TRIAL PROTOCOL

ACCURE-UK 2

An international multicentre randomised controlled trial to assess the effect of Appendectomy on the Clinical Course of UlceRativE colitis; UK Arm

This protocol has regard for the HRA guidance and is compliant with SPIRIT.

Version Number:	**2.0**
Version Date:	**9th July 2019**

Protocol Development

Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**

Funding and Support in Kind	
Funder	National Institute for Health Research (NIHR)
Funding scheme	Efficacy and Mechanism Evaluation (EME)
Funder's reference number	16/61/35
The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research, Health Education England or the Department of Health. The funder had no role with respect to study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.	

Protocol Sign Off

CI Signature Page	
The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol. I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor. I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained. The protocol has been approved by:	
Trial Name:	ACCURE-UK 2
Protocol Version Number:	Version: 2.0
Protocol Version Date:	9th July 2019
CI Name & Role: **Signature and date:**	Professor Thomas Pinkney - Chief Investigator _____ __ __ / __ __ / __ __ __ __
Sponsor statement: As formally delegated by the University of Birmingham, the sponsor confirms approval of this protocol. Compliance statement: This protocol describes the ACCURE-UK 2 trial only. The protocol should not be used as a guide for the treatment of participants not taking part in the ACCURE-UK 2 trial. The study will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research 2017, the General Data Protection Regulations (GDPR), and the principles of Good Clinical Practice as defined by the European Good Clinical Practice (GCP) Directive. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.	

PI Signature Page	
The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator agrees to conduct the trial in compliance with the approved protocol. I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor. This protocol has been approved by:	
Trial Name:	ACCURE-UK 2
Protocol Version Number:	Version: 2.0
Protocol Version Date:	9th July 2019
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REFERENCE NUMBERS	
Sponsor number	RG_18-149
ISRCTN reference number	<<to be inserted>>
IRAS reference number	254954
REC reference number	19/EM/0191

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ABBREVIATIONS

Abbreviation	Term
5-ASA	5-aminosalicylic acid
AMC	Academic Medical Centre, University of Amsterdam
BCTU	Birmingham Clinical Trials Unit
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CV	Curriculum Vitae
DCF	Data Clarification Form
DMC	Date Monitoring Committee
EME	Efficacy and Mechanism Evaluation
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GP	General Practitioner
HRA	Health Research Authority
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
ILC	Innate Lymphoid Cells
ISF	Investigator Site File
NHS	National Health Service
NIHR	National Institute for Health Research
PI	Principal Investigator
PIS	Participant Information Sheet

QALY	Quality-Adjusted Life Year
QMS	Quality Management System
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGT	Research Governance Team
SCFA	Short Chain Fatty Acids
SIV	Site Initiation Visit
SOP	Standard Operating Procedure
TCR	T-cell Receptor
TMG	Trial Management Group
TSC	Trial Steering Committee
UC	Ulcerative Colitis
UoB	University of Birmingham

DEFINITIONS

Term	Abbreviation	Description
Quality Management System	QMS	A Quality Management System (QMS) is a system that includes procedures and policies to describe how certain tasks should be performed and that encapsulate any standards and/or regulatory requirements that may apply to those tasks. By adhering to the Quality Management System, the user and the UoB will be assured that applicable regulations are adhered to.
Standard Operating Procedures	SOP	Standard Operating Procedures are detailed written instructions to achieve uniformity in the performance of a specific function. They define tasks, allocate responsibilities, detail processes, indicate documents and templates to be used and cross-reference to other work instructions and guidance or policy documents. They are standards to which the UoB may be audited or inspected.
Source data		All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.
Birmingham Clinical Trials Unit	BCTU	The co-ordinating centre for the trial.

TRIAL SUMMARY

Title

The effect of Appendectomy on the Clinical Course of UlceRativE colitis; UK arm.

Objectives

To evaluate the short-term and medium-term effectiveness of appendicectomy to maintain remission in patients with an established diagnosis of ulcerative colitis who have had a relapse successfully treated within 12 months pre-randomisation.

Trial Design

The UK arm of a multi-centre, phase 3, 2-arm, outcome-assessor blinded, prospective randomised controlled trial.

Participant Population and Sample Size

The Dutch ACCURE trial is powered on a reduction in relapse rate. To increase the power from 80% to 90% requires an additional 60 patients (including 10% attrition). This UK arm will recruit 90 patients, to both increase the power of the trial and help complete the main trial recruitment in a more expedient manner.

Key Eligibility Criteria

Inclusion Criteria

- Histologically confirmed diagnosis of ulcerative colitis
- Disease relapse within 12 months of randomisation medically treated until remission
- In clinical remission at time of randomisation with partial Mayo score <3 and endoscopic Mayo subscore of 0 or 1
- Aged 18 or over
- Able and willing to provide written informed consent

Exclusion criteria

- Prior appendicectomy or major abdominal surgery which precludes safe laparoscopy appendicectomy
- Any suspicion of Crohn's disease
- Disease recently treated with biologicals (within 3 months of randomisation)
- Severe disease ever treated with biologicals and stopped due to secondary non-response
- Toxic megacolon or severe ongoing active colitis at time of randomisation
- Medical comorbidity (e.g. COPD) that precludes safe laparoscopy

Intervention

Patients will be randomised between laparoscopic day-case appendicectomy with standard medical therapy and standard medical therapy only.

Outcome measures

Primary outcome:

The one-year UC relapse rate (defined both clinically and endoscopically as Mayo-score ≥5 with endoscopy score of 2 or 3).

Secondary outcomes:

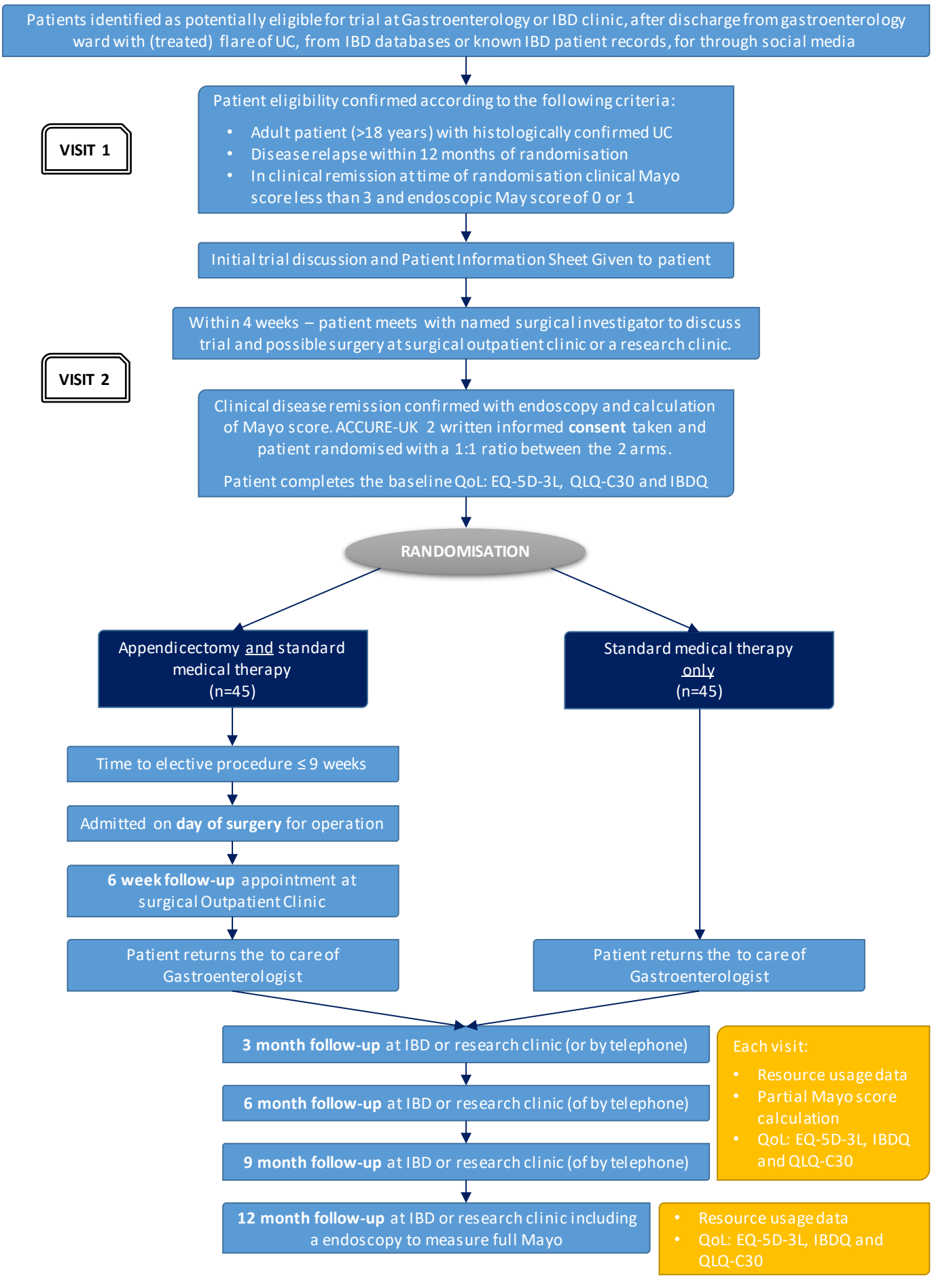
- Number of relapses per patient at 12 months.
- Time to first relapse.
- Health related quality of life and costs (EQ-5D-3L, EORTC-QLQ-C30-QL and IBDQ) at 3, 6, 9 and 12 months post-randomisation.
- Disease activity, as measured with the Mayo score at 12 months or relapse.
- Colectomy rate at 12 months.
- Number of semesters (6 month period) in remission since beginning of disease and current relapse.
- Resource usage, including medication usage, diagnostic tests undergone outside of the trial (laboratory work, radiological and endoscopic assessments), inpatient costs and health professional interactions.

Mechanistic sub-study

The research questions for the mechanistic sub-study are:

- Can analysis of (1) SCFA concentration, (2) mucosa-associated microbiome, or (3) Th1:Treg ratio predict response to appendicectomy?
- Can the direct mechanism by which appendicectomy impacts upon inflammatory activity in UC be verified?

ACCURE-UK 2 – Schema and Patient Flowchart



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1. BACKGROUND AND RATIONALE

1.1 Background

Chronic relapsing diseases such as ulcerative colitis (UC) incur considerable long-term health burden to the patient and the state. Early interventions that reduce the rate of relapse could provide considerable benefits to patients and the health service. Around 150,000 people suffer from UC in the UK at present. Most can be treated effectively with medical therapy, but when the disease is unresponsive, major surgery is indicated. Around 25% will ultimately require colectomy surgery; this takes place as an emergency if the patient suffers a severe refractory attack of colitis[1]. This surgery is high risk with a complication rate of >30% and many months of recovery[2]. Patients may also be left with a stoma.

The majority of UC patients will remain on long term medication to maintain lifestyle and prevent relapse. Even on maintenance therapy the annual disease relapse rate is at least 40%[3]; these require escalation to high dose steroids with their incumbent risks and toxicity. The peak age of onset of UC is 20-35 years old, so as well as a long potential period of disease activity, there are additional impacts on working life, procreation and childcare[4].

There is a need to develop new treatment options for UC patients for whom drug treatment aimed at inducing or maintaining remission is either ineffective or associated with unacceptable side effects.

1.2 Existing research around the role of therapeutic appendicectomy in UC

UC is regarded as multifactorial, involving an interaction between genetic and environmental factors that gives rise to an inappropriate immunological response. This immune response is known to be Th2-mediated and characterised by the presence of autoantibodies.

The interaction between intestinal epithelial cells, gut flora, innate and T cells is important in gut homeostasis; a disruption in any of these components can result in chronic mucosal inflammation[5].

The appendix has a unique role in the regulation of intestinal immune mechanisms, which may explain the emerging body of evidence demonstrating interaction between the appendix and UC disease activity. The following immune mechanisms have been postulated to explain this interaction:

1. <u>The appendix as a source of bacterial load in the induction and regulation of colitis</u>

   In numerous animal models of colitis, the driving force for intestinal inflammation is the intestinal flora[6]. Antibiotics have been shown to attenuate the severity of colitis in a colitis-liable mouse model[7], suggesting that the bacterial load is a key driver for intestinal inflammation. The appendix has recently been shown to be the most abundant source of microbial biofilms compared to other parts of the colon[8]. This supports the hypothesis that appendicectomy would reduce the bacterial load and thereby affect UC activity.

2. <u>Appendix as a source of innate lymphoid cells</u>

   In the past decade, there has been much interest in the role of innate lymphoid cells (ILC) in the development of UC. The appendix is a rich source of ILC, which can function as effector cells in the

development of colitis[9]. Reducing these cell numbers would potentially reduce the pro-inflammatory drive.

Several animal experiments have explored the effect of appendicectomy on UC activity. In TCRa-/- mice, in which the alpha chain of the T-cell receptor (TCR) is deleted, mice develop a colitis exhibiting a Th2 cytokine profile similar to UC. In this model appendicectomy performed at one month of age reduces the incidence of colitis. Furthermore, when mice undergo appendicectomy aged 3-5 weeks there is a reduction in the number of mesenteric nodes compared to control, and the incidence of colitis was only 3.3% compared to 80% in controls[10]. This supports the hypothesis that the appendix is a source of bacterial load, which is important in mucosal inflammation and also the development of T-cell mediated pathways via the draining mesenteric lymph nodes.

In summary, the appendix is a source of bacterial load and innate cells which are important constituents in mucosal inflammation. The suggestion that appendicectomy may affect UC activity is biologically plausible.

1.3 Clinical evidence of the interaction between the appendix and UC activity

There is a strong inverse relationship between prior appendicectomy and the development of UC, documented through multiple large-scale epidemiological and case-control studies from diverse populations[11-13].

A recent systematic review of retrospective cohort studies also suggests a beneficial effect from appendicectomy in patients with established UC although the heterogeneity of the studies and subjective nature of the endpoints made interpretation difficult[14].

There is an emerging body of clinical evidence presenting outcomes from appendicectomy performed as a therapeutic intervention in treating active UC in humans. This evidence, whilst restricted to single-centre series, is directly aligned with our research and is outlined below.

Bolin and colleagues undertook appendicectomy in 30 adults with UC and found significant improvement in clinical activity index in 90% of patients with a median disease score of 9 pre-operation reducing to 2 post-operation ($p<0.0005$)[15]. Furthermore 12 of 30 patients (40%) experienced complete resolution of symptoms by 12 months and stopped all medications. This complete resolution of symptoms was attained at a median of 3 months post-appendicectomy and all remained symptom-free up to the end of follow-up.

In a second Australian study, Radford-Smith employed appendicectomy as a treatment for refractory distal colitis in 15 patients and found significant improvements in clinical activity index ($p=0.015$), endoscopic activity ($p=0.02$) and need for medication at 12 months ($p=0.02$)[16]. Further smaller series or individual cases have appeared from Japan, Korea, France and Sweden[17-20]. These all involved patients with active or treatment-resistant UC and they universally reported a significant improvement in symptoms and disease activity, some with complete symptom resolution.

This evidence undoubtedly suffers from publication bias, but as a collective body does provide compelling support for the hypothesis that appendicectomy may improve the clinical course of UC. This novel

intervention requires evaluation in a prospective multicentre randomised controlled trial (RCT). It is not currently employed as a therapeutic treatment for UC. If we can demonstrate that appendicectomy is an efficacious and cost-effective strategy that is acceptable to patients and their clinicians, widespread uptake can be anticipated.

1.4 Trial Rationale

UC is a chronic disease with a significant burden amongst young patients. Existing treatments are often based on either on drugs with extensive side effect profiles or major high-risk surgery. If appendicectomy reduced the likelihood of relapse in UC, and consequent need for burdensome drugs, hospital admission and major surgery, then patients will benefit from substantially improved quality of life, whilst reducing their health resource usage. This would outweigh the low risk of morbidity and minor costs associated with the initial appendicectomy.

Our group has already demonstrated in our NIHR RfPB-funded randomised external pilot study that the appendicectomy intervention is attractive to patients and clinicians, and is safe with minimal morbidity[21]. There is significant and sustained interest in this potential new therapy for UC. Our Dutch collaborators are already midway through the main ACCURE trial (ISRCTN 56523019), a phase III trial exploring the clinical effectiveness of the intervention. This protocol represents the UK arm of this same ongoing trial in The Netherlands, both to shorten the time until this final result is available, and to strengthen the generalisability of the result by increasing the number of centres involved and the statistical power of the study from 80% to 90%.

2 AIMS AND OBJECTIVES

2.1 Aims and Objectives

The aim of the ACCURE-UK 2 trial is to evaluate the short- and medium-term effectiveness of appendicectomy in maintaining remission in adult patients with an established diagnosis of UC, who are currently in a remission phase.

Clinical Hypothesis:

Appendicectomy will result in an improved clinical course in UC compared to those undergoing standard care, with an increased chance of maintaining remission and an associated improvement in overall symptoms.

Clinical research question:

In UC patients who are in remission, compared to standard medical therapy, does laparoscopic appendicectomy lower the rate of relapse and/or prolong the time to relapse?

Specimens for future mechanistic studies will be taken and biobanked in selected sites, aiming to confirm the mechanism of action and stratify responders to the therapy.

3 TRIAL DESIGN AND SETTING

3.1 Trial Design

The ACCURE-UK 2 trial is the UK arm of a multicentre, outcome-assessor blinded randomised controlled trial comparing laparoscopic appendicectomy plus standard medical therapy with standard medical therapy alone for patients with confirmed UC who have had a disease flare-up within the past 12 months and are currently in remission.

3.2 Trial Setting

The ACCURE-UK 2 Trial is the UK arm of the Dutch ACCURE trial.

It is anticipated that 10 centres from across the UK will open to recruitment to the ACCURE-UK 2 arm of the trial. Ideally, each centre will recruit 9 patients, on average, to the trial.

3.3 Identification of participants

Potentially eligible patients will be identified from one of four scenarios:

- **Gastroenterology and surgical outpatient clinics.**

  At the outpatient clinics, the approach to potential participants will be made by either the surgeon or the gastroenterologist. Engagement from both specialties at each site will be required for delivery of the trial.

- **Inpatients who are being discharged home, having recovered from a flare of UC activity that has been successfully treated medically.**

  Upon discharge, the local ACCURE-UK 2 team will be informed of the discharge of patients who had been admitted with a flare of UC. The local site research team will then be responsible to identify when patients return for follow-up outpatient appointments (at 6 – 8 weeks, for example), at which point complete response can be confirmed and the patient can be asked for consent for entry into the trial.

- **IBD databases, review of IBD patient medical records and local IBD helpline users.**

  Patient records that are available to the local ACCURE-UK 2 team will be screened for potential patients who will then be contacted by the IBD/research nurse (via a telephone call and/or an invitation letter) to introduce the trial and invite them to meet with a gastroenterologist or surgeon involved in the trial. Patients who engage with the local IBD helpline (or equivalent) will be screened for potential participation, who will then be contacted by the IBD/research nurse (via a telephone call and/or an invitation letter) to introduce the trial and to meet with a gastroenterologist or surgeon involved in the trial.

- **Social media by way of Ulcerative Colitis patient forums, Facebook, Twitter, etc.**

  Ethically approved material aimed at potentially eligible ACCURE-UK 2 participants will be posted on social media sites related to UC and ACCURE-UK 2. Potential patients will be asked to contact the ACCURE-UK 2 Trial Office for further information. The Trial Office will direct the patient to the nearest site open for the trial or inform the patient how to be referred to an open site.

3.4 Sub-studies

A future mechanistic sub-study is planned with the objective to try to establish the mechanism of action of the intervention and stratify responders to the therapy.

The hypothesis of the mechanistic study is that dysbiosis in the appendix is associated with dysregulated production of short chain fatty acids (SCFA), leading to aberrant immune activation and persistent/reactivated colonic inflammation. This effect can be suppressed by the removal of the appendix. SCFA quantification may predict response to appendicectomy in UC and so stratify patients for prophylactic surgery.

The research questions for the mechanistic sub-study are:

1. Can analysis of (1) SCFA concentration, (2) mucosa-associated microbiome, or (3) Th1:Treg ratio predict response to appendicectomy?
2. Can the direct mechanism by which appendicectomy impacts upon inflammatory activity in UC be verified?

Whilst this study will be subject to a future funding application for the analyses and associated work, this current trial will include biobanking of specimens from selected sites.

3.4.1 Sub-study procedures for specimen collection and biobanking

The future mechanistic study will be undertaken by analysis of appendix tissues, peripheral blood and mucosal biopsy samples from patients recruited to the ACCURE trial UK arm. Samples will be taken and biobanked at baseline, 3 months and 12 months, with half of the patients having been randomised to undergo appendicectomy in the interim. Addition of clinical outcomes data for those in the intervention arm (treatment response versus non-response) is a central component of the analyses.

Specimens will be collected from 20 patients randomised to the control arm and 40 in the intervention arm (60 patients in total):

- **Colonic biopsies** will be taken at baseline and trial exit (12 months) at the same time as the primary clinical endpoint assessment. We propose that the microbiomes in these specimens will be sequenced using 16S RNA and shot gun metagenomic techniques. Metabolomes will be studied with quantification of short chain fatty acids (SCFA).

- Patients randomised to the intervention arms will have their appendices flushed out following excision. **Appendiceal effluent** and **appendix mucosal biopsy** microbiomes and metabolomes will be biobanked for future assessment. Greater SCFA concentration (specifically butyric acid), decreased microbial diversity and greater gram-negative anaerobe concentrations are postulated as predictors of response to appendicectomy.
- **Peripheral blood samples (10ml)** will be taken at baseline, 3 months and 12 months. These will be spun and stored for phenotyping using flow cytometry to identify Th1, Th17 and Treg cell concentrations. Greater Th1:Treg and Th17:Treg concentrations are postulated as predictors of response to appendicectomy.

This will be undertaken at selected centres and commenced during recruitment phase of the trial. Sample will be sent to and stored at the Human Biomaterials Resource Centre at the University of Birmingham.

3.5 Assessment of Risk

The primary ethical issue relates to the appendicectomy operation; we are offering patients a surgical operation as an alternative to traditional medical therapies. This operation carries with it inherent risk, both from the general anaesthetic and from the surgery itself.

An important part of our feasibility study was to quantify these risks in this population as there was previously no published information available. Expert consensus is that the risks of an adverse event after an elective appendicectomy performed by a consultant surgeon on a systemically well patient are likely to be very low (<1 in 100). It is important to note that the medications used to treat a flare-up of UC are themselves fairly toxic and carry side-effect and complication risks. In addition, a proportion of patients suffering a relapse will not respond to medical therapy and will require an emergency colectomy operation. This is a major operation with an appreciable risk to life and significant complication profile. These risks must be offset against those for the appendicectomy.

Our feasibility study showed that the appendicectomy intervention was safe and acceptable. There were 4/26 minor complications (Clavien-Dindo grade 1-2), and no major complications or adverse events. We also confirmed that the operation conferred minimal impact on patient's lives in terms of pain or decreased activity, with all patients reporting being back to full activities by 6 weeks, and often much sooner.

The risk assessment therefore concluded that this trial is of no higher than the risk of standard medical care.

4 ELIGIBILITY

4.1 Inclusion Criteria

- Histologically confirmed Ulcerative Colitis
- Disease relapse within 12 months of randomisation medically treated until remission
- In clinical remission at time of randomisation with partial Mayo score less than 3 and presumptive endoscopic Mayo subscore of 0 or 1, identified by endoscopy (within 3 months). The endoscopy will be either:
    - Colonoscopy examining the full length of the colon and rectum
    - Sigmoidoscopy examining the last part of the colon (sigmoid and rectum) with faecal calprotectin less than 150 µg/g
- Aged 18 or over
- Patient able and willing to give written informed consent

4.2 Exclusion Criteria

- Previous appendicectomy or other major abdominal surgery precluding safe laparoscopic appendicectomy
- Any suspicion of Crohn's disease
- Disease recently treated with biologicals (within 3 months of randomisation)
- Severe disease ever treated with biologicals and stopped due to secondary non-response
- Toxic megacolon or severe ongoing active colitis at time of randomisation
- Patients with significant comorbidity (e.g. unstable heart failure, liver or kidney failure, major lung co-morbidity)

4.3 Co-enrolment

Patients can be in both ACCURE-UK 2 and other non-interventional trials.

If the patient has been part of another interventional trial for the treatment of UC, they can still be recruited to ACCURE-UK 2 provided a period of at least six months has passed since completion of all treatment and follow-up in the other trial.

Please contact the ACCURE-UK 2 Trial Office to discuss these patients' eligibility prior to randomisation.

5 CONSENT

It will be the responsibility of the Investigator to obtain written informed consent for each participant prior to performing any trial related procedure.

Consent may be taken by the PI or delegate (consultants, registrars, research nurses) as captured on the ACCURE-UK 2 Site Signature and Delegation Log. All those delegated to take consent must have undertaken Good Clinical Practice (GCP) training.

A Patient Information Sheet (PIS) will be provided to facilitate this process. Investigators or delegate will ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the participant. They will also stress that participation is voluntary and that the participant is free to refuse to take part and may withdraw from the trial at any time. The participant will be given adequate time to read the PIS and to discuss their participation with others outside of the site research team. The participant will be given the opportunity to ask questions before initialling, signing and dating the latest version of the Informed Consent Form (ICF).

If the participant expresses an interest in participating in the trial they will be asked to initial, sign and date the latest version of the ICF. The participant must give explicit consent for the regulatory authorities, members of the research team and or representatives of the sponsor to be given direct access to the participant's medical records.

The Investigator or delegate will then sign and date the ICF. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, a copy sent to the ACCURE-UK 2 Trial Office and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the ISF. In addition, if the participant has given explicit consent a copy of signed ICF will be sent to the ACCURE-UK 2 Trial Office for review.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant and version number of ICF signed and date consent received.

At each visit the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the ACCURE-UK 2 Trials Office and will be printed or photocopied onto the headed paper of the local institution. Details of all patients approached about the trial will be recorded on the ACCURE-UK 2 Patient Screening Log.

With the participant's prior consent, their General Practitioner (GP) will also be informed that they are taking part in the trial.

6 ENROLMENT AND RANDOMISATION

The trial is designed as a multicentre randomised clinical trial and will involve both gastroenterologists and colorectal surgeons.

Potentially eligible patients will be identified from one of four scenarios:

- Gastroenterology and surgical outpatient clinics.
- Inpatients who are being discharged home, having recovered from a flare of UC activity that has been successfully treated medically.
- IBD databases, review of IBD patient medical records and local IBD helpline users.
- Social media by way of Twitter or Facebook and patient groups.

Once identified, patients may be invited to attend an appointment at an outpatient or research clinic to discuss the trial with the consultant gastroenterologist or research nurse.

At this first appointment the patient will be given the PIS. If needed, a further gastroenterology medical or research appointment will be offered to further discuss the trial.

6.1 Enrolment and Screening

If patients are willing to consider entry to the trial, they will meet with a consultant colorectal surgeon within the 4 weeks following the initial approach by a member of the ACCURE-UK 2 site team, to further discuss the trial and possible surgery (if randomised to the intervention arm). If a joint IBD clinic is held at the site, this could take place on the same day as the above initial discussion.

At the second assessment visit, if patients are still willing to enter ACCRUE-UK 2, written informed consent for participation in the trial can be obtained.

Prior to randomisation, confirmation of eligibility and clinical disease remission is required via endoscopy (either a colonoscopy or a sigmoidoscopy with a measurement of faecal calprotectin less than 150 µg/g). **The investigation(s) used to confirm must be within 3 months prior to randomisation so if participants have had suitable investigations as part of their ongoing routine care within the required timeframe, they can be used to confirm eligibility.** If the investigations to confirm are additional to standard care, written informed consent must be obtain before they can be undertaken.

6.2 Randomisation

6.2.1 Randomisation Methodology

Participants will be randomised by computer at the level of the individual in a 1:1 ratio to either:

1. Laparoscopic appendicectomy + Standard medical therapy
2. Standard medical therapy

A minimisation algorithm will be used within the computerised randomisation system to ensure balance in the treatment allocation over the following variable:

- Extent of disease (Rectum; left sided colon; pancolitis)

A 'random element' will be included in the minimisation algorithm, so that each patient has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received. Full details of the randomisation specification will be stored in a confidential document at the Academic Medical Centre, University of Amsterdam (AMC).

6.2.2 Blinding

It is not feasible to blind participants to the randomised allocation.

However, the gastroenterologist performing the follow-up assessment at 12 months or at relapse, will be blinded to the randomised treatment allocation.

The blinded gastroenterologist must not have been involved in the participant's care over the preceding 12 months. The site research team is responsible for arranging an assessment of the patient at 12 months by a gastroenterologist blinded to the randomised allocation and to ensure that the gastroenterologist remains blinded to the patient's treatment until the completion of the 12 month follow-up assessment.

6.2.3 Randomisation process

After written informed consent has been received and eligibility has been confirmed, the patient can be randomised into the trial.

Randomisation will be provided by a secure randomisation system managed by the AMC. The toll-free telephone randomisation service will be available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days.

Randomisation Forms will be provided to investigators and should be used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation Form must be answered before a Trial Number can be given. Only when all eligibility criteria and baseline data items have been provided will a Trial Number be allocated.

6.2.4 Randomisation records

Following randomisation, a confirmatory e-mail will be sent to the local PI, research nurse and responsible clinician.

Investigators will keep their own study file log which links patients with their allocated trial number in the ACCURE-UK 2 Participant Recruitment and Identification Log. The Investigator must maintain this document, which is not for submission to the Trial Office.

The Investigator will also keep and maintain the ACCURE-UK 2 Patient Screening Log which will be kept in the ISF, and should be available to be sent to the Trial Office upon request. The ACCURE-UK 2 Participant Recruitment and Identification Log and ACCURE-UK 2 Patient Screening Log should be held in strict confidence.

6.3 Informing the participant's GP

If the participants has agreed, the participant's GP should be notified that they are in the ACCURE-UK 2 trial. A specimen "GP Letter" is supplied for use by investigators.

7 TRIAL INTERVENTION

Patients with an established diagnosis of UC (any extent of disease) and a disease relapse, within 12 months of randomisation medically treated until remission, will be randomised to laparoscopic appendicectomy or to no appendicectomy. Patients in both the intervention and control arm will receive standard medical therapy.

7.1 Intervention arm: laparoscopic appendicectomy

The trial intervention is laparoscopic appendicectomy with standard medical therapy.

Patients randomised to the intervention arm will undergo standard 3-port laparoscopic appendicectomy performed by a colorectal surgeon with sufficient experience in the procedure (>20), as a planned day-case procedure.

This operation will be undertaken within 9 weeks of randomisation.

The appendix will be removed using a laparoscopic endostapler enabling a safe and complete appendicectomy with the cross-stapling line at the base of the appendix at the junction with the caecal pole.

7.2 Control arm

Patients in the control arm will receive the standard medical therapy only.

7.3 Standard Medical Therapy (both arms)

During the 12 month period that participants are in the trial, participants in both arms are to continue with the maintenance therapy medications they are taking at trial entry as part of standard of care. Modifications

to the medications the participants receive are to be as clinically indicated and will be recorded on in the case report forms.

7.4 Management of disease relapse

In case of exacerbation, faecal calprotectin will be measured. Faecal calprotectin will be measured locally. If faecal calprotectin >150 µg/g an endoscopy will be performed and the Mayo score will be assessed by a gastroenterologist blinded to the treatment allocation.

Further medications subsequently required according to local gastroenterologists for the treatment of UC during the study period, such as steroids, immunosuppressants, or biologics will be allowed but their usage (start date, duration and dose) will be carefully recorded and collected on the 3, 6, 9 and 12 month follow-up CRFs.

8 OUTCOME MEASURES AND STUDY PROCEDURES

8.1 Outcome Measures

8.1.1 Primary Outcome

The primary outcome is the one year UC relapse rate (defined both clinically and endoscopically as Mayo-score ≥5 with endoscopy subscore of 2 or 3).

8.1.2 Secondary Outcomes

- Number of relapses per patient at 12 months.
- Time to first relapse.
- Health related quality of life and costs (EQ-5D-3L, EORTC-QLQ-C30-QL and IBDQ) at baseline, 3, 6, 9 and 12 months post-randomisation.
- Disease activity, as measured by the Mayo score at 12 months or relapse (if earlier).
- Number of semesters (6 month period) in remission since beginning of disease and current relapse.
- Colectomy rate at 12 months.
- Resource usage, including medication usage, diagnostic tests undergone outside of the trial (laboratory work, radiological and endoscopic assessments), inpatient costs and health professional interactions.

8.2 Study Procedures

Screening and randomisation

Patients will undergo either an endoscopy (either colonoscopy or a sigmoidoscopy with a measurement of faecal calprotectin) at inclusion to confirm remission. If a patient has undergone an endoscopy as part of standard care up to 3 months prior to randomisation, this is to be used to confirm remission.

Intervention

Participants randomised to the intervention will be under the care of the surgical team for pre-op assessment and appendicectomy. The laparoscopic appendicectomy will be under taken in the recruiting/randomising centre within 9 weeks of randomisation.

During the 12 month study period, patients in both arms will continue with the maintenance therapy medications they are taking at trial entry as part of standard of care.

Follow-up (6 weeks, 3, 6 and 9 and 12 months post-randomisation)

At 6 weeks following surgery, participants in the intervention arm will be followed up in surgical outpatient clinics to assess post-operative complications and surgical morbidity.

Both groups (intervention and control) will be followed up in gastroenterology outpatient clinics, research clinics or by phone at 3, 6 and 9 months post-randomisation to access medication usage, complications, additional interventions, re-admissions, duration of hospital stay and visits to the outpatient clinic, number of days of sick leave and of social non-attendance and to ensure completions of the questionnaires.

During these contacts at 3, 6 and 9 months the non-invasive 9-point partial Mayo score will also be assessed.

Participants will be asked to complete health-related quality of life questionnaires (EQ-5D-3L, EORTC-QLQ-C30-QL and IBDQ) at inclusion and every 3 months thereafter for one year.

Follow-up at 12 months post-randomisation / Assessment of relapse

Patients will undergo an endoscopy (colonoscopy or a sigmoidoscopy with a measurement of faecal calprotectin) after 12 months or at relapse to assess mucosal appearance with the Mayo score, performed by a gastroenterologist blinded to the treatment allocation.

As the relapse rate / maintenance of remission is the primary outcome it is important that disease relapses are robustly confirmed prior to commencement of medical therapy. Patients who feel that they are developing symptoms of a flare will be asked to contact their local investigator team who will arrange an urgent clinic appointment for clinical review, blood tests +/- endoscopy. Their gastroenterologist will make decisions regarding further therapy on the basis of the results of these tests.

Long term follow-up

Patients will be prospectively consented for long-term follow-up using routinely collected NHS data. This will allow the collection of key endpoints to test whether any benefit from appendicectomy is maintained in the longer term. Endpoints will include i) admission for treatment of disease flare-ups, ii) administration of

biological medications, iii) colectomy rates and (iv) diagnoses of colorectal cancer. However, this will be dependent of additional funding being secured.

8.2.1 Clinical monitoring of disease activity using Mayo Score

The Mayo scoring system (see Appendix 1) is a widely used multimodal disease activity index which incorporates patient reported factors, endoscopic appearance and a clinician's global assessment in a 12-point tool[22]. There is no established core outcome set for the evaluation of UC disease activity, and the linked document recommended by the COMET Initiative highlights the fact that 13 different scoring systems have been described, none of which are fully validated[23]. The Mayo score, however, is favoured by the FDA for UC trials due to its ability to detect changes in symptoms following an intervention. It was used in the pivotal ACT I and ACT II studies exploring the use of biological therapies in the treatment of UC[24]. We will use the full Mayo scoring system at the following time points:

1. At baseline, to verify disease remission and thereby confirm eligibility for the trial
2. At the one year final follow-up (trial exit) stage

Intermediate clinical assessments will take place at 3, 6 and 9 months after randomisation and at each stage incorporate a 'non-invasive' 9-point partial Mayo score calculation as endoscopic mucosal assessment will not routinely be performed unless clinically indicated.

8.3 Schedule of Assessments

Visit		Prior to randomisation	Baseline - prior to treatment	At Surgery	6 weeks post-op (+/- 2 weeks)	3 months post-randomisation (+/- 2 weeks)	6 months post-randomisation (+/- 2 weeks)	9 months post-randomisation (+/- 2 weeks)	12 months post-randomisation (+/- 1 month)
Written informed consent		x							
Endoscopy	Colonoscopy **OR** Sigmoidoscopy with calprotectin	x *							x **
Routine bloods[1]		x							
Randomisation			x						
QoL questionnaire[3]			x			x	x	x	x
Pre-operative assessment[2]			x						
Appendicectomy[2,4]				x					
Surgical Morbidity[3]					x				
Resource usage						x	x	x	x
Relapse evaluation						x	x	x	x
Serious adverse events		Evaluate throughout 3 months post-randomisation							

*Screening investigations to confirm eligibility and remission must be within 3 months prior to randomisation

** Or earlier than 12 months should the patient relapse

[1] Full blood count (FBC), Renal function and Potassium

[2] Patients randomised to receive appendicectomy only

[3] EQ-5D-3L, EORTC-QLQ-C30-QL and IBDQ questionnaires to be completed at all designated time points.

[4] Must occur within 9 weeks of randomisation

8.4 Participant Withdrawal

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process; participants should be asked about their ongoing willingness to continue participation and this documented in the participant's medical notes.

Participants should be aware at the beginning of the trial that they can freely withdraw (discontinue participation) from the trial (or part of) at any time.

Types of withdrawal as defined are:

- The participant would like to withdraw from trial treatment, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis)
- The participant would like to withdraw from trial treatment and does not wish to attend trial visits in accordance with the schedule of assessments but is willing to be followed up at standard clinic visits and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected at standard clinic visits and used in the trial analysis, including data collected as part of long-term outcomes)
- The participant would like to withdraw from trial treatment and is not willing to be followed up in any way for the purposes of the trial and for no further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis)

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source data.

Patients who withdraw from trial treatment, but continue with ongoing follow-up and data collection should be followed-up in accordance with the protocol.

9 ADVERSE EVENT REPORTING

9.1 Definitions

Adverse Event	AE	Any untoward medical occurrence in a participant or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event		An event which resulted from the administration of any of the research procedures.

Serious Adverse Event	SAE	An untoward occurrence that: • Results in death • Is life-threatening. • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly/ birth defect • Or is otherwise considered medically significant by the Investigator.
Unexpected and Related Event		An event which meets the definition of both an Unexpected Event and a Related Event
Unexpected Event		The type of event that is not listed in the protocol as an expected occurrence.

9.2 Reporting Requirements

The collection and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care (2017) and the requirements of the Health Research Authority (HRA). Definitions of different types of AEs are listed in the table of definitions. The Investigator should document all AEs experienced by the trial participant in the source data and assess the seriousness and causality (relatedness) of all AEs experienced by the trial participant with reference to the protocol.

9.3 Adverse Events (AE) requiring reporting in ACCURE-UK 2

The safety profile for this trial population and intervention are well established so although the severity and causality of all AEs should be recorded in the source data, a strategy of targeted recording of AEs will therefore not affect the safety of participants. The recording of only a subset of AEs via the Case Report Forms (CRFs), for the duration of the participant's inclusion in the trial, is consistent with aims of the trial.

9.4 Serious Adverse Event (SAE) Reporting in ACCURE-UK 2

All events which meet the definition of serious will be collected and recorded in the participant notes and the follow-up CRF. SAEs will in addition be reported to the trials office immediately and within 24 hours of being made aware of the event.

For the purposes of this study, serious adverse events include, but are not limited to:

- Intra-operative complications such as bleeding, bowel injury or anaesthetic complication
- Post-operative complications such as wound infection or cardiac event
- Death

Disease relapse is a trial end point but should not be reported as an SAE. Instead, relapse will be captured on the relevant Relapse case report form.

Expected SAEs

The following are SAEs that could be reasonably expected for this group of patients during the course of the trial:

- Hospitalisations for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Hospitalisations for treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study, and did not worsen
- Admission to a hospital or other institution for general care, not associated with any deterioration in condition
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

For the purposes of this trial these expected SAEs do **NOT** require reporting on an SAE form. These events should continue to be recorded in the source data according to local practice and be included on the routine follow-up CRFs.

9.5 Reporting period

SAEs must be followed up at least until the final outcome is determined, even if it implies that the follow-up continues beyond the planned period of follow-up. SAEs will be reported for 3 months post randomisation.

9.6 Reporting Procedure – At Sites

9.6.1 Reporting procedure for Serious Adverse Events

AEs defined as serious and which require reporting as an SAE should be reported on an SAE Form. When completing the form, the PI will be asked to define the causality and the severity of the AE.

A five point scale will be used when reviewing causality: definitely related; probably related; possibly related; unlikely to be related or unrelated.

All events considered at the site to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported by the ACCURE-UK 2 Trial Office as 'related'; all events considered at site to be 'unlikely' or 'unrelated' to the intervention will be reported by the ACCURE-UK 2 Trial Office as 'unrelated'.

On becoming aware that a participant has experienced an SAE, the Investigator or delegate(s) should report the SAE to their own Trust in accordance with local practice and to the BCTU trials office.

To report an SAE to the ACCURE-UK 2 Trial Office, the Investigator (or delegate) must complete, date and sign the ACCURE-UK 2 specific SAE form. The completed form together with any other relevant, appropriately anonymised, data should be faxed, or scanned, to the ACCURE-UK 2 Trial Office using the contact details listed below as soon as possible and no later than 24 hours after first becoming aware of the event for expedited SAEs:

To report an SAE, fax the SAE Form to:
0121 415 8871

Or scan and email the SAE Form to:

accure@trials.bham.ac.uk

On receipt of an SAE form, the ACCURE-UK 2 Trial Office team will allocate each SAE a unique reference number and return this via email to the site as proof of receipt. If the site has not received confirmation of receipt of the SAE from the BCTU or if the SAE has not been assigned a unique SAE identification number within 1 working day, the site should contact the ACCURE-UK 2 Trial Office. The site and the ACCURE-UK 2 Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the Site File.

Where an SAE Form has been completed by someone other than the Investigator initially, the original SAE form will need to be countersigned by the Investigator to confirm agreement with the causality and severity assessments.

9.6.2 Provision of follow-up information

Following reporting of an SAE, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the BCTU trials team. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, the final version of the original SAE form(s) completed at site must be returned to the BCTU trials office and a copy kept in the Site File.

9.7 Reporting Procedure – ACCURE-UK 2 Trial Team

On receipt of a faxed SAE form from the site, the ACCURE-UK 2 trial team will allocate each SAE form with a unique reference number and enter this onto the SAE form in the section for office use only. The SAE form (containing the unique reference number completed) will be forwarded to the site as proof of receipt within 1 working day. The SAE reference number will be quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the TMF.

On receipt of an SAE Form, the Chief Investigator (CI) (or delegate) will independently determine the seriousness and causality of the SAE. An SAE judged by the PI or CI (or delegate) to have a reasonable causal relationship with the intervention will be regarded as a related SAE. The causality assessment given by the PI will not be downgraded by the CI (or delegate). If the CI (or delegate) disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

The CI (or delegate) will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

9.8 Reporting to the Research Ethics Committee

9.8.1 Unexpected and Related Serious Adverse Events

BCTU will report all events categorised as Unexpected and Related SAEs to the main Research Ethics Committee (REC) and RGT within 15 days.

9.8.2 Other safety issues identified during the course of the trial

The main REC and RGT will be notified immediately if a significant safety issue is identified during the course of the trial.

9.9 Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to PI. A copy of any such correspondence should be filed in the site file and TMF.

9.10 Data Monitoring Committee

All SAEs will be reviewed by the independent Data Monitoring Committee.

10 DATA HANDLING AND RECORD KEEPING

10.1 Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

The source data is retained at site in the participants' medical notes. In addition for the ACCURE-UK 2 Trial, source date also includes participants-completed questionnaires and endoscopy images.

Data	Source
Patient Reported Data (EQ-5D-3L, EORTC-QLQ-C30-QL and IBDQ questionnaires)	The original participant-completed paper form is the source data and will be forwarded directly to the ACCURE-UK 2 Trial Office.
Lab results (calprotectin, FBC, U&E, potassium, CRP)	The original lab report, which may be electronic, is the source data and will be kept and maintained, in line with normal local practice.
Endoscopy images	The original electronic images are the source data. They will be kept and maintained in line with normal local practice.
Clinical event data	The original clinical annotation is the source data. This may be found on clinical correspondence, or electronic or paper patient records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source data.

CRF are not to be considered source data. Any information collected on CRFs should be documented in the medical notes.

10.2 Case Report Form (CRF) Completion

A CRF is required and should be completed for each individual participant. ACCURE-UK 2 will use paper CRFs to collect participant data. The data held on the completed original CRFs are the property of the respective local PIs whilst the data set as a whole is the property of the Sponsor.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs. The ACCURE-UK 2 Site Signature and Delegation Log will identify all those personnel with responsibilities for data collection.

The CRFs will comprise of the following forms:

Form Name	Schedule for submission
Consent, baseline and randomisation CRF	At the point of randomisation
Operative and follow-up CRFs	As soon as possible after each follow-up assessment time point
Serious Adverse Event CRF	Faxed/emailed within 24hrs of research staff at site becoming aware of event
Change of status CRF	At the point of discontinuation or withdrawal

Paper CRFs must be completed, signed/dated and returned to the ACCURE-UK 2 Trial Office by the Investigator or an authorised member of the site research team (as delegated on the ACCURE-UK 2 Trial Signature & Delegation Log) within the timeframe listed above. Entries on paper CRFs should ideally be made in ballpoint pen, in black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form will be consistent with the source data and any discrepancies will be explained. If information is unknown, this must be clearly indicated on the CRF. Staff delegated to complete CRFs will be trained to adhere to CRF completion guidance provided by the ACCURE-UK 2 Trial Office.

In all cases it remains the responsibility of the site's PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the site's PI on the CRF.

10.3 Participant completed questionnaires

Patients will fill in a health-related quality of life (QoL) questionnaires (EQ-5D-3L, EORTC-QLQ-C30-QL and IBDQ) at baseline (i.e. after consent and randomisation) and every 3 months post-randomisation for one year.

The baseline and 12-month (or relapse) QoL questionnaires will be completed by the patient in clinic, with the support of the research nurse, if necessary. The 3, 6 and 9-months post-randomisation QoL questionnaires will be posted to the participants for completion and return to the ACCURE-UK 2 Trial Office using pre-paid, addressed envelopes supplied to with the questionnaires.

Patients will be contacted by telephone every 3 months by a trial nurse to assess medication usage, complications, additional interventions, re-admissions, duration of hospital stay and visits to the outpatient clinic, number of days of sick leave and of social in attendance and to ensure completions of the questionnaires.

10.4 Data Management

Processes will be employed to facilitate the accuracy of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan. Coding and validation will be agreed between the trial team and the trial database will be signed off once the implementation of these has been assured.

Missing and ambiguous data will be queried using a Data Clarification system in line with the ACCURE-UK 2 Data Management Plan, and will focus on data required for trial outcome analysis and safety reporting. Single data entry with central monitoring will be employed.

CRFs will be completed in hard copy at each site with originals forwarded to the BCTU when completed. A copy will be kept at the local site. The ACCURE-UK 2 Trial Office will be responsible for uploading the data from hard copy into the electronic CRF.

The electronic CRF will be held on the ACCURE-UK 2 database. This is a secure online database that allows research teams to collect and store research data. The software is hosted on University of Birmingham secure servers and only accessible via controlled username and password access.

Data reported on each CRF should be consistent with the source data or the discrepancies should be explained. Completed CRFs will be reviewed by the ACCURE-UK 2 Trial Office for completeness. All missing and ambiguous data will be queried. A database system will be used to generate data clarification forms (DCFs). These will be generated on a regular basis by ACCURE-UK 2 Trial Office staff and reported to the site for clarification.

The process of entering data on to the database, itself forms a data quality check, as ranges are put in place to ensure that only viable data values can be input.

Questionnaires completed remotely by participants will be received by BCTU and will be transcribed directly onto the database. Given that these are patient reported outcomes, a data query process cannot be implemented.

Self-evident corrections by the ACCURE-UK 2 Trial Office will only be used following agreement with the local PI.

CRFs may be amended and the versions updated by the ACCURE-UK 2 Trial Office, as appropriate, throughout the duration of the trial. Whilst this may not constitute a protocol amendment, new versions of the CRFs must be implemented by participating sites immediately on receipt.

10.5 Data Security

The security of the System is governed by the policies of the University of Birmingham. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the University of Birmingham have to be registered with the Data Protection Officer and data held in accordance with the General Data Protection Regulations 2018 (GDPR). The University will designate a Data Protection Officer

upon registration of the study. The Study Centre has arrangements in place for the secure storage and processing of the study data which comply with the University of Birmingham policies.

The System incorporates the following security countermeasures:

- Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.
- Logical measures for access control and privilege management: including restricted accessibility, access-controlled servers, separate storage of identifiable data etc.
- Network security measures: including site firewalls, antivirus software and separate secure network protected hosting etc.
- System Management: the System shall be developed by the BCTU Programming Team and will be implemented and maintained by the BCTU Programming Team.
- System Design: the system shall comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.
- Operational Processes: the data will be processed and stored within the Study Centre (University of Birmingham).
- Data processing: Statisticians will have access to anonymised data.
- System Audit: The System shall benefit from the following internal/external audit arrangements:
    - Internal audit of the system
    - An annual IT risk assessment
- Data Protection Registration: The University of Birmingham has Data Protection Registration to cover the purposes of analysis and for the classes of data requested. The University's Data Protection Registration number is Z6195856.

10.6 Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, ISF, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years. No documents will be destroyed without prior approval from the ACCURE-UK 2 Trial Office.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Site Set-up and Initiation

All PIs will be asked to sign the necessary agreements including an ACCURE-UK 2 Site Signature and Delegation Log between the PI and the BCTU and supply a current CV and GCP certificate to BCTU. All members of the site research team are required to sign the ACCURE-UK 2 Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of site initiation, either a meeting or a teleconference. At the site initiation visit (SIV), which key members of the site research team are required to attend, the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping will be discussed.

Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The BCTU ACCURE-UK 2 trials team must be informed immediately of any change in the site research team.

11.2 Monitoring

The monitoring requirements for this trial have been developed following trial specific risk assessment by BCTU and as documented in the ACCURE-UK 2 monitoring plan.

11.3 Onsite Monitoring

On-site monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan. Any monitoring activities will be reported to the trials team and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations (also defined in the monitoring plan).

If a monitoring visit is required, investigators will allow the ACCURE-UK 2 trial staff access to source documents as requested.

11.4 Central Monitoring

ACCURE-UK 2 will be centrally monitored, however on-site monitoring may occur if triggered. The ACCURE-UK 2 Trial Office will be in regular contact with the site research team to check on progress and address any queries that they may have. The ACCURE-UK 2 Trial Office will check incoming CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

11.5 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The investigator will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections.

11.6 Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial. Sites are therefore requested to notify the Trials Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring will be reported to the Trial Management Group, Trial Steering Committee and the REC. A copy is sent to the University of Birmingham Clinical Research Compliance Team at the time of reporting to the REC.

12 END OF TRIAL DEFINITION

The end of trial is defined as the last participant's last visit, i.e. the 12 month post-randomisation visit of the last participant.

The ACCURE-UK 2 Trials Office will notify the REC and RGT within 90 days of the end of trial. Where the trial has terminated early, the Trials Office will inform the REC within 15 days of the end of trial. The Trials Office will provide them with a summary of the clinical trial report within 12 months of the end of trial.

13 STATISTICAL CONSIDERATIONS

13.1 Sample Size

The Dutch ACCURE trial is powered on a clinically relevant reduction in relapse rate from an expected 40% in the control group to 20% in the intervention group. Testing for a difference in proportions and using an alpha of 0.05, we find that 164 patients are needed (82 per arm) to detect such a difference at 80% power. Allowing for a 10% attrition, our Dutch collaborators intend to randomise 182 patients (91 per arm).

To increase the power from 80% to 90% requires around an additional 60 patients (including 10% attrition) for a total of 244 patients (122 per arm). We therefore propose to recruit 90 patients in the UK, to both power up the trial and help complete main recruitment.

13.2 Analysis of Outcome Measures

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below. The primary comparison groups will be composed of those randomised to laparoscopic appendicectomy versus those randomised to standard medical therapy. In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised irrespective of compliance or other protocol deviation. For all major outcome measures, summary statistics and differences between groups (e.g. relative risks) will be presented, with 95% confidence intervals and p-values from two-sided tests also given. No adjustment for multiple comparisons will be made.

13.2.1 Primary Outcome Measure

The relapse rate in the two groups will be compared using a chi-squared test. The relative risk and 95% confidence interval will be provided alongside the p-value.

13.2.2 Secondary Outcome Measures

Time to relapse will be analysed using standard survival analysis techniques. Medication usage will be compared using the Mann-Whitney U test. Differences in quality of life, disease activity and morbidity will be analysed using mixed-models analysis of variance for repeated measures.

13.2.3 Subgroup Analyses

No subgroup analyses are planned.

13.2.4 Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk.

13.3 Planned Interim Analysis

An interim review will be performed at 25, 50, 100, 150 and 200 included patients. At 9 weeks after inclusion of these patients the trial's safety data should be evaluated. The DMC will be supplied the number of (serious) adverse events in both groups at the three mentioned time points.

If there is a skewed distribution of the number of (serious) adverse events between the two groups, an efficacy analysis can be performed at the discretion of the DMC.

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the study. The committee will meet prior to study commencement to agree the manner and timing of such analyses but this is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (SAEs) at least at annual intervals. Criteria for stopping or modifying the study based on this information will be ratified by the DMC. Details of the agreed plan will be written into the Statistical Analysis Plan. Further details of DMC arrangements are given in section 14.5.

13.4 Planned Final Analyses

The primary analysis for the study will occur once all participants have completed the final assessment and corresponding outcome data has been entered onto the study database and validated as being ready for analysis.

13.5 Health economics analysis

The economic evaluation will be performed from a societal perspective as a cost-effectiveness and cost-utility analysis. Primary outcomes in the economic evaluation are costs per patient related to the appendicectomy and the non-surgical treatment and costs per QALY gained. Additional one way sensitivity analyses will determine how changing treatment costs might impact the results. Standard unit prices will be used when available, complemented by results from cost calculations where needed. The cumulative total costs will be calculated for the 12 month study period. Furthermore the cost effectivity (costs per prevented relapse) will be calculated.

Direct medical costs and indirect costs arising from losses in productivity will be assessed.

14 TRIAL ORGANISATIONAL STRUCTURE

14.1 Sponsor

The University of Birmingham is the sponsor for the ACCURE-UK 2 trial. It takes overall responsibility for initiation, management and financing of the trial.

ACCURE-UK 2 is the UK arm of the Dutch ACCURE trial.

14.2 Coordinating Centre

The ACCURE-UK 2 office is based at the University of Birmingham Clinical Trials Unit.

14.3 Trial Management Group

The ACCURE-UK 2 TMG is responsible for the day to day management of the trial. Membership of the TMG is listed at the front of the protocol. The role of the TMG is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

Representatives from the UK TMG (Mr Tom Pinkney and Dr Laura Magill) will also be members of the Dutch ACCURE TMG.

14.4 Trial Steering Committee

The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial.

An ACCURE-UK 2 TSC will be convened. Membership is listed at the front of this protocol and responsibilities are outlined in the TSC Charter. In summary, the TSC will provide overall oversight of the trial, including the practical aspects of the study, as well as ensuring that the study is run in a way which is both safe for the participants and provides appropriate feasibility data to the sponsor and investigators. The TSC will consider and act, as appropriate, upon the recommendations of the DMC. The TSC ultimately carries the responsibility for deciding whether the trial needs to be stopped on grounds of safety or efficacy.

The TSC will meet early at the start of the trial, ideally prior to the start of recruitment in the UK. The TSC will then meet annually by teleconference or at face-to-face meetings.

14.5 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) has been established by the sponsor of the Dutch ACCURE trial. The data from the ACCURE-UK 2 trial will be pooled with the Dutch data; for this reason a separate UK DMC will not be established.

The DMC performed an interim analyses at 25, 50, 100, 150 and 200 patients randomised. Subsequent meetings will be held annually until the trial closes to recruitment.

The membership of the DMC is:

1. M. Koelemay, MD, PhD, surgeon AMC, clinical epidemiologist
2. T. Karsten, MD, PhD, surgeon Onze Lieve Vrouwe Gasthuis
3. J. van der Meer, MD, PhD, internist AMC

Data analyses will be supplied in confidence to the independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC operate in accordance with a trial specific charter based upon the template created by the Damocles Group.

The DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. The DMC will report directly to the Trial Steering Committee. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety. The trial will stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community.

14.6 Finance

The ACCURE-UK 2 trial is funded by the Efficacy and Mechanism Evaluation programme of the NIHR.

Funding will be provided to sites on a recruited and followed-up per patient basis. The funding will provide support for the costs associated with the endoscopies; research nurse time for sample and data collection and follow-up visits; Mayo score assessment by clinicians at relapse, plus the cost of laparoscopic staplers for those patients allocated to the intervention arm.

The ACCURE-UK 2 trial has been adopted onto the NIHR CRN portfolio; sites will receive support for each patient recruited into the trial.

15 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996.

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the General Data Protection Regulations and Human Tissue Act 2008) and the Principles of GCP.

Before any participants are enrolled into the trial, the PI at each site is required to obtain local R&D approval/assurance. Sites will not be permitted to enrol participants until written confirmation of R&D approval/assurance is received by the BCTU trials team.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

16 CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation 2018.

Participants will always be identified using their unique trial identification number and initials on the CRF and correspondence between the BCTU. The full name and birth date of the patient will only be recorded on the ICF and baseline CRF.

Participants will give their explicit consent for the transfer of their ICF, giving permission for BCTU to be sent a copy from the site where they were entered into the trial. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to BCTU (e.g. Participant Recruitment and Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

Representatives of the ACCURE-UK 2 trial team and sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

As the ACCURE-UK 2 trial is the UK arm of the Dutch ACCURE trial, data analysis will be performed by the ACCURE team at the Academic Medical Center (AMC) in Amsterdam. To enable the analysis, anonymised data will be transferred to the AMC. Data will be transferred for analysis by the DMC and for the final analysis. Patients will be made aware of the transfer of data in the PIS.

17 FINANCIAL AND OTHER COMPETING INTERESTS

This is an investigator-led trial funded by the Efficacy and Mechanism Evaluation programme of the NIHR. The members of the trial oversight committees (TMG, TSC and DMC) have no financial or other competing interests.

18 INSURANCE AND INDEMNITY

The University of Birmingham has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

19 PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the UK and Dutch Trial Management Group.

All primary outputs relating to the combined Clinical Trial and UK Clinical Trial will be coordinated by AMC and published under a corporate authorship group (the name of such group will be agreed by the in advance), preceded by first authors as determined by the ACCURE Steering Committee. Each publication will include a detailed description of exact contributions of each Party, following accepted guidelines for collaborative authorship models. Only participating doctors from other centres will participate in publication if a substantial contribution to the trial (e.g. patient accrual, full completion of CRF or intellectual input) is made.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of The University of Birmingham and funding from the National Institute for Health Research. Intellectual property rights will be addressed in the ACCURE-UK 2 Clinical Study Site Agreement between Sponsor and site.

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21 APPENDIX 1: Calculation of Mayo score

Parameter	Subscore
A. Stool pattern?	
Patient reports a normal number of daily stools	0
1 to 2 stools more than normal	1
3 to 4 stools more than normal	2
5 or more stools than normal	3
B. Most Severe Rectal Bleeding of the Day?	
None	0
Blood streaks seen in the stool less than half the time	1
Blood in most stools	2
Pure blood passed Note: A score of 3 for bleeding requires patients to have at least 50% of bowel motions accompanied by visible blood and at least one bowel motion with blood alone.	3
C. Endoscopic Findings?	
Normal or inactive colitis seen	0
Mild colitis: mild friability, erythema, decrease in vascuality	1
Moderate colitis: friability, marked erythema, vascular pattern absent, erosions seen	2
Severe colitis: ulcerations and spontaneous bleeding	3
D. Global assessment by Physician?	
Normal	0
Mild colitis	1
Moderate colitis	2
Severe colitis	3
PARTIAL Mayo Score (A+B+D)	**0-9**
FULL Clinical Mayo Score (A+B+C+D)	**0-12**

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