Determining post-operative morbidity and mortality following gynecological oncology surgery: protocol for a multicenter, international, prospective cohort study (Global Gynaecological Oncology Surgical Outcomes Collaborative—GO SOAR)

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ABSTRACT

Background The Global Gynaecological Oncology Surgical Outcomes Collaborative (GO SOAR) aims to develop a network of gynecological oncology surgeons, surgical departments, and other interested parties that will have the long-term ability to collaborate on outcome studies. The protocol for the first collaborative study is presented here.

Primary Objective To evaluate international variation in 30-day post-operative morbidity and mortality following gynecological oncology surgery between very high/high and medium/low human development index country settings.

Hypothesis There is no variation in post-operative morbidity and mortality following gynecological oncology surgery between very high/high and medium/low human development index country settings.

Study Design International, multicenter, prospective cohort study. Patient data will be collected over a consecutive 30-day period through gynecological oncology multidisciplinary teams/tumor boards and clinics across different human development index country groups. All data are collected on a customized, secure, password protected, central REDCap database.

Major Inclusion/Exclusion Criteria Inclusion criteria include women aged ≥18 years undergoing elective/emergency, curative/palliative surgery for primary/recurrent tubo-ovarian/peritoneal, endometrial, cervical, vulval, vaginal, gestational trophoblastic malignancies. Surgical modality may be open, minimal access (laparoscopic/robotic), or vaginal.

Primary Endpoint 30-day post-operative morbidity and mortality defined as per Clavien-Dindo classification system.

Sample Size 1100 (550/arm).

INTRODUCTION

In 2018 globally, the prevalence, incidence, and mortality of gynecological oncology cancers (cervix, endometrial, tubo-ovarian, vulval, vaginal) were 25.18 per 100 000 (954 439 cases), 29.35 per 100 000 (1 309 165 cases), and 13.03 per 100 000 (609 377 cases), respectively. Gynecological cancers collectively, after breast cancer, account for the second greatest disease burden among all female cancers, and by the year 2040 incidence is set to rise by 69%. Annually, 45% of all individuals diagnosed with cancer undergo surgery with curative intent. This amounts to 589 124 cases per annum of gynecological cancer surgery worldwide. Hence, due to the current and growing disease burden of gynecological malignancies, surgical care for gynecological malignancies is an indispensable component of a functioning health system.1-4 However, surgery has historically had a disproportionately low profile in global health priorities at the WHO due to the erroneous perception that it is a high cost intervention benefiting a small segment of society. The recent interest in surgical outcomes has been prompted by the recognition that conditions amenable to surgery such as gynecological malignancies are important public health conditions.
Clinical trial

and that there are disparities in access to life saving and disabil-
ity preventing surgeries particularly for rural and marginalized
populations in medium/low human development index countries
representing unmet surgical needs. The WHO and the World Bank
have highlighted surgery as an important component for global
health development.3 However, surgical care requires coordination
of skilled human resources, specialized supplies and infrastruc-
ture including multicentered, international collaborations for the
purpose of research to inform international policies.4 It is estimated
that <25% of patients with cancer have access to safe, affordable,
and timely surgery. While death rates from cancer are decreasing
in very high/high human development index countries, the opposite
is true in medium/low human development index countries and up
to 1.5% gross domestic product is lost because of cancer in some
medium/low settings.5 6

Despite 45% of women with gynecological malignancies
receiving surgical care with curative intent, safety and quality of
care remain poorly measured and a low priority in many medium/
low human development index countries. In addition, there is a lack
of standardized gynecological oncology surgical data globally and
a shortage of patient level data. Gynecological oncology surgical
outcomes data are not located or reported in any standardized way
and require information to be compiled from multiple agencies,
ministries, health reports, and published literature, as there is no
central source for collecting or reporting. In addition, collected data
do not take into account country specific epidemiological factors.

Detecting variations associated with outcomes following gyneco-
logical oncology surgeries, and modifiable practices associated
with these variations, are likely to act as surrogate markers for best
performance of gynecological oncology surgical units.7 8 Globally
relevant risk factors for variations in outcomes relate to the training
of the operating surgeon, availability of investigations, use of safety
checklists, equipment, and access to critical care facilities.9 11

A prospective audit of surgical outcomes following gynecological
oncology surgery in the UK (UKGOSOC: United Kingdom Gynaeco-
logical Oncology Surgical Outcomes and Complications),12–14 a very
high human development index country, may lack relevance and
comparability in medium/low human development index countries
or indeed other very high/high human development index countries
which do not have a nationalized government funded healthcare
system but private healthcare. While the GlobalSurg collaborative
has set up a consortium of general surgeons investigating surgical
outcomes following general surgery, this has not included gyneco-
logical oncology.

The Global Gynaecological Oncology Surgical Outcomes Collabor-
ative (GO SOAR) aims to supplement the WHO Global Initiative for
Emergency and Essential Surgical Care by providing risk adjusted
patient level outcome data to advise human development index
country group specific policy formation and develop educational
resources to reduce morbidity and mortality from gynecological
oncology surgery, thereby addressing an urgent unmet need
within gynecological oncology. In addition, GO SOAR will develop
a network of gynecological oncology surgeons, surgical departments,
and other interested parties that will have the long-term ability to
Collaborate on future outcome studies, including randomized trials.
Widespread provision of protocols and supporting educational
materials will empower individual practitioners to participate and
will facilitate audit and research capacity building in regions that
currently lack local opportunities for development.

We present the protocol for the first GO SOAR collaborative
study (GO SOAR1) which evaluates international variation of post-
operative morbidity and mortality rates following gynecological
oncology surgery between country groups defined by human
development index. The full protocol has also been registered at
https://clinicaltrials.gov/ct2/show/NCT04579861 (ClinicalTrials.gov
registry: NCT04579861).

Our hypothesis is that there is no variation in morbidity and
mortality following gynecological oncology surgery among human
development index country groups.

METHODS

Study Design

Study design is that of an international, multicenter, prospective,
observational, cohort study. There are 100 sites planned (nine
currently active and an additional 56 participating sites currently
in the set up phase). Sites may register to join the study using the
following link: https://redcap.abdn.ac.uk/surveys/?s=NFFCAE4FTX

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Medtronic; Karl Storz.

Participants

Inclusion criteria include women aged ≥18 years undergoing cura-
tive, curative attempted but then abandoned (open/close lapa-
rotomy) or palliative surgery for primary or recurrent tubo-ovarian/
peritoneal, endometrial, cervical, vulval, vaginal, gestational troph-
oblastic malignancies. Surgical modality may be open, minimal
access (laparoscopic/robotic), minimal access converted to open,
or vaginal. Both elective and emergency cases are included.
Surgeries where pre-operative pathology was thought to be benign
but malignancy was subsequently confirmed on histopathology
post-operatively are also eligible.

Objectives

The primary objectives are to evaluate international variation in
post-operative morbidity and mortality rates following gynecological
oncology surgery between country groups defined by the human
development index. This is a composite index of life expectancy,
education, and per capita income indicators, used to rank countries
into four tiers of human development: very high, high, medium, low.
Secondary objectives include intra-operative morbidity/mortality
and histological clearance rates following cytoreductive surgery,
and to identify human development index group specific modifiable
surgical processes associated with best care taking into account
resource availability/infrastructure.

Endpoints

Primary endpoints are 30-day post-operative morbidity/mortality
defined as per the Clavien-Dindo classification system.15 Secondary
endpoints include intra-operative morbidity/mortality, tumor clear-
ance, and comparison of current practice against selected tumor
specific audit standards derived (where available) from the Euro-
pean Society of Gynaecological Oncology guidelines for the diag-
nosis, investigation, and management of gynecological cancers
(Box 1).
Clinical trial

Site Selection Strategy
To ensure surgical outcome data collected are representative of care received in each country, attempts will be made where possible to recruit large/medium/small centers performing gynecological oncology surgery in a 1:1:1 ratio. Centers will be defined according to surgical caseload as follows: large >150, medium 75–149, small ≤74 new surgical gynecological cancer cases per annum. Large center threshold of >150 was set as per European Society of Gynaecological Oncology training center accreditation criteria.

Patient data will be collected over a consecutive 30-day period through gynecological oncology multidisciplinary teams/tumor boards and clinics across different human development index country groups. This collaborative model for a snapshot clinical audit is well established. It is vital that all patients operated on during the consecutive 30-day period are entered onto the database. Data will not be presented at the level of individual surgeon/site. Additional data entry (beyond 30 days) is encouraged and may take place at the discretion of the participating site. All patients are followed up as per local protocols for 30 days post-operatively to identify post-surgical morbidity/mortality. In the absence of established local follow-up protocols, at the very minimum, a telephone call to the patient within the 30-day follow-up period from surgery is required to capture morbidity data (Figure 1).

Data Quality and Validation
To ensure high data quality, a detailed protocol has been produced and published online (https://clinicaltrials.gov/ct2/show/NCT04579861). Collaborators are encouraged to perform data input in real time using the REDCap system. Data quality rules built into the REDCap database will also ensure data quality and highlight disparities in data fields to the local collaborator for review. Training is available to collaborators prior to the commencement of data collection and entry.

Data validation is completed in three stages across a representative sample of centers. First, centers self-report key processes used to identify and follow-up patients. Second, independent validators locally not part of the recruiting teams quantitatively report case ascertainment and sampled data accuracy. Third, local teams are interviewed by the central coordinating team to qualitatively assess collaborator engagement and data collection processes.

Box 1  Tumor specific measurable audit standards

Ovarian
- Surgery performed by a gynecologic oncologist or a trained surgeon specifically dedicated to gynecological cancer management
- Treatment planned and reviewed at a multidisciplinary team meeting

Endometrial
- Complete macroscopic cytoreduction and comprehensive staging is recommended in advanced endometrial cancer
- Multimodality management should be considered for the treatment of advanced endometrial cancer when surgery may significantly impair vaginal function

Cervical
- Surgery performed or supervised by a certified gynecologic oncologist or a trained surgeon dedicated to gynecological cancer
- Treatment discussed at a multidisciplinary team meeting

Vulval
- Surgery performed or supervised by a certified gynecologic oncologist or a trained surgeon dedicated to gynecological cancer
- Treatment discussed at a multidisciplinary team meeting

Vaginal—in the absence of international guidelines on surgical management, the following is proposed:
- Surgery performed or supervised by a certified gynecologic oncologist or a trained surgeon dedicated to gynecological cancer
- Treatment discussed at a multidisciplinary team meeting

Gestational trophoblastic malignancies—in the absence of international guidelines on surgical management, the following is proposed:
- Surgery performed or supervised by a certified gynecologic oncologist or a trained surgeon dedicated to gynecological cancer
- Treatment discussed at a multidisciplinary team meeting

Figure 1  Study flowchart. FIGO, International Federation of Gynecology and Obstetrics; GO SOAR, Global Gynaecological Oncology Surgical Outcomes Collaborative.
Clinical trial

Sample Size
While there is a paucity of data on morbidity and mortality following gynecological oncology surgery in medium/low human development index country settings, data for very high/high human development index country settings suggest morbidity is 26% and mortality 2%. Using this as a baseline, a sample size of 1100 (550/arm) inflated by 20% to account for missing data and loss to follow-up, at 90% power, \( \alpha = 0.05 \), will be able to determine a 10% point difference in 30-day post-operative morbidity and mortality following gynecological oncology surgery between very high/high human development index countries and medium/low human development index country settings.

Statistical Methods
Baseline characteristics will be calculated using descriptive statistics. Appropriate statistical tests will be used for analyses. \( \chi^2 \) tests will compare categorical variables, and t-test (parametric) and Mann-Whitney (non-parametric) tests will compare continuous outcome variables between groups. Random effects models adjusted for covariates/confounders will be used to compare outcomes between human development index groups over time. Progress on data collection and summary statistics will be reported to the international steering committee at their regular meetings. Analysis of the full data set will be undertaken at the end of the study.

DISCUSSION
The GO SOAR Collaborative plans to implement a series of internationally collaborative studies. This protocol describes the first GO SOAR collaborative study which is a multicenter, prospective cohort study evaluating international variation in post-operative morbidity and mortality following gynecological oncology surgery between human development index country groups.

The WHO’s analysis of excess surgical mortality established three significant findings. First, surgical interventions take place on a massive and previously unrecognized scale in all countries and resource settings. Second, the inequity in service provision among countries and settings is dramatic. Third, little is known about the indications for, quality, safety, and outcomes of surgical care. While the GlobalSurg Collaborative has made headway investigating these issues within the context of general surgery, for gynecological oncology there is a paucity of comparable international data across different human development index country groups on surgical outcomes. The first GO SOAR study aims to generate data to help fill this knowledge gap. Despite the likely increased risk of morbidity and mortality for patients undergoing gynecological oncology surgery in medium/low human development income country settings, robust, empirical data are currently unavailable. Additionally, in countries with limited resources, the applicability of gynecological oncology surgical guidelines is yet to be tested. By using a collaborative model and a 30-day snapshot data collection period, our study will recruit sufficient patients to measure this, while avoiding over burdening low resource centers that may otherwise be unable to participate. Investigating the morbidity and mortality caused by gynecological oncology surgery globally, this study will provide a platform to build future quality improvement programs and interventional trials. A detailed study protocol, training, data quality control, and validation will ensure standardization to deliver a reliable and accurate data set. This study will be delivered using an international multidisciplinary collaborative network of healthcare researchers and clinicians.

The four key mandates of the GO SOAR Collaborative are to: (1) set the research agenda through research prioritization in gynecological oncology; (2) gather high quality data via a centralized database accessible to all sites that perform gynecological oncology surgery; (3) build sustainable international research by producing protocols/guidelines; and (4) train the researchers and leaders of tomorrow by providing open access to all GO SOAR training materials. In combination, this in turn will help provide safe and effective surgical care in gynecological oncology globally.

The GO SOAR international database will help standardize surgical outcome reporting. Standardized reporting renders comparable data across different healthcare systems for more extensive research and analysis. The international database will also allow all participating centers/units performing gynecological oncology surgery to audit their local practice and implement local changes while at the same time contribute patient level data reported using standardized electronic forms for use in global GO SOAR studies which will help inform and drive policy change internationally.

Often research in gynecological oncology takes place within very high/high human development index country settings with outcomes difficult to reproduce and recommendations difficult to implement in medium/low human development index countries with limited resources. Inclusion of medium/low human development index country partners are vital to be able to identify context specific solutions and to ensure high quality surgical care in a low resource setting.

In conclusion, the GO SOAR Collaborative aims to improve surgical outcomes through collaborative research. It will provide risk adjusted patient level outcome data collected via a centralized database to advise human development index country group specific policy formation.

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**Ethics approval** The study has been approved and registered with the Quality Improvement & Assurance Team (QAT) at NHS Grampian (project ID 5009), UK.

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