Global evaluation and outcomes of cholecystectomy
NIHR Global Health Research Unit on Global Surgery

DOI:
10.1136/bmjopen-2023-079599

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Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Link to publication on Research at Birmingham portal

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Global evaluation and outcomes of cholecystectomy: protocol for a multicentre, international, prospective cohort study (GlobalSurg 4)

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ABSTRACT

Introduction Cholecystectomy is one of the most common operations performed worldwide. Although laparoscopic surgery has been the ‘gold-standard’ approach for this operation, there is a paucity of global evidence around the variations of safe provision of cholecystectomy, including low-income and middle-income countries. This international collaborative study will allow contemporaneous data collection on the quality of cholecystectomies using measures covering infrastructure, care processes and outcomes, with the primary aim defining the global variation in compliance with preoperative, intraoperative and postoperative audit standards.

Methods and analysis Global Evaluation of Cholecystectomy Knowledge and Outcomes is a prospective, international, multicentre, observational cohort study delivered by the GlobalSurg Collaborative. Consecutive patients undergoing cholecystectomy between 31 July 2023 and 19 November 2023 will be recruited, with follow-up at 30 days and 1-year postoperatively. The study will be undertaken at any hospital providing emergency or elective surgical services for biliary disease. The primary endpoint of this study is compliance with preoperative, intraoperative and postoperative audit standards. Secondary outcomes include rates of 30-day and 1-year postoperative complications, achievement of critical view of safety and rates of gallbladder cancer.

Ethics and dissemination This project will not affect clinical practice and has been classified as clinical audit following research ethics review at University Hospital Birmingham NHS Trust. The protocol will be disseminated through the international GlobalSurg and CovidSurg network.

Trial registration number NCT06223061.

INTRODUCTION

Cholecystectomy is among the most common surgical operations performed worldwide. Common indications include biliary colic, cholecystitis and gallstone pancreatitis.1 2

In patients who are deemed fit for surgery, cholecystectomy can be performed in three main settings: (1) emergency setting at index admission; (2) elective setting with no previous admissions or (3) delayed setting with one or more previous gallbladder-related admissions.2

The advent of laparoscopy fundamentally altered biliary surgery and quickly became the ‘gold-standard’ approach. Recent multicentre collaborative studies2 3 have demonstrated that the burden imposed on healthcare systems by laparoscopic cholecystectomies is primarily due to patient readmissions and complications arising from the operation, rather than the perioperative mortality burden that was more commonly seen in open surgery.4 As a result, national and international societies5 6 have shifted their focus towards creating a culture of safety around this procedure, with the overarching goal of improving patient satisfaction and reducing hospital costs. The universal establishment

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will be delivered globally across centres from high-income, middle-income and low-income countries performing cholecystectomy.

⇒ The collaborative methodology adopted by our group, has previously delivered two large high-quality studies while avoiding overburdening low-resource centres that may otherwise be unable to participate in such projects.

⇒ Definitions of quality in cholecystectomy care are disputed and little evidence exists of their validity or appropriateness in low-income and middle-income countries; high-quality data will help identify specific measures for cancer care in resource-limited settings.

⇒ This study will include a unique 1-year follow-up to evaluate the incidence and outcomes of patients with bile duct injury and gallbladder cancer on a global scale which has not been described to date.

⇒ As strict primary data monitoring is not possible within the limitations of the study, we will use a previously developed mixed-methods validation process.
of safe cholecystectomy is a complex process that relies not only on the operation itself, but also on various other factors such as promoting adequate training, improving hospital infrastructure and enhancing perioperative patient care.7

There remains a paucity of evidence around the variations of safe provision of laparoscopic surgery for gallbladder disease internationally, including low-income and middle-income countries (LMICs). To bridge this knowledge gap, the Global Evaluation of Cholecystectomy Knowledge and Outcomes (GECKO) study (GlobalSurg 4) will be an international collaborative effort, delivered by the GlobalSurg network8 9 that will allow contemporaneous data collection on the quality of cholecystectomies using measures covering infrastructure, care processes and outcomes. It will be disseminated via contacts from the National Institute for Health and Care Research (NIHR) Global Surgery Unit, leading emergency general surgeons and specialist organisations.

**Primary aim**

The primary aim of this study is to assess the global variation in compliance with preoperative, intraoperative and postoperative standards during cholecystectomy (table 1).

**Secondary aims**

The secondary aims of this study are to:

1. To determine the quality of safe provision of cholecystectomy, including the rates of intraoperative imaging (eg, cholangiogram).
2. To assess adverse events following cholecystectomy (eg, bile duct injury) and their management.
3. To determine rates and outcomes of unsuspected gallbladder cancer.
4. To evaluate the global variation in the availability of cholecystectomy services and training among included hospitals.
5. To assess sustainable practices in laparoscopic cholecystectomy globally.

**METHODS AND ANALYSIS**

The GECKO study is a prospective, international, multicentre, observational cohort study delivered by the GlobalSurg Collaborative. Data on consecutive patients undergoing cholecystectomy will be collected, between 31 July 2023 and 19 November 2023, with 30-day and 1-year follow-up postoperatively. The study period includes eight 2-weeks data collection periods. Mini teams of up to five collaborators per 2-week data collection period will prospectively collect data at each participating centre. Centres may choose to collect data for on selected or all data collection periods. There are no restrictions to the centre participation.

**The GlobalSurg collaborative**

GlobalSurg (http://globalsurg.org/) is a collaboration between practising surgeons from around the world, performing research in surgery to foster local, national and international research networks. The collaborative model is described elsewhere10 and has already facilitated three multicentre, international, prospective cohort studies including a total of 46186 patients undergoing emergency and elective abdominal surgery.8 9 11 The NIHR Global Health Research Unit on Global Surgery was established in 2017 and is a consortium between the Universities of Birmingham, Edinburgh and Warwick, together with international partners based in seven countries (Benin, Ghana, India, Mexico, Nigeria, Rwanda and South Africa). The objective of the unit is to advance the education of medical students and doctors in surgical science, clinical research, by promoting participation in collaborative clinical research.

**Study setting**

The study is open to any hospital worldwide that performs emergency and/or elective cholecystectomy. Eligible hospitals will collect data on consecutive patients undergoing cholecystectomy during the specified study period, following appropriate registration of the study according to local hospital regulations. Included centres will ensure data collection is >90% complete. Centres with >10% missing data, when including all data points, will be excluded from the final analysis and removed from the authorship. There is no minimum number of patients per centre, though all eligible patients treated during the study period will be included.

**Inclusion and exclusion criteria**

The study population includes consecutive adult patients (aged ≥18 years), admitted to hospital within the prespecified data collection periods, undergoing cholecystectomy as the index operation. Any operative approach may be used. Each patient will only be included once and patients with known preoperative gallbladder malignancy will be excluded. The inclusion and exclusion criteria are presented in Box 1.

**Outcome measures**

The primary endpoint of this study is compliance with preoperative, intraoperative and postoperative audit standards (table 1).

The secondary endpoints include:

> Rates of different bailout procedures initiated when safe cholecystectomy is compromised.
> 30-day and 1-year rates of outcomes for cholecystectomy, which includes postoperative complications (Clavien-Dindo classification), intraoperative complications (including bile duct and vascular injuries), length of stay, readmission, mortality and postoperative imaging or intervention.
> Unsuspected gallbladder cancer rates and their 30-day and 1-year outcome rates, which include:
  - Complication rates (Clavien-Dindo classification).
  - Time-to-recurrence rates (time from surgery to recurrence).
| Table 1 | Summary of preoperative, intraoperative and postoperative audit standards |
|-----------------|-----------------|-----------------|
| **Audit standard** | **Guidelines** | **Reporting in GECKO** |
| **Preoperative** | | |
| Interventional radiology service: There should be 24-hour access to interventional radiology to support the delivery of an emergency HPB service | AUGIS<sup>13</sup> | We will report presence of 24-hour access to interventional radiology (yes/no) on a hospital-level basis. |
| Risk Stratification: For patients with acute cholecystitis, surgeons need to risk stratify using the Tokyo Guidelines 18 (TG18) | SAGES<sup>5</sup> | We will determine use of risk stratification on an individual patient basis. This will be used for further analyses at the hospital, country, and World Bank Income Group level. |
| Timing of surgery: In patients presenting with acute cholecystitis, the optimal timing for cholecystectomy is within 48 hours. | WSES<sup>12</sup> | We will determine timing of surgery on an individual patient basis. This will be reported as within 48 hours, 48 hours to 10 days, and >10 days of admission. |
| **Intraoperative** | | |
| Critical safety view (CVS): The use of the CVS during laparoscopic cholecystectomy (achieving all three components) is the recommended approach to correctly identify relevant anatomy and minimise the risk of bile duct injuries. | WSES<sup>7,12</sup> | We will determine whether all components of the critical view of safety is achieved on an individual patient basis. |
| Intraoperative imaging: in patients with uncertainty of biliary anatomy or suspicion of bile duct injury, intraoperative imaging (eg, cholangiogram, laparoscopic ultrasound and incisionless cholangiography with fluorescence) may help delineate relevant anatomy and decrease the risk of bile duct injury. | WSES<sup>12,15,16</sup> | We will determine the use of intraoperative imaging on an individual patient basis. This will be used for further analyses at the hospital, country, and World Bank Income Group level. |
| Bailout procedures: When CVS cannot be achieved during laparoscopic cholecystectomy, a bailout procedure (eg, subtotal cholecystectomy or total cholecystectomy by the fundus-first (top down) approach) should be considered. | WSES<sup>12</sup> | We will determine the rates of subtotal cholecystectomy when CVS was not achieved on an individual patient basis. This will be used for further analyses at the hospital, country, and World Bank Income Group level. |
| Antibiotic use: Antibiotics are not required in low-risk patients undergoing laparoscopic cholecystectomy but may reduce the incidence of wound infection in high-risk patients. | SAGES<sup>14</sup> | We will determine the rates of antibiotic use on an individual patient basis. This will be used for further analyses at the hospital, country, and World Bank Income Group level. |
| Use of drains: drains are not needed after elective laparoscopic cholecystectomy. | SAGES<sup>14</sup> | We will determine the rates of abdominal drains during elective cholecystectomy. This will be used for further analyses at the hospital, country, and World Bank Income Group level. |
| **Bile duct injury (BDI):** | | |
| 1. If major BDI occur, outcomes are improved by early recognition and immediate referral to experienced hepatobiliary specialists for further treatment before any repair is attempted by the primary surgeon, unless the primary surgeon has significant experience in biliary reconstruction. | | |
| 2. If considering all types of BDIs, rates are <0.4% and <0.8% for elective and emergency settings, respectively. | | |
| 3. It is recommend knowing Strasberg’s classification (ie, documenting the classification during each operation), which remains the most used classification for BDIs | WSES<sup>5,15,16</sup>, SAGES<sup>14</sup> | We will determine bile duct injury on an individual patient basis. This will be used for further analyses at the hospital, country and World Bank Income Group level. We will identify the overall reporting of the Strasberg classification as recorded in the patient’s notes/case report form. |
| **Postoperative** | | |
| 30-day readmission: rate should be <10%. | AUGIS<sup>13</sup> | We will determine the rates of readmission on a hospital-level basis. This will be used for further analyses at the hospital, country and World Bank Income Group level. |

Continued
Table 1 Continued

<table>
<thead>
<tr>
<th>Audit standard</th>
<th>Guidelines</th>
<th>Reporting in GECKO</th>
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<tbody>
<tr>
<td>Critical care: There should be access to critical care beds with on-site renal support.</td>
<td>AUGIS(^{13})</td>
<td>We will determine the access to critical care beds on a hospital-level basis. This will be used for further analyses at the country and World Bank Income Group level.</td>
</tr>
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AUGIS, Association of Upper Gastrointestinal Surgeons; GECKO, Global Evaluation of Cholecystectomy Knowledge and Outcomes; SAGES, Society of American Gastrointestinal and Endoscopic Surgeons.

- Revisional surgery rates (liver resection, bile duct resection and/or lymph node dissection).
  - A description of the global variation in the availability of cholecystectomy services, training and sustainable practice.

**Site survey**
To describe local infrastructure, processes and resources, each site will be asked to complete an online site survey questionnaire to delineate the variation of cholecystectomy services and training among included hospitals (online supplemental Appendix a, full protocol).

**Data points**
Collaborators will collect data on consecutive eligible patients undergoing cholecystectomy within the prespecified data collection periods. Data collectors will use a combination of the GECKO Case Report Form (online supplemental Appendix b, full protocol) alongside the data dictionary (online supplemental Appendix c, full protocol) to successfully record required data on all eligible patients. Definitions of the data points are provided in online supplemental Appendix d (full protocol). Collaborators will create clear mechanisms appropriate to their institution to identify and include all eligible patients, involving daily review of operating logbooks, multidisciplinary team meeting, admission and handover lists. Local arrangements may include daily review of the patient and notes focused on included data points. Data will be collected and stored online via the Research Electronic Data Capture (REDCap) web application, hosted and managed by the University of Edinburgh, UK. No patient identifiable data will be uploaded or stored on the REDCap database.

Centres will undertake patient follow-up at two time points:
1. 30-day follow-up will be performed for all recruited patients. Each patient will be followed up for 30 days starting on the day of surgery (day 0).
2. One-year follow-up to assess bile duct injury and unsuspected gallbladder cancer outcomes, we will collect 1-year follow-up data on all recruited patients with these diagnoses.

Local arrangements for successful 30-day and 1-year follow-up may include reviewing patient notes, reviewing patient status in outpatient clinics or via telephone interview at 30 days (if this is normal practice) and checking for readmission through handover lists. Follow-up will be performed in line with current routine practices of each hospital. No additional telephone, in-person or questionnaire-based follow-up is required. Source data may be acquired from hospital in-patient notes, clinical electronic systems or outpatient letters.

**Box 1 Patient inclusion and exclusion criteria**

**Inclusion criteria**
- Age: All adult patients (aged ≥18 years).
- Procedure: Primary cholecystectomy, where this is the main procedure planned.
- Approach: Open, laparoscopic (standard and single port) and robotic. Gasless laparoscopic and robotic approaches are included. Laparoscopic and robot converted cases are eligible.
- Urgency: Elective, delayed and emergency procedures.

**Exclusion criteria**
- Procedure: Patients having a cholecystectomy as a part of another surgical procedure; for example, Whipple’s procedure, bariatric, antireflux or transplant operations.
- Indication: Patients with Mirizzi syndrome.
- Secondary operation: Each patient should only be entered into the study once. Any patient returning to theatre and requiring a cholecystectomy for whatever indication following index surgery should not be included.
- Known gallbladder malignancy: When the diagnosis of gallbladder cancer is established preoperatively, the patient should be excluded. If gallbladder cancer is found unexpectedly during or after cholecystectomy (ie, on histology), the patient should be included.

**Investigators**
Each registered centre must have a supervising consultant/attending to ensure adequate data quality. In the case that the hospital lead is a registrar/resident then they must recruit a consultant/attending to supervise the study. The hospital lead will also ensure that they recruit independent data validators to perform the data validation outlined below. For data collection, the hospital lead will recruit a ‘mini-team’ of up to five local collaborators for each data collection period. Medical students, doctors (non-registrars/residents or consultants/attendings) and nurses can act as local collaborators and their participation is encouraged. The same ‘mini-team’ can cover different time periods at each hospital if they wish to. Each team will include at least one qualified doctor to provide additional local support for participating medical students or nurses.
Data quality
To ensure high data quality, this protocol was written with guidance from an expert cross-speciality advisory group and published online. Protocol translations into multiple languages will be performed to ensure geographical representation. Countries with multiple sites will be assigned a national lead, who will be responsible for coordinating multiple teams across sites to ensure duplication of data does not occur. GECKO National Leads are encouraged to hold any local meetings with collaborating teams to ensure they are up to date on the protocol as well as to provide feedback on any local issues or questions raised to the central management team.

Data validation
The present collaborative methodology has been widely validated across multiple datasets internationally and has demonstrated high levels of case ascertainment (≥90%) and data accuracy (≥95%). Validation will be performed to ensure a high level of data accuracy.

Validation by primary data collection teams includes:

- Follow-up methodology at patient level: all hospitals will self-report the methods used to determine 30-day outcomes.
- Patient identification methodology: all hospitals will self-report the methods used to identify patients who fulfil the inclusion criteria.

Validation by independent teams includes:

- Case ascertainment: hospital records will be reviewed to identify patients fulfilling the inclusion criteria within a 2-week data collection period and compare this to the actual number of cases submitted. This will be performed by individuals not involved in collecting the primary data. By comparing samples, a quantitative estimate of case ascertainment will be produced by the central data team.
- Data accuracy: a subset of collected variables will be validated by individuals who are independent of the primary data collection process. Following the ‘case ascertainment stage, validators will be asked to provide data for a subset of key variables: two patient variables, two operation variables and two outcome measures.

Bias and confounding
Data will be collected on perioperative standards on promoting safety during cholecystectomy and to account for potential confounding factors through risk-adjusted analyses. These include age, sex, body mass index, American Society of Anesthesiologists grade and relevant comorbidities. Variables including operative urgency, operative contamination and operative approach will also be collected. This will minimise the risk of bias associated with patient factors and allow for outcome comparison across the international cohort.

A full list of required data fields is available in online supplemental Appendix c (full protocol) and on the REDCap database.

Statistical analysis and power calculation
Variation across different international health settings will be tested using the World Bank Country group a composite statistic of life expectancy, education and income indices published by the United Nations. This will be defined as high income, middle income, lower middle income and low income. Initially, data will be reported using descriptive analyses. Comparisons between groups will be undertaken using appropriate parametric and non-parametric analyses. Multilevel logistic regression models will be constructed to account for case mix, with population stratification by hospital and country as random effects. Further prespecified subgroup analyses will be made by operative approach (open, laparoscopic and converted, robotic), and operative urgency (elective, emergency and delayed surgery). Perioperative standards on improving the safety of cholecystectomy and site survey (online supplemental Appendix a, full protocol) will guide exploratory analysis into the global variation in the provision of cholecystectomy and available resources. However, it is acknowledged that some standards are designed for high-income settings, and therefore, their attainment will not be considered mandatory or a potential definitive measure of quality in global cholecystectomy. Identification of hospital or surgeon-specific performance will not be reported. Following analysis, results will be fed back to participants at the centre level, but no other centres will be identifiable.

Based on previous GlobalSurg studies,10–16 GECKO was anticipated to include around 500 centres globally. At the time of submission for the publication, 2084 centres have expressed interest in participation, across 134 countries. With consideration to recent figures provided by previous collaborative studies on cholecystectomy,2 a sample of approximately 15000 patients is anticipated. The recent multisociety practice guidelines on prevention of bile duct injury7 advised that a study adequately powered to detect and report on bile duct injury would require at least 9000 patients.

Patient and public involvement
The relevance of these research topics was discussed with patients who have had gallstone disease. Patients identified the study was important to the community, especially the sustainability practices. Patient representatives will be involved throughout the study in activities such as data interpretation, producing patient-facing materials after data analysis and presentation at conferences.

Ethics and dissemination
Research ethics approval
The primary audit standards in this prospective cohort study stem from the World Society of Emergency Surgery,12 Association of Upper Gastrointestinal Surgeons13 from the UK and the Society of American Gastrointestinal and Endoscopic Surgeons14 from the USA for the safe management of patients undergoing cholecystectomy (table 1). As this study will not change local clinical
practice and is limited to using data obtained as part of usual care, it has been classified as an audit by the University Hospital Birmingham National Health Service (NHS) Trust. Therefore, this may be considered a global audit or global service evaluation. Local investigators will be responsible for ensuring the study is registered appropriately and approval is gained from the relevant local clinical audit departments, research and development department or institutional review boards. If such departments are unavailable, written permission should be supplied by the chief of surgery or the responsible supervising consultant/attending physician. All data will be handled in accordance with national and local data governance policies. For instance, collaborators in the UK will seek their Caldicott Guardian permission to submit data.

Data will be collected and stored online through a secure server running the REDCap web application. REDCap allows collaborators to enter and store data in a secure system. Collaborators will be given secure REDCap project server login details, allowing safe anonymised data storage on the REDCap database. The service is managed by the Global Surgery REDCap system hosted by the University of Edinburgh, UK. REDCap access privileges will be managed and maintained by the NIHR Global Health Research Unit on Global Surgery to ensure that users can only access data relevant to their site. Collaborator access will be limited to their site only. Personnel handling data collection are professional medical students and health staff (consultants and doctors on site). There are no new data collected directly from patients; data from routine practice will be collected. A named consultant or attending will ensure data completeness and accuracy, and data collection will be completed by a team of local surgical trainees or medical students working at that hospital. No data will be uploaded to REDCap prior to written approval from the Caldicott Guardian (or equivalent) or ethical board.

Protocol dissemination
The protocol will be disseminated throughout the GlobalSurg network. This consists of surgeons, other clinical staff and medical students throughout the globe. Prior studies using this network have included over 2000 centres. National leads will be primary audit standards responsible for local dissemination within their country. Social media, including the use of Facebook, Twitter and YouTube, will be used for further dissemination.

Dissemination of results
We aim to publish study results in an open-access format. Data shall be presented in ways to maintain anonymity of individual countries, hospitals and surgeons. On completion of the study, participating centres will be provided with their own benchmark performance. All authors will be credited in accordance with National Research Collaborative Authorship guidelines, and research outputs from GECKO will be listed under a single corporate authorship of ‘GlobalSurg Collaborative, NIHR Global Health Research Unit in Global Surgery’. Full requirements for authorship on GECKO outputs can be found at https://www.globalsurgeryunit.org/clinical-trials-holding-page/project-gecko/.

DISCUSSION
In this protocol, we describe a multicentre, global prospective cohort study investigating the quality and outcomes of patients undergoing cholecystectomy. The advent of laparoscopy as the ‘gold standard’ has shifted outcome focus to that of safety and risk mitigation, and global variation of such outcomes, along with adherence to perioperative standards internationally, are sparsely reported.

The use of collaborative methodology and the brevity of eight, 2-week data collection periods, the GECKO study will include ample patients to measure this, while mitigating risk of burn-out among data collectors and promoting parity between large specialist centres and smaller local units. Therefore, enabling recruitment and participation of all interested centres across the globe. The GlobalSurg Network has already built a substantive platform to deliver the GECKO study, and this work will further ratify the ability to deliver not only global observational studies but also build interventional projects and continue to advance this global network. GECKO will be delivered using this network and platform, with the former having proven its ability to produce high-impact outcomes in international studies. The present protocol has already been reproduced in multiple languages, along with mandatory training, data quality control and validation period to ensure standardisation to deliver a reliable data set. In its delivery, the aim is to galvanise a global community of surgeons to collect and analyse prospective, observational data for one of the most performed operations worldwide. There is a gap in knowledge on delivery of ‘safe’ cholecystectomy, especially in LMICs, and GECKO aims to bridge such a gap. Quantification of differences in infrastructure, care processes and outcomes across participating countries will allow collaborators to compare their individual (and centre) practice to a global standard for preoperative, intraoperative and postoperative outcomes. However, this study has limitations which need to be acknowledged. Firstly, selection bias will exist in the cholecystectomies captured in the cohort; for instance, there is an expected bias towards central hospitals at the expense of district hospitals and ambulatory care facilities, across high-income, middle-income and low-income settings. Secondly, ascertainment of certain standards such as a critical view of safety is inherently difficult, and for some, we are reliant on clinician reporting rather than an objective measure. Third, due to the observational nature of the study, it will not be possible to determine a causative link between laparoscopic surgery and complications, and therefore, comparisons of incidence and risk factors across different Human Development Index settings will
be hypothesis-generating only. Finally, delivering long-term follow-up is likely to be challenging, particularly in health systems where there is low availability of health records.

The GECKO cohort study will be a large, multicentre international cohort study using a GlobalSurg collaborative model with a track record of producing high-impact cohort studies which have subsequently delivered successful international randomised controlled trials such as FALCON and CHEETAH. This work will seek to build on a major trial aiming to improve global outcomes after cholecystectomy.

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Acknowledgements
SKK and OK are joint first authors. SKK, OK, EG, AR-DIM, DGM and EMH developed a draft of the protocol. SKK, OK, PA, NA, MC, ADawson, ADermanis, DG, EG, PH, LK, SL, JM, AR-DIM, AMB, DGM, RP, JP, KR, AS, SS, CS, RS, NWH and EMH have critically reviewed and edited the manuscript.

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Contributors
All authors within the NIHR Global Health Group on Global Surgery contributed to the design, drafting and review of this study protocol. In addition to this, SKK and EH is the overall guarantor for this article.

Funding
This study is funded by the NIHR Global Health Research Unit on Global Surgery (NIHR16.136.79).

Competing interests
GlobalSurg is run by the Surgical Research Gateway (SuRG) Foundation. The SuRG Foundation is a registered charity (charity number 1159898) whose object is to advance the education of medical students and doctors in surgical science, clinical research by promoting participation in collaborative clinical research and audit studies.

Patient and public involvement
Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Provenance and peer review
Not commissioned; externally peer reviewed.

Supplemental material
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