Trial Title: Managing Gallstone Disease in the Elderly: Comparing Quality of Life and Outcomes after Operative and Non-Operative Treatment

Internal Reference Number / Short title: The MANGO Trial

Ethics Ref: 22/NS/0026

IRAS Project ID: 301556

Date and Version No: 12/10/2022, v1.3

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Funder:	Rosetrees Trust

Chief Investigator signature

Prof Simon KC Toh

The investigators have no conflicts of interest

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee and Regulatory Authorities unless authorised to do so.

Protocol signatures continued (PI for each site needs to sign)

Trial Title: The MANGO Trial
EudraCT Number: NA
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Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator (Please print name)	**Signature**	**Site name or ID number**	**Date**

Following any amendments to the protocol, this page must be updated with the new protocol version number and date and re-signed by the site PI.

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1. KEY TRIAL CONTACTS

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Clinical Trials Unit	N/A
Statistician	N/A
Committees	N/A

2. LAY SUMMARY

Patient over 70 are very commonly admitted to hospital with problems caused by gallstones, such as pain, infection, jaundice and pancreatitis (inflammation of the pancreas, a digestive organ which can get blocked by gallstones). Some people have their gallbladder removed during their initial admission and others are treated first with medical therapy (such as antibiotics or an endoscopy) then brought back later to have their gallbladder removed as a planned (or "elective") operative. This usually prevents further problems caused by gallstones. A third group of patients may not be offered surgery at all, usually because they are elderly, frail or have other medical problems which make surgery more risky. Very little is known about what happens to these patients – such as whether the gallstones do cause more problems and how this affects their quality of life. This study aims to follow up patients who were admitted to hospital with gallstone disease to assess how this has affected them for up to three years after their initial diagnosis and compare those who did and those who didn't have surgery. Patients will be contacted regularly to ask whether they have any ongoing symptoms and how this affects their quality of life. This is an observational study which will not affect which treatment each patient receives – this will be decided as normal by the team treating them in hospital. A better understanding of what happens to patients after surgical and non-surgical treatment would allow doctors to have more informed discussions with patients about the likely outcomes of each treatment and improve their ability to make a joint decision about whether surgery is the best option.

3. SYNOPSIS

Trial Title	**Managing Gallstone Disease in the Elderly: Comparing Quality of Life and Outcomes after Operative and Non-Operative Treatment**

Internal ref. no. (or short title)	MANGO		
Trial registration	To be registered on clinicaltrials.gov		
Sponsor	Portsmouth Hospitals University NHS Trust Queen Alexandra Hospital, Cosham, Portsmouth PO6 3LY		
Funder	Rosetrees Trust		
Clinical Phase	Observational		
Trial Design	Observational		
Trial Participants	All patients aged 70 and over admitted acutely with gallstone disease		
Sample Size	290 (assuming readmission rate of 5% vs 30% with alpha of 0.05 and power of 0.9)		
Planned Trial Period	Recruitment period of 1 year with follow up of 3 years (study period 4 years in total)		
Planned Recruitment period	April 2022 – March 2023		
	Objectives	Outcome Measures	Timepoint(s)
Primary	Compare gallstone-related readmission rates among operative and non-operative groups	Number of patients readmitted with gallstone-related problems	30 days, 1 year, 3 years
Secondary	Morbidity Mortality Quality of Life	Number of patients with complications Number of patients who have died Gastrointestinal Quality of Life Index (GIQLI)	30 days, 1 year, 3 years
Intervention(s) • IMP(s) • nIMP(s)	None		

• Other intervention(s)	
Comparator	N/A

4. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GP	General Practitioner
GTAC	Gene Therapy Advisory Committee
HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB	Independent Review Board
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
RES	Research Ethics Service
PI	Principal Investigator

PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File

5. BACKGROUND AND RATIONALE

Gallstone disease is the most common surgical cause of hospital admission in developed countries[1] and the most common indication for abdominal surgery[23]. The prevalence increases progressively with age [1,2,4]. The incidence of gallstones in those aged 80 or over is as high as 38-53%[5,6], and has been reported to be as high as 80% for patients over 90 years of age[7]. Older patients are known to be at greater risk of complications of gallstones than younger patients, and are more likely to present with cholecystitis, choledocholithiasis and pancreatitis[8], as opposed to uncomplicated biliary colic. While modern guidelines[9,10] advise surgical management of gallstone disease in the typical patient, it is unclear whether these should also apply to the elderly, who often have pre-existing conditions and diminished physiological reserve which may affect their suitability for surgery.

Currently, published reports suggest that older patients are less likely to be managed surgically, with up to 30% of older patients managed non-operatively[11–13]. In cases where intervention is required, ERCP for ductal stones or cholecystostomy are considered. However, up to a third of patients may have recurrent problems when managed non-operatively[14]. Long term follow-up in these patients is lacking and there is

no real data comparing mid- to long-term outcomes, readmission rates or quality of life in patients undergoing these procedures compared with the definitive management of cholecystectomy.

This study aims to investigate the differences in outcomes, readmission rates and quality of life when comparing older patients (defined as at least 70 years of age) who are admitted with acute biliary disease (including biliary colic, cholecystitis, cholangitis, choledocholithiasis and pancreatitis) and are treated operatively compared with those who are managed with medical treatment only.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To compare the rate of gallstone-related hospital re-admission between patients treated operatively and non-operatively	Number and percentage of patients readmitted to hospital with gallstone-related disease by each timepoint.	30 days, 1 year, 3 years
Secondary Objectives 1. To compare morbidity in operative and non-operative groups 2. To compare mortality in operative and non-operative groups 3. To compare quality of life in operative and non-operative groups	Number and percentage of patients with complications in each group Number and percentage of patients who have died in each group Gastrointestinal Quality of Life Index (GIQLI) in each group	30 days, 1 year, 3 years
Exploratory Objectives To assess the result of frailty on		

morbidity, mortality and quality of life (as defined above) To assess whether frailty affects whether or not surgery is carried out	Morbidity, mortality and quality of life according to Rockwood frailty score Comparison of Rockwood frailty score in operative and non-operative groups both before and after surgery.	30 days, 1 year, 3 years

7. TRIAL DESIGN

This is an observational multicentre cohort study which will take place in a number of hospitals in Wessex. Patients will be recruited to the trial during admission for gallstone disease and followed up for 3 years after this admission. At each follow up timepoint patients will be contacted and asked to complete a quality of life questionnaire and will also be asked whether they have had any further admissions with gallstone related disease. Follow up information may also be obtained from hospital and GP records where appropriate.

8. PARTICIPANT IDENTIFICATION

8.1. Trial Participants

Participants aged 70 or over who are admitted acutely to hospital with gallstone disease (including biliary colic, cholecystitis, gallstone pancreatitis, choledocholithiasis and cholangitis)

8.2. Inclusion Criteria

- Male or Female, aged 70 years or above.
- Diagnosed with biliary colic, cholecystitis, gallstone pancreatitis, choledocholithiasis or cholangitis.
- In the Investigator's opinion, is able and willing to comply with all trial requirements.
- Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the trial.

8.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Participant is unwilling or unable to give informed consent for participation in the trial.

9. TRIAL PROCEDURES

None

9.1. Recruitment

Recruitment centres will be selected from the Wessex Deanery via the Wessex Research Collaborative. Each site will have a trainee associate PI who will be responsible for identifying patients presenting with gallstone disease from the emergency take list. Patients will be approached during their index admission and given information about the study. If they agree to participate, they will be consented and registered by an appropriately trained member of the research team. Patients will only be approached on multiple occasions if they have specifically asked to be given more time to consider their decision or discuss with others.

9.2. Screening and Eligibility Assessment

There is no specific time limit between screening and registration but the patient must be recruited and registered during their index hospital admission.

Screening will involve reviewing the patient's medical notes and imaging results to ensure that there is a clear diagnosis of gallstone-related disease. If the diagnosis is unclear (e.g. pancreatitis without confirmation of gallstones) the patient should either be excluded or rescreened once further investigations have been carried out. A screening log will be maintained at each site, documenting eligibility and if eligible, the reasons for patients not recruited (e.g. not approached, declined).

9.3. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing the nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the trial site.

9.4. Randomisation

Not applicable – observational trial

9.5. Blinding and code-breaking

Not applicable – observational trial

9.6. Baseline Assessments

Demographic data will be collected from the participant's medical records. Frailty will also be assessed at baseline

9.7. Subsequent Visits

Patients will be contacted by telephone at 30 days, 1 year and 3 years from registration. Prior to any contact, the hospital EPR and CHiE will be checked to ensure that the patient is still alive.

9.8. Sample Handling

Not applicable

9.9. Early Discontinuation/Withdrawal of Participants

During the course of the trial a participant may choose to withdraw their consent, meaning that they wish to withdraw from the study completely. Participants will have the following three options for withdrawal:

1) Participants may withdraw from active follow-up and further communication but allow the trial team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care; i.e., scans, blood results and GP records.
2) Participants can withdraw from the study but permit data and samples obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal.
3) Participants can withdraw completely from the study and withdraw the data and samples collected up until the point of withdrawal. The data and samples already collected would not be used in the final study analysis.

9.10. Definition of End of Trial

The end of trial is the point at which all the 3-year follow up data has been entered and all queries resolved.

10. TRIAL INTERVENTIONS

N/A – observational trial

10.1. Investigational Medicinal Product(s) (IMP) Description

N/A

10.1.1. Blinding of IMPs
N/A

10.1.2. Storage of IMP
N/A

10.1.3. Compliance with Trial Treatment
N/A

10.1.4. Accountability of the Trial Treatment
N/A

10.1.5. Concomitant Medication
N/A

10.1.6. Post-trial Treatment
N/A

10.2. Other Treatments (non-IMPS)
N/A

10.3. Other Interventions
N/A

11. SAFETY REPORTING
As this is an observational trial no adverse events are anticipated.

11.1. Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

	All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	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' 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. NOTE: 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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

11.2. Assessment results outside of normal parameters as AEs and SAEs

N/A

11.3. Assessment of Causality

N/A

11.4. Procedures for Reporting Adverse Events

Adverse events will not be reported as this is an observational trial.

11.5. Reporting Procedures for Serious Adverse Events

Serious adverse events will not be reported as this is an observational trial.

11.5.1. Events exempt from immediate reporting as SAEs

N/A

11.5.2. Procedure for immediate reporting of Serious Adverse Events

N/A

11.6. Expectedness

N/A

11.7. SUSAR Reporting

N/A

11.8. Development Safety Update Reports

N/A

12. STATISTICS

12.1. Statistical Analysis Plan (SAP)

The plan for the statistical analysis of the trial are outlined below. There is not a separate SAP document in use for the trial.

12.2. Description of Statistical Methods

Continuous data will be summarized using descriptive statistics (mean, median, standard deviation, quartiles, minimum and maximum) and categorical data will be summarized using counts and

percentages. The proportion of patients undergoing operative compared to non-operative treatment will be reported.

Primary endpoint

The primary endpoint will be reported as the percentage of patients re-admitted with gallstone related problems after operative vs non-operative management during their index admission.

Secondary endpoints

Data will be reported at 30 days, 1 year and 3 years. Patients who have had complications or have died in each group will be reported as a number and percentage. Comparison between groups will be carried out using Chi squared test. Gastrointestinal Quality of Life Index (GIQLI) in each group will be reported as a median and range. Paired T test will be used to compare groups.

12.3. Sample Size Determination

From previous studies, we estimate an approximate readmission rate of at least 30% in patients who do not have surgery compared to 5% in those who do. We estimate that approximately 10% of patients over 70 will not have surgery therefore the enrolment ratio is likely to be 1:9. Using an alpha of 0.05 and a power of 0.9 the number of patients required would therefore be 260. We would aim to recruit a minimum of 290 patients to account for a maximum of 10% lost to follow up.

12.4. Analysis Populations

All patients as registered. Comparisons will be made between groups who had surgery during/after their index admission and those who were treated non-operatively in assessing the primary endpoint.

12.5. Decision Points

No interim analysis is planned.

12.6. Stopping Rules

N/A

12.7. The Level of Statistical Significance

The level of statistical significance will be set at 0.05.

12.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

Any concerns about incomplete or spurious data will be discussed directly with the person responsible for data collection at the site and an attempt to verify the data will be made (e.g. through re-review of medical records).

12.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation from the original statistical plan will be reported in any publication resulting from the trial.

12.10. Health Economics Analysis

N/A

13. DATA MANAGEMENT

The plan for the data management of the study are outlined below. There is not a separate Data Management document in use for the trial.

Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number, not by name.

13.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

13.2. Data Recording and Record Keeping

Data will be collected from medical records and direct patient questioning if necessary (e.g. in assessing frailty, if this information is not already available in the medical record). Quality of life data will be collected via a questionnaire sent to patients at 30 days, 1 year and 3 years. A named Surgical Registrar at each site

will be responsible for data collection and CRF completion. Completed CRFs will be sent to the Wessex Research Collaborative and data will be entered onto Microsoft Excel.

The participants will be identified by a unique trial specific number in any database. The name and any other identifying detail will NOT be included in any trial data electronic file. Electronic CRFs will be kept for 5 years after recruitment has ended in case of need for re-review. Any concerns about incomplete or incorrect data will be discussed directly with the person responsible for data collection at the site and an attempt to verify the data will be made (e.g. through re-review of medical records).

All CRFs and data records in the database to be only identifiable by trial number. The list of trial numbers and link to patient details will be stored separately using fully secured computers within the research office of each site and will not be shared with the sponsoring organisation or the Wessex Research Collaborative.

14. QUALITY ASSURANCE PROCEDURES

14.1. Risk assessment

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

14.2. Monitoring

Regular monitoring will be performed according to the trial specific Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the trial specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

15. PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file.

16. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trial) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial".

In the event that 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 REC committee, Regulatory authority and the relevant NHS host organisation within seven calendar days.

17. ETHICAL AND REGULATORY CONSIDERATIONS

17.1. Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

17.2. Guidelines for Good Clinical Practice

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

17.3. Approvals

Following Sponsor approval the protocol, informed consent form, participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

17.4. Other Ethical Considerations

N/A

17.5. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

17.6. 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.

17.7. Expenses and Benefits

All additional follow up will be carried out by telephone. No expenses will therefore be payable.

18. FINANCE AND INSURANCE

18.1. Funding

There are no financing arrangements or supporting organisations for this trial

18.2. Insurance

:

NHS bodies are legally liable for the negligent acts and omissions of their employees. If participants are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the trial team this liability cover would apply.

18.3. Contractual arrangements

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

19. PUBLICATION POLICY

Results will be published in a peer reviewed journal. All trainees recruiting patients to the trial will be eligible for collaborative authorship.

Patients will be asked if they would like to receive results from the trial and if so, to provide contact details. A lay summary of findings will be disseminated to all patients who have indicated their interest.

20. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable

21. ARCHIVING

CRFs will be retained for 5 years following the end of recruitment. The anonymised data in the database will be retained indefinitely.

22. REFERENCES

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23. APPENDIX A: SCHEDULE OF PROCEDURES

Procedures	**Visits**				
	Visit timing				
	Screening	**Baseline**	**30 Day Follow up**	**1 Year Follow up**	**3 Year Follow up**
Identify potential participant	X				
Eligibility checks	X				
Approach participant		X			
Take informed consent		X			
CRF/eCRF completion		X	X	X	X
Follow up phone call			X	X	X

24. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
AM01	1.3	12/10/2022	Amy Lord	Addition of Schedule of Procedures

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC / MHRA / HRA submission.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, HRA (where required) or MHRA.