C-GALL

laparoscopic Cholecystectomy with observation/conservative management for preventing recurrent symptoms and complications in adults with uncomplicated symptomatic GALLstones. (C-GALL trial)

HEALTH ECONOMICS ANALYSIS PLAN

Version 1, 4th October 2021

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1. Background on the Trial

Gallstone disease (cholelithiasis) is one of the most common gastrointestinal disorders in industrialised societies, with prevalence rates for gallstone disease ranging from 5.9% to 25% [1-4] and tending to increase with age. In the UK prevalence rates of 12% among men and 22% among women over 60 years of age have been reported.[3] Natural history studies have shown low mortality from gallstone disease, with typically less than 1% of people dying from gallbladder-related causes.[5] 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).[5] The most common complications associated with gallstones are acute cholecystitis, common bile duct (CBD) stones and acute pancreatitis.

From a patient perspective, the defining symptom of gallstone disease is pain.[6-7] 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. Even though removal of the gallbladder is considered the standard treatment for symptomatic gallstones, it does not guarantee eradication of symptoms.[8] Up to approximately 40% of people may continue to experience pain and abdominal symptoms after surgery.[9] A 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.[10] 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.[11] Similarly, in a RCT conducted in the UK, 19% of people complained of biliary pain five years after open cholecystectomy.[12]

Trial rationale

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 in the UK. However, medical 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, recent studies stated that half of the people

treated medically were eventually symptom free after 5 years;[13] therefore, some cholecystectomies could possibly be avoided with potential important savings for the NHS.

2. Aims and Objectives of the economic evaluation[i]

The ***primary economic objective*** is to assess the cost-effectiveness of medical management versus cholecystectomy. The ***primary economic outcome measure*** is the incremental cost per quality adjusted life years (QALY).

The ***secondary economic objectives*** are:

1) to compare medical management with surgical treatment (cholecystectomy) in terms of health care resource use and costs at up to 24 months after randomisation.[ii]

2) Model the longer-term cost-effectiveness of medical management versus cholecystectomy

3. Methods

3.1 Study design and participants

Details of the trial design are provided in the study protocol.[14] 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.

Adult patients with confirmed (by imaging) symptomatic gallstones electively referred to a secondary care setting for consultation are eligible for the study. Individuals consenting to participate are randomised 1:1 to receive either laparoscopic cholecystectomy or

[i] *Primary aim of the study*: to assess the clinical and cost effectiveness of medical management with cholecystectomy for preventing recurrent symptoms and complications in adults presenting with uncomplicated symptomatic gallstones in a secondary care setting. *Primary patient objective:* to compare medical 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.

[ii] The 24-month timepoint has been selected because 24-month was the data collection timepoint that was closer to the timepoint used for the definition of the primary patient outcome measure (i.e., 18-month) but was long enough to allow for relevant cost and consequences due to the interventions.

observation/conservative management (Figure 1). Treatment allocation is minimised by centre, gender and age (<35; 35-64; ≥ 65).

3.2 Cost and outcome assessment

Costs and outcomes will be assessed via the trial case report forms (CRFs) and participant completed questionnaires (Figure 1). 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 and 6 months thereafter, post randomisation, till end of trial. QALYs will be estimated from patients' responses to the SF-36 at 3, 9, 12- and 18-months and 6 months thereafter, post randomisation, till end of trial. The schedule for economic data collection is shown in Table 1.

Figure 1: Flow diagram of the trial (as for C-Gall Protocol - Version 10.0, 07.05.2020**)**

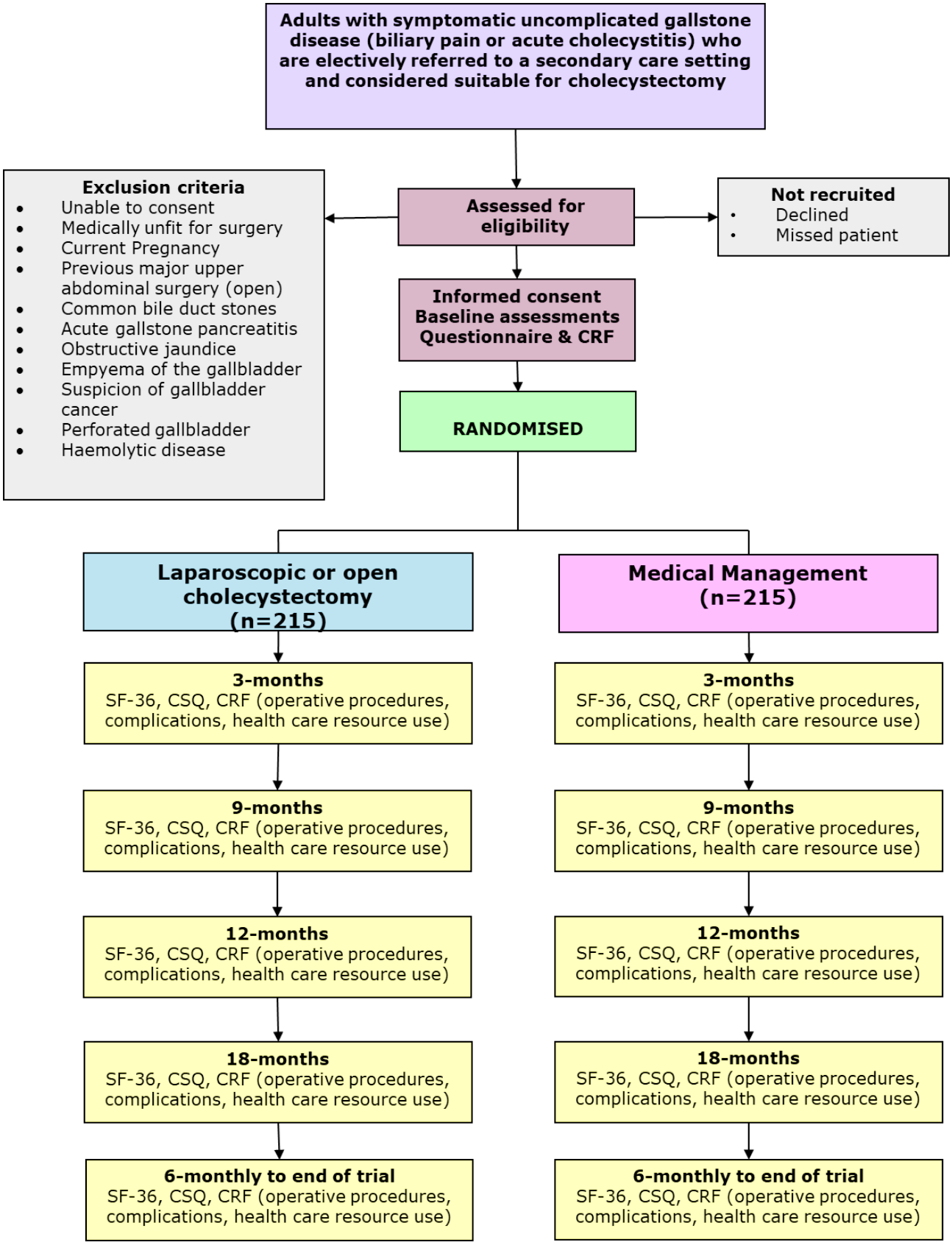


Table 1: Schedule of economic data collection

	Baseline	Surgery*	3 M	9 M	12 M	18 M	6 monthly thereafter
SF-36	X		X	X	X	X	X
CRF	X	X	X	X	X	X	X
Resources use questionnaire			X	X	X	X	X
Time and travel questionnaire						X	

*Surgery CRF completed where appropriate

A Markov model, based on within trial data supplemented by available published data on the requirement for further interventions over time, will be developed and used to extrapolate cost-effectiveness beyond 24 months post randomisation.

3.3 Assessment of health service costs

NHS costs for health service use in both secondary and primary care by the trial participants will be estimated. Since the economic evaluation seeks to inform the efficient allocation of the NHS budget, the base case analysis will adopt a health service perspective. Cost will be expressed in British Pound Sterling and the price year will be 2019-2020.

3.3.1 Cost of the primary interventions

Cholecystectomy

Costs of the initial surgical intervention will be estimated from resource use data recorded in the C-Gall Surgery CRF for each participant. The CRF captures type of procedure carried out (Lap, Open, conversion to open), operation time (i.e., incision to skin closure), grade of surgeon, intra-operative complications, anaesthetic complications, and destination post-operation or recovery room.

The primary costing approach will assign costs to individual components of resource use to capture patient level variation in costs. Laparoscopic Cholecystectomy is one of the most

common NHS operational procedures.[iii] C-Gall Surgery CRF asked for time from *incision to skin closure*. Time in the anaesthetic room will be assumed based on clinical opinion and costed using the cost per hour (incorporating overheads) for a consultant anaesthetist and an anaesthetist nurse.[15] For time in theatre, clinical opinion will be used to allow for additional time in theatre from the collected *incision to skin closure* time; the unit cost of the recorded grade of surgeon and a consultant anaesthetist will be applied to the final total time in theatre.[15] Nursing staff will be costed at the requirement for general day surgery: one aesthetic nurse, a scrub nurse, and two further theatre nurses.[iv] In addition, a published unit cost will be applied for time in theatre to reflect the average cost of other staff, supplies and consumables, and allocated capital charges and overheads.[16] This detailed unit cost of theatre time is only available for Scottish hospitals. However, the average cost per theatre hour in general hospitals in Scotland (£1,144 including medical and nursing staff) is comparable with a previously published estimate for England (£1,200 per hour).[17] Therefore, the average Scottish estimate (£596 per hour, excluding medical and nursing staff) will be applied to time in the base case analysis. In addition to this, we will apply the unit costs of major consumable items specific to the alternative procedures.[v]

Time in recovery following surgery will be costed using the unit cost of grade six nurse (inclusive of overheads) assuming one to one care. Time on the ward following recovery will be costed using an estimate of the cost per excess bed day (transformed to an hourly rate) following Cholecystectomy.[18]

As an alternative approach to costing the initial Cholecystectomy procedure episode, each patient record will be mapped to the appropriate Health Care Resource Group (HRG), and costed using the relevant NHS reference cost.[18] The core HRG code for Cholecystectomy[vi] is

[iii] Surgical Workload Outcome Audit Database (SWORD). An Internet-based platform which collects up to date NHS Hospital episodes statistics data. Accessed through AUGIS (Association of Upper Gastrointestinal Surgery of Great Britain and Ireland)

[iv] Jamie McAllister (NHS Grampian) (through Irfan) is collecting data for micro-costing.

[v] Jamie McAllister (NHS Grampian) (through Irfan) is collecting data for micro-costing. Supplemented by literature search.

[vi] HRG coding different for tariffs 2014-15: GA10C, Open Cholecystectomy without CC; GA10D, Laparoscopic Cholecystectomy with length of stay 1 day or more without CC; GA10E, Laparoscopic Cholecystectomy with length of stay 0 days without CC; GA10F, Open or Laparoscopic Cholecystectomy with CC; Also, checked CholeS RCT Economic evaluation (used these codes but

GA10K (Laparoscopic Cholecystectomy, 19 years and over, with CC Score 0). The reference costs for this procedure will be applied as either a day case (patient discharged same day) or an inpatient admission (stay ≥ 1 day) adjusted for length of stay.

NHS outsourced Cholecystectomies

There are a number of procedures that have been performed on a private basis as NHS outsourced capacity in order to reduce waiting lists for surgery. A surgery CRF will not be available for these interventions. Therefore, we will:

a) assess the number and proportion of procedures that have been conducted on a private basis;

b) explore through consultation with clinical and other collaborators the unit costs for these interventions (i.e. the tariff paid by NHS).

c) assess the impact on costs of incorporating these interventions costed as being conducted in a private or NHS hospitals. We will conduct scenario analysis with extreme cases where most interventions are conducted in private or NHS hospitals.

Medical management

Medical management involves the prescription of analgesics to relieve the biliary pain (paracetamol, nonsteroidal anti-inflammatory drugs NSAIDs -e.g. ibuprofen etc.-, narcotic analgesics -e.g. opiates-, antispasmotics -e.g. Buscopan-), together with generic lifestyle advice.(C-Gall protocol) Furthermore, active monitoring is recommended for individuals without symptoms. This means participants should let their GP know if any changes in symptoms happen.

Data on medications and GP visits are collected through patient questionnaires. The British National Formulary (BNF) will be used to value medications.

allowed for excess days as we did in HEALTH). However, HRG codes for National Schedule of NHS Costs - Year 2018-19 will be used.

3.3.2 Costs of perioperative complications and readmissions

In the context of perioperative complications leading to prolonged hospital stay, the clinical management costs will be based on the NHS reference cost for any additional procedures and adjusted for prolonged length of stay. The information on the type of complications experienced and any procedures undertaken will be obtained from the C-Gall Operation form, Hospital CRF and associated Serious Adverse Event (SAE) forms.

Data on any hospital readmissions will be obtained from the Hospital CRF and associated serious adverse event forms. These events will be costed using HRG based reference costs.[18]

3.3.3 Costs of subsequent health care utilisation

Related primary and secondary outpatient care incurred over the 24-month follow-up period will be collected from the patient questionnaires at 3, 9, 12, 18, and 24 months post-randomisation. Medications prescribed for any on-going problems related to the patient's gallstone condition are also recorded in these questionnaires. All the primary care contacts will be costed using the Unit cost of Health and Social Care,[15] and outpatient visits will be costed using the NHS reference cost for general surgery outpatient visit.[18] For each patient the number of visits will be multiplied by the appropriate unit cost. The list of medications and quantities prescribed will be costed using prices recorded in the British National Formulary (BNF).[19]

Table 2 Unit costs (NHS perspective)

Resource	How measured	Source of measurement	Unit cost	Source of valuation
Time in anaesthetic room	Time in hours	Assumption based on clinical opinion	£151 per hour	Band 6 nurse (£45) + consultant anaesthetist (£106); Unit Costs of Health and

				Social Care, 2017.[15]
Time in theatre	Time in hours	C-Gall operation form		
Surgeon time			Consultant (£107 per hour); Associate specialist (£101); Registrar (£43 per hour); Foundation FY2 (£30); Foundation FY3 (£26); Nurse consultant (£62) Nurse (floor) (£62)	Unit Costs of Health and Social Care, 2017.[15]
Anaesthetist time			Consultant: (£106 per hour) Anaesthetic nurse (£62)	Unit Costs of Health and Social Care, 2017.[15]
Theatre costs (excluding medical and nursing staff)			£596 per hour	Table R140, ISD 2017.[16]
Procedure consumables	*Source*: Aberdeen Royal Infirmary General Surgery Service.			
Perioperative complication costs	See 3.2.2	C-Gall Operation form	Various based on recorded reasons and procedures	NHS Reference costs.[18]

Readmissions	See 3.2.2	Hospital admission CRFs; Patient questionnaire	Various based on recorded reasons and procedures	NHS Reference costs.[18]
Outpatient appointments	See 3.2.3	Patient questionnaires		NHS Reference costs.[18]
Non-Admitted Face-to-Face Attendance, First			£155 per attendance	
Non-Admitted Face-to-Face Attendance, Follow-up			£130 per attendance	
Primary care contacts	See 3.2.3	Patient questionnaires		Unit Costs of Health and Social Care, 2017.[15]
GP visits			£37 per visit	
GP home visits			£45.98	
GP phone / video consultation			£37 per visit	
Medications	See 3.2.3	Patient questionnaires	Various	British National Formulary.[19]

NOTE: These unit costs will be updated to the latest available at the time of analysis.

3.3.4 Indirect costs

Data on time off work were not collected within the C-Gall study. A literature search will be conducted to retrieve information on absenteeism for individuals waiting for Cholecystectomy and after surgery. These data will inform a model-based sensitivity analysis.

3.4 Outcome measures: health related quality of life and utilities

Effectiveness will be measured in terms of quality adjusted life years (QALYs), estimated using the SF-36 questionnaire completed by participants measured at baseline, 3, 9, 12, 18 months post randomisation and 6-monthly thereafter (Table 1). Participant responses will be assigned

a utility score based on the SF-36 UK tariff. SF-36 version 2 has been used; therefore, the algorithm sf6d_sf36v2_mod[vii] will be updated in STATA to obtain QALYs which will be estimated using the area under the curve approach, assuming linear change in utility between the observed follow-up time points.

3.5 Statistical Analysis of trial economic data

3.5.1 Aggregating costs and effects

Resource use, cost, and health outcome data will be summarised and tabulated for comparison by treatment allocation group, following the principles of intention to treat analysis (Dummy Tables 3-5). Continuous and count variables will be presented as means (± standard deviations), and dichotomous and categorical variables will be presented as absolute numbers and percentages. All cost elements will be summed over the follow-up period (to 24 months post randomisation) to estimate a total costs per patient.

3.5.2 Missing data

Reliance on complete case data for cost-effectiveness analysis can introduce bias unless the data are missing completely at random. The total estimated cost is the sum of numerous components over the observed follow-up period of the trial. Besides, QALYs can only be computed where participants have responded to the relevant quality of life questionnaires at every follow-up point. Therefore, economic evaluations based on participant level trial data are likely to encounter problems with missing data. Multiple imputation will be implemented as part of the primary analysis, using chained equations to generate multiple datasets with plausible fitted values assigned for missing cost and utility elements.[20] The imputation model will include all of the variables in the analysis model and a number of auxiliary variables that may help to explain missingness. Rubin's rules will be used to pool estimates across the multiple imputation datasets.[21]

3.5.3 Incremental Cost-effectiveness analysis

The trial based economic analysis will estimate the incremental cost and QALYs between Laparoscopic Cholecystectomy and Medical management up to 24 month post

[vii] SF6D downloaded documentation University of Sheffield webpage, *Outline of SF-6D programmes.doc*

randomisation. General linear regression models (GLM) with appropriate variance and link functions will be used, with adjustment for minimisation factors (centre, age) and, when appropriate, baseline measures. Recycled predictions will be used to recover adjusted mean values by treatment allocation group, and the incremental differences between groups.[22] The incremental cost-effectiveness ratio (ICER) for Laparoscopic Cholecystectomy and Medical management will be calculated as the incremental cost divided by incremental QALY (Dummy Table 5). Variance surrounding the joint incremental costs and effects will be characterised using non-parametric bootstrapping, with the simulation results presented graphically using the cost-effectiveness plane and cost-effectiveness acceptability curves. The probability of Laparoscopic Cholecystectomy being cost-effective at 24 months will be expressed for threshold ratios of willingness to pay per QALY that are typically applied in the UK health technology appraisals.[23]

Scenario analyses will be conducted according to initial findings and discussions with the Project Management Group (PMG). (Dummy Table 6).

Subgroup analysis will be conducted to explore cost-effectiveness of medical management vs surgical management according to gender (male/ female), age (<35; 35-64; ≥ 65) and ethnicity (white; mixed/multiple ethnic groups; Asian/Asian British; Black/African/Caribbean/Black British; Other). Treatment and ethnic group interaction terms will be used in the regression models for this analysis. (Dummy Table 7). Further subgroups will be explored upon agreement within the project management group (i.e., individuals with or without diabetes, individuals with BMI ≥30 or not).

3.6 Decision modelling

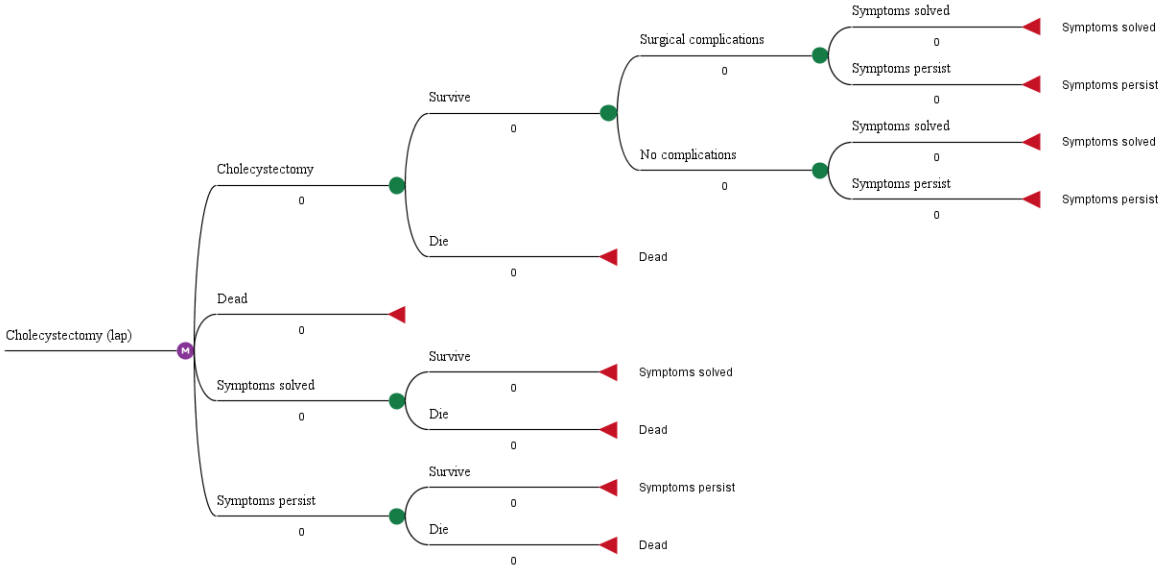
While informative the within trial analysis might not consider all relevant cost and consequences for a definitive answer on cost-effectiveness of Laparoscopic Cholecystectomy against Medical management. Cross over might occur, symptoms (e.g., pain) and emergency procedures can happen, and post-operative chronic pain continue after 24-month follow-up period. A Markov model will be developed to extrapolate cost and quality of life up to 10

years.[viii] [24] The model structure will be decided through review of existing model in the area.[14] A schematic of the possible model is provided below (Figure 2).

A final decision on reporting results for the modelling exercise will be taken by the PMG depending on the results of the within RCT analysis. If the modelling extrapolation shows an already cost effective or dominant alternative being more cost-effective or dominant, the PMG can decide on not reporting such outcome data[ix].

Figure 2a. Schematic of the Decision model

Cholecystectomy arm

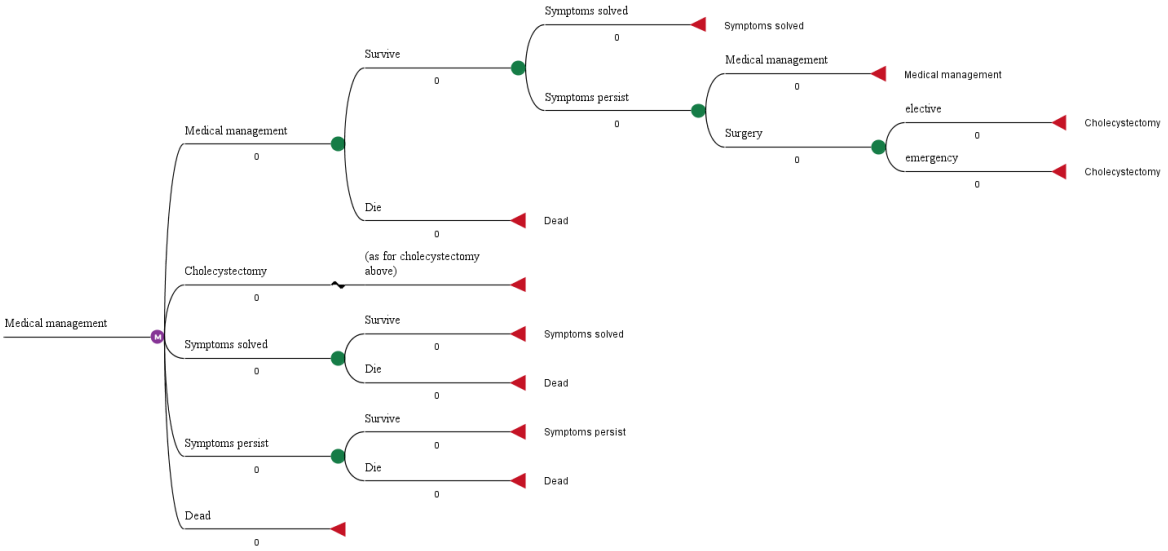


viii Schmidt et al. (2011) "*Virtually no cholecystectomy was performed after 5 years of follow-up, and no clear escalation in the severity of the disease was observed*". So, 10-year time horizon should be enough to allow for all costs and consequences.

[ix] Modelling might also inform the effect of the intervention for a non Covid-19 times e.g. by assuming alternative waiting time to those experienced in the trial.

Figure 2b. Schematic of the Decision model

Medical management arm



Probabilistic and deterministic sensitivity analysis will be carried out to characterise the uncertainty surrounding the model-based estimate of incremental cost-effectiveness of Laparoscopic Cholecystectomy against Medical management (Dummy Tables 9 and 10). For the probabilistic analysis, an appropriate distribution will be assigned to each model input parameter (reflecting the degree of uncertainty surrounding it due to sampling variation), and the model will be analysed a large number of times, each time randomly drawing a value for each input parameter from its assigned distribution.[25] The number of times for this analysis will be defined according to the stability of results (e.g., the ICER varying within £1000 range). This process will generate a large number of estimates of incremental costs and effects. Cost-effectiveness scatterplots and acceptability curves will be used to summarise the findings of the PSA. Further deterministic analysis will assess the sensitivity of the model-based estimates to further choices over sources of parameter estimates and other structural assumptions required when constructing the model. Sensitivity analysis will focus on expected key result drivers such as long-term cross overs, the risk of emergency procedures and assumptions for the survival curve estimation for these key variables.

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Planned Results Tables and Figures

Table 3: Health service resource use and costs by treatment allocation

Variable	**No of Observations**	**N=**	
		Medical management	**Surgical management**
Resource use			
Time in theatre; mean (SD)			
Length of stay; mean (SD)			
Hospital readmission; n (%)			
Readmission days; mean (SD)			
Outpatient visits			
GP contacts			
Face to face visits; mean (SD)			
Phone consultations; mean (SD)			
Home visits; mean (SD)			
Medication prescribed; n (%)			
Costs			
Index surgical episode cost; mean (SD)			
Readmission costs for adverse events; mean (SD)			
Readmission costs for further treatment; mean (SD)			
Outpatient costs; mean (SD)			
Primary care costs; mean (SD)			
Medication costs; mean (SD)			
Total NHS cost; mean (SD)			

Table 4: Health state utility and QALYs by treatment allocation

Variable	No of Observations	N=	
		Medical management	Surgical management
SF-6D			
Baseline; mean (SD)			
Three months post-randomisation; mean (SD)			
Nine months post-randomisation; mean (SD)			
12 months post-randomisation; mean (SD)			
18 months post-randomisation; mean (SD)			
24 months post-randomisation; mean (SD)			
Quality adjusted life years (SF-6D); mean (SD)			

Table 5: Trial based incremental cost-effectiveness analysis (NHS perspective)

Intervention	Total cost (£)	Incremental cost (£)	Total QALYs	Incremental QALY	Incremental cost-effectiveness ratio
Surgical management					
Medical management					

Table 6: Trial based sensitivity analysis

Intervention	Total cost (£)	Incremental cost (£)	Total QALYs	Incremental QALY	Incremental cost-effectiveness ratio
Base case analysis					
Surgical management					
Medical management					

1. HRG based reference costs to cost initial surgical episode					
Surgical management					
Medical management					
2. Other relevant scenarios					
Surgical management					
Medical management					

Table 7: Trial based incremental cost-effectiveness analysis by predefined subgroups

Intervention	Total cost (£)	Incremental cost (£)	Total QALYs	Incremental QALY	Incremental cost-effectiveness ratio
Base case analysis (full cohort)					
Surgical management					
Medical management					
Females					
Surgical management					
Medical management					
Males					
Surgical management					
Medical management					
Age 35 year and younger					
Surgical management					
Medical management					
Age 35 to 64 years					
Surgical management					
Medical management					
Age 65 years and older					
Surgical management					
Medical management					
Ethnicity (to be defined)					
Surgical management					
Medical management					

Table 8: Markov model input parameters

Structure to be confirmed

Table 9: Markov model based probabilistic incremental cost-effectiveness analysis (NHS perspective)

Design as per Table 5

Table 10: Markov model based deterministic sensitivity analysis

Design as per Table 6

List of planned figures

Figure 3: Trial based incremental cost-effectiveness scatter-plot for Medical management versus Surgical management

Figure 4: Trial based cost-effectiveness acceptability curve for Medical management versus Surgical management

Figure 5: Schematic of the Markov decision model

Figure 6: Model based incremental cost-effectiveness scatter-plot for Medical management versus Surgical management (extrapolated to five years)

Figure 7: Model based cost-effectiveness acceptability curve for Medical management versus Surgical management (extrapolated to five years)