RIPASA Treatment Without Operation (TWO) – A Non-Inferiority Prospective Randomised Clinical Controlled Trial of Antibiotic Non-Operative Management Strategy versus Surgery Management Strategy for Early Uncomplicated Acute Appendicitis.

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ABSTRACT

Introduction: The role of an antibiotic non-operative management strategy (AMS) in managing early-uncomplicated acute appendicitis (EUAA) is still debatable and most meta-analysis have not shown significant benefit of AMS over SMS, partly due to variable treatment efficacy, high recurrence rate within a year and a lack of agreement of whom would constitute a group of EUAA. This research proposal provides the framework to investigate the role of AMS versus Surgical Management Strategy (SMS) in patients with clinical diagnosis of EUAA. The primary aim of the study is to compare treatment efficacy of both treatment arms.

Design: A single centre, prospective non-inferiority Randomised Controlled Clinical Trial comparing AMS with SMS in the main tertiary referring hospital in Brunei Darussalam.

Participants and Interventions: Patients aged more than 12years old with a clinical diagnosis of EUAA with RIPASA score from 7.5-11.5, will be invited to participate in the trial. Once consented, participants will be randomised to either AMS or SMS using a computer-based randomisation allocation programme. Recruitment is planned to start in October 2017 and will recruit 228 patients over a 2 year period. Patients randomised to the AMS arm will receive intravenous (IV) amikacin 1.5mg/kg/day given in 2 doses for 48 hours followed by oral ciprofloxacin 500mg twice daily (bd) for 5 days. Patients randomised to SMS will receive standard antibiotics combination of IV cefuroxime 1.5g and metronidazole 500mg three times a day (tds) and surgery.

Outcomes: Primary outcome is treatment efficacy within 30 days in each arm and compliance with RIPASA guidelines. Secondary outcomes include length of stay, 30-days treatment related complications, recurrence rate from 1 month up to 1 year, treatment cost, defining effective RIPASA score range for AMS and medical sick leave days taken.

Analysis: Data analysis will be carried out based on intention-to-treat principle combine with per protocol analysis for non-inferiority of AMS arm. Non-inferiority margin is set based on FDA approved 50% reduction of treatment efficacy for AMS arm

Novelty and Significance: The novelty of this research study is that it is the only non-inferiority RCT comparing AMS with SMS that uses a clinical prediction rule (CPR) such as RIPASA Score for clinical diagnosis of EUAA. The significance of this research study is that it will complete the final and third part of the creation and validation of the RIPASA score as a CPR by assessing its impact on change behavior in managing patients with EUAA with AMS rather than SMS and hence improves patient outcomes by reducing unnecessary negative appendicectomy rate, complications related to undergoing emergency appendicectomy and ultimately reducing cost of managing acute appendicitis surgically.

Keywords: Appendicectomy, Antibiotic Management strategy, Clinical Prediction Rule, Early Uncomplicated Acute Appendicitis, RIPASA Score.

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INTRODUCTION

Acute appendicitis (AA) is a very common surgical emergencies. The life time prevalence of AA is approximately 1 in 7 with a reported incidence of 1.5-1.9 per 1000 in male and female population and is approximately 1.4 times greater in men than in women. [1,2]

Diagnosis of AA can be difficult to establish, particularly in the young, elderly and female of reproductive age where a host of other genitourinary and gynaecological inflammatory conditions can also present with signs and symptoms similar to AA.[3] Improving diagnostic accuracy through radiological investigations may lead to delay in appendicectomy and risks appendicular perforation and sepsis, which increases morbidity and mortality.[4] Similarly early appendicectomy in favour of diagnostic accuracy may lead to an increase in unnecessary surgery and reported negative appendicectomy rate is 20-40%.[5]

Several clinical prediction rules (CPR) such as the Alvarado, modified Alvarado or RIPASA scores have been developed to aid in the rapid and accurate diagnosis of AA.[5-10] The RIPASA score has been well validated across the world with sensitivity, specificity and diagnostic accuracy of 98%, 82% and 92% respectively and is significantly better at diagnosing AA than Alvarado score and with significantly reduced negative appendicectomy rate.[9–33]

The standard management of AA has remained unchallenged since it was first introduced in the late 19th century, largely because of the belief that if left untreated surgically, acute uncomplicated appendicitis will progress to perforation and peritonitis with increased morbidity and mortality.[34] However since 1990s, antibiotic non-operative therapy has been increasingly proposed as an alternative management strategy for early uncomplicated acute appendicitis (EUAA), driven by evidence from the routine conservative management of diverticulitis (with or without perforations) with antibiotics. [35]

However, despite multiple randomised controlled trials (RCT) and meta-analysis, the role of antibiotics in the management of EUAA remains controversial. [36–48] Earlier RCT have reported treatment efficacy for antibiotic non-operative management strategy (AMS) of EUAA as high as 88-91% with recurrence rate of acute appendicitis at 13-14% at 1 year follow up, which supported the AMS.[37,38] However in one RCT, the high treatment efficacy of 91% was based on per protocol analysis which is generally not recommended but based on intention-to-treat analysis, the efficacy for AMS dropped to 48%.[38] More recent RCTs comparing AMS versus early surgery management strategy (SMS) have not confirmed the non-inferiority status of the former strategy.[39-41] These later findings have also been supported by multiple recent meta-analysis.[42–48]

Thus this study is designed with the primary objectives of investigating the efficacy of AMS compare to SMS in patients with a clinical diagnosis of EUAA and effectiveness of RIPASA score in guiding clinical management decisions.

METHODOLOGY

Trial Design

This study is designed as a single centre, non-inferiority, prospective randomised clinical controlled trial to compare 2 management strategies for suspected EUAA, AMS versus SMS, using RIPASA score to identify the group of patients with EUAA and to monitor progression of disease and guiding surgical decision based on the participants' RIPASA score.

Population and Study Setting

The study setting is based at the tertiary referral centre of the Department of General Surgery at Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital. All staffs of the Department

of General Surgery and Accident & Emergency Department at RIPAS Hospital will be brief of the trial design and purpose.

Eligibility Criteria

All patients presenting to Accident & Emergency Department at RIPAS Hospital, with right iliac fossa pain suspected of acute appendicitis,

Inclusion criteria

1. More than 12 years of age,
2. Clinical diagnosis of EUAA with confirmed RIPASA score of 7.5-11.5, by on-call surgeon

Exclusion criteria

1. 12 years of age or less,
2. RIPASA score 7 or less, or greater than 12,
3. Confirmed diagnosis of acute complicated appendicitis with perforation (based on ultrasound or CT investigation) or signs of generalised peritonitis.
4. Refusal to consent for study

Recruitment and Retention

Patients with right iliac fossa pain will be triaged and seen by the Casualty Officer on duty. RIPASA score will be derived. Patients with RIPASA score between 7.5-11.5 will be referred onto the on-call surgeon on duty for recruitment to the study. Antibiotics will be withheld until patients have been seen by the on-call surgeon and the RIPASA score has been confirmed to be between 7.5-11.5. The on-call surgeon will inform and explain to the patient and family of the study and a study information sheet will be provided to the patient and family. Upon written signed consent, patients will be randomised to either arms – AMS or SMS.

Allocation concealment

A variable block randomisation sequence stratified to two RIPASA score range, 7.5-9.5 and 10.0-11.5, will be used to randomly allocate participants to either AMS or SMS. Randomisation codes will be generated using computer generated variable random sequence. The block randomisation sequence will be contained within a programme specifically designed for randomisation allocation. Access to the programme is via secured Log-in, which can only be accessed by doctors from the Department of General Surgery, using individually provided username and password. The programme will screen all potential patients to ensure they satisfy the inclusion and exclusion criteria before accessing their randomisation allocation arm and code. Once the randomisation code and arm have been obtained, the on-call surgeon will inform the participants of their allocation.

Study Protocol

Upon allocation, the patient will then be admitted to surgical wards. Patients randomised to AMS arm will receive the allocated antibiotic treatment. (Figure 1 – Consort flow chart). Those randomised to SMS arm will receive the usual Departmental antibiotic policy of preoperative antibiotics prior to appendicectomy.

Patients randomised to AMS arm

For patients in the AMS arm, the RIPASA score will be repeated to monitor progression of the patient's condition after 24 hours. If RIPASA score remain stable or decreasing, the patient will continue on the allocated IV antibiotic treatment. If RIPASA score is increasing but remain below 11.5, the team looking after the patient can consider ordering further investigations such as ultrasound or CT scan to confirm the diagnosis based on the RIPASA score guidelines, but patient will continue at this point on the antibiotic. If the RIPASA score increases to above 12, the surgeon can consider appendicectomy as suggested by RIPASA score. Alternatively the surgeon can consider surgery for RIPASA score between 7.5 and 11.5 if there are clinical signs of perforation or generalised peritonism.

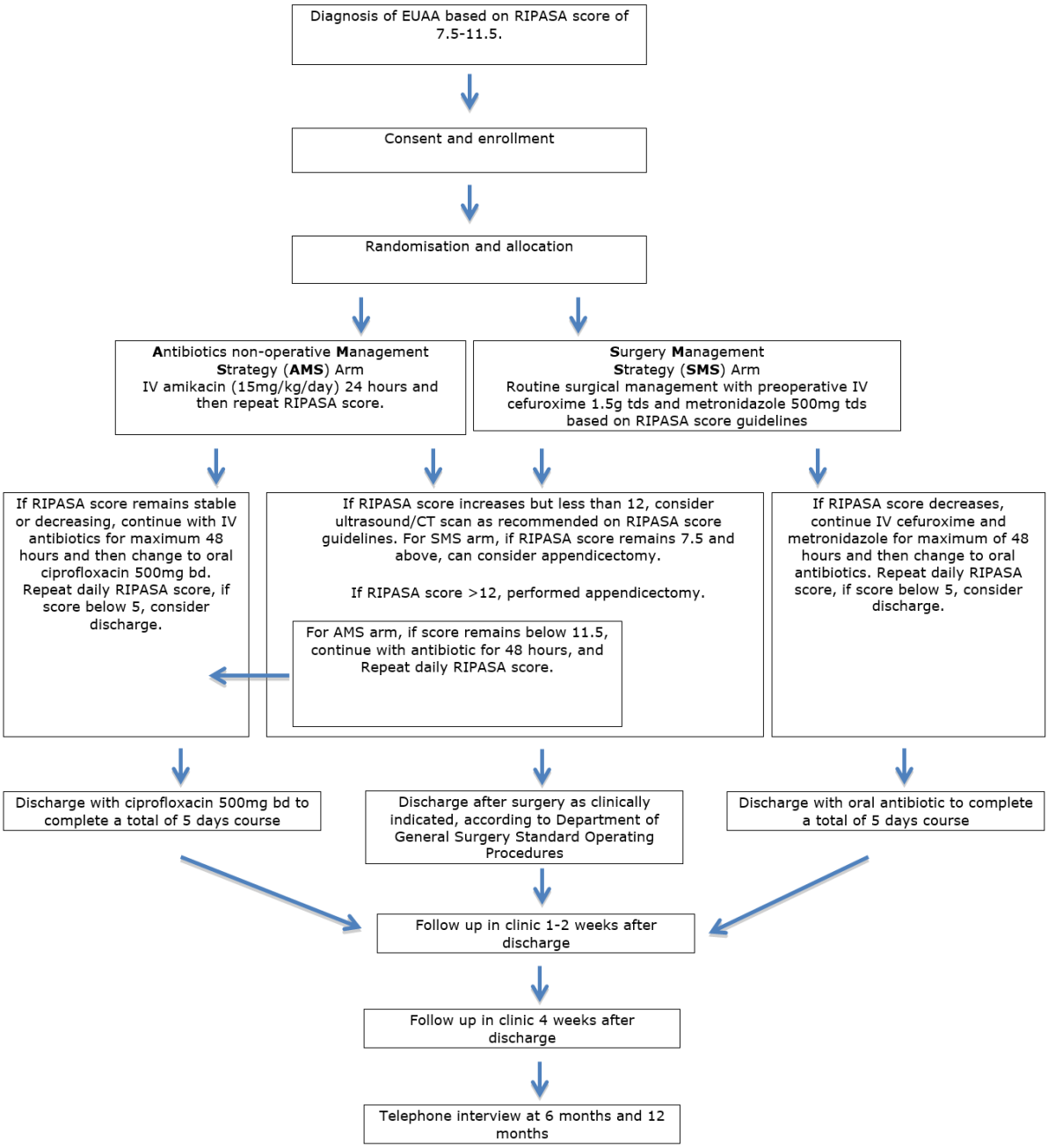

Figure 1: RIPASA TWO Non-Inferiority Prospective Randomised Clinical Controlled Trial study protocol consort diagram.

For patients in the AMS arm who have not cross over to surgery, they will continue with iv antibiotics for 48 hours and if symptoms improved with decreasing RIPASA score to below 7.5, the antibiotic will be changed to oral route and patient monitor. If RIPASA score goes below 5, patient can be considered for discharge and follow up in 1 week in clinic with oral antibiotic for 5 days.

Patients randomised to SMS arm

For patients randomised to SMS arm, the patients will receive the usual Departmental antibiotic policy as preoperative antibiotics prior to surgery. If patients are admitted during office hours or before 12 midnight, appendicectomy can be considered immediately. For admission after 12 midnight, the patients will remain on preoperative antibiotics and get review the

next morning with repeat RIPASA score. If RIPASA score is increasing but remain below 11.5, the team looking after the patient can consider ordering further investigations such as ultrasound or CT scan to confirm the diagnosis based on the RIPASA score guidelines, but patients will continue at this point on the antibiotic. Alternatively the surgeon can consider surgery if there are clinical signs of perforation or generalised peritonism. If the RIPASA score increases to above 12, the surgeon can consider appendicectomy as suggested by RIPASA score guidelines.

For patients in the SMS arm whose symptoms improved with decreasing RIPASA score to below 7.5, their antibiotic will be changed to oral route and patient monitor. If RIPASA score goes below 5, patient can be considered for discharge and follow up in 1 week in clinic with oral antibiotic for 5 days.

Antibiotic

Selection of the antibiotic of choice for the AMS arm is based on the microbial antibiotic sensitivity from pus swab taken for all appendicectomy specimens from previous year (2016: Figure 2). Microbiological data showed that the 3 commonest microbes were *Escherichia Coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*. Based on recommendation from the clinical microbiologist, IV Amikacin 15mg/Kg/day given in two divided doses per day for the first 48 hours and then converted to oral ciprofloxacin 500mg bd for 5 days will be the antibiotic regime for AMS arm.

A prospective registry for microbial antibiotic sensitivity of all appendicectomy specimens from the trial will be kept to monitor changes in antibiotic sensitivity. Based on data from this registry, the AMS antibiotic proposed can be changed as the trial progresses. Any changes propose will be discussed with the Data Safety Management Board (DSMB) and submitted to Medical and

				S %	I %	R %
Escherichia coli	39	Amikacin	37	94.872	2.5641	2.564
		Amoxy/Clavu Acic	28	71.795	15.385	10.26
		Ceftazidime	34	87.179	5.1282	7.692
		Cefepime	19	48.718	0	2.564
		Cefoperazone	31	79.487	5.1282	15.38
		Ciprofloxacin	30	76.923	0	23.08
		Ceftriaxone	33	84.615	2.5641	10.26
		Cefuroxime oral	20	51.282	28.205	10.26
		Cefuroxime parer	31	79.487	0	10.26
		Ertapenem	19	48.718	0	0
		Gentamicin	31	79.487	0	20.51
		Imipenem	39	100	0	0
		Meropenem	39	100	0	0
		Netilmicin	34	87.179	2.5641	0
		Piperacillin	11	28.205	2.5641	38.46
		Co-trimoxazole	18	46.154	0	46.15
		Piperacillin/Tazob	12	30.769	0	0
		Ampicilin/Sulbact	12	30.769	28.205	15.38
Pseudomonas aerugi	9	Amikacin	8	88	0	0
		Ceftazidime	9	100	0	0
		Ciprofloxacin	9	100	0	0
		Gentamicin	9	100	0	0
		Imipenem	9	100	0	0
		Meropenem	9	100	0	0
		Netilmicin	7	77	0	0
		Piperacillin/Tazob	3	100	0	0
Klebsiella pneumonia	4	Amikacin	4	100	0	0
		Amoxy/Clavu Acic	4	100	0	0
		Ceftazidime	4	100	0	0
		Cefoperazone	4	100	0	0
		Ciprofloxacin	4	100	0	0
		Ceftriaxone	4	100	0	0
		Cefuroxime oral	3	75	25	0
		Cefuroxime parer	4	100	0	0
		Gentamicin	4	100	0	0
		Imipenem	4	100	0	0
		Meropenem	4	100	0	0
		Netilmicin	3	75	0	0
		Piperacillin	3	75	0	25

Figure 2: Antibiotic sensitivity for common microbials isolated from pus swab taken at time of appendicectomy for year 2016.

(MHREC) for approval.

Outcomes

The primary outcomes are treatment efficacy (Rate of treatment success) between the two management strategies, AMS versus SMS within 30 days of randomisation and effectiveness of RIPASA score in guiding clinical management decisions.

Treatment efficacy in the AMS group is defined as successful treatment of EUAA with antibiotics from time of randomisation till discharge and follow-up to 30 days without incurring surgery and cases of negative appendicectomy if surgery is performed. Treatment failure for AMS is defined as cases where surgery is carried out despite antibiotic therapy from time of admission or surgery performed at anytime up to 30 days follow up after discharge with histology confirmation of acute, suppurative or gangrenous or perforated appendicitis.

Treatment efficacy for SMS group is defined as all cases of confirmed acute, suppurative or gangrenous or perforated appendicitis on histology specimen. Treatment fail-

ure for SMS group is defined as cases of negative appendicectomy and cases successfully treated with antibiotics and discharged and follow-up to 30 days without incurring surgery. Negative appendicectomy is defined as an unnecessary operation performed where the outcome is one of normal appendix or periappendicitis on histological examination.

Effectiveness of RIPASA score in guiding clinical management decisions will be based on compliance and adherence to RIPASA score guidelines. Non-compliance or non-adherence is defined as action performed outside the RIPASA score guidelines, for example, not performing appendicectomy for cases with RIPASA score >12 or performing surgery when RIPASA score is less than 7.5 and this will be considered as loss of effectiveness.

Secondary outcome measures are length of hospital stay, 30 days treatment related complications (For AMS group: appendiceal perforation, peritonitis, abscess or phlegmon formation and for SMS group: surgical site infection, bowel obstruction secondary to adhesions or sepsis), recurrence rate* at any time of follow up > 1 month, and up to 12 months, number of medical sick leave days taken related to condition of study, defining a group with RIPASA score range where AMS is most beneficial and treatment cost in US dollar, calculated at completion of study and follow up at 1-year post randomisation, which will include all radiological examinations carried out during the study period related to the condition of study.

Data collection and management

All clinical details, RIPASA score, daily entry, surgery details, discharge details, complications and outcomes will be entered into Bru-HIMS patient electronic management system and can be retrieved later for analysis. Data entry into Bru-HIMS will be carried out daily by the attending surgeon and his/her team and checked for completion and accuracy by one of the investigators (or research assistant if this is available). Data will be entered into an Access database/Excel for analysis at the end of the study.

Bru-HIMs patient electronic management system can only be accessed onsite via intranet and is protected by firewall. All computers are protected by antivirus software. The Access database/Excel file will be kept in a laptop and locked in a secure office at the end of everyday by the principal investigator.

Statistical methods

Sample size calculation

Based on our previous study, the expected negative appendicectomy rate based on the RIPASA score was 14.7%, giving surgical treatment efficacy of 85.3%.[10] Hence using the FDA approved non-inferiority margin of 50% reduction in efficacy, we would accept an approximate 7.3% reduction of treatment efficacy for the AMS, thus the non-inferiority margin will be set at 22% and a treatment failure between 14.7-22% will be considered as confirmation of non-inferiority.[49] A treatment failure of less than 14% will be considered as superiority. Thus based on a difference in treatment efficacy rate of 7.3% (22% vs 14.7%), with a sample size powered at 80% at 5% significance, the sample size needed to show non-inferiority is 91 patients in each group.[50] Assuming a dropout rate of 25%, we plan to recruit a total of 228 patients, based on a 1:1 recruitment; each arm will have 114 patients.

On completion of the study, the main analysis will be carried out based on intention-to-treat principle but per-protocol analysis will also be carried out to ensure robustness of the results and that substandard treatment has not been provided to the SMS arm. The

*(Recurrence is defined as readmission for suspected AA or proven AA on histological specimen following surgery for AMS group after discharge. Recurrence will not be categorised as treatment failure in the AMS group since the appendix has not been surgically removed and patients in this group although at a higher rate of recurrence of about 13-14% at 1-year follow up, does not represent failure of treatment for the initial episode of AA.[47,48])

intention-to-treat analysis will include all randomised patients with outcome results, excluding those lost to follow-up and those who have withdrew from the study and have prespecified that they do not wish for their data to be used.

All statistical analysis will be performed using SPSS statistical programme. Categorical data will be presented using frequencies and percentages. Continuous data will be presented as mean ± SD. Statistical analysis for categorical data will be carried out using Chi Square exact test. Differences between groups with normally distributed variables will be tested using independent sample t -test. Variables with no normal distribution will be tested using Mann-Whitney test. Non-inferiority for AMS will be tested using one-sided Wald tests with an α level of 0.05.

Duration of Study

Based on our previous study, we recruited 200 consecutive patients over 8 months.[10] But only 192 were included in the study final analysis. Out of these 192 patients, 96 had RIPASA score from 7.5-11.5, which accounted for over 50% of the study sample size of 192. Thus for a sample size of 228, we expect to recruit the required sample size over a period of 19 months. Hence the study will be expected to complete within 2 years.

Funding

This study will be carried out by the Department of General Surgery and in collaboration with Accident and Emergency Department. Deputy Head of Department of Accident and Emergency Department as Co-Investigator for this trial, will oversee the recruitment process in Accident and Emergency Department. The Head of Department of General Surgery as Co -Investigator, will oversee the recruitment and allocation of treatment group when patients are admitted to General Surgical Wards.

Care and subsequent follow up provided to participants will be part of the clinical care package provided by the Department of General Surgery which should not be any different from the general care provided to other patients. The Department of General Surgery has been given permission to conduct this trial by the RIPAS Hospital Administrative Head. Hence cost of antibiotics and any investigations will be covered by the hospital as routine cost of managing patients admitted with AA in general.

No other sources of funding from any external parties or organisations will be sought for, to conduct this study.

RIPASA Score Registry

Participants who have not consented to be recruited for the trial or those who withdraw from the trial after randomisation and are not analyse in the trial, as well as those who are excluded from the trial (see exclusion criteria) will be entered into the RIPASA Score Registry. Data from this registry can be analysed at a later date to obtained real world experience of RIPASA score practice as well as comparison of the two arms.

Interim Analysis

Interim analysis will be conducted at 2 time points. For changes to antimicrobial sensitivity, the interim analysis will be conducted at every 6 monthly and any changes will be discussed with the DSMB for propose changes to the antibiotic regime. Proposed changes and all interim reports will be submitted to MHREC for approval. The main study interim analysis will be conducted at 1-year post recruitment to assess safety efficacy of the trial. This is to ensure that we are not getting more cases of acute complicated appendicitis (ACA) in the AMS arm, which is set at a cutoff of 30%. This 30% cutoff is chosen as it would mean a treatment efficacy difference of 15% from current surgical management based on the RIPASA score of 14.7% failure rate, suggesting that the AMS arm is no better than place-

bo.

Ethical Consideration

Participants' Rights, Consent and Confidentially

This study will be conducted in accordance with the principles of Good Clinical Practice Guidelines according to the Declaration of Helsinki, to ensure that all clinical research participants are not exposed to undue risk, and the data generated from the research are valid and accurate.[51]

The participant's free and voluntary involvement in the trial will be stressed at the time of recruitment. The patients will be reassured that their decision whether or not to take part or continue in the study will not affect the standard or availability of their care in anyway. The participants and their family will also be informed that they can withdraw from the study at anytime if they feel the need to do so and that they can contact the MHREC via address and email given on the participants information sheet, should they have any concerns during working hours. Participants who withdrew from the trial will not be included in the final analysis if they have specified instruction not to be included but their data will be entered into the RIPASA Score Registry.

Patients' confidentiality will be maintained by using their randomised allocation code as their unique identifier, linked to their Bru-HIMs number. Patient's name will not be recorded down in the Access database/Excel file to ensure confidentiality. Bru-HIMs number is secure as access is via intranet and only accessible via allocated staff's username and password.

Ethics approval for the study was approved by MHREC based in RIPAS Hospital (MHREC/2017/3/4) and the study is registered with the ClinicalTrial.gov registry for RCT (NCT03169114).

Reimbursement

There will be no proposed payment or reimbursement for the participants. All care and follow up will be carried out as part of the Department of General Surgery standard clinical care provision upon recruitment and admission. Private patients who consented to be recruited will have to cover the usual cost of their care and surgery during their hospital stay and subsequent follow up.

Monitoring (Interim data, auditing, Harm and adverse event reporting)

Monitoring for safety will be carried out throughout the duration of the study as part of the participants' clinical care during their admission and follow up. Current standard of care for patients seen in Accident & Emergency Department at RIPAS Hospital who are suspected to have acute appendicitis generally will have a RIPASA score taken at time of consultation and based on the RIPASA score, the appropriate action taken based on the RIPASA guidelines.[10] For RIPASA score 7.5 or greater, patients are given iv antibiotics prophylactically and referred onto the on-call surgeon who will review the patient and reassess their RIPASA score. Once confirmed to be 7.5 or greater, the patients will be admitted to the surgical ward and a decision for appendicectomy will be made by the on-call surgeon or upon discussion with the consultant on-call. If there is any uncertainty, an ultrasound or CT abdomen may be requested to confirm the diagnosis of acute appendicitis. If the on-call surgeon feels that the patient has ACA, the decision will be to consent the patient for appendicectomy.

The same standard of care pathway above will be applied to all patients recruited to the trial. Thus there should not be any major concerns in general with regards to care provided to patients involved in the trial. The only major concern is for the AMS arm, which is the possibility of progression of disease to ACA with perforation and generalised peritoni-

tis. The study protocol includes daily assessment of RIPASA score to monitor progression of participants condition and guided by RIPASA score guidelines to cross over to the SMS arm for appendicectomy or not. If the RIPASA score progressed to above 12, then based on the RIPASA guidelines, the indication is for performing surgery and patients will cross over to SMS arm. For scores up to 11.5, if the trend for the RIPASA score is increasing, management options include radiological investigations such as ultrasound or CT scanning and if confirmed presence of acute appendicitis and patients' clinical picture is not improving, then based on the RIPASA score guidelines, the attending surgeon has the option of performing surgery. If radiological investigations are negative, options is either continue with antibiotics or if clinical indications is there, to proceed with surgery.

Harm and adverse events monitoring will be carried out by 3 senior clinicians (Gastroenterologist Physician, Orthopaedic Surgeon and Clinical Microbiologist), as part of the DSMB and are not involved with recruitment or as investigators. The principal investigators will provide the DSMB with interim data at the mid point of the study period (1-year interim analysis) or every 6 months and whenever requested by DSMB, on: recruitment and retention rates, any protocol violations and any harm or adverse events and other unintended events, which will be reported as soon as it is ascertain to have occurred.

The main function of the DSMB is to alert both the principal investigator and MHREC via interim reports (6 monthly and at 1 year) on issues of participant recruitment, trial conduct and safety of participants. Any serious adverse events reported by participants or observed by the staffs or investigators will be clearly documented on pre-specify adverse events clinical trial forms and reported to the principal investigator who will notify the DSMB immediately (during working hours) or within 24 hours. Any adverse events deemed severe by the DSMB will be discussed with the principal investigator and reported directly to the MHREC. The board may recommend trial termination or suspension pending an MHREC review.

Protocol amendments

Any protocol amendments will be made by applications through MHREC and these changes will be communicated to the DSMB. Protocol amendments which affect participants in terms of what is required of them or what is consented to will be communicated to the participants with renewed consent sought where appropriate. Trial registries will be updated and materials amendments noted in any subsequent publications.

Ancillary and post-trial care

Any post-trial care required by participants will be provided by the admitting surgeon as part of RIPAS Hospital patient care policy, which will not be any different from other patients not taking part in the trial.

Dissemination Policy

The protocol for this study has been registered on ClinicalTrials.gov under the ClinicalTrial.gov identifier number of NCT03169114. The findings of this study will also be presented at local, regional and international conferences. The protocol and outcomes of the study will be published in local and international journals.

Expected Outcomes, Novelty and Significance

Based on our previous publications, the negative appendicectomy rate based on RIPASA score is 14.7%, giving surgery a treatment efficacy rate of 85.3%.[10] Accepting an increase of 50% more failure rate for AMS arm would give a treatment failure rate of about 22% and a treatment efficacy rate of 78% for AMS arm. From our previous publications, for RIPASA score range from 7.5-11.5, the rate of

perforated and gangrenous appendicitis, a group, which is unlikely to benefit from antibiotic therapy alone, is 21%. The remaining 79% consisted of EUAA, which is the group that will most likely to benefit from AMS and hence giving a probable treatment efficacy rate of 79%, which is just 1% more than the predicted non-inferiority treatment efficacy rate. Thus we are confident our trial will achieve non-inferiority of AMS to SMS.

Since the trial will be conducted based on RIPASA score guidelines, all doctors, surgeons and staffs will be fully brief and instructed to achieve compliance to the RIPASA score guidelines. Any deviation or non-compliance will be considered as failure of RIPASA score to influence change on physician behavior. To ensure compliance, weekly support and reinforcement of compliance sessions will be carried out in the Department of General Surgery weekly meeting.

The novelty of this research study is that it is the only non-inferiority RCT comparing AMS with SMS, that uses a CPR such as RIPASA Score to define a group with EUAA. Previous and pending non-inferiority RCTs on the same theme of comparing AMS with SMS have always used clinical judgement to define the group of patients with EUAA. As most cases of AA are seen first by the most junior member of the surgical team, there is always a margin of error in defining this group. Using a CPR such as RIPASA score with a define range of score that predicts high probability of AA, will objectively eliminate this margin of error.

The significance of this research study is that it will complete the final and third part of the creation and validation of the RIPASA score as a CPR by assessing its impact on changing physician behavior in terms of an AMS for treatment of EUAA and hence improves patient outcomes by reducing unnecessary negative appendicectomy rate, complications related to undergoing emergency appendicectomy and ultimately reducing cost of managing AA surgically. Thus results of this study will go as far as to consolidate RIPASA score as a good validated and effective CPR for the diagnosis of AA, not just locally but worldwide and also determine the role of AMS in a specific group of patients with RIPASA score that defines them as EUAA.

RIPASA TWO Non-Inferiority Randomised Controlled Trial Study Group and Roles (RIPAS Hospital)

Mr CHONG Chee Fui, **Principal Investigator:** Role is to oversee the whole project and ensure data collection are kept and maintain for the duration of the trial, to liaise with DSMB members and provide interim reports to them and to MHREC via DSMB.

Mr TAN Lian Tat, HoD, Department of General Surgery, **Co-Investigator:** Role to oversee recruitment in General Surgery Department and coordination with Accident & Emergency Department.

Dr Linawati JUMAT, HoD, Accident and Emergency Department, **Co-Investigator:** Role to oversee recruitment in Accident & Emergency Department and coordination with General Surgery Department.

Recruiting, admitting and Follow up Consultant Surgeons and team

Unit 1: Samuel YAPP Kai Seng, CHONG Chean Leong and Amy THIEN.

Senior Medical Officer/Medical Officer: Role to recruit, inform and consent patients, allocate randomization, ensure minimally required trial data entry

AUNG Kyaw Phyo, KOH Kai Shing, Anis AHMED, Nurul Ayu Elmi MOHD YUNUS.

Unit 2: TAN KK, TAN Lian Tat and Mohd Ady Adillah AHMAD.

Senior Medical Officer/Medical Officer: Role to recruit, inform and consent patients, allocate randomization, ensure minimally required trial data entry

Sonal TRIPATHI, Ahamed Jiffri AHAMED MACKIE, Shahriman HUSAIN, CHUA Hong Sang.

Data Safety Monitoring Board Members

CHONG Vui Heng (Gastroenterologist)

Ketan PANDE (Orthopaedic Surgeon)

Terence Rohan CHINNIAH (Microbiologist)

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