Portsmouth Hospitals University NHS Trust

A single-centre, randomised clinical trial assessing non-inferiority of surgical techniques: robotic multi-port cholecystectomy versus conventional laparoscopic multi-port cholecystectomy for benign gallbladder disease. [STaRLING trial]

Surgical **T**echniques: **R**obotic versus conventional **L**aparoscopic cholecystectomy **IN** benign **G**allbladder disease.

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Surgical **T**echniques: **A**ssisted by **R**obot or **L**aparoscopy **In** **G**allbladder Surgery

A randomized controlled, open, parallel, non-inferiority, single centre trial

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Amendment History

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

CBD	Common bile duct
CI	Chief Investigator
CRF	Case Report Form
CT	Computed Tomography scan
DSMB	Data Safety Monitoring Board
EQ-5D	EuroQol 5D questionnaire
ERCP	Endoscopic Retrograde cholangiopancreatography
FU	Follow-up
GDPR	General Data Protection Regulation
GCP	Good Clinical Practice
HRA	Health Research Authority
HR-QOL	Health related quality of life
ICU	Intensive Care Unit
IOUSS	Intra-operative ultrasound
IU	International Units
LC	Laparoscopic cholecystectomy
MRCP	Magnetic Resonance Cholangiopancreatography
O-CSQ	Otago condition specific questionnaire
OTC	On-table cholangiogram
PHU	Portsmouth Hospitals University NHS Trust
PI	Principal Investigator
PPI	Patient Public Involvement
POD	postoperative day
PROMs	Patient Reported Outcome Measures
QA Hospital	Queen Alexandra Hospital, Portsmouth, UK
QOR-15	Quality of Recovery 15 questionnaire
RC	Robot assisted cholecystectomy
REC	Research Ethics Committee
SAE	Serious Adverse Event
SURG-TLX	Surgical Task Load Index
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAP	Transverse Abdominis Plane
UK	United Kingdom
US	Ultrasound

SUMMARY

Rationale: Robotic surgery is increasingly being adopted for gallbladder removal, despite no randomized trial available to assess patient safety and outcomes in comparison to the current gold standard: laparoscopic gallbladder removal. A literature review found several case-series that showed no difference in outcomes for postoperative complications and postoperative recovery between robotic cholecystectomy and laparoscopic cholecystectomy.

Objective: To study whether robotic multi-port cholecystectomy is non-inferior compared to conventional laparoscopic cholecystectomy with regard to morbidity and complications occurring within 30-days of the procedure. Alongside, we aim to compare both procedures with regards to peri-operative data, patient reported outcome measures (PROMs) such a health-related quality of life and patient satisfaction.

Study design: The STARLING trial is a non-inferiority parallel randomised controlled trial.

Study population: All adult patients with benign gallbladder disease with an indication for cholecystectomy.

Intervention: Patients will be randomly assigned to two groups. One group of patients will undergo robot-assisted multi-port cholecystectomy, whereas the other group of patients will undergo conventional laparoscopic multi-port cholecystectomy.

Main study parameters/endpoints: The primary endpoint will be the frequency and severity of postoperative complications occurring within 30 days of cholecystectomy. Secondary endpoints will be peri-operative outcomes, total health care utilisation, health related Quality of Life (HR-QoL) as measured in PROM's; EuroQol 5D (EQ-5D), Quality of Recovery 15 (QoR-15) and Otago Gallstones condition specific questionnaire (O-CSQ) along with cost-effectiveness.

Short summary (300 words)

Robotic surgery is increasingly being adopted for gallbladder removal, whereas no randomized trial has been performed to assess patient safety and outcomes in comparison to the current gold standard: laparoscopic gallbladder removal. The STARLING trial is a prospective randomized clinical trial, in which adult patients with benign gallbladder disease (e.g. gallstones), will be randomized between robotic multiport gallbladder removal and conventional laparoscopic multiport gallbladder removal. The primary outcome will be complications within 30 days postoperatively. Secondary outcomes include intra-operative outcomes, patient recovery (including return to work), patient reported outcomes measures (PROMs) for quality of life and recovery and cost-effectiveness. Peri-operative care and work-up will be similar in both groups.

When adopting a novel technique, this technique should be as safe as the current standard. Robotic cholecystectomy should be non-inferior in complication rate to conventional laparoscopic cholecystectomy. The sample size for non-inferiority is based on previous literature; taking into account a two-sided 90% confidence interval a total of 276 patients are to be randomized.

All operations will be performed by surgeons with experience in both conventional laparoscopic, and robotic multiport cholecystectomy. Eligible surgeons have to have performed at least 32 robotic cholecystectomies which is based on previously reported learning curve data. We expect to complete recruitment and primary analysis within 18 months.

1. INTRODUCTION AND RATIONALE

Cholecystectomy is one of the most common general surgical procedures performed, with over 75,000 cholecystectomies performed annually in the UK [1]. Since the first successful laparoscopic cholecystectomy (LC) in 1985, laparoscopic techniques have been implemented widely, and laparoscopic cholecystectomy is considered the gold standard for gallbladder removal, with low rates of conversion and low incidence of bile duct injury [2].

Robotic surgery can help overcome the limits of laparoscopy due to wristed instrumentation, enhanced ergonomics and a stable magnified visual field [3]. However, the adoption of a novel surgical technique comes with a learning curve, often resulting in longer surgical time with a potential increased morbidity. Beyond "standard" cholecystectomy, robot-assisted techniques are likely to aid more complex biliary procedures such as common bile duct exploration [4]. It is imperative to establish whether robotic cholecystectomy (RC) is safe, and at least non-inferior to laparoscopic cholecystectomy before implementing such a technique and exploring more advanced options.

A systematic review undertaken by our research group revealed that the available evidence is scarce and generally of poor quality [5]. The studies indicate that the operating time for RC is longer but may lead to a lower conversion rate compared to LC. Postoperative recovery and complication rates were similar in both groups. Taking into account the scarce evidence, in the context of increasing evidence for, and the adoption of, robotic techniques in advanced procedures such as robotic oesophagectomy [6] and robotic pancreaticoduodenectomy [7], the value of routine robotic cholecystectomy should not be underestimated.

Robotic cholecystectomy may further aid as a "level 1" procedure to train surgeons and their teams in robotic skills and setup and thereby diminish learning curves for more advanced procedures [8]. A

similar training pattern has long been established for laparoscopy, where trainees start with appendicectomy and cholecystectomy before progressing to advanced laparoscopic procedures [9]. With the adoption of robotics in more elaborate and advanced procedures, surgeons are looking to create standardized learning pathways to adapt robotic skills in a safe way [10]. Robotic cholecystectomy could play an important role in such a learning pathway. Further to this, the benefits afforded by the robotic approach may indeed have clinical benefits, although a trial to assess this has not been performed to date. In order to progress the use of robotics adequate assessment of robotic versus laparoscopic multiport cholecystectomy is important.

Another observation from the available evidence for RC comes from a recent report, which has highlighted a further issue with regards to the implementation of robotic technology in the context of cholecystectomy. The IDEAL framework has published a systematic review assessing whether IDEAL criteria were adhered to in the implementation of robotic cholecystectomy [11]. This study did not set out to compare RC to LC, including multi- and single-port procedures reports on RC. Instead, the study was performed to assess whether the evidence-based IDEAL framework was adhered to in the context of adopting new technology. The study highlighted several issues. The first was that the IDEAL framework was not adhered to in most cases, with no IDEAL stage mentioned in any of the studies and most of the available studies were of retrospective nature. The second issue it highlighted was the vast difference observed between the recorded outcomes with over 800 different outcomes reported, of which 198 outcomes were only reported on once. A similar observation was made in a recent assessment of the implementation of robotic surgery for anti-reflux surgery [12]. In this study 157 different outcomes were reported across 23 studies; 95 (61%) of these were only used once. The implication of these results is that formal assessment of the value of robotic technology is difficult and inherently heterogenous with a lack of standardized reporting for defining selection criteria and outcomes.

In summary, with the current available literature, it can be concluded that robotic cholecystectomy is safe and feasible. The observation that it may lead to a reduction in the risk of conversion to open, although statistically true, is likely to reflect the poor quality of the studies. With increasing evidence supporting the application of robotic surgery in more complex upper gastrointestinal (and other) procedures such as oesophagectomy, the role of robotic cholecystectomy should not be under-estimated.

Here we present the trial protocol for the STARLING trial, with the aim to thoroughly assess robotic versus conventional laparoscopic multi-port cholecystectomy with regards to 30-day morbidity, peri-operative outcomes and patient recovery, health related quality of life, health care utilization and costs.

2. OBJECTIVES

2.1 Primary objective

Based on current literature, robotic multiport cholecystectomy (RC) is feasible and appears safe. A novel surgical technique for benign gallbladder disease should be at least non-inferior with regard to complications and morbidity. In the STARLING trial, robotic multiport cholecystectomy will be compared with conventional laparoscopic cholecystectomy (LC) with regards to 30-day morbidity, peri-operative outcomes and patient recovery, health related quality of life, health care utilisation and costs.

- Primary outcome: 30-day complications and morbidity, taking into account any complication as graded by the Clavien-Dindo classification [13].
    1. Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
    2. Requiring pharmacological treatment with drugs other than such allowed for grade I complications.

       Blood transfusions and total parenteral nutrition are also included.
    3. Requiring surgical, endoscopic or radiological intervention
        i. intervention not under general anaesthesia
        ii. intervention under general anaesthesia
    4. Life-threatening complication (including central nervous system complications), requiring management in an Intensive Care Unit (ICU).
    5. Death of a patient

  Data on all complications will be recorded, allowing for comparison of the frequency of complications, severity of individual complications and in the case of multiple complications: assessment of the comprehensive complication index number for each patient [14].

2.2 Secondary objectives

intra-operative outcomes

The following data will be collected on intra-operative outcomes:

- Duration of the procedure: In order to allow for assessment of robotic set-up times, two measurements will be performed; time between arrival and exit of the operating theatre, and time from knife to skin to closure of the skin.
- Peri-operative blood loss (Measured both in millilitres and the number of tonsil swabs used)
- Intra-abdominal pressure (mmHg insufflation)
- Perforation of the gallbladder (i.e. bile spillage)
- Intra-operative complications
- Technical difficulty of the procedure (as per Nassar et al.) [15]
    - Grade 1:
        - Gallbladder—floppy, non-adherent
        - Cystic pedicle—thin and clear
        - Adhesions—Simple up to the neck/Hartmann's pouch
    - Grade 2:
        - Gallbladder—Mucocele, Packed with stones
        - Cystic pedicle—Fat laden
        - Adhesions—Simple up to the body
    - Grade 3:
        - Gallbladder—Deep fossa, Acute cholecystitis, Contracted, Fibrosis, Hartmann's adherent to common bile duct (CBD), Impaction
        - Cystic pedicle—Abnormal anatomy or cystic duct—short, dilated or obscured
        - Adhesions—Dense up to fundus; Involving hepatic flexure or duodenum

- Grade 4:
    - Gallbladder—Completely obscured, Empyema, Gangrene, Mass
    - Cystic pedicle—Impossible to clarify
    - Adhesions—Dense, fibrosis, wrapping the gallbladder, Duodenum or hepatic flexure difficult to separate

- Assessment of liver parenchyma
    - Normal, large, Steatosis, Cirrhotic
- Assessment of common bile duct (CBD) performed?
    - If yes: indication on table cholangiogram (OTC) or ultrasound (IOUSS)?
        - Deranged liver function tests in pre-operative blood sampling
        - Abnormalities in CBD seen on ultrasound
- Cholangiogram performed? Yes/no
    - Cholangiogram performed with cholangiogram (X-ray), or intra-operative ultrasound
    - Stones seen in the bile ducts
    - If stones seen: bile duct exploration performed?
    - Other abnormalities seen?
- Use of peri-operative antibiotics. Prophylactic antibiotics not indicated as per current evidence. Any deviations from this during the procedure should be recorded.
- Placement of drain (number or drains if multiple).
- Surgical perceived effort with SURG TLX (Surgical Task Load Index).

<u>Peri-operative recovery</u>

Data on peri-operative outcomes will be compared as a marker for postoperative recovery:

- Analgesia needed in recovery.
- Opioids prescribed upon discharge.
- Frequency of same day discharge.

- Time from theatre departure to stage 3 recovery

30-day follow-up

- Quality of life
- Return to work / normal daily activities

Morbidity

When assessing overall morbidity, not only complications should be taken into account, but also added morbidity because of necessary additional procedures and interventions, and possible complications from these added procedures. RC and LC will be compared for readmission rates, needed interventions after cholecystectomy and overall health care utilization.

Patient satisfaction

Patient's wishes, satisfaction and quality of life should be taken into account, as this will help in deciding which procedure is preferred from a patient perspective. The patient journey may provide important insights for the role of RC in clinical settings. The following questionnaires will be used

- EuroQol 5D-5L (EQ-5D)
- Quality of Recovery – 15 (QOR) questionnaires
- Preoperative assessment of Otaga condition specific questionnaire (O-CSQ)
- Specific questions: Which wound (port-site) is most painful. (see Appendix 4).

Timings of the different questionnaires are depicted in the figure below. All questionnaires will be added alongside to this protocol.

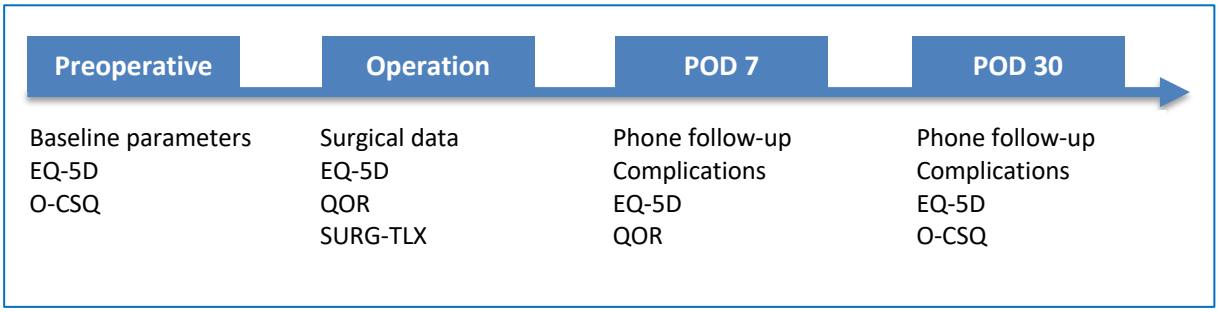


Figure 1: *Timings of measurements of data collection and patient reported outcome measures. Abbreviations: phone FU = telephone follow-up appointment, POD = postoperative day*

Cost-effectiveness

In order to assess the effect of implementation of robotic multi-port cholecystectomy on hospital costs, case data will be collected and compared in the conventional laparoscopic and robotic cholecystectomy group. Operative costs, admission costs and additional treatment costs (i.e. total health care utilization) will be assessed from index operation to 30 days postoperatively.

3. STUDY DESIGN

Design

The STARLING trial is a randomised controlled, parallel, single-centre, non-inferiority trial. Patients over 18 years of age, presenting with benign gallbladder disease with an indication for elective cholecystectomy will be randomised in two groups.

- Robotic multiport cholecystectomy (RC)
- Conventional laparoscopic multiport cholecystectomy (LC)

Design and timing of the investigations are presented in Appendix 1 and 2, respectively. Further information regarding the procedures and methods are described in chapter 8.

Setting

In order to create a homogenous environment with regards to peri-operative care (work-up, anaesthesia, peri-operative care) this study is set up as a single-centre study. Patients are included in the Queen Alexandra (QA) Hospital in Portsmouth. This hospital currently has the largest series of both benign and malignant robotic Upper GI experience in the UK. The QA hospital is one of very few UK hospitals providing routine robotic cholecystectomy and has ample experience with advanced robotic surgery, including bile duct explorations, oesophagectomy and advanced hiatal hernia surgery.

Complication rates, the duration of an operation and procedure related morbidity can all be a result of a learning curve of the operating surgeon, potentially causing bias. In order to prevent surgeon bias, participating surgeons will have sufficient experience in both LC and RC. Based on literature it is required that the participating surgeon has performed at least 200 conventional laparoscopic multi-port cholecystectomies (as based on a recent systematic review) and at least 32 robotic multi-port cholecystectomies [16, 17] in order to ensure they have gone through the learning curve .

Quality assurance of the procedures will be ensured through collection of unedited video data from five robotic cholecystectomy procedures for each participating surgeon. Videos will be anonymized and assessed by Mr. G.I. van Boxel and Mr N.C. Carter as most senior robotic surgeons and proctors.

4. STUDY POPULATION

4.1 Population (base)

The study population encompasses all adult patients with benign gallbladder disease. Exact inclusion- and exclusion criteria are listed below.

4.2 Inclusion criteria

- Age equal to or above 18 years
- Benign gallbladder disease: diagnosis of gallbladder polyps or symptomatic gallstones proven on imaging (ultrasound, CT (computed tomography) scan or MRCP (Magnetic resonance cholangiopancreatography)).
- Capacity to give informed consent.

4.3 Exclusion criteria

- Minimally invasive procedure is not deemed possible by the operating surgeon
- Evidence of acute cholecystitis
- Known stones in the common bile duct.
- Suspicion of possible malignancy
- Pregnancy
- Diagnosis of liver cirrhosis, stage III or IV.
- Insufficient language skills to be able to perform the quality-of-life questionnaires.

4.4 Sample size calculation

When considering a new technique, such as robotic cholecystectomy, these new techniques should be safe for patients. We performed a systematic review and meta-analysis of available literature comparing robotic multiport cholecystectomy with conventional laparoscopic cholecystectomy, we

found no difference in the rate of overall complications, and no difference in the rate of bile duct injuries [5]. Although there was marked heterogeneity in definitions used, this does give us an overall idea of complication rates.

Overall postoperative complications were reported in nine out of the fourteen studies and showed no statistically significant differences between LC and RC, with a weighted odds ratio of 1.21 (95% CI = -0.80 – 1.84), with P=0.86. Complications were reported in 42 out of 526 patients who underwent RC (7.9%) and in 62 out of 790 patients who underwent LC (7.8%).

Bile duct injuries were reported in 11 studies and showed no statistically significant differences between RC (6/1380 patients) and LC (15/1437 patients), with a weighted odds ratio of 0.54 (95% CI = -0.21 – 1.42), with P=0.21.

Based on postoperative complications, using a frequentist approach; If there is truly no difference between the standard conventional laparoscopic approach and robotic multiport cholecystectomy (7.9% in RC and 7.8% in LC), then 250 patients in total are required to be 90% sure that the upper limit of a one-sided 95% confidence interval (or equivalently a 90% two-sided confidence interval) will exclude a difference in favour of the standard group of more than 10%. Taking into account a 10% loss to follow-up, a total of 276 patients will be included [18]. The data is to heterogeneous and data on quality adjusted life years is scarce, which means we are unable to apply a decision theory approach to the sample size calculation [19].

Bile duct injuries are associated with high morbidity rates for patients, and it would be very interesting to power the trial base on bile duct injuries. As seen in our systematic review, the incidence is low and there is a marked heterogeneity in definitions used for bile duct injury. When applying the non-inferiority model with a frequentist approach, using the same limits as above, the model states only 12 patients are needed per group. There is no adequate data to perform a decision theory sample size calculation [19]. For the sake of comparison we calculated for a superiority design (i.e. hypothesis that RC might lead to less bile duct injuries) a total of 4861 patients would need to be included in each group.

Overall, the low incidence and heterogeneity in definitions used in the previous studies do not allow us to perform a sample size calculation based on bile duct injuries and we have hence chosen to power the trial for overall complications. This means a total of 276 patients will need to be randomized to either LC or RC.

5. PARTICIPANTS INTERVENTION

5.1 Description of Study Intervention

The investigational treatments are robotic multi-port cholecystectomy and conventional laparoscopic multi-port cholecystectomy. Specific details regarding both operative procedures are provided in section 6.3.

5.2 Schedule of Assessments

Overview of different time-points for data collection in the trial with a list of collected data (marked X) for each time point. POD = Postoperative day

Timing	Outpatient department	Admission	Discharge	Follow-up POD 7	Follow-up POD 30
Pre-operative work-up - Demographics - History - Bloods - Ultrasound	 X X X X				
Informed consent	X	check			
Clinical parameters		X			
Operative data		X			
Data on morbidity and complications (if applicable)		X	X	X	X
Quality of Life (PROMs)	EQ-5D O-CSQ		EQ-5D QOR	EQ-5D QOR	EQ-5D QOR O-CSQ
Survival			X	X	X

5.3 Concomitant Medication/Therapies

Patients are allowed to use their own prescription drugs, unless the anaesthetist advises differently. The majority of the patients included in the study will be day-case procedures – the rate of elective day-case cholecystectomy in the Queen Alexandra hospital is 80% over the past two years. If patients are admitted following cholecystectomy (i.e. not day case), these patients will receive anti-thrombotic prophylaxis according to local protocol, consisting of Enoxaparin 4000 IU (40 mg) subcutaneously, once daily for the duration of the admission. This dosage may be adapted according to the patient's needs (i.e., patient weight, renal protection). Peri-operative antibiotics are given at discretion of the surgeon and use of antibiotics will be recorded in the trial.

6. METHODS

6.1 Study parameters/endpoints

This study will be conducted in accordance with the principles of the Declaration of Helsinki and 'good clinical practice' (GCP) guidelines [20]. The independent ethics committee will need to approve the final protocol. Oral and written informed consent in form will be obtained from all patients before inclusion in the trial.

6.1.1 Main study parameter/endpoint

- 30-day complications
    - All complications, graded by Clavien-Dindo Classification [13].
    - Comprehensive complication index

    An extensive description of the main endpoint is provided in chapter 2.1.

6.1.2 Secondary study parameters/endpoints

<u>intra-operative outcomes</u>

Duration of the procedure, peri-operative blood loss, perforation of the gallbladder (i.e. bile spillage), intra-operative complications, difficulty of procedure (grade 1-4 [15]), assessment (and if applicable: treatment) of common bile duct stones, placement of drains. Analgesia used in theatre, use of peri-operative anti-biotics. SURG-TLX score.

<u>Peri-operative recovery</u>

Analgesia needed on recovery, opioids prescribed upon discharge, frequency of same day discharge. Time from departing theatre to discharge.

<u>Morbidity</u>

Readmission, additional procedures needed, health care utilisation.

<u>Patient satisfaction</u>

Measured with patient reported outcome measures: EuroQol 5D (EQ-5D), Quality of Recovery 15 (QoR-15) and Otago Gallstones condition specific questionnaire (O-CSQ)

Cost-effectiveness

Taking into account all health-care utilisation in the follow-up of these patients.

An extensive description of secondary endpoints is provided in chapter 2.2.

6.1.3 Other study parameters

- Other study parameters will include baseline characteristics: age, sex, medical history, previous surgery, smoking and alcohol habits, height and weight and comorbidities. The American Society of Anaesthesiologists (ASA) grade and the Charlson-comorbidity index will be recorded for all patients.

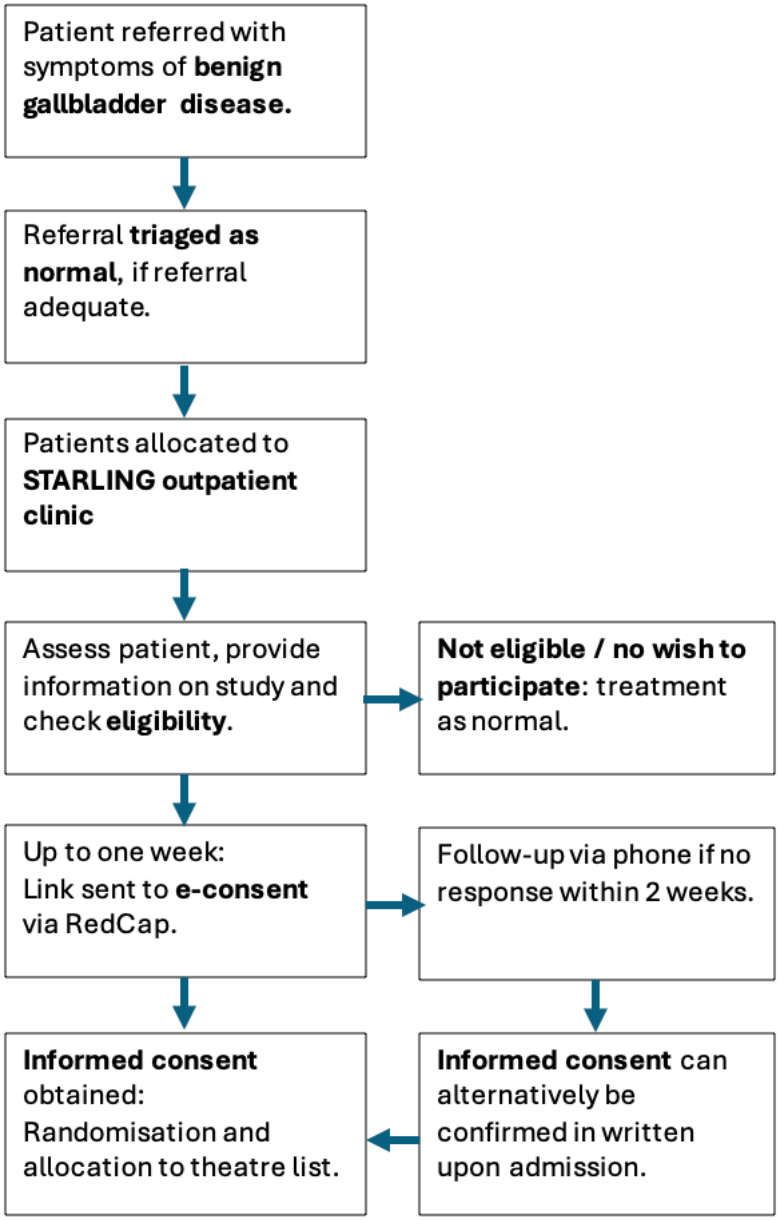
6.2 Recruitment and consent

Patients can be referred via GP or after attending the surgical ambulatory unit. All patients are triaged by a consultant upper GI surgeon, as is already normal practice. Patients referred with symptoms and examinations pointing to benign gallbladder disease, will be allocated to additional gallbladder outpatients clinics, these clinics are run by members of the study team. Patients will be assessed, informed about the study and assessed for eligibility.

If eligible, patients will be informed about the study. Receiving both verbal information and an additional leaflet with patient information, which the patient can study at home and discuss with their relatives. Beyond this, the patient can obtain additional information from their physician, the investigators, or the independent physician. The participant information will be used to explain risks and benefits of study participation before the patient is entered in the study.

Potential participants will be contacted up to a week after the initial contact with a link where they can sign the e-consent, this ensures patients have time to think about participating and discuss the information with their friends and family. There is also the possibility to call the study team if they have additional questions. If the patient does not respond to the link within 2 weeks, the study team

will contact the patient and check whether they have received the information. During this phone call any additional questions can be answered and the coordinating researcher can confirm whether the patient would want to participate. If the patient wishes to participate, the link to the informed consent form will be sent to the participant via email and signed digitally via RedCAP. Alternatively, participants can also consent on paper at admission. The delegated study team are responsible to obtain informed consent from each patient with appropriate signature and dates, prior to the performance of any protocol procedure. Please find a flow chart for screening patients below.



6.2 Randomisation, blinding and treatment allocation

In order to allow for preparation of the surgical teams and materials, patients can be randomised as soon as informed consent is obtained. After randomisation, the patient can be allocated to the appropriate theatre list (robotic or conventional laparoscopic). The patients nor the surgeon will be blinded to the treatment.

The randomisation process will be managed using the built-in module within the project's REDCap eCRF database managed by Portsmouth Hospitals University NHS Trust. See section above for detailed screening and recruitment pathways. After consent is received the patient can be randomised, via the dedicated study database on REDCap. After randomisation, the patient will be scheduled to the appropriate STARLING dedicated theatre lists. Pre- and postoperative workup is similar in both groups and further described in chapter 6.4.

6.4 Study procedures

Preoperative work-up

Preoperative work-up is the same for all patients, consisting of assessment of history and complaints, laboratory assessment of inflammation markers (white blood cell count, C-reactive protein) and liver function tests (total bilirubin, albumin, alkaline phosphatase, alanine transaminase), abdominal ultrasound with assessment of gallbladder and bile ducts. If there is doubt about stones in the bile ducts, an additional MRCP (may be performed. All patients are reviewed by the preoperative assessment team to assess them for fitness for surgery.

Patients with a BMI over 35 kg/m^2 will have a two-week liver shrinkage diet prescribed preoperatively, as is standard practice in our hospital.

Operation

Anaesthesia

Patients will have a general anaesthetic. Anaesthesia is the same for patients undergoing RC or LC, and the same anaesthetists will be involved in both RC and LC cases. Patients will receive standard pre-medication as per local protocol in the Queen Alexandra Hospital, consisting of paracetamol 1000 mg tablets, Ibuprofen 400 mg tablet and Omeprazole 20 mg tablet. Patients will receive peri-operative dexamethasone. Antibiotic prophylaxis will not be administered routinely, as per the findings of a recent meta-analysis these are not routinely indicated in patients operated electively for benign gallbladder disease [21]. Based on peri-operative findings, such as ongoing infection and bile leak, peri-operative antibiotics may be administered. Use of antibiotics will be monitored in this trial.

Surgery

The patient is placed in supine position with reverse Trendelenburg position and the procedure will be performed as described below. During the procedure local anaesthetics can be administered, a total of 60 millilitres of Bupivacaine 0.25% will be available. This can be used at the discretion of the surgeon and can be applied locally to the port sites and/or as a TAP (Transverse Abdominis Plane) block. Data will be collected on use of local anaesthetics.

Conventional laparoscopic cholecystectomy

Intra-abdominal entry is achieved by means of an open cut-down at the umbilicus and placement of 12 mm trocar. Where there is a contra-indication/difficulty of entry, the surgeon may opt to use a Veress needle or direct optical entry, mode of entry will be documented in the operation note. A further 12 mm trocar in the epigastric area, and 2x 5 mm trocar in the right flank. An overview of possible trocar placement is depicted in appendix 3, deviations in placement may occur based on surgeon preferences.

After placement of trocars, the abdomen is inspected. If applicable, any adhesions from the gallbladder are released. The gallbladder is retracted upwards, allowing for a view of the base of the gallbladder. The peritoneal layer is opened and dissected free with the aim of obtaining a critical

view of safety, referring to Callot's triangle, where a view is obtained with the cystic duct, cystic artery going to the gallbladder and a free space between the liver parenchyma. Both cystic duct and artery are clipped with hem-o-lok clips (Weck®, Teleflex inc.) and the gallbladder is then dissected free from the gallbladder fossa and extracted through the umbilical incision using a Bert bag (200ml, Fannin Ltd, UK).

Robotic cholecystectomy

Intra-abdominal entry is achieved by means of an open cut-down at the umbilicus and placement of a 12 mm assistant port, and 3 DaVinci 8 mm trocars. An overview of possible trocar placement is depicted in Appendix 3 and described in more detail in our peer-reviewed publication on the techniques for robotic cholecystectomy [van Boxel et al 2024] [22], slight deviations in placement may occur based on surgeon preferences.

After placement of trocars the robot is docked and the abdomen is inspected. If applicable, any adhesions from the gallbladder are released. The gallbladder is retracted upwards by the assistant, allowing for a view of the base of the gallbladder. The peritoneal layer is opened and dissected free with the aim of obtaining a critical view of safety, referring to Callot's triangle, where a view is obtained with the cystic duct, cystic artery going to the gallbladder and a free space between the liver parenchyma. Both cystic duct and artery are clipped by the assistant with hem-o-lok clips (Weck®, Teleflex inc.) and the gallbladder is then dissected free from the gallbladder fossa and extracted through the umbilical incision using a Bert bag (200ml, Fannin Ltd, UK).

<u>Assessment of common bile duct stones</u>

Assessment of the common bile duct is performed at discretion of the surgeon. To get a better understanding of the indication for assessment: the highest measured previous bilirubin level and

measured diameter of the CBD on ultrasound will be recorded. CBD assessment can be performed in two ways;

- Ultrasound of CBD (US-CBD) is the primary mode of assessment; in this case a small ultrasound probe is introduced in the abdomen and used to assess the common bile duct to the duodenum, as previously described Glaysher et al. [23].
- If ultrasound is not available, or views are not adequate with the probe, an on-table cholangiogram (OTC) can be performed; in this case a small catheter is inserted in the cystic duct and radiopaque contrast dye administered. With a C-arm the flow of the dye is assessed to see if there is free flow in the hepatic ducts, common bile duct and through to duodenum.

If stones in the CBD are observed during this assessment, additional treatment is indicated to prevent complications arising from these stones. Treatment may consist of

- Direct treatment: intra-operative exploration of the common bile duct: A small incision is made in the CBD allowing for introduction of a choledochoscope. The inside of the CBD is viewed and stones can be retrieved with a basket, which is introduced via the choledochoscope. Alternatively, stones can be retrieved by means of a trans-cystic approach, where the choledocoscope is inserted into the CBD though the cystic duct.
- Delayed treatment: Endoscopic retrograde cholangio- and pancreaticography (ERCP): This would entail an additional procedure by a gastro-enterologist. Retrieving the stones via endoscopy through the duodenal ampulla.
- Expectant management: small stones are likely to pass and an interval post-operative MRCP can be planned to assess the ducts.

Management of CBD stones is at the discretion of the surgeon, and any treatment will be recorded in the trial.

<u>End of the procedure</u>

The gallbladder is removed. The abdominal wall fascia is to be closed at the site of retrieval of the specimen. The skin will be closed with an intra-cutaneous absorbable suture. Either plasters or wound-glue may be applied as wound protection at the end of the procedure.

Specimen

All removed gallbladders will be sent for histo-pathological assessment as per local protocol.

Surgeon experience

A total of 6 surgeons will participate in the trial: G.I. van Boxel, J. Straatman, M.G. Glaysher, S.J. Mercer, P. Pucher and N. Carter. These surgeons all have ample experience in both laparoscopic and robotic cholecystectomy. According to available literature, the learning curve for robotic cholecystectomy is between 16 – 32 cases [16]. At the time of writing this protocol version (January 2025) all abovementioned surgeons completed at least 80 robotic cholecystectomies. The participating surgeons will submit a video of a robotic cholecystectomy to be reviewed by GvB and NCC as most experienced team members and active proctors for the Da Vinci robotic systems. To ensure that there is no surgeon bias: theatre lists will be allocated in a way where each surgeon will have an equal number of laparoscopic and robotic lists.

Postoperative management

Patients in both investigated groups will receive the same post-operative treatment and recommendations, unless a deviation from this is warranted on clinical grounds (in which case this will be documented). Postoperative patients will be monitored on our recovery ward, and information on administered pain medication will be collected. All patients will go home with the same pain medication, consisting of: Co-codamol 30mg/500mg tablets, Tramadol 50 mg tablets and Prochlorperazine 3 mg buccal tablets. Alterations can be made based on patient requirements, such as allergies and comorbidities.

Patients are operated on in a day case setting. Patients can be discharged if the following discharge criteria are met:

- Ability to fully ambulate without assistance
- Adequate pain control with no or only oral analgesics
- Ability to tolerate oral diet
- Able to urinate, no signs of urinary retention
- Acceptance of the patient

If patients require admission after their surgery, this will be recorded in the trial. If all discharge criteria are met, but due to other reasons the actual discharge is delayed a note will be made in the CRF.

Follow-up

In order to assess for the occurrence of postoperative complications: all included patients are called at 7 and at 30 days after the procedure. The following data will be collected;

- Occurrence of complications
- Patient reported outcome measures for recovery and quality of life
- Return to work or normal daily activities.

6.5 Withdrawal of individual participants

Participants can withdraw from the study at any time for any reason if they wish to do so without any consequences. The investigator can also decide to withdraw a participant from the study for urgent medical reasons. Follow-up in terms of primary outcome of those participants will be performed as usual. Included patients will be analysed according to the intention to treat.

6.6 Replacement of individual participants after withdrawal

Once individual participants are withdrawn from the study before resection of the gallbladder, they will be replaced. Withdrawn patients will not be included in follow-up for this study. Patients withdrawn from the study will go back to routine NHS care and receive follow-up as appropriate.

6.7 Definition of End of Study

The end of the study is the date of the last follow-up contact with the last participant. Which will be at 30 days after the operation date of the last participant.

7. SAFETY REPORTING

7.1 Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening*
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.
- Other important medical events**

*The term “life-threatening” in the definition of “serious” refers to an event in which the participant 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.

**Other ‘important medical events’ may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was ‘related’ (resulted from administration of any of the research procedures) and ‘unexpected’ in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the sponsors serious adverse event form. Please refer to PHURDSOP007 for further guidance.

7.2 Adverse and serious adverse events

7.2.1 Adverse Events

An adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease in any participant in a clinical trial (including those in an untreated control group), whether or not considered related to the intervention investigational medicinal product. Adverse events will be captured from the time of a participant's enrolment into the study until the end of their participation. All adverse events will be recorded in the participant's medical notes and reported in the CRF. The following information should be provided as a record: description, start time, end time, duration, severity, treatment and outcome. There are no specified timelines for AE reporting however this should be done in a timely manner.

List of Anticipated Adverse Events

Cholecystectomies can lead up to certain postoperative complications, the rate of postoperative complications is around 7.9% [5]. Complications such as:

- wound infections
- bile duct stone requiring postoperative ERCP
- fluid collection requiring drainage
- bile leak requiring treatment
- pneumonia
- Pain management requiring prolonged admission / re-admission

Will not be separately mentioned as AEs as these are complications that are generally known complications of a cholecystectomy and therefore exempt from safety reporting within this study. All patients undergoing gallbladder surgery in the Queen Alexandra hospital are informed on the above risks and possible complications prior to giving informed consent for the procedure (see patient information leaflet).

7.3 Follow-up of adverse events

All adverse events will be followed up until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

7.4 Data Safety Monitoring Board (DSMB)

The protocol committee thinks that the involvement of a DSMB is not necessary, unless the medical ethics committee decides otherwise (see chapter 13). The study Sponsor, Portsmouth Hospitals University NHS Trust, will monitor study data according to a risk-based monitoring and plan and Good Clinical Practice (GCP). The informed consent of selected individual participants will be checked. Source data verification will be performed during monitoring (in order to verify if all data on the Case Report Form are in accordance with the source data). The intensity of verification is in relation to the risk associated with the intervention investigated. The monitor will also verify if all SAEs are reported adequately and within the time determined by the sponsors standard operating procedures, and regulations.

A Trial Management Group (TMG) will convene quarterly and will oversee the day-to-day co-ordination and progress of the study. The TMG will consist of study representatives selected from the Chief Investigator which will include members of the study research team and the members of the sponsor's research office based at the lead/Sponsor site. The TMG will be the primary point of contact for the study with responsibility for the delivery of approvals and permissions, initiation and training of sites, adverse event and progress reporting to the Sponsor. All relationships and any delegation of duties will be formalised in written agreements facilitated by the Sponsor.

7.5 Interim assessment

An interim data assessment will be conducted at the half way point (136 patients included) of the data to allow for early identification of any concerning trends between the two study arms.

8. STATISTICAL ANALYSIS

The STARLING trial is a non-inferiority trial. Patients who undergo a robotic multiport cholecystectomy will be compared to patients who undergo a conventional laparoscopic multiport cholecystectomy for the primary and secondary endpoints. Data will be analysed based on intention to treat. Continuous variables will be described as means and standard deviations in normal distributions, and as medians and interquartile ranges in non-normal distributions. For comparison T-test and ANOVA analysis will be used as appropriate. Categorical variables will be summarised with frequencies and percentages. For analysis chi-square and McNemar analysis will be used as appropriate. A p-value of 0.05 is considered appropriate. Linear and logistic regression models will be used to assess for confounders and effect-modifiers.

8.1 Primary study parameter

The primary objective of this project is to assess 30-day complications following cholecystectomy. In order to assess this, all complications as graded by the Clavien-Dindo classification will be recorded. The frequency of complications will be compared using Chi-square and McNemar tests as appropriate. Multivariate assessment will be performed using logistic regression models.

8.2 Secondary study parameters

Statistical analysis will be performed using SPSS statistical software (IBM statistics). Continuous data will be presented as mean and standard deviation in the case of a normal distribution, comparison between RC and LC will be performed using a Student's T-test. For continuous data with a non-normal/skewed distribution, data will be presented as median and interquartile range. Comparison between RC and LC will be performed with a Mann-Whitney U test. Linear regression techniques will be used to correct for confounders and effect-modifiers.

For parameters measured in frequency, the percentage of this frequency will be presented and comparison between RC and LC will be performed with Chi-square tests and McNemar tests as

appropriate. Logistic regression techniques will be used to correct for confounders and effect-modifiers.

9. ETHICAL CONSIDERATIONS

9.1 Declaration of Helsinki

The investigator will ensure that this study is conducted according to the principles of the Declaration of Helsinki [20],

9.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

9.3 Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

9.4 Benefits and risks assessment, group relatedness

Both operations are standard clinical practice and are therefore no experimental treatment.

9.5 Incentives

No incentives are used.

10 PATIENT PUBLIC INVOLVEMENT (PPI)

The protocol for the STARLING trial was designed by clinicians, taking into account active feedback from our service users. Before designing the trial, we wanted to know:

a) Whether patients would consider participating in such a trial?

b) What information is important to them, and how would they like it presented?

c) What outcome parameters are important to our patients?

d) How would they prefer to participate (i.e. active in house follow up versus a telephone call)

Mr van Boxel asked these questions in the outpatient surgical department to twelve patients who were being seen for gallbladder problems.

In summary: All patients reported they would be interested to participate in such a trial. Before considering participation, they would like to be informed on current available evidence. All patients preferred a printed leaflet, 50% of patients would like the information to be available online as well, for instance on a dedicated website. The outcomes most important to patients were: Complications, postoperative pain and postoperative recovery. Based on the literature and patient input we have made complications our primary endpoint and have ensured that pain and recovery are measured appropriately within the trial. With regards to follow-up, patients preferred to be contacted over the phone. Our researchers will follow up with these patients over the phone at 7 and 30 days after surgery. This questionnaire process really helped us ensure that we are measuring what is important to our patients.

Additionally, we have involved Sharon Court, Patient and Public involvement (PPI) facilitator who allowed us to present our protocol at one of the monthly PPI meetings. Additionally, the patient information leaflet, and gallbladder surgery leaflet were sent out to a group of volunteers in the PPI committee. The presentation was received well, and there were no remarks on the design of the trial. Our team was praised for its inclusivity of patients, and awareness of stakeholders in the whole chain of the study.

Following the presentation, we received some corrections to our leaflets via email, which were helpful to ensure that the leaflets are written in a good and comprehensive way.

We have agreed to organise another presentation in the PPI meeting, when we have the results of the trial. We hope that the PPI team can help us with interpretation of the results (especially, what would this mean for our patients) and dissemination of results. The PPI team is keen to help us organise a meeting for any interested stakeholders (including patients who participated) to attend and discuss the results of the trial. The PPI team was further interested in future applications of robotics, and with the results we hope to collaborate on the next steps forward.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11 .1 Data Management

The plan for the data management of the study is outlined below. Please note that the aforementioned quality of life questionnaires may be collected on paper if the patient is unable to utilise the questionnaires via REDCap.

All data will be handled within the conditions of the General Data Protection Regulations (GDPR) which came into force in May 2018. Required data for this study (including data collected from patient care records) will be entered onto an internet-facing instance of REDCap, administered by Portsmouth Technologies Trials Unit (PTTU) and hosted by AIMES, an ISO 2700 Information Security Management System. The Data Manager, supported by the study team, will design and build the database and eCRF. They will also create two-factor authenticated, password-protected user accounts for study members on the delegation log, at the request of the PI.

Data Security

The REDCap system hosted by AIMES is fully validated in accordance with industry and regulatory standards and incorporates controlled access security. Web servers are secured by digital certificates. Data integrity is assured by strictly controlled procedures, including secure data transfer procedures. Data is backed up on-site nightly with a 7-day retention period. AIMES is an ISO 2700 Information Security Management System certified, NHS IG Toolkit Compliant, G-Cloud Assured Supplier, NHS Digital Accredited Commercial N3 Aggregator, Data Centre Alliance Class 3 Facility.

Database usage and sharing procedures

There will be a trial master file (TMF) which will contain a delegation log of approved users. Access to the database will only be provided to members of the study team with approval of the Chief Investigator (CI) of the study. The CI, PI and trial coordinator will have access to all research data

collected in this study in order to perform the data analyses required. All standard safeguards such as locked workstations and password protected files will be applied. Where possible all study data will be captured and stored electronically and will comply with regulations of the Data Protection Act 2019 (DPA 2018) and Data Protection Regulation 2016/679 (GDPR).

Data Monitoring

Regular data quality control checks, reporting and statistics will be performed using tools built into the REDCap platform. The Chief Investigator will facilitate access to study records for the purpose of monitoring, audits, and regulatory inspections. Participant's consent to this will be sought at the time of enrolment into the study.

The database will prevent the entry of spurious or invalid data at the point of data entry due to pre-defined validation rules. A comprehensive audit trail will be maintained throughout the study detailing data changes, reasons for changes, dates that the changes made, and who made the changes. This audit trail will be exported and stored in the TMF at study close. For data points that are incomplete or data that violates the validation rules, a query will be generated, which can then be assigned to a user to resolve. The database cannot be locked while queries remain open. Reports for missing data will be scheduled monthly.

11. 2 Data Handling and Storage

All data will be entered and stored on a specialised, online, secure database (REDCAP). The CI & PI can access all data on a secured laptop. The laptop and paperwork will be stored in a secured space, which is only accessible to the researcher. Data will be handled confidentially. A subject identification code is used to link the data to the subject. A code is generated randomly by the online module in REDCap. The handling of personal data will comply with the General Data Protection Regulation (GDPR).

11.3 Source Data

Source data is defined as the first place that data is recorded. It is the place from which participants research data will be obtained. In the study the following data will be collected from the following sources:

- Hospital records (minestrone): baseline parameters, comorbidities and preoperative assessment.
- Laboratory: preoperative bloods, accessed via Minestrone
- Radiology: preoperative imaging, accessed via Minestrone
- Operation notes: to ensure that our surgeons operating in the trial report all the necessary data a surgical checklist will be made including the data points mentioned in section. The operation notes will be on Minestrone.
- Patient reported outcome measures, for quality of life and postoperative recovery. Stored in REDCap directly.

11.4 Monitoring and Audit

Portsmouth Hospitals University NHS Trust, as Sponsor, operates a risk-based monitoring and audit programme, to which this study will be subject. As part of the quality management process, the study will be subject to a risk assessment and a monitoring plan will be developed by the Sponsor in accordance with the level of risk identified to participant safety, integrity of the study and study data validity. All study monitoring will be conducted in accordance with the monitoring plan and will be undertaken by the study Sponsor or their delegate. All monitoring will be performed by staff who are ICH/GCP trained and are competent in monitoring to all applicable regulatory guidelines.

11.5 Amendments

A substantial amendment is defined as an amendment to the terms of the ethical review application, or the protocol or any other supporting documentation, which is likely to affect to a significant degree.

- The safety or physical or mental integrity of participants of the trial
- Scientific value of the trial
- Conduct or management of the trial
- Quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the REC and HRA the Research Office. Non-substantial amendments will not be notified to the HRA and actioned accordingly via the Research Office

11.6 End of study report

The investigator will notify the accredited REC of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit. In case the study is ended prematurely, the investigator will notify the accredited REC, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited REC.

11.7 Public disclosure and publication policy

After completion of the study an analysis of the data, the results will be made publicly without restriction, independent of the outcome. They will be submitted for publication to an international, peer-reviewed journal. The principal investigators and study coordinators will prepare the manuscript together with those who substantially contributed to the study. Being a (co-)investigator on this trial does not automatically result in co-authorship of the manuscript reporting the study result

12. STRUCTURED RISK ANALYSIS

12.1 Summary of known and potential risks

Current available literature shows no differences in risks between robotic multiport cholecystectomy and conventional multiport cholecystectomy. The risks of participation in the trial are therefore not believed to be different from patients undergoing gallbladder surgery outside of the trial. A list of expected adverse events/complications is listed below.

12.2 Expected frequency of adverse events/complications

Common complications after cholecystectomy include: wound infections, bruising or haematoma around the incisions and postoperative pain in the abdomen and at the shoulder tip. Generic complications after any type of surgery include: thrombo-embolic events, pneumonia and constipation in the first period after surgery.

Severe complications are less common, and include: a bile leak, which may require drainage or even a re-operation, frequency 0 – 1.6% in recent meta-analysis [24]. Intra-abdominal collections which may require drainage. Damage or perforation to other organs in the abdominal cavity, which usually require re-operation.

If the gallbladder is friable and stones fall out of the gallbladder, there is a small risk of a retained stone, which usually does not require any additional intervention. In very rare cases, new stones may form in the stump of the gallbladder duct or the common bile duct, causing similar symptoms in the future, this is usually treated with ERCP [24].

12.3 Control and reversibility of adverse events

Postoperative complications will be graded according to the Clavien-Dindo classification, which grades postoperative complications with respect to the treatment necessitated. Some complications may require medicinal treatment, whereas others require invasive treatment such as percutaneous drainage, reoperation and intensive care admission. Based on currently available literature, as

assessed in our systematic review, no differences are seen in complication rates between conventional laparoscopic and robotic multiport cholecystectomy.

12.4 Physical, psychological and social stress

No differences in psychological and social stress is expected. However, participation may cause some psychological stress. To prevent this from occurring, patients will be provided with all the necessary study information before inclusion. Patients will have the opportunity to ask questions and discuss participation with the principal investigators, study-coordinators and/or the independent physician. To prevent any form of psychological pressure on decision-making, the treating physician will emphasize that the patient's decision on participation will not in any way influence their doctor-patient relationship.

12.5 Study population

All in- and exclusion criteria are identified in chapter 4.2 and 4.3. In summary, all patients who present with benign gallbladder disease and an indication for elective surgery are eligible for inclusion. Informed consent is obligatory. Patients who are legally or mentally incapable or unable to give informed consent, regardless of their age, are excluded. By defining in- and exclusion criteria we aim to get a real-life representation of all patients undergoing elective cholecystectomy, thereby ensuring that data from the STARLING trial can be used for future assessment in robotic programs.

12.6 Risk of protocol violation

Patients included in the STARLING-trial will be randomly assigned to robotic or conventional laparoscopic multi-port cholecystectomy. During surgery, intra-operative findings such as adhesions or variations in anatomy (for instance due to previous surgery) may warrant conversion to an open procedure. Conversion will be registered. Analysis will occur according to the intention to treat principle. Postoperative treatment as described above does not differ from treatment in patients who decide not to participate in the trial.

After discharge the patient will be monitored by the research coordinator up to the 30th postoperative day. No additional hospital visits are required.

12.7 Protocol Deviations

A deviation is a departure from the protocol that has been identified retrospectively, which is neither critical or major and so not likely to effect to a significant degree:

- The safety or physical or mental integrity of the trial participant
- The scientific value of the trial

Any deviations from the protocol will be documented in a protocol deviation form, sent to the sponsor organisation and filed in the trial master file.

12.8 Serious protocol breaches

A 'serious breach' is defined by the Medicines for Human Use (Clinical Trials) Regulations 2004 as a breach which is likely to affect to a serious degree:

- The safety or physical or mental integrity of the subjects of the trial; and/or
- The scientific value of the trial.

If a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the CI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

13. FINANCE AND INSURANCE

13.1 Funding

This study is funded by the Intuitive Foundation following a competitive grant application.

13.2 Insurance

PHU is a member of the NHS Clinical Negligence Scheme for Trusts. Under this scheme, PHU will accept full financial liability for any harm caused to participants in the clinical trial due to the negligence of its employees and honorary contract holders. In the event of harm caused by the protocol design or non-negligent harm arising from participation in the clinical trial, PHU will arrange appropriate insurance coverage. This ensures that participants are protected and that any potential risks are mitigated effectively.

13.3 Sponsorship

This study will be sponsored by Portsmouth Hospitals University NHS Trust (PHU). As the sponsor, PHU will oversee the study's conduct, ensuring compliance with regulatory and ethical standards.

13.4 Contractual Arrangements

Appropriate contractual arrangements will be put in place with all third parties, if required.

14. DISSEMINATION

The results of the study will be published in a peer-reviewed journal. Our aim is to raise awareness on the results, and (if the results confirm this) further educate our community. Engaging our community is important to ensure adequate uptake.

Dissemination will focus on our different stakeholders.

- Colleagues in hospital: presentation of results on local clinical governance meetings
- Healthcare professionals elsewhere: publishing of paper, presentation of results on both national and international conferences. Healthcare professionals can come on work visits to see our techniques and get more information on how introduce such a procedure in their local hospitals.
- Public, and especially our patients: A newsletter will be sent out to all participants of the study to inform them of the results of the study. Patients and other interested individuals may sign up to the newsletter via our trial website. Information leaflets on gallbladder removal surgery will be updated to reflect the results of the trial, ensuring that new patients are receiving up to date information. The results will be presented in the PPI team, with the aim of establishing further pathways of dissemination (see section on patient involvement).

Further uptake of robotic cholecystectomy

The results may warrant further uptake of robotic cholecystectomy. Internally, this means ensuring all staff is up to date and trained in working with the robotic systems. Training pathways are in place to ensure training of surgeons who are naïve to robotic surgery.

Externally, our techniques for robotic surgery have already been published in a peer reviewed journal for others to assess and use. Surgical teams may wish to visit our hospital to get acquainted with the setup and organisation. Several of our surgeons are already involved as proctors and frequently visit

surgical teams who are training in robotic surgery, and the team is keen to help other hospitals get set up and learn these techniques in the safest possible way.

As uptake increases, it will be important to keep reviewing the outcomes: ensuring our patients get the best possible care. Uptake can be reviewed via the NHS England model hospital portal and will allow for comparison of techniques nationally.

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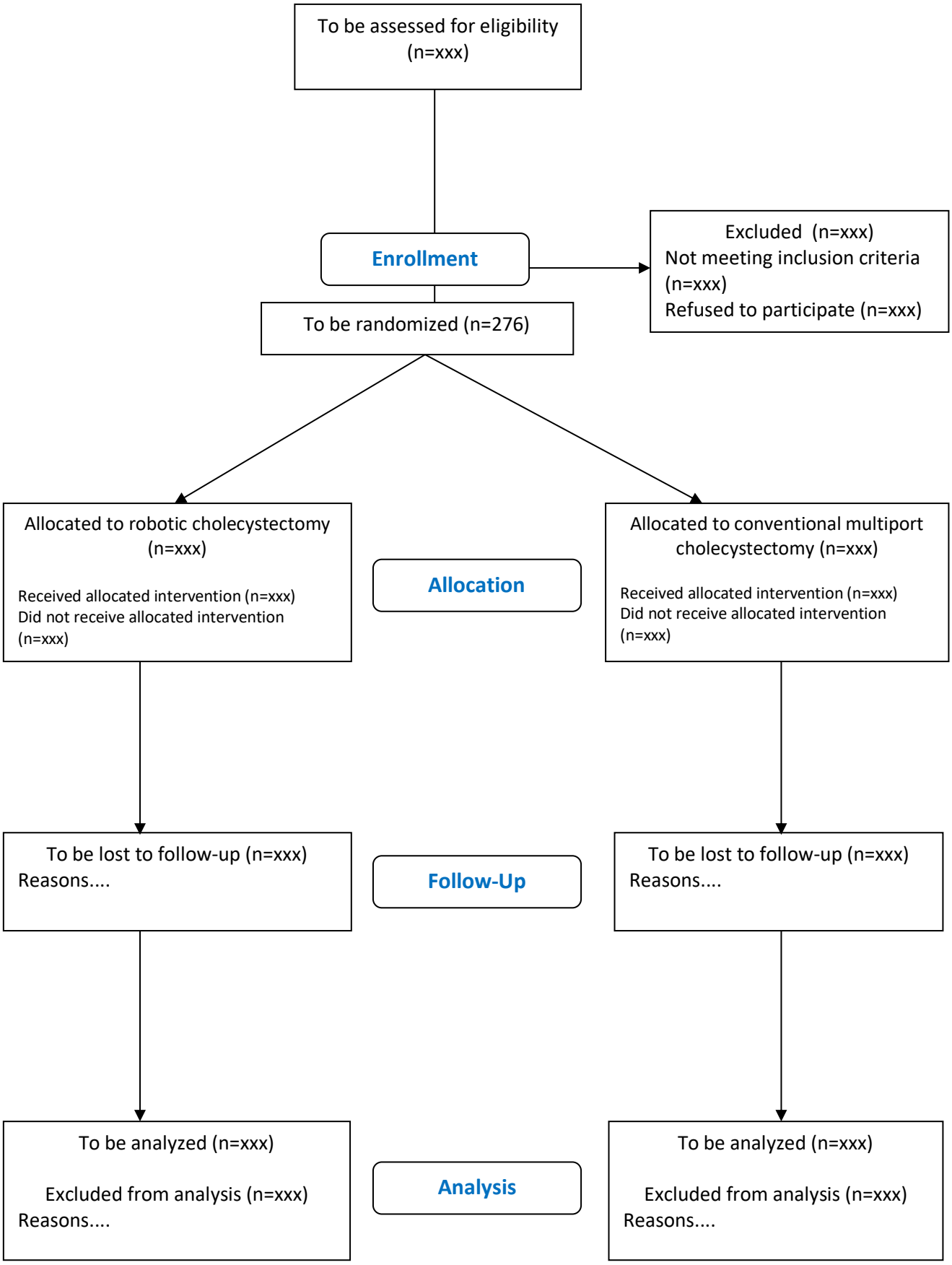
Appendix 1: STARLING trial according to CONSORT criteria.



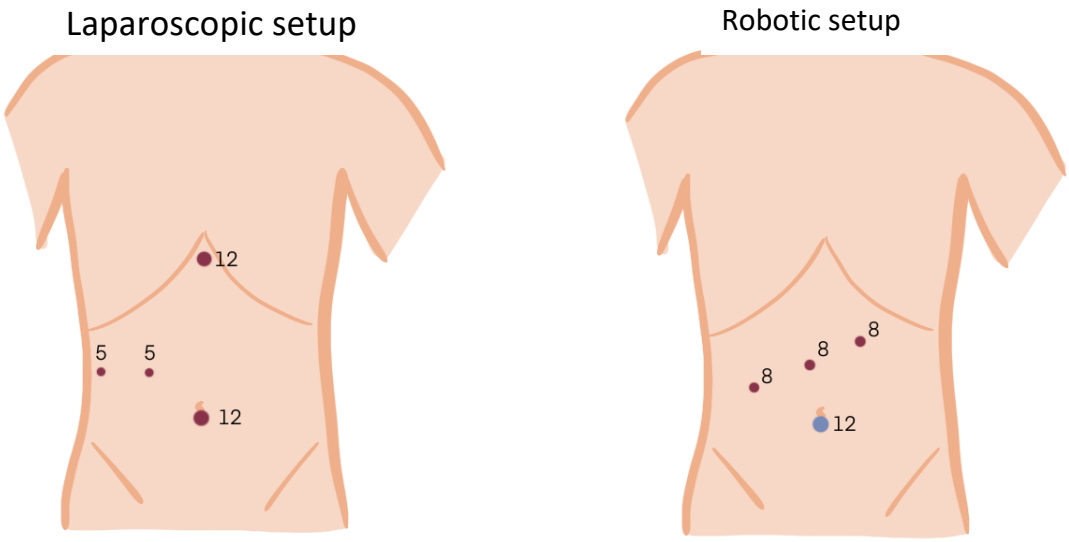
Appendix 2: Overview of different time-points for data collection.

Collected data (marked X) for each time point. POD = Postoperative day

Timing	Outpatient department	Admission	Discharge	Follow-up POD 7	Follow-up POD 30
Pre-operative work-up - History - Bloods - Ultrasound	 X X X				
Informed consent	X				
Clinical parameters		X			
Operative data		X			
Data on morbidity and complications (if applicable)		X	X	X	X
Quality of Life (PROMs)	EQ-5D O-CSQ		EQ-5D QOR	EQ-5D QOR	EQ-5D QOR O-CSQ
Survival			X	X	X

Appendix 3 Trocar placement for cholecystectomy.

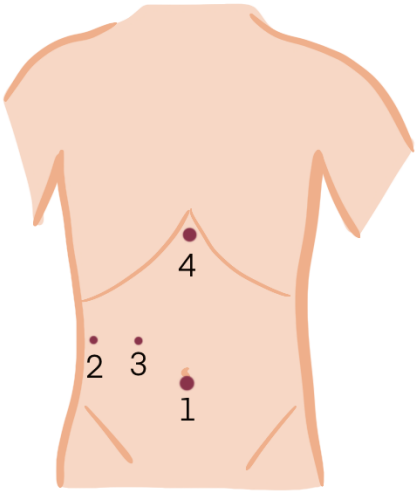
Local deviations in placement may occur. A) placement for conventional multiport laparoscopic cholecystectomy on the left, and placement for robotic cholecystectomy on the right. The numbers in the image reflect trocar sizes in mm. In the robotic image, the assistant port is depicted in blue.



Appendix 4 – questionnaire to assess pain at wound site.

Laparoscopic cholecystectomy

Which wound is most painful at this moment?



Robotic cholecystectomy

Which wound is most painful at this moment?