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Study Protocol

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Feasibility of Predicting Incidental Gallbladder Cancer: a protocol for a UK multicentre feasibility diagnostic modelling study for incidental gallbladder cancer in adult cholecystectomy

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Abstract

Background: In the UK, gallbladder specimens are routinely sent for histological examination to exclude incidental gallbladder cancer (iGBC) and other clinically relevant pathology. Although rare, gallbladder cancer requires early detection to improve outcomes. Existing risk stratification tools miss cases or are not tailored to the UK population. Predicting Incidental Gallbladder Cancer (P-iGBC) is an adaptive, multicentre, cross-sectional, trainee-led collaborative study designed to develop a diagnostic score to stratify iGBC risk in adult cholecystectomy. This feasibility phase, fP-iGBC, evaluates the methods and procedures of the overall study, ensuring its robustness and practicality before full-scale implementation. **Methods:** fP-iGBC comprises an internal pilot of P-iGBC with a parallel qualitative study. The internal pilot investigates recruitment, data collection and study procedures in adults undergoing cholecystectomy for benign disease. The qualitative study explores attitudes of patients and professionals towards iGBC risk and selective histological analysis. **Outcomes:** The primary objectives were to evaluate screening processes, recruitment and data completeness. Additionally, the incidence of clinically relevant histological abnormalities will be compared against published evidence. A collaborator survey will identify challenges in study procedures. The qualitative study will explore the study's value. Interim analysis will assess screening and recruitment targets against predefined progression criteria. **Ethics and Registration:** P-iGBC is approved by the London-Central National Health Service Research Ethics Committee (24/LO/0504), the University of Plymouth Faculty Research Ethics and Integrity Committee (PEOS 5550) and is registered at ClinicalTrials.gov (NCT06531408). **Conclusion:** fP-iGBC will assess the feasibility of P-iGBC and inform necessary protocol amendments to ensure successful implementation of subsequent research phases.

Keywords: gallbladder neoplasms; gallbladder; cholecystectomy; diagnostic techniques and procedures; clinical decision making; risk

INTRODUCTION

Incidental gallbladder cancer (iGBC) is found unexpectedly at histopathology after routine cholecystectomy and is diagnosed in fewer than 1 in 500 specimens in the UK [1, 2]. It is considered 'truly' incidental when there has been no suspicion of malignancy pre- or peri-operatively [3]. Gallbladder cancer (GBC) is a rare disease, and approximately half of all GBC diagnoses are incidental [4–6]. Current guidelines suggest that index cholecystectomy is adequate operative treatment for early-stage disease; however, surgically fit patients with iGBC above stage T1b should undergo re-resection of the gallbladder fossa, lymphadenectomy and chemotherapy [7]. Less than half of iGBC is considered early stage, and the index cholecystectomy may inadvertently upstage disease or worsen prognosis, for example, by gallbladder perforation [3, 8, 9]. Survival, even with re-resection and systemic anticancer therapies, is poor [4, 10].

Missing a diagnosis or underestimating an individual patient's risk of iGBC may, therefore, have significant clinical consequences. Consequently, early, robust identification of high-risk patients is crucial. Each year, approximately 70 000 patients undergo cholecystectomy in England, and the majority do so for benign conditions such as gallstone disease [11, 12]. Identifying iGBC poses a key diagnostic challenge, and strategies need to be considered in light of their financial, systematic and personal costs.

Diagnosis of iGBC in the UK is currently achieved by routine histological analysis (RHA) of all removed gallbladders, which additionally identifies other clinically significant pathology, including dysplasia [13, 14]. Whilst RHA is a robust method of

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diagnosis, it imposes substantial costs and workload pressures on histopathology services. We estimate that RHA in England alone costs over £5 000 000, and there is a well-recognized shortage of histopathologists across the country [11, 15, 16]. Selective histological analysis (SHA) limits histopathology testing to high-risk cases based on risk stratification and has been proposed as an alternative to RHA. It is sporadically performed in other countries, such as Sweden and the Netherlands. SHA has been shown to be cost-effective compared to RHA based on the number of life-years saved and the incremental cost of RHA and SHA [17]. The Dutch FANCY study demonstrated that a 78.1% reduction in specimens sent for analysis was feasible. However, they also found that the strategy was oncologically safe despite identifying eight gallbladder malignancies in the untested cohort—seven of which were deemed clinically consequential—from a total of 36 gallbladder malignancies in the whole study population [18]. This concern is echoed in recent literature, which has highlighted that traditional risk stratification methods such as clinical judgement and post-operative macroscopic examination of specimens by the operating surgeon can be inconsistent and miss up to one-third of iGBC cases [3, 8].

Two diagnostic scores have been developed to improve risk stratification. A Swedish team drew on data from the GallRiks registry to create a predictive model and stratified patients into low-risk, medium-risk and high-risk categories. However, in development, 8 of 249 patients with iGBC were included in the low-risk group [19]. Subsequently, a Dutch group combined data from multiple healthcare databases and registries to produce an externally validated score. In validation, their score also included two from 75 cases of iGBC in the lowest risk group. However, as these cases were early stage and would not have required further treatment, the Dutch team therefore argued that histological analysis would be inconsequential [20].

Despite this positive progress, both of these studies have limitations in their approach. Their reliance on non-purposefully collected data from registries and databases exposes them to variability in data input and coding practices, which may undermine the real-world reliability of their models. Neither score made use of the full range of data available preoperatively and intraoperatively, including imaging and operative findings. Furthermore, as SHA is already a widespread practice in both countries, there is a risk of sampling bias as patients deemed at low risk of iGBC may not have had histological reports available. These concerns are compounded by higher numbers of patients with inflammatory conditions and significantly longer waiting times for cholecystectomy in the UK [21–25]. Subsequently, these existing scores are difficult to generalize to the UK population. Nonetheless, the potential for equivalent cost and workload reductions in the UK remains considerable, provided a robust and generalisable diagnostic score can be developed.

Therefore, we are conducting Predicting Incidental Gallbladder Cancer (P-iGBC), a UK-based diagnostic modelling study with broad inclusion criteria to gather the data required to develop a UK diagnostic score for iGBC in adult cholecystectomy patients. This feasibility phase, Feasibility of Predicting Incidental Gallbladder Cancer (fP-iGBC), aims to evaluate the methods and procedures of the overall study, ensuring its robustness and practicality before full-scale implementation.

METHODS AND ANALYSIS

The reporting guideline 'SPIRIT2013 Statement: Defining standard protocol items for clinical trials' has been used to report our study protocol [26, 27].

Trial design

fP-iGBC is a multicentre feasibility diagnostic modelling study comprising an internal pilot of P-iGBC and a parallel qualitative study. It utilizes a trainee collaborative model for patient identification, screening, recruitment and data collection.

Trial setting

The internal pilot study will be undertaken in up to eight NHS organizations in the southwest of England. The parallel qualitative study will identify patient participants from units participating in the internal pilot, while professional participants will be identified across the UK. Formal recruitment for the qualitative study and all interviews will be undertaken in person or remotely from University Hospitals Plymouth NHS Trust.

The study is designed to be surgical trainee-led with the support of an appropriate Principal Investigator at each participating site. fP-iGBC is being conducted by the first author for a doctoral degree at the University of Plymouth.

Participant eligibility criteria

Inclusion criteria

All adult patients (≥18 years of age) undergoing cholecystectomy for benign indications, including symptomatic gallstone disease and gallbladder dyskinesia, during the recruitment period.

Exclusion criteria

The following criteria are associated with an increased risk of gallbladder malignancy.

- Suspected/confirmed type III/IV Mirizzi syndrome.
- Any preoperative clinical suspicion or history of gallbladder or biliary tree malignancy.
- Presence of gallbladder polyps ≥5 mm.
- Biliary tree abnormalities, including primary sclerosing cholangitis and choledochal cysts.

The following criteria imply that cholecystectomy is performed for reasons other than symptomatic gallbladder disease and may imply an additional risk of malignancy.

- Patients undergoing cholecystectomy as a part of, or incidental to, another procedure.

Trial procedures

Recruitment

Potential participants will be identified by collaborating trainees and allied healthcare professionals from operating lists and waiting lists. Participants will be informed of the study through posters in clinical areas, social media notifications (on Twitter/X), via the study website (www.p-igbc.org) and in communication with their clinicians. As all data required for the study will be collected routinely by the direct care team and can be fully de-identified before export, participants will not be consent. However, detailed participant information sheets will be available in a printed format and via the study website (www.p-igbc.org), and patients may exercise an opt-out by contacting collaborating units up until the end of the recruitment period. Information for participants and contact details for collaborating units will be made available through the study website.

Data collection

Collaborating units will maintain a screening and enrolment log, cross-referencing patient identifiers with a study ID. De-identified

Table 1. Criteria for retention of data points

	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 eCRF)	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 sample size calculations to accommodate level of completeness achieved in pilot	Consider whether omitting data point from full study is justified

Table 2. Red-Amber-Green criteria for progression to full diagnostic modelling study, subject to adequate funding

	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 eCRF)	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 2 years	Sufficient centres to meet recruitment target* within 3 years (aim to recruit centres to shorten data collection period)	Insufficient centres to meet recruitment target* within 3 years.

data will be collected from medical records and entered into electronic case record forms (eCRF) in REDCap [28, 29].

Study assessments

Sample size calculation

The internal pilot study will recruit up to 500 patients over 6 months to provide operational assessments of the study processes and assess the recruitment and data completeness rates. At this sample size, the rate of iGBC, assuming a 0.2% incidence, will be estimated with a margin of error of $+-0.4\%$. A provisional sample size of 30 000 has been set for the total research programme. It will be recalculated based on data completeness, the confirmed incidence of histological abnormalities and the expected number of diagnostic parameters required for the eventual diagnostic model.

Statistical analysis

As this is a feasibility study, there will be no formal hypothesis testing. Data collected will be reported using descriptive statistics. Rates of screening and recruitment will be assessed against a minimum monthly target of 10.5 cases per collaborating unit per month of recruitment. Data completeness will be evaluated overall and for each data point. Individual data points which do not achieve a minimum of 80% completeness will be assessed in light of the effect size suggested by previous literature and considering the responses from the collaborator survey. Data points which are both unlikely to have a large effect size and meet a minimum level of completeness will be removed from the study (Table 1). An assessment of the remaining data points will be made, and recruitment rates will be considered. Where necessary, recommendations will be made for changes to the eCRF. Subject to appropriate financing and recruited centres, the outcomes will be assessed against pre-defined criteria, and a final statement will be made on the overall feasibility of P-iGBC (Table 2).

Data integrity

The integrity of the data collected will be ensured through a double-data entry exercise. Collaborators who have not been involved in the primary data collection will duplicate data collection for core data points from 10% of patients recruited to the observational study, and will be blinded to the original data collected. An assessment of concordance will be undertaken, and where necessary, adjudication of identified differences will be made. The need for ongoing quality assurance will be assessed following the analysis of the feasibility study.

Parallel qualitative study

fP-iGBC includes a parallel qualitative study, in line with the Medical Research Council's framework for complex interventions [30]. This component describes experiences and attitudes towards iGBC in cholecystectomy and the barriers and enablers to SHA.

Participants from groups including 10–15 patients, 8–10 surgeons and 5–8 other relevant healthcare professionals will be invited to participate in recorded semi-structured interviews undertaken by the first author. Interviews will occur virtually or face-to-face, and interview guides have been developed to align with the study's aims. Interviews are expected to last 30–45 minutes and will be transcribed ad verbatim, after which recordings will be deleted. Transcripts will be analyzed in NVivo using thematic analysis to identify themes and subthemes aligning with the study aims. The experiences and opinions of each participant group will be triangulated to inform an understanding of the risk of iGBC in routine cholecystectomy and the barriers to selective analysis in the UK.

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AUTHOR CONTRIBUTIONS

O.D.B. developed and drafted this protocol with oversight from all other authors. T.M. contributed significantly to the protocol development, quality assurance and data integrity. J.M.L. and L.S. provided key expertise in qualitative research and statistical rigour and are Academic Supervisors for the doctoral degree. S.A. is the Chief Investigator and Director of Studies for the doctoral degree. All named authors have reviewed and approved the final draft of this manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest or financial ties to declare.

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ETHICS AND DISSEMINATION

Research ethics and approval

The protocol for the full study, which includes fP-iGBC, has been approved by the London-Central Research Ethics Committee, reference (24/LO/0504), and the University of Plymouth Faculty Research Ethics and Integrity Committee, reference (PEOS 5550). P-iGBC is registered on ClinicalTrials.gov, registration number (NCT06531408). (University Hospitals Plymouth NHS Trust is the study's sponsor.

Patient and public involvement and engagement

Patients and the public have been involved in developing this protocol as co-designers, collaborators and consultees. Their ongoing input has informed the study's design and supported the development of patient-facing documents.

Reporting and dissemination

The study results will be disseminated in Plain English to interested parties and presented to the scientific community through publications, conferences or other appropriate means. Where published, observational data will be reported in line with the Strengthening and Reporting of Observational Studies in Epidemiology (STROBE) guidance for cross-sectional studies [31]. Qualitative data will be reported in line with the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist [32].

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