SHORT TITLE

P-iGBC

(Predicting Incidental Gallbladder Cancer)

FULL TITLE OF THE TRIAL

Identifying predictive factors of incidentally detected gallbladder cancer and prospective validation of a scoring system to allow selective histological analysis of the gallbladder.

Version 1.3: 04 November 2024

IRAS Number:	334671
REC Reference:	24/LO/0504
FREIC Reference:	5550
SPONSORS Number:	23SUR879
FUNDERS Number:	TBC

This protocol describes the study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS UK Policy Framework for Health and Social Care Research (2017). It will be conducted in compliance with the protocol, the Data Protection Act (2018) and other regulatory requirements as appropriate.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature:  Date: 05/11/2024

Name (please print): Muchineripi Kanengoni

Position: Research Governance Manager

Chief Investigator:

Signature:  Date: 04/11/2024

Name (please print): Mr Somaiah Aroori

KEY CONTACTS

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Funder(s):	Peninsula Medical Foundation
	Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
	University Hospitals Plymouth NHS Trust

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GLOSSARY OF ABBREVIATIONS

AE	Adverse event
BHA	Benign Histological Abnormalities
BMI	Body Mass Index
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CRF	Clinical Research Fellow
fP-iGBC	Feasibility/Pilot phase of P-iGBC (qP-iGBC and pP-iGBC together)
GBC	Gallbladder Cancer
GBD	Gallbladder Dysplasia
GPo	Gallbladder Polyp(s)
HRA	Health Research Authority
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ICJME	International Committee of Medical Journal Editors
iGBC	Incidental Gallbladder Cancer
NHS	National Health Service
NRES	National Research Ethics Service
PES	Plain English Summary
PI	Principal Investigator
P-iGBC	Predicting Incidental Gallbladder Cancer (short title/acronym for full study)
PIS	Participant/ Patient Information Sheet
PPIE	Patient and Public Involvement and Engagement
pP-iGBC	Pilot P-iGBC Component
qP-iGBC	Qualitative P-iGBC Component

R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RHA	Routine Histological Analysis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SHA	Selective Histological Analysis
SOP	Standard Operating Procedure
TBC	To Be Confirmed
UHP	University Hospitals Plymouth NHS Trust
UK	United Kingdom
XC	Xanthogranulomatous Cholecystitis

KEY WORDS

Incidental Gallbladder Cancer, Gallbladder Cancer, Cholecystectomy, Histology, Gallbladder, Selective Histological Analysis, Histopathology, Adaptive design

STUDY SUMMARY

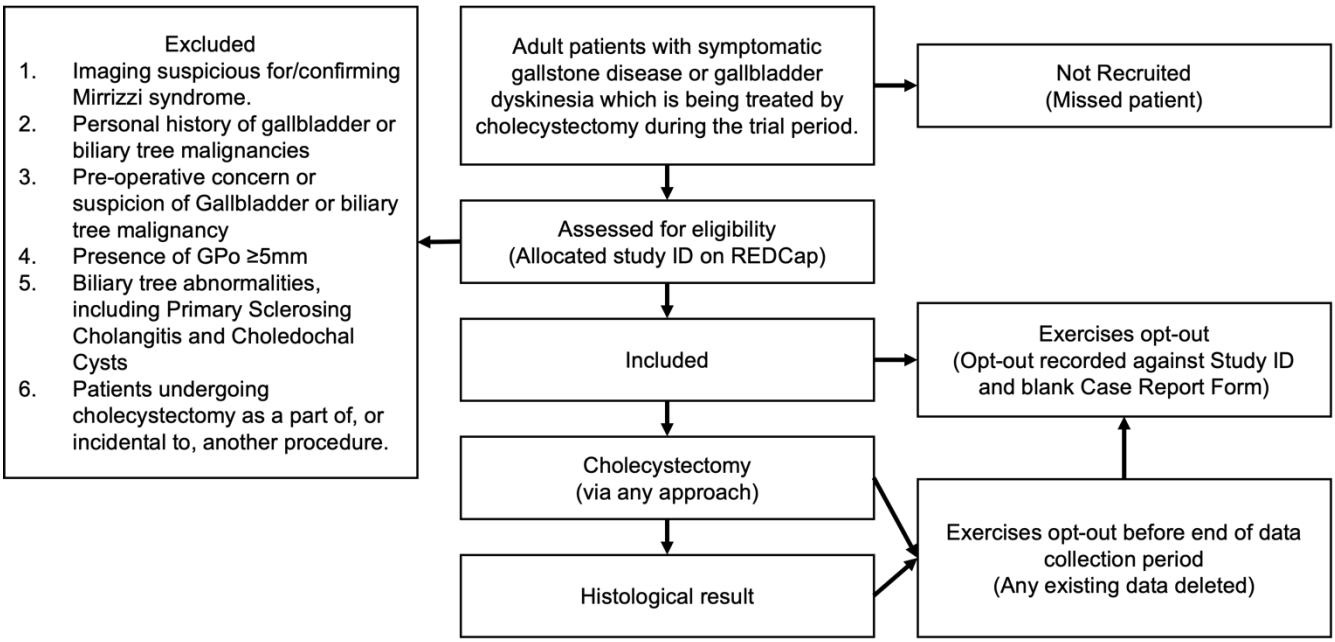
Study Title	Identification of **P**redictive factors of **I**ncidentally detected **G**all**b**ladder **C**ancer and prospective validation of a scoring system to allow selective histological analysis of the gallbladder (**P-iGBC**).
Study Design	Prospective, Multi-centre, Observational & Modelling Study with an internal pilot and adaptive design. Parallel, embedded qualitative study
Study Participants	Adults undergoing cholecystectomy during the trial period, Biliary pathway patients and professionals involved in their care.
Eligibility Criteria	Inclusion Criteria: All adult patients (>=18 years of age) undergoing cholecystectomy (including subtotal and remnant cholecystectomy) for benign indications: 1. Symptomatic Gallstone Disease 2. Biliary dyskinesia Exclusion Criteria: 1. Imaging suspicious for/confirming type III & IV Mirrizzi syndrome. 2. Previous or current diagnosis of biliary tree malignancies 3. Pre-operative concern or suspicion of Gallbladder or biliary tree malignancy 4. Presence of gallbladder polyps ≥5mm 5. Biliary tree abnormalities, including Primary Sclerosing Cholangitis and Choledochal Cysts 6. Patients undergoing cholecystectomy as a part of, or incidental to, another procedure.

Planned Sample Size	300-500 (internal pilot) up to 30,000 (TBC on the result of an internal pilot)
Follow-up Duration	Ends on report of histopathology result. No longitudinal follow-up.
Planned Study Period	June 2024-June 2029
Primary Objective	Development and validation of a diagnostic score for incidental gallbladder cancer
Secondary Objectives	Evaluation of willingness for and barriers to selective histological analysis of the gallbladder Incidence of incidental Gallbladder Cancer and associated benign abnormalities. Identification of the risk factors for incidental Gallbladder Cancer.

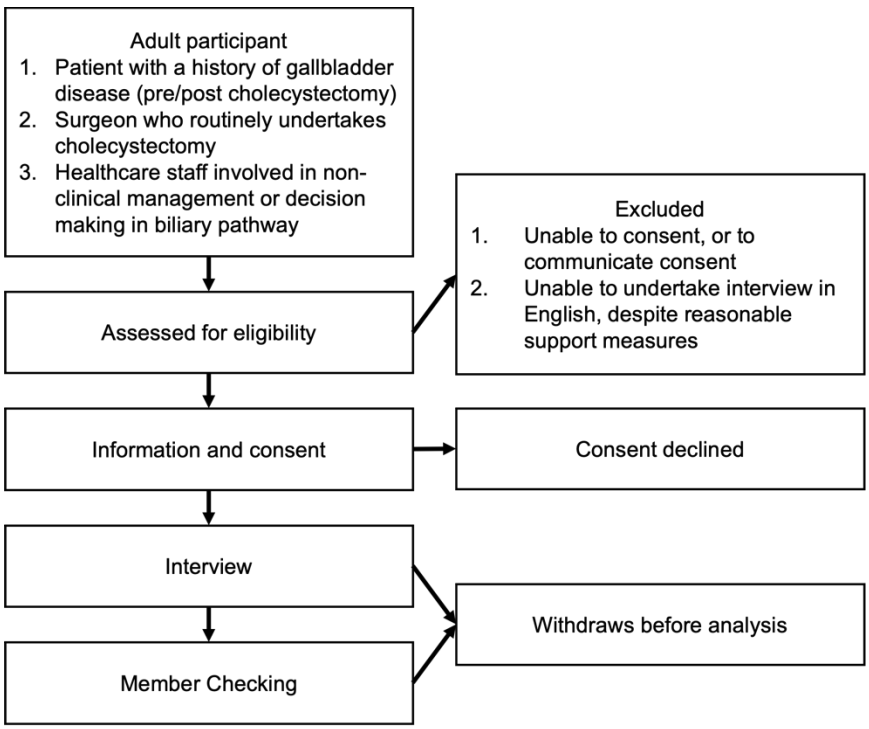
Date and Version No: 04/11/2024; Version 1.3

STUDY FLOW CHARTS

Quantitative component



Qualitative component



1. INTRODUCTION

1.1 BACKGROUND

Incidental Gallbladder Cancer (iGBC) is a rare diagnosis following cholecystectomy, which is a common operation normally performed for symptomatic gallstone disease (1,2). Less common benign indications include gallbladder dyskinesia and gallbladder polyps. Overall, 67,819 cholecystectomies were performed in NHS England and Wales in the year to March 2022 and it is standard practice in the UK for cholecystectomy specimens to be sent for Routine Histological Analysis (RHA) to exclude underlying iGBC(1,3). The United Kingdom (UK) has a low incidence of iGBC of between 0.14-0.3%, which contrasts with high-incidence countries, for example in South America and South Asia, where it is as high as 1.18% (4–12). Other, non-cancerous abnormalities, termed Benign Histological Changes (BHC), such as Xanthogranulomatous Cholecystitis (XC) and Gallbladder Dysplasia (GBD), can be challenging to diagnose or differentiate from cancer macroscopically and therefore require histological examination. Combined, iGBC and BHC have an incidence in the UK of around 2% (4,6,13).

RHA is not unique to the UK, and is practised in most high-income countries, however it is expensive and requires examination of thousands of unremarkable gallbladders to diagnose relatively few patients with iGBC(1,8,10,14). We conservatively estimate that the cost of RHA in routine cholecystectomy is at least £5,055,228.26 annually, based on an historic estimate of the cost of processing individual specimens multiplied by the volume of cholecystectomies quoted above (1,8). In addition to the financial costs incurred by RHA, processing so many gallbladder specimens puts enormous pressure on histopathology services who are acknowledged to be overburdened and under resourced(15,16). This volume of specimens is particularly significant at present, as subsequent delays in processing NHS cancer specimens can anecdotally reach 4- 6 weeks, potentially delaying decisions on adjuvant treatment (e.g. chemotherapy) which, in some cases, may affect overall survival(17). As the incidence of iGBC is so low, it has been argued that sending every gallbladder specimen for RHA is unnecessary and could be replaced with Selective Histological Analysis (SHA), whereby gallbladders with no significant risk of iGBC or BHC would not be sent for histopathology(3,5,8–11,18–20).

Whilst SHA has the potential to significantly reduce costs and mitigate high pathological workloads, its safety is intrinsic to its success. Key to this is a good, clinically applicable method of risk-stratification, and current methods require improvement. Some centres in high-income countries already practice SHA, however the risk stratification methods and criteria by which gallbladders are selected for histopathology are not always clear (7,20). Proponents of SHA suggest that it is safe when specimen

selection is based on macroscopic inspection or uses a defined, algorithmic approach (5,9,11,14,21). However, review data suggests that macroscopic inspection misses between 23.1 and 33.3% of iGBC and that there are higher incidences of iGBC in RHA centres than in SHA centres. This implies that current selection methods lead to missed diagnoses(5,7,20). Although it is not clear why SHA has not been adopted in the UK, it has been suggested that UK surgeons are averse to taking responsibility for a missed diagnoses(21,22). Further, whether SHA is acceptable to patients in the UK is yet to be evaluated.

The risk factors for GBC are well recognised. Cholelithiasis is a pre-disposing factor, and there is a strong association with chronic cholecystitis, while acute cholecystitis confers a poorer prognosis (23–25). Other risk factors include age, ethnicity, female gender, jaundice, a raised alkaline phosphatase, certain intra-operative factors and findings (including macroscopic cholecystitis or a thick-walled gallbladder and a need for lengthy or open operations), a history of typhoid infection or pre-existing disorders of the biliary tree, such as Primary Sclerosing Cholangitis and Choledochal Cysts(7,10,13,14,19,26–28). Gallbladder polyps are also associated with GBC, with a well described relationship between the size of the polyp and likelihood of cancer. The risk is negligible in polyps under 5mm but rises above the 0.2% UK incidence of iGBC to a 1.2% risk of GBC when the polyp is between 5-10mm, and increases to 8.5% in polyps over 10mm(29). It is therefore recommended that patients with high-risk polyps over 5mm or any polyps over 10mm undergo prophylactic resection(30,31). In Mirrizzi Syndrome, in which impacted stones fistulate into the Common Hepatic Duct, the risk of GBC and cholangiocarcinoma occur is even higher, occurring in up to 28% of patients(32–34).

Although these multiple risk factors for GBC are well recognised, there is no robust risk-stratification method which is suitable for use in routine cholecystectomy in the UK. If a clinically applicable diagnostic score was able to stratify patients by their risk of iGBC, it could facilitate SHA, but importantly may also enable early identification, intervention, or investigation in high risk patients. These two major benefits of a risk-stratification or diagnostic score have clear potential benefits for patients and the health service, so it is perhaps unsurprising that there are already two such diagnostic scores in existence. Both, however, are limited in their reliability by their methodology and in their generalisability to the UK because of the settings in which they were developed. The first study, from a Swedish group, developed a diagnostic score based on age, sex, presence of cholecystitis and jaundice(19). A Dutch group recently published a more methodologically sound, retrospective, multi-centre study (18). From a methodological viewpoint, the data from which both were derived were limited and poorly complete - the Dutch study was missing 30.9% of data - and

both resultant scores consequently failed to identify all patients with iGBC in validation. Furthermore, the studies relied on existing or prospectively collected registry variables and, as a result, neither captured or were able to utilise many of the multiple known pre- and intra-operative risk factors. Further, both studies were conducted in settings in which SHA is already sporadically practiced, which may have meant that iGBC diagnoses were missing from their datasets leading to skewed data.

When comparing the populations in question, a further problem with the use of these scores arises. Compared to other European countries where patients are often operated within days of presentation, NHS patients wait longer for their cholecystectomies and therefore risk recurrent inflammation (35–43). In this post-COVID-19 era, a higher proportion of UK cholecystectomies are being performed for inflammatory indications, and this may suggest that the UK prevalence of iGBC will increase or the prognosis be poorer(7,23,35). As a consequence, we are unable to generalise the findings of the Swedish and Dutch studies to our own population and there is, therefore, a need for a high quality and comprehensive diagnostic modelling study of UK patients, to accurately identify and stratify the risk of iGBC.

This study aims to collect the data required to develop a high-fidelity, clinically applicable diagnostic score with a high negative predictive value, and has the potential to facilitate SHA and early identification of patients at high-risk of iGBC in this country.

1.2 RATIONALE FOR CURRENT STUDY

Stratifying patients undergoing routine cholecystectomy by their risk of iGBC could facilitate SHA, enabling significant financial savings and reduced histopathological workloads, and allow identification of the highest-risk patients, meaning that their care could be prioritised appropriately. Published diagnostic scores and historical techniques, such as macroscopic inspection, either fail to identify all cases of iGBC or are poorly generalisable to our population and, as such, are inadequate for use in the UK. Multiple risk and predictive factors are well established, but no dataset adequately encompasses them to develop and validate such a robust, UK-based diagnostic score for iGBC.

This study aims to build a dataset from which a validated diagnostic score could be developed.

1.3 PARTICIPANT AND PUBLIC INVOLVEMENT AND ENGAGEMENT

Fortunately, we have had the support of a patient representative (AB) who has critically reviewed the study design and documents, and has provided valuable feedback. A second patient representative

(HW) has assisted in developing Plain English Summaries (PES) for formal PPIE consultation and grant applications.

The overall hypotheses and aims of the study were discussed with the PENPeg PPIE group's "Ideas Cafe" in its early development stages. The group unanimously supported the project, with several members expressing surprise at the current practice of routine histological analysis in cholecystectomy.

A formal PPIE consultation has been undertaken, in which five patients agreed to participate. Patients were provided with pertinent study documents and a PES before one-to-one meetings were held. For full report on the PPIE consultation, including full methodology and detailed results, please see appendix 12.

Overall, consultation participants were very supportive of the study, stating that they were, "so much in favour of what you're doing," and that the study would be, "helpful for patients and… the medical profession". Most commented that they were surprised that gallbladders were routinely sent for analysis, and that they had not considered that cancer may, "complicate," their procedure. There was a general consensus that non-consented data collection was both justified and acceptable, as it was felt that the research was, "for the greater good," and that attempting to consent all patients would be, "impractical if [the protocol adopted] too formalised a route… [it] would cost too much and take a huge amount of time".

Some further changes to the protocol were made following PPIE consultation. One participant commented that the original initialism, PIGBC, and the associated logo read to them as "pig" and had a negative association with obesity as their perceived cause of gallstone disease. They suggested that the revised acronym P-iGBC held a much weaker association, and subsequently approved this and a revised logo. The opinion was supported by subsequent consultees. The original arrangements for non-consented data collection and informing patients of the study have also been revised. Although there was unanimous support for non-consented data collection, consultees felt that the wording of the protocol needed to be changed to encourage active informing of patients by clinicians in participating units. Consultees understood that this was different from informed consent but were satisfied that clinicians would be encouraged to draw patients' attentions to public notices of the study during the process of normal consultation and consent. Other minor changes to study documents resulting from the PPIE consultation include revisions to the PIS for the qualitative study and re-wording of public facing documents to improve clarity.

Given that this project affects histopathological services in that hypothesised changes to histological analysis protocols may affect their workload, we have sought and have been granted the support of our local histopathology department.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

- To develop and validate a diagnostic score for iGBC in patients undergoing cholecystectomy for benign indications.

2.2 SECONDARY OBJECTIVES

- To establish the pre- and peri-operative risk factors for iGBC and BHC in a UK population
- To define the incidence of iGBC and BHC in a UK population
- To explore the views of patients and healthcare professionals regarding the risk of iGBC in routine cholecystectomy and their acceptance of selective histological analysis of the gallbladder

2.3 OUTCOME MEASURES

- Rates of iGBC
- Rates of BHC
- Internal pilot: Feasibility of conducting a large multi-centre prospective study.
- Internal pilot: Feasibility of developing a diagnostic scoring system for the diagnosis of incidental gallbladder cancer based on pre- and intra-operative factors.
- Completed study: Validation of a diagnostic score for incidental gallbladder cancer.

3. STUDY PARTICIPANTS

Cross sectional study: All adult patients undergoing routine cholecystectomy within the study period at participating sites (subject to inclusion and exclusion criteria below).

Qualitative study: Participants will be recruited from patient lists at study sites, from within the NHS and through specialty association mailing lists. Each group will consist of participants who have been

purposively selected to represent a cross section of the population. For example, by incorporating a range of ages or career stages, rural and urban settings, and from primary, secondary, and tertiary care settings. Contingency arrangements, including convenience sampling and snowballing, are outlined in section 6.2.

Participant groupings will include:

1. Patients with a history of benign gallbladder disease, either pre- or post-cholecystectomy including, if possible, at least one post-operative patient with an iGBC diagnosis (5-7 pre-operative and 5-7 post-operative)
2. Surgeons who undertake adult cholecystectomy as part of their routine practice, including, if possible, at least two who have experience with patients with iGBC (8-10 participants)
3. Healthcare staff involved in non-clinical management and decision-making (3-5 participants)

a. Clinical Commissioners
b. Managers

3.1 SCREENING PROCEDURES

Cross-sectional study:

All patients aged 18 and over who are being considered for cholecystectomy at participating sites during the study period should be screened.

Qualitative study:

Participants will be purposively selected to represent a cross-section of the relevant populations, for example, by incorporating a range of ages or career stages, rural and urban settings, and primary, secondary, and tertiary care settings.

3.2 INCLUSION CRITERIA

Cross-sectional Study:

All adult patients (>=18 years of age) undergoing cholecystectomy (including subtotal and remnant cholecystectomy) for benign indications:

- Symptomatic Gallstone Disease (includes Gallstone Pancreatitis)
- Biliary Dyskinesia

Embedded Qualitative Study

Consenting adult participants (>=18 years of age) will be purposively selected into groupings, which will include,

- Patients with a history of gallbladder disease, either pre- or post-cholecystectomy, including, if possible, at least one post-operative patient with an iGBC diagnosis (10-15 participants)
- Surgeons who undertake adult cholecystectomy as part of their routine practice, including, if possible, at least two who have experience with patients with iGBC (8-10 participants)
- Healthcare staff involved in non-clinical management and decision-making (5-8 participants)
    - Examples include,
        - Clinical Commissioners
        - Managers
        - Histopathologists

3.3 EXCLUSION CRITERIA

Cross-Sectional Study:

Participants may not enter the study if ANY of the following apply:

- Imaging suspicious for/confirming type III/IV Mirrizzi syndrome.
- History of gallbladder or biliary tree malignancies
- Any pre-operative clinical suspicion of Gallbladder or biliary tree malignancy, (even if subsequently dismissed or disproven)
- Presence of Gallbladder polyps ≥5mm
- Biliary tree abnormalities, including Primary Sclerosing Cholangitis and Choledochal Cysts
- Patients undergoing cholecystectomy as a part of, or incidental to, another procedure.

Embedded Qualitative Study:

Participants may not participate in interviews if ANY of the following apply:

- Unable to consent, or to communicate consent.
- Unable to undertake interview in English, despite reasonable support measures.

4. STUDY DESIGN, PROCEDURES, AND INTERVENTIONS

4.1 STUDY DESIGN

Multi-centre, cross-sectional study for diagnostic modelling with an integrated internal pilot, an embedded, parallel, interview-based, qualitative study, and an adaptive design.

The internal pilot and parallel qualitative workstreams will form a feasibility phase of this study (fP-iGBC). Following this feasibility phase, data collection will pause for 18 to 24 months to allow time for analysis of the feasibility phase, additional funding to be secured, expansion of the study team and for centres to be recruited and registered.

4.2 RECRUITMENT

Cross-Sectional Study

Patients will be identified from waiting lists and emergency admissions within the relevant departments of participating centres during the study period by clinicians undertaking cholecystectomy and those participating in the research (all of whom will be members of the direct care team). As data collection is non-consented, all patients who pass screening against the inclusion and exclusion criteria may be recruited, however patients will be able to opt-out of inclusion in the study as detailed in section 4.3, below.

Qualitative Study

Patients will be recruited from existing patient waiting and clinic lists and historical patient lists at participating sites. Professional participants will be recruited through speciality association mailing lists, direct approach and those who have expressed an interest in participation in the recruitment stages of the cross-sectional study.

Where potential participants are identified by a collaborator at a participating site, the collaborator will make initial contact with the potential participant to inform them about the study and to invite them to take part in an initial conversation with the central research team. If they are willing to receive more information, the collaborator will ask the potential participant to contact the central research team either by telephone or email, on receipt of which the central research team will take over contact with potential participants to undertake a formal invitation to participate and the informed consent process, as laid out below. Collaborators may alternatively offer to share a contact detail (e.g. an email address or a telephone number) with the central study team, using the encrypted NHS.net email, with the express consent of the potential participant.

4.3 CONSENT

Cross-sectional Study

Data will be collected from patients and patient records without their consent. Patients will be informed about the study and provided with an opt-out mechanism as outlined below.

Rationale for non-consented data collection.

The cross-sectional component of this study exclusively requires the collection of de-identified information which would normally be recorded during patient care. This will be extracted from the patient's record by members of the direct care team. The volume of patients required is felt to make individual consent impractical and prohibitively expensive, and would therefore prevent sufficient recruitment. It is subsequently felt to be both justified and necessary to collect the de-identified data without individual patient consent, as per the Confidentiality Advisory Group pre-application checklist, and guidance received in communication with them.

Local arrangements for informing patients about the study.

When data is collected without informed consent, is good practice to publicise the study and provide a mechanism for patients to opt-out. Participating units will be required to display notifications (see example in appendices) in appropriate areas, such as outpatient, inpatient, and pre-operative areas. These notifications must include the contact details of the local study team and must expressly state the right to opt-out. Following feedback from our PPIE consultation, we recommend that consenting clinicians inform patients of their eligibility for inclusion, and right to opt-out of the study. This is especially important in the event that a patient does not speak English and is being consented for surgery with the help of a translator (see below). Clinicians in participating units should direct patients to further information, such as the website, a poster, or the PIS if asked. Whilst it will not be mandatory, clinicians may wish to record that the patient has been informed, for example by noting the conversation in the patient's record, on a clinic letter or other clinical documents related to the episode of care.

Patients who do not speak English.

Patients who do not speak English should be informed of the study during the operative consent conversation, which is normally with a translator. Within the feasibility phase, there is no specific information available in languages other than English. If and where there is any doubt over the participant's understanding, the participant should be recorded on RedCAP as having opted out, given

that other opportunities for that patient to opt out may be more limited than for those who speak English. Provision will be made to ensure that this reason can be specifically identified, to inform whether multi-lingual participant information sheets should be funded and developed following the feasibility phase. Welsh Language information will be developed following the feasibility phase, if and where centres in Wales participate.

National arrangements for informing patients about the study.

During periods of recruitment and data collection, the central study team will post monthly notices of the study to Twitter/X (see example in appendices), and maintain notifications on the website. Collaborating units, are advised to share these notifications, which will include a link to the study website where the PIS, and information about opting-out of the study, will be posted. Following PPIE consultation, notifications will make a distinction between the pilot phase and the full national study.

Arrangements for patient opt-out.

Patients have a right to opt-out of the study. As the central research team will not have access to identifiable patient information, it will not be possible for the opt-out mechanism to be centrally administered. Instead, local study teams will be required to field requests for study opt-out. The contact details for the study team at each unit will be made available on local notifications, and on the study website. On receiving a study opt-out request from a patient, units are required to respond and confirm the request within ten working days. In case of a non-response from the local unit, patients will be able to contact the central study team via the study website. This will require the patient to share a single contact address (such as a telephone number or email address) with the central study team, which will in turn be shared with the local unit. The central study team will contact the local team by any or all additional means at their disposal and will require the local team to confirm the opt-out directly with the patient, and then confirm with the central team. As a contingency, and to safeguard patients, in the event that contact cannot be established with the local team, data entry by collaborators in that unit will be paused and data from that unit will not be included in export, until the opt-out request has been satisfactorily fulfilled.

If an eligible patient exercises their right to opt-out before they are identified for inclusion in the study, or before any data is collected, units should still allocate a study ID in REDCap. After screening for inclusion, the CRF will ask, “has the patient opted out?”, which will both allow monitoring of opt-out rates and act as a barrier to further data entry in the event of an affirmative response. When data has already been collected, any locally held information, except for the study ID and cross-referenced identifiers, should be deleted and/or destroyed in line with local policy. Changing the response to the

opt-out question will automatically prompt the deletion of any remaining data associated with that study-ID. As an additional safeguard, alongside checks for outlying data points, the central study team will regularly check the database for opt-outs and manually remove any remaining data held against the study-ID.

It will not be possible for patient data to be removed once the data collection period for each phase of the study has ended (i.e. six to eight weeks after the end of the recruitment period in each unit).

Qualitative study

Consent to enter the study must be sought from each participant only after a full explanation has been given, a participant information sheet offered, and time allowed for consideration. Signed participant consent should be obtained and, to minimise hard-copy and to facilitate remote consent, eConsent will be obtained using the relevant REDCap modules*. The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the interview, without giving reasons and without prejudicing their clinical treatment or professional situation.

4.4 STUDY ASSESSMENTS/ INTERVENTIONS

Cross-sectional study:

No deviation from routine patient care is required. The cross-sectional study will collect baseline information about the patient's background, including age, ethnicity, co-morbidity, BMI, pre-operative investigations and intra-operative findings, which will largely be available from the patient's written and digital records. The diagnosis/diagnoses of the postoperative histopathology report will be collected once available and is considered a result from the event of interest (the cholecystectomy). Consequently, there is no longitudinal follow-up required.

Qualitative Study:

The embedded qualitative study consists of carefully designed, semi-structured interviews which follow an interview guide, and can be found in the appendices. The analysis will occur contemporaneously, and the interview guide may be adjusted where appropriate, to maximise data richness, as the study progresses.

The fundamental questions to be answered are:

* eConsent forms will exactly match the wording of approved paper consent forms.

- What are the participant's attitudes, experiences, and beliefs towards the risk of GBC?
- How supportive are participants of the concept of SHA in routine cholecystectomy?
- What perceived problems and barriers exist around introducing SHA in the UK?

Participants will undergo contact by the research team or by collaborators at the following time points. All events may be either face-to-face, or remotely.

1. Identification
   Participants will be contacted either by a member of the research team at University Hospitals Plymouth NHS Trust, or by a collaborator at a participating unit, as previously described. At this stage, they will be informed of the study and invited to make contact with the central research team to obtain more information.
2. Initial information, including provision of PIS
   Participants will be contacted by an appropriate researcher from the central team, and provided with an explanation of the study, a copy of the PIS and an opportunity to ask any questions pertinent to their decision to participate. A minimum of 24 hours for the participant to consider their decision is required and the participant should indicate their agreement in principle before an interview is arranged.
3. Possible further liaison regarding logistics of interview arrangements
   Further contact may be necessary, to make suitable arrangements for an interview to take place, or to answer any supplementary questions.
4. Interview
   A qualitative researcher will meet with participants, either face to face or via MS Teams, as outlined elsewhere. At this contact, a final opportunity to ask questions will be offered, the consent form will be completed and the interview will be conducted.
5. Member checking (optional)
   As outlined elsewhere, participants will be emailed transcripts and reports and invited to comment on them. This activity is strictly optional.

4.5 DEFINITION OF END OF STUDY

This is defined as the date of the last visit of the last participant undergoing the study. The Sponsor will notify the REC, in writing, within 90 days of the end of the study.

5. SAFETY REPORTING

Given the purely observational nature of this study, safety reporting is not applicable and there are no defined or undefined Serious Adverse Events.

6. STATISTICS

6.1 THE NUMBER OF PARTICIPANTS

Cross-sectional study:

The required power to develop a diagnostic score for iGBC, assuming a 0.2% prevalence, Nagelkerke's R^2 of 0.3 and 20 diagnostic parameters, is 20,996. Allowing for a 20% rate of incomplete data, 26,245 participants would be required. It is possible that, following the feasibility study, it will be clear that more than 20 diagnostic parameters are required. The study will, therefore, aim to recruit up to 30,000 participants to ensure adequate power.

An internal pilot study will be undertaken between 8 participating units to ensure the feasibility of recruiting so many participants and calibrating the final recruitment target. Data collection will be paused at the first of 500 participants between all participating units or six months of completed data collection in each participating unit, allowing for the internal pilot to be evaluated. For a sample size of 500, an iGBC incidence of 0.2% will be estimated with a margin of error of +/- 0.39%. Rates of recruitment, completeness of data, and events will be evaluated. The assumptions above will be adjusted, and the corrected data will be used to re-calculate the final recruitment target before data collection for the complete cross-sectional study begins.

Qualitative Study:

Saturation is typically considered to occur after 20 interviews, however multiple participant groups are being included in this analysis. The total number of purposely selected participants will therefore be between 23 and 33, as outlined in the group descriptions in section 3.2. If data saturation is felt to have occurred, participants will only be interviewed if the minimum group size has not been met. If a participant withdraws and the minimum number for any group falls below the sample sizes described in section 3.2, participants will be replaced. If, however, the minimum numbers are maintained the participant will not be replaced.

6.2 SAMPLING

Cross-sectional study:

Trainee collaboratives are a well-proven data collection method which limits the patient burden and encourages broad participation, as well as ensures that only the direct care team accesses identifiable information. A trainee collaborative model will be used, with a Lead Trainee or Associate PI[†] and a Principal Investigator or Co-Investigator responsible for data collection in each unit (see section 9).

Local clinicians will identify patients from elective and emergency general surgical operating lists occurring during the study period. All patients undergoing cholecystectomy during the study period should be screened for inclusion by any clinical team member.

Data will be prospectively collated in a Microsoft Excel Spreadsheet, and de-identified information will be entered directly into REDCap at each study site. A minimum dataset cross-referencing a study ID and patient identifiers will be kept locally. The local investigators will be responsible for ensuring that the spreadsheet is kept and maintained according to local data security guidelines, and, as a bare minimum, the spreadsheet should be held on a secure, institution-approved drive location and password protected. Patient identifiers held locally will be excluded from transfer to the main trust undertaking analysis, and sites will be encouraged to keep a secure cross-referencing database so that patients can be locally identified for internal validation or obtaining missing data. Data will be submitted to the primary investigating team centrally at UHP using REDCap to facilitate secure transfer and assess the dataset's completeness. Individual surgeons will not be centrally identified and will strictly remain anonymous.

Qualitative study:

Participants will be selected from patient lists at study sites, from public support groups, from within the NHS and through specialty association mailing lists. Each group will consist of participants who have been purposively selected to represent a cross-section of the relevant population.

As a contingency, in the event of either an un-representative mixture of participants, or the minimum number for any group not being achieved, convenience sampling will be used to identify and recruit participants from the relevant staff and patient groups at UHP. If required, snowballing will be used to aid recruitment.

[†] This definition is dependent on whether the study is adopted by the NIHR and accepted to the Associate Principal Investigator scheme.

6.3 ANALYSIS OF ENDPOINTS

Cross-sectional Study

a. Internal pilot analysis

Descriptive statistics (including means, standard deviations, medians, inter-quartile ranges and ranges, as appropriate for continuous variables and frequency and percentage for categorical variables) will be summarised for all demographics and potential predictive factors of iGBC collected.

The prevalence of iGBC and BHC will be presented as a percentage with confidence intervals.

The number of patients undergoing cholecystectomy, the number of patients eligible, the number of patients (and percentage) recruited, and the number of patients (and percentage) undergoing the procedure will be summarised overall and by site.

The level of data completeness (demographics, potential risk factors and outcomes) will be summarised by frequency and percentages overall and by site.

Descriptive statistics will be used for

- rates of iGBC and BHC in the pilot population
- rates of recruitment of patients to the study
- data completeness

The dataset will be evaluated to identify commonly incomplete data points (core data points for which completeness is <80%). Units and collaborators will then be surveyed to evaluate the challenges associated with these areas. Following the result of this survey, the study team will discuss each incomplete data point and make suitable adjustments to the power calculation and data points for collection according to the figure below.

	Variable with large effect size or significance for iGBC in pilot, or in previous studies	Variable with low or uncertain effect size or significance for iGBC
Completeness likely to improve to >80% following intervention (e.g. change in the phrasing of a question or definition, change to patient record sheet)	Retain data point for full study	Retain data point for full study
Completeness unlikely to improve following intervention	Retain data point for full study, consider adjusting power calculations to accommodate level of completeness achieved in pilot	Consider whether omitting data point from full study is justified

Rates of recruitment will be considered in the context of the power calculation and the time initially allocated to complete data collection. Where necessary, proposed timeframes will be adjusted in the context of the power calculation and with details of potential participating units, prior to data collection for the full study beginning.

Feasibility of the study may be hypothetically established, however adequate funding and sufficient participating centres with at least firm expressions of interest are required for actual progression. A final analysis and assessment against the following criteria (see table) will inform whether it is considered practically feasible to progress and therefore seek funding to continue the study.

	Green (Progress to full trial)	Amber (May progress, subject to revision and review)	Red (Not to progress without further evaluation and/or development)
Variables	Sufficient variables completed >80% for meaningful diagnostic score development	Insufficient variables completed >80% for meaningful diagnostic score development, likely to resolve with adaptations (e.g. changes to CRF)	Insufficient variables completed >80% for meaningful diagnostic score development, and unlikely to improve with adaptations
Centres *Time to meet recruitment target based on mean per-centre recruitment rate in fP-iGBC.	Sufficient centres to meet recruitment target* within two years	Sufficient centres to meet recruitment target* within three years (aim to recruit centres to shorten data collection period)	Insufficient centres to meet recruitment target* within three years.

b. Full prospective study analysis

A summary of the demographics, potential predictive factors and outcomes will be presented.

A multivariable predictive model will be developed using potential risk factors available before the decision to send cholecystectomy specimens for RHA to identify patients with iGBC. The predictive model will be in the form of a logistic regression model and, therefore, will be interpreted using odds ratios. A post-estimation method to reduce the possibility of overfitting will be implemented.

Internal validation of the predictive model will be performed using a method of resampling from the original data (e.g. cross-validation or bootstrapping). Measures of model performance, including discrimination, calibration statistics and clinical usefulness (e.g. net benefit), will be presented.

A complete, detailed statistical analysis plan (SAP) for each of the pilot and the complete study will be available at a later date.

Qualitative Study:

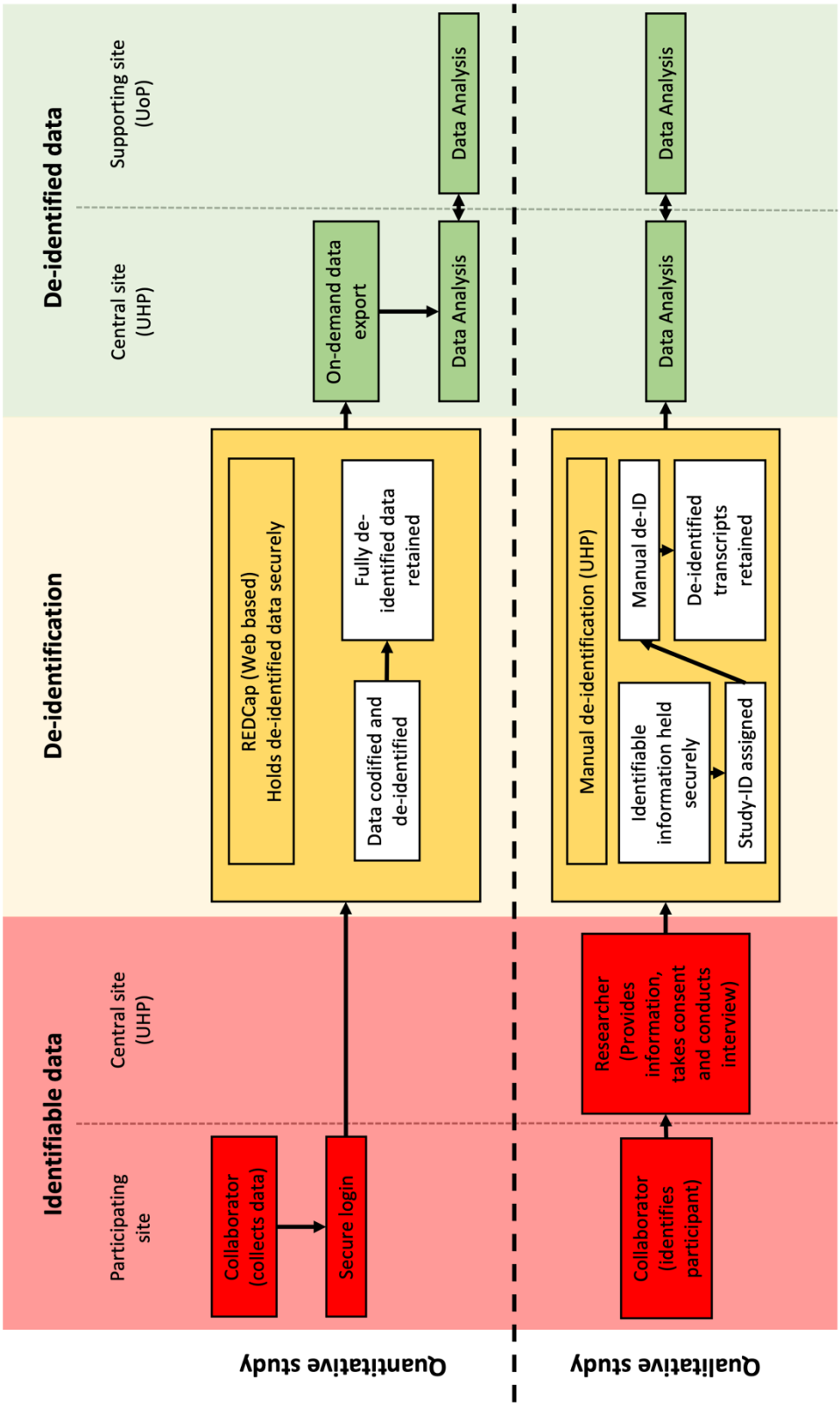
Thematic analysis of interview transcripts will be performed using dedicated qualitative analysis software and data-driven to reduce the potential for interviewer bias. The analysis will start after the first 3-4 interviews to inform subsequent interviews and actively assess data saturation. Where appropriate, the interview guide may be adjusted to maximise the richness of the data. Data extracts will be coded and categorised into themes, following proper guidance. Coded data will be reviewed and agreed upon by at least two researchers. A provisional summary will be sent to 3 patient participants and to 3 professional participants, for member checking. Outcomes of interest will be aligned with the aims of the qualitative study as defined previously.

7. DATA MANAGEMENT AND DATA SHARING PLAN

To comply with the Data Protection legislation, information will be collected and used fairly, stored safely and not disclosed to any unauthorised person. This applies to both manual and electronically held data.

The Chief Investigator will preserve the confidentiality of participants taking part in the study and ensure the EU General Data Protection Regulation (GDPR), in conjunction with the UK Data Protection Act 2018, which sets out the statutory requirements for processing personal data, is adhered to.

7.1 DATA FLOW DIAGRAM



7.2 DESCRIPTION OF THE DATA

The following discrete data points will be collected. Data points will be re-evaluated following the pilot, and the feasibility of collection of each data point will be considered.
A summary of these data points is presented in the table below, and a fully exploded list of variables is available in the appendices. Not all data points will be applicable to all patients, for example where variation in practice exists. These dependent data points, and their sub-points are marked with an asterisk (*).

Core data points (all patients)	Study ID Patient Factors Referral Pathway Indication for Surgery Laboratory findings Intra-operative Findings Histology
Semi-dependent data points (minimum dataset required per patient)	Imaging findings (minimum one modality, include all directly relevant to patient's cholecystectomy pathway).
Dependent data points (applicable patients) *	Pre-operative interventions Intra-operative imaging Progression to CBD exploration

7.3 COLLECTION OF DATA AND STUDY MATERIALS

Cross-sectional Study:

Trainee collaboratives are a well-proven data collection method that limits the patient burden and encourages wide participation. A trainee collaborative model will be used, with a Lead Trainee or Associate Principal Investigator (PI)‡ responsible for data collection in each unit under the supervision of a formal PI. Each unit will be asked to recruit as many patients as possible, and will be provisionally asked to target a minimum of 10 recruited patients per month of inclusion.

‡ This definition is dependent on whether the study is adopted by the NIHR and accepted to the Associate Principal Investigator scheme.

Data will be prospectively collected on a digital Case Report Form (CRF), and may either be initially collated in a Microsoft Excel Spreadsheet, or entered directly onto REDCap at each study site. A separate, minimum dataset cross-referencing a study ID and patient identifiers must be kept locally to allow data validation and identification and/or recovery of missing variables. The local investigators will be responsible for ensuring that the spreadsheet is kept and maintained according to local data security guidelines, and, as a bare minimum, the spreadsheet should be held on a secure, institution-approved drive location and password protected. Only de-identified information will be exported to the central team at UHP using REDCap. This tool facilitates secure data transfer, can help to ensure de-identification and has the facility to assess the dataset's completeness. Individual surgeons will not be centrally identified and will strictly remain anonymous.

In order to ensure the integrity of the data, the dataset will be subject to a regular review process during data collection periods to identify outliers, which may be the result of typographic errors. This will allow timely feedback to the collaborating researchers and ensure that the final datasets are of high quality.

To further validate the dataset, units will be asked to perform an internal validation exercise. As outlined in section 9, this will be conducted in each participating unit by a collaborator who is not otherwise involved in data collection and will act independently from the other collaborators at the site. For the feasibility phase, 10% of patients will undergo this exercise. For a unit achieving the provisional target of 10 patients each month, this will equate to six records. The data validator will be asked to review the clinical record of the recruited patient and re-enter data from several core data points on a new CRF. This duplication of data entry will allow an assessment of concordance and give an idea of the quality of the dataset. The need for ongoing internal validation, and the proportion of patients required to validate the dataset will be reviewed following the feasibility phase.

Qualitative Study:

Semi-structured interviews will be conducted in a private setting, either face-to-face in a suitable, mutually convenient location, which might be, for example, the participant's home (subject to the relevant sections of the University of Plymouth's *Guidance for Assessor/Supervisors and learners when carrying out unaccompanied home visits and for the use of learners' vehicle for placement activity*), a room in a hospital or academic setting, or remotely over Microsoft Teams. Settings for interviews must be private, quiet, and comfortable, and measures must be in place to limit interruption, such as switching off telephones. In each instance, the interview will be recorded using an audio

recording device or the built-in recording function of MS Teams. Where appropriate, the researcher(s) will collect observational field notes.

The interviews will be transcribed into a pseudonymised Microsoft Word document, with each individual identified by a study ID. Auto-transcription software may be used to assist transcription, subject to manual checking and correction against the original recording. A separate Microsoft Excel spreadsheet will be maintained, cross-referencing the study ID and patient identifiers. All recordings and documents will be digitised, kept and maintained according to local data security guidelines and will be held on a secure, institution-approved drive location and password protected.

7.4 DATA STORAGE AND SECURITY

Electronic data captured in the Trust's web-based system, REDCap Community, will be stored on Microsoft Azure servers in the UK South and uses Locally Redundant Storage, meaning that the data is stored in three separate locations within this data centre. All electronic data are regularly backed up and retained for 30 days.

7.5 ARCHIVING, PRESERVATION, AND CURATION

Archiving will be authorised by the Sponsor following the submission of the end-of-study declaration. Upon completion of the study, study documents will be digitised (Hard Copies will be destroyed) and archived for a minimum of 10 years, and as per the participating Trust's Research Archiving SOP. Once the archiving retention period has been reached, the Sponsor will liaise with the sites regarding destruction.

7.6 DATA SHARING

Requests for data sharing can be made after the publication of the primary results papers. Requests should be made to the Chief Investigator in the first instance. Requesters will be asked to complete an application form detailing specific requirements, rationale, and proposed usage. The CI and study sponsor (including the Sponsor's Research Governance Manager (or deputy), the Information Governance Team, Caldicott Guardian, IM&T Security Officer and the researcher funder, as appropriate) will review all requests.

Consideration will be given to:

- The viability and suitability of the request
- Appropriate steps have been taken to minimise the risk of identifying participants

- Data security policies and procedures of recipient organisation (including country if aboard) and other regulatory requirements are applicable
- The credentials of the requestor

Where access to requested data is granted, requester's organisations must sign a data sharing agreement before accessing any data.

Subject to appropriate data sharing agreements, individual participants' data that underlie the results will be made available (after de-identification) on a controlled access basis. Requested data will be made available, along with supporting documentation (e.g., data dictionary), on a secure server or through other secure data transfer methods.

8. ETHICAL AND REGULATORY COMPLIANCE

8.1 ETHICS AND HRA APPROVAL

The Chief Investigator has obtained approval from the Health Research Authority (HRA) and Research Ethics Committee (REC). The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the UK Policy Framework for Health and Social Care Research (2017), which have their basis in the Declaration of Helsinki.

8.2 INDEMNITY

This is an NHS-sponsored research study. If an individual suffers negligent harm as a result of participating in the study, NHS indemnity covers NHS staff and those responsible for the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS cannot agree in advance to pay compensation, but an *ex-gratia* payment may be considered in the event of a claim.

8.3 SPONSOR

UHP will act as the main Sponsor for this study, assuming overall responsibility for the initiation and management of the trial. Delegated responsibilities may be assigned to other relevant parties taking part in this study and appropriately documented.

8.4 FUNDING

Funding and costing will be considered in two stages – feasibility and full study. At this point, funding and costing has been performed for the feasibility phase only. If the feasibility phase of the study is a success, and meets criteria for progression, additional funding and costing will be required to continue the study.

Arrangements, as they stand at present, are outlined below.

University Hospitals Plymouth NHS Trust are funding fP-iGBC (the pilot and qualitative studies) as detailed below.

- The salary of a Clinical Research Fellow (CRF) is being provided by the Trust, the CRF's responsibilities predominantly include the delivery of the internal pilot and qualitative study, which will be conducted as part of their Medical Doctorate at the University of Plymouth.
- UHP are providing the use of REDCap and oversight of f-P-iGBC free of charge for the feasibility phase.

The Peninsula Medical Foundation and the Association of Upper Gastrointestinal Surgeons are supporting the research associated costs of the feasibility phase. Further funding will be sought following the feasibility phase.

There will be no per-participant payments for the qualitative study.

8.5 MONITORING

The study will be subject to monitoring by UHP under their remit as Sponsor to ensure adherence to the UK Policy Framework for Health and Social Care Research (2017). All UHP studies will be initially monitored approximately 25 days after local R&D Confirmation of Capability and Capacity has been given. The subsequent level of monitoring will be determined by a risk assessment, or on a for-cause basis. The study may also be audited/ inspected by regulatory bodies to ensure compliance with national regulations.

9. STUDY MANAGEMENT

The day-to-day management of fP-iGBC (the pilot and qualitative study) will be co-ordinated through a UHP Clinical Research Fellow. A Clinical Trials Unit will be engaged to assist with completion of the quantitative study once feasibility has been established.

9.1 STUDY SITES AND PERSONNEL

Study sites for the will be recruited based on a number required to meet patient recruitment targets. 8 units, including University Hospitals Plymouth NHS Trust, will be recruited from within England for the feasibility phase. Each study site requires at least 3 collaborators adopting

Principal Investigators and Co-Investigators

Each organisation will require a Principal Investigator (PI). When an organisation has more than one study site, a single principal investigator will oversee study activities across the organisation. However, a Co-Investigator or, if possible, a Co-PI may be registered in the event that more than one surgical department operates across the organisation, but will not be required if a single team operates across multiple locations. This is likely to occur when NHS Hospital Trusts merge for organisational reasons, for example.

Lead Trainees

Each PI, Co-PI or Co-Investigator will be required to identify and recruit a Lead Trainee for their unit, who will be put forward for an Associate PI scheme if the study is adopted by the NIHR. The Lead Trainee should be a trainee, or locally employed doctor in an equivalent non-training grade, in an appropriate specialty. The study team recognises that trainees join and leave units frequently because of their rotational or contractual commitments, and therefore acknowledges that Lead Trainees may have a time-limited involvement with the study. There may, therefore, be more than one Lead Trainee over the course of a site's involvement with the study. However, There should only be one Lead Trainee at any given point in time. A Lead Trainee should remain in that role for a minimum of six months, but ideally a minimum of a year, except when a data collection period starts or ends part way through a rotation. It is the responsibility of the PI to decide on the suitability of the Lead Trainees, however they should be in a position to recruit and lead their trainee peers, and consideration should be given to their seniority, ability to deliver the project and other commitments. Lead Trainees are not required during quiescent periods of the project.

Roles of the Lead Trainee include

1. Identification, recruitment and management of collaborators.

2. Active involvement in identification, recruitment and data collection of patient participants.
3. Oversight and management of the locally delivered opt-out process (with support form the PI as required).
4. Increasing awareness of the project within the organisation, particularly with regards to ensuring that relevant clinicians are aware of the project and inform patients about it as outline in the relevant section above.
5. Liaison with the central research team.
6. Confirmation of collaborators' contribution to the project (in association with the PI).

Collaborators – Data Collection

Lead Trainees and PIs are required to recruit sufficient (trainee) collaborators to monitor operating lists and to identify, recruit and collect data from patients for each component of the study. Collaborators include the Lead Trainee and PI, and can be recruited from any grade of doctor or the allied health professions, including Physician Associates, Nurses etc, however must:

1. Be drawn from members of the direct care team for patients undergoing cholecystectomy.
2. Ordinarily have access to review necessary results.
3. Have sufficient training and/or experience to provide the knowledge and understanding of common terminology found in reports and letters, which may need to be interpreted before input to the data collection tool.
4. Meet any generic organisational requirements for involvement in research within the participating organisation.

There is no centrally defined maximum number of collaborators per organisation, as in common with Lead Trainees it is recognised that many collaborators will be rotational, and that organisations will vary in their surgical volumes. However, to be considered for authorship each collaborator should be able to identify and collect data from 2 patients each month. For example, in a unit meeting the initial feasibility target of 10 cholecystectomies each month, 5 local collaborators (including the PI and Lead Trainee) would be suggested as an appropriate maximum. Data collectors should remain actively involved with the study for a minimum of one rotation (but not less than four months, as applicable to their job role, unless data collection starts or finishes mid-rotation), or one year for permanent staff. Collaborators are not required to remain involved outside of data collection periods.

Collaborators – Data Validation

Lead Trainees and PIs will also be required to recruit a data validator. These collaborators will undertake the data validation exercise described in the relevant sections above. Data validators

should meet the same requirements as data collectors however should not otherwise be involved in the identification or data collection processes, in order that their independence may be maintained.

Collaborators – Limited role

Where it may assist local teams to utilise other members of the direct care team to identify and screen patients, or to permit "live" operative data entry by the performing team, a limited access role will be available in REDCap in order for accurate, prospective recording of intraoperative events. These collaborators will be able to access the screening and operative findings sections of the eCRF. The Lead Trainee and PI are responsible for determining whether their contribution is sufficient to qualify for authorship, through comparison to those collaborators undertaking data collection and validation.

10. PUBLICATION POLICY

It is proposed that the study team will prepare a Plain English Summary of the study results, which will be sent to interested study participants as soon as possible after the end of the study. The study's final results will be disseminated via presentations at appropriate scientific meetings and conferences and publication in appropriate peer-reviewed journals.

10.1 AUTHORSHIP

This is a collaborative project. In all cases, collaborators will be considered for authorship if they meet the requirements of the International Committee of Medical Journal Editors' (ICJME) statement on defining the role of authors and contributors. Briefly, the requirements are that an author should have made a "substantial contribution" to the work, which may include acquisition of data, have drafted, or critically reviewed the work, have approved the final version and agree to be accountable for it. In light of the design of the study, it is likely that all Principle Investigators and Trainee Collaborators will be able to meet the requirements[§]. Where they do not but have nonetheless been significant collaborators in the presented work, they will be listed as Contributors. Collaborators will only be considered for authorship if they have contributed to the segment of work being presented. For example, if a further analysis is performed on feasibility data after the full study is completed, only collaborators who contributed to the feasibility stage will be eligible for authorship.

[§] To facilitate compliance with these requirements, collaborators will be asked to review and approve drafts, and to agree to accountability statements.

How collaborators are listed as co-authors will depend on the rules and requirements of specific journals. Where only a limited number of individuals will be listed as authors by the journal, collaborators will be grouped as below. Whenever possible, the members of each group will be individually named, but will otherwise be known as the "writing group" or the "collaborative". In MEDLINE, facility exists for collaborators to be individually associated with group, or collaborative authorship and, where this is acceptable, the group names below may be used. Individual listing of members of the Writing Group will take precedent over individual listing of members of the Collaborative.

1. P-iGBC Writing Group

   Authors in this category are those who have contributed significantly to the writing of the paper. These authors will typically be part of the central research team or major collaborators from other participating units or universities and will meet ICJME authorship requirements by having made significant contributions to the conception and design, or analysis and interpretation of the presented work. Collaborators who have solely been involved in data collection or internal validation are unlikely to meet the requirements of this group.
2. P-iGBC Collaborative

   Authors in this category are either central research team members who meet authorship requirements but do not meet writing group requirements, or those who have otherwise collaborated. They will typically meet ICMJE authorship requirements by virtue of significant contribution to the acquisition of data for the presented work. Where appropriate or required, their roles will be further defined as below.
   a. Members of the central research team
   b. Principle Investigators and Lead Trainees/Associate Principal Investigators**
   c. Trainee Collaborators††
      i. Data collection
      ii. Data validation
   d. Other collaborators, including limited role for identification, screening, recruitment and "live" operative data entry.

** This definition is dependent on whether the study is adopted by the NIHR and accepted to the Associate Principal Investigator scheme.

†† NB This "trainee" collaborative allows for non-training grade and non-medical grade collaborators.

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APPENDICIES

Pease see Links to other appendices for hyperlinks to the most recent versions of the documents below.

Appendix 1. Schedule of Events
Appendix 2. Amendment History
Appendix 3. P-iGBC Participant Information Sheet
Appendix 4. P-iGBC Consent Form (redundant)
Appendix 5.
a. qP-iGBC Participant Information Sheet
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Appendix 6. qP-iGBC Consent Form
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Appendix 9. Public Notification Poster (Example)
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APPENDIX 1 – SCHEDULE OF EVENTS

Quantitative Component

Procedures	- 2 weeks	Start of recruitment period	Operating List Planned	Day of operation	End of recruitment period	Histology	+ 8 weeks
Public Announcements	X	X	X	X	X		
PIS available online + paper	X	X	X	X	X		
Start of data collection		X					
Demographics, Imaging, Bloods			X	X			
Intra-operative findings				X			
Histology						X	
Monthly local performance updates		X	X	X			
Fortnightly data upload reminders					X		
Data upload ended (locked)							X

Qualitative Component

Procedures	Screening	Initial Contact	Interview	Week 2
Basic Demographics	X			
PIS Provided		X		
Informed Consent			X	
Interview Undertaken			X	
Transcript Provided				X

APPENDIX 2 – AMENDMENT HISTORY

List details of all protocol amendments here whenever a new version of the protocol is produced.

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of changes made
1	1.1	19/07/2024	O Brown	• Addition of REC reference number • Updated hyperlinks to Supplementary Participant Information Sheet, Participant Information Sheet for the qualitative workstream and Poster • Addition of print-format (hyperlink free) version of Supplementary Participant Information Sheet (Appendix 5b)
2	1.2	06/09/2024	O Brown	• Addition of University of Plymouth Faculty Research Ethics and Integrity Committee reference number. • Addition of the Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland as funders for the feasibility phase. • Clarification on the separation of funding arrangements between the feasibility phase and main study.

LINKS TO OTHER APPENDICES (APPENDIX 3-13)

Appendix 3.

a. P-iGBC Participant Information Sheet
b. P-iGBC Participant Information Sheet (Print Format, hyperlinks removed)

~~Appendix 4. P-iGBC Consent Form (redundant)~~

Appendix 5. gP-iGBC Participant Information Sheet

Appendix 6. gP-iGBC Consent Form

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