GlobalSurg

GlobalSurg 3

Quality and outcomes in global cancer surgery:

a prospective, international cohort study

GlobalSurg Collaborative

NIHR Unit on Global Surgery

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This protocol is available in other languages.

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wellcome

Abbreviations

AJCC	American Joint Committee on Cancer
ASA	American Society of Anaesthesiologists score
ASTRO	American Society for Radiation Oncology
BMI	Body mass index
CD	Clavien-Dindo classification
CDC	Centers for Disease Prevention and Control
CRM	Circumferential Resection Margin
CT	Computerised Tomography scan
DCIS	Ductal Carcinoma in-situ
ER	Oestrogen receptor
GIST	Gastrointestinal stromal tumour
HER2	Human epidermal growth factor receptor 2
HDI	Human Development Index
HIPEC	Hyperthermic intraperitoneal chemotherapy
ICU	Intensive Care Unit
LMICs	Low- and middle-income countries
MDT	Multidisciplinary team
MRI	Magnetic Resonance Imaging
NICE	National Institute for Health and Care Excellence
OGJ	Oesophagogastric junction
PR	Progesterone receptor
SSI	Surgical site infection
SSO	Society of Surgical Oncology
USS	Ultrasound scan
WAIC	Widely-applicable information criterion
WLE	Wide local excision

1 Key facts

Aim: The aim is to determine the variation in quality of cancer surgery worldwide. Quality will be determined using measures covering infrastructure, care processes, and outcomes. We will concentrate on the most common surgically-treated cancers worldwide: breast, gastric and colorectal cancer. The primary aim focusses on 30-day mortality and complication rates after cancer surgery. The secondary aim is to characterise infrastructure and care processes in the treatment of these cancers worldwide.

Primary outcome measure: 30-day mortality and complication rates after cancer surgery.

Primary comparison: Between country groups defined by human development index.

Hospital eligibility: Any hospital in the world performing surgery for breast, gastric or colorectal cancer.

Patient eligibility: Consecutive patients undergoing surgery for breast, gastric, or colorectal cancer. Surgery can be with palliative or curative intent.

Team: Individual hospital teams with up to three people, collecting data for four weeks. Several teams collecting data over multiple four-week periods in the same centre is encouraged.

Time period: Patients will be identified, and data collected on all patients during the time-period with follow-up to 30-days. The study will run from 1st April 2018 to 31st October 2018 (with follow-up of the last period to 30th November 2018).

Validation: Data validation will be in two parts. First, hospitals will self-report the key processes used to identify and follow-up patients. Second, independent validators will quantitatively report case ascertainment and sampled data accuracy.

Registration: Interested participants should subscribe at globalsurg.org/subscribe. If you are motivated and wish to act as a local or national lead for your country (either alone or as part of a team with your colleagues), please contact: enquiry@globalsurg.org.

2 Introduction

2.1 What is GlobalSurg

The GlobalSurg Collaborative was established to allow individuals from around the world to lead and participate in global research aimed at improving outcomes after surgery. The ethos of GlobalSurg is inclusive and collaborative – our international cohort studies are open to all collaborators from anywhere in the world.

2.2 GlobalSurg 3: Why cancer surgery?

Of the 15.2 million individuals diagnosed with cancer in 2015, over 80% will need surgery (1). In tumours amenable to surgical resection, surgery often offers the best chance of cure, particularly in early-stage disease. It has been estimated that 45 million surgical procedures are needed each year worldwide, yet, fewer than 25% of patients with cancer have access to safe, affordable, and timely surgery. While death rates from cancer are decreasing in high-income countries, the opposite has been demonstrated in low- and middle-income countries (LMICs) (2). Up to 1.5% of the gross domestic product is lost because of cancer in some LMIC regions (3).

General surgeons manage patients with the most common cancers on a day-to-day basis. Breast cancer (global incidence ranked 1st, global mortality ranked 5th), gastric cancer (incidence ranked 5th, mortality ranked 3rd), and colorectal cancer (incidence ranked 3rd, mortality ranked 2nd), represent a significant burden of disease across income settings (1). Yet, most studies that examine the global distribution and outcomes of solid cancers use simulated methods due to the absence of robust data, including country-specific epidemiological data, stage distribution, and treatment approaches (1).

2.3 Research priority setting by the GlobalSurg network

The GlobalSurg collaborative is a growing network of over 5000 clinicians across 106 countries. We have now delivered two international cohort studies of over 24,000 patients undergoing emergency and elective abdominal surgery.

GlobalSurg 1 launched in 2014 and showed that mortality after emergency abdominal surgery is up to three times higher in low compared with high Human Development Index (HDI) countries (4). This difference was not attributable to patients' baseline clinical characteristics alone. An analysis of children showed that mortality rates following emergency abdominal surgery were seven times greater for children in low-income countries compared to high-income countries (5).

GlobalSurg 2 was conducted in 2016 and examined the incidence of surgical site infection (SSI), which remains the remains the most common complication following surgery (6). Our *Lancet Infectious Diseases* publication showed that patients in low-income countries carry a disproportionately greater burden of SSI and suggested higher rates of antibiotic resistance.

A three-stage research prioritisation exercise was performed by the network through 2017. This focussed on the priorities of LMIC surgeons and incorporated views across country development levels. This culminated in a research prioritisation workshop in Johannesburg, November 2017. Cancer surgery was highlighted as a major research priority and this study is the first of a series addressing this need.

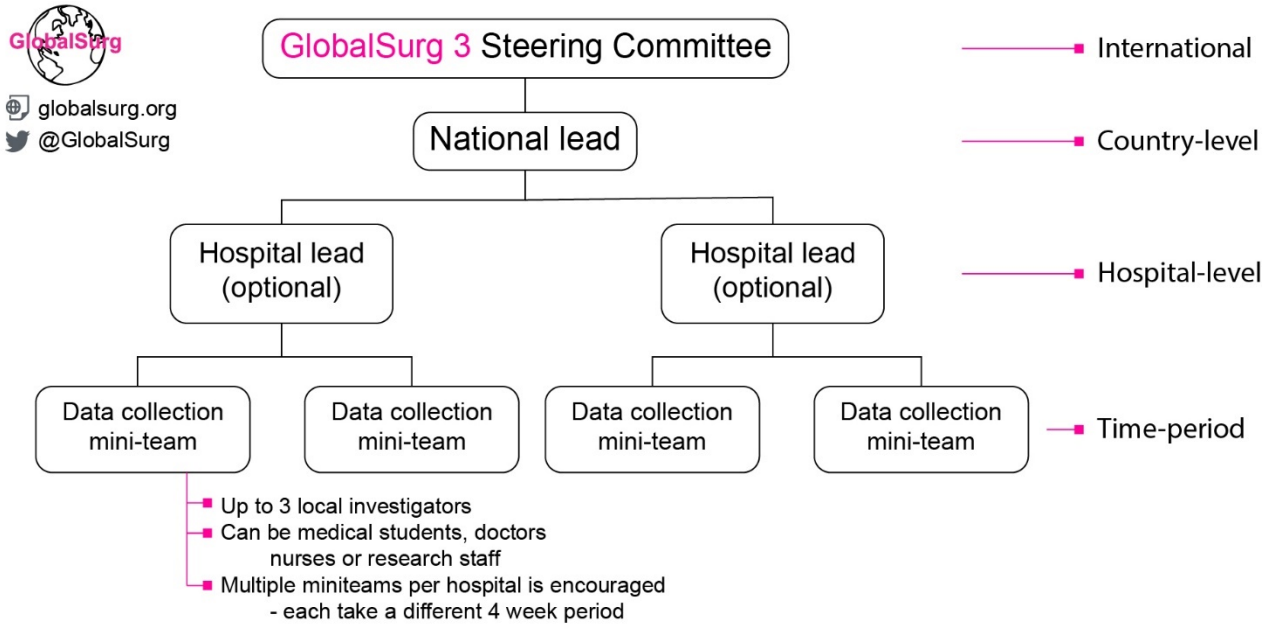
The aim of the GlobalSurg 3 Study is to determine variation in the quality of cancer surgery worldwide, focusing on patient outcomes, infrastructure, and care processes.

3 Roles, responsibilities and authorship

GlobalSurg represents an international network of like-minded clinicians around the world. Participation in GlobalSurg projects results in co-authorship on primary publications, with a PubMed citable ID attributed to all collaborators.

3.1 Roles and responsibilities

The project is administered by the GlobalSurg 3 Steering Committee (see figure below). The committee is here to help you run the study and can assist you with technical issues, ethics applications and more. Each country will have an overall GlobalSurg lead who can provide help and information on how to set up the study at your centre and will be your main point of contact. In large hospitals planning multiple data collection periods, a “Hospital lead” may be appointed by the National lead. The Steering committee should be informed via enquiry@globalsurg.org. Data collection mini-teams include up to 3 members, who can be medical students, doctors, nurses, or search staff. For details of local investigator data collection responsibilities, see section 8.1.



3.2 Authorship

Publication will be authored under one main group name ('GlobalSurg Collaborative') on the authorship by-line underneath the title, recognising all contributor efforts[1]. All collaborator names will then be listed at the end of primary publications. Secondary publications are encouraged. These may focus on a geographic area, a particular disease, or a patient subgroup. The inclusion of collaborators on secondary publications is decided on a study-by-study basis, for instance, it would make no sense to include European data collectors on a study using only African data.

Wherever possible, manuscripts will be published as fully open access. This authorship model has been successful in all our previous collaborative projects.

Help and support is always available from your country lead and the GlobalSurg steering group.

Go to www.globalsurg.org for more help and information.

[1] https://www.ncbi.nlm.nih.gov/pubmed/29452941

4 Methods

4.1 Primary aim

The primary aim is to audit 30-day mortality and complication rates after cancer surgery across low-, middle- and high-human development index[2] (HDI) countries.

4.2 Secondary aim

The secondary aim is to measure the quality of surgical cancer care and is designed to be relevant in low-, middle-, and high-income settings. Conditional data points will be dependent on the specific resources available in a hospital and will include infrastructure (e.g. imaging), care process measures (e.g. multidisciplinary team decision making), and outcomes (e.g. surgical margin involvement). Cancer-specific quality metrics are described in section 4.5.3.

When registering your team on globalsurg.org, you will require an ORCID ID (orcid.org). This takes just 30 seconds to receive. Make sure your name is correct as this is how it will appear in publications.

Do not register more than once.

4.3 Time-period

The study will run from 1st April 2018 to 31st October 2018 (with follow-up for the last period ending in 30th November 2018). Individual hospital teams will have a maximum of three people and collect data for four weeks. Each local team may select a convenient four-week time-period. Multiple teams covering different, non-overlapping, time-periods from a single institution are encouraged, and the same team can continue for more than one four-week block if they wish.

[2] http://hdr.undp.org/en/content/human-development-index-hdi

Teams may consist of medical students, doctors, nurses, and research staff. Including a supervising consultant or attending surgeon in the team is encouraged. Supervisors must be registered for the study prior to data collection to be included as collaborators. Multiple data collection periods are encouraged as a means of increasing the number of collaborators and patients included at each centre.

4.4 Inclusion criteria

4.4.1 Hospital inclusion criteria

- Hospitals regularly performing elective or emergency surgery for breast, gastric, or colorectal cancer anywhere in the world are eligible to enter. An eligible hospital is not required to perform surgery for all three conditions; however, in hospitals where two or three of the diseases are treated by surgery, all patients are required to be enrolled during the study period.
- All participating centres will be required to register their details and all collaborators must complete an online training module prior to commencing data collection (training.globalsurg.org). The module includes a standardized description of the different data variables to be collected and how to use the online study data entry system.
- For inclusion in the study, centres must include consecutive (i.e. one after the other) patients and provide greater than 90% overall data completeness (i.e. no cases should be missed). Centres who fall below the 90% overall data completeness threshold will be removed from data analyses and authorship lists.
- There is no minimum number of patients per centre, as long as all eligible patients treated during the study period are included.

4.4.2 Patient inclusion criteria

Inclusion Criteria

- All consecutive patients undergoing therapeutic surgery (curative or palliative) for breast, gastric, and colorectal cancer should be included.
- Surgery is defined as a procedure requiring a skin incision performed under general or neuraxial (e.g. regional, epidural or spinal) anaesthesia.
- Both elective and emergency procedures should be included.
- Include patients in whom the pre-operative diagnosis was thought to be benign, but was subsequently found to be cancer, e.g. bowel obstruction found to be due to cancer during surgery.
- Include patients in whom the pre-operative diagnosis was thought to be cancer but was subsequently found to be benign disease (ensure the "pathology" variable indicates **not** cancer; will not be included in primary analysis).
- Laparoscopic, laparoscopic-converted, robotic, and open cases should be included.
- Patients aged 18 years and over should be included[3].
- Surgery may be with curative or palliative intent. Include patients in whom curative surgery was attempted but abandoned, e.g. open/close laparotomy.

Exclusion criteria

- Operations where breast, gastric, or colorectal cancer is not **suspected to be** the primary pathology should be excluded.
- Patients undergoing a procedure purely for diagnosis or staging should be excluded, e.g. open breast biopsy, staging laparoscopy.

[3] This can be adjusted to "aged 21 years and over" in countries where 21 is the age of majority, to avoid the complexity of seeking ethical approval to include "children".

- Patients undergoing a procedure which **does not** require a skin incision should be excluded, e.g. colonoscopy/endoscopy alone, chemo/radiotherapy alone.
- Patients with recurrence of breast, colorectal or gastric cancer should be excluded.

4.5 Outcome Measures

4.5.1 Primary outcome measures

We will use dual primary outcome measures; 30-day mortality rate and 30-day major complication rate (see 9.1 for details on statistical power).

30-day mortality rate

Defined as death within 30-days of index operation, where day of operation is day 0.

30-day major complication rate

Defined as the occurrence of a Clavien-Dindo grade III or IV complication within 30-days of index operation.

Clavien-Dindo grade III: Unplanned surgical, endoscopic or radiological intervention –

IIIa: intervention **not** under general anaesthesia;

IIIb: intervention under general anaesthesia.

Clavien-Dindo grade IV: Life-threatening complication requiring unplanned critical care / intensive care unit (ICU) management –

IVa: single organ dysfunction (including dialysis);

IVb: multiorgan dysfunction.

How to identify a complication

Adverse post-operative events may be divided up into treatment failures, sequelae and complications. **Failure of treatment** occurs when the original surgery fails to achieve its intended benefits; for example, tumour recurrence following cancer surgery. **Sequelae** are the recognised consequences of a given procedure; for example, gut malabsorption following a large small bowel resection or immune deficiency following splenectomy. Any deviation from the normal post-operative course that has an adverse effect on the patient and is not either a treatment failure or sequelae, is a **complication**.

In the Clavien-Dindo classification, the factor determining the severity of a complication is the treatment required. Consequently, a given complication may be graded differently depending on how it has been managed. For example, an anastomotic leak may be managed just with antibiotics if it is contained (grade II) or it may require re-operation under anaesthetic (grade IIIb). Some other considerations:

- Intra-operative complications are **not** considered unless they have an adverse effect on the patient post-operatively. The only exception to this is **intra-operative death**; this is classified as grade V.
- **All post-operative adverse events** are included, even when there is no direct relationship to the surgery.
- **All adverse events within the follow-up** period (30 days) are included, even if they occur following discharge.
- **Diagnostic procedures** are **not** included. For example, a diagnostic endoscopy to look for a source of bleeding without any intervention **would not** be considered a complication, but a therapeutic endoscopy with clipping of a bleeding vessel would be considered a grade IIIa complication. Since **negative exploratory laparotomies** are diagnostic procedures, they **should not** be recorded as complications.

Clavien Dindo Grade	Definition (examples listed in italics)
I	Any deviation from the normal postoperative course without the need for pharmacological (other than the "allowed therapeutic regimens"), surgical, endoscopic or radiological intervention. Allowed therapeutic regimens are: selected drugs (antiemetics, antipyretics, analgesics, diuretics and electrolyte replacement), physiotherapy and wound infections opened at the bedside but **not** treated with antibiotics. ***Examples****: Ileus (deviation from the norm); hypokalaemia treated with oral potassium replacement; nausea treated with an anti-emetic (e.g. cyclizine); acute kidney injury treated with intravenous fluids.*
II	Requiring pharmacological treatment with drugs beyond those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included. ***Examples****: Surgical site infection treated with antibiotics; myocardial infarction treated medically; deep venous thrombosis treated with enoxaparin; pneumonia or urinary tract infection treated with antibiotics; blood transfusion for anaemia.*
IIIa	Requiring surgical, endoscopic or radiological intervention, **not under** general anaesthetic. ***Examples****: Therapeutic endoscopic therapy (do not include diagnostic procedures); interventional radiology procedures.*
IIIb	Requiring surgical, endoscopic or radiological intervention, **under** general anaesthetic. ***Examples****: Emergency re-laparotomy for bleeding.* Note some procedures are staged, requiring a planned return to theatre and **should not** be considered a complication, for example, damage-control laparotomy in trauma with planned re-look. .
IVa	Life-threatening complications requiring critical care management – **single organ** dysfunction, or neurological complications including brain haemorrhage and ischemic stroke (excluding TIA). This may include a requirement for mechanical ventilation, high-flow oxygen therapy, haemofiltration, vasopressor support or continuous invasive monitoring. In some centres, planned or routine admission to critical care is normal following major operations. These instances **should not** be included. In centres without critical care facilities, Clavien-Dindo grade IV can be assigned in the presence of a life-threatening complication where critical care admission would have occurred facilities had been available ***Examples****: Single organ dysfunction requiring critical care management, e.g. pneumonia with ventilator support, renal failure with filtration; stroke.*
IVb	Life-threatening complications requiring critical care management – **multi-organ** dysfunction.
V	Death of a patient

4.5.2 Secondary outcome measures

Cancer-specific quality measures

These are described in section 4.5.3

30-day minor complication rate

Defined as the occurrence of a Clavien-Dindo grade I or II complication within 30-days of index operation.

Clavien-Dindo grade I: Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.

Clavien-Dindo grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusion sand total parenteral nutrition are also included.

Surgical Site Infection

Surgical site infection will be defined according to the Centers for Disease Prevention and Control (CDC) surgical site infection guidelines (7) which specifies the following:

1. Infection involves skin, superficial and deep tissues of incision

   AND

2. Patient has **at least one** of the following:
   a. Purulent drainage from the incision
   b. Organisms identified from aseptically obtained specimen by culture or non-culture based testing for the purposes of clinical diagnosis and treatment

c. Reopening of incision **AND** patient has **at least one** of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat.
d. an abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathological examination, or imaging test.

Anastomotic leak

Anastomotic leak is defined as the presence of a communication between the lumen of stomach or bowel and the chest/abdomen/pelvis at the site of a previously formed anastomosis. Detection of anastomotic leak may be detected radiologically (with CT, MRI, contrast studies), endoscopically (through endoscopy or laparoscopy) or on operation.

Length of follow up

Follow-up will be measured up to and including 30-days after surgery where possible (either in person or chart review), or by the point of discharge if not possible. The day of surgery will be considered as day 0.

Feasibility studies

We will work with **some** hospitals to perform additional feasibility studies (see Section 4.6). **Not all hospitals will be required to take part in these**. Feasibility studies will investigate the collection of other outcome measures. These will include overall and disease-free survival at 3, 6, and 12 months; quality of life and other patient-centred outcome measures; and an assessment of the economic cost of cancer care to patients. Please indicate to your National Lead whether you can support these objectives. It is **not** a requirement for **all hospitals** to take part in feasibility studies.

4.5.3 Cancer-specific quality measures

The measures used to determine the quality of surgical cancer care are controversial and subject to on-going debate. Guidelines produced by bodies such as the National Institute for Health and Care Excellence (NICE, UK) and American College of Surgeons (US) in high-income countries provide some consensus. However, there is little evidence on the appropriateness of such guidelines in LMICs or what specific measures may indicate quality in cancer surgery in resource-poor settings.

The measurement of perioperative mortality and complication rate may act as surrogate measures for quality, such as surgical site infection rates in breast cancer surgery (8). The following quality measures taken from national cancer guidelines will be used:

4.5.3.1 Breast cancer

Infrastructure/Care processes

- Availability/performance of pre-operative fine needle aspiration/core biopsy to diagnose breast cancer.
- Availability/performance of breast/axillary MRI for staging.
- Availability/performance of breast conservation surgery for AJCC stage 0/I/II breast cancer.
- Availability/ performance of axillary/breast radiotherapy and axillary lymph node clearance (at least 10 lymph nodes for analysis).
- Availability/performance of sentinel lymph-node biopsy for early invasive breast cancer.

- Availability/performance of progesterone receptor (PR), oestrogen receptor (ER), human epidermal growth factor receptor 2 (HER2) receptor and Ki67 status for invasive cancers.
- Availability/treatment with adjuvant treatment where appropriate within 31 days of completion of surgery.
- Availability/plan for radiotherapy for all with breast conserving surgery with clear margins (including DCIS).
- Treatment decisions made within multidisciplinary team meeting / tumour board.

Outcomes

- 30-day mortality rate.
- 30-day complication rate. This will include surgical site infection, abscess formation, seroma, unplanned reoperation, unplanned readmission and requirement for unplanned critical care.
- Margin involvement. “Tumour on inked margin” is considered positive (SSO/ASTRO consensus guidelines for early stage breast cancer (9)) or a margin <2 mm in DCIS in surgery [or ability to measure this locally].

4.5.3.2 Gastric cancer

Infrastructure/Care processes

- Availability/performance of endoscopy and biopsy to reach a diagnosis of cancer.
- Availability/performance of CT chest, abdomen and pelvis scan performed for pre-operative staging.
- Availability/treatment with pre- or post-operative chemotherapy for gastric cancer.
- Treatment decisions made within multidisciplinary team meeting / tumour board.

Outcomes

- 30-day mortality rate.
- 30-day complication rate. This will include surgical site infection, anastomotic leak, unplanned reoperation, and requirement for unplanned critical care.
- At least 15 regional lymph nodes removed and pathologically examined for resected gastric cancer [or ability to measure this locally].

4.5.3.3 Colorectal cancer

Infrastructure/Care processes

- Availability/performance of CT chest, abdomen and pelvis scan performed for pre-operative staging.
- Availability/performance of pre-operative MRI for rectal cancer.
- Availability/planning/treatment with post-operative chemotherapy following resection for lymph node positive colon cancer.
- Availability/treatment with pre-operative chemotherapy/radiotherapy.
- Treatment decisions made within multidisciplinary team meeting / tumour board.
- Stoma formation rate.

Outcomes

- 30-day mortality rate
- 30-day complication rate. This will include surgical site infection, anastomotic leak, unplanned reoperation, unplanned readmission and requirement for unplanned critical care.
- Circumferential resection margin (CRM) >1mm [or ability to measure this locally].
- At least 12 regional lymph nodes removed and pathologically examined for resected colon cancer [or ability to measure this locally].

4.6 Feasibility studies

The feasibility studies will complement the primary objectives of GlobalSurg3, aiming to further explore related quality and outcome measures beyond the initial 30-day follow-up period. Recently, large simulated datasets have been used to explore such measures, however locally collected, prospective data on a global scale has yet to be performed.

It is not a requirement for local teams to perform these feasibility studies, however we would hope the majority would be able to collect data on one or more additional outcomes. Those measured will fall into three broad categories:

Patient survival

- Disease-free survival at 3, 6 and 12-months post-operatively
- Overall survival at 3, 6 and 12-months post-operatively

Patient-reported outcome measures

- Cancer-specific patient-reported quality of life following cancer surgery
- Explore which outcome measures patients feel are important when undergoing surgery for cancer

Estimating the economic cost of cancer surgery to patients

- Proportion of patients who suffer catastrophic costs following surgery (measured by the total number of days work required to pay medical bill)
- Length of time before patient can return to paid work and/or perform family care

5 Local approval/ Ethical considerations

Different countries and hospitals will have differing mechanisms in place to gain permission for this study. All data collected will measure current practice, and no changes to normal patient management will be required. Data will not be presented at the level of individual surgeon, hospital or country.

In many centres, this study will not require formal ethics approval. In the United Kingdom for example, ethical review has confirmed this project is considered an audit, and it will be registered at each participating hospital centre as a clinical audit or service evaluation (see letter from ethics board at end of this protocol).

Local investigators must gain approval from one of the following, guided by local policy:

- Clinical Audit Department (as either audit or service evaluation);
- Research Departments/Institutional Review Boards (as either observational research, or as service evaluation);
- Some hospitals may not have these departments, in which case written or emailed permission should be provided to the local investigator from the next best available source. This may include the Chief of Surgery or a supervising consultant/attending physician. Local investigators will be solely responsible for ensuring they have followed the correct mechanisms for this and will be asked to confirm local approval when their data is submitted.

Prior to collecting data, you must have approval to do so.

In the UK you will require Caldicott guardian approval.

6 Audit standards

In many countries this is a clinical audit or service evaluation, as the study is comparing practice to 'gold-standard', without using identifiable data or changing patient care. On completion of the study, participating centres will be provided with their own benchmark performance for which to use for quality improvement or subsequent re-audit. This study will use standards taken from the following published guidelines:

6.1 Breast cancer

- American College of Surgeons Commission of Cancer Quality of Care for Breast Cancer (10);
- National Institute for Health and Care Excellence (NICE): Early and locally advanced breast cancer: diagnosis and treatment; Clinical Guideline CG80 (11).

6.2 Gastric cancer

- American College of Surgeons Commission of Cancer Quality of Care for Gastric Cancer (10);
- National Institute for Health and Care Excellence (NICE): Oesophago-gastric cancer: assessment and management in adults (12).

6.3 Colorectal cancer

- American College of Surgeons Commission of Cancer Quality of Care for Colorectal Cancer (10);
- National Institute for Health and Care Excellence (NICE): Colorectal cancer: diagnosis and management; Clinical Guideline CG131 (13).

7 Governance and data sharing

Data will be collected via a secure online system, provided by the University of Edinburgh, Edinburgh, UK, using the REDCap system[4]. REDCap is used around the world to securely gather research data. All patient data will be transmitted and held anonymously; the data will not be analysed at identifiable hospital or surgeon level. Submitting centres with >10% missing data will result in exclusion of that centre from the study.

All collaborators will be asked to agree to a data handling and storage Code of Conduct prior to participating in GlobalSurg 3. Our formal policy on data governance can be found online (globalsurg.org/gs3).

8 Collecting data

8.1 Local investigator responsibilities

Local investigators are responsible for data collection within their hospital. A "data collection mini-team" comprise up to three individuals, who can be medical students, doctors, nurses, or research staff. Local investigators will be specifically responsible for:

- Gaining local audit, service evaluation, or research ethics approval;
- Forming a team of up to three people (including themselves) to identify patients and collect data;
- Creating clear mechanisms to identify and include eligible patients;
- Identifying clear pathways to establish outcome;
- Submitting data to the online REDCap system, including team member names.

[4] http://project-redcap.org

Methods to identify consecutive patients:

- Daily review of operating theatre lists;
- Daily review of team handover sheets, emergency admission lists and ward lists;
- Daily review of multidisciplinary team meeting / tumour board lists;
- Daily review of theatre logbooks;
- National Leads can help with alternative country-specific methods.

8.2 Follow-up

All investigators are encouraged to actively monitor patients to identify post-operative complications to 30-days, with day 0 considered as the day of surgery. This is part of standard practice as recommended by many hospitals and national organisations (e.g. NICE). Centres should be proactive in identifying postoperative events (or an absence of them). We will ask the method used to obtain 30-day follow-up status. Local arrangements may include:

- Daily review of patient status and notes during admission, and before discharge;
- Reviewing the patient status in outpatient clinic or via telephone at 30 days (if this is normal practice);
- Checking hospital records (electronic or paper) or handover lists for re-attendances or re-admissions;
- Checking for Emergency Department records for re-attendances.

Where local approval exists, record the hospital patient identity number in REDCap.

Alternatively, securely store a file matching the REDCap study ID with the patient's hospital ID so follow-up can be performed. Keep a record of where the linked identifiers are held for future follow-up

9 Statistical analysis

9.1 Sample size

A prospective design analysis has included an exploration of statistical power. Estimates of 30-day mortality for gastrointestinal cancer resection were determined using data from the GlobalSurg 1 and 2 studies. Stratification of results by human development index was performed. Prominent variation in 30-day mortality rate was seen after cancer surgery in both emergency surgery (high HDI, 75/644 (11.6%) vs. low/middle HDI, 59/216 (27.3%)) and elective surgery (high HDI,30/1501 75/644 (2.0%) vs. low/middle HDI, 23/416 (5.5%)). An indicative sample size calculation using the smaller of these estimates suggests around 500 per group at 80% power (p1=0.020, p2=0.055, alpha=0.05) or 640 per group at 90% power would be required to conclude a difference in 30-day mortality rate between HDI groups.

9.2 Analysis

Variation across different international health settings will be assessed by stratifying participating centres by country according to the Human Development Index rank (HDI). This is a composite statistic of life expectancy, education, and income indices published by the United Nations (hdr.undp.org/en/statistics). Further pre-specified subgroup analyses will be made by geographical country grouping, cancer-type, emergency vs. elective surgery, performance status, palliative vs curative surgery, extent of staging, and extent of pathological analyses. Initial univariable analyses will by with Pearson chi-squared tests, Kruskal-Wallis tests, and logistic regression. Bayesian multilevel logistic regression models will be constructed to account for case mix (differing patient, disease, and operative characteristics). We will use weakly-informative priors with sensitivity analyses performed on alternative priors and different chain initiation points/chain lengths, as previous. Models will be constructed using the following principles: 1. Variables associated with outcome

measures in previous studies will be accounted for; 2. Demographic variables will be included in model exploration; 3. Population stratification by hospital and country of residence will be incorporated as random effects with constrained gradients; 4. All first order interactions will be examined and included in final models if found to be influential; 5. Final model selection will be performed using a criterion-based approach by minimising the widely-applicable information criterion (WAIC) and discrimination determined using the c-statistic (area under the receiver operator curve). First-order interactions are expected and will be explored during model building.

Data will not be analysed or reported at an individual surgeon or hospital level. Results will be fed back to participating centres at the centre level. No other centres will be identifiable. Data will not be identifiable to the centre or country that submitted it in any other subsequent analyses.

10 Quality assurance and validation

To ensure high-quality data, several steps will be taken to ensure all data entered is accurate and valid.

10.1 Data validation

Validating data is important to ensure the results obtained for the study are of high quality. Data validation will be performed in two parts as per the structure used in the GlobalSurg 2 study (6).

1. Validation by primary data collection teams:

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

2. Validation by independent teams:
    a. Case ascertainment: hospital records will be reviewed to identify patients fulfilling the inclusion criteria. This will be performed by individuals not involved in collecting the primary data (i.e., doctors, nurses, or medical students who were not part of the recruiting teams). By comparing samples, a quantitative estimate of case ascertainment will be produced by the central data team.
    b. 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 variables, two patient variables, two operation variables, and two outcome measures

If you wish to help with the data validation study, please contact your national GlobalSurg lead via globalsurg.org.

10.2 Pilot phase

An internal pilot will be undertaken to test the REDCap system to ensure that every individual field is operating correctly prior to commencing the study. If you wish to help with the internal pilot and testing phases, please contact the GlobalSurg team.

10.3 Minimum data entry requirements

For inclusion in the study, centres must include consecutive (i.e. one after the other) patients and provide greater than 90% overall data completeness (i.e. no data points should be missed). Centres will fall below the 90% overall data completeness threshold will be removed from data analyses. Collaborators must complete electronic learning beforehand.

Be sure to complete the electronic learning packages on GlobalSurg 3, information governance and outcome assessment at:

globalsurg.org/gs3

11 Appendix A: Key steps for successful inclusion of your hospital

- Subscribe to the GlobalSurg mailing list if you have not already done so: globalsurg.org/subscribe.
- Consider forming a team of up to three people, to help identify patients, collect data, and look for post-operative outcomes. Any healthcare professional is eligible to be part of the team. Medical students are also eligible collaborators, although they must form a team with a local doctor.
- Register your mini-team for the project: globalsurg.org/gs3.
- Your hospital can form multiple teams (up to three people), covering different times.
- Ensure that you gain approval from your hospital. This may involve Clinical Audit Departments, Research and Development Offices, Institutional Review Boards, or responsible individuals (e.g., Head of Department of Surgery). You should use this protocol to complete and support your application. You should begin this process soon because it can take a substantial amount of time. You are responsible for ensuring this is undertaken via the most suitable mechanism and you will be asked to confirm this at the time of data submission.
- Collect complications up to 30 days, either as an inpatient or during a readmission. You should be active in identifying these (review notes, admission lists, other reporting systems).
- Be proactive in identifying postoperative complications (e.g. review patients on the ward, daily checking of hospital notes, review for readmissions etc.). This will prevent under-estimating the true event rate.
- Avoid missing data; complete all fields. If there is >10% of overall missing data at your centre, your centre and name cannot be included in the study.

12 Appendix B: Datafields

Patient characteristics	
Patient ID	Local hospital field
Primary method of patient identification	Multidisciplinary team meeting / tumour board list, outpatient clinic list, theatre logbook, planned operating list, ward/handover list, staff memory
Age	Completed years
Gender	Male, Female, Unknown
Body mass index (weight (kg) / height^2 (metres))	Underweight (BMI <18.5) Normal weight (BMI 18.5 to 24.9) Overweight (BMI 25 to 30) Obese (BMI >30)
Unintentional weight loss (≥10% over 6 months, include clothes size ref in key)	No, Yes, Unknown
Performance status	0, 1, 2, 3, 4, Unknown
ASA score	I, II, III, IV, V, Unknown
Smoking status	No-never, Stopped >6 weeks ago, Yes-current smoker, Unknown
Diabetes	No Diet controlled Medication (non-insulin) controlled Insulin Controlled Unknown
Human Immunodeficiency Virus (HIV) tested	No, Yes-NEGATIVE, Yes-POSITIVE
Pathway	
Presentation	Symptomatic, screening, detected incidentally, unknown
Date of first consult for cancer symptoms (may be estimated)	DD/MM/YYY
Who did the patient first consult for cancer symptoms?	Local clinic: family doctor / general practitioner Local clinic: nurse Local clinic: specialist doctor Hospital: out-patient clinic Hospital: in-patient Other/non-medical/traditional healer Unknown
Distance from home to hospital	< 10 km, 10-20 km, 20-50 km, 50-100 km, >100 km, Unknown
Disease characteristics	
Location	Breast, Gastric, Colorectal
Cancer specific information	Fixed fields for each cancer (see specific cancer variables)
Diagnosis (what tests were performed pre-operatively, please tick all that apply)	Fixed fields for each cancer (see specific cancer variables)
Clinical stage	TNM classification / Essential TNM Classification
Neoadjuvant therapy	Fixed fields for each cancer (see specific cancer variables)
Operative characteristics	
Date of admission	DD/MM/YY, 24 hour clock
Date and time of operation	DD/MM/YY, 24 hour clock
Urgency of operation	Elective, Emergency
Surgical intent (at completion of procedure)	Palliative, Curative
Was a surgical safety checklist used?	No-but available in this hospital, No-but available in this hospital, Yes, Unknown
Primary operation performed	Fixed fields for each cancer (see specific cancer variables)
Pathology	
Most valid basis for cancer diagnosis	Clinical only Imaging Exploratory surgery/endoscopy without histology Tumour specific markers Cytology

	Histology of metastasis (secondary deposit) Histology of primary
Histology	Fixed fields for each cancer (see specific cancer variables)
Size of invasive tumour	Centimetres
TNM (pathology)	
Number of INVOLVED lymph nodes in specimen	
TOTAL number of lymph nodes in specimen	
Histological grade	1, 2, 3, 4
Lymphatic or vascular invasion	No, Yes, Unknown
Resection margins	Fixed fields for each cancer (see specific cancer variables)
Outcomes and adjuvant treatment	
Length of postoperative stay	Continuous number of days
How was 30-day follow-up status achieved? (dropdown box)	Still an inpatient OR re-admitted Clinic review Telephone review Community/home review Discharged before 30 days and not contacted again
30-day mortality (if alive at the point of discharge and no follow-up information available, indicate Alive)	Alive, Dead (date of death), Unknown
30-day cancer-specific complications	Fixed fields for each cancer (see specific cancer variables)
30-day minor complication (CD I)	No, Yes, Unknown
30-day minor complication (CD II)	No, Yes, Unknown
30-day unexpected re-intervention (CD III)	No, Yes-NOT under general anaesthetic, Yes-under anaesthetic, Unknown
30-day unplanned critical care admission (CD IV)	No, Yes-single organ failure, Yes-multi organ failure, Unknown
30-day unplanned hospital readmission	No, Yes, Unknown
Surgical site infection	No Yes, no treatment/wound opened only (CD I) Yes, antibiotics only (CD II) Yes, return to operating theatre (CD III) Yes, requiring critical care admission (CD IV) Yes, resulting in death (CD V) Unknown
Post-operative haemorrhage	No Yes, no intervention required (CD I) Yes, drug treatment only (CD II) Yes, intervention required (CD III) Yes, critical care admission &/- intervention required (CD IV) Yes, resulting in death (CD V) Unknown
Planned adjuvant treatment	Fixed fields for each cancer (see specific cancer variables)

Shaded boxes represent variables which have cancer-specific drop-down boxes

12.1 Breast cancer-specific variables

Disease characteristics	
Diagnosis (what tests were performed pre-operatively, please tick all that apply)	> USS (No-not available, No-not indicated, No-indicated and facilities available, but patient not able to pay, Yes, Unknown) > CT (No-not available, No-not indicated, No-indicated and facilities available, but patient not able to pay, Yes, Unknown) > MRI (No-not available, No-not indicated, No-indicated and facilities available, but patient not able to pay, Yes, Unknown) > Mammogram (No-not available, No-not indicated, No-indicated and facilities available, but patient not able to pay, Yes, Unknown) > Fine needle aspiration (No-not available, No-not indicated, No-indicated and facilities available, but patient not able to pay, Yes, Unknown) > Core biopsy (No-not available, No-not indicated, No-indicated and facilities available, but patient not able to pay, Yes, Unknown) > Open/excision biopsy (No-not available, No-not indicated, No-indicated and facilities available, but patient not able to pay, Yes, Unknown) > ER, PR, Ki-67, HER2 status assessed (No-not available in this hospital, No-but available in this hospital, Yes-NEGATIVE, Yes-POSITIVE, Unknown)
Stage (dropdown box)	TNM classification / Essential TNM classification Unknown
Neoadjuvant chemotherapy	No, patient does not need it No, patient needs it, but not available No, patient needs it, facilities available, but patient not able to pay No, planned but not given Yes, NO anthracycline, NO taxane Yes, anthracycline, NO taxane Yes, anthracycline AND taxane Yes, regimen unknown Unknown
Neoadjuvant radiotherapy	No, patient does not need it No, patient needs it, but not available No, patient needs it, facilities available, but patient not able to pay No, planned but not given Yes (Cobalt) Yes (Linear accelerator) Yes (type unknown) Unknown
Other neoadjuvant treatment (tick all that apply)	Hormone therapy Biological therapy (HER2 inhibitor) Oophrectomy Other (free text)
Operation	
Primary operation	Mastectomy Partial mastectomy / wide local excision / lumpectomy Open biopsy of breast Other operations on breast
Sentinel lymph node biopsy	No, not available in this hospital No, but available in this hospital Yes, single technique Yes, dual technique Unknown
Axillary lymph node biopsy	No, Yes, Unknown
Resection margins checked at time of surgery	No, not available in this hospital

	No, but available in this hospital Yes, by x-ray Yes, by frozen section Unknown
Reconstruction	No, not available in this hospital No, but available in this hospital Yes, immediate – prosthesis Yes, immediate – flap Yes, planned at later stage
Pathology	
Histology	Invasive ductal carcinoma Invasive lobular carcinoma Ductal carcinoma in-situ (DCIS) Other CANCER (specify) Other BENIGN (specify) Unknown, not available in this hospital Unknown, but available in this hospital
Receptor status	ER, PR, Ki67, HER2 No-not available in this hospital, No-but available in this hospital, Yes-NEGATIVE, Yes-POSITIVE, Unknown
Resection margins	< 1 mm / tumour on inked margin 1-5 mm (NO tumour on inked margin) >5 mm Margins confirmed clear, but no distance given Unknown, not available in this hospital Unknown, but available in this hospital
Outcomes and Adjuvant treatment	
Post-operative seroma	No Yes, no intervention/aspiration only (CD I) Yes, antibiotic treatment only (CD II) Yes, intervention required (CD III) Yes, critical care admission &/- intervention (CD IV) Yes, resulting in death (CD V) Unknown
Planned adjuvant treatment (tick all that apply)	No, patient does not need it No, patient needs it, but not available No, patient needs it, facilities available, patient unable to pay Yes, in this hospital Yes, in another hospital in this country Yes, in another hospital in a different country Chemotherapy Radiotherapy Biological therapy (HER2 inhibitor) Hormone therapy Other (free text)

12.2 Gastric cancer

Disease characteristics	
Diagnostic (what tests were performed pre-operatively, please tick all that apply)	> USS (No-not available, No-not indicated, No, indicated and facilities available, but patient not able to pay), Yes, Unknown) > CT (No-not available, No-not indicated, No, indicated and facilities available, but patient not able to pay), Yes, Unknown) > MRI (No-not available, No-not indicated, No, indicated and facilities available, but patient not able to pay), Yes, Unknown) > Endoscopy (No-not available, No-not indicated, No, indicated and facilities available, but patient not able to pay), Yes, Unknown) > Biopsy (No-not available, No-not indicated, No, indicated and facilities available, but patient not able to pay), Yes, Unknown) > Staging laparoscopy (No-not available, No-not indicated, No, indicated and facilities available, but patient not able to pay), Yes, Unknown)
Stage (dropdown box)	TNM classification / Essential TNM classification
Neoadjuvant chemotherapy	No, patient does not need it No, patient needs it, but not available No, patient needs it, facilities available, but patient not able to pay No, planned but not given Yes Unknown
Neoadjuvant radiotherapy	No, patient does not need it No, patient needs it, but not available No, patient needs it, facilities available, but patient not able to pay No, planned but not given Yes (Cobalt) Yes (Linear accelerator) Yes (type unknown) Unknown
Other neoadjuvant treatment (tick all that apply)	Other (free text)
Operation	
Primary operation	Abdomen: Laparotomy with no other procedure Abdomen: Diagnostic laparoscopy with no other procedure Stomach: Total excision of stomach Stomach: Partial excision of stomach Stomach: Connection of stomach to jejunum Stomach: Other open operations on stomach
Site	Upper third (cardia/fundus) Middle third (body) Distal third (antrum/pylorus) Entire stomach Unknown
Cancer specific information	> Anastomosis: Not performed, handsewn, stapled, unknown > D2 lymphadenectomy performed: No, Yes, Unknown > Obstructed: No, Yes, Unknown > Perforated: No, Yes, Unknown
Pathology	
Histology (dropdown box)	Adenocarcinoma Lymphoma Gastrointestinal stromal tumour (GIST) Carcinoid Other CANCER (specify) Other BENIGN (specify)

	Unknown, histology not available in this hospital Unknown, but histology available in this hospital
HER2 receptor status tested (on surgical resection specimen)	No-not available in this hospital, No-but available in this hospital, Yes-NEGATIVE, Yes-POSITIVE, Unknown
Resection margins	No residual disease (R0) Microscopic residual disease (R1) Macroscopic residual disease (R2) Unknown, not available in this hospital Unknown, but available in this hospital
Outcomes and adjuvant treatment	
Intra-abdominal abscess	No Yes, no intervention (CD I) Yes, antibiotics only (CD II) Yes, surgical/radiological drainage (CD III) Yes, critical care admission (CD IV) Yes, resulting in death (CD V) Unknown
Anastomotic leak	No Yes, no intervention required (CD I) Yes, drug treatment only (CD II) Yes, intervention required (CD III) Yes, critical care admission &/- intervention required (CD IV) Yes, resulting in death (CD V) Unknown
Planned adjuvant treatment (tick all that apply)	No, patient does not need it No, patient needs it, but not available No, patient needs it, facilities available, patient unable to pay Yes, in this hospital Yes, in another hospital in this country Yes, in another hospital in a different country Chemotherapy Radiotherapy Biological therapy (HER2 inhibitor) Hormone therapy HIPEC Other (free text)

12.3 Colorectal cancer

Disease characteristics	
Diagnostic (what tests were performed pre-operatively, please tick all that apply)	> USS (No-not available, No-not indicated, No-indicated and facilities available, but patient not able to pay, Yes, Unknown) > CT (No-not available, No-not indicated, No-indicated and facilities available, but patient not able to pay, Yes, Unknown) > MRI (No-not available, No-not indicated, No-indicated and facilities available, but patient not able to pay, Yes, Unknown) > Endoscopy (No-not available, No-not indicated, No-indicated and facilities available, but patient not able to pay, Yes, Unknown) > Biopsy (No-not available, No-not indicated, No-indicated and facilities available, but patient not able to pay, Yes, Unknown) > Staging laparoscopy (No-not available, No-not indicated, No-indicated and facilities available, but patient not able to pay, Yes, Unknown)
Stage	TNM classification / Essential TNM classification Unknown
Neoadjuvant chemotherapy	No, patient does not need it No, patient needs it, but not available No, patient needs it, facilities available, but patient not able to pay No, planned but not given Yes Unknown
Neoadjuvant radiotherapy	No, patient does not need it No, patient needs it, but not available No, patient needs it, facilities available, but patient not able to pay No, planned but not given Yes (Cobalt) Yes (Linear accelerator) Yes (type unknown) Unknown
Other neoadjuvant treatment (tick all that apply)	Other (free text)
Operation	
Primary operation	Abdomen: Laparotomy with no other procedure Abdomen: Diagnostic laparoscopy with no other procedure Small bowel: Formation of ileostomy only Colon: Total excision of colon and rectum Colon: Total excision of colon Colon: Extended excision of right hemicolon Colon: Excision of right hemicolon Colon: Excision of transverse colon Colon: Excision of left hemicolon Colon: Excision of sigmoid colon Colon: Other excision of colon Colon: Formation of any colonic stoma Colon: Other open operations on colon Rectum: Abdominoperineal resection Rectum: Resection with anastomosis of colon to anus Rectum: Anterior resection with anastomosis Rectum: Resection with closure of rectal stump (Hartmann's) Rectum: Other open operations on rectum
Cancer specific information	> Site: Caecum, Ascending colon, Transverse colon, Descending colon, Sigmoid colon, High rectum (>10 to 15cm from anal verge), Middle Rectum (>5 to 10cm),

	Low rectum (≤5cm), Unknown > Anastomosis: Not performed, handsewn, stapled, unknown > Obstructed: No, Yes, Unknown > Perforated: No, Yes, Unknown
Stoma formation	No, Yes, loop ileostomy Yes, end ileostomy Yes, loop colostomy Yes, end colostomy Unknown
Pathology	
Histology (dropdown box)	Adenocarcinoma Squamous cell carcinoma Carcinoid Lymphoma Other CANCER (specify) Other BENIGN (specify) Unknown, histology not available in this hospital Unknown, but histology available in this hospital
Perineural invasion	No, Yes, Unknown
Resection margins	No residual disease (R0) Microscopic residual disease (R1) Macroscopic residual disease (R2) Unknown, not available in this hospital Unknown, but available in this hospital
Circumferential margin (CRM)	Millimetres
Outcomes and adjuvant treatment	
Anastomotic leak	No Yes, no intervention required Yes, intervention required Yes, critical care admission +/- intervention required Unknown
Planned adjuvant treatment (tick all that apply)	No, patient does not need it No, patient needs it, but not available No, patient needs it, facilities available, patient unable to pay Yes, in this hospital Yes, in another hospital in this country Yes, in another hospital in a different country Chemotherapy Radiotherapy Biological therapy (HER2 inhibitor) Hormone therapy Liver resection (metastasis) Lung resection (metastasis) HIPEC Other (free text)

13 Appendix C: Optional feasibility studies

Oncological outcomes	
Disease-free survival	Assessment of signs, symptoms, and imaging results for evidence current disease at: 3, 6, 12 months
Overall survival	Death from any cause at: 3, 6, 12-months
Patient-centred / quality of life outcomes	
EQ-5D	Quality of life questionnaire administered at: 3 +/- 6 months
Disease-specific quality of life questionnaire	Administered at: 3 +/- 6 months
Economic costs of treatment questionnaire	Administered at: 3 +/- 6 months

Appendix D: Required data fields - Glossary of Terms

This section provides a data dictionary for key terms in the required data fields where they are not self-explanatory. It also provides information on where will be best to find this data, shown in italics. Much of this data can be collected after becoming familiar with the system. Some of it may be supported by input from the junior doctor(s) in your mini-team.

13.1 Patient data collection form

Record ID: A unique ID automatically generated by REDCap for each of your patients.

Patient ID (notes): Enter your patient ID here. Only you will have access to this secure field. Use the official hospital ID if you have permission. If you don't have hospital IDs at your centre, enter an identifying number here that you can match to the patient (e.g. 1, 2, 3).

Age, Sex (notes): As standard.

Body mass index (BMI) (direct observation, notes): Weight (kg) / Height^2 (metres) (height is squared/to the power two).

Recent weight loss (notes): The weight that the patient has lost compared to their usual body weight, over the preceding 6 months, prior to the date of operation. >10% or estimated with patient dropping a clothes size / 2x belt buckle holes.

Performance status (direct observation, notes):

0. Fully active, able to carry on all pre-disease performance without restriction.
1. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2. Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hour.
3. Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.

4. Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

American Society of Anaesthesiologists score (take from anaesthetic chart, filed in notes):

1. Normal healthy patient.
2. Patient with mild systemic disease.
3. Patient with severe systemic disease.
4. Patient with severe systemic disease that is a constant threat to life.
5. Moribund patient not expected to survive without the operation.

Presentation (direct observation, clinical notes, admission records): Was the patient symptomatic or not? If not, did they come through a screening programme, where healthy individuals without symptoms undergo an investigation for cancer.

Date of first consult for cancer symptoms (direct observation, clinical notes, admission records): This refers to the first date on which the patient's cancer was diagnosed, whether that was through an Emergency Department or directly with surgical services.

13.2 Disease and neoadjuvant treatment data collection form

Cancer specific information (notes or on computer): See Appendix E for cancer specific glossary of terms.

Clinical stage (clinic letter, notes, MDT discussion): This relates to the most advanced clinical stage for the patient's cancer prior to surgery. If the patient has been staged with the TNM classification, this should be used. However, if the TNM classification is not available, the **Essential TNM Classification**[5] should be used instead.

[5] http://www.hoofdhalskanker.info/wpavl/wp-content/uploads/TNM-Classification-of-Malignant-Tumours-8th-edition.pdf

Surgical intent (direct observation, operation note, filed in notes or on computer): This refers to the aim of the cancer surgery, whether for cure or to alleviate symptoms/reduce tumour bulk without the potential for cure.

13.3 Operation data collection form

Was a surgical safety checklist used? (direct observation, clinical notes): This related to the WHO surgical safety checklist (or an equivalent local checklist)

Primary operation performed (operation note, filed in notes or on computer): This should record the main procedure performed.

Cancer specific operation information (notes or on computer): See Appendix E for cancer specific glossary of terms.

13.4 Outcomes data collection form

Length of stay following surgery (notes): The day of surgery counts as Day 0, and the day of discharge as a whole day, (e.g., staying from Monday to Friday counts as a 4-day length of stay and “4” should be entered).

30-day peri-operative mortality (direct observation, computer, notes): Defined as the number of all-cause deaths during operation or within 30 days of operation, or at the point of final discharge if out-patient mortality status unknown.

Unplanned admission to critical care (direct observation, computer, notes): Critical care (level 2 or 3) is defined as the unexpected requirement for support of one or more body systems or organs. This may consist of the requirement for mechanical ventilation, high-flow oxygen therapy, haemofiltration, vasopressor support and continuous invasive monitoring.

30-day re-intervention (direct observation, computer, notes): This relates to surgical, endoscopic or radiological re-intervention, by Day 30. The entry field allows which method used to be specified.

Unplanned readmission to hospital post-discharge (direct observation, computer, notes): Unplanned readmission is defined as the requirement to return as a hospital inpatient within **30 days of the primary index operation**.

Wound infection (direct observation, computer, notes, outpatients): We advise adherence to the Centre for Disease Control's definition of surgical site infection (7), which is **any one of**:

(1) Purulent drainage from the incision;

(2) **At least two of**: pain or tenderness; localised swelling; redness; heat; fever; **AND** the incision is opened deliberately to manage infection or the clinician diagnoses a surgical site infection;

(3) Wound organisms AND pus cells from aspirate/swab

Intra-abdominal/Pelvic abscess (direct observation, computer, notes, radiology systems, outpatients): Detected clinically/symptomatically, radiologically, or intra-operatively.

13.5 Pathology and adjuvant treatment data collection form

Pathology (clinical notes, or operation note, filed in notes or on computer): This should record the main pathology of the resected specimen.

Resection margins (clinical notes, or operation note, filed in notes or on computer):

- R0: No cancer cells seen microscopically at resection margin
- R1: Cancer cells present at resection margin (microscopic positive margin)

- R2: Gross examination by the naked eye shows tumour present at the resection margin

Circumferential resection margin (CRM): Refers to the minimum distance (in millimetres) of normal tissue that lies between the resection margin and the tumour following surgical resection

14 Appendix E: Cancer-specific glossary of terms

14.1 Breast cancer

14.2 Breast Clinical Classification (TNM 8)

The clinical staging of breast cancer:

- T categories: Physical examination and imaging
- N categories: Physical examination and imaging
- M categories: Physical examination and imaging

14.2.1 T – Primary Tumour

- T1 Tumour 2 cm or less in greatest dimension
- T2 Tumour more than 2 cm but not more than 5 cm in greatest dimension
- T3 Tumour more than 5 cm in greatest dimension
- T4 Tumour of any size with direct extension to chest wall and/or to skin (ulceration or
- skin nodules)

14.2.2 N – Regional Lymph Nodes

- N0 No regional lymph node metastasis
- N1 Movable ipsilateral level I, II axillary lymph node(s)
- N2 Fixed ipsilateral level I, II axillary lymph node(s);
    - or ipsilateral internal mammary lymph node(s) in the absence of clinically evident axillary lymph node metastasis
- N3 Ipsilateral infraclavicular (level III axillary) lymph node(s);
    - or ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastasis;
    - or ipsilateral supraclavicular lymph node(s)

The regional lymph nodes are:

1. Axillary (ipsilateral): interpectoral (Rotter) nodes and lymph nodes along the axillary vein and its tributaries, which may be divided into the following levels:
    a. Level I (low axilla): lymph nodes lateral to the lateral border of pectoralis minor muscle
    b. Level II (mid axilla): lymph nodes between the medial and lateral borders of the pectoralis minor muscle and the interpectoral (Rotter) lymph nodes
    c. Level III (apical axilla): apical lymph nodes and those medial to the medial margin of the pectoralis minor muscle, excluding those designated as subclavicular or infraclavicular
2. Infraclavicular (subclavicular) (ipsilateral)
3. Internal mammary (ipsilateral): lymph nodes in the intercostal spaces along the edge of the sternum in the endothoracic fascia
4. Supraclavicular (ipsilateral)

14.2.3 Essential TNM

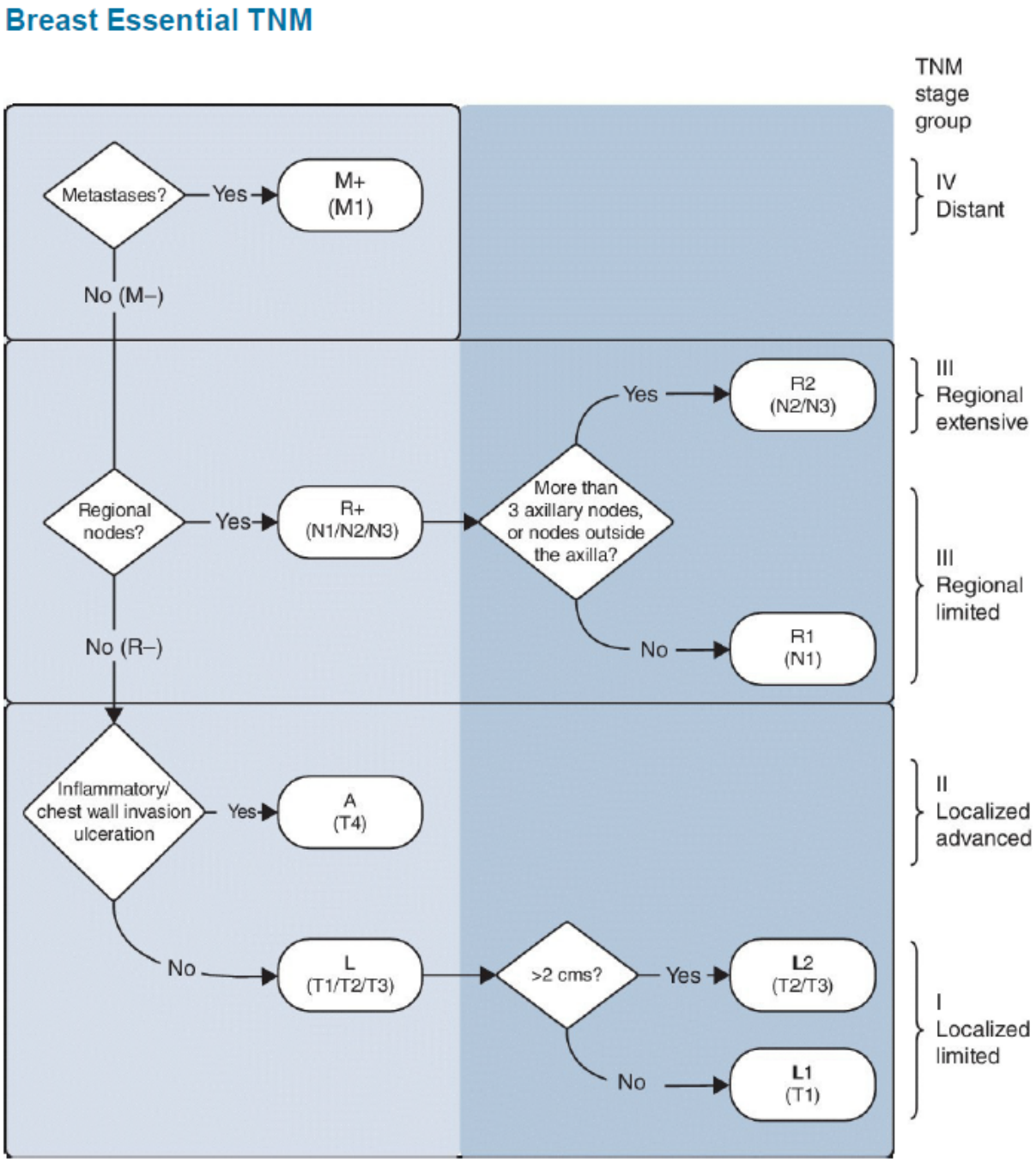


Figure 3 Breast essential TNM.

Seroma (direct observation, clinical notes, or operation note): is a pocket of clear fluid which collects within the surgical tissue cavity created following breast cancer excision. This can be diagnosed clinically with or without the use of radiological tests.

14.3 Gastric cancer

The classification applies only to carcinomas. There should be histological confirmation of the disease. For cancers at the oesophagogastric junction (OGJ), only include those whose epicentre is in the stomach (defined as more than 2 cm distal from the OGJ).

The following are the procedures for assessing the T, N, and M categories.

- T categories: Physical examination, imaging, endoscopy, and/or surgical exploration
- N categories: Physical examination, imaging, and/or surgical exploration
- M categories: Physical examination, imaging, and/or surgical exploration

- T1 Tumour invades lamina propria, muscularis mucosae, or submucosa
    - Tumour has grown through lining (mucosa) of stomach
- T2 Tumour invades muscularis propria
    - Tumour has grown into thick inner muscle layer
- T3 Tumour invades subserosa
    - Tumour invades visceral peritoneum of stomach but has not perforated it
- T4 Tumour perforates serosa (visceral peritoneum) or invades adjacent structures
    - Tumour perforates outer layer or invades adjacent structures

Tumour site (direct observation, endoscopy report, operation note, filed in notes or on computer): This refers to where within the stomach the greatest proportion of the tumour is located and is determined according to the Japanese Gastric Cancer Association classification system (14):

- Upper third: Tumours located predominantly in the cardia or gastro-oesophageal junction
- Middle third: Tumours located predominantly in the midbody

- Distal third: Tumours located predominantly in the pylorus
- Entire stomach: Tumours which span all three regions (upper, middle, lower) of the stomach

D2 lymphadenectomy (direct observation, operation note, filed in notes or on computer): This refers to the en-bloc resection of local gastric lymph nodes and those around the coeliac axis, splenic hilum and hepatoduodenal ligament during gastrectomy, according to the Japanese Gastric Cancer treatment guidelines (14).

Anastomotic leak (clinical notes, operation note, filed in notes or on computer): Anastomotic leak is defined as the presence of a communication between the lumen of the stomach and the chest/abdomen/pelvis at the site of a previously formed anastomosis.

14.4 Colorectal cancer

The classification applies only to carcinomas. There should be histological confirmation of the disease.

The following are the procedures for assessing the T, N, and M categories.

- T categories Physical examination, imaging, endoscopy, and/or surgical exploration
- N categories Physical examination, imaging, and/or surgical exploration
- M categories Physical examination, imaging, and/or surgical exploration

- T1 Tumour invades submucosa
    - Tumour has grown through lining (mucosa)
- T2 Tumour invades muscularis propria
    - Tumour has grown into thick inner muscle layer

- T3 Tumour invades subserosa or into non peritonealized pericolic or perirectal tissues
    - Tumour invades visceral peritoneum but has not perforated it, or where there is no peritoneum, has invaded fatty tissues around colon or rectum.
- T4 Tumour directly invades other organs or structures and/or perforates visceral peritoneum

N0 No regional lymph node metastasis

N1 Metastasis in 1 to 3 regional lymph nodes

N2 Metastasis in 4 or more regional lymph nodes

Essential TNM

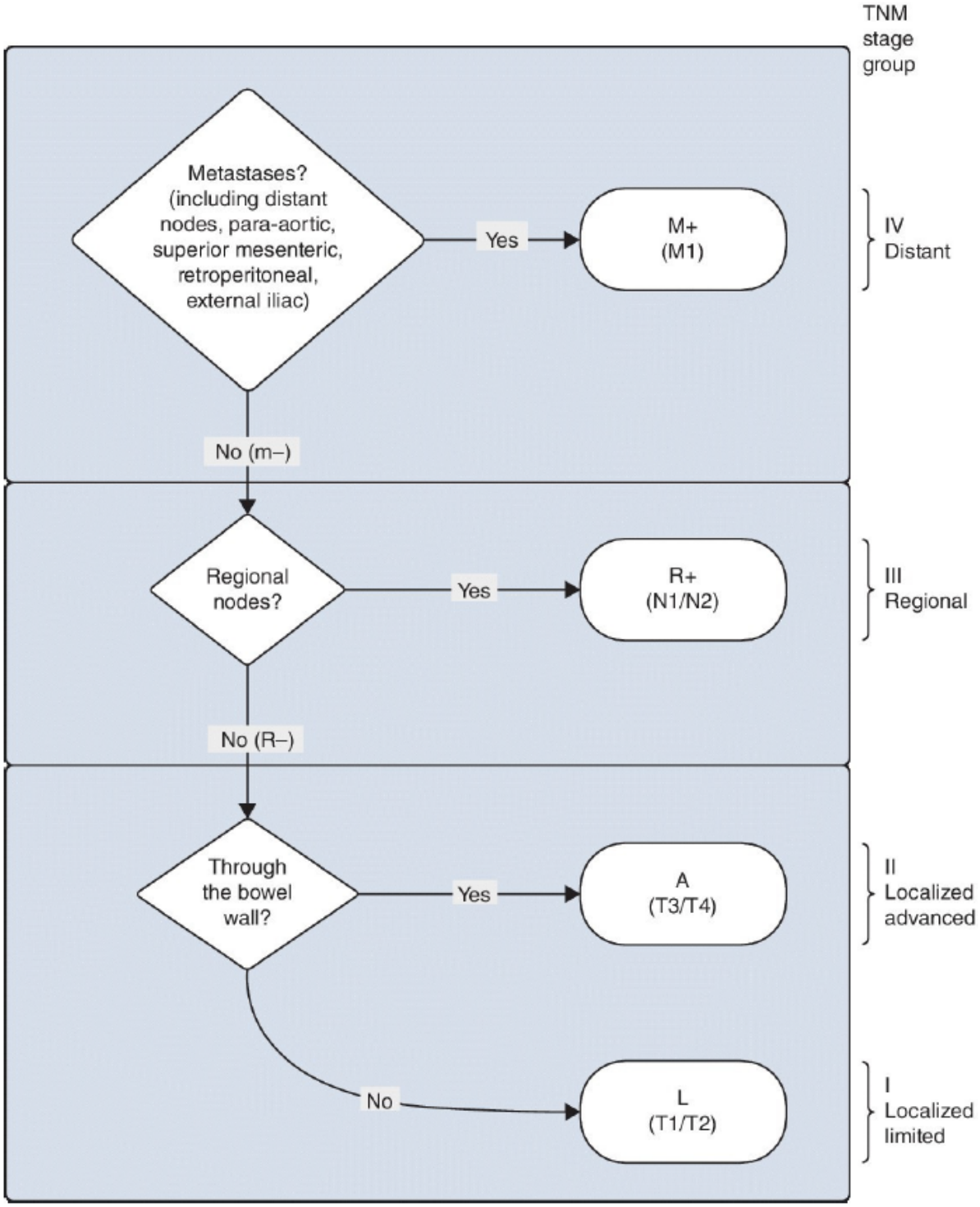


Figure 2 Colon and rectum essential TNM.

Endoscopy (clinical notes, or operation note, filed in notes or on computer): This includes both flexible sigmoidoscopy and colonoscopy (whether completed or attempted).

Rectal tumours (clinical notes, or operation note, filed in notes or on computer): These are classified by the distance between the most distal aspect of tumour and the anal verge (15).

- High rectal: 10.1 – 15 cm
- Middle rectal 5.1 – 10 cm
- Low rectal ≤5 cm from anal verge

Obstructed tumour (clinical notes, or operation note): A tumour which has caused complete occlusion of the bowel lumen, blocking both the passage of faeces and gas.

Perforated tumour (clinical notes, or operation note): Loss of the integrity of the bowel lumen and spillage of bowel content into the abdomen due to erosion of the bowel wall by the tumour.

Stoma formation (direct observation, operation note, filed in notes or on computer): These are categorised in the main groups. If a mucous fistula type stoma is made in addition to any category, this does not need to be recorded.

Anastomotic leak (clinical notes, operation note, filed in notes or on computer): Anastomotic leak is defined as the presence of a communication between the lumen of the stomach and the chest/abdomen/pelvis at the site of a previously formed anastomosis.

15 Appendix F: Data collection system information for local approvals / ethical review boards

15.1 How is the data collected?

Data will be collected via a secure online system run by University of Edinburgh using the REDCap software (http://project-redcap.org/). REDCap is used around the world to securely gather research data. This is designed specifically around HIPAA-Security guidelines.

15.2 Where is the data being stored and used?

REDCap is run by the Surgical Informatics research group (The University of Edinburgh) within the University of Edinburgh Virtual Machine architecture which is physically secured.

Data is stored in MySQL databases on a separate server. This server is behind a firewall and can only be accessed from the IP address of the web server. An SSL-tunnel encrypts communication between the web and databases servers. File upload is secured between servers using the WebDAV protocol with SSL. “At rest” encryption is in place on the database server (aes-xts-plain64:sha256 with 512-bit keys). Operating security updates are installed automatically. Antivirus software runs to a scheduled protocol on the web server.

Raw data will be stored and will remain at the Edinburgh site – it will not be offshored to any other location.

15.3 What kind of access control and auditing is in place?

All collaborators will be issued individual accounts with secure logins. Collaborators from the same hospital can view data entered by other investigators at the same hospital (but not other hospitals in the same country). REDCap has a built-in audit trail that automatically logs all user activity and logs all pages viewed by every user, including contextual information (e.g. the project or record being accessed). Whether the activity be entering data, exporting data, modifying a field, running a report, or add/modifying a user, among a plethora of other activities, REDCap logs all actions. The built-in audit trail in REDCap allows administrators to be able to determine all the activity and all the data viewed or modified by any given user.

User passwords are managed directly. Accounts are disabled after 5 failed login attempts. Users are auto logged out after 30 mins of no activity. Users are forced to change password after 90 days. Password strength: at least 9 characters in length and must consist of at least one lower-case letter, one upper-case letter, and one number. Daily audit tracking of users is in place with removal of unused user accounts.

South East Scotland Research Ethics Service

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Ewen M Harrison

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NIHR Unit on Global Surgery (Universities of Birmingham, Edinburgh and Warwick)
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Date: 19/02/2018
Your Ref:
Our Ref: NR/161AB6
Enquiries to:
Direct Line: 0131 465 5679
Email:

Dear Mr Harrison,

Project Title: "GlobalSurg 3: Quality and outcomes in global cancer surgery: a prospective, international cohort study"

You have sought advice from the South East Scotland Research Ethics Service on the above project. This has been considered by the Scientific Officer and you are advised that, based on the email correspondence it does not need NHS ethical review under the terms of the Governance Arrangements for Research Ethics Committees (A Harmonised Edition).

If the project is considered to be health-related research you will require a sponsor and ethical approval as outlined in The Research Governance Framework for Health and Community Care. You may wish to contact your employer or professional body to arrange this. You may also require NHS management permission (R&D approval). You should contact the relevant NHS R&D departments to organise this.

For projects that are not research and will be conducted within the NHS you should contact the relevant local clinical governance team who will inform you of the relevant governance procedures required before the project commences.

This letter should not be interpreted as giving a form of ethical approval or any endorsement of the project, but it may be provided to a journal or other body as evidence that NHS ethical approval is not required. However, if you, your sponsor/funder feel that the project requires ethical review by an NHS REC, please write setting out your reasons and we will be pleased to consider further. You should retain a copy of this letter with your project file as evidence that you have sought advice from the South East Scotland Research Ethics Service.

Yours sincerely,

Helen Newbery
Scientific Officer
South East Scotland Research Ethics Service

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