer, MD, David Cibula, MD, PhD, Ignace Vergote, MD, PhD, and On behalf of the member trial groups of the European Network of Gynaecological Oncological Trial Groups (ENGOT)

Abstract: The first version of ENGOT's Requirements for Trials Between Academic Groups and Industry Partners in Europe was published 2010. This first update integrates the experiences made by the ENGOT network and the cooperative group studies while performing, analyzing, and publishing -among others - three large phase III trials. Furthermore, progress in European legislation and its impact on clinical studies in Europe have been considered in this update process.

Key Words: Academic groups, ENGOT, Requirements, Trials

Received April 14, 2015, and in revised form Month DD, YYYY.
Accepted for publication April 15, 2015.

(Int J Gynecol Cancer 2015;00: 00–00)

The European Network of Gynaecological Oncological Trial Groups (ENGOT) is a research network of the European Society of Gynaecological Oncology, which was founded in 2007. Currently, 19 European trial groups are members of ENGOT (Appendix). As a network of European national or regional clinical trials groups, ENGOT promotes clinical trials within Europe in women with gynecological cancer. This coordination is particularly relevant not only for academic clinical trials, translational research, and research on rare diseases, but also for clinical trials in cooperation with

the industry desiring to perform multinational studies with academic groups in Europe.

The primary version of this article was a consensus document published in the *International Journal of Gynecologic Cancer* in 2010, and its recommendations have been widely adopted.¹ It has served as a blueprint for the planning of several phases II and III studies with ENGOT involvement. The manuscript has been reevaluated following further general experiences within ENGOT and the conclusion of several large randomized phase III trials that were planned and conducted based on that manuscript. The reevaluation process started during the general assembly in October 2013, and an ENGOT working group including a statistician, administrative representatives, and physicians worked on suggestions for an update. These suggestions were discussed twice in the general assembly again, and the updated manuscript was finalized. The manuscript was sent to all groups to include further modifications before being approved by the ENGOT groups.

Requirements for Trials Between Academic Groups and the Industry

European Network of Gynaecological Oncological Trial Groups, Geneva, Switzerland.

Address correspondence and reprint requests to Andreas du Bois, MD, PhD, ENGOT Office, Rue François-Versonnex 7, PO Box 1726, 1207 Geneva, Switzerland. E-mail: engot@esgo.org.

The authors declare no conflicts of interest.

Copyright © 2015 by IGCS and ESGO

ISSN: 1048-891X

DOI: 10.1097/IGC.0000000000000478

1. One protocol developed and agreed upon by the lead study group and the industry partner, reviewed, and approved by the trial steering committee.
2. Both the industry partner and the lead study group will agree on 1 common statistical analysis plan (SAP) or produce their own SAPs. In case of 2 different SAPs, the leading study group's SAP will be the basis for all academic publications.
3. One database agreed on by the lead study group and the industry partner.
4. One set of case report forms, preferably a Web site-based electronic case report form, agreed upon by the lead study group and the industry partner.
5. Sponsor: both the lead study group or industry partner may be sponsor; however, sponsorship by the lead study group should be preferred and will guarantee the highest possible credibility and independence. The sponsor has the overall responsibility as defined by the European Union Directive (2001/20/EC).
6. Monitoring:
 - a. Preferably organized by the academic group, but monitoring by industry (possibly through a contract research organization [CRO] in mutual agreement with the academic group) is allowed.
 - b. Risk-based central monitoring may be allowed over on-site monitoring, depending on the group policies of quality control and assurance, and if stated in the protocol. The financial budget available for such quality controls and legal requirements of the territories covered by each group need to be considered.
7. Database property:
 - a. Legal ownership: sponsor. The sponsor can be an industry partner or an ENGOT group (leading on behalf of all ENGOT groups recruiting into the study).
 - b. Contracts and organizational structures must ensure
 - i. that the sponsor receives all information needed for pharmacovigilance. The industry partner will maintain the global safety reporting for the drug trial database. This will contain only serious adverse events, which may be unblinded only by patient safety personnel as required for regulatory reporting.
 - ii. serious adverse events should be regularly reviewed by the steering committee and the independent data monitoring committee (IDMC).
 - iii. that neither the investigators of the ENGOT study groups nor the industry medical research team has access to data regarding study endpoints before predefined time points for analysis. In order to allow timely programming of analysis scripts, academic data management gets early access to database exports, in particular before database lock. This might be facilitated within the framework of regular database updates (cf. 7.b.v.) and should be negotiated and confirmed within the contract. The interim data analyses (eg, for IDMC) should be performed by departments/persons not involved in the study conduct if possible.
 - iv. that both the lead study group and the industry partner have the opportunity to follow any changes made in the database (cleaning, queries etc).
 - v. that the trial steering committee gets regular trial status reports.
 - vi. that the lead study group obtains quarterly updated copies of the database and in the case of double-blind trials also quarterly updates of the randomization list. The latter must be kept strictly confidential and separate from those personnel who must remain blinded to treatment groups.
 - vii. that no party provides access to the database to any third party unless after mutual agreement and in accordance with a signed contract (eg, for the European Medicines Agency or the Federal Drug Agency reporting).
 - viii. the lead study group is responsible for the publication and use of the database for educational and scientific purposes, irrespective of sponsor.
 - ix. contracts with third parties (eg, for central imaging reviews) can be made by the sponsor, in mutual agreement between the ENGOT groups and the industry partner.
- c. The database could be organized as
 - I. Option A: the database itself at the lead study group
 - i. quality assurance and certified database software
 - ii. audits by company or company assigned auditors
 - iii. transfer of database to the company for registration issues and analysis.
 - II. Option B: the database at the CRO; the CRO is contracted by the lead study group. The choice of a CRO is made in mutual agreement between the lead group and the industry.
 - i. quality assurance and certified database software
 - ii. audits by the company and by the lead study group, if deemed necessary
 - iii. installation of standard operating procedures (SOPs) for the respective protocol and information system for any violation to the sponsor
 - iv. transfer of the complete database to the lead study group for scientific analysis and to the company for registration purposes.
 - III. Option C: database at the CRO; the CRO is contracted by the company. The choice of a CRO is made in mutual agreement between the lead group and the industry. Every transfer of the database for analysis must be agreed on by the leading group.
 - i. quality assurance and certified database software with 100% tracing of any access or changes made
 - ii. audits by study group or study group-assigned auditors, if deemed necessary
 - iii. installation of SOPs for the respective protocol and information system for any violation to the lead group
 - iv. transfer of complete database for further scientific evaluations to the lead study group after final analysis of predefined endpoints
8. Statistical analysis and publication:
 - a. The lead study group is responsible for the independent analysis of the complete database for primary and secondary endpoints:
 - i. The database may be used later for further meta-analyses or subgroup analyses of or within an intergroup consortium.

- ii. The publication is the sole responsibility of the lead study group.
 - iii. The company may comment within a predefined period but cannot prohibit any publication.
- b. Intergroup trials:
- i. Each ENGOT group should receive a data set of patients recruited by the respective study group after final analysis.
 - ii. Separate analyses by 1 participating group on their included patients should not include primary or secondary objectives, and the intergroup study leading committee (steering committee) and the principal investigator should be informed about each project prior to conducting the analysis.
 - iii. Further subgroup analysis of the whole population should be prospectively discussed and agreed among the participating groups.
- c. The industry partner may perform all the analyses necessary for regulatory purposes or economic purposes.
- d. The official study report must be agreed upon by the leading study group.
- e. The company is not allowed to publish in a scientific journal or to transfer the database to any third party for scientific publishing, unless mutual agreement has been reached with the lead study group.
- f. In the publication, it should be mentioned that the trial was performed according to the principles of this document, and it should state which database property model (paragraph 7.c option A, B, or C) was assigned.
9. Non-European Countries
Institutions from non-European countries can participate; 2 models are possible:
- a. A non-European academic study group participates in the intergroup consortium (either ad hoc or as long-term cooperation partner assigned the status as privileged partner of ENGOT).
 - b. Single non-European centers may participate if they are adopted by 1 of the participating ENGOT study groups (these centers act as study group member centers), or the company is the sponsor for these centers (these centers do not have the same rights as study groups in intergroup studies).
10. Independent Data Monitoring Committee:
The IDMC is appointed by the lead study group in mutual agreement with participating groups and industry partner (applies for trials when an IDMC is needed).
11. Standard operating procedures have to be agreed upon by the study groups and the industry partner, preferably based on the leading group's SOPs (which may be modified according to the needs of the protocol); however, industry SOPs may be acceptable as basis as well.
12. A contract needs to be agreed upon between
- the industry partner and lead study group,
 - cooperating groups and lead study group, and
 - industry partner and cooperating groups.
- This contract must indicate the database property model (paragraph 7.c option A, B, or C), the role of the trial steering committee and rules for publication, presentation, and possible

press releases. Furthermore, handling of potential conflicts, for example, the wish of early stopping a trial without getting an agreement between industry partner and study groups, should be defined.

The Roadmap for the European Network of Gynaecological Trial Groups (ENGOT) Trials suggested frameworks may be beneficial when planning such cooperative trials and designing contracts and SOPs.²

Clauses mentioned within this document can be negotiated within a contract as some may not be applicable in all situations.

REFERENCES

1. Vergote I, Pujade-Lauraine E, Pignata S, et al; European network of gynaecological oncological trial groups' requirements for trials between academic groups and pharmaceutical companies. *Int J Gynecol Cancer*. 2010;20:476–478.
2. Vergote I, Elser G, Votan B, et al; on behalf of the member trial groups of the European Network of Gynaecological Trial Groups (ENGOT). Roadmap for the European Network of Gynaecological Trial Groups (ENGOT) Trials. *Int J Gynecol Cancer*. 2013;23:1339–1343.

APPENDIX: ENGOT GROUPS (Alphabetically)

Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO-Study Group, Germany),
Austrian Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO-Austria),
Belgian and Luxemburg Gynaecological Oncology Group (BGOG),
Central and Eastern European Gynecologic Oncology Group (CEGOG),
Dutch Gynaecological Oncology Group (DGOG),
European Organisation for Research and Treatment of Cancer – Gynaecological Cancer Group (EORTC-GCG),
Grupo Español de Investigación en Cáncer de Ovario (GEICO),
Groupe d'Investigateurs Nationaux pour les Etudes des Cancers de l'Ovaire (GINECO),
GROningen International Study on Sentinel nodes in Vulvar cancer, The Netherlands (GROINS),
Hellenic Cooperative Oncology Group (HECOG),
All Ireland Cooperative Oncology Research Group (ICORG),
Israely Society of Gynecologic Oncology (ISGO),
Mario Negri Gynecologic Oncology group (MANGO),
Multicenter Italian Trials in Ovarian cancer and gynaecological malignancies group (MITO),
National Cancer Research Institute (NCRI/MRC UK),
Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO),
Nordic Society of Gynaecological Oncology (NSGO),
Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK),
Scottish Gynaecological Clinical Trials Group (SGCTG),
Turkish Gynaecological Oncology Group (TRSGO).