A randomised controlled trial comparing laparoscopic **c**holecystectomy with observation/conservative management for preventing recurrent symptoms and complications in adults with uncomplicated symptomatic **gall**stones. (C-Gall trial)

PROTOCOL

A UK Collaborative Trial funded by the HTA
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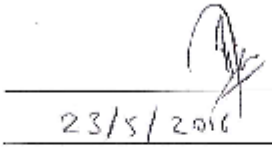
[Irfan Ahmed]:  signature

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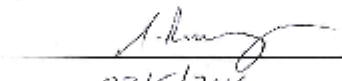
[Craig Ramsay]:  signature

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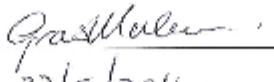
[Graeme MacLennan]:  signature

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PROTOCOL SUMMARY

Question addressed	Is there any difference between observation /conservative management and cholecystectomy in terms of participant quality of life and cost-effectiveness in terms of incremental cost per QALY?
Considered for entry	All Adults with symptomatic uncomplicated gallstone disease who are referred to a secondary care setting and considered suitable for cholecystectomy.
Populations	Adults with symptomatic uncomplicated gallstone disease
Trial entry	Eligible and consenting male and female adult patients.
Interventions	1.Laparoscopic cholecystectomy 2.Observation/conservative management with analgesia
Outcome assessment	The patient reported outcomes (SF-36; CSQ) will be assessed by participant-completed questionnaires at baseline, 3, 9, 12 and 18 months post randomisation.
Co-ordination	**Local**: by local surgical teams, local Research Nurse or Recruitment Officer. **Central**: by Trial Office in Aberdeen (Telephone 01224 43xxxx). **Overall**: by the Project Management Group, and overseen by the Steering Committee and the Data Monitoring Committee.

GLOSSARY OF ABBREVIATIONS	
AE	Adverse Event
AUC	Area under the curve
AUGIS	Association of Upper Gastrointestinal Surgeons
BNF	British National Formulary
CBD	Common bile duct
CEAC	Cost-effectiveness Acceptability Curve
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSQ	Condition Specific Quality of Life
CTU	Clinical Trial Unit
DCE	Discrete Choice Experiment
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GP	General Practitioner
GREPCO	Italian Group for the Epidemiology and Prevention of Cholelithiasis
HPB	Hepato-Pancreato-Biliary
HRQoL	Health Related Quality of Life
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
ISD	Information Statistics Division
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IVR	Interactive Voice Response (randomisation)
MRC	Medical Research Council
NCT	National Clinical Trial
NHS	National Health Service
NHSG	National Health Service Grampian
NIHR	National Institute Health Research
NRES	National Research Ethics Service
NSAIDS	Nonsteroidal anti-inflammatory drugs
PI	Principal Investigator
PIL	Patient Information Leaflet
PMG	Project Management Group
PPI	Patient and Public Involvement
PQ	Participant Questionnaire
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF36	Short form 36
SOP	Standard Operating Procedure
TMF	Trial Master File
TSC	Trial Steering Committee
UK	United Kingdom
UKCRC	United Kingdom Clinical Research Collaboration
UoA	University of Aberdeen

TRIAL PERSONNEL

Co-Chief Investigators

1 Craig Ramsay (Programme Director HSRU)

2 Irfan Ahmed (Consultant HPB Surgeon)

Grant Holders

1	Jane Blazeby (Professor Of Surgery)	6	Katie Gillies (MRC Methodology Research Fellow)
2	John Norrie (Director of CHaRT)	7	Bernie Croal (Patient and Public Representative)
3	Rodolfo Hernandez (Health Economic Research Fellow)	8	Peter Murchie (Academic GP)
4	Alison Avenell (Clinical Chair in Health Services Research)		
5	Miriam Brazzelli (Senior Research Fellow)		

Project Management Group (PMG)

This group is comprised of the grant holders along with representatives from the C-Gall central trial team:

1	Senior Trials Manager, CHaRT	5	C-GALL Data co-ordinator
2	Senior IT Manager, CHaRT	6	
3	Quality Assurance Manager	7	
4	C-Gall Trial Manager	8	

Trial Steering Committee (TSC) Members

The membership of this committee comprises of four independent members along with the Chief Investigators (Ahmed/Ramsay) or a nominated delegate. The other C-GALL grant-holders and key members of the central office (e.g. the trial manager) may attend TSC meetings.

Independent TSC Members

1	David Beard (Chair)	3	Dr Ian Beckingham (Consultant Surgeon)
2	Mrs Dee McDonald (PPI)	4	Dr John Leeds (Consultant gastroenterologist)

Data Monitoring Committee (DMC) Members

This committee is comprised of three independent members and the trial statistician contributes as appropriate. The CI and/or a delegate may contribute to the open session of the meetings as appropriate.

1	To be confirmed (Chair)	3	To be confirmed (Gastroenterologist)
2	Prof Kenneth Walker	4	

(Consultant Surgeon)

Trial Office Team

1 Co-Chief Investigators
2 CHaRT Director
3 Trial Manager
4 Data Co-ordinator
5 Senior Trials Manager
6 Senior IT Manager
7 Trial statistician

1. INTRODUCTION

1.1 Background

Gallstone disease (cholelithiasis) is one of the most common gastrointestinal disorders in industrialised societies. The prevalence of gallstones in adult populations is approximately 10 to 15%. Gallstones are more common in women and people over the age of 40.

Clinical surveys conducted in Europe, North and South America, and Asia indicate that the prevalence rates for gallstone disease range from 5.9% to 25%[1-4] and tend to increase with age. A clinical ultrasound survey conducted in the UK reported prevalence rates of 12% among men and 22% among women over 60 years of age.[3] A multicentre population-based study conducted in Italy has reported a cumulative incidence of gallstone disease of 0.67% per year (0.66% in men and 0.81% in women).[5]

Natural history studies have shown low mortality from gallstone disease with typically less than 1% of people dying from gallbladder-related causes.[6] In a recent population-based study the overall frequency of symptom development in asymptomatic people was around 20% over a long follow-up period (mean: 8.7 years).[6]

In people with symptomatic uncomplicated gallstone disease, the annual rates of developing complications have been reported to be as low as 1 to 3%.[7-9] The Italian Group for the Epidemiology and Prevention of Cholelithiasis (GREPCO) study reported an annual incidence of complications of 0.7% for symptomatic people.[10]

In the UK and in North America, the number of surgical procedures for gallstone disease increased steadily between the 1950s and 1990s, reflecting both the rise in prevalence of gallstone disease and the use of cholecystectomy as the treatment of choice. Rates of surgical procedures stabilised in both countries towards the end of the twentieth century.

1.1 Impact of health problem

From a patient perspective, the defining symptom of gallstone disease is pain.[11, 12] Commonly, general abdominal symptoms intensify over a period of time and become regular pain attacks (biliary colic) and may require medical attention. Best medical therapy includes the prescription of analgesics and when necessary antibiotics.

The most common complications associated with gallstones are acute cholecystitis, common bile duct (CBD) stones and acute pancreatitis. CBD stones are found in up to 15% of people who undergo cholecystectomy. They may be asymptomatic or accompanied by biliary pain, jaundice, pancreatitis or cholangitis.[13] CBD stones can cause acute pancreatitis by obstructing the main pancreatic duct.[14]

Even though removal of the gallbladder is considered the standard treatment for symptomatic gallstones, it does not guarantee eradication of symptoms.[15] Up to approximately 40% of people may continue to experience pain and abdominal symptoms after surgery.[16] In particular, marked biliary pain has been described in 4-9% of people after cholecystectomy while persistent abdominal pain or non-specific pain persists in about 13%-37% of people.[17-22] A recent systematic review of the literature found that up to one-third of people suffered continuing pain after cholecystectomy and up to 14% of people experienced *de novo* pain.[23] Some investigators have also reported a persistent pain similar to that experienced pre-operatively in about 20% of people with gallstones. In a prospective study conducted in Denmark, 21% of people experienced the same type of pain after surgery.[24] Similarly, in a RCT conducted in the UK,

19% of people complained of biliary pain five years after open cholecystectomy.[25] No difference has been observed between open and laparoscopic surgery in terms of persistent pain.

The term ‘post-cholecystectomy syndrome’ is an umbrella term which has been widely used to describe, though not accurately, the range of symptoms, which occur after cholecystectomy.[26] The term 'persistent post-cholecystectomy symptoms' has been suggested as a more accurate description of these symptoms.[27] These symptoms include: biliary and non-biliary abdominal pain, gastrointestinal disorders, dyspepsia, heartburn, nausea, vomiting, jaundice, and cholangitis. Severe symptoms that occur early after surgery may represent complications of cholecystectomy whilst those that manifest later (over months or years) are probably unrelated to cholecystectomy and can be explained by no biliary causes. Recent research has suggested that, in some people, functional gastrointestinal disorders and not gallstone disease may be the cause of persistent post-surgery symptoms.[28] Nevertheless, there is not a consistent pathophysiological explanation for persistent post-cholecystectomy symptoms and, in about 5% of people, the reason for persistent abdominal pain remains unknown.[29]

1.2 Rationale for the trial

At present cholecystectomy is the default option for people with symptomatic gallstone disease and one of the most common and costly surgical procedures performed in the NHS UK. Some 73,065 cholecystectomies were performed in England between 2012-2013 and 63,288 in 2014. Although some patients are operated in the acute hospital settings but still in many hospitals patients with uncomplicated symptomatic gallstone disease are put on a waiting list and operated electively.

However, conservative management may be a valid therapeutic option in people presenting with uncomplicated disease depending on their age, clinical presentation, and evolution of symptoms over time. Moreover, as these symptoms are usually not urgent, it may therefore be reasonable to take into consideration a non-surgical option first, which could save a considerable amount of NHS resources.

Recent studies stated that half of the people treated conservatively were symptoms free; therefore, up to 30,000 cholecystectomies per year could potentially be avoided with a potential saving for the NHS of £68 million annually. These resources could be freed (disinvestment) and allocated to fund alternative health care within the NHS.

Early natural history studies[6] and more recent observational and population-based studies have suggested that there is probably a proportion of people with symptomatic gallstone disease who no longer experience biliary pain after onset of symptoms. Larsen and colleagues[5] found that 45% of symptomatic people on watchful waiting were totally relieved from symptoms during a one-year observation period. Similarly, Festi and colleagues[6] observed that 58% of people with initially mild symptoms and 52% of those with more severe symptoms did not experience further episodes of pain during a follow-up period of 10 years and the severity of the disease did not increase over time.[30, 31] A recent NIHR Technology Assessment Report[32] found that on average cholecystectomy is more costly but more effective than conservative management for the treatment of symptomatic gallstones or cholecystitis. Nevertheless, half of the people treated conservatively were symptom free and did not require surgery long term indicating that there are probably a proportion of patients with uncomplicated symptoms who could benefit from conservative management. The specific results were that participants randomised to observation were significantly more likely to experience gallstone-related complications [risk ratio 6.69; 95% CI 1.57 to 28.51; p=0.01], in particular acute cholecystitis (risk ratio 9.55; 95% CI 1.25 to 73.27; p=0.03); but less likely to undergo surgery (risk ratio 0.50; 95% CI 0.34 to 0.73; p=0.0004), experience surgery-related complications (risk ratio 0.36; 95% CI 0.16 to 0.81; p=0.01) than those randomised to surgery. Fifty-five per cent of people randomised to observation did not require an operation during the 14-year follow-up period and 12% of people randomised to cholecystectomy did not undergo the scheduled operation. These results were

subject to major uncertainties in the reported economic model. Even when cholecystectomy occurred, on average, cost-effective, conservative management had between 40% and 60% chance of being cost-effective for alternative values of willingness to pay for an additional QALY. Furthermore, results were heavily sensitive to the proportion of individuals originally followed with conservative management that needed surgery. In their base case, the authors assumed that 44% of the cohort would need surgery within 5-years. If this proportion was reduced to 25% conservative management became, on average, cost-effective. The report was based on the findings of the only two RCTs[31, 33] available in the literature and included only 201 participants in total. Both RCTs were conducted in Norway by the same research team. Due to the limited evidence available and the current lack of UK NHS data the investigators highlighted the need for a large, well-designed trial assessing the effects and safety of conservative management compared with cholecystectomy.

2. AIMS AND OBJECTIVES

The ***primary aim*** of the study is to assess the clinical and cost effectiveness of observation/conservative management compared with cholecystectomy for preventing recurrent symptoms and complications in adults presenting with uncomplicated symptomatic gallstones in a secondary care setting.

The ***primary patient objective*** is to compare observation/conservative management with cholecystectomy in terms of participants' quality of life using the SF-36 short-form health survey bodily pain domain at up to 18 months after randomisation.

The ***primary economic objective*** is to assess the cost-effectiveness of observation/conservative management versus cholecystectomy in terms of the incremental cost per QALY.

The ***secondary objectives*** are to compare observation/conservative management with surgical treatment (cholecystectomy) in terms of condition specific quality of life; SF-36 domains (excluding bodily pain domain); complications; need for further treatment; persistent symptoms; health care resource use; costs.

The null hypothesis being tested is that there is no difference between observation/conservative management and cholecystectomy. The alternative hypothesis is that cholecystectomy is superior.

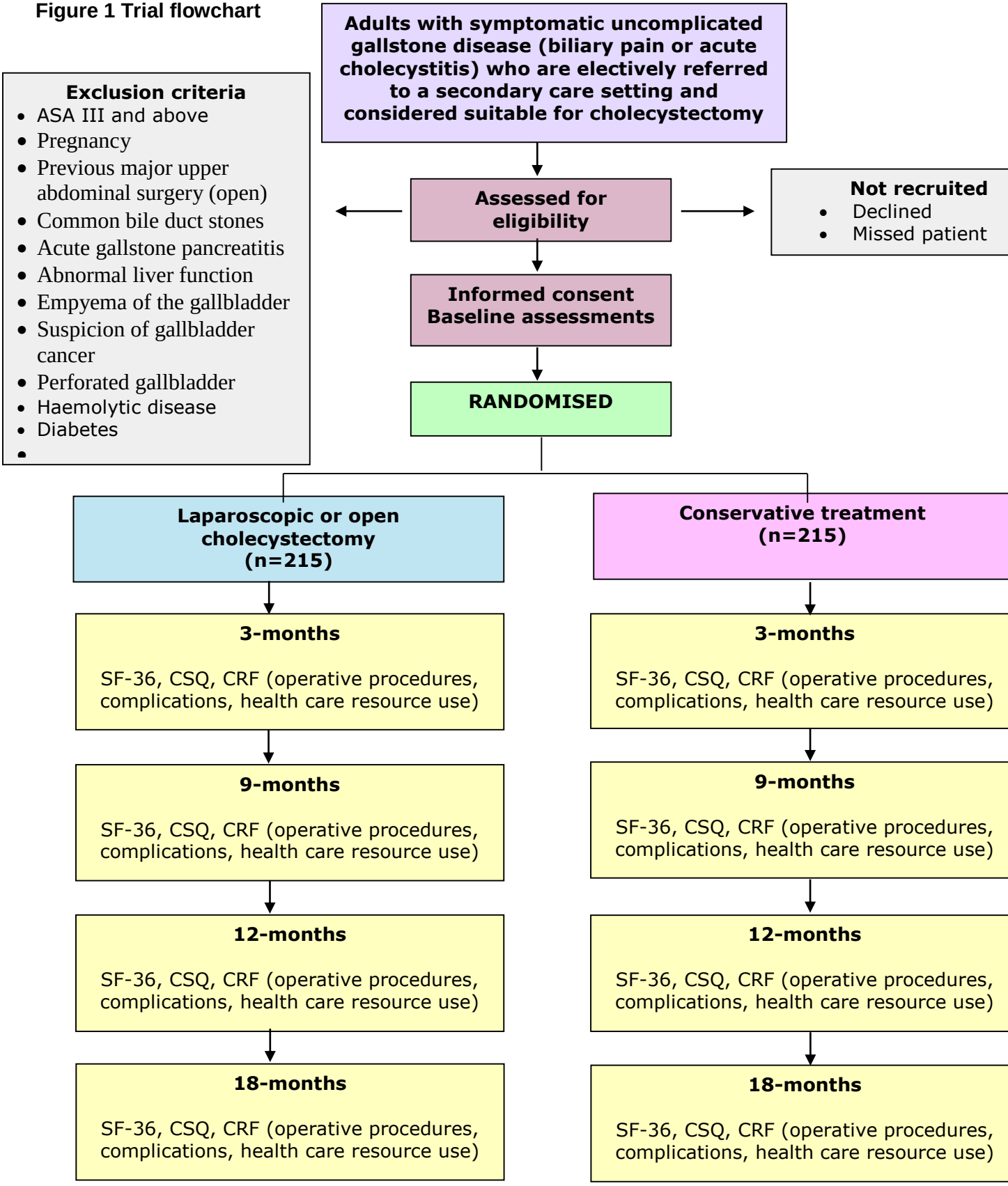
3. TRIAL DESIGN

A pragmatic, multi-centre parallel group patient randomised superiority trial (with internal pilot phase) to test if the strategy of standard cholecystectomy is more (cost-) effective than observation/conservative management at 18 months post randomisation. Other than the collection of outcome data, participant care will follow standard care pathways in participating NHS secondary care sites. A within trial economic evaluation will be conducted. Linear regression models will be used for this. Extrapolation beyond the trial follow-up period will be considered if a definite answer on cost-effectiveness cannot be reached from this within trial analysis.

The patient reported outcomes (SF-36; CSQ) will be assessed by participant-completed questionnaires at baseline, 3, 9, 12 and 18 months post randomisation. A case report form (CRF) will be completed at the time of surgery providing details of the operative procedures, complications and resource use in hospital. Costs of the initial intervention procedures will be estimated from resource use data recorded on the case report forms coupled with routine unit cost data. Costs associated with subsequent contacts with primary and secondary care (due to symptomatic gallstones) will be estimated from patient questionnaires at 3, 9, 12 and 18 months

post randomisation and checked at source. QALYs will be estimated from patients' responses to the SF-36. The trial flowchart is shown in Figure 1.

Figure 1 Trial flowchart



Embedded qualitative research will identify any challenges during the internal pilot related to design or conduct that can then be addressed and modified during progression to full trial. Fuller details are given in Appendix 1. Additionally, we are proposing to develop a core outcome set for uncomplicated symptomatic gallstones (see Appendix 2).

3.1 Interventions to be evaluated

(i) Laparoscopic cholecystectomy: is the current standard surgical procedure for the management of symptomatic gallstone disease. The gall bladder is removed with the stones within it using keyhole techniques (laparoscopy). The procedure is undertaken under a general anaesthetic. It usually involves three to four small incisions in the abdomen, which allow the surgeon to dissect the gallbladder from its attachments and safely divide the key anatomical structures (the cystic duct and artery) that link it to the biliary tree. The gallbladder is then separated from the under surface of the liver. Usually the gallbladder (containing the stones) is removed within a retrieval bag via one of the small incisions. The operation takes between 45 and 120 minutes, many patients are admitted for one night although day case laparoscopic cholecystectomy is safely undertaken in an otherwise fit patients with appropriate social support.

(ii) Observation/conservative management: Observation/conservative management in the context of gallstone disease involves the prescription of analgesics to relieve the biliary pain. Typical therapy includes paracetamol, antispasmotics (e.g. Buscopan), nonsteroidal anti-inflammatory drugs NSAIDs (e.g. ibuprofen etc.), narcotic analgesics (e.g. opiates) together with generic lifestyle advice.[15, 34-37] In the longer term, conservative management also may involve these strategies for symptom management if required, as well as advice to eat a healthy diet with regular meals (http://www.nhs.uk/Conditions/Gallstones/Pages/Treatment.aspx). For the purpose of this trial a standard protocol for conservative management will be agreed with the PPI group and used in all centres. Safety advice for patients in the observation/conservative management group will be aligned with the current advice given via the NHS choice website (www.nhs.uk).

3.2 Trial population

Adults with symptomatic uncomplicated gallstone disease (biliary pain) who are electively referred to a secondary care setting and considered suitable for cholecystectomy.

3.3 Setting

Adult patients with diagnosed gallstone disease electively referred to a secondary care setting via GP referral or A&E department, not requiring emergency surgical or endoscopic intervention will be approached by the research teams.

3.4 Planned inclusion and exclusion criteria

Inclusion criteria: *Inclusion criteria:* All adult patients with confirmed gallstones electively referred to a secondary care setting for consultation.

Clinical diagnosis of gallstone disease will be confirmed by imaging. Transabdominal ultrasonography is the standard imaging technique for the diagnosis of gallbladder stones, but diagnosis by any imaging technique is acceptable.

Exclusion criteria*:*

Unable to consent, ASA III and above, pregnancy, previous open major upper abdominal surgery, gallstones in common bile duct or evidence of previous choledocholithiasis, a history of acute pancreatitis, abnormal liver function tests (with the exception of GGT <90u/L)[38] evidence of empyema of the gallbladder, perforated gallbladder or Haemolytic disease

3.5 Recruitment and Trial Procedures

3.5.1 Identifying participants

General practitioners within the study area have an important role in awareness raising among those potential recruits to the study that they are referring or admitting to hospital. We will provide information about the study to all referring GPs within the study areas. In Scotland we will contact and attend the relevant health board's GP subcommittees. Subsequently we will work with the board's primary care directorate to cascade information to individual GP practices and registered locums. In England we will contact the relevant Clinical Research Network primary care leads and seek permission to contact referring GPs within their grouping. Additionally, in the regions where the study is taking place we will liaise with the relevant Clinical Commissioning Groups as a further means of cascading information to relevant GPs. We will provide GPs with standardised information about the study and make the protocol available to them. We will encourage GPs to make patients aware of the study and why it is being conducted when they refer or admit potential recruits to the study. Participants will be identified by the local research team at participating centres. Local procedures at the participating hospitals are different and the timing and mode of approach to patients and the consent process may vary in order to accommodate both the specific circumstances at each site and the needs of the patients.

Following identification of potential participants, an invitation letter and patient information leaflet (PIL) detailing the trial will be sent out, inviting them to attend an outpatient clinic visit where the trial and their treatment will be discussed. Potential participants not identified prior to a clinic visit or at sites that are unable to send the PIL in advance, will be given the PIL at the outpatient clinic visit. The PIL will also highlight that the clinical consultation may be audio-recorded, if participants consent to do so. At the clinic consultation, the research team will outline the trial and ask the patient if they are willing to discuss participation and have their conversation audio-recorded. For those patients who are happy with this proposal the process will follow as described. A member of the local research team will complete a trial screening form using information from the prospective participant and from the clinical record to document fulfilment of the entry criteria. Eligibility criteria will be cross-checked with the clinical record. If the patient is eligible and in provisional agreement, a local research team member will meet with the patient immediately in the clinic. Eligible participants who express interest in participating will have the study explained to them by local research staff and asked if they have any questions or concerns about participating in the trial. If they agree to take part they will give written consent to be randomised. Standard local arrangements concerning pre-assessment, admission, consent for surgery, conduct of surgery and after care will continue unimpaired. Eligible participants who are not willing to consider randomisation will not be contacted about any further research.

The PIL and consent form refer to the possibility of long term follow up to determine the incidence of future operations. The PIL and consent form also refer to the possibility of participants being contacted in the future to participate in other relevant research. Eligible and randomised participants may be contacted to participate in a semi-structured audio recorded interview (See Appendix 1 for details of Qualitative Research).

The patient information leaflet provides clear details of the anticipated risks and benefits of trial participation. Risks associated with both treatment arms are explicitly mentioned. The risk and benefits of the study will also be discussed by the local research nurses and the patient's own Consultant as part of the process of obtaining informed consent.

3.5.2 Informed consent

Informed consent to participate in the trial will be sought and obtained according to Good Clinical Practice (GCP) guidelines. Informed signed consent forms will be obtained from the

participants in all centres, by an appropriately trained individual. Participants will be given sufficient time to accept or decline involvement and will be free to come out of the study at any time. Patients may make a decision to participate during an initial consultation, during a subsequent visit to hospital, or alternatively at home. If the patient agrees to be contacted at home he/she may receive a telephone call from the local Research Nurse to discuss any queries. Patients who decide to participate following telephone counselling can either send their completed documents (consent form and baseline questionnaire) through the post to the local team at their treating hospital or bring it with them if they are returning to hospital for another consultation.

A significant qualitative component is proposed for this study to underpin its development and to inform how best to interpret the results of the trial. The qualitative component is entirely optional but consent will be sought to audio record the initial consultation when the trial is discussed and for interviews with both those who consent and refuse randomisation.

Participants who cannot give informed consent (e.g. due to their mental state) are not eligible for either the randomised trial or the qualitative work.

3.5.3 Randomisation and allocation

Eligible and consenting participants will be randomised to one of the two intervention groups using the proven 24-hour telephone Interactive Voice Response randomisation application or via the web-based application, both hosted by CHaRT. The randomisation algorithm will use recruitment site, gender (male/female) and age (<35; 35-64; ≥65) as minimisation covariates to allocate treatment to intervention and control groups in a 1:1 ratio. A random element will be incorporated into the randomisation algorithm. The PI at site, or individual with delegated authority, will access the telephone or web-based system. Patient screening identification, initials and recruiting site (the stratifying variable) will be entered into the voice-activated or web-based system, which will return the allocation status. After obtaining patient consent, randomisation will happen in the clinic and participants will be informed of their allocated treatment group following randomisation. If the participants are not present in the clinic, they will be contacted by the research teams to inform them of the allocated treatment group after randomisation.

3.5.5 Follow-up procedures

The patient reported outcomes (SF-36; CSQ) will be assessed by participant-completed questionnaires at baseline, 3, 9, 12 and 18 months post randomisation. A case report form (CRF) at the time of any gallstone surgery providing details of the operative procedures, complications and resource use in hospital. Costs of the initial intervention procedures will be estimated from resource use data recorded on the case report forms coupled with routine unit cost data. Costs associated with subsequent contacts with primary and secondary care (due to symptomatic gallstones) will be estimated from patient questionnaires at 3, 9, 12 and 18 months post randomisation and checked at source. QALYs will be estimated from patients' responses to the SF-36.

3.5.6 Change of Status/Withdrawal procedures

Participants will remain in the trial unless they choose to withdraw consent or if they are unable to continue for a clinical reason. All changes in status with the exception of complete withdrawal of consent will mean the participant is still followed up for all trial outcomes wherever possible. All data collected up to the point of complete withdrawal will be retained and used in the analysis.

3.5.7 Subsequent arrangements

Informing key people

Following formal trial entry:

The Study Office will:

i) inform the participant's General Practitioner (GP) (by letter) enclosing information about C-Gall and the Study Office contact details.

The local Research Nurse/Recruitment Officer and/or PI will:

i) file the Hospital Copy of the Consent form in the hospital notes along with information about C-Gall.
ii) inform the ward and theatre staff as appropriate of the participant's entry to the trial and details of the intervention allocation (theatre only).
iii) use the C-Gall internet database to enter data regarding the participant, including data required to complete randomisation; and intra-operative and postoperative information abstracted from local medical records.
iv) maintain and archive Study documentation at the site. A copy of the signed consent form is returned to the Study Office in Aberdeen after database entry.
v) provide any relevant follow-up clinical data.

Monitoring the participants

Participants will be contacted by phone, post or email as appropriate. In case of non-return of questionnaires, or non-attendance at outpatient appointments, attempts will be made by staff at the Study Office to trace the participant directly using these means or indirectly by contacting the GP.

Notification by GPs

GPs are asked to contact the Study Office if the participant moves, becomes too ill to continue or dies, or any other notifiable or adverse event occurs. Alternatively, staff at the Study Office may contact the GP.

Offices for National Statistics (HES [Hospital Episode Statistics] data in England, ISD [Information Statistics Division] data in Scotland)

Consent will be sought from all participants to trace their medical records and addresses from local records and centrally held computerised databases. This should facilitate long term follow up.

4. SAFETY

4.1 Definitions

An **adverse event** (AE) is any untoward medical event affecting a clinical trial participant. Each initial AE will be considered for severity, causality or expectedness and may be reclassified as a serious event based on prevailing circumstances.

A **serious adverse event** (SAE), is any AE, that:

- results in death;
- is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect,
- is otherwise considered medically significant by the investigator

Note: Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an AE. Complications occurring during such hospitalisation will be AEs or SAEs as appropriate.

C-Gall specific expected adverse events:

In this trial the following adverse events are potentially expected.

Adverse events during or after laparoscopic cholecystectomy. (8-10%)

Intraoperative complications.

1. Bleeding > 500 ml. (1-2%)
2. Injury to the bowel. (0.5%). Requires corrective surgery and might requires major operation if not detected during initial surgery.
3. Anaesthetic complications (<1%) including hypersensitivity to the general anaesthesia and /or any of the medications or material used. Change of procedure and / or type of anaesthesia.
4. Injury to the bile duct. (0.2%). Requiring further major operation

Immediate post operative complications.

1 Wound Infection (2-3%). Requiring antibiotics or drainage
2 Pain. Requiring additional analgesia (2-5%)
3 Bile leak. (1-2%) Requiring insertion of drain or return to operation theatre
4 Thrombosis/DVT/PE (<1%). Requires anti-coagulation
5 Urinary retention. Requiring urinary catheter. (<1%)
6 Infection (sepsis, septicaemia, abscess) (<1%)

Late post operative complications.

1. Incisional / port site hernia (1-2%). Requires further corrective surgery.
2. Chronic wound pain (1-2 %). Requiring long term pain medication.
3. Infection (sepsis, septicaemia, abscess) (<1%)
4. Re-admission (5%)
5. Death (rare)

Furthermore 4-9% of the surgical patients might continue experiencing biliary pain after surgery (post cholecystectomy syndrome) and 13-37% of the patient might continue to have non specific abdominal pain.

Potential adverse event during conservative treatment.

There will be 0.7% / year risk of developing potential adverse event in the conservative management group that might require further surgery or endoscopic treatment.

1. Acute cholecystitis
2. Empyema/mucocele
3. Gallbladder perforation.
4. Acute pancreatitis
5. CBD stone

6. Obstructive jaundice.

4.2 Procedures for detecting, recording, evaluating & reporting AEs, SAEs

4.2.1 Detecting AEs and SAEs

All AEs and SAEs must be recorded from the time a participant consents to join the trial until the end of follow-up.

Non-serious events will be recorded in the case report forms (CRFs) and participant questionnaires. Planned primary care or hospital visits for conditions other than those associated with symptomatic uncomplicated gallstone disease will not be collected or reported.

Any SAEs related to the participants' gallstone disease treatment that are not further interventions (eg if a participant is admitted to hospital for treatment of infection) will be recorded on the serious adverse event form. In addition all deaths for any cause (related or otherwise) will be recorded on the serious adverse event form.

Within C-GALL, 'relatedness' is defined as an event that occurs as a result of a procedure required by the protocol, whether or not it is either a) the specific intervention under investigation or b) it is administered outside the study as part of normal care.

4.2.2 Recording AEs and SAEs

Depending on severity, when an AE/SAE occurs, it is the responsibility of the Investigator (or delegate) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator (or delegate) should then record all relevant information in the CRF and on the SAE form.
Information to be collected includes, type of event, onset date, Investigator assessment of seriousness, causality, and expectedness, treatment required, investigations needed and outcome.

4.2.3 Evaluating AEs and SAEs

Assessment of Seriousness

The Investigator should make an assessment of seriousness as defined in Section 4.1.

Assessment of Causality

The Investigator must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

- **Related**: resulted from administration of any of the research procedures
- **Unrelated**: where an event is not considered to any of the research procedures.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

Assessment of Expectedness

When assessing expectedness refer to the expected events (Section 4.1).

4.2.4 Reporting AEs and SAEs

Reporting responsibilities of the CI

When an SAE form is uploaded onto the trial website, the Trial Manager will be automatically notified. If, in the opinion of the local PI and the CI, the event is confirmed as being *serious* and *related* and *unexpected*, the CI or Trial Manager will notify the sponsor within 24 hours of receiving the signed SAE notification. The sponsor will provide an assessment of the SAE. A Sponsor cannot downgrade an assessment from the PI or CI. Any disparity will be resolved by further discussion between these parties.

The CI or delegate will report any related and unexpected SAEs to the REC within 15 days of the CI becoming aware of it. All related SAEs will be summarised and reported to the Ethics Committee, the Funder and the Trial Steering Committee in their regular progress reports.

If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

5. OUTCOME MEASURES

5.1 Primary outcome measure

The *primary patient outcome measure* will be quality of life as measured by area under the curve (AUC) at up to 18 months post-randomisation using the SF-36 bodily pain domain (AUC measures at 3, 9 and 18 months).

The *primary economic outcome measure* will be incremental cost per QALY.

5.2 Secondary outcome measures

The secondary outcomes measures will include:
Condition specific quality of life; SF-36 domains (excluding bodily pain domain) complications; need for further treatment; persistent symptoms; health care resource use; costs.

In addition, routinely collected national data on further surgery will be sought in the future to update longer term estimates of cost-effectiveness.

6. DATA COLLECTION AND PROCESSING

6.1 Measuring outcomes

The Patient Reported Outcome Measurement Group at the University of Oxford published recommendations to the Department of Health on the appropriate patient reported outcomes to consider for patients undergoing cholecystectomy.[39] The report concludes that the SF-36 has good evidence in assessing general quality of life in patients undergoing cholecystectomy in the UK. In addition the report states that "the Otago Gallstones Condition-Specific Questionnaire is worthy of consideration above the other condition-specific measures." We are proposing to use both in this study. The Otago gallstones condition-specific questionnaire (CSQ)[40] devised a conceptual model for gallstone-specific quality of life, with four underlying domains: Physical Functioning (pain, dyspepsia and diet changes), Systemic Functioning (fatigue), Social Functioning (daily duties, leisure, relationships) and Emotional Functioning (mood). The CSQ contains 12 items, each with a 5-point Likert response scale. The CSQ is succinct, has high patient acceptance and can be used in conjunction with the generic SF-36.[40]

The patient reported outcomes (SF-36; CSQ) will be assessed by participant-completed questionnaires at baseline, 3, 9, 12 and 18 months post randomisation. The research nurse will complete a case report form (CRF) at the time of surgery providing details of the operative procedures, complications and resource use in hospital. Costs of the initial intervention procedures will be estimated from resource use data recorded on the case report forms coupled with routine unit cost data. Costs associated with subsequent contacts with primary and secondary care (due to symptomatic gallstones) will be estimated from patient questionnaires at 3, 9, 12 and 18 months post randomisation. QALYs will be estimated from patients' responses to the SF-36 at 3, 9, 12 and 18 months post randomisation. The components and timing of follow-up measures are shown in Section 6.2.

6.2 Schedule of data collection

	Baseline	Surgery	3 months	9 months	12 months	18 months
SF-36	X		X	X	X	X
CSQ	X		X	X	X	X
CRF		X				
Resources use questionnaire			X	X	X	X
Time and travel questionnaire						X

6.3 Data processing

Research nurses will enter locally collected data in the centres. Staff in the Trial office will work closely with local Research Nurses to ensure the data are as complete and accurate as possible. Follow-up questionnaires to participants will be sent from and returned to the Trial Office in Aberdeen. Extensive range and consistency checks will further enhance the quality of the data.

7. SAMPLE SIZE, PROPOSED RECRUITMENT RATE AND MILESTONES

7.1 Sample size

Any attacks will likely be intermittent and of relatively short duration, so an outcome measure at a single point in time is unlikely to be sensitive enough to detect real differences. A more comprehensive outcome would incorporate the total quality of life of the participant throughout the study. Therefore, the primary outcome is the area under the curve (AUC) of the SF-36 bodily pain domain up to 18 months post randomisation. In order to detect a 0.33 SD difference, 90% power with alpha 5%, 194 participants per group (388 total) are required. Such a difference in generic health status is considered clinically relevant and in terms of treatment effect size, in the small to medium range as observed in other clinical studies. To allow for the anticipated approximately 10% of participants for whom outcome data is completely missing, and therefore the AUC cannot be calculated, it is proposed to randomise 430 participants.

Whilst recognising that follow-up beyond 18 months may be useful for the longer term symptoms and outcomes of gall bladder disease, the use of 18 months in this study reflects the primary key considerations for the effectiveness and cost-effectiveness of the interventions. These considerations are (i) estimating the quality of life for patients after cholecystectomy versus those on conservative management – such a comparison holds at 18 months (approximately 12 months after surgery) where only a small proportion of conservative management patients will likely have received surgical treatment and (ii) the cost savings of a conservative management policy largely depend on the number of patients managed conservatively who never require surgical treatment.

The current evidence suggests that around 44% of patients will not receive surgery with a conservative management policy at 5 years follow-up (11% per year).[32] The economic modelling also suggests that if around 25% or less of the conservative management group receives surgery by 5 years, the medical management strategy becomes cost effective. This would equate to approximately 5% per year. We have therefore also considered how precisely the proportion of conservatively managed patients going on to have surgery can be estimated in the study when considering the sample size. A trial with 200 conservatively managed patients estimates this proportion to within 5% with 95% statistical confidence. If the current best evidence of 10% at 12 months post surgery is realised, we would be able to rule out a 5% rate or less.

7.2 Recruitment rates and Milestones

Most recent NHS Hospital Episode Statistics suggest that around 70,000 people have surgical treatment for gallstones each year in England. The trial centres conduct an average of 500 cholecystectomies per year. Based upon surgeon estimates, at least 10-20% (50-100) of the patients would be symptomatic, uncomplicated disease. We propose a 24 month recruitment period (months 7-30 inclusive) based on a conservative throughput of 50 eligible patients per year in 20 centres with the assumption that 50% of eligible patients in the first month and 50% in August and December will be missed. We expect that 40% of the remaining eligible patients will be willing to be randomised. The projection detailed below allows for a staggered study site set-up with all centres active by the end of month 18.

7.3 Recruitment projection

The recruitment projection is based on approximately 20 active centres participating across a 24 months recruitment period with the expectation that they will contribute an estimate of 2 participants per month per site in steady state. Recruitment at all sites is reduced in the first month and in the peak holiday months of July/August and December. The first 20 patients recruited by Month 12, 111 patients by Month 18 and the remaining 319 patients by Month 30 making a total of 430 patients. The projected recruitment is modelled below in Figure 1. Note first six months (months 1 to 6) of project, no recruitment is expected and is not included in Figure 2.

Figure 2 Recruitment projection

7.4 Internal pilot study

The internal pilot is primarily designed to verify that recruitment is possible. There are three areas of uncertainty that we propose to verify during the internal pilot study. These areas are (i) the generalisability of the randomised participants (ii) the willingness to randomise and (iii) ability to scale-up the number of centres. To address these areas we are proposing to initially set-up three selected pilot centres in the first 12 months of the study. Within these three centres, detailed clinical screening logs will be implemented. The screening logs will record the number of screened participants, the number ineligible and number eligible. The three centres will also be undertaking embedded qualitative research to understand barriers and facilitators to recruitment during this phase (see Appendix 1). From months 12 to 18, the internal pilot will continue with the scaling-up of the trial to the rest of the trial centres.

7.5 Stop/go criteria

During the internal pilot phase we are proposing two decision points - one at month 12 and another at month 18. By month 12, 14 centre months of recruitment should have occurred and 20 participants randomised across the three centres. By end month 18, 94 centre months of recruitment should have occurred and 111 participants randomised across 20 centres. After the internal pilot, we are also proposing an early check of the AUC assumption, average recruitment rate and rate of crossovers during follow-up. The proposed stop/go criteria are:

At 12 months

- recruited projected participants (currently 20)
- recruited at least 20% of eligible patients

At 18 months

- Recruited the appropriate number of centres to achieve recruitment target (currently 20)
- The average recruitment rate per site per month is at least one

At 24 months

- The AUC estimate is no more than 10% larger than current estimate of 0.33
- The crossover rate is greater than 50%

Full details of the stop-go criteria for the progression to the main trial will be developed in a detailed progression plan in the Statistical Analysis Plan, in consultation with the HTA Board.

A green/amber/red approach to progression at 12 and 18 months has been included in the trial:

- Green: 100% of target recruitment achieved (20 at 12 months and 111 at 18 months and centres recruiting average of at least 1 participant per month) - automatic progression.

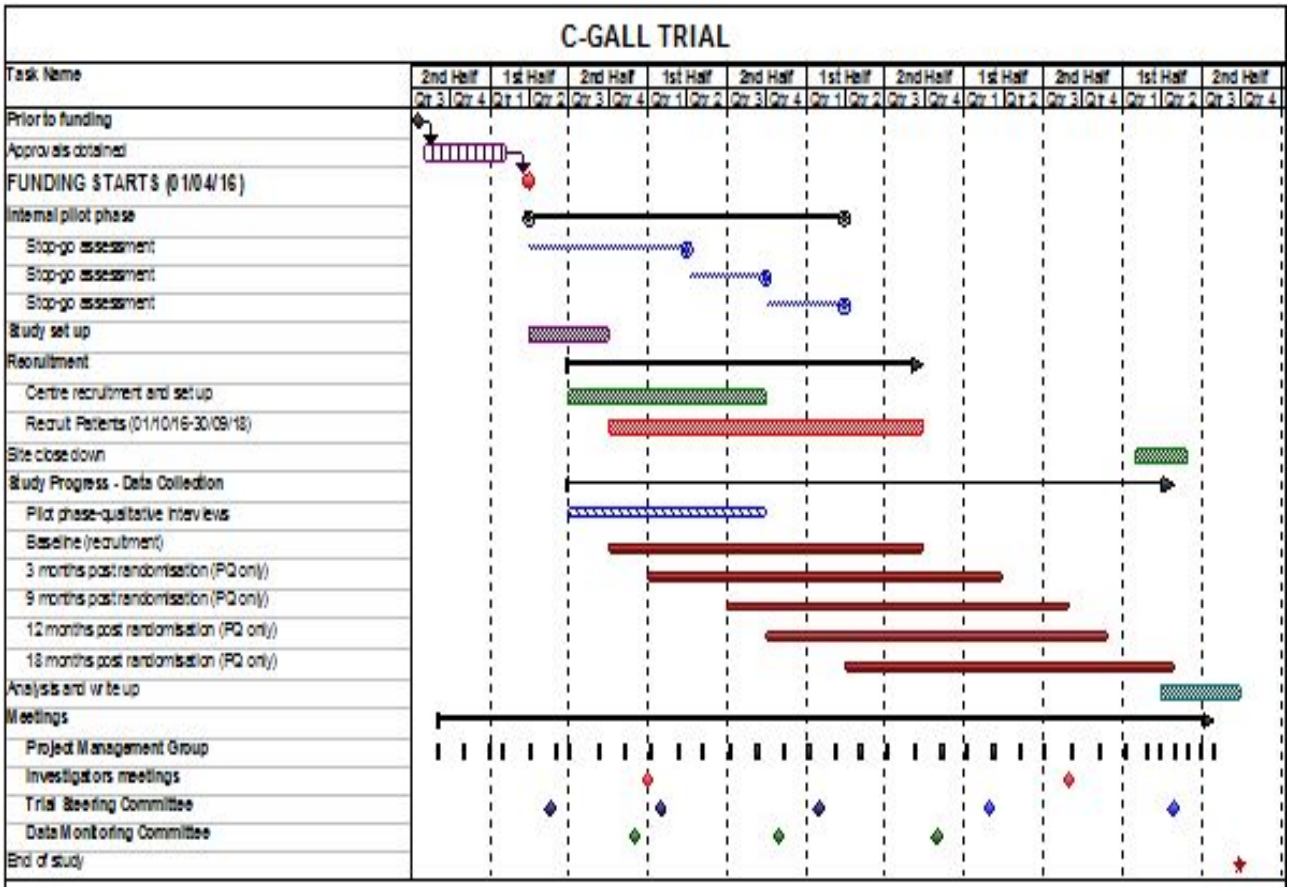
- Amber: 50-100% recruitment achieved (10-20 at 12 months or 55-111 or centres recruiting average between 0.5 and 1 participant per month at 18 months) - identify remediable factors and submit recovery plan to HTA with new targets for the following 6 months.

- Red: less than 50% recruitment achieved (<10 at 12 months or <31 at 18 months or centres recruiting average of less than 0.5 participants per month)- stop the trial unless there is a strong case that unanticipated remediable factors have been identified and can be addressed.

Project timetable and milestones

The projected start date for the study is 1 April 2016: the study duration will be 54 months. Milestones are:
Pre-funding: multicentre research ethics and central R&D approvals; Month 1-6: Study set-up authorisations; Months 7-30: patient recruitment; Month 18 core outcome set and qualitative findings completed. Months 25-48 patient follow up at 18 month; Months 49-54 analysis of data, interpretation of results and report writing. The Gantt chart is shown below in Figure 3.

Figure 3: Gantt Chart



8. STATISTICAL ANALYSIS

The primary outcome, area under the curve (AUC) for the SF-36, will be generated for each participant using Simpson's rule. Score data for participants who have missed a scheduled questionnaire will be estimated using a multiple imputation approach to make use of partial outcome data. Sensitivity analyses will be conducted to assess the robustness of the treatment effect estimate to these approaches. Missing items on the health-related outcome measures will be treated as per the instructions for that particular measure. The primary outcome measure will be analysed using linear regression with adjustment for the minimisation variables (site of recruitment, gender and age). Secondary outcomes will be analysed using generalised linear models with adjustment for minimisation and baseline variables as appropriate. Statistical significance will be at the 2-sided 5% level with corresponding confidence intervals derived. Subgroup analyses will explore the possible modification of treatment effect by clinically important factors; gender and age. This will be done by including treatment-by-factor interactions in the model and they will be classified as exploratory analyses. All analyses will initially be performed on an intention to treat basis, although we will consider additional analysis groups such as per-protocol. The main statistical analyses will be based on all participants as randomised, irrespective of subsequent compliance with the treatment allocation. From the internal pilot phase we will report estimates of recruitment rates and potential participant availability, together with appropriate confidence intervals. There are no planned interim outcome analyses; all analyses will occur following completion of trial follow up. Interim analyses will be performed if requested by the Data Monitoring and Ethics Committee (DMC).

9. ECONOMIC EVALUATION

This study will include an economic evaluation of cholecystectomy against medical management to assess the relative efficiency of these care pathways. A within trial cost-utility analysis will be conducted. The need to extrapolate beyond the study follow-up period will be

considered if a definite answer on cost-effectiveness cannot be obtained from the within trial analysis.
Brazzelli et al[32] identified a number of uncertainties in their modelling based economic evaluation. Particularly, there was uncertainty in the resources used by, as well as the quality of life of, individuals that followed a medical management strategy. In addition, there was uncertainty in the proportion of individuals having surgery after being allocated to a medical management care pathway. Cholecystectomy was, on average, cost effective for their base case analysis. However, the mentioned uncertainties in the economic evaluation model resulted in a 50% probability of cholecystectomy being cost-effective at a £30,000 willingness to pay for a QALY threshold[32] (the usual threshold used for decision making in the UK[41] This study will inform these uncertainties and aim to provide a more precise answer to this decision problem.

The economic analysis
The economic analysis will rely on participant responses to the SF-36 to estimate quality adjusted life years (QALYs) at 18 months. Resource use and costs will be estimated for each participant. The evaluation will consider the costs of the care pathways that patients follow; i.e. the costs of the surgery (e.g. cholecystectomy) as well as the cost of simultaneous and subsequent use of primary and secondary NHS services (including additional interventions received) by participants. Personal costs such as purchase of medications, particularly analgesics, will be estimated. The clinical condition affects adult individuals that might still be in their working age; therefore, time off work will be also retrieved to estimate indirect costs (e.g. human capital approach). The incorporation of indirect costs into the economic evaluation is debatable; however, the collection of these data will open the possibility to include these costs into the analysis or report them separately following reporting practice at the time of analysis.

Collection and valuation of data
Hospital inpatient and outpatient resource used data (e.g. hospital admissions by type of service; outpatient visits, etc.) will be retrieved from participants' hospital case notes. In addition, primary care resource use (e.g. GP visits) time off work, out of pocket purchases of medications and quality of life data (e.g. SF-36) will be obtained from patient questionnaires at 3, 9, 12 and 18 months. The analysis will be conducted from the UK NHS and personal social services perspective. Therefore, resource used will be valued using appropriate unit prices obtained from national sources, including the NHS reference costs,[42] the Unit cost of health and social care.[43] British National Formulary[44] will be used to obtain unit costs to value medications and wage categories to value time off work. Preference based measures of health related quality of life can be obtained from the responses to the SF-36 questionnaire using parametric[45-47] or non-parametric techniques.[48] This is an evolving area of research; hence, the most up to date techniques at the time of analysis will be used. The utility scores used to value the SF-36 health states were obtained using standard gamble techniques with a representative sample for the UK population. These utility scores will be used to calculate quality adjusted life years (e.g. the area under the curve) for each trial participant.

Assessment of cost-effectiveness
Cost-effectiveness will be measured in terms of costs of the care pathways and quality adjusted life years (QALYs) at 18 months post randomisation for the within trial analysis. Mean NHS costs, patient costs and QALYs will be compared between randomised groups at 18 months. Incremental costs and QALYs will be estimated for cholecystectomy versus medical management using linear regression with adjustment for minimisation variables and baseline variables (e.g. baseline utility scores) as appropriate. Final decision on what regression model to use is data dependent. However, methodological guidelines will be used to define the best approach at the time of analysis.[49] Uncertainty surrounding joint estimates of incremental cost and effects will be characterised and presented graphically using cost-effectiveness acceptability curves.[50, 51] Guidelines for economic evaluation advocate for a long enough time horizon to consider all cost and consequences relevant for the analysis.[41] However, a definite answer on cost-effectiveness could be obtained from the analysis at 18 months follow-up. This would be the case, for instance, if very small or very high number of individuals in the medical

management group actually receives surgery. Consequently, a final decision on extrapolating the analysis beyond the clinical trial follow-up will be done depending upon the within trial analysis result. The extrapolation analysis might involve the development of a simple state transition model (e.g. Markov model).

10. ORGANISATION: TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

10.1 Trial office in Aberdeen

The Trial Office is in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen and provides day to day support for the clinical centres. The Trial Manager in CHaRT at Aberdeen will take responsibility for the day to day transaction of trial activities. The Data co-ordinator will provide clerical support to the trial, including organising all aspects of the postal questionnaires (mailing, tracking, and entering returned data using the trial web data entry portal).

The C-Gall Trial Office Team will meet formally at least monthly during the course of the trial to ensure smooth running and trouble-shooting. Finally, we intend to produce a yearly C-Gall Newsletter for participants and collaborators to inform everyone of progress and maintain enthusiasm.

Any modification to the project shall be approved by the Sponsors and funder before application to REC and R&D unless in the case of immediate safety measures when the Sponsor shall be notified as soon as possible.

10.2 Local organisation in sites

The Local PI and research nurse will be responsible for all aspects of local organisation including identifying, consenting, and randomising the participants, along with facilitating the delivery of the intervention and notification of any problem or unexpected developments for the duration of the trial. The research nurse will be responsible for ensuring that study data is collected for baseline assessments, collecting and recording participant study data on study specific Case Report Forms, provide any relevant follow-up clinical data, and will log details onto the remote web-based data capture system in a timely manner.

10.3 Project Management Group (PMG)

The trial is supervised by its Project management Group (PMG). This consists of the grant holders and representatives from the Trial Office. Observers may be invited to attend at the discretion of the PMG. We will meet/teleconference every two months on average.

The research team has the expertise to cover the clinical and surgical aspects of the research

10.4 Trial Steering Committee (TSC)

The trial is overseen by a Trial Steering Committee (TSC). The membership of this Committee is comprised of four independent members along with the Chief Investigator (Ahmed/Ramsay) or a nominated delegate. The trial sponsor(s) other grant-holders and key members of the central office (e.g. the trial manager) can participate in TSC meetings but are not members. The funders will be notified in advance of meetings and a representative invited to attend. Other relevant experts may be invited to attend as appropriate. Details of the membership of the TSC can be found at the start of this protocol. CHaRT has adopted the TSC Charter adapted from the DAMOCLES Charter for DMCs and suggests to the independent TSC members that they adopt the Terms of Reference contained within. The TSC will meet approximately yearly. A copy of the TSC minutes will be forwarded to the sponsor.

10.5 Data Monitoring Committee (DMC)

The independent Data Monitoring Committee (DMC) is made up of members listed at the start of this protocol, one of whom is an experienced statistician. After the trial has been initiated the DMC will initially meet to agree its terms of reference and other procedures. CHaRT has adopted the DAMOCLES Charter for DMCs and suggests to the independent DMC members that they adopt the Terms of reference contained within.

The Committee will meet regularly (at least yearly) to monitor the unblinded trial data and serious adverse events and make recommendations as to any modifications that are required to be made to the protocol or the termination of all or part of the trial.

11. RESEARCH GOVERNANCE, DATA PROTECTION AND SPONSORSHIP

11.1 Research Governance

The trial will be run under the auspices of CHaRT based at HSRU, University of Aberdeen. This will ensure compliance with Research Governance, and provide centralised trial administration, database support and economic and statistical analyses. CHaRT is a registered Clinical Trials Unit with particular expertise in running multicentre RCTs of complex and surgical interventions.

The CI will ensure, through the TSC, that adequate systems are in place for monitoring the quality of the trial (compliance with appropriate governance) and appropriate expedited and routine reports, to a level appropriate to the risk assessment of the trial. The Sponsors Standard Operating Procedures shall be followed.

11.2 Data protection

Data collected during the course of the research will be kept strictly confidential and accessed only by members of the trial team. Participant's details will be stored on a secure database under the guidelines of the 1998 Data Protection Act and regular checks and monitoring are in place to ensure compliance. Data are stored securely in accordance with the Act and archived to a secure data storage facility. The senior IT manager (in collaboration with the Chief Investigator) will manage access rights to the data set. Participants will be allocated an individual specific trial number and their details will be anonymised on the secure database. We anticipate that anonymised trial data may be shared with other researchers to enable international prospective meta-analyses. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose for which it has been acquired.

11.3 Sponsorship

The University of Aberdeen and Grampian Health Board (NHS Grampian) are the co-sponsors for the trial.

12. ETHICS AND REGULATORY APPROVALS

The North of Scotland Research Ethics Committee (2) has reviewed this trial. The trial will be conducted according to the principles of good clinical practice provided by Research Governance Guidelines. Annual progress reports and a final report at the conclusion of the trial will be submitted to XXXX REC within the timelines defined in the regulations. A copy of the Annual progress report and the final report shall be forwarded to the Sponsors.

13. QUALITY ASSURANCE

The trial will be monitored to ensure that the trial is being conducted as per protocol, adhering to Research Governance, and the appropriate regulations. The approach to, and extent of, monitoring (specifying both central and on-site monitoring) will be specified in a trial monitoring plan which is usually initially determined by a risk assessment, undertaken prior to start of trial. Investigators and their host Trusts will be required to permit trial related

monitoring and audits to take place by Sponsors and/ or regulatory representatives providing direct access to source data and documents as requested.

13.1 Risk assessment

An independent risk assessment has been carried out by the sponsor. The trial will be monitored to ensure that the study is being conducted as per protocol, adhering to Research Governance, and the appropriate regulations. The approach to, and extent of, monitoring is specified in the trial monitoring plan and is appropriate to the risk assessment of the study.

14. FINANCE AND INSURANCE

The trial is funded by a grant awarded by the NIHR Health Technology Assessment programme.

The necessary trial insurance is provided by the University of Aberdeen.

15. END OF TRIAL

The end of follow-up for each participant is defined as the final data capture to answer the research question. The end of the trial is defined as the end of funding.

The end of the trial will be reported to the REC within 90 days, or 15 days if the trial is terminated prematurely. The end of the trial will be reported to the Sponsors within 90 days. The Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved.

A summary report of the trial will be provided to the Sponsors as well as the REC within one year of the end of the trial. An end of trial report will also be issued to the funders at the end of funding.

16. DATA HANDLING, RECORD KEEPING AND ARCHIVING

Clinical data will be entered into the database by the local investigator and/or research nurse working in each hospital site, together with data from questionnaires completed at clinic. Questionnaires returned by post to the trial office will be entered there. Staff in the trial office will work closely with local research nurses to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

The co-sponsors are responsible for ensuring that trial data is archived appropriately. All essential data and documents (electronic, hard copy and audio recordings) shall be retained for a period of at least 10 years after close of trial according to the relevant UoA/NHSG Sponsor and CHaRT archiving SOPs. The archiving procedures for local sites will be performed as documented in the Sponsor site agreement.

17. SATELLITE STUDIES

It is recognised, that the value of the trial may be enhanced by smaller ancillary studies of specific aspects. Plans for these will be discussed in advanced with the Project Management Group. REC approval will be sought for any new proposal, if appropriate. Sponsorship will be sought for any new proposal if appropriate prior to any application to REC.

18. AUTHORSHIP PUBLICATION

All RCTs conducted by CHaRT have a commitment to publish the findings of the research. At a minimum this trial will have a results paper published in a peer-reviewed medical/scientific journal. If all grant-holders and researcher staff fulfil authorship rules, group authorship will be used under the collective title of ‘the C-Gall Trial Group’. If one or more

individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to the named individual(s) and the C-Gall Trial Group.

For reports which specifically arise from the trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to the named individual(s) for the C-Gall Trial Group.

To safeguard the integrity of the main trial, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the Project Management Group.

We intend to maintain interest in the trial by publication of C-Gall newsletters at intervals for staff and collaborators. Once the main report has been published, a lay summary of the findings will be sent in a final C-Gall Newsletter to all involved in the trial. Further details on the publication policy can be found in Appendix 3.

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APPENDIX 1 Qualitative study

This trial plans to compare surgery (cholecystectomy) versus conservative management. Due to the interventions being very different it is likely that the trial will face a number of challenges, particularly around informed consent and recruitment, from both the perspective of patients and recruiting clinicians. There are now several surgical trials (funded by the HTA) that include embedded qualitative research that aims to elucidate and inform trial processes and procedures.[52-54]

The aim of the embedded qualitative research is to identify any challenges during the internal pilot relating to design or conduct that can then be addressed and modified before progression to full trial. This may include changes to the way the trial information is presented, recruitment consultations are framed or requirements for staff training. As per the details above relating to the internal pilot, 3 sites will be established during the pilot and these sites will be the focus of this embedded qualitative research. The use of a small number of sites will allow significant investment in establishing the process requirements for embedding this qualitative work. Moreover, demonstrating successful buy-in and implementation of this work across three sites in the pilot should lead to more effective delivery across the remainder of sites during the main trial.

Equipoise, recruitment and retention
In depth semi-structured interviews will be conducted to understand perspectives of participation and equipoise with a range of individuals: 1. Participants consented for the RCT(including those who consent who go on to cross-over to the surgical intervention) ; and 2. Clinical and recruitment staff at participating centres. Topic guides will be developed for each group and cover aspects of trial rationale, design and conduct with a specific focus on illuminating the trial recruitment pathway (originating from primary care) and considerations of consent for potential participants. Analysis will take the form of constant comparison alongside case study methods both within and across sites and individuals to determine problem areas or identify aspects of good practice. An in depth analysis of participant flow at each recruiting site will be conducted. For example, screening logs (containing information on number of participants screened, number of participants eligible, and number of participants randomised) will be assessed alongside discussions with staff to identify areas of complexity and protocol compliance. These data will be compared across sites to illustrate any variation between centres and again identify areas of good practice that can be shared.

In addition to individual interviews, where possible, recruitment consultations will be audio-recorded and analysed appropriately (e.g. conversation analysis techniques to identify aspects of informed consent that are problematic). The analysis will focus on aspects of the consultations that are deemed modifiable e.g. eligibility of participants, exploration of preferences. The audio-recordings will contribute to determining models of ‘good practice’ for consent discussions which can be used for site training.

With regard to exploring aspects of trial retention, the audio-recordings and observations described above will also be analysed for discussions relating to trial follow-up procedures and the importance placed on the commitment to the trial across the entire timeline. Specific analysis methods will be as described above. In addition, participants who intentionally withdraw from the trial during the internal pilot will be contacted and asked to participate in in-depth semi-structured interviews to investigate whether there were specific aspects of trial design or conduct that led to their decision to terminate their involvement.

Impact of embedded qualitative research
Results from all aspects of the qualitative work will be fed back (as anonymised summaries) to the Project Management Group (PMG) both during and at the end of the first stop/go phase of the internal pilot (month 12). Potential solutions in the form of action plans will be developed by

the qualitative team and PMG in tandem, implemented and evaluated (through improvements in recruitment and retention) on a rolling case basis. The qualitative work will further extend into the next phase (months 12-18) and can be used during site set up to identify areas of concern and during periods of follow up to improve retention across sites.

APPENDIX 2 Development of core outcome set

Recommendations from the recent NICE guideline on Gallstone Disease[55] has clearly demonstrated insufficient information for patients on the effect of cholecystectomy on patient outcomes. The Guideline recommends "research is needed to establish the long-term patient benefits and harms, so that appropriate information can be provided to patients to aid decision-making and long-term management of their condition." The only disease specific outcome measure with good measurement properties in gallstone disease is the Otago gallstones condition-specific questionnaire. The questionnaire was developed on patients that were being considered for a cholecystectomy and covered a range of disease severity. It was not however, developed using patients that had undergone a cholecystectomy or long term conservative management once eligible for surgery. Therefore key important outcomes for longer term follow-up may be missing. Given our proposed trial study will be working with an independent PPI group, we propose to tackle the Guideline recommendation cost-efficiently by developing a core outcome set for symptomatic uncomplicated gallstone disease using a Nominal Group Technique.

Core outcome sets are agreed standardised sets of outcomes that represent the minimum that should be measured (and reported) in trials of a specific condition.[72] There is currently no agreed published core outcome set for symptomatic uncomplicated gallstone disease. Generally, the methodology describing the development of a core outcome set encompasses three key stages: 1. A review of the literature to identify outcomes reported to date; 2. Interviews with patients to explore additional outcomes of importance; and 3. A consensus based approach to determine which outcomes should be considered core. This methodology will be adopted to develop a core outcome set for symptomatic uncomplicated gallstone disease alongside the main trial.

A recent systematic review led by our team[32] identified two trials of cholecystectomy versus conservative management. This review will be supplemented with additional randomised studies that report outcomes in symptomatic uncomplicated gallstone disease (e.g. trials of early versus delayed laparoscopic cholecystectomy for uncomplicated biliary colic). The qualitative interviews in the embedded qualitative research component of the trial (see Appendix A), will be used as a way to identify additional potential outcomes of importance (to both patients and clinicians) that are not identified from the literature search. These outcomes (identified in the review and qualitative interviews) will be generated into a list and distributed by postal questionnaire to upper GI surgeons and the study PPI group. Responders will be asked to rate the importance of each outcome for inclusion in a core outcome set. Initial analysis of the questionnaire will aim to identify a shortlist of outcomes for further discussion at consensus meeting. Following initial analysis of this questionnaire a Nominal Group Technique (NGT), a face-to-face meeting of stakeholders that aims to generate consensus, will be conducted. The NGT will involve key stakeholders (patients and clinicians) and will summarise and discuss the questionnaire results with an additional round of anonymised rating to determine the final core set. It is anticipated that this set will consist of no more than 10 individual outcomes. This core outcome set work will be registered with the COMET Initiative, an international initiative to bring together people interested in developing core outcome sets (http://www.comet-initiative.org/).

APPENDIX 3: Authorship Policy

1. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals (see references) and are in accordance with the rules of the international Committee of Medical Journal Editors.

a. Group authorship

Group authorship will be appropriate for some publications, such as main reports. This will apply when the intellectual work underpinning a publication 'has been carried out by a group, and no one person can be identified as having substantially greater responsibility for its contents than others'.[1] In such cases the authorship will be presented by the collective title - The C-Gall Trial Group - and the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. In some situations one or more authors may take responsibility for drafting the paper but all group members qualify as members; in this case, this should be recognised using the by-line 'Jane Doe *and* the Trial Group'.[2] Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the by-line would read 'Jane Doe *for* the Trial Group').[2]

b. Individual authorship

Other papers, such as describing satellite studies, will have individual authorship. In order to qualify for authorship an individual must fulfil the following criteria[1]:

i. each author should have participated sufficiently in the work represented by the article to take public responsibility for the content.

ii. participation must include three steps:

- conception or design of the work represented by the article OR analysis and interpretation of the data OR both; AND
- drafting the article or revising it for critically important content; AND
- final approval of the version to be published.

Participation solely in the collection of data is insufficient by itself. Those contributors who do not justify authorship may be acknowledged and their contribution described.[1]

c. Determining authorship

Tentative decisions on authorship should be made as soon as possible[1]. These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Steering Committee.

2. AUTHORSHIP FOR PUBLICATION ARISING FROM C-GALL TRIAL

a. Operationalising authorship rules

We envisage two types of report (including conference presentations) arising from the C-Gall trial and its associated projects:

i. *Reports of work arising from the main C-Gall trial*

If all grant-holders and research staff fulfil authorship rules, group authorship should be used under the collective title of 'The C-Gall Trial Group'; if one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to 'Jane Doe and the C-Gall Trial Group'.

ii. *Reports of satellite studies and subsidiary projects*

Authorship should be guided by the authorship rules outlined in Section 1 above. Grant-holders and research staff not directly associated with the specific project should only be included as authors if they fulfil the authorship rules. Grant-holders and research staff who have made a contribution to the project but do not fulfil authorship rules should be

recognised in the Acknowledgement section. The role of the C-Gall Trial Group in the development and support of the project should be recognised in the Acknowledgement section. The lead researcher should be responsible for ratifying authorship with the Project Management Group.

For reports which specifically arise from the C-Gall trial but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to 'Jane Doe for the C-Gall Trial Group'. If individual members of the group are dissatisfied by a decision, they can appeal to the Management Group for reconciliation. If this cannot be achieved, the matter should be referred to the Steering Group.

b. Quality assurance

Ensuring quality assurance is essential to the good name of the trial group. For reports of individual projects, internal peer review among members of the Project Management Group is a requirement prior to submission of papers. All reports of work arising from the C-Gall trial including conference abstracts should be peer reviewed by the Project Management Group.

The internal peer review for reports of work arising from the C-Gall project is mandatory and submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. The Project Management Group will be responsible for decisions about submission following internal peer review. If individual members of the group are dissatisfied by decisions, the matter may be referred to the Steering Group.

The Project Management Group undertakes to respond to submission of articles for peer review at the Project Management Group Meeting following submission (assuming the report is submitted to the trial secretariat in Aberdeen at least two weeks prior to the meeting).

3. REFERENCES

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