Roadmap for the European Network of Gynaecological Trial Groups (ENGOT) Trials

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Abstract: The European Network for Gynaecological Oncological Trial groups (ENGOT) is a research network of the European Society of Gynaecological Oncology and was founded in Berlin in October 2007. Earlier, we reported on the ENGOT minimal requirements for trials between academic groups and pharmaceutical companies. In this paper, we summarize the roadmap for performing trials in the ENGOT framework. In this roadmap, we define how an ENGOT trial should be set up and discuss the following items: What are the conditions to classify a study as an ENGOT trial? What is an ENGOT protocol? How are an ENGOT protocol, informed consent (ICF), and case report form (CRF) produced? How is the center selection and feasibility performed in ENGOT trials? How are regulatory and operational tasks handled? How should a confidentiality agreement between the industry and the whole ENGOT network be negotiated? How are contracts made between the industry and ENGOT and between ENGOT groups? How are funding, insurance, and communication flow arranged in ENGOT trials? What are the requirements for conducting substudies and what are the tasks for the leading group in an ENGOT trial? A template of a confidentiality agreement, a checklist of ENGOT criteria for new study proposals, and guidelines for authorship are also provided.

Key Words: ENGOT, Clinical trials, Gynecologic oncology, Trial, Management, Academic

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The European Network for Gynaecological Oncological Trial groups (ENGOT; Table 1) is a research network of the European Society of Gynaecological Oncology and was founded in Berlin in October 2007. Earlier, we reported on the ENGOT minimal requirements for trials between academic groups and pharmaceutical companies.[1] In this paper, we summarize the roadmap for performing trials in the ENGOT framework.

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1. What are the conditions to classify a study as an ENGOT trial?
   - There is an ENGOT lead group
   - Preference to join the study will be given to other ENGOT groups.
   - It is possible for groups who are not part of the ENGOT collaboration to join an ENGOT trial.
   - What if other non-ENGOT isolated centers wish to join the study? This is possible (see ENGOT minimal requirements for a trial[1]).

However:

1. Most of the centers and the recruited patients are estimated to come from ENGOT group centers. This is not necessarily applicable for academic studies (ie, those without industry partner as sponsor).
2. Other centers should be approved by the ENGOT lead group or adopted by one of the participating ENGOT groups.
3. Flexibility on both requirements 1 and 2 is possible.

TABLE 1. European Network of Gynaecological Oncological Trial Groups (alphabetically arranged)

Arbeitsgemeinschaft für Gynäkologische Onkologie Studiengruppe (AGO),
Austrian Arbeitsgemeinschaft für Gynäkologische Onkologie (A-AGO),
Belgian Gynaecological Oncology Group (BGOG),
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),
Hellenic Cooperative Oncology Group (HECOG),
All Ireland Cooperative Oncology Research Group (ICORG),
Mario Negri Gynecologic Oncology Group (MaNGO),
Multicenter Italian Trials in Ovarian Cancer and Gynaecological Malignancies Group (MITO),
National Cancer Research Institute (NCRI),
Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO),
Nordic Society of Gynaecological Oncology (NSGO),
Scottish Gynaecological Clinical Trials Group (SGCTG),
Turkish Gynaecological Oncology Group (TGOG).

- In principle, it will not be possible to run a trial without the cooperation of the local ENGOT group in one of the countries represented in ENGOT. However, if isolated centers affiliated to the local ENGOT group want to do the study *and* there is approval of the local ENGOT group, this might be possible.
- If a national or regional ENGOT group is performing a study in cooperation with the industry, it is not possible for individual non-ENGOT institutions from that country or region to join the study outside the ENGOT collaboration.
- There should be at least cooperation between 2 ENGOT groups to call a trial an ENGOT trial.
- In principle, the principal investigator should be appointed by the leading ENGOT group. However, in exceptional circumstances, ENGOT can decide to accept a principal investigator not belonging to ENGOT.

2. How is the center selection and feasibility performed in ENGOT trials?
   - When an ENGOT group is represented in a country and an interest in the trial has been expressed, the trial should be coordinated with the ENGOT group in that country. The ENGOT requirements should be discussed first before the collaboration between the ENGOT groups and an industry partner (technical or other).
   - Early global discussion on the maximum number of sites and number of patients per trial per ENGOT group and per country is recommended.
   - The lead ENGOT group should receive, as a minimum requirement, a letter of intent (LOI) from the industry partner, which details and ensures costs for all participating groups (or with each group before center selection).
   - Technical requirements for the centers (described upfront as clear as possible, eg, imaging techniques, e-CRF . . .) should be available before center selection.
   - Final responsibility for center selection belongs to the ENGOT group in each country or region. Nonacceptance of centers should be discussed and agreed upon by the groups and the industry partner.
   - Minimal requirements of center selection are:
   - Center agrees to collaborate with the group.
   - Center has staff with clinical trial experience; adequate staffing resources: aside from investigator, the center also has a study coordinator or study nurse to handle documentation and organization of the study.
   - Center is willing to conduct clinical trials according to the protocol and the principles of International conference on harmonization good clinical practice (ICH-GCP), local rules and regulations including documented GCP training (as applicable).
   - Center has the adequate infrastructure resources (laboratory, radiology, etc.) to conduct the trial according to the protocol (*to be defined per protocol*).

3. How are contracts made between the industry and ENGOT and between different ENGOT group?
   1. Initially, an LOI describing the development of the protocol discussion should be in place. This could be an independent contract or an LOI with the specific tasks documented. It should be mentioned that the ENGOT group name should appear in every presentation and publication.
   2. Minimal requirements for the contract between the lead ENGOT group and the industry partner are:
      - Ownership and publication rights for trials between academic groups and industry partners should be mentioned in the main contract between the lead ENGOT group and the industry partner based on the chosen model of collaboration.[1]
      - The clinical study database should be the property

of the lead ENGOT group and in case of option C[1] of the industry partner as well.
- When the industry partner is the sponsor, the industry partner will have the ownership of arising intellectual property and patentable inventions, whereas the participating ENGOT groups (and the lead group in particular) will have the right to use and publish the results for academic purposes and for the planning of further trials.
- Collaborative groups can have access to their specific national subsets to allow them to use that data for national-level research (eg, epidemiology).
- Roles & responsibilities, as well as obligations & duties of each contract partner should be described clearly.

3. Further contracts:
   - Intergroup agreements to be signed between the lead ENGOT group and the cooperating groups.
   - Center contracts are preferably signed between the cooperating group and their centers directly. These may eventually be cosigned by the industry partner or their delegate.
   - The contract between an ENGOT group and the center should include data ownership, publication rules, and intellectual property, if applicable.
4. Funding of an ENGOT trial
   - Discussion should start as early as possible in the negotiations.
   - The lead ENGOT group will investigate the amount required by each cooperative group to commence the trial in their area.
   - The funding will be centrally negotiated by the lead ENGOT group after negotiation with the other ENGOT groups (each cooperating group can decide how their funds will be spent depending on their specific requirements).
   - Sponsorship is separate from clinical trials insurance. Each cooperating group should obtain insurance or indemnity for all of the trials that they are collaborating in.
5. Requirements for conducting sub-studies in an ENGOT trial

The main results of the study will be the responsibility of the trial writing committee, which will have input from the study investigators, biostatisticians, data management, and (if appropriate) clinical epidemiologists. However, after the final analysis has been performed, interested cooperating groups can seek to use the data or human biological materials to generate new hypotheses and/or explore relationships between clinical, biomarkers, quality of life, and patient-related characteristics and outcomes.

The following principles are proposed to ensure that appropriate substudies are undertaken on behalf of the group together with a high quality of statistical analysis and a balanced interpretation of the results:

The steering committee of the main study as a whole or a working group set up by the steering committee for this

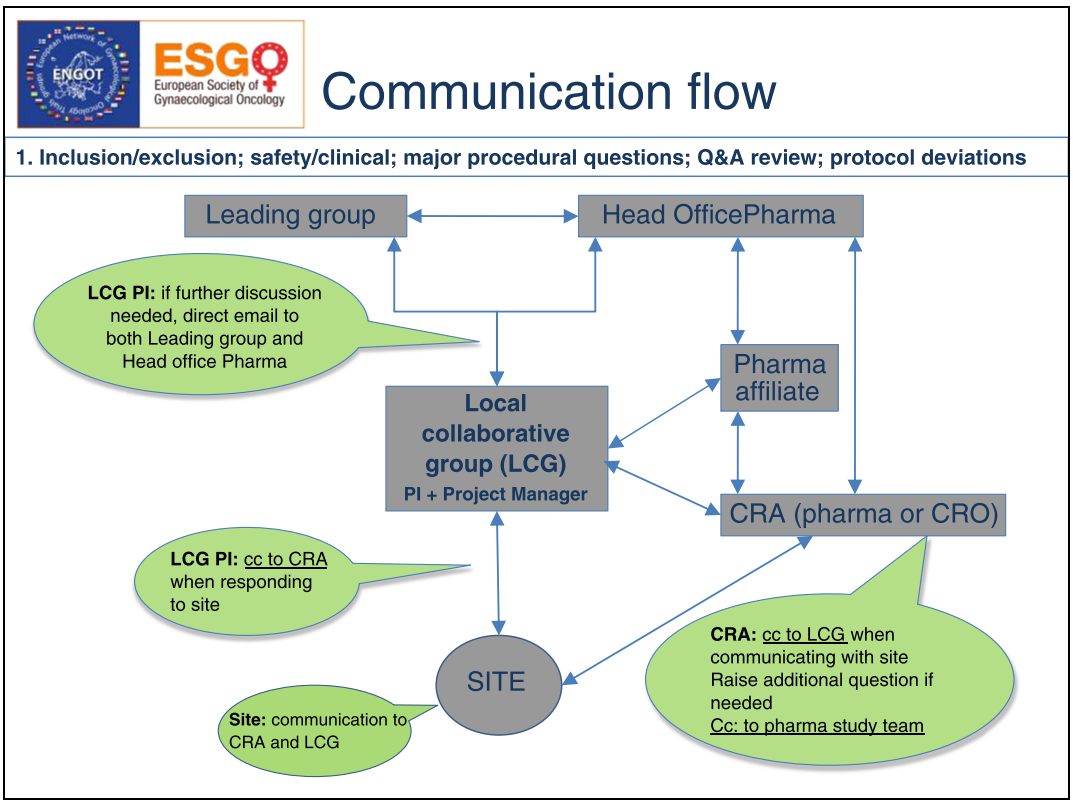

FIGURE 1. Communication flow for inclusion/exclusion; major procedural questions; questions/answers review and protocol deviations.

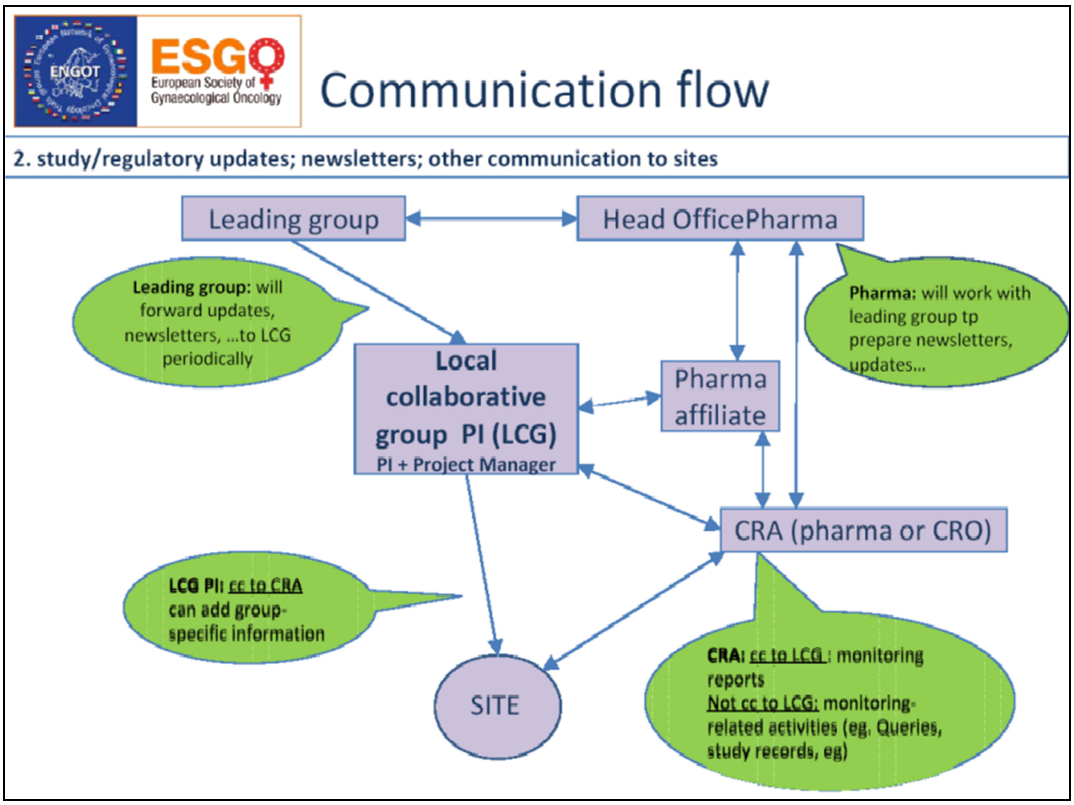

FIGURE 2. Communication flow for study/regulatory updates, newsletters, and other communications to centers.

FIGURE 3. Communication flow for intergroup communication between leading ENGOT group and local ENGOT groups.

purpose will decide whether a substudy is appropriate. The steering committee or working group will review all proposals and evaluate the feasibility of the substudy. The methodology and analysis plan should be agreed on before granting the material.

1. Close collaboration between the lead statistician and the subproject must be established.
2. Draft/final manuscripts will be made available through this substudy committee to the trial management committee or group for comment and approval before submission for publication.

6. Communication flow

Guiding principles:

- Communication flow should be discussed upfront between the lead ENGOT group and the industry partners.
- Strong intergroup communication between the lead ENGOT Group and local collaborative group (LCG) should exist.
- If queries arise, the participating centers and clinical research assistants should first consult with the relevant LCG.
- The LCG should be the primary contact for protocol eligibility questions, avoiding deviations, safety/clinical questions and recruitment strategies, etc. Deviations should always be discussed with the principal investigator of the lead group and the medical monitor of the study.
- The group PI may delegate to other LCG representatives or industry partner. The LCG and the CRA should be copied into all correspondence with the centers.
- Roles and responsibilities between the affiliates and the local groups should be clearly defined.
- Local project management has to be done by the groups in agreement with the affiliate.
- Regular teleconferences are to be planned.
- Updates and newsletters should be distributed by the lead ENGOT group to the LCG and then from the local group to the centers (if appropriate, in agreement with the industry partner).
- Medical queries should be first sent to the LCG and the industry partner- recommendation to put Questions & Answers log on a website (eg, on lead ENGOT group website or study-specific website).
- Information flow on Serious Adverse Events/Suspected Unexpected Serious Adverse Reactions to LCGs should be defined.
- It is recommended to build up a communication flow according to Figures 1–3.

The complete roadmap for ENGOT trials including also guidelines on an ENGOT protocol, informed consent form, regulatory issues, operational tasks, insurance, authorship, case report forms, tasks for the lead group, a template of a confidentiality agreement, and a checklist of criteria for new study proposals can be downloaded at http://www.esgo.org/Documents/ENGOT_Roadmap_for_trials_version01.06.12.pdf

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