CLINICAL TRIAL PROTOCOL

PROTOCOL TITLE:
A randomised controlled trial comparing conventional open haemorrhoidectomy and laser haemorrhoidoplasty in the treatment of symptomatic haemorrhoids: COHLAH trial

PROTOCOL NUMBER:
CIRB: 2019/2930
Clinicaltrials.gov ID:

PROTOCOL VERSION: 2
PROTOCOL DATE: 07/03/2020

PRINCIPAL INVESTIGATOR:
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PROTOCOL SIGNATURE PAGE

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Sponsor Name:
NA

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: Foo Fung Joon_____

Principal Investigator Signature: _____

Date: _____

1 BACKGROUND AND RATIONALE

1.1 General Introduction

Haemorrhoids or piles are the most common colorectal condition in the local population. Patients often present with bleeding with bowel movement or anal discomfort, both of which causes significant anxiety and stress. For symptomatic sizeable piles, the treatment of choice still remains the conventional open excision (COH). However, this technique carries with it a significant risk of bleeding and pain immediately after the operation, leading to some period of discomfort for the patients. The laser haemorrhoidoplasty procedure (LAH) has been shown in preliminary studies to have less pain, and less complications compared to COH. This study aims to directly compare these two techniques in a local Asian population.

1.2 Rationale and Justification for the Study

We would be conducting a single-centre RCT simultaneously comparing the conventional open Milligan-Morgan haemorrhoidectomy (COH) and the laser haemorrhoidoplasty procedure (LAH) for the treatment of symptomatic grade ll-lV haemorrhoids. Primary outcomes will be post-operative pain while secondary outcomes include post-operative bleeding, readmission and/or reoperations, haemorrhoid-related quality of life (QoL) results and recurrence of symptoms up to a year post procedure.

1.2.1 Rationale for the Study Purpose

Treatment of haemorrhoids have long been associated with significant postoperative pain as well as laden with complications, including bleeding and pelvic sepsis, which usually results in patients' distress and readmission back to hospital. The open Milligan Morgan technique has long been regarded as the gold standard treatment for non-circumferential grade ll-IV haemorrhoids.

Newer techniques, including doppler haemorrhoidal dearterialization, has yield mixed results with a high recurrence rate.

Laser haemorrhoidoplasty has recently been studied and have shown promising results which has addressed the problems of the open Milligan-Morgan technique. These preliminary studies have shown a significant decrease in post-operative pain scores, less bleeding risk. There have yet to be any well-designed randomised controlled trial (RCT) looking into the longer-term outcomes of this technique.

1.2.2 Rationale for Doses Selected

NA

1.2.3 Rationale for Study Population

Patients would be recruited if they are:

a. between 21-70 years old
b. presents with symptomatic haemorrhoids as evident from clinical assessment
c. never had any haemorrhoid-related operations performed on them before
d. fit for general anaesthesia

e. able to give informed consent
f. willing to be randomized
g. willing to fill in post-operative questionnaires and be compliant to follow up

We will be excluding individuals who:
a. Are pregnant
b. Are prisoners
c. Intellectually, mentally or emotionally deemed not able to provide an informed consent and/or are unable to fill up the post-procedure questionnaires/VAS score
d. Have had previous haemorrhoid procedural treatment before (except Rubber Band Ligation)
e. Declined endoscopic evaluation
f. Are on anti-platelets and/or anti-coagulation
g. Have history of thrombophilia
h. Are on steriods
i. Have haemorrhoids which are incidentally found on endoscopy/clinical examination but are asymptomatic from it

1.2.4 Rationale for Study Design

We would be conducting a single-centre RCT simultaneously comparing the conventional open Milligan-Morgan haemorrhoidectomy (COH) and the laser haemorrhoidoplasty procedure (LAH) for the treatment of symptomatic grade ll-lV haemorrhoids. Primary outcomes will be post-operative pain while secondary outcomes include post-operative bleeding, readmission and/or reoperations, haemorrhoid-related quality of life (QoL) results and recurrence of symptoms up to a year post procedure.

This would allow us to study this cohort prospectively while comparing the short- and long-term outcomes of both techniques in parallel.

2 HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

The study team hypothesize that LAH has significantly less pain and bleeding and better QoL scores at 1- and 3-months post-operatively.

2.2 Primary Objectives

Daily visual analogue pain scale (VAS) in the first 10 days after surgery.

2.3 Secondary Objectives

- Operative duration
- Incidence of post-operative bleeding
- Incidence of readmission to haemorrhoidectomy/haemorrhoidoplasty related symptoms/condition (pain/pelvic symptoms/bleeding)
- Procedure-related complications (thrombosis, fistulation, incontinence, stenosis)
- Incidence and timing of recurrence of haemorrhoid-related symptoms
- Haemorrhoid-specific QoL questionnaire (Haemorrhoid Severity Score)

2.4 Potential Risks and Benefits:

2.4.1 Potential Risks

Risk of the participation in the trial include:
- Breach of patient confidentiality and personal data

Risk of General Anaesthesia for both procedures is in keeping with that of those patients not involved in the study. These includes but not limited to:
- Major adverse cardiac events (MACE)
- Cerebral vascular accidents (stroke)
- Barotrauma
- Damage or loss of dentition

Risk of Operation:
a. Conventional open haemorrhoidectomy (COH):
    i. Bleeding
    ii. Anal sphincter injury which may lead to fecal incontinence
    iii. Anal stenosis
    iv. Pelvic sepsis
    v. Recurrence of haemorrhoids
b. Laser haemorrhoidoplasty procedure (LAH):
    i. Bleeding
    ii. Thrombosis
    iii. Anal sphincter injury which may lead to fecal incontinence
    iv. Pelvic sepsis
    v. Bowel injury which may necessitate emergency surgery and/or stoma creation
    vi. Intestinal obstruction which may necessitate stoma creation

2.4.2 Potential Benefits

The benefits of participation in this trial is that patients will be closely monitored post procedure for their pain and symptoms and will receive a phone calls outside the regular follow up period, up to a year post-procedure, to follow up on their haemorrhoid-related symptoms.

They will also potentially may receive a procedure that could potentially cause less pain and have a lower risk of post-operative bleeding.

3 STUDY POPULATION

3.1 List the Number and Nature of Subjects to be Enrolled

Based on previous studies, as well as unpublished results from surgeons who have performed LAH around the South East Asian region, we are expecting 50% of the patients in the COH arm to have a VAS score of more than 7.5. We expect to see 25% patients in the LAH arm having a VAS score of more than 7.5.

With a power of 80%, chance of type 1 error (alpha) less than 5% and accounting for 10% of loss to follow up rate, the sample size required for the study to be adequate powered is having 64 patients in

each arm (N=128).

3.2 Criteria for Recruitment and Recruitment Process

Patients who are seen in the specialist outpatient clinics (SOC) or who are admitted for haemorrhoid-related symptoms/complications will be evaluated by one of the PI/co-PIs. All of them would need to have the usual clinical and endoscopic assessment of the colon to ascertain that the haemorrhoids are the only cause of their symptoms. They also should not have previous operation for haemorrhoids, excluding rubber band ligations. Only after the above would they be eligible for recruitment into the study.

3.3 Inclusion Criteria

a. between 21-70 years old
b. presents with symptomatic haemorrhoids as evident from clinical assessment
c. never had any haemorrhoid-related operations performed on them before
d. fit for general anaesthesia
e. able to give informed consent
f. willing to be randomized
g. willing to fill in post-operative questionnaires and be compliant to follow up

3.4 Exclusion Criteria

a. Are pregnant
b. Are prisoners
c. Intellectually, mentally or emotionally deemed not able to provide an informed consent and/or are unable to fill up the post-procedure questionnaires/VAS score
d. Have had previous haemorrhoid procedural treatment before (except Rubber Band Ligation)
e. Declined endoscopic evaluation
f. Are on anti-platelets and/or anti-coagulation
g. Have history of thrombophilia
h. Are on steriods
i. Have haemorrhoids which are incidentally found on endoscopy/clinical examination but are asymptomatic from it

3.5 Subject Replacement

Subjects who drop out are accounted for in the sample size calculation and will not be replaced.

4 STUDY DESIGN

This is a single-center, double-blind randomized controlled trial to be conducted in Sengkang General Hospital.

All patients presenting to the clinic or admitted for symptomatic haemorrhoids would be assessed for recruitment.

Figure 1 shows the enrolment process of the study population in the trial. Patients will be seen in the

clinic or in the wards for symptomatic haemorrhoids. All these patients would be approached and be introduced to this study but not recruited yet.

Patients older than 40 years-old with no recent colonoscopy (within 5 years) would need to have a colonoscopic evaluation of the colon after the index admission/clinic visit.

Those younger than 40 would be advised to have a rigid sigmoidoscopy on the day of the operation during the examination under anaesthesia. Only after agreement to the above, the patient would be recruited into the study. They would then be educated on the peri-operative questionnaire separately by a research administrator after recruitment into the trial.

The peri-operative package is split into pre- and post-operative components and will include basic demographics, baseline haemorrhoid-specific QoL questionnaires[1-3], VAS scales for POD0-10 and details of the intraoperative procedure and intraoperative description of the haemorrhoids.

Patients who fit the inclusion and exclusion criteria would be recruited into the study. We will perform a 1:1, block-of-4 randomization using a computer-generated programme performed by an independent research administrator who is not part of the surgical team.

They will be allocated only after they are examined under anaesthesia. Allocation is provided in a concealed opaque envelope that is provided by the research administrator on the day of the operation. Thus, the patient is blinded to the procedure. There will also be no cross-over from one study arm to another.

Potential Difficulties and Alternative Approaches to achieve the aims:

Difficulty of recruitment of patients into the trial may be potentially present especially for a procedure that is new in Singapore. Patient counselling and explanation of the procedure would be important and offering a short video clip of the procedure may be helpful. The procedurists/co-investigators of the study team would also be trained by a regional practitioner of the technique before the initiation of the trial to ensure proficiency for reassurance.

Accurately assessing the pain scores and QoL measures may be subjective and laden with the potential of recall and interviewer biases. In order to mitigate this, the patients will be instructed on the proper way of performing a VAS assessment of their pain before the procedure when they are not bothered by any sort of discomfort from the procedure. In addition, our research administrators would be briefed and trained to conduct an objective QoL assessment prior to the initiation of the trial.

4.1 Randomisation and Blinding

Patients who fit the inclusion and exclusion criteria would be recruited into the study. We will perform a 1:1, block-of-4 randomisation using a computer-generated programme performed by an independent research administrator who is not part of the surgical team.

They will be allocated only after they are examined under anaesthesia. Allocation is provided in a concealed opaque enveloped that is provided by the research administrator on the day of the operation. Thus, the patient is blinded to the procedure. There will also be no cross-over from one study arm to another.

An independent research administrator, not part of the randomisation process, will also contact the patient 3 months and 1 year after the procedure as mentioned above.

4.2 Contraception and Pregnancy Testing

For females of childbearing age included in the trial, they will be asked whether they are pregnant and for their last menstrual period. They will be offered a UPT to test for pregnancy during recruitment into the trial but there are no requirements to perform the test.

4.3 Study Visits and Procedures

4.3.1 Screening Visits and Procedures

Patients will be seen in the clinic or in the wards for symptomatic haemorrhoids. All these patients would be approached and be introduced to this study but not recruited yet.

Figure 2 illustrates the visits commitment throughout the study process. After the completion of surgery, patients typically would already have a follow up appointment at 4-6 weeks after the procedure. The clinician will assess the patients progress and examining them for any complications. If their recovery is smooth, most of these patients would be discharged from follow up. During the same setting, the research administrators would collect back the peri-operative package from the patient.

Research administrators would then conduct a phone interview with the patients at 3-month and 1-year after surgery to perform the QoL survey and also looking out for late-onset complications and recurrence of symptoms. If present, they will be offered to have an appointment booked with their primary surgeon. Patients would be informed of the allocation at the clinic review at 4-6 weeks. As none of the visits are outside of normal practice, no remuneration is required.

4.3.2 Study Visits and Procedures

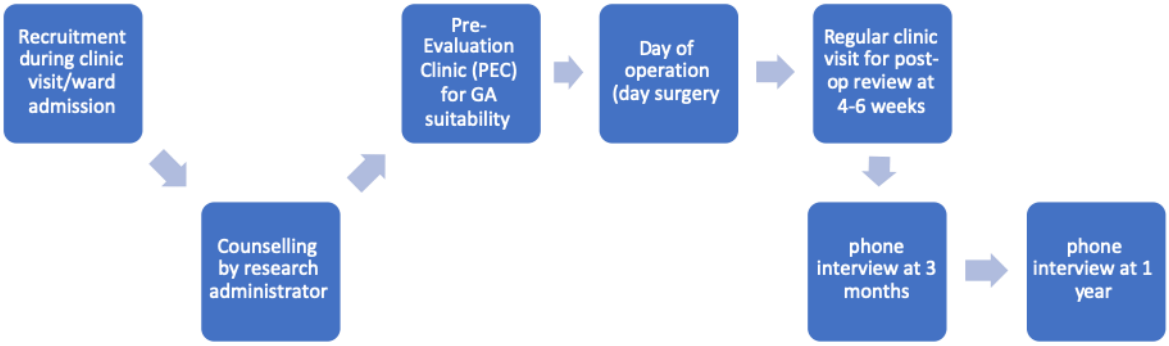

Figure 2. Timeline of participation. Those in the 1st row are regarded as within normal clinical

practice. Those in the 2nd row are regarded as outside of normal clinical practice.

4.3.3 Final Study Visit:

The final physical study visit for individuals without complications/recurrence will be at 4-6 weeks post operatively. As none of the visits are outside of normal practice, no remuneration is required.

4.3.4 Post Study Follow up and Procedures

The phone interview at 3-months and 1-year post-operatively would not be regarded as a visit. However, if the patients highlight symptoms suggestive of a complication or recurrence of symptoms, they would be offered to return for an evaluation by a colorectal specialist. It would then be dependent on the patient if they would like to take up this offer.

4.4 Discontinuation/Withdrawal

4.4.1 Discontinuation Criteria

Discontinuation criteria of the trial would either be due to:

a. Safety issues of LAH techniques
b. Significant number and severity of the complications
c. Statistically overwhelming evidence that 1 method is superior over the other

4.4.2 Discontinuation Visit and Procedures

Upon voluntary withdrawal, participants would resume regular follow up as per clinical requirement. These patients would not receive a phone interview at 3-months and a year after the procedure. These patients would also be given an open date in the clinic to allow them a year in duration to return to the clinic for evaluation if there are recurrence of symptoms or development of a previously unrecognised complication from either of the procedures.

5 TRIAL MATERIALS

5.1 Trial Product (s)

NA

5.2 Storage and Drug Accountability

NA

6 TREATMENT

6.1 Rationale for Selection of Dose

NA

6.2 Study Drug Formulations

NA

6.3 Study Drug Administration

NA.

6.4 Specific Restrictions / Requirements

NA

6.5 Blinding

Patients will be allocated only after they are examined under anaesthesia. Allocation is provided in a concealed opaque enveloped that is provided by the research administrator on the day of the operation. Thus, the patient is blinded to the procedure. There will also be no cross-over from one study arm to another.

An independent research administrator would conduct a phone interview with the patients at 3-month and 1-year after surgery to perform the QoL survey and also looking out for late-onset complications and recurrence of symptoms. If present, they will be offered to have an appointment booked with their primary surgeon. Patients would be informed of the allocation at the clinic review at 4-6 weeks.

6.6 Concomitant therapy

NA

7 SAFETY MEASUREMENTS

7.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

7.2 Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to CIRB

Only related SAEs (definitely/ probably/ possibly) will be reported to CIRB. Related means there is a reasonable possibility that the event may have been caused by participation in the clinical trial. Please refer to the CIRB website for more information on Reporting Requirement and Timeline for Serious Adverse Events.

The investigator is responsible for informing CIRB after first knowledge that the case qualifies for reporting. Follow-up information will be actively sought and submitted as it becomes available.

Related AEs will not be reported to CIRB. However, the investigator is responsible to keep record of such AEs cases at the Study Site File.

7.3 Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to the Health Science Authority (HSA)

All SAEs that are unexpected and related to the study drug will be reported to HSA. Please refer to the HSA website for more information on Safety Reporting Requirements for Clinical Trials.

7.4 Safety Monitoring Plan

The Data Safety Monitoring Plan (DSMP) for this study can be divided into individual events and collated events.

Every individual complication will be evaluated by all members of the study team immediately after the event has occurred. The study team would review the case and its proceedings to determine whether the event was a direct result of the procedure or its technique, and whether this could have been prevented. The complication would also be scored for its severity based on the Clavien-Dindo Classification of Complications. If there is a severe complication, or if the complication is a direct result of the procedure or its technique, a technical pause would be called for in order to re-clarify the technical aspects as well as processes to avoid a repeat complication before the trial is resumed.

Interim analysis would also be carried out in a timely fashion (after 50% and 75% of the required sample size has been randomised. This would allow statistically significant differences in the outcome of the procedures to be identified. If one arm is grossly different from the other, the study team would convene to evaluate whether this outcome difference is regarded as a safety hazard to subsequent patients. If so, the trial would be halted or terminated prematurely.

7.5 Complaint Handling

All complaints will be handled in accordance with the Sengkang General Hospital Service Quality Department policy and aid. They will provide advice on the management strategies in such instances. If the complaint is related to a safety issue, the above (7.4) would apply.

8 DATA ANALYSIS

8.1 Data Quality Assurance

All data collected is prospective and the study team members and research administrators will convene to go through the peri-operative package, as well as the variables which are going to be

collected for the study. This will help standardise the method of assessment and finetune the method of administering the phone-based questionnaire.

All the study co-investigators would have also completed the CITI-training workshop and would be cognisant of the need for uniformity in terms of assessment of intraoperative and post-operative variables.

8.2 Data Entry and Storage

Data will be entered into a data collection sheet by the study team or on the peri-operative package by the patient. All these data will be scanned in and images stored in a dedicated encrypted external hard-drive for archiving purposes. Hard-copy forms will be stored in a ring-file that is kept under lock-and-key by the PI. The data on the 2 data collection forms will be separately entered into an password-protected excel document, not having any patient identifiers, and stored in the dedicated encrypted hard-drive in a separate folder for the purposes of data analysis.

Only the study administrators and study co-investigators will have access rights for data entry and analysis though the PI.

9 SAMPLE SIZE AND STATISTICAL METHODS

9.1 Determination of Sample Size

Based on previous studies, as well as unpublished results from surgeons who have performed LAH around the South East Asian region, we are expecting 50% of the patients in the COH arm to have a VAS score of more than 7.5. We expect to see 25% patients in the LAH arm having a VAS score of more than 7.5.

With a power of 80%, chance of type 1 error (alpha) less than 5% and accounting for 10% of loss to follow up rate, the sample size required for the study to be adequate powered is having 64 patients in each arm (N=128).

9.2 Statistical and Analytical Plans

a. General Considerations

All analysis would be conducted with the assistance or validation of a biostatistician. SPSS or Strata would be used to conduct the analysis. All categorical data would be analysed using the Fisher Exact Test. All continuous variables would be analysed using the Mann-Whitney U test. The level of statistical significance would be set as $p<0.05$.

b. Safety Analyses

Every individual complication will be evaluated by all members of the study team immediately after the event has occurred. The study team would review the case and its proceedings to determine whether the event was a direct result of the procedure or its technique, and whether this could have been prevented. The complication would also be scored for its severity based on the Clavien-Dindo Classification of Complications. If there is a severe complication, or if the complication is a direct result of the procedure or its technique, a technical pause would be called for in order to re-clarify the technical aspects as well as processes to avoid a repeat complication before the trial is resumed.

c. Interim Analyses

Interim analysis would also be carried out in a timely fashion (after 50% and 75% of the required sample size has been randomised. This would allow statistically significant differences in the outcome of the procedures to be identified. If one arm is grossly different from the other, the study team would convene to evaluate whether this outcome difference is regarded as a safety hazard to subsequent patients. If so, the trial would be halted or terminated prematurely.

d. Describe the types of statistical interim analyses, including their timing.

Interim analysis would also be carried out in a timely fashion (after 50% and 75% of the required sample size has been randomised. This would allow statistically significant differences in the outcome of the procedures to be identified. If one arm is grossly different from the other, the study team would convene to evaluate whether this outcome difference is regarded as a safety hazard to subsequent patients. If so, the trial would be halted or terminated prematurely.

10 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data and document.

11 QUALITY CONTROL AND QUALITY ASSURANCE

All data collected is prospective and the study team members and research administrators will convene to go through the peri-operative package, as well as the variables which are going to be collected for the study. This will help standardise the method of assessment and finetune the method of administering the phone-based questionnaire.

All the study co-investigators would have also completed the CITI-training workshop and would be cognisant of the need for uniformity in terms of assessment of intraoperative and post-operative variables.

12 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Clinical Trial Protocol, including the final version of the Participant Information Sheet and Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB) and regulatory approval from Health Sciences Authority (HSA), prior to enrolment of any patient into the study.

The principle investigator is responsible for informing the CIRB and HSA of any amendments to the

protocol or other study-related documents, as per local requirement.

12.1 Informed Consent

Upon satisfaction of the inclusion and exclusion criteria, the primary surgeon (co-investigator) would introduce the trial to the patient in their preferred language either themselves or through a proxy. Upon interest, the research administrators will provide further details of the trial to the patient in a separate room in the clinic/wards. The patient will have ample time to read the patient information form (in the language that the patient can read) and consider enrolment into the trial. After the decision to participate, he/she would be invited to sign on the recruitment consent forms.

The research administrator and co-investigators would have to document the consult and the risks that of participation and of the techniques that were explained. In obtaining and documenting informed consent, the investigator should comply with the GCP guidelines and to the ethical principles that have their origin in the Declaration of Helsinki.

12.2 Confidentiality of Data and Patient Records

Data will be entered into a data collection sheet by the study team or on the peri-operative package by the patient. All these data will be scanned in and images stored in a dedicated encrypted external hard-drive for archiving purposes. Hard-copy forms will be stored in a ring-file that is kept under lock-and-key by the PI. The data on the 2 data collection forms will be separately entered into an password-protected excel document, not having any patient identifiers, and stored in the dedicated encrypted hard-drive in a separate folder for the purposes of data analysis.

Only the study administrators and study co-investigators will have access rights for data entry and analysis though the PI.

13 PUBLICATIONS

The study team owns the data and analysis. The manuscript would be written by a member of the study team and approved by the PI before presentation at an international/regional and local scientific conference.

The details of analysis would be published in a peer reviewed journal that is also registered in at least MEDLINE.

14 RETENTION OF TRIAL DOCUMENTS

Records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.) as well as IRB records and other regulatory documentation should be retained by the PI in a secure storage facility. The records should be accessible for inspection and copying by authorized authorities.

All these data will be scanned in and images stored in a dedicated encrypted external hard-drive for archiving purposes. Hard-copy forms will be stored in a ring-file that is kept under lock-and-key by the PI. The data on the 2 data collection forms will be separately entered into an password-protected excel document, not having any patient identifiers, and stored in the

dedicated encrypted hard-drive in a separate folder for the purposes of data analysis.

Only the study administrators and study co-investigators will have access rights for data entry and analysis though the PI.

15 FUNDING and INSURANCE

En-Life has agreed to sponsor 40 laser probes to initiate the study. Grants will be applied to cover the remaining cost of the other 14 laser probes. En-life has agreed to loan the Laser Generator for free.
Singhealth research indemnity insurance – for utility to cover for the management of any complications during the trial

List of Attachments

Appendix 1 Study Schedule

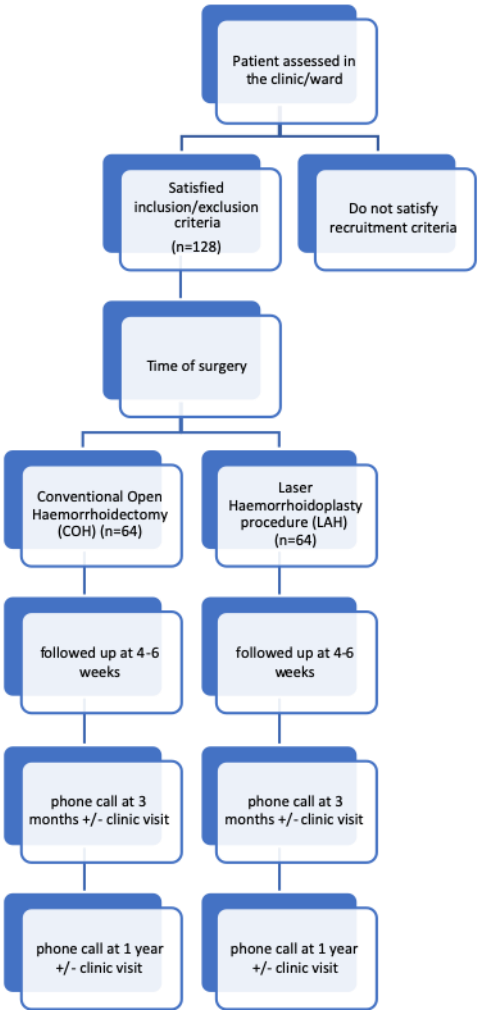

Figure 1. CONSORT diagram of patient involvement in COHLAH trial

Appendix 2 Post-procedure Questionnaire Package

(Attached separately)