A randomised controlled trial to establish the clinical and cost effectiveness of expectant management versus pre-operative imaging with MRCP in patients with symptomatic gallbladder disease undergoing laparoscopic cholecystectomy at low or moderate risk of common bile duct stones

The SUNFLOWER Study

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Details of Sponsor

Research & Innovation Department, Research & Innovation Centre
The Leeds Teaching Hospitals NHS Trust
St James's University Hospital
Beckett Street
Leeds, LS9 7TF
Email: leedsth-tr.researchgovernance@nhs.net

Chief Investigators & Research Team Contact Details

Chief Investigator & Consultant Surgeon
Professor Giles Toogood
Department of Hepatobiliary and Transplantation Surgery
Leeds Teaching Hospitals NHS Trust
St James's University Hospital
Beckett Street
Leeds, LS9 7TF

Tel: 0113 206 5175
Email: giles.toogood@nhs.net

Professor of Surgery, Consultant Upper GI Surgeon & Co-Applicant
Professor Jane Blazeby
Bristol Medical School
Population Health Sciences
University of Bristol, Office 4.05
Canynge Hall,39 Whatley Road,
Bristol, BS8 2PS

Tel: 0117 928 7332
Email: j.m.blazeby@bristol.ac.uk

Trialist/Medical Statistics & Co-Applicant
Professor Chris Rogers
Bristol Trials Centre
1-5 Whiteladies Road
Bristol
BS8 1NU

Tel: 0117 455 7909
Email: chris.rogers@bristol.ac.uk

Trialist/Epidemiologist & Co-Applicant
Emeritus Professor Barnaby Reeves
Bristol Trials Centre
1-5 Whiteladies Road
Bristol
BS8 1NU

Tel: 0117 456 0234
Email: barney.reeves@bristol.ac.uk

Professor of Applied Health and Care Research & Co-Applicant
Professor Kerry Avery
Bristol Medical School
Population Health Sciences
University of Bristol
39 Whatley Road, Bristol, BS8 2PS

Tel: 0117 455 8070
Email: Kerry.Avery@bristol.ac.uk

Professor of Surgery and honorary consultant surgeon& Co-Applicant
Miss Natalie Blencowe
Centre for Surgical Research
Population Health Sciences
Bristol Medical School
University of Bristol
39 Whatley Road, Bristol, BS8 2PS

Tel: 0117 331 3933
Email: Natalie.Blencowe@bristol.ac.uk

Consultant Surgeon & Co-Applicant
Mr Ravinder Vohra
Trent Oesophago-Gastric Unit
Nottingham University Hospitals NHS Trust
City Hospital, Hucknall Rd,
Nottingham, NG5 1PB

Tel: 0115 969 1169
Email: ravinder.vohra@nuh.nhs.com

Consultant Surgeon & Co-Applicant
Mr Neil Jennings
Sunderland Royal Hospital
Kayll Road, Sunderland
Tyne & Wear
SR4 7TP

Tel: 0191 565 6256
Email: Neil.Jennings@chsft.nhs.uk

Professor of Health Economics & Co-Applicant
Professor William Hollingworth
Bristol Medical School
Population Health Sciences
University of Bristol, Office Room 1.11
Canynge Hall, 39 Whatley Road,
Bristol, BS8 2PS

Tel: 0117 928 7355
Email:
william.hollingworth@bristol.ac.uk

Associate Professor in Qualitative Health Science & Co-Applicant
Dr Marcus Jepson
Bristol Medical School
Population Health Sciences
University of Bristol, Office 4.03
Canynge Hall, 39 Whatley Road,
Bristol, BS8 2PS

Tel: 0117 455 4379
Email: marcus.jepson@bris.ac.uk

Radiologist & Co-Applicant
Dr Ashley Guthrie
Leeds Teaching Hospitals NHS Trust
Leeds General Infirmary
Great George Street
Leeds, West Yorkshire, LS1 3EX

Tel: 0113 206 7167
Email: ashguthrie@hotmail.com

Patient Representative & Co-Applicant
Mrs Elizabeth Leinhardt

Tel: 07752 251121
Email: lizbooth59@googlemail.com

Academic clinical lecturer in HpB and general surgery, honorary specialist registrar
Mr Samir Pathak
Centre for Surgical Research
Population Health Sciences
Bristol Medical School
University of Bristol
39 Whatley Road, Bristol, BS8 2PS

Tel: 0117 331 3933
Email: drsamirpathak@gmail.com

Consultant Surgeon & Co-Applicant
Mr Ian Beckingham
Nottingham University Hospitals NHS Trust
Hucknall Road
Nottingham
NG5 1PB

Tel: 07753 679873
Email: ian.beckingham@mac.com

Trial Methodologist & Co-Applicant
Dr Lucy Culliford
Bristol Trials Centre
1-5 Whiteladies Road
Bristol
BS8 1NU

Tel: 0117 455 3487
Email: lucy.culliford@bristol.ac.uk

Consultant Upper GI Surgeon & Co-Applicant
Mr Ewen Griffiths
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital Birmingham
Mindelsohn Way, Edgbaston
Birmingham, B15 2GW

Tel: 0121 371 5886
Email: Ewen.Griffiths@uhb.nhs.uk

Consultant Radiologist & Co-Applicant
Dr Raneem Albazaz
Leeds Teaching Hospitals NHS Trust
Leeds General Infirmary
Great George Street
Leeds, West Yorkshire, LS1 3EX

Tel: 0113 20 67167
Email: r.albazaz@nhs.net

Study Manager
Mr Stephen Palmer
Bristol Trials Centre
1-5 Whiteladies Road
Bristol
BS8 1NU

Tel: 0117 455 5321 / 07929 771395
Email: sunflower-study@bristol.ac.uk

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Glossary / abbreviations

A&E	Accident and Emergency
BTC	Bristol Trials Centre
CBD	Common bile duct
CC	Critical care
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trial
CRF	Case report form
CT	Computed tomography
DI	Diagnostic imaging
DMSC	Data Monitoring and Safety Committee
EM	Expectant management
ERCP	Endoscopic retrograde cholangiopancreatography
GBIHPBA	Great Britain & Ireland Hepatopancreatobiliary Association
GCP	Good Clinical Practice
GP	General practitioner
HES	Hospital Episode Statistics
HRA	Health Research Authority
HRG	Healthcare Resource Group
HRQoL	Health related quality of life
HTA	Health Technology Assessment
IOC	Intra-operative cholangiogram
IOUS	Intra-operative ultrasound
IP	Inpatient
ITT	Intention to treat
LC	Laparoscopic Cholecystectomy
LFT	Liver function tests
MRC	Medical Research Council
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NIHR	National Institute for Health Research

OP	Outpatient
PI	Principal Investigator
PIL	Patient information leaflet
PPI	Patient and public involvement
QALY	Quality adjusted life year
QRI	Quintet Recruitment Intervention
RCT	Randomised controlled trial
REC	Research ethics committee
SAE	Serious adverse event
SMG	Study management group
SOP	Standard operating procedure
SSC	Study steering committee
STC	Surgical trainee collaborative
UK	United Kingdom
ULN	Upper Limit of Normal
USS	Ultrasound scan

1. Study summary

Surgery to remove the gallbladder is required if it contains gallstones that cause problems. About 70,000 operations are performed annually in England. Sometimes, gallstones cause other problems if they pass from the gallbladder into the nearby bile duct (e.g. jaundice or inflammation of the pancreas). In the bile duct, stones may pass without issue or they may lead to problems. If stones are found in the bile duct, it is generally recommended that they are removed before or during the gallbladder operation. Because of this, patients requiring gallbladder surgery are assessed for risk of bile duct stones. If the risk is high, further tests are performed to identify if bile duct stones are present. If the risk is moderate or low (although it can be difficult to distinguish between the two), then it is uncertain whether further tests to look for bile duct stones are necessary. It is difficult to know the risk of bile duct stones in these groups and it is estimated that around 4% of ‘low risk’ patients may have stones (1). As a result, some surgeons choose to perform tests in all or some patients, and others don’t.

A United Kingdom (UK)-wide research study found that a third of patients undergoing gallbladder surgery were tested for bile duct stones, usually before surgery using a Magnetic Resonance Imaging (MRI) scanner. This test involves a 1-hour visit to hospital and costs the National Health Service (NHS) about £365. The test identifies bile duct stones but may delay gallbladder surgery (approximately by 2 months) which can lead to increased problems with gallstones whilst waiting. There are other uncertainties about the need for testing. Even if the test shows bile duct stones, the stones can pass into the bowel spontaneously usually with no consequence; and removing the stones can cause complications. Not having the test avoids these risks but can lead to bile duct stones being left behind after surgery, which may also cause complications. Research is needed to establish if going straight to gallbladder surgery without testing the bile duct beforehand is appropriate.

The Sunflower Study will find out whether testing for bile duct stones before gallbladder surgery is worthwhile or not in patients with a low or moderate risk of having stones. Over the course of the study, about 20,000 eligible patients in participating UK hospitals will receive information about the study. Patients who consent to participate (approximately 7,500 expected) will be divided into two groups. One group will go straight to surgery (i.e. no additional test) and the other will be tested before surgery. The groups will be selected by a process called randomisation to ensure that groups have similar patients in terms of general

health, age, gender etc. This allows a fair comparison to be made between the two groups. The “straight to surgery” group will have twice as many people in as the “tested” group to reduce the number of MRI tests performed. Both groups will be followed for 18 months and information about the need for treatment of bile duct stones, complications of surgery and costs collected.

Many surgeons in the UK are unfamiliar with participating in research studies like this one, so the study will include support and training for surgeons to ensure they communicate information about the study information clearly and fairly. The number of patients agreeing to take part and being followed up successfully will be checked in each centre and, after a probationary period, the information will be reviewed to make sure that it is possible to complete a full study.

This study will be carried out by an experienced multi-disciplinary team of surgeons, radiologists, researchers and patient representatives. We expect it will take at least six years to complete. Independent people will review the study regularly and provide advice. The results will be made publicly available to inform future care of patients with gallbladder disease.

2. Background

2.1 Surgery for symptomatic gallbladder disease

Laparoscopic cholecystectomy (LC) is the one of the most common operations undertaken in the Western world. It is indicated in patients with symptomatic gallstones in the gallbladder. About 70,000 LCs are performed annually in England (2). Indications for surgery are based on symptoms and on finding gallbladder stones on trans-abdominal ultrasound scan (USS). Gallbladder stones may pass from the gallbladder into the common bile duct (CBD) where they may remain without symptoms, cause problems of pain, jaundice, infection and acute pancreatitis, or, they may pass spontaneously into the gut. When patients are assessed for gallbladder stones with USS, information about the CBD is also obtained. A risk of CBD stones is assigned (high/moderate/low) on the basis of the USS findings and results of liver function
tests (LFTs). When symptomatic patients are classified as having a high risk of CBD stones it is national and international practice to recommend further investigation and treatment (3-7) and stones are found in at least 20% of these patients (8). Further investigation of patients at moderate or low risk of CBD stones is, however, controversial, and guidance and practice varies; fewer than 10% actually have CBD stones (3-5, 7, 8). There is controversy because CBD imaging (or not) may lead to subsequent over (or under) treatment with significant risks to the patient in terms of morbidity and Health Related Quality of Life (HRQoL), and costs to the health service.

2.2 Over-investigation and treatment of patients at moderate or low risk of CBD stones

Over treatment may occur if CBD imaging identifies CBD stones that would subsequently pass if untreated. Overtreatment occurs because national guidance recommends extraction of CBD stones identified by imaging before or during LC. Extraction is most frequently performed with an endoscopic retrograde cholangiopancreatography (ERCP) before LC. ERCP is usually carried out as a day case or short stay admission. An ERCP involves endoscopy under sedation and instrumentation of the CBD. At the time of the ERCP, however, it may become apparent that the stones have passed spontaneously. This means

that the ERCP was unnecessary, but its risks and costs will have been borne. Risks of ERCP are significant (pancreatitis, perforation, cholangitis and occasionally death in 0.05% of patients). The procedure is inconvenient for patients and impacts on quality of life, and healthcare resource use (about £1,600). In this situation, in addition to over treatment, Magnetic Resonance Cholangiopancreatography (MRCP) and ERCP can also delay the LC because of the time required to organise and perform investigations. A delay in LC could increase problems related to stones in the gallbladder (e.g. cholecystitis and a more complex LC).

2.3 Under-investigation and treatment of patients at moderate or low risk of CBD stones

If patients at low or moderate risk of CBD stones do not undergo CBD imaging (i.e. Expectant Management (EM)) there is a risk of under treatment because CBD stones may be present and lead to complications before or after LC. If CBD complications present after LC (after excluding a bile duct injury) they are attributed to retained CBD stones. Complications related to CBD stones include pain, jaundice, infection and acute pancreatitis. When these occur, an unscheduled admission to hospital is required for an ERCP to extract the stones (although at the time of the ERCP the stones may have already passed as described above). The risks and costs of an ERCP in this setting are as described above.

2.4 Uncertainties and gaps in current knowledge

The question of whether to undertake additional imaging to identify CBD stones in patients with
symptomatic gallbladder disease is the central uncertainty that this study will address. It will provide information to optimise treatment benefits and minimise harms in patients awaiting LC who are at moderate or low risk of CBD stones. This study will provide an estimate of the risk of complications of gallstones whether these arise from over or under treatment, across the entire care pathway including at least 12 months after LC. The study will also estimate the cost effectiveness of EM versus MRCP.

Some CBD stones pass spontaneously before or after LC. Estimates of the spontaneous passage of CBD stones are difficult to obtain and this study will be able to provide these. In patients classified as being at moderate and low risk for CBD stones, it is thought that up to 75% of CBD stones may pass spontaneously (9-12).

Where CBD stones are retained after LC they may lead to complications or pass spontaneously without problems. Complications include post-operative bile leak due to CBD stone impaction causing raised intrabiliary pressure and clip failure in the first few days before the cystic duct has sealed; this is uncommon. Most retained CBD stones do not become symptomatic until several months after LC. Then they may cause pain, jaundice, cholangitis or pancreatitis. A study of 10,000 LCs in Switzerland identified that the immediate risk of acute postoperative pancreatitis was 0.34% and was due to CBD stones in only 4 cases (0.04%) (13). Rates of retained symptomatic stones up to 4% have been reported (14, 15).

3. Rationale

There are two predominant imaging strategies, namely;

A. Pre-operative imaging (by MRCP) with (usually/almost always) a pre-operative intervention to remove CBD stones, if present, by ERCP before LC;
B. Intra-operative imaging (intra-operative cholangiogram, IOC or intra-operative ultrasound, IOUS) with extended intervention during surgery to remove CBD stones, if identified.

Either imaging strategy contrasts with EM, i.e. no preoperative or intra-operative imaging, dealing with retained CBD stones after LC if they become symptomatic.

We discounted strategy B as a potential NHS-wide imaging strategy, even though it is sometimes usual practice, e.g., in Australia. This strategy is not widely used in the UK (IOC used in 12% of all LC (8); IOUS used even less often than IOC). Most patients with gallstones are treated by general surgeons and not within specialist centres. Intra-operative imaging requires additional time in the operating theatre and depends on having an expert radiographer available (as well as being dependent on operator expertise). It is not practical or desirable to include IOC because it is only performed regularly in a few specialist centres. The limited availability of IOC would severely restrict the success of a study in terms of timeliness or power.

A variant of strategy A is “request MRCP when there is a suspicion of a CBD stone.” This is, in effect, current practice; most surgeons request some MRCPs rather than a few surgeons always requesting MRCPs. The LC audit shows that surgeons do this successfully, to the extent that the risk of a CBD stone in patients who have MRCP is higher than in patients who do not have MRCP. However, factors causing suspicion of CBD stones are not established and the threshold of suspicion triggering a MRCP request varies across surgeons. Four key facts/gaps in evidence emerge from this situation:

1) current practice (i.e. criteria for requesting a MRCP) cannot be defined;
2) there is no way to avoid ‘creep’ in practice in the future (i.e. decrease in decision criterion threshold leading to an increase in MRCP requests);
3) the natural history of CBD stones identified by MRCP is unknown (i.e. the proportion that pass uneventfully versus the proportion that become symptomatic);
4) the overall benefits and risks of MRCP, also taking into account the benefits and risks of ERCP in patients found to have CBD stones, are unknown.

The Sunflower study comparing MRCP versus EM will answer all but the first uncertainty.

Although MRCP is only carried out in about 25% of all patients having LC, we regard this as usual care since, by adopting a cautious decision criterion (low threshold), surgeons generally succeed in selecting for MRCP patients with a higher risk of CBD stones (at the cost of frequent false positives, with the risk of harm to these patients). Therefore, we consider that it is necessary to test whether a policy of EM (avoiding any preoperative imaging) is non-inferior to MRCP. We are testing EM against MRCP for everyone allocated to MRCP (rather than just those in whom surgeons would anyway order MRCP) because it is not possible to define criteria for MRCP and in order to answer evidence gaps 3 and 4 (above).

Preoperative imaging with MRCP (a non-invasive, out-patient procedure) is in principle easily implemented (but would require more MRI resource, both equipment and staff, if implemented universally in patients at low to moderate risk of CBD stones). It should allow patients to proceed to LC with peace of mind that any post-operative CBD complication will be avoided, i.e. LC should be the “end of their problem”. However, many CBD stones that

are identified by MRCP “pass” uneventfully (the absolute frequency of retained symptomatic CBD stones in low and moderate risk patients is <4% (14, 15)) and there are several potential disadvantages of preoperative MRCP:

a) Potential delay in admission for LC. Instead of proceeding directly to surgery (as for EM), patients need to have MRCP as an out-patient first, and then ERCP if CBD stones are identified by MRCP, before being booked for LC. Any delay compared to EM increases the risk of complications of the underlying gallbladder disease or from CBD stones if present. (N.B. the increased risk here arises simply because of the delay in having LC; the rate of complications is constant.)
b) If CBD stones are identified by MRCP, it is usual practice to remove the stones by ERCP before having LC. ERCP is expensive (£1,600) and carries a 3% risk of a serious complication (bleeding; pancreatitis; bowel perforation) requiring hospital and, sometimes, intensive care unit admission.

While EM might be superior to MRCP, we believe that it would be sufficient for EM to be non-inferior to MRCP with respect to a future guideline/policy since EM removes a step (and the associated cost) from the care pathway. Unless later consequences of removing this step, i.e. treating retained CBD stones after LC, outweigh the short-term benefits there is no need for EM to be superior to MRCP providing the non-inferiority margin is set appropriately. The non-inferiority hypothesis is supported by the views of expert surgeons, the study team, the wider upper GI surgical community (e.g. the Great Britain & Ireland Hepatopancreatobiliary Association (GBIHPBA)) and the patient and public involvement (PPI) group.

4. Aims and objectives

4.1 Aim

The Sunflower study will compare the effectiveness and cost-effectiveness of EM versus pre-operative imaging with MRCP in patients with symptomatic gallbladder disease undergoing LC at low or moderate risk of CBD stones. The study will test the hypothesis that EM is non-inferior to MRCP with respect to hospitalisation for treatment for a complication of gallstones up to 18 months after randomisation.

4.2 Objectives

1. To estimate the difference between groups in the proportion of participants requiring a hospital admission for treatment of a complication of gallstones in the gallbladder or CBD, and complications related to their subsequent LC and possible ERCP.

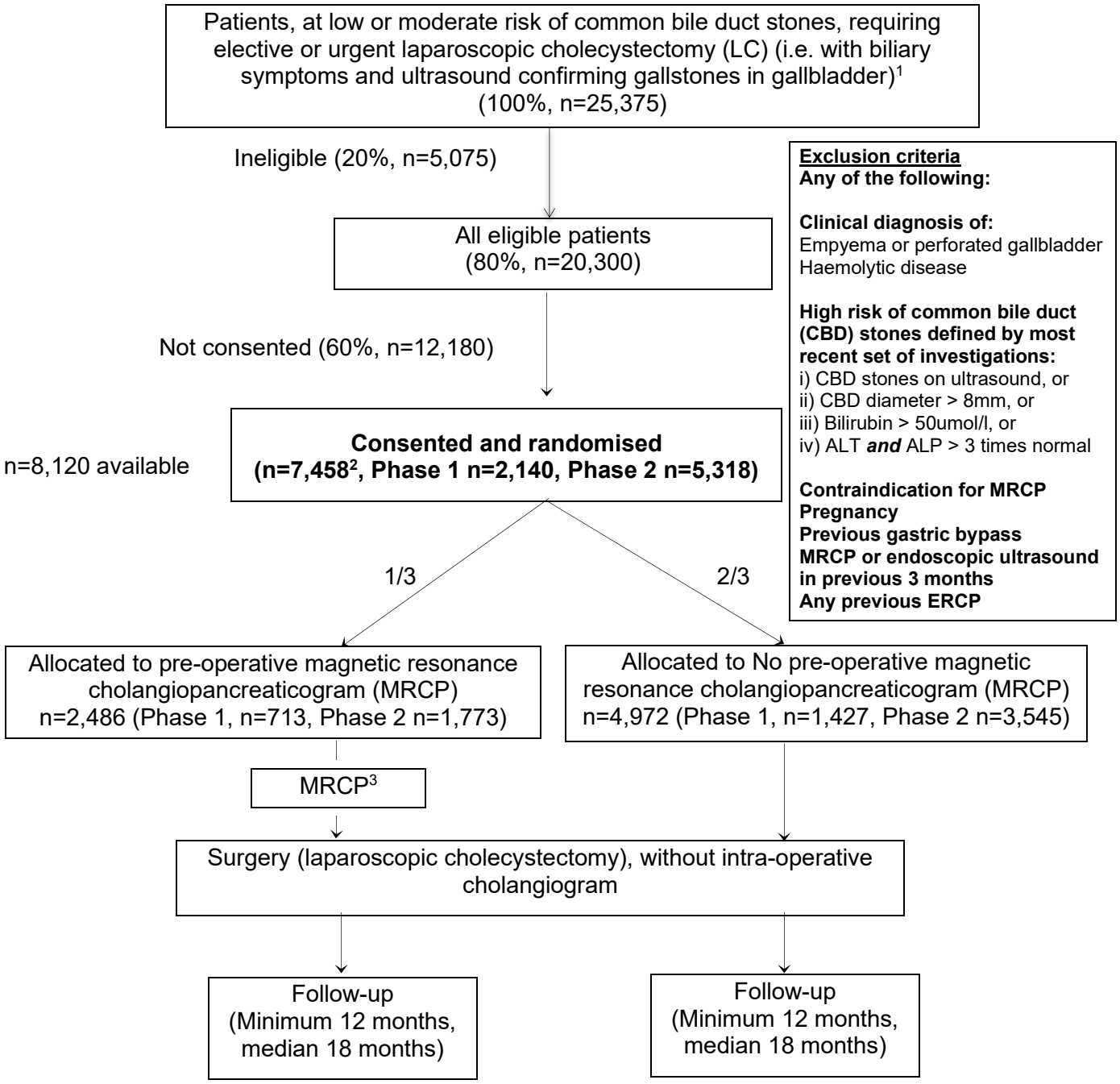
2. To estimate the difference between groups with respect to a range of secondary outcomes, including symptoms related to complications of gallstones in the gallbladder or CBD, and symptoms related to complications related to their subsequent LC and possible ERCP.

3. To estimate the cost-effectiveness of MRCP compared to EM.

5. Plan of Investigation

5.1 Study schema

Figure 1 Study schema – Revised after the target sample size was reduced



[1] CBD diameter and LFTs are used to determine if there is a moderate or low risk of CBD stones.
[2] The total sample size was reduced from 13,680 to 7,457.
[3] If CBD stones are detected on MRCP the patient will either undergo ERCP to clear common bile duct before surgery or undergo intra-operative bile duct clearance in accordance with local practice.

5.2 Study design

The Sunflower study is a multi-centre pragmatic open parallel group randomised controlled trial (RCT) with an internal pilot phase and a Quintet Recruitment Intervention (QRI). Participants will be allocated to MRCP or no MRCP (i.e. EM) in a 1:2 ratio. A 1:2 ratio (MRCP: EM) was chosen to make the study easier for centres to implement, by matching the requirement for MRCP more closely to the existing level of provision (13-26% of patients at low or moderate risk of CBD stones currently have MRCP (8)); it also reduces the excess treatment costs for MRCP (and subsequent ERCP when indicated by the MRCP).

There are two phases to the study;

Phase 1: Set-up and recruit across 36 centres with integrated QRI to optimise recruitment, and integrated monitoring and feedback to maximise adherence.

Phase 2: Increase the number of centres to 50 and continue recruitment using the optimum methods of recruitment and adherence established in Phase 1 until recruitment is complete, along with integrated QRI to optimise recruitment in new centres, following participants for a median of 18 months after randomisation (minimum 12 months).

5.3 Setting

The study will be run in secondary and tertiary care in at least 50 NHS hospital Trusts in England, Wales, Scotland and Northern Ireland. All sites will require access to MRI facilities. A Principal Investigator (PI), participating consultant surgeons, surgeons in training, participating radiologist/s, research nurses and a Research & Development contact will be identified at each site as appropriate.

5.4 Key design features to minimise bias

(a) Bias arising from the randomisation process (selection/allocation bias)
(systematic differences between baseline characteristics of the groups that are compared)
This bias is ruled out by allocation concealment; randomisation will be via a secure website. The allocation will be stratified by centre to minimise confounding due to centre.

(b) Bias due to deviations from intended interventions (performance bias)
(systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest)
This bias will be minimised by: i) defining the intervention and comparator, as well as standard protocols for other procedures undertaken during the study (see section 5.6); ii) defining procedures for participant follow-up (see section 6.11); and iii) monitoring adherence to protocol (see section 8.2).

Participants, clinicians and other hospital staff caring for participants will not be ‘blind’ to their allocation, because of the need to attend hospital for the MRCP. Attempts to blind participants and undertake a ‘sham’ imaging in participants randomised to EM would have added significant additional research cost and created logistical issues. Because sham imaging would also cause a delay to LC (if it were to be realistic), it would also prevent the study from assessing the wider impact on outcomes of adding MRCP to the care pathway.

(c) Bias in measurement of the outcome (detection bias) (systematic differences between groups in how outcomes are determined)
This bias will be minimised by using an objective primary outcome measure (see section 6.6).

(d) Bias due to missing outcome data (attrition bias) (systematic differences between groups in withdrawals from a study)
This bias will be minimised by i) using routine data for the primary outcome (see section 5.7.1); ii) using established Bristol Trials Centre, methods to maximise the proportion of participants for whom secondary outcome data are available, and the proportion of participants who receive the intervention to which they were allocated (see section 6.12); iii) implementing measures to promote adherence to random allocations (see section 6.12); iv) documenting non-adherence to random allocations (see section 7.1); using intention to treat analysis and investigating sensitivity to attrition bias in statistical analysis and implementing appropriate imputations for missing data (see section 7.1).

(e) Bias in selection of the reported result (reporting bias)
This type of bias will be minimised by having pre-specified outcomes (see section 0) and a pre-specified analysis plan (see section 7.1).

5.5 Study population

The target population is adults referred for surgery for symptomatic gallbladder disease at low or moderate risk of CBD stones, based on abdominal ultrasound and LFTs.

5.5.1 Inclusion criteria

Participant may enter study if ALL of the following apply

1. Aged 18 years or older;
2. Symptomatic gallbladder disease (including, for example, biliary colic, cholecystitis, mild and severe gallstone pancreatitis, gallbladder polyps, gallbladder dyskinesia *etc.*) confirmed by trans-abdominal USS or computed tomography (CT) scan;
3. Scheduled and fit for LC as an elective or urgent procedure;
4. Low or moderate risk of CBD stones, i.e.
    a) CBD diameter ≤8mm on USS, and
    b) bilirubin ≤50umol/l, and
    c) alanine transferase less than three times the upper limit of normal (≤ 3 x ULN) **and/or** alkaline phosphatase ≤ 3 x ULN.

    N.B. If a patient doesn't meet the definition of low or moderate risk of CBD stones solely because **both** alanine transferase and alkaline phosphatase are > 3 x ULN, if repeat blood tests are carried out and at least one of the second or subsequent test results is within range (i.e. ≤ 3 x ULN) the patient may be recruited at that time.
    N.B. If a patient doesn't meet the definition of low or moderate risk of CBD stones solely because bilirubin > 50umol/l, if repeat blood tests are carried out and at least one of the second or subsequent test results is within range the patient may be recruited at that time.
    N.B. If CBD cannot be seen on USS or CT scan, the patient may be recruited as long as all the other inclusion criteria are met and there is no intrahepatic duct dilatation reported.

5.5.2 Exclusion criteria

Participant may not enter study if ANY of the following apply

1. Unable to undergo MRCP;
2. Evidence of empyema or perforated gallbladder requiring urgent intervention;
3. High risk of CBD stones (CBD stones identified on USS, or CBD diameter >8mm on USS, or bilirubin >50umol/l, or both alanine transferase and alkaline phosphatase > 3 x ULN);
4. Previous gastric bypass;
5. Previous MRCP or endoscopic ultrasound (EUS) within last 3 months;
6. Any previous ERCP;
7. Haemolytic disease;
8. Pregnancy;
9. Unwilling to participate in follow up;
10. Unable to provide written informed consent.
11. Prisoner.

5.6 Study interventions

The study interventions are pre-operative MRCP (a type of MRI exam that produces detailed images of the hepatobiliary and pancreatic systems, including the liver, gallbladder, bile ducts, pancreas and pancreatic duct) and expectant management (EM).

The MRCP group will have an MRCP arranged, prior to their listed LC date. The participants will be required to attend as an out-patient for this scan. The study will make no changes to the usual hospital radiology protocols used for MRCP. If CBD stones are identified on MRCP they are commonly treated by ERCP, an endoscopic procedure used to enter the lower end of the common bile duct in order to remove possible bile duct stones. The participants will be required to attend as an in-patient for this procedure. The study will make no changes to usual hospital surgical and anaesthetic protocols associated with the ERCP. It is also possible for CBD stones identified on MRCP to be removed at the time of LC (as is usual practice in some centres) and again there will be no change to usual protocols for this procedure.

EM will simply involve listing patients for LC (keyhole surgery to remove the gallbladder) without any imaging, although the study team suspect that clinicians will order MRCP for a very small percentage of patients in this group for clinical/safety reasons (about 3%). This percentage will be monitored. Intraoperative imaging will only be carried out if there is an anatomical reason to do so.

In both study groups, LC will proceed as per usual hospital surgical and anaesthetic protocols – the study will make no changes to the LC procedure in either group.

5.7 Primary and secondary outcomes

5.7.1 Primary outcome

The primary outcome for the study is any of the following:

i. Any hospital admission within 18 months of randomisation for treatment of a complication of gallstones whether in the CBD or gallbladder;
ii. Complications of LC either during the admission for LC or any readmission for complications of the LC within 18 months of randomisation Complications will include, but not be limited to, a) need to return to theatre post LC for any cause related to the LC or CBD, b) need for percutaneous radiological drainage, c) bile duct reconstruction; d) and ERCP post laparoscopic cholecystectomy.
iii. Complications of any ERCP for the treatment for gallstones within 18 months of randomisation. Complications will include but not be limited to, a) bleeding requiring blood transfusion post ERCP, b) need for percutaneous radiological drainage, c) treatment of a perforation occurring during ERCP, d) acute pancreatitis.

This outcome will be derived using data from Hospital Episode Statistics (HES), or the equivalent in the devolved nations. The final specification of qualifying events (i.e. combinations of Office of Population Censuses and Surveys-4 procedures and International Classification of Diseases-10 diagnostic codes) for identifying the primary outcome from HES will be developed and validated during the study. Events identified in routine data will be compared with events identified from a clinical review of the medical records at 90 days post-LC. The data will be reviewed by an independent group of clinicians, blinded to the allocation.

5.7.2 Secondary outcomes

Secondary outcomes will include:

a) Any hospital admission within 18 months of randomisation for treatment of a complication of gallstones in the CBD (i.e. excluding complications of gallstones in the gallbladder) or complications of any ERCP for the treatment for gallstones within 18 months of randomisation. This will include but not be limited to, a) bleeding requiring blood transfusion post ERCP, b) need for percutaneous radiological drainage, c) treatment of a perforation occurring during ERCP, d) acute pancreatitis.
b) HRQoL measured using the EQ-5D-5L questionnaire completed at time of randomisation, admission for LC (for admissions up to September 2021 only) and 3, 6, 12 and 18 months after randomisation (collected for a 20% sample). Of note, participants will not be asked to complete the questionnaire at the time of admission for LC if they have completed their baseline questionnaire within the previous two days;
c) Items in the LC core outcome set* (16)
    i. Common bile duct injury
    ii. Biliary leak
    iii. Haemorrhage
d) NHS resource use to 18 months post randomisation.

*Items from the core outcome set are limited to those that apply in the period to 90 days following discharge from the index admission for LC.

5.7.3 Exploratory endpoints/outcomes

Exploratory outcomes will include:

a) Time from randomisation into the trial to LC
b) Time from randomisation into the trial to MRCP
c) Number and size of stones in the common bile duct seen on MRCP
d) Stones in the common bile duct found and removed under ERCP
e) Use of ERCP, its timing relative to MRCP and LC, ERCP findings and complications following ERCP

5.8 Sample size calculation

The study team hypothesise that EM will be non-inferior to pre-operative imaging with MRCP with respect to the primary outcome, i.e. hospital admission for treatment of a complication of gallstones or retained CBD stones. The sample size has been chosen to test this hypothesis. In estimating the sample size, the study team considered the proportion of patients that would be expected to experience the primary outcome, as identified in the CholeS (8) audit (5% to 10%) and the exploration of a sample of HES data, noting that this range includes patients at high risk of CBD stones. The consensus amongst clinicians on the study team at the time the study was designed was that the non-inferiority margin should be set at 1.5%, i.e. that the risk of the primary outcome with EM should not exceed 8.5% assuming a risk of 7% after MRCP. Further exploration of HES data for Sunflower participants suggests that the risk of the primary outcome is closer to 15% rather than the 7% assumed in the original calculation. Waiting times for LC have increased since the COVID-19 pandemic and it is plausible that events due to gallbladder disease and its treatment may explain the increased risk of the primary outcome as such events are expected to occur before surgery and equally often in both groups. Increasing the non-inferiority margin proportionally in line with the anticipated increased risk (i.e. from 1.5% to 3.2% (=15 x 1.5/7)) reduces the sample size required to test the hypothesis from 13,680 to 5,889 (Table 1).

However, as EM could only plausibly increase complications due to CBD stones alone (a secondary outcome), a final sample size of 7458 has been chosen to also provide 80% power to test the non-inferiority of this secondary outcome. The non-inferiority margin for this secondary outcome has been set at the original 1.5% and the outcome frequency has been assumed to be 5% in the MRCP group. These sample sizes shown in Table 1 assume 2.5% one-sided statistical significance, and a 1:2 allocation ratio (MRCP:EM).

Patient reported outcomes (see section 0) will be collected for a sample of 2,736 participants with a minimum 18 months follow-up in the study. The sample will be stratified by allocation. This sample will have >90% power to detect a difference of 0.12 standard deviation between groups.

Table 1 Proportion experiencing a gallstone-related complication

Proportion experiencing a Gallstone/CBD-related complication in the MRCP group (%)	Non-inferiority margin (%)	Sample size (total) Power	
		90%	80%
5.0	1.5	9984	7458
7.0	1.5	13,682	10,220
15.0	3.2	5889	4398

The random allocation to MRCP or EM will be stratified by centre, so that each centre will have approximately a 1:2 ratio of participants allocated to MRCP and EM. As the study is not evaluating the surgery per-se, surgical experience is not a criterion for participation (all participants will be under the care of a consultant surgeon). In the context of the Sunflower study, clustering by surgeon is not relevant to the sample size and can be ignored (on the basis that the intra-class correlation is negligible, personal communication with Prof D Altman for a previous trial).

6. Study methods

6.1 Description of randomisation

Randomisation will be carried out after eligibility has been confirmed and consent given. Randomisation will be performed by an authorised member of the local research team using a secure internet-based randomisation system to ensure allocation concealment. CTEU, Bristol Trials Centre, will develop the randomisation system. The allocation will be computer generated. Stratification will be used to ensure balance across the groups by centre. The key data required to characterise a participant's current clinical status and HRQoL at recruitment (20% sample only) will be collected before randomisation.

Concealed randomisation will protect against selection bias.

Code breaking will not be required, as participants, clinicians and other hospital staff caring for participants will not be 'blind' to their allocation. This is due to the need for participants allocated to the MRCP group to attend hospital for the MRCP.

6.2 Blinding

Participants and clinical personnel will not be blind to allocation and the study will be at risk of performance bias.

An algorithm will be applied to routine data to identify the primary outcome, in effect "blind" to allocation.

In the pilot phase of the study, hospital admissions identified from HES data, or the equivalent in the devolved nations, will be validated against data obtained from the clinical review of the medical records at 90 days post-LC. The data will be reviewed by an independent group of clinicians, blind to the allocation.

6.3 Research procedures

Participants will be required to do, or undergo, the following tasks or investigations specifically for the research:

- Read a patient information leaflet (PIL) about the main study and the QRI.
- Provide written, informed consent to participate in the main study and/or the QRI.
- Have consultations where Sunflower is discussed and audio recorded (optional).
- Complete the EQ-5L-5L questionnaire at baseline, on admission for LC (for admissions up to September 2021 only) and at 3, 6, 12 and 18 months after randomisation (20% sample).
- Allow access to hospital records for medical history information to be collected, as well as information relating to their surgery and recovery.

- Allow MRCP images to be transferred to radiologists at the Sponsor site for review (10% sample).
- Allow linkage and access to routinely collected data on hospital care held by NHS Digital in England and equivalents in the devolved nations.

Participants randomised to pre-operative imaging will undergo MRCP at an outpatient or inpatient appointment, depending on their initial presentation. If stones are identified, most patients will have them removed during hospital admission for an ERCP before LC surgery. This will be at the discretion of the clinical team. Some participants will undergo intra-operative imaging – IOC or IOUS – with extended intervention during the surgery to remove the CBD stones. Participants randomised to EM will proceed directly to LC surgery.

6.4 Duration of treatment period

The treatment period will end when the participant is admitted for their LC surgery.

6.5 Definition of end of study

The study ends for participants once they have completed follow-up. Study participants will be followed up for a minimum of 12 months (i.e. those recruited in the last year of recruitment will only be followed to 1 year, participants recruited earlier in the recruitment phase will be followed for longer). All participants will be followed postoperatively to discharge and through linkage with routine data to the end of the study.

The definition of the overall end of the study is the date when all data collection has been completed (including patient follow-up), the database is locked and all data analysis is complete.

6.6 Data collection

Patients will either be referred by their GP (either to be seen at an outpatient clinic or to be seen urgently), or they will have an urgent admission to hospital via the Emergency Department with severe abdominal pain. Eligibility will be assessed by the research nurse/team, surgical trainee or consultant after potential participants have undergone routine LFTs and abdominal USS to assess the nature of their pain and risk of CBD stones, either as an outpatient or after admission to hospital.

Data will be collected on the numbers of patients screened, eligible and consented, including reasons for ineligibility and reasons for declining the study. During the pilot phase of the study, the screening data to be collected will include duct size in mm from the USS (where reported) and the results of routine LFTs (bilirubin, alanine transferase and alkaline phosphatase). Data will be entered in a purpose-designed secure database, with in built real-time validation, which will be developed by the Bristol Trials Centre, to support the study.

Data collected in the period from recruitment to discharge from hospital after LC surgery will be collected by the research nurse/team or surgical trainee using study case report forms (CRFs). The CRFs will capture key details (e.g. MRCP date, report, ERCP details if performed; LC: admission/discharge dates, duration of surgery) in order to describe the process of care and derive costs.

Clinical events and resource use after discharge will be ascertained through review of the medical notes at 90 days post-LC and through linkage with routine data sources (e.g. HES,

Information Services Division Scotland, Patient Episode Database for Wales, Trust level data for Northern Ireland). Data collection from review of the medical notes will include collection of information on LFTs, and hospital admissions and interventions in the 90 days post LC. It is expected that local surgical trainees registered with the study will facilitate this data collection. The 90 day data collection time point will continue until data have been received from NHS Digital (and the equivalents in the devolved nations) and the study team are able to demonstrate that the primary outcome events can be reliably identified from these routine data sources. Once this is confirmed by the Study Steering Committee (SSC), active data collection at study sites at 90-days post-LC will cease.

Consent for linkage to HES (and devolved nation equivalents) datasets (diagnostic imaging, DI; inpatient, IP; critical care, CC; outpatient, OP; Accident and Emergency, A&E) and mortality data will be sought at recruitment. The DI dataset provides information on diagnostic test date, modality, region of body and NHS provider. The IP, CC, OP, A&E datasets provide information on date of admission, procedure codes, healthcare resource group.
See Table 2 for schedule of data collection.

Data collection will include the following elements:

(a) A log of patients requiring elective or urgent LC and those who are approached for the study (including the date when they are given the PIL);

(b) Patients approached and assessed against the eligibility criteria and, if ineligible, reasons for ineligibility. During the pilot phase, duct size and results of routine LFTs will also be collected;
(c) Patients approached for the QRI and consent for audio recording of their consultations;

(d) Consent and baseline information (e.g. medical history, scheduled operation) collected prior to randomisation;

(e) If applicable, MRCP, ERCP, IOC and IOUS details;

(f) Information relating to index hospital admission for LC (e.g. admission/discharge dates, duration of surgery);
(g) For a 20% sample of participants, EQ-5D-5L questionnaire, days lost from work/usual activities and primary care use due to symptoms of gallbladder disease or CBD stones completed at baseline, admission for LC (for admissions up to September 2021 only) and 3, 6, 12 and 18 months post randomisation. Of note, participants will not be asked to complete the admission for LC questionnaires if they have completed their baseline questionnaires within the previous two days;

(h) Items in the LC core outcome set;

(i) At 90 days post surgery, data collection from patients' medical records relating to LFTs, admissions and interventions;

(j) Clinical events and resource use after discharge, obtained using HES or equivalents in the devolved nations.

To minimise bias, outcome measures are defined as far as possible on the basis of objective criteria.

Table 2 Data collection

Data item	Pre-Randomisation	Pre-Surgery	Hospital Admission for LC	90 days post LC	3 months*	6 months*	12 months*	18 months*
Eligibility	✓							
Written informed consent	✓							
Medical history	✓							
EQ-5D-5L, productivity & primary care use questionnaire	✓		✓***		✓	✓	✓	✓
MRCP, ERCP, IOC and IOUS details, if applicable		✓						
Operative and post-operative details			✓					
Items in the LC core outcome set				✓				
Safety data collection				✓				
Study consultations audio recorded**	✓							

**These timepoints are months post randomisation. The 3-month timepoint could be before hospital admission for LC, depending on patient pathway.*
***In phase 1 of the study, consultations will be audio recorded at two high volume sites (Leeds & Bristol) from opening and at a further 4 centres based on screening levels. Thereafter consultations will be recorded at centres where their recruitment rates fall below target (initially 30% of eligible patients, rising to 50% after 6 months and following targeted recruitment training).*
****For admissions up to September 2021 only*

6.7 Source data

The primary data source will be the participant's medical notes. The reports will be the primary data source for MRCP, ERCP, LC and IOC/IOUS results.

The EQ-5D-5L, productivity and primary care use questionnaire will be considered source data.

The data provided by HES, or the devolved nation equivalents, will be considered source data for hospital admissions after discharge following LC surgery.

6.8 Planned recruitment rate

Recruitment to the study is expected to last for approximately five and a half years. The study is multi-centre, and there will be a staggered start across the centres. The study team anticipate that 36 centres will be open to recruitment by month 16 of the study, and that ultimately 50% of patients who are screened will be eligible. Recruitment to the study will

now continue at all open centres until the target recruitment end date 31st May 2024. The required rate will be calculated on a monthly basis by the study team and shared with all participating centres.

6.9 Participant recruitment

Sunflower will be a large study, conducted in at least 50 centres and involving at least 180 surgeons and teams. Study participants will be identified and recruited by the research team (e.g. research nurse, surgical trainee, consultant) to ensure that eligible patients admitted out-of-hours are not missed. All potential participants will be sent or given an invitation letter and PIL (approved by the local Research Ethics Committee (REC)) describing the study. The patient will have time to read the PIL and to discuss their participation with others outside the research team (e.g. relatives or friends) if they wish. Most elective patients will have at least 24 hours to consider whether to participate. However, as it will be important to include patients who are admitted to hospital in an urgent manner, some patients (including elective) may have less than 24 hours to consider the study. In these circumstances, patients will only be enrolled if they confirm that they feel they have had enough time to consider their participation.

Patients who feel they have not had enough time to consider the study will be invited to take the consent form and baseline questionnaire (where applicable) home, and to complete and return them if they decide to take part. Patients will be provided with a stamped addressed envelope to use to return the form(s). The local research team may telephone the patient after the clinic appointment to check if they wish to participate and answer any queries. Randomisation will take place once the completed consent form has been received and countersigned, and the patient will then be informed of their study allocation.

Where possible, before agreeing to take part, patients will be seen by a member of the local research team who will answer any questions, confirm the patient's eligibility and take written informed consent if the patient decides to participate. Some of these processes may take place via telephone or electronically (see below). Consent may be taken at a clinic appointment, when the patient is in hospital, alternatively it may also be completed at home using the postal consent or e-consent form. Details of all patients approached for the study and reason(s) for non-participation (e.g. reason for being ineligible or patient refusal) will be documented. The participants' GP will be informed of their enrolment in the study.

Postal consent can also be used alongside a telephone conversation with the patient, where a face-to-face consultation is not possible (e.g. where clinics are being held remotely due to COVID-19). In this circumstance, the patient will be provided with a study PIL, postal consent form, return envelope and invitation letter in the post. Within a few days of posting the study information, a member of the local research team will contact the patient via telephone to ask if they are interested in participation. If so, the patient will have the opportunity to ask any questions and discuss their participation. If relevant, the baseline questionnaire will then be posted to the patient. If the patient is happy to enter the study, they will complete the postal consent form and return this to the local research team in the provided envelope. As above, randomisation will take place once the completed consent form has been received and countersigned, and the patient will then be informed of their study allocation.

Patients may also be offered the option to complete an e-consent form. In this circumstance, following a discussion with the patient either in the clinic or via telephone, the patient will be provided with a study PIL in the post or via email. Within a few days, this will be followed up by a telephone call from a member of the local research team to discuss the study, answer

any questions, confirm the patients' interest, and begin the consent process. An e-consent form will be sent to the patient for them to complete and the study recruiting team will remain on the phone throughout to answer questions on any or all of the consent statements The eConsent process will be conducted via REDCap on University of Bristol servers. Potential participants email addresses will be stored outside of the main study database and will be deleted if the patient does not proceed to consent to the study. Randomisation will take place once the e-consent form has been completed and the patient will then be informed of their study allocation.

6.9.1 Trainee-led research collaboratives

Firstly, the study team will work with surgical trainees in surgical trainee collaboratives (STCs), which have been established under the umbrella of the National Research Collaborative. These STCs have pioneered a novel approach to surgical research in the UK. To date, they have designed, conducted and reported two large RCTs (17, 18), which both recruited ahead of target; completed multiple large cohort studies (8, 19, 20); are currently conducting another study (https://nwresearch.org/our-projects/packing-of-perianal-abscesscavities-ppac/); and recently undertook a survey of dressings use in general surgery for another National Institute for Health Research (NIHR) funded project (21). As well as their unprecedented track record in delivering multicentre studies, working with STCs has the added advantage of maximising the recruitment of eligible patients, because trainees routinely work unsocial as well as normal working hours, ensuring that the study can recruit patients admitted in an urgent manner. The study research team will work together closely to ensure patients are not missed (and not approached independently by different team members).

6.9.2 Quintet Recruitment Intervention

Most of the surgeons will have little experience of studies and of explaining randomisation to patients. Variation in practice and preferences for imaging (or not) in the Sunflower population are anticipated. Patients may also have preferences for imaging (or not). The PPI group confirmed that some patients would rather go straight to surgery, while others preferred detailed imaging before surgery. Therefore, the study team plan to support surgeons and nurses to optimise informed consent and recruitment with the support of the QRI, which is incorporated into the study (22).

The QRI will have two components, i) initial recruiter training, and ii) targeted qualitative interventions to optimise informed consent and recruitment, with ongoing review. Initiation of these components will be based on regular scrutiny of the data from each hospital regarding patients screened for eligibility, reasons for ineligibility, number of participants recruited and reasons for non-randomisation.

i. Training for PIs, recruiting surgeons and research nurses

The QRI researcher will provide training based on common recruitment challenges (interpretation of eligibility criteria; demonstrating equipoise; managing recruiter/patient preferences; presenting study information clearly and concisely). Training will be provided at investigators' meetings, and at site initiation visits. During the study, targeted training will then be provided based on rates of recruitment in each centre assessed with study screening logs.

ii. Targeted QRI

Contextual interviews will be undertaken with the Chief Investigator (CI) and members of the study management group (SMG) to understand potential recruitment challenges before

recruitment begins. Thereafter, the QRI researcher will work closely with the Clinical Trials Unit (Bristol Trials Centre) to review detailed logs of potential RCT participants as they proceed through screening and eligibility phases, to identify points at which patients do not continue with recruitment to the RCT. Where centre randomisation rates fall below target (initially 30%, rising to 50% after 6 months with feedback and training), the QRI team will use established methods of data collection and analysis to identify specific barriers to recruitment. Methods will involve:

a) Interviews with site PI, surgeons and nurses, Interviews will explore respondents' perspectives on the RCT, and their experiences of recruitment. Key topics explored will include perspectives on the study design and protocol; views about the evidence on which the study is based; perceptions of uncertainty/equipoise in relation to the RCT groups; views about how the groups/protocol are delivered in their clinical centre; methods for identifying eligible patients; views on eligibility, and examples of actual recruitment successes and difficulties.
b) Analysis of audio-recorded recruitment discussions: Appointments during which the study is discussed will be audio-recorded with consent. The audio recordings will be analysed to explore information provision, recruitment techniques, management of patient treatment preferences, and study participation decisions to identify recruitment difficulties and improve information provision (see section 0 for more information).
c) Mapping of eligibility and recruitment pathways: Detailed eligibility and recruitment pathways will be compiled for participating centres, noting the point at which patients receive information about the study, which members of the clinical team they meet, and the timing and frequency of appointments. Recruitment pathways will be compared with details specified in the study protocol and pathways from other centres to identify practices that are potentially more/less efficient.

When recruitment challenges are identified, the QRI team will work closely with the CI or local PI to formulate a 'plan of action' to improve recruitment and information provision. The plan for a particular centre will be grounded in the findings from the data collection/analysis. Forms of intervention may include 'tips' about how to explain study design and processes. Supportive feedback will be a core component of the plan of action, with the exact nature and timing of feedback dependent on the issues that arise. Centre-specific feedback may cover institutional barriers, while multi-centre group feedback sessions may address widespread challenges that would benefit from discussion. All group feedback sessions will be aided by displaying anonymised data extracts from interviews and audio-recorded consultations. Individual confidential feedback will also be offered – particularly when recruiters experience specific difficulties, or where there is a need to discuss potentially sensitive issues.

6.10 Discontinuation/withdrawal of participants

Each participant has the right to withdraw at any time.

In addition, the investigator may withdraw the participant from their allocated treatment pathway if there are changes in the patients' clinical condition (e.g. their LFTs change) and they have increasing concerns about the presence of CBD stones. In this circumstance the patient will remain in the study and **will not** be withdrawn, unless the patient expresses a wish to do so. In this case, a withdrawal CRF must be completed to document the reasons for withdrawal from the study.

If a participant wishes to withdraw, the study will continue to analyse any data already collected. The participant will not be contacted to participate in any further study related follow up and will remain in the care of their surgeon/GP for clinical follow up.

6.11 Frequency and duration of follow up

A 20% sample of participants will be asked to complete the EQ-5L-5L questionnaire at baseline (time of randomisation), on admission for LC* and at 3, 6, 12 and 18 months after randomisation. Of note, participants will not be asked to complete the questionnaire at the time of admission for LC questionnaire if they have completed their baseline questionnaire within the previous two days, and this suspended in September 2021 and not restarted. Study participants will be followed up for a minimum of 12 months (i.e. those recruited in the last year of recruitment will only be followed to 1 year), participants recruited earlier in the recruitment phase will be followed for longer. All participants will be followed postoperatively to discharge and through linkage with routine data to the end of the study.

6.12 Likely rate of loss to follow-up

Attrition bias, that is systematic differences in withdrawals from the study between the groups, will be minimised by using routine data for the primary outcome. There is likely to be significant attrition for secondary outcomes (especially self-reported outcomes) over the duration of the study and the study will prespecify methods (such as multiple imputation) to manage this in the statistical analysis plan. Collecting data at repeated time points will maximise the number of patients with HRQoL data. Nevertheless, the study team will maintain contact with participants throughout the duration of the study to maximise the proportion of participants for whom all outcome data are available and the proportion of participants who adhere to the allocation and will implement measures to promote adherence (e.g. stickers on participant records or clinical alerts for digital patient records to remind the care team that participants are in the study).

In estimating the target sample size, the study has not allowed for loss to follow-up as the study intends to follow-up all participants for the primary outcome using routine data. The only participants for whom this should present an issue are those who receive treatment that is not captured in the routine data sets, e.g. patients recruited in a devolved nation but treated for a complication in England or vice versa; the number of such instances is expected to be very small.

6.13 Expenses

There will be no participant reimbursement for travel expenses as participants will already be scheduled to receive surgery. MRCP and ERCP are part of routine care.

7. Statistical analyses

7.1 Plan of analysis

Non-adherence to random allocations will be documented. The study will be analysed on an intention-to-treat (ITT) basis, i.e. outcomes will be analysed according to the treatment allocation, irrespective of future management and events, and every effort will be made to include all randomised participants. Follow-up for the outcomes measures during the participant's stay in hospital should be complete for all participants.

7.1.1 Data analyses to estimate effectiveness

The primary analysis will be by ITT and will follow the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines for a non-inferiority study. An analysis limited to those participants who followed the allocated image pathway (i.e. a per-protocol analysis) will also be performed for the primary outcome and for secondary outcome a). As recommended, both analyses will be considered when assessing whether the hypothesis is met (23). The primary outcome and secondary outcome a) relating to complications of CBD stones will be compared using a generalised linear model (Poisson family with log link) with estimates conditional on time in the study (i.e. to allow for censoring).Follow-up of participants without a qualifying primary outcome event, will be censored at 18 months post randomisation (or sooner if recruited in the last 12 months of recruitment). Other secondary outcomes will be compared using a mixed linear or logistic regression model as appropriate, adjusted for baseline measures when available. Changes in treatment effect with time since randomisation will be assessed by adding a treatment by time interaction to the model and comparing models using a likelihood ratio test. Model fit will be assessed and alternative models and/or transformations (e.g. to induce normality) will be explored where appropriate. Sensitivity analyses using multiple imputation for missing data will be explored. The primary outcome is any hospital admission for treatment of a complication of gallstones. The frequencies of and reasons for admission will be described. Analyses will be adjusted for centre fitted as a random effect where possible. Where the analysis software does not support this centre will be adjusted for using a clustered sandwich estimator. Treatment differences will be reported with 95% confidence intervals.

A detailed analysis plan will be prepared. There is no intention to compare any outcomes between groups at the end of phase 1; the only analyses will be descriptive statistics to summarise eligibility and recruitment to decide whether the study satisfies the progression criteria (see section 7.4).

7.1.2 Exploratory analyses

Exploratory analyses will include:

a) Relationship between number and size of stones in the CBD seen on MRCP and the primary outcome and secondary outcome a) (cohort undergoing MRCP only)
b) Relationship between stones in the CBD removed under ERCP or not (e.g. ‘necessary’ vs. ‘unnecessary’ ERCP) and the primary outcome and secondary outcome a) (cohort undergoing ERCP only)
c) Impact of the COVID-19 pandemic on the
    i. waiting time from randomisation to MRCP (group randomised to MRCP only)
    ii. time from randomisation to LC
    iii. primary outcome and secondary outcome a)
    iv. characteristics of the study population, including the number of urgent and elective referrals and on follow-up rates

    Timeframes describing the pre, during and post COVID-19 pandemic will be defined in the statistical analysis plan.

Use of ERCP, its timing relative to MRCP and LC, ERCP findings and complications following ERCP will be described.

7.1.3 Qualitative analysis of audio recordings

All qualitative data will be audio-recorded using digital encrypted recorders, transcribed verbatim and edited to ensure anonymity of respondent. Interview data will be managed using NVivo software (QRS International) and analysed thematically using constant comparative approaches derived from Grounded Theory methodology. Consultation data will be analysed using novel approaches, including targeted conversation analysis (24) and appointment timing (the 'Q-Qat method') (25). There will be a focus on aspects of information provision that are unclear, disrupted, or potentially detrimental to recruitment and/or adherence. Analysis will be led by the qualitative researcher, with a sample of transcripts independently coded by a second qualitative methodologist.

7.2 Subgroup analyses

The subgroup analyses will evaluate the primary outcome and secondary outcome a) in subgroups of participants defined by characteristics. The main subgroup analysis will be in patients with low versus moderate risk of common bile duct stones. Low and moderate risk will be defined following the pilot phase of the study, and will be a composite of baseline LFTs, baseline common bile duct diameter on ultrasound scan and whether the participant is an elective or urgent admission for laparoscopic cholecystectomy. The information will be compiled to produce a risk score.

Further subgroups will be defined:

(a) Patients referred for elective surgery versus patients undergoing urgent surgery;
(b) Patients with normal LFTs at baseline versus patients with abnormal (outside of upper and/or lower normal limits) LFTs at baseline (i.e. low versus moderate risk);
(c) Patients with a history of pancreatitis versus patients with no history of pancreatitis.

7.3 Frequency of analyses

The primary analysis will take place when follow-up is complete for all recruited participants. Safety data will be reported to the Data Monitoring and Safety Committee (DMSC) every 6 months, together with any additional analyses the committee request. In these reports the data will be presented by group. Any interim analyses will be decided in discussion with the DSMC.

7.4 Criteria for the termination of the study

The study may be terminated early on the instruction of the DMSC, the SSC or the funder or if the results of another study supersede the necessity for completion of this study.

The study will continue into Phase 2 if it can demonstrate that, by month 16 of recruitment:

a) At least 30 centres are opened and have started recruiting. The criterion of 30 centres represents >80% of the target 36 centres for this stage of the study and 60% of the total;
b) 2140 participants have been randomised. The study team would consider the study unfeasible if fewer than 1750 participants have been randomised by this point. This criterion represents >80% of the target sample size at this stage of the study and 13% of the total recruitment target;
c) At least 90% of participants will have followed the allocated pathway (i.e. will have had or not had MRCP as allocated);

d) The study team have demonstrated that they can identify the primary outcome, admission for treatment of a complication of gallstones or CBD stones, reliably from routine data. The study team will compare the routine datasets to data collected at the 90 day time point, which will allow identification of false positives and false negatives.

7.5 Economic analyses

The primary economic evaluation will compare NHS costs and patient outcomes, measured by Quality Adjusted Life Years (QALYs), between the MRCP and EM groups on an ITT basis. This analysis will explore whether the initial cost savings due to not using MRCP are subsequently offset by higher treatment costs and worse patient outcomes due to LC complications and/or retained symptomatic stones. Secondary economic analyses will compare NHS costs and hospitalisations due to complications of gallstones, LC, or ERCP (i.e. the primary clinical outcome).

Resource use data will be obtained from NHS Digital HES data sets (and equivalent data sets in the devolved nations) for all consented patients. The health economists will use English NHS tariffs (https://www.england.nhs.uk/resources/pay-syst/national-tariff/) for outpatient MRCP to estimate the cost to NHS commissioners. Likewise, the health economists will initially use NHS tariffs to estimate the cost of LC. These tariffs are based on Healthcare Resource Groups (HRGs) and distinguish between open/laparoscopic, elective/urgent and day case/inpatient LC. However, they are not sufficiently granular to measure the impact on costs of small differences in theatre time or post-surgical length of stay which might be evident between MRCP and EM. Therefore, the health economists will micro-cost any incremental differences in LC length of stay using long stay per diem payments and theatre time or procedures using estimates from NHS trust finance departments. The health economists will use HRG codes and NHS tariffs to estimate the costs of all other secondary care during follow up. The health economists will use standard unit costs to estimate the costs of primary care contacts reported by patients. The health economists will use EQ-5D-5L value sets for England, linear interpolation between time-points and adjust for baseline imbalances to calculate QALYs (26).

Costs and outcomes beyond 12 months will be discounted at standard rates (27). The health economists will describe the prevalence of missing cost and EQ-5D-5L data and use multiple imputation techniques as appropriate. The health economists will estimate the incremental cost per QALY of MRCP versus EM groups over the 18-month follow up period and use non-parametric bootstrapping techniques to estimate 95% confidence intervals. The health economists will use regression (e.g. Seemingly Unrelated Regressions) to estimate the incremental net monetary benefit and cost-effectiveness acceptability curve of MRCP at conventional National Institute for Health and Care Excellence thresholds after controlling for key baseline covariates (28). In sensitivity analyses, the health economists will explore the robustness of the conclusions to plausible differences in key costing assumptions (e.g. the unit cost of MRCP). If there is evidence that costs and outcome differences between study groups persist between 6 and 18 months, the health economists will consider a simple extrapolation model to estimate cost-effectiveness beyond the study follow up period. In secondary analyses the health economists will estimate the cost-effectiveness acceptability curve of MRCP for the primary clinical outcome (hospitalisations for complications of gallstones, LC or ERCP avoided), describe the impact of care pathways on patient productivity costs and discuss how any differences might alter the interpretation of the primary analyses.

8. Study management

The study will be managed by the Bristol Trials Centre. The Bristol Trials Centre is an UK Clinical Research Collaboration registered Clinical Trials Unit. The BTC will prepare all the study documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the study progresses, monitor recruitment and carry out some study analyses in collaboration with the clinical investigators.

8.1 Day-to-day management

The study will be managed by a SMG, which will meet face-to-face approximately bi-monthly. The SMG will be chaired by the CI and will include all members of the named research team (see Chief Investigators & Research Team Contact Details).

An appropriately qualified person by training will be responsible for identifying potential study participants, seeking informed participant consent, randomising participants, liaising with radiology, collecting study data and ensuring the study protocol is adhered to.

8.2 Monitoring of sites

8.2.1 Initiation visit

Before the study commences, training sessions will be organised by Bristol Trials Centre. These sessions will ensure that personnel involved fully understand the protocol, CRFs and the practical procedures for the study. Due to the large number of participating centres, investigators will be trained at regional initiation meetings or via Skype (or equivalent).

8.2.2 Site monitoring

The study coordinating centre (Bristol Trials Centre) will carry out regular monitoring and audit of compliance of centres with Good Clinical Practice (GCP) and the data collection procedures described in section 6.6. The QRI programme will provide recruitment training and monitor recruitment targets.

8.3 Study Steering Committee, and Data Monitoring and Safety Committee

An independent SSC will be established to oversee the conduct of the study. It is anticipated that the SSC will comprise the lead investigators, an independent chair and at least two additional independent members, at least one of whom will be a patient/public representative. The SSC will develop terms of reference outlining their responsibilities and operational details. The SSC will meet before recruitment begins and regularly (at intervals to be agreed with the Committee) during the study.

A DMSC will be established to review safety data during the course of the study and will advise on interim analyses. The DMSC will develop a charter outlining their responsibilities and operational details. The DMSC will meet (before or jointly with the SSC) before the study begins and they will meet regularly thereafter (at intervals to be agreed with the Committee). Termination criteria for the study will be discussed at the first DMSC meeting, and decisions documented in the DMSC Charter.

9. Safety reporting

Serious and other adverse events will be recorded and reported in accordance with the GCP guidelines and the Bristol Trials Centre, Standard Operating Practice (SOP) GE-12 Serious Adverse Events (SAEs) and Safety Reporting.

In gallbladder surgery, post-operative transient complications are not unexpected and are not infrequent, often causing an extension of the patient's hospital admission. These complications are classified as anticipated. There are also some known complications of ERCP, also classified as anticipated events, and known complications of MRCP, classified as expected events in this study. Any event classified as anticipated or expected will not require expedited reporting to the Sponsor or REC, unless in the event of a participant death. Bristol Trials Centre will only notify unanticipated or unexpected SAEs to the study Sponsor.

At the conclusion of the study, all adverse events recorded during the study will be subject to statistical analysis, and the analysis and subsequent conclusions will be included in the final study report.

An SAE is defined as an untoward event that is not necessarily related to the study intervention and that: a) results in death; b) is life-threatening; c) requires hospitalisation or prolongation of existing hospitalisation; d) results in persistent or significant disability or incapacity; e) consists of a congenital anomaly or birth defect; or f) is otherwise considered medically significant by the investigator.

For all SAEs requiring expedited reporting, the subject will be actively followed up, and the investigator (or delegated person) will provide a follow-up report five working days after the initial report. Further SAE reports will be sent when there is a change to the participants condition, until the SAE has resolved or the Sponsor confirms no further reports are required.

Note: Elective interventions (e.g. planned surgery) during the follow-up period that was scheduled prior to recruitment to the study will not be reported as an unexpected SAE.

9.1 Adverse events

The following adverse events and treatments are 'anticipated'.

Anticipated adverse events associated with the patient's condition/surgery:

Body System	Adverse Event
Cardiovascular	Acute myocardial infarction
	Dysrhythmia
	Cardiac arrest
	Heart failure
Circulatory	Bleeding requiring reoperation or blood transfusion
	Bleeding requiring acute endoscopy +/- possible injection for bleeding/ clipping/diathermy
	Bleeding not requiring intervention
	Interventional radiology for bleeding or biliary injury (complications including damage to arteries/ haematoma / intimal tear and loss of distal perfusion and function / loss of limb)

Body System	Adverse Event
	Iatrogenic injury to major blood vessels in abdomen requiring intervention
	Thromboembolic complications, including deep vein thrombosis and pulmonary embolus
	Fluid/electrolyte problems
	Hyponatraemia causing confusion
	Hypoglycaemia
	Hyperglycaemia
	Iron deficiency/anaemia
	Complications related to central line insertion - Bleeding / pneumothorax / perforation of central vein or heart
	Complications related to arterial line – Intimal tear leading to damage to wrist artery and further surgery
Lymphatic	Iatrogenic injury to spleen requiring intervention
Gastrointestinal	Iatrogenic injury to liver requiring intervention
	Iatrogenic injury to bowel requiring intervention
	Oesophagitis
	Upper gastrointestinal bleed
	Stomach ulcer
	Small bowel obstruction
	Port site hernia
	Infective intra-abdominal collection
	Small bowel obstruction or perforation requiring re-operation
	Division of adhesions requiring re-operation
	Diagnostic laparoscopy alone requiring re-operation
	Bile leak requiring intervention
	Bile Duct Injury requiring intervention
	Bleeding from gallbladder bed/liver requiring re-operation
	Infected intra-abdominal collection requiring re-operation
	Small bowel resection requiring re-operation
	Laparoscopic drain placement requiring re-operation
	Post laparoscopic Cholecystectomy Pancreatitis requiring endoscopic/percutaneous/open necrosectomy re-operation
	Upper gastrointestinal endoscopy
	Laparoscopy / laparotomy
	Enteral feeding
	Total parenteral nutrition feeding
	ERCP post laparoscopic cholecystectomy
	Cholangitis/common bile duct stones post laparoscopic cholecystectomy
	Fistula
	Retained gallstones post laparoscopic cholecystectomy
	Abandoned laparoscopic cholecystectomy
	Non-specific abdominal pain requiring admission
	Adhesions
Generalised disorders	Anaphylaxis to anaesthetic agent or drug given during surgery or during recovery prior to discharge
Pulmonary	Intubation and ventilation for any reason

Body System	Adverse Event
	Initiation of mask continuous positive airway pressure ventilation after weaning from ventilation
	Pneumonia
	Haemothorax / Pneumothorax (post central line)
	Damage to larynx
	Tracheostomy
	Damage to oesophagus
Renal	Urinary retention
	Acute renal failure
	New haemofiltration/dialysis
	Urinary catheterisation stricture
	Urinary stricture
Infections and infestations	Wound infection/breakdown
	Port site infection
	Urinary tract infection
	Other infection
	Abscess
Neurological	Permanent stroke
	Transient ischaemic attack
Interventions/Investigations	Radiological drain placement requiring re-operation
	Placement of chest drain requiring re-operation
	Chest X-ray
	Abdominal X-ray
	CT scan
	MRI
	MRCP
	ERCP
	Endoscopic ultrasound
	Doppler ultrasound
	Unplanned admission to Intensive Treatment Unit/High Dependency Unit
	Complications relating to epidural – Infection / paralysis / chronic back pain
Skeletal	Rhabdomyolysis
	Joint replacement or repair requiring re-operation
Generalised disorders	Fever
	Claustrophobia

Anticipated adverse events associated with ERCP:

Body System	Adverse Event
Gastrointestinal	Oropharyngeal/oesophageal/gastric/duodenal perforation
	Biliary / pancreatic duct perforation and leakage
	Pancreatitis
	Bleeding from papilla
	Cholangitis
	Retained Dormier basket or other instrument
Cardiovascular	Myocardial infarction
	Respiratory arrest

Immune	Anaphylaxis due to sedation

The following adverse events and treatments are 'expected'.

Expected adverse events associated with MRCP

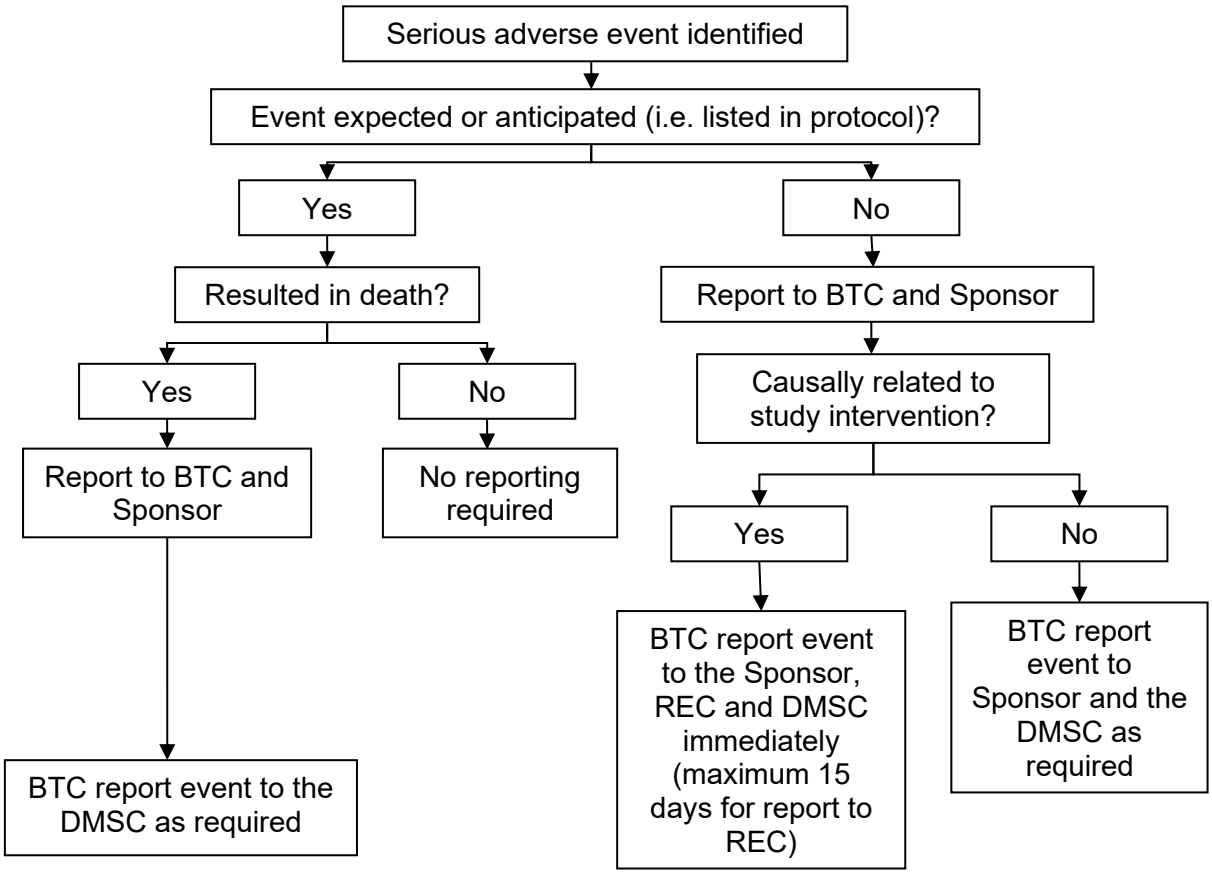
Body System	Adverse Event
Immune	Claustrophobia
	Thermal burn

Data on these adverse events collected during the study will be reported regularly to the DMSC for review.

9.2 Period for recording serious adverse events

Data on adverse events will be collected for the duration from randomisation to hospital discharge from the participant's index admission for their LC. For patients who do not undergo LC for any reason, data on adverse events will be collected for a period of 9 months from randomisation. Unanticipated or unexpected SAEs will be reported to the study Sponsor and Bristol Trials Centre, at the same time, via email or fax. No patient identifiers will be included with SAE reports. BTC will manage any onward reporting to the REC and/or DMSC as required.

Figure 2 Serious adverse event reporting flow chart



10. Ethical considerations

10.1 Review by an NHS Research Ethics Committee

Ethics review of the protocol for the study and other study related essential documents (e.g. PIL and consent form) will be carried out by a UK REC.

Any amendments to these documents, after a favourable opinion from the REC has been given, will be submitted to the REC for approval prior to implementation.

The question of whether to undertake additional imaging to identify CBD stones in patients with
symptomatic gallbladder disease is the central uncertainty that this study will address. There is clinical equipoise around this question. The study will provide information to optimise treatment benefits and minimise harms in patients awaiting LC who are at moderate or low risk of CBD stones. This study will provide an estimate of the risk of complications of gallstones, whether these arise from over or under treatment, across the entire care pathway including at least 12 months after patients join the study.

10.2 Risks and anticipated benefits

Potential benefits to participants:

There is unlikely to be any direct benefit as a result of participation in the study. Investigation of whether to undertake additional imaging to identify CBD stones in patients with symptomatic gallbladder disease will help to inform future treatment of patients undergoing gallbladder surgery.

Possible adverse effects of each intervention:

Patients randomised to the ‘testing’ group will undergo a MRCP. The test is usually well tolerated but some patients may experience claustrophobia.

If the MRCP identifies bile duct stones, the participant will often be referred to have them removed via ERCP before their gallbladder surgery, which can cause problems such as bleeding, infection or pancreatitis. The MRCP and ERCP may delay gallbladder surgery (by 1-3 months), which can lead to increased problems with gallstones whilst waiting. For some participants, this ERCP may have been unnecessary as bile duct stones can pass into the bowel safely on their own.

Participants randomised to the ‘straight to surgery’ group and who do not have the test may have bile duct stones left behind after their gallbladder surgery, which may also cause problems (e.g. jaundice, infection or pancreatitis) later that require further treatment or readmission to hospital.

Benefits to society:

The main benefit to society is the provision of high quality evidence to address this important area of clinical uncertainty.

10.3 Informing potential study participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the PIL.

10.4 Obtaining informed consent from participants

All participants will be required to either give written informed consent in person or via post, or consent via an electronic process. These processes, including the information about the study given to patients in advance of recruitment, is described above in section 6.9.

The research team (e.g. research nurse/PI/consultant/surgical trainee) will be responsible for the consent process, which will be described in detail in the Study Manual.

10.5 Co-enrolment

Participants can be co-enrolled into the Sunflower study and another study, providing that the burden on the patient is not too great. Co-enrolment will be considered on a study-by-study basis, in discussion with the CI and other members of the SMG. Participants can be enrolled into observational studies.

11. Research governance

This study will be conducted in accordance with:

- GCP guidelines;
- Research Governance Framework for Health and Social Care.

11.1 Sponsor approval

Any amendments to the study documents must be approved by the sponsor prior to submission to the REC and Health Research Authority (HRA).

11.2 NHS approval

Confirmation of capacity and capability from the local NHS Trust is required prior to the start of the study.

Any amendments to the study documents approved the REC and the HRA will be submitted to the study sites, as required by the HRA.

11.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual, and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor, Bristol Trials Centre, or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their study team of any amendments to the study documents approved the REC and the HRA that they receive, and ensure that the changes are complied with.

11.4 Monitoring by sponsor

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the Research Governance Framework and the Medicines for Human Use (Clinical Trials) Regulations 2004. All study related documents will be made available on request for monitoring and audit by Bristol Trials Centre (who has been delegated this by the sponsor, see 8.2.2), the relevant REC and for inspection by other licensing bodies.

11.5 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

11.6 Clinical Trial Authorisation

The intervention is not classed as an investigational medicinal product and a Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency is not required.

12. Data protection and participant confidentiality

12.1 Data protection

Data will be collected and retained in accordance with the EU General Data Protection Regulation 2018.

12.2 Data handling, storage and sharing

12.2.1 Data handling

Data will be entered onto a purpose designed database and data validation and cleaning will be carried out throughout the study. SOPs for database use, data validation and data cleaning will be available and regularly maintained.

Data will be submitted to the Bristol Trials Centre, directly into the database.

12.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. Where study related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the study in accordance to the Sponsor's policy. If paper records are no longer in use at a specific site, the same information must be recorded using the appropriate local online system (e.g. clinical alerts). In compliance with the Medical Research Council (MRC) Policy on Data Sharing, relevant 'meta'-data about the study and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely

(University server). A secure electronic ‘key’ with a unique participant identifier, and key personal identifiers (e.g. name, date of birth and NHS/CHI number) will also be held indefinitely, but in a separate file and in a physically different location (NHS hospital server). These will be retained because of the potential for the raw data to be used subsequently for secondary research.

For a sample of participants in the MRCP group (10%), the MRCP images will be transferred for independent review by the study core team of radiologists, based in Leeds. At the end of the study these images will be deleted.

12.2.3 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be retained for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body. Patient identifiers would not be passed on to any third party.

13. Dissemination of findings

A full report will be written for the NIHR Health Technology Assessment (HTA) programme. The study team will write up the methods and study findings for conference presentation and publication in peer-reviewed journals. The study team will provide progress reports to organisations contributing to the PPI group, to collaborating surgical associations (e.g. GBIHPBA) and work with the group to draft lay progress reports for dissemination to participants and more widely (e.g. newsletters). The study team will use social networking media to publicise and disseminate the study via a website, Facebook and Twitter streams.

The health economic analyses will inform the cost effectiveness of preoperative MRCP for managing patients referred for cholecystectomy in the NHS. The study team expect that the results of the study will be used by NHS England to formulate a commissioning policy and will inform national and international guidelines.

14. Funding

The Sunflower Study team, which includes researchers at the Bristol Trials Centre, Royal College of Surgeons Bristol Surgical Trials Centre and the Medical Research Council ConDuCT-II Hub for Trials Methodology Research collaborated in designing the study and securing funding. The Sunflower Study is funded by the NIHR HTA programme (project number 16/142/04) and supported by the Royal College of Surgeons Bristol Surgical Trials Centre and NIHR CTU support funding.

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16. Amendments to protocol

Amendment number (i.e. REC amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
Substantial Amendment 1	1.0	14 August 2018	2.0	08 March 2019	Clarification of inclusion and exclusion criteria. Addition of postal consent. Safety reporting updated.	09 April 2019

Amendment number (i.e. REC amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
					Minor wording changes.	
Substantial Amendment 2	2.0	08 March 2019	3.0	25 November 2019	Changes to inclusion and exclusion criteria. Clarification of primary outcome wording. Minor wording changes.	20 December 2019
Substantial Amendment 3	3.0	25 November 2019	4.0	18 August 2020	Clarified that 90-day data collection will continue until NHS Digital data received and validated. Changes to postal consent processes. Minor wording changes.	10 September 2020
Substantial Amendment 4	4.0	18 August 2020	5.0	8 September 2021	Changes to details of EQ-5D-5L frequency (temporary removal of Index Admission timepoint)	20 October 2021
Substantial Amendment 5	5.0	8 September 2021	6.0	11 July 2022	Changes to text on consent process – to clarify eConsent	26 July 2022
Substantial Amendment 6	6.0	11 July 2022	7.0	7 September 2023	Changes to the study sample size and duration of recruitment. Addition of a secondary outcome of	13 October 2023

Amendment number (i.e. REC amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
					complications due to CBD stones. End date of recruitment and study grant have been extended by 18 months. Removal of reference to CTEU after full name change to Bristol Trials Centre	
N/A	7.0	7 September 2023	8.0	10 October 2024	The protocol was amended but the amendment was withdrawn before approval was granted and all study activity reverted to protocol v7.0.	N/A
Substantial amendment 7	7.0	7 September 2023	9.0	16 December 2025	Primary outcome points ii) and iii) removed the restriction that complications had to lead to a hospital stay of >2 days to be considered, to better reflect varying clinical practice across the UK. In point ii), Added 'within 18 months of	

Amendment number (i.e. REC amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
					randomisation' and removed "non-diagnostic reasons" from ERCP criterion. Bile duct reconstruction also added in primary outcome point ii). Clarified the examples in points ii) and iii) to better define the complication and not just the action arising from it. Removed 'other' from primary outcome point iii) as this is inferred from the earlier text. Clarified the outcomes on the core outcome set will be reported for the period to 90-days post LC discharge and removed intra-abdominal collections from the list. For exploratory outcome a)	

Amendment number (i.e. REC amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
					clarified that time to LC will be measured from randomisation. In exploratory outcomes c) and d) and in analysis section 7.1.2 clarified that stones in the CBD are of interest. Added exploratory outcomes b) and e). Clarified that collection of EQ-5D-5L data at LC admission will not be reinstated following its temporary suspension in Sept 2021. Added time from randomisation to MRCP and exploratory analyses investigating the impact of COVID-19 on the time to MRCP, time to LC, the primary outcome and secondary outcome a). Updated the statistical	

Amendment number (i.e. REC amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
					analysis section to reflect current guidance regarding non-inferiority designs, planned modelling of the primary outcome and secondary outcome a) and include additional exploratory analyses planned Minor formatting and grammatical corrections	

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