

Joint ENGOT and GOG Foundation requirements for trials with industry partners

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HIGHLIGHTS

- The European Network of Gynaecological Oncological Trial Groups (ENGOT) and The GOG Foundation present for the first time the joint requirements for trials with industry.
- Guidelines are presented for sponsorship, trial steering committee, and development of a protocol, database, and statistical plan.
- A roadmap is presented for site selection, contracts, press releases, publications, and a communication plan.

These guidelines were developed by The European Network of Gynaecological Oncological Trial Groups (ENGOT) and The GOG Foundation and are published jointly in *Gynecologic Oncology* and the *International Journal of Gynecological Cancer*. The European Network of Gynaecological Oncological Trial Groups (ENGOT) is a research network of the European Society of Gynaecological Oncology (ESGO), which was founded in 2007 and published earlier its requirements for studies with industry and a roadmap for ENGOT studies.^{1–3} The GOG Foundation, Inc. (GOG-F) is non-profit 501(c)³ corporation based in the District of Columbia, USA, which serves as the organizational body for the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP)-funded NRG Oncology and GOG-Partners (GOG-F industry) trials. The legacy Gynecologic Oncology Group cooperative group was established in 1969 and held its first official meeting in 1970 under the guidance and support of the US NCI.⁴ In 2010, the NCI announced its intention to restructure and consolidate the cooperative group system for federally funded research following a study by the Institute of Medicine (IOM) highlighting efficiencies and cost reduction. This process led to the consolidated group, NRG Oncology Foundation, Inc. ('NRG Oncology'), formed in 2011 by the National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG) to conduct federally-funded government research; NRG Oncology Philadelphia East is the branch of this group, which houses the legacy GOG cooperative group. To avoid confusion of the new groups at that time, the corporate name 'Gynecologic Oncology Group

Inc.' was changed to The GOG Foundation, Inc. (GOG-F), and its industry-sponsored trials are conducted under the brand name of "GOG-Partners". The GOG-Foundation, Inc. is the non-profit organization collectively bridging NRG Oncology and GOG-Partners. The GOG Foundation has designated GOG Partners to oversee non-CTEP funded investigative ventures, including collaborative functions with ENGOT.

The ENGOT and GOG-F Liaison Committee was created in June 2016 to provide a venue where discussion of the best research framework whereby resources, with patients being the most important, would be most effectively engaged in order to best strategically answer key clinical and scientific questions that advance the care of women afflicted with gynecologic malignancies. In the past, a number of studies have been duplicative, and efforts were poorly coordinated in different regions of the world. This liaison committee was created to address these issues via improved communication and coordination. The mission of the ENGOT/GOG-F Liaison Committee is to promote communication between ENGOT and GOG-F, to provide transparency, and to discuss potential ENGOT-GOG-F collaborations early in the negotiation process with industry partners (ENGOT/GOG-F Model A, B or C studies),^{1–3} as well as for academic studies with ENGOT (ENGOT Model A) or GOG-F serving as the sponsor. This liaison committee will help to determine which organization, ENGOT or GOG-F, will lead a particular trial, pending approval by the ENGOT Steering Committee and GOG-F leadership, and it will strive to create a fair balance between ENGOT and GOG-F led-trials in the future based on which group was first involved in the

study, origin of concept, and other agreed on factors. This liaison's goal is to build trust and solidarity, while enabling efficiencies for trial investigators, industry partners, and other relevant research stakeholders.

The current ENGOT and GOG-F draft statement was approved by the General Assembly meeting of ENGOT and GOG-F leadership in the spring of 2018, and supports the earlier ENGOT statements.¹⁻³ In short, for ENGOT and GOG-F studies there will be one protocol developed and agreed on by the organizations and administered by the lead study group, one statistical plan with simultaneous analysis of the primary endpoint by the sponsor and the lead study group (models B and C, see below and 1-3),¹⁻³ one electronic case report form (CRF), and one database approved by the lead study group. The sponsor can be the an academic or cooperative group member (model A or B) or an industry partner (model C). In model A, the database resides with, and is owned by, the lead study group. In model B, the database resides at a contract research organization (CRO) but owned by the lead study group (which is also the sponsor). In model C, the database resides at a CRO, and the CRO is contracted by the industry partner (sponsor). The choice of a CRO is made by mutual agreement between ENGOT and GOG-F, and the industry partner. The lead study group is responsible for the independent analysis of the complete database for primary, secondary, exploratory, and translational endpoints and the database may be used later for further meta-analyses or subgroup analyses of the study group or within an intergroup consortium. The publication is the responsibility of the Trial Steering Committee (TSC), and authors are appointed according to publication rules outlined below. According to these publication rules, ENGOT and GOG-F will appoint authors, where the number of authors will be largely related to the number of patients accrued per group following the order outlined below. Each ENGOT group and GOG-F should receive a dataset of patients recruited by the respective study group after final analysis. Further subgroup analysis of the whole population should be prospectively discussed and agreed on within the TSC. In each publication, it should be referenced that the trial was performed according to the principles of this document, and it should specify which model (A, B or C) or design was utilized. Monitoring can be done by the lead study group, but monitoring by the industry partner (through a CRO in mutual agreement with the lead study group) is also allowed. The Independent Data Monitoring Committee (IDMC) is appointed by the lead study group and the industry partner in mutual agreement (applies for trials when an IDMC is needed). The industrial partner is not a member of the IDMC. When biological samples are required in a study, the informed consent and master contract should stipulate that residual samples will be transferred to the lead study group for future additional translational research.

In addition to the above summarized statements, ENGOT and GOG-F want to add:

a. Sponsorship

The sponsor can be the industry partner or the lead study group. If a lead study group is the sponsor, ENGOT will serve as the sponsor for ENGOT-led studies through its lead ENGOT group, and GOG-F will serve as the sponsor for GOG-F led studies.

Many studies will include an investigational agent, which generally requires a sponsor-filed Investigational New Drug (IND) application with the US Food and Drug Administration (FDA). If the lead study group is serving as the sponsor, the lead study group will need to file and hold the IND, and will be responsible for IND reporting.

b. Trial Steering Committee (TSC)

The TSC will have the opportunity to review and provide feedback on protocol, database, statistical plan and CRF development. The Steering Committee may propose additional analyses with final approval by the industry partner.

In ENGOT led studies, the ENGOT lead study group will appoint the chair of the TSC and appoint the Principal Investigator (PI) of the study, while in GOG-F led studies, GOG-F will appoint the chair of the TSC and the PI. The number of TSC study group representatives will be proportional to the anticipated number of sites (or the planned number of patients, if the recruitment plan has been finalized and the anticipated number of patients to be accrued by each group is defined). For organization and representation, ENGOT will elect one group member as its representative lead on behalf of ENGOT. This group member will represent ENGOT during all negotiations with GOG-F and sponsors. The other ENGOT groups will be participating cooperative groups in the study. Other cooperative groups outside ENGOT and GOG-F can be members of the TSC. Industry partners can participate in the TSC as well.

Recommendations of the TSC, especially on early closure of a trial, should be formally and accurately presented in the minutes in order to be used for internal and external discussions, for example, with regulatory authorities. The sponsor should respond point by point to the TSC recommendations, which will be documented. These points should be stated in the master contract with the lead study group.

c. Protocol, database, case report form (CRF), and statistical data plan development

The lead study group will be primarily responsible with the industry partner for development of the protocol including the database, statistical plan, and CRF. Preferentially, the contributing organization will be engaged in the protocol development as well. A summary of key data elements (standardized report format) together with a full database copy that coincides with pre-determined database locks will be shared between the organizations. In model C, the pharmaceutical company can also maintain an internal database rather than use a CRO database.

d. Clinical Research Organization (CRO) selection

Industry can establish a relationship with a CRO for a study after mutual agreement with the lead study group. Furthermore, the infrastructure and experience of the local/national ENGOT groups and GOG-F should be considered, and the agreement may be modified accordingly. It will be encouraged that discussions with industry regarding CRO selection occur with the lead study group (or both ENGOT and GOG-F) before contract award to enable a clear overview of regulatory intent.

e. Site selection, study start-up and monitoring

The industry partner will negotiate with each ENGOT group in Europe and GOG-F in the USA regarding study start up, monitoring, and data management services to be provided by their respective regions. GOG-F will serve as the central negotiating

body for its member sites. No US sites outside of the GOG-F network will be involved in the trial, but if new sites are interested, they will be vetted by GOG-F for membership. Within Europe, this will be performed in close collaboration with the ENGOT lead study group and other ENGOT members. ENGOT lead study group and GOG-F will negotiate the number of sites and groups with the industry partner. Site selection in Europe is done per country after mutual agreement between the industry partner and the local ENGOT group. Site selection in the USA will be done following review of interest, past performance, and patient/trial availability.

f. (S)AE's review

Details of AE review (blinded and unblinded) will be defined within the IDMC Charter and Steering Committee Charter.

g. Contracts

In general, we prefer one master contract for ENGOT and one master contract for GOG-F (industry partner and lead study group) together with multiple sub-contracts. The high-level items (database, TSC charter, publication rules, IDMC, transfer of samples) must be covered in the master contract.

h. Press releases

Any results should be analyzed and approved by the TSC before press-release, first presentation, and publication. The statistical analysis of the primary endpoint should be done simultaneously by the statisticians of the lead study group and the industry partner. Press releases in the USA are mandated by the Securities and Exchange Commission (SEC) for publicly-traded corporations whenever a primary endpoint analysis has been performed. Statistical analysis at the lead study group and CRO (or pharmaceutical company) must be done simultaneously and approved by the industry partner and the lead study group. At a minimum, ENGOT and GOG-F should be quoted in the press release. In the master contract, the mandatory SEC (and EU) requirements will be stipulated, but will also include the mandatory requirements of independent simultaneous statistical analysis.

i. Publications

It is acknowledged that each organization (ENGOT and GOG-F) has a publication policy that governs the distribution and number of authors for the clinical trials in which they participate. Authorship in ENGOT-GOG-F clinical trials will generally follow the ENGOT guidance documents, reflecting patient accrual and leadership in protocol development and its conduct. The proportion of authors in the publication stream will reflect the actual accrual contribution as a whole at accrual closure; the appointment of specific authors within this allotment from each group will follow the publication policies of the respective group. This will allow ENGOT and GOG-F to adjust authorship based on additional factors such as intellectual contribution, mentorship, junior-PI development, and other strategic factors, in addition to accrual. The lead study group PI would normally serve as first author and this position, as well as the trial statistician, would not count in the calculation of authors per group. The contributing study group would likewise assign their PI, who would get the second highest prominent authorship position (eg, second or senior author, or in exceptional cases of equal scientific and enrollment contribution, co-first and/or co-senior) if the group is the best or second best recruiting group, or if arrangements are made otherwise. The author number will reflect the max-

imal number allowed by the intended publication journal; the positions of prominence (first, last) will be adjudicated based on the desired contribution of each group and where possible and appropriate be co-represented by individuals from both groups (if ENGOT and GOG-F are the two largest groups in accrual of participants in this trial). All other authorship positions granted to ENGOT will be distributed to the ENGOT groups according to the ENGOT publication rules and will reflect proportional accrual. Co-authorship positions of a potential industrial sponsor (not a study group) will be foreseen and vetted on a case by case basis by the TSC. For ENGOT-led studies, the ENGOT lead study PI (chair of the TSC) will present and publish the primary analysis as first author. For GOG-F led studies, the GOG-F will select the person who will present and publish the primary analysis as the first author.

j. Communication plan

Communication (eg, newsletters) to the US sites will be done through GOG-F. For ENGOT sites this will be done via the ENGOT member lead study group and the other ENGOT groups.

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