The feasibility of undertaking Appendicectomy to impact upon the Clinical Course of Ulcerative Colitis - The ACCURE-UK Trial Feasibility study

ACCURE-UK TRIAL PROTOCOL
Version 3.0 10/12/2014

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Funder: Research for Patient Benefit (RfPB)
ISRCTN: ISRCTN56523019
Main REC Ref. No.: 14/NE/1143
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### Abbreviations

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<tr>
<td>AE</td>
<td>Adverse event</td>
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<td>AR</td>
<td>Adverse reaction</td>
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<td>BCTU</td>
<td>Birmingham Clinical Trials Unit at the University of Birmingham</td>
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<td>CI</td>
<td>Chief Investigator</td>
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<td>DMEC</td>
<td>Data Monitoring and Ethics Committee</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>ISRCTN</td>
<td>International Standard Randomised Controlled Trial Number</td>
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<td>MREC</td>
<td>Multicentre Research Ethics Committee</td>
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<td>PI</td>
<td>Principal Investigator</td>
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<td>PIS</td>
<td>Participant Information Sheet</td>
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<td>RR</td>
<td>Relative Risk</td>
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<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>SOP</td>
<td>Standard Operating Procedure</td>
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<td>TMG</td>
<td>Trial Management Group</td>
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<td>TSC</td>
<td>Trial Steering Committee</td>
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<td>UC</td>
<td>Ulcerative Colitis</td>
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</table>
## CONTENTS

1. BACKGROUND .................................................................................................................. 1
  1.1. Ulcerative Colitis ........................................................................................................ 1
  1.2. The role of the appendix in ulcerative colitis .......................................................... 1
  1.3. Clinical evidence of the interaction between the appendix and UC activity ........... 2
  1.4. Potential benefits to patients and the NHS ............................................................... 3
  1.5. The need for the ACCURE-UK feasibility study ..................................................... 3
  1.6. The future phase III trial ......................................................................................... 3

2. TRIAL DESIGN .................................................................................................................. 4
  2.1. Trial Objectives ......................................................................................................... 4

3. ELIGIBILITY ....................................................................................................................... 5
  3.1. Inclusion and Exclusion Criteria ............................................................................... 5
  3.2. Centre eligibility ....................................................................................................... 5

4. PATIENT ENTRY ............................................................................................................... 5
  4.1. Identifying potential participants for consent ......................................................... 5
    4.1.1 ACCURE-UK qualitative research study ........................................................... 6
  4.2. Obtaining consent .................................................................................................... 7
  4.3. Informing the participant’s GP ................................................................................ 7
  4.4. Screening logs and acceptance rate ........................................................................ 7
  4.5. Baseline investigations ........................................................................................... 8

5. RANDOMISATION ............................................................................................................ 8
  5.1. Randomisation ......................................................................................................... 8
  5.2. Randomisation method ............................................................................................ 8

6. TREATMENT ALLOCATIONS ......................................................................................... 8
  6.1. Standard Treatment .................................................................................................. 8
  6.2. Experimental Arm .................................................................................................... 8
  6.3. Withdrawal of treatment or protocol violation ...................................................... 9
  6.4. Compatibility with other studies ............................................................................ 9

7. CLINICAL FOLLOW-UP ................................................................................................. 9
  7.1. Follow-up assessments and data collection ............................................................ 10
  7.2. Timing of assessments ............................................................................................ 10
  7.3. Data management and validation ........................................................................... 10
  7.4. Confidentiality of personal data ............................................................................ 11
  7.5. Definition of the End of Trial ................................................................................ 11

8. QUALITATIVE RESEARCH ARM .................................................................................. 11
  8.1. Interview schedule .................................................................................................. 11
  8.2. Summary of qualitative interviews and timings ..................................................... 12

9. SAFETY MONITORING PROCEDURES ...................................................................... 12
  9.1. General Definitions .................................................................................................. 12
9.2. Reporting SAEs ............................................................................................................ 14
9.3. Timeframes for reporting of SAEs ............................................................................ 14
9.4. Notification of deaths ............................................................................................... 14
9.5. Pharmacovigilance responsibilities ......................................................................... 14
9.6. Notification of Serious Breaches of GCP and/or the protocol ................................... 15
10. STATISTICAL CONSIDERATIONS ............................................................................ 15
10.1. Sample size .............................................................................................................. 15
10.2. Projected accrual and attrition rates ....................................................................... 16
10.3. Statistical Analysis .................................................................................................. 16
10.3.1 Feasibility and Acceptability ............................................................................... 16
10.3.2 Outcome Data ....................................................................................................... 16
10.4. Qualitative Analysis ............................................................................................... 17
10.5. Cost-effectiveness Analysis .................................................................................... 17
11. DATA ACCESS AND QUALITY ASSURANCE ............................................................ 17
11.1. Confidentiality of personal data ............................................................................. 17
11.2. In-house Data Quality Assurance ......................................................................... 17
11.2.1 Monitoring and Audit ......................................................................................... 17
11.2.2 Statistical monitoring throughout the trial ............................................................ 17
11.3. Long-term storage of data ..................................................................................... 18
12. ORGANISATION AND RESPONSIBILITIES .............................................................. 18
12.1. Principal Investigator at each centre ....................................................................... 18
12.2. Research Co-ordinator at each centre .................................................................. 18
12.3. The ACCURE-UK Trial Office .............................................................................. 19
13. RESEARCH GOVERNANCE ...................................................................................... 19
13.1. Regulatory and Ethical Approval ........................................................................... 19
13.2. Funding and Cost implications .............................................................................. 20
13.3. Sponsor ................................................................................................................... 20
13.4. Indemnity ............................................................................................................... 20
13.5. Clinical Trials Unit ............................................................................................... 20
13.6. Confidentiality of Personal Data ........................................................................... 21
13.7. Publication ............................................................................................................. 21
14. REFERENCES ............................................................................................................ 22
1. BACKGROUND

1.1. Ulcerative Colitis

Chronic relapsing disease such as ulcerative colitis (UC) incurs 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. UC carries an annual incidence of 8-15/100,000 new cases and a prevalence of 100-200/100,000 in the United Kingdom. At least 50,000 people are suffering from UC in the UK at present.1-3

Most UC patients can be treated effectively with medical therapy, but when the disease is unresponsive surgery is indicated usually requiring a total colectomy. Up to 25% will ultimately require surgery; this takes place as an emergency if the patient suffers a severe refractory attack of colitis. This surgery is high risk with a complication rate in excess of 30% and many months of recovery.4 Patients may also be left with a stoma.

A significant proportion 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 around 40% which will require escalation to high dose steroid medication with its incumbent risks and toxicity.5 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.2

Treatment of UC falls into two main categories – maintenance therapy (preventing disease relapse) and breakthrough therapy (treating active disease relapses). Almost all patients will remain on long-term maintenance therapy with 5-ASA tablet medication unless their disease has been quiescent for some time. Treatment of disease relapse normally follows a stepwise approach with escalation of 5-ASA, topical therapies and potentially oral steroids. Severely unwell patients require hospital admission for intravenous steroids. Refractory patients may require immunomodulatory therapy and there is emerging evidence exploring the role of biological therapy for these patients. Those patients who are unresponsive to maximal medical therapy will require surgical resection of the whole colon and rectum.

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

1.2. The role of the appendix in ulcerative colitis

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. 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:

a. The appendix as a source of bacterial load in the induction and regulation of colitis

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-prone 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\textsuperscript{8}.

b. The appendix as a source of innate lymphoid cells

Recently 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\textsuperscript{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 TCR\textsubscript{a/-} 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\textsuperscript{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.

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\textsuperscript{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\textsuperscript{14}.

There is now 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 the research described in this protocol and is outlined below.

Bolin and colleagues undertook appendicectomy in 30 adults with UC and found significant improvement in ‘simple clinical activity index’ in 90\% of patients with a median disease score of 9 pre-operation reducing to 2 post operation (p<0.0005)\textsuperscript{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)\textsuperscript{16}. Further smaller series or individual cases have appeared from Japan, Korea, France and Sweden\textsuperscript{17-21}. 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.
1.4. Potential benefits to patients and the NHS
The evidence discussed suffers from publication bias, but as a collective body provides support for the hypothesis that appendicectomy may improve the clinical course of UC. This novel intervention requires evaluation in a prospective multicentre RCT as it is not currently employed as a therapeutic treatment for UC.

If an appendicectomy can protect UC patients from future use of medication, hospital admission and thereby the need for major colonic re-sectional surgery, the initial minor morbidity from appendicectomy will be offset by substantial long-term gain in health and quality of life, as well as reduced health resource usage.

If it can be demonstrated that appendicectomy is an efficacious and cost-effective strategy that is acceptable to patients and their clinicians, widespread uptake can be anticipated.

1.5. The need for the ACCURE-UK feasibility study
A feasibility study is required before a definitive phase III randomised control trial (RCT) can be undertaken. The aim of the ACCURE-UK trial will be to determine the feasibility of randomising patients between standard medical therapy and appendicectomy (plus standard therapy).

The feasibility study will evaluate accrual and retention rates and establish throughput rates of eligible patients. Patients will be followed for a one year period after randomisation allowing evaluation and optimisation of the patient pathway and follow-up strategy. Full 30 day post-operative adverse event data for the patients undergoing appendicectomy will be collected to establish the safety profile of the intervention in this group of patients. The relapse rate in the control arm over the one-year period will be established, which will be important to inform the sample size for a phase III trial. A qualitative research study is embedded within Accure-UK which is primarily designed to explore patient and clinician acceptability regarding both the intervention and the trial.

1.6. The future phase III trial.
If the feasibility study suggests that appendicectomy is an acceptable treatment option for UC patients and clinicians, a major multicentre randomised trial to investigate the clinical efficacy of this intervention would be anticipated.

A future phase III study, would aim to answer the following questions:

1. Does laparoscopic appendectomy lower the relapse rate of patients with an established diagnosis of UC and recent disease flare-up?

2. Does laparoscopic appendectomy prolong the time to relapse?

3. Do patients with UC treated with appendectomy have an overall better health-related quality of life compared to those patients treated with standard medical care?

4. Is laparoscopic appendectomy a cost-effective strategy in the treatment of UC compared to standard medical care?
2. TRIAL DESIGN

ACCURE-UK is an external feasibility study. It is designed as a prospective, multi-centre randomised controlled trial.

The objective of the ACCURE-UK feasibility study is to assess the feasibility and inform the design of a large, phase III, multi-centre randomised trial comparing standard medical therapy versus appendicectomy plus medical therapy.

2.1. Trial Objectives

- Explore whether appendicectomy is an acceptable treatment option to UC patients and clinicians and if patients are willing to be randomised to a trial where appendicectomy forms one treatment arm
- Determine the numbers of eligible, approached and randomised patients and ascertain the optimal recruitment pathways
- As it is likely that relapse rate would be the primary outcome measure in a phase III trial, this feasibility study will provide estimates of relapse rate in the control arm and inform the sample size calculations for a future phase III trial.
- Estimate the morbidity profile of the appendicectomy operation
- Patient-related outcomes, e.g. patients will be asked about disease-related work absence and loss of earnings to try and establish the ability to collect social economics data.
- Determine the suitability of the QoL outcome measures
- Pilot bespoke health economic evaluation questionnaires
- Test the one-year follow-up strategy for the future phase III trial. This will assess the acceptability of the follow up tools for a future phase III RCT. This will assess the utility and acceptability of the follow-up tools while exploring alternative options
3. ELIGIBILITY

3.1. Inclusion and Exclusion Criteria

In order that patients are randomised into the ACCURE-UK trial, patients must fulfil all eligibility criteria. Investigators will be asked to confirm eligibility criteria at randomisation.

Inclusion criteria
1. Histologically confirmed ulcerative colitis
2. Disease relapse within 12 months of randomisation, requiring steroid medication prescribed by hospital or GP.
3. In clinical remission at time of randomisation with clinical Mayo score less than 3 and presumptive endoscopic Mayo score of 0 or 1 (to be confirmed later at baseline endoscopy)
4. Aged 18 or over
5. Patient able and willing to give written informed consent.

Exclusion criteria
1. Previous appendicectomy
2. Previous major abdominal surgery which would preclude safe laparoscopic appendicectomy
3. Uncertain histological findings or any suspicion of Crohn’s disease
4. Infective diarrhoea confirmed by positive stool culture
5. Ongoing active colitis at time of randomisation
6. Patients still on steroid medication for ongoing active or previously active colitis at time of randomisation.
7. Patients with significant comorbidity that prevents surgery (e.g. unstable heart failure)

3.2. Centre eligibility

This feasibility study will be performed in at least 6 major UK National Health Service hospitals and will involve both gastroenterologists and general surgeons at each site.

4. PATIENT ENTRY

4.1. Identifying potential participants for consent

This feasibility study will be performed in at least 6 major UK NHS trusts and will involve both gastroenterologists and general surgeons at each site.

It is envisaged that potentially eligible patients will be identified from one of two scenarios:
- Gastroenterology outpatient clinic
- Inpatients on the gastroenterology wards (who are being discharged home, having recovered from a flare of UC activity that has been successfully treated medically).

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 patient information sheet (PIS). If needed, a further gastroenterology medical or research appointment will be offered to further discuss the trial.
If patients are willing to consider entry to the trial, they will meet with a consultant colorectal surgeon within the following 4 weeks 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 this second assessment visit, once clinical disease remission and eligibility has been confirmed, written informed consent can be obtained for the main study.

Patients randomised to the intervention will be under the care of the surgical team for pre-op assessment and appendicectomy. At 6 weeks following surgery the patients will then be followed up in surgical outpatient clinics. Both groups will then be followed up in gastroenterology outpatient clinics, research clinics or by phone at 3, 6, 9 and 12 months post-randomisation.

4.1.1 ACCURE-UK qualitative research study

The qualitative research study will aim to understand the perspectives and experiences of patients that are approached to take part in the randomised study, including those who subsequently reject entry to the trial, and those who agree to participate. The anticipated pathway is detailed below and a script will be provided to the research team to introduce the qualitative study to the patients.

Patients will be told about the qualitative study at the same first appointment where they are given the PIS for the randomised study. Patients who reject entry to the trial (either at the first appointment, or at a subsequent appointment with a surgeon), and who have expressed an interest in taking part in an interview will be given the relevant interview PIS for trial non-participants at that point, and asked to complete a contact details form (to be forwarded to the qualitative research fellow).

Patients who agree to take part in the trial and who have expressed an interest to take part in an interview will be given the relevant interview PIS for trial participants, and similarly asked to complete a contact details form. Patients will also be asked to complete the relevant section of the consent form.

The contact form will be returned to the ACCURE-UK trial office together with the consent form. All patients who have completed contact details forms will then be contacted by the qualitative research fellow who will make arrangements for the interviews, and take informed consent for the qualitative study prior to commencement of the interviews.

4.1.2 ACCURE-UK Mechanistic Research Study

Some patients entering the trial will be approached for participation in an additional mechanistic sub-study. This would be an optional extra extension and would involve their donation of blood samples and bowel mucosal biopsies at baseline and at 12 months. This is likely to be undertaken primarily at the primary site of Queen Elizabeth Hospital, Birmingham, but other local West Midlands sites may also be involved at a later date. These samples, as well as the appendix specimens from those randomised to the intervention arm, will be centralised to our research laboratories at the University of Birmingham for analysis.
It is important to highlight that no extra research visits are needed, and the only additional invasive element is the blood tests, as trial participants will already be undergoing endoscopic mucosal evaluation as part of the standard trial protocol. Separate consent for donation of these specimens and involvement in this sub-study will be obtained (appendix YY), and it will be made clear that patients do not need to participate in this component of the research if they do not want to; and they can remain in the main ACCURE-UK trial alone.

This exploratory mechanistic sub-study has been funded separately by a small grant from the Bowel Disease Research Foundation (BDRF). The over-arching aim is to try and determine the mechanism of action of an appendicectomy intervention in chronic Ulcerative Colitis patients, using a hypothesis-driven investigation of a novel mucosa lymphocyte subset. We will focus on the immune regulatory mechanism governed by mucosa-associated invariant T (MAIT) cells and explore their putative role in potentiating UC. Further information about the mechanistic study can be found in Appendix B

4.2. Obtaining consent
The patient’s written informed consent to participate in the trial must be obtained before randomisation and after a full explanation has been given of the study. Written informed consent will be obtained by a trained member of the research team (with GCP training, knowledge of the trial protocol, and delegated authority from the local PI). Within the ACCURE-UK trial, it is anticipated that consent will usually be obtained by a surgeon, gastroenterologist or research nurse at site (once they have seen the surgeon).

Once written informed consent is obtained, the original copy should be kept in the ACCURE-UK study site file, one given to the patient, one kept in the patient’s notes and one sent to the ACCURE-UK study office.

Written informed consent for the research interviews will be obtained by the qualitative fellow prior to commencement of the interviews.

Informed consent must be obtained before any trial-related procedures are undertaken.

4.3. Informing the participant’s GP
The patient’s GP should be notified, with the patient’s consent, and a specimen “Letter to GP” is supplied for use by investigators.

4.4. Screening logs and acceptance rate
In order to ascertain throughput and further assess acceptability, a screening log will be kept by the research team at each participating site. Details will be recorded of all patients considered eligible, those approached and recruited and also on those who decline randomisation. Details recorded will also include the reason for non-randomisation and subsequent management plan.

Twelve patients who have declined randomisation will be approached to participate in the ACCURE-UK qualitative study which (Section 8).
4.5. Baseline investigations
Prior to randomisation and any treatment, all study patients will undergo baseline assessments:

- Quality of Life questionnaires: EuroQol EQ-5D, EORTC-QLQ-C30 and IBDQ
- Baseline endoscopy examination to confirm disease remission macroscopically and microscopically if last endoscopic examination has not been within the last 3 months.

5. RANDOMISATION
5.1. Randomisation
48 patients will be randomised into the ACCURE-UK trial by the Birmingham Clinical Trials Unit in a 1:1 ratio between standardised medical therapy and standardised medical therapy plus interval appendicectomy.

5.2. Randomisation method
Once eligibility has been confirmed and after written informed consent has been obtained, patients can be randomised into the trial.

Patients are randomised into the trial online at the ACCURE-UK website, [https://www.trials.bham.ac.uk/ACCURE](https://www.trials.bham.ac.uk/ACCURE)
Or by telephone call to the randomisation service (0800 953 0274)

Telephone randomisation is available Monday-Friday 0900-1700.
Online randomisation is available 24 hours a day, 7 days a week apart from short periods of scheduled maintenance and occasional network problems.
For the secure online randomisation website, each randomiser will be provided with a unique username and password.
Randomisation notepads will be provided to investigators and should be used to collate the necessary information prior to randomisation. The person randomising will need to answer all of the questions before a treatment allocation and a trial number is given.

6. TREATMENT ALLOCATIONS
6.1. Standard Treatment
Patients in both arms of this study will receive standardised medical maintenance therapy in the form of oral 5-ASA at a dose of 2g per day.
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.

6.2. Experimental Arm
Patients in the intervention arm will undergo laparoscopic appendicectomy. This will be performed by a consultant general surgeon on an elective (planned) theatre list using a standardised 3-port technique. This will be performed within 6 weeks of randomisation.
In addition to the operation, from the date of randomisation patients in this arm will also receive the same standardised medical maintenance therapy in the form of oral 5-ASA at a dose of 2g per day.

**6.3. Withdrawal of treatment or protocol violation**

Patients may withdraw at any time during the trial if they choose not to continue, or if their clinical team feel that continued participation in the trial is inappropriate.

There are different types of withdrawal:

- The patient would like to withdraw from the randomised treatment allocation, but is willing to be followed-up according to the trial protocol (i.e. has agreed that follow-up data can be collected)

- The patient does not want to attend trial specific follow-up visits, but has agreed to be followed-up according to standard practice (i.e. has agreed that follow-up data can be collected at standard clinic visits)

- The patient is not willing to be followed up for trial purposes at any further visits (i.e. has agreed that any data collected prior to the withdrawal of consent can be used in the trial final analysis)

Full details of the reason(s) for withdrawal should be recorded on the Case Report Forms (CRFs) if healthcare professional-initiated, otherwise a simple statement reflecting patient preference will suffice. Patients who withdraw from trial treatment, but continue with ongoing follow-up and data collection should be followed-up in accordance with the protocol.

**6.4. Compatibility with other studies**

Patients can be in both ACCURE-UK 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 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 trial office to discuss these patients’ eligibility prior to randomisation.

**7. CLINICAL FOLLOW-UP**

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

CRFs can be entered online at [http://www.trials.bham.ac.uk/ACCURE](http://www.trials.bham.ac.uk/ACCURE). Authorised staff at sites will require an individual secure login username and password to access this online data entry system. If data is being collected on paper CRFs, these must be completed, signed/dated and returned to the ACCURE-UK Trial Office by the Investigator or an authorised member of the site research team (as delegated on the ACCURE-UK Trial Signature & Delegation Log) within the timeframe listed below. Entries on paper CRFs should 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 CRF should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the CRF. All missing and ambiguous data will be queried. All sections are to be completed.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

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

### 7.1. Follow-up assessments and data collection

Clinical follow-up and data collection will be undertaken up to 1 year from randomisation. Data will be collected at baseline, postoperative, 6-week post-op, 3, 6, 9 and 12 months post-randomisation.

All patients will have an endoscopy examination at baseline and at 12 months post-randomisation.

#### 7.2. Timing of assessments

<table>
<thead>
<tr>
<th></th>
<th>Prior to randomisation</th>
<th>Baseline – prior to treatment</th>
<th>At discharge: post-surgery</th>
<th>6 weeks post-op</th>
<th>3 months post-randomisation</th>
<th>6 months post-randomisation</th>
<th>9 months post-randomisation</th>
<th>12 months post randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Written informed consent a</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>QoL b</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Surgical morbidity c</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Relapse evaluation</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Evaluate throughout the course of the study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. For both the feasibility and qualitative study

b. EQ-5D, EORTC-QLQ-C30 and IBQQ questionnaires to be completed at all designated time points.

c. Surgical morbidity only relevant for those patients randomised to appendicectomy

### 7.3. Data management and validation

Data should be collated directly from the patient or the patient hospital notes using the ACCURE-UK case report forms. Data should be entered as soon as possible onto the ACCURE-UK database as soon as possible after collection by the Research Coordinator, investigator or local PI, who will be allocated personal usernames and passwords that restrict access to only
participants at their centre. Alternatively, paper forms can be sent to the ACCURE-UK Trial Office for central input. Data validation is built into the database so that range, date and logic checks are performed at the point of data entry. Email and letter reminders will be sent to the investigator and research coordinator for missing CRFs, missing data or data inconsistencies.

7.4. Confidentiality of personal data
All data will be handled in accordance with the UK Data Protection Act 1998. All CRFs, with the exception of the consent form, will not bear the participant’s name. The participant’s initials, date of birth and trial identification number will be used for identification.

7.5. Definition of the End of Trial
The end of the trial for regulatory purposes is defined as the date of the last visit of the last patient undergoing protocol based treatment. Within ACCURE-UK, this is once the last participant has reached 1 year follow-up.

Long-term follow-up to at least one year post-trial entry will constitute the end of the non-interventional phase of the trial.

8. QUALITATIVE RESEARCH ARM
Qualitative research with patients and clinicians will provide a detailed picture of key stakeholder perspectives on trial acceptability, design and processes, thereby contributing to the design of the definitive phase III study.

8.1. Interview schedule
In-depth interviews with patients consenting to be randomised and allocated to appendicectomy (n≈12) and standard treatment (n≈12), will be carried out following randomisation. These will provide data on patient perspectives regarding consent to participate, understanding of trial aims and processes, expectations for participation, outcome preferences and priorities, and views on treatment allocation. These interviews will also explore participants’ personal experience and history of ulcerative colitis, such as previous treatment and flare ups, in order to place perspectives on trial participation within this context.

Trial participants will be invited to repeat interview at 12 months follow up where their experience of trial participation, treatment and outcomes will be explored. Interviews will also be conducted with a sample (n≈15) of patients who refused consent to participate in order to understand this decision-making. For example, whether non consent is influenced by personal and disease related factors or by understanding of trial aims and processes.

Colorectal surgeons and gastroenterologists (n≈12) from participating centres will be interviewed at the end of the feasibility study to gather data focusing on trial participation across the centres. Together with the follow up patient interviews this will provide a qualitative trial process evaluation. We will also interview clinicians who did not participate (n=12), sampled via the West Midlands NIHR IBD network, to ensure that we have a broad understanding of trial acceptability amongst the clinical community. These clinician interviews will also allow the research team to understand clinical outcome preferences, whether these are concordant with patient preferences, and if they are encompassed by the primary and
secondary endpoints detailed in our proposal. Data will be collected until a point of analytic saturation. Sample size estimates are based on previous research experience. All data will be analysed by the qualitative researchers using Framework analysis. Emerging findings will be discussed amongst the broader research team, thereby providing multiple perspectives on the data.

There is no planned formal cost-effectiveness analysis in this small feasibility study, but we will explore the ease, variability and acceptability of obtaining the data relevant to these analyses, as above.

### 8.2. Summary of qualitative interviews and timings

<table>
<thead>
<tr>
<th>Population</th>
<th>Baseline</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients entering the trial, randomised to control arm (n=12)</td>
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<td>✓</td>
</tr>
<tr>
<td>Patients entering the trial, randomised to intervention arm (n=12)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Patients refusing to enter trial (n=15)</td>
<td>✓</td>
<td>-</td>
</tr>
<tr>
<td>Clinicians participating in the trial (n=12)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Clinicians not participating in trial (n=12)</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

### 9. SAFETY MONITORING PROCEDURES

The collection and reporting of data on adverse events and serious adverse events will be in accordance with ICH GCP and the Research Governance Framework 2005. It is imperative that all investigators have a thorough understanding of anticipated adverse events and the reporting process of these events.

There are no Investigational Medicinal Products (IMPs) used as part of this trial. As all of the surgical techniques being tested in this trial are used as standard practice there are no (serious) adverse events which would be anticipated as a unique consequence of participation in the trial.

Any trial-related serious adverse events (SAEs) which require immediate reporting will be reported on a trial-specific SAE form and will follow the procedure/timeframes outlined in this section of the protocol.

For the purposes of this study, 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
- Medication reaction (either arm)

### 9.1. General Definitions

**Adverse Events (AEs)**

An AE is any untoward medical occurrence in a subject to whom a research treatment or procedure has been administered, including occurrences which are not necessarily caused by or related to that treatment or procedure.
**Adverse Reactions (ARs)**
An AR is any untoward and unintended response in a subject which is caused by or related to a research treatment or procedure.

**Serious Adverse Events (SAEs)**
An SAE is an untoward event which:
- Results in death
- Immediately threatens the life of participant*
- Results in hospitalisation or a longer than anticipated stay in hospital
- Results in a persistent or significant disability
- Results in any congenital anomaly or birth defect in any pregnancy

*Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

**Non-serious adverse events/reactions**
Most AEs that occur in this trial, whether they are serious or not, will be ‘expected’. Non-serious adverse events/reactions will be recorded in the medical records and routine follow-up CRFs.

**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.

Routine treatment or monitoring of a pre-existing condition that has not worsened will NOT be considered as SAEs and should NOT be reported to the Trial Office.
9.2. Reporting SAEs

All SAEs must be recorded on the SAE Form and faxed to the ACCURE-UK Trial Office on 0121 415 8871 within 24 hours of the research staff becoming aware of the event.

The assessment of relatedness and expectedness to the trial intervention is a clinical decision and will be based on all available information at the time.

The Principal Investigator (or other nominated clinician) has to assign seriousness, causality and expectedness to the SAE before reporting.

For each SAE, the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates; times, if applicable)
- action taken
- outcome
- causality, in the opinion of the investigator*
- whether the event would be considered expected or unexpected*

*Assessment of causality and expectedness must be made by a doctor. If a doctor is unavailable, initial reports without causality and expectedness assessment should be submitted to the BCTU by a healthcare professional within 24 hours, but must be followed up by medical assessment as soon as possible thereafter, ideally within the following 24 hours.

The local investigator and others responsible for patient care should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors and provide further follow-up information as soon as available. If a participant dies, any post-mortem findings must be provided to the BCTU. The BCTU will report all deaths to the DMEC for continuous safety review.

9.3. Timeframes for reporting of SAEs

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. Events will be reported for 3 months post randomisation. The BCTU will report all SAEs to the DMEC approximately 3-monthly, to the main REC annually, and to the Trial Steering Committee 6-monthly.

Local Investigators are responsible for reporting SAEs to their host institution, according to local regulations but they do not need to inform the main REC as this will be done by the BCTU.

9.4. Notification of deaths

All deaths will be reported to the BCTU on the SAE Form irrespective of whether the death is related to disease progression or an unrelated event. If a participant dies, any post-mortem findings must be provided to the BCTU with the SAE form. The BCTU will report all deaths to the DMEC for continuous safety review.

9.5. Pharmacovigilance responsibilities

Local Principal Investigator (or nominated individual in PI’s absence):

- Medical judgement in assigning seriousness, expectedness and causality to SAEs.
- To fax SAE forms to BCTU within 24 hours of becoming aware, and to provide further follow-up information as soon as available.
- To report SAEs to local committees if required, in line with local arrangements.
To sign an Investigator’s Agreement accepting these responsibilities.

Chief Investigator (or nominated individual in CI’s absence):

- To assign causality and expected nature of SAEs where it has not been possible to obtain local assessment
- To review all events assessed as SAEs in the opinion of the local investigator

Birmingham Clinical Trials Unit:

- To prepare annual safety reports to main REC and TSC.
- To prepare SAE safety reports for the TSC-DMEC at X-monthly intervals.
- To report all fatal SAEs to the TSC-DMEC for continuous safety review

Joint Trial Steering and Data Monitoring and Ethics Committee (TSC-DMEC):

- To provide independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies.
- To review data, patient compliance, completion rates, adverse events (during treatment and up to end of follow-up).
- To review overall safety and morbidity data to identify safety issues which may not be apparent on an individual case basis
- To determine whether the trial should continue unchanged, continue with protocol modifications, or stop.

9.6. Notification of Serious Breaches of GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree:
(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial.

The BCTU on behalf of the Sponsor shall notify the MREC in writing of any serious breach of:
(a) the conditions and principles of GCP in connection with the trial; or
(b) the protocol relating to the trial, as amended from time to time, within 7 days of becoming aware of that breach.

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

10. STATISTICAL CONSIDERATIONS

10.1. Sample size

The target recruitment of this feasibility study was set at 48 patients as it was felt this was the minimum number needed to satisfy the objectives. By recruiting 48 patients, 24 will be randomised to the intervention arm. This will provide an estimation of operative morbidity rate and generalisable evidence about the length of stay, time off work and impact upon HRQL.

The full cohort (both arms) will provide information on follow-up acceptability and attrition rates. Running the trial at 6 centres will generate a better understanding of likely patient
acceptance rates for the intervention and understand potential barriers to recruitment in different settings.

10.2. Projected accrual and attrition rates
Active recruitment to the trial will take place over six months. Over this time we intend to recruit a total of 48 patients from the six sites that have already given letters of intent to open for this study. This figure is readily achievable on an estimated rate of 2 patients per month per site once open. We fully appreciate the potential difficulties of getting sites open and active, and have built into our recruitment model the conservative rate of site opening at one per month (in addition to the initial 4 month overall set-up period).

An audit of UC patient activity at University Hospital Birmingham has already been performed in late 2012 to estimate throughput rates of potentially eligible patients for this trial. This showed that around 5-6 patients per month are successfully medically treated for a UC relapse, who would thus be eligible for this trial. Our rate of two patients per month (33-40% successfully recruited) seems a realistic target. A final point to note is that patients are eligible for up to a year after a disease relapse, as such they can be approached any time in this period when they routinely attend follow-up outpatient clinic, further increasing the achievability of these recruitment targets.

10.3. Statistical Analysis
A detailed Statistical Analysis Plan will be written for the feasibility trial. A summary of the planned analyses is provided here.

10.3.1 Feasibility and Acceptability
Data from screening logs completed by each centre will provide information on the participant screening process, and will be analysed descriptively. The logs will provide information on the number of patients randomised compared to the number screened at each centre. Reasons for non-entry into the trial will also be assessed.
Patient retention rate will be investigated through the collection of data on patients who do not complete the trial. Both the number and the proportion of patients who did not complete the trial will be analysed - overall and by treatment arm. Reasons for non-completion will be analysed descriptively.
Adherence to randomised allocation will be monitored throughout the trial and reasons for non-adherence will be collected and analysed descriptively.

10.3.2 Outcome Data
Data from this feasibility study will be used to inform suitability of outcome measures, provide data to inform a sample size calculation, and explore possibilities for future cost-effectiveness analyses for the full scale trial.
Data return rates at each time point will be assessed, along with data completeness of the various outcomes measures. The outcome data collected will be summarised using summary statistics and an exploratory analysis will be performed. Any analyses performed will be by intention to treat. Data at each time point for each arm will be presented as numbers and percentages, or means with standard deviations as appropriate.
10.4. Qualitative Analysis
Interviews will be recorded with the consent of patients and transcribed clean for analysis. Analysis will be conducted within the qualitative research team with reference to recordings, transcripts and field notes taken at the time of data collection. A thematic analysis of content will be informed by the Framework analytical approach. Following initial familiarisation with the interview data, development of thematic frameworks and data coding will proceed in an iterative manner. Thematic charts / grids will be used to aid interrogation of patterning within the qualitative data. Analysis and discussion within the qualitative team, and in partnership with patient stakeholders will provide multiple perspectives on the data during the development of this thematic analysis. Data collection and analysis will run concurrently so that emergent analytical themes can inform further data collection.

10.5. Cost-effectiveness Analysis
There is no planned formal cost-effectiveness analysis in this small feasibility study, however the ease, variability and acceptability of obtaining the data relevant to these analyses will be determined.

11. DATA ACCESS AND QUALITY ASSURANCE
11.1. Confidentiality of personal data
Personal data and sensitive information required for the ACCURE-UK Trial will be collected directly from trial participants and hospital notes. Participants will be informed about the transfer of this information to the ACCURE-UK trial office at the BCTU and asked to sign a consent form to show their agreement. The data will be entered onto a secure computer database, either directly via the internet using secure socket layer encryption technology or indirectly from paper by BCTU staff. All personal information received in paper format for the trial will be held securely and treated as strictly confidential according to BCTU policies. All staff involved in the ACCURE-UK Trial (clinical, academic, BCTU) share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be stored on a secure server at Birmingham Clinical Trials Unit (BCTU) under the provisions of the Data Protection Act and/or applicable laws and regulations.

11.2. In-house Data Quality Assurance
11.2.1 Monitoring and Audit
Investigators and their host Trusts will be required to permit trial-related monitoring and audits to take place by the ACCURE-UK trial office, providing direct access to source data and documents as requested. Trusts may also be subject to inspection by the Research and Development Manager of their own Trust and should do everything requested by the Chief Investigator in order to prepare and contribute to any inspection or audit. Trial participants will be made aware of the possibility of external audit of data they provide in the participant information sheet.

11.2.2 Statistical monitoring throughout the trial
As this study is a small, feasibility study extensive statistical monitoring is not required. Incoming data will be checked and queried throughout the duration of the trial.
11.3. Long-term storage of data
Archiving will be authorised by the BCTU on behalf of the Sponsor following submission of the end of trial report.
Principal Investigators are responsible for the secure archiving of essential trial documents (for their site) as per their NHS Trust policy. All essential documents will be archived for a minimum of 5 years after completion of trial.
Destruction of essential documents will require authorisation from the BCTU on behalf of the Sponsor.

11.4 External long-term follow-up
This study will include optional consent to allow future linkage to patient data available in NHS routine clinical datasets, including primary care data (e.g. CPRD, THIN, QResearch), secondary care data (Hospital Episode Statistics; HES) and mortality data from the Office of National Statistics (ONS) through The Health and Social Care Information Centre and other central UK NHS bodies. The consent will also allow access to other new central UK NHS databases that will appear in the future. This will allow us to extend the follow-up of patients in the trial and collect long-term outcome and health resource usage data without needing further contact with the study participants. This is important as it will link a trial of a treatment that may become a clinical standard of care to long-term outcomes that are routinely collected in clinical data, but which will not be collected during the follow-up period of the trial.

12. ORGANISATION AND RESPONSIBILITIES
To ensure the smooth running of the trial and to minimise the overall procedural workload, it is proposed that each participating centre should designate individuals who would be chiefly responsible for local co-ordination of clinical and administrative aspects of the trial.
All investigators are responsible for ensuring that any research they undertake follows the agreed protocol, for helping care professionals to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research and for reporting any failures in these respects, adverse reactions and other events or suspected misconduct through the appropriate systems.

12.1. Principal Investigator at each centre
Each centre will nominate both a Lead Gastroenterologist and a Lead Surgeon. Either one of these may act as the Local Principal Investigator.
The local PI shall bear responsibility for the conduct of research at their centre. The responsibilities of the local Principal Investigator will be to ensure that all medical and nursing staff involved in the care of patients are well informed about the study and trained in trial procedures, including obtaining informed consent. The local Principal Investigator should liaise with the Trial Coordinator on logistic and administrative matters connected with the trial.

12.2. Research Co-ordinator at each centre
Each participating centre should also designate a researcher as local Research Coordinator; this is usually a research nurse. This person would be responsible for ensuring that all eligible patients are considered for the study, that patients are provided with study information sheets and have an opportunity to discuss the study if required. The coordinator may be responsible
for collecting the baseline patient data and for administering the follow-up evaluations. Again, this person would be sent updates and newsletters and would be invited to training and progress meetings.

12.3. The ACCURE-UK Trial Office
The ACCURE-UK trial office will assist local PIs in obtaining relevant Trust approvals. The ACCURE-UK trial office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing collaborating centres with the following trial materials:

- The Site File, containing all documentation required under ICH GCP to define the involvement of the centre in the trial.
- An Investigators folder containing printed materials, including participant information sheets, consent forms and trial schema.
- An online randomisation system, including individual log-ins and passwords and guidance.

All of the above will be supplied to each collaborating centre, after relevant Trust approval has been obtained. Additional supplies of any printed material can be obtained on request. The ACCURE-UK trial office also provides the central randomisation service and is responsible for collection and checking of data (including reports of serious adverse events thought to be due to trial treatment), for reporting of serious adverse events to the sponsor and/or regulatory authorities and for analyses. The Trial Office will help resolve any local problems that may be encountered in trial participation.

13. RESEARCH GOVERNANCE
The trial will be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP), the UK Data Protection Act and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

All centres will be required to sign an Investigator’s Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. Deviations from the agreement will be monitored and the TSC-DMEC will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre.

The Trial Office will ensure researchers not employed by an NHS organisation hold an NHS honorary contract for that organisation.

13.1. Regulatory and Ethical Approval
The ACCURE-UK trial office will obtain a favourable ethical opinion from a Multi-centre Research Ethics Committee (MREC), determining that the trial design respects the rights, safety and wellbeing of the participants.

The Local Comprehensive Research Network will conduct governance checks and assess the facilities and resources needed to run the trial, in order to give host site permission. The Trial Office is able to help the local Principal Investigator in the process of the site specific assessment by completing much of Site Specific Information section of the standard IRAS form as possible. The local Principal Investigator will be responsible for liaison with the Trust management with respect to locality issues and obtaining the necessary signatures at their Trust.
As soon as Trust approval has been obtained, the Trial Office will send a folder containing all trial materials to the local Principal Investigator. Potential trial participants can then start to be approached.

13.2. Funding and Cost implications
The research costs of the trial are funded by a grant from the Research for Patient Benefit programme of NIHR awarded to the University of Birmingham.

13.3. Sponsor
Sponsorship will be provided by the University of Birmingham upon signing of the Clinical Study Site Agreement with each trial site.

13.4. Indemnity
ACCURE-UK will be coordinated by the Birmingham Clinical Trials Unit and is funded by the Research for Patient Benefit programme of NIHR.

The University of Birmingham is the trial ‘sponsor.’

The Sponsor (University of Birmingham) holds Public Liability (negligent harm) and Clinical Trial (negligent harm) insurance policies, which apply to this trial. Participants may be able to claim compensation, if they can prove that the University of Birmingham has been negligent. However, as this clinical trial is being carried out in a hospital setting, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Compensation is only available via NHS indemnity in the event of clinical negligence being proven. University of Birmingham does not accept liability for any breach in the hospital’s duty of care, or any negligence on the part of hospital employees.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University of Birmingham or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor’s Insurers, via the Sponsor’s office.

There are no specific arrangements for compensation made in respect of any serious adverse events occurring though participation in the trial, whether from the side effects listed, or others yet unforeseen.

Hospitals selected to participate in this trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary should be provided to University of Birmingham, upon request.

13.5. Clinical Trials Unit
Data from this trial will be handled by the BCTU at the University of Birmingham. BCTU is a full-time research facility dedicated to, and with substantial experience in, the design and conduct of randomised clinical trials. The BCTU recognises the responsibilities of a data management centre with respect to the ethical practice of research and the adequate protection of human subjects.
13.6. Confidentiality of Personal Data
The trial will collect personal data about participants, and medical records will be reviewed for all patients and routine physical examinations will be performed. Participants will be informed that their trial data and information will be securely stored at the trial office at the BCTU and will be asked to consent to this. The BCTU abides by the UK law Data Protection Act 1998. The data will be stored on a secure computer database and all personal information obtained for the study will be held securely and treated as strictly confidential. Any data processed outside of the BCTU will be anonymised.

13.7. Publication
A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. Centres will be permitted to publish data obtained from participants in the ACCURE-UK Trial that use trial outcome measures but do not relate to the trial randomised evaluation and hypothesis.
14. REFERENCES

APPENDIX A Patient Pathway

ACCURE-UK Trial feasibility study - Schema and Patient Flowchart

Patients identified as potentially eligible for ACCURE-UK trial at Gastroenterology or IBD clinic

Patient eligibility confirmed according to the following criteria:
- Adult patient (>18yr) with histologically confirmed UC
- Disease relapse within 12 months of randomisation
- In clinical remission at time of randomisation with clinical Mayo score less than 3 and endoscopic Mayo score of 0 or 1

Initial trial discussion and Patient Information Sheet given to patient

Within 4 weeks - patient meets with a named surgical investigator to discuss trial and possible surgery at surgical outpatient clinic or a research clinic

ACCURE-UK Trial consent taken and patient randomised with a 1:1 ratio between the 2 arms
Patient completes baseline QoL Forms: EQ-5D, QLQ-C30

RANDOMISATION

Appendectomy and standard medical therapy  
\( n=24 \)

Time to elective procedure ≤ 5 weeks

Admitted on day of surgery for operation

6 week follow up appointment at surgical Outpatient Clinic

3 month follow up at IBD clinic, research clinic or by phone

6 month follow up at IBD clinic, research clinic or by phone

9 month follow up at IBD clinic, research clinic or by phone

12 month follow up at IBD clinic or research clinic including flexible sigmoidoscopy to measure Mayo Score

Standard medical therapy  
\( n=24 \)

PT returns to the care of Gastroenterologist

At each visit:
- Resource usage data
- Partial Mayo score calculation
- QoL questionnaires x2
Appendix - ACCURE-UK Mechanistic Evaluation [“ACCURE-ME” Study]

Premise - There is increasing evidence that the appendix can affect the level of inflammatory activity in Ulcerative Colitis (UC) and its removal (appendicectomy) can result in an improved disease course1. We know that in the appendix of UC patients, the CD4/CD8 ratio is significantly increased, and the proportion of CD4+CD69+ T cells is also significantly elevated. Alterations in mucosal immune responses resulting from appendicectomy presumably affect the mucosal immunology and pathogenetic mechanisms of UC although the exact immunological pathway by which the appendix impacts upon disease activity in UC remains unknown.

Much research investment has resulted in the development of immunological therapies for the treatment of UC and these have been used for past decade with reasonable clinical success. These agents include infliximab, an anti-TNF agent, and Ustekinumab, a monoclonal antibody to IL-12 and IL-23. The fact that some patients do not respond to these treatments while others lose responsiveness to them suggests that there may an alternative overarching group of mucosal immune cells and an immune regulation pathway that is as yet undiscovered.

MAIT cells - Very recently, mucosa-associated invariant T cells (MAIT) have been implicated to play a major role in epithelial barrier protection and inflammatory bowel diseases. It has recently been proven that there is an increase in frequency of MAIT cells in patients with Ulcerative Colitis2. However, exploring MAIT cells in mucosal immunology in this setting is in its infancy and has centred on peripheral blood only. One mouse model has suggested that Vα19-Jα33 MAIT cells are involved in colitis3.

Currently, our group is investigating regulatory T cells and IFN & IL-17 dual secreting MAIT cells balance in human autoimmune liver inflammation. Our preliminary data has suggested that human explanted livers in patients with Primary Sclerosing Cholangitis and Ulcerative Colitis are enriched with IL-17, IL-22, TNF and IFN polysecretor MAIT cells. These MAIT cells express gut homing integrin α4β7, supporting the hypothesis of a gut origin4 (also see figure 1 below). We therefore feel that this may be the ‘missing link’ pathway that is responsible for driving inflammation in UC. We have the unique opportunity and expertise to bring together the emerging clinical observations of the impact of appendicectomy on UC activity and these emerging immunological theories. No other group in the UK or overseas has ever explored the relationship of the appendix and MAIT cells in UC.

Figure 1 - Comparison of the production of various cytokines produced after stimulation by CD3, CD8 and MAIT lymphocyte subsets. Bars: control blood (white), Ulcerative colitis patient blood (grey) and PSC diseased liver (black).

A. IL-17 production by CD3, CD8 and MAIT lymphocyte subsets show MAIT cells produce the greatest amount (5.5%) of IL-17 in peripheral blood of UC patient and around 4% in the PSC liver. B. IL-22 production is low amongst CD3, CD8 and MAIT cells across all patient samples. C. TNF-α production was around 60% in MAIT cells derived from the colitis blood and diseased liver. D. IFN-γ was produced in large amounts by all lymphocyte subsets. E. MAIT cells produced the largest amount of IL-17 and IFN-γ. F. MAIT cells...
Mechanistic study - research aims:
1) To determine the frequency, tissue localization and phenotype of MAIT cells in the appendix and colonic tissue in UC as compared to normal controls.
2) To investigate the mechanism by which MAIT cells may trigger a flare-up of UC activity.
3) To investigate how removal of the appendix may modulate mucosal immune regulation pathways and lead to improved clinical outcomes in some UC sufferers.

We hope to subsequently answer the following direct research questions:
1) Can analysis of MAIT cells in the appendix predict response to surgical resection?
2) Can analysis of MAIT cells in blood and tissue select for a definable subgroup of UC patients who will not respond to appendicectomy?
3) Can subtypes of (1) and (2) help direct 2nd line medical therapy?
4) Can large bowel mucosal biopsies microarray and microbiome be correlated with appendix mucosal lymphocyte population and response to appendicectomy?
5) Can systemic mucosa lymphocyte populations be investigated (in the light of appendix data) to provide a non-invasive marker / signature to help direct medical therapy?

The study will be undertaken by analysis of appendix tissues, peripheral blood, faeces and mucosal biopsy samples from patients recruited to the ACCURE-UK randomised feasibility trial. Samples will be taken at baseline 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.

Please refer to the flowcharts demonstrating the interplay of this mechanistic evaluation with the ACCURE-UK trial and a schematic depiction of our overall analysis strategy.

Mechanistic study - experimental design and methodology
1) Localization and phenotype of MAIT cells in the normal and Ulcerative Colitis appendices:
   a) We will investigate the frequency, tissue localization of MAIT cells in lamina propria and submucosa tissue from appendix in patients from control and intervention arm of ACCURE trial. Previous study suggested that histological findings of the appendix from ulcerative colitis patients have higher CD3+CD4+CD25+, CD3+CD4+CD45RO+, and CD3+CD8+CD45RO+ lymphocytes than in acute appendicitis and in normal appendix13. We will perform immunohistochemistry on frozen and paraffin tissue sections of appendix tissue and bowel mucosa from biopsy samples with Vα7.2 antibody. We will then investigate MAIT cells and dendritic cells tissue co-localization with Vα7.2, CD3/CD4/CD8 and CD11c dendritic cells markers with 4-colour confocal microscopy. Different FITC, PE, CY5 and DAPI conjugation will be applied for these experiments. Quantification of cells numbers will be carried out with the assistance from gastro-histopathologists.
b) Frequency and phenotypic analysis of intraepithelial and peripheral blood CD4, CD8, double negative MAIT cells subsets will be investigated with Fortessa 12-colour flow cytometry. Appendix tissue from patients with Ulcerative Colitis vs. appendix from appendicitis patients vs. normal appendix from colorectal cancer will be compared. We have established expertise to apply well-compensated 12 colours of flow cytometry to determine the phenotype of small population of lymphocytes. These studies will determine the MAIT cells activation marker CD69, exhaustion marker PD1, chemokine receptors focusing on gut homing CCR9 along with other chemokine receptors. CCR9 is well known to be a gut homing receptors in both murine and human studies14-16. We will also determine the integrins such as LFA1, VLA-4 and gut homing α4β7 on MAIT cells. These integrins are crucial for migration across mucosa tissue and homing to colonic gut mucosa. Effector memory, central memory and naïve phenotype of MAIT cells will be determined by using CCR7, CD62L and CD45RA, CD45RO markers.

c) We will then explore the cytokines receptors, transcription factors RORc, Tbet and intracellular cytokines profile of cells by intracellular staining on freshly isolate cells from blood and appendix and analyse phenotype by flow cytometry.

2) To investigate the mechanism by which MAIT cells may trigger a flare-up of UC activity.

Increased CD4/CD8 ratio and predominant infiltration of CD4+CD69+ T cells in the appendix suggested that the appendix is a priming site in the development of UC17. Experimental colitis model also demonstrated that preferential migration of CD62L+CD4+ naïve T cells into the appendix as compared to the colon. This migration pattern correlated with upregulation of integrin alpha4beta7 on T cells4. Thus, we will carry out co-culture functional experiments with antigen presenting dendritic cells from appendix from patients (control and intervention arm of ACCURE-UK trial) with CD4MAIT, CD8MAIT cells to explore whether appendix is the site of priming to effector mucosa cells. Microbial flora is enriched with E coli and E fecalis and these bacteria will be presented to MAIT cells via MR1 expressing appendix dendritic cells.

a) Cell sorting method will be used applying CD3, Valpha 7.2 and CD161 antibodies to isolated MAIT cells from freshly isolated lymphocytes from Appendix.

b) Appendix is enriched with microbioata and bacterial pathogens. Vitamin B6 expressing bacterial antigen such as E coli (control E fecalis) will be used to present bacterial antigen to MAIT cells via MR1 expressing appendix dendritic cells. We will first carry out cytokine receptors expression of MAIT cells (such as IL12R, IL18R and IL23R) by flow cytometry. We will then investigate the production of IFN, TNF, IL17 and IL22 from MAIT cells by co-culturing bacterial infected DC in the presence/absence of IL12, IL18, IL23 cytokines to determine the specific cytokines or cytolytic proteins (granzyme, perforin) secretion response from MAIT cells.

3) To define predictive markers of treatment responder and non-responder

a) Multi-plex cytokines, chemokines analysis, will be performed in peripheral blood of patients from ACCURE trial. Phenotypic markers and differential frequency of CD4, CD8, double negative MAIT cells in pre and post appendectomy (intervention arm) and control arm (without appendectomy) of patients along with Luminex findings may provide us with some predictors of treatment response in Ulcerative Colitis.
b) Microbiota profiling of faecal samples of pre and post appendectomy in both study arm and control arm will be analysed. Microarray analysis of bowel biopsy will be carried out to detect the treatment response group as well.

We will also addressed the aforementioned research questions using the following techniques and analyses:

i) Can analysis of MAIT cells in the appendix predict response to surgical resection?
   We will address this question by analysis of frequency and phenotype of Va7.2 CD161++ MAIT lymphocyte subtypes (CD4/CD8/Double negative). We will investigate the difference in the cytokines receptors (IL-12R, IL18R, IL6R and IL1R), chemokine receptors (focusing on CCR9) and integrins (alpha4 beta7), surface markers (CD69, PD1) and intracellular cytokines expression (IL-17, IL-22, IL33, TNF, IFN) and cytolytic enzyme profiles (Granzyme B, K and perforin) and CD107 in MAIT cells subsets.
   These analyses will be carried out in a) control group appendix (appendectomy for colorectal tumour) and intervention group (appendectomy for Ulcerative Colitis) in ACCURE trial.

ii) Can analysis of mucosal lymphocyte subtypes select for a definable subgroup of UC patients who do not respond to surgical resection?
   We will answer this research question by comparing the phenotype and frequency of peripheral blood MAIT cells subsets in control arm and appendix tissue and peripheral blood (before and after appendectomy) of appendectomy arm (both responder and non-responder) of ACCURE trial patients.

iii) Can subtypes of 1 and 2 help direct 2nd line medical therapy?
    This question will be answered by intracellular cytokines (IL17/IL22/TNF/IFN) expression profile of appendix and peripheral blood MAIT cells; Luminex cytokines/chemokines result of blood from responder and non-responder group. This will define the patient group for either anti-TNF (infliximab) or anti-IL12/anti-IL23 (Ustekinumab) therapy.

iv) Can large bowel mucosal biopsies and microbiome be correlated with appendix mucosal lymphocyte population and response to surgery?
   We will investigate the microarray profiles of bowel mucosa tissue and microbiome profiles before and after appendicectomy and compare to the control arm of ACCURE trial. These results will be correlated with the phenotype and frequency of appendix MAIT cells. These data may provide predictors for response to intervention.

v) Can systemic mucosa lymphocyte populations be investigated (in the light of appendix data) to provide a non-invasive marker / system to help direct medical therapy?
   Frequency and phenotype profile of Va7.2 CD161+ MAIT subtypes (CD4/CD8/Double negative) in responder and non-responder group may potentially
provide us with non-invasive mucosal immunological markers in peripheral blood to predict the responder and may stratify the patient groups for appropriate anti-TNF or anti-IL17 therapy.

**Mechanistic study - Methodology**

The study will be undertaken by analysis of appendix tissues, peripheral blood and mucosal biopsy paired samples from patients recruited to the ACCURE-UK randomised feasibility trial. Samples will be taken at baseline 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) will form a central component of the analyses.

Patients who have agreed to enter the trial will be approached and they agree to donate specimens, separate collection and storage consent will be taken, before the following specimens are obtained:

**A** - At Baseline: i) Blood - 5 small bottles (total approximately 30ml) on trial entry, after consent and on the same day as randomisation. These will be centralised to the biorepository at the University of Birmingham. Some of these blood samples will then be analysed fresh by 12 colours Fortessa immunophenotyping, other bottles will be spun at the biorepository to separate serum/plasma (3 aliquots each) and PBMC components then stored for analysis later during the study. This will be Luminex analysis later for serum and plasma and genomic analysis for cells. ii) Colonic mucosal biopsies - A necessary prerequisite to enter the main ACCURE-UK feasibility trial is the undertaking of a direct mucosal visualisation, via flexible sigmoidoscopy, at baseline and at 12 months. This is necessary to confirm remission at trial entry and to calculate full Mayo scoring at baseline and at 12 months. In this additional mechanistic study, we are simply asking for mucosal biopsies to be taken at these same endoscopy procedures, then stored appropriately and centralised to the biorepository for analysis. All patients with established UC will have had previous endoscopy examinations and biopsies to assess their disease and establish the primary diagnosis. The biopsies required for this research are the same routine, painless biopsies with minimal risk of causing any bowel damage or other ill effect. We require 2 biopsy samples from 2 different levels - the rectum and the sigmoid/descending colon. These will be placed directly into cryovials containing RNAlater®. They will then be preserved safely for one week at 25°C or one month if kept in a fridge at 4°C. The samples will be returned later to the biorepository in batches via a courier. Here they will be stored at -80 degrees for subsequent transcriptomic analysis during the study.

**B** – Appendix specimens: The patients who are randomised to the intervention arm of the feasibility trial will undergo laparoscopic appendicectomy within 6 weeks of randomisation. These resected appendix specimens form an important part of this mechanistic evaluation. After removal, the whole appendix will be put straight into an RPMI-containing media pot in theatre. Returned to biorepository within 24 hours and on arrival small samples cut from appendix and put into formalin and liquid nitrogen. The majority of the appendix will undergo fresh analysis with 12 colour flow cytometry. The other specimens will undergo Immunohistochemistry analysis, transcriptomic analysis, 4- colour confocal microscopy and Laser capture microdissection.

**C** – At 12 months: For all patients (both intervention and control arms) the exact same specimens of blood and bowel mucosal biopsies will be obtained at the end of
an individual patient's involvement in the trial. These will be centralised, stored and analysed in the same fashion as above.

D – Other appendix specimens for validation and control purposes: Alongside the specimens above from patients within the ACCURE-UK trial, we intend to obtain and analyse additional appendix specimens for control and validation purposes. These will be requested from appropriate patients after obtaining their specific consent for this using the pre-existing biobanking and specimen research consent form and approved pathway already in place. We intend to obtain 30 of these additional appendix specimens: 10x appendicitis (inflamed appendix) - 10x cancer resections (normal appendix) - 10x UC total colectomy (UC appendix).
Initial trial discussion and Patient Information Sheet given to patient

Patient eligibility confirmed according to the following criteria:
- Adult patient (>18yrs) with histologically confirmed UC
- Disease relapse within 12 months of randomisation
- In clinical remission at time of randomisation with clinical Mayo score less than 3 and endoscopic Mayo score of 0 or 1

Patients identified as potentially eligible for ACCURE trial at Gastroenterology or IBD clinic, or after discharge from gastroenterology ward with (treated) flare of UC

Within 4 weeks - patient meets with a named surgical investigator to discuss trial and possible surgery at surgical outpatient clinic or a research clinic

Clinical disease remission confirmed with endoscopy/biopsies and calculation of Mayo score. ACCURE-UK Trial consent taken and patient randomised with a 1:1 ratio between the 2 arms

Patient completes baseline QoL Forms: EQ-5D, QLQ-C30 and IBDQ

Appendicectomy and standard medical care
n=24

Time to elective procedure ≤ 6 weeks

Admitted on day of surgery for operation

6 week follow up appointment at surgical Outpatient Clinic

3 month follow up at IBD clinic or research clinic

6 month follow up at IBD clinic or research clinic

9 month follow up at IBD clinic or research clinic

12 month follow up at IBD clinic or research clinic including a colonoscopy and biopsies to measure full Mayo Score

ACCURE-UK Randomised feasibility study:

ACCURE-ME parallel mechanistic study:

Consent also taken for ACCURE-ME and baseline blood, mucosa and stool samples taken and returned to Bham

Appendix specimens (intervention arm) centralised to Bham

Randomisation

PT returns to the care of Gastroenterologist

Follow-up blood, mucosa and stool samples taken and returned to Bham

At each visit:
Resource usage data
Partial Mayo score calculation
QoL questionnaires x3

Visit 2

Visit 1
ACCURE TRIAL

Intervention arm (appendicectomy)

Baseline specimens at trial entry

Repeat specimens after 12 months

RESPONDER (decreased or no relapses)

NON-RESPONDER (no change in relapse rate)

A1 – Combined analysis of baseline immunological characteristics

A2 – Differences after 12 months (due to intervention)

A3 – Differences between responder and non-responder in intervention arm

A4 – Differences between responder and control

A5 – Differences between non-responder and control

Then add in clinical outcomes data:

(Control arm)

Together these 3 analyses will establish an understanding of the mechanisms of both a responder and a non-responder to the appendicectomy intervention