CLARITY: SurgiCaL educAtion to Reduce IncorrecT care pathwaYs and enhance patient outcomes in right iliac fossa pain.

An implementation-effectiveness trial of an educational intervention for surgical teams.

Study Protocol

Version 1.0, Jan 7, 2024

TRIAL NEWS AND INFORMATION

All trial documents, news and information can be found at: claritytrial.co.uk/hub

SITE REGISTRATION

Expression of interest and site registration: claritytrial.co.uk/register

QUICK START GUIDE

The CLARITY trial quick-start guide is available here: **claritytrial.co.uk/CLARITY-quick-start.pdf**.

This is a step-by-step guide and checklist to setting up and running CLARITY at your centre.

CLARITY TRIAL HUB

The CLARITY Trial Hub has all the relevant information and forms you will need to set up and run CLARITY at your centre. It can be found here: **claritytrial.co.uk/CLARITY-hub**.

It may be useful to bookmark this page and the REDCap data collection tool in your computer and phone internet browsers.

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FUNDING AND SPONSOR

Sponsor	
The University of Birmingham	**CLARITY Trial**
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Sponsor statement	
As formally delegated by the University of Birmingham, the sponsor confirms approval of this protocol.	
ISRCTN	16757238
Sponsor reference number	RG_24-022
Compliance statement This protocol describes the CLARITY study only. The protocol should not be used as a guide for the treatment of patients not taking part in the CLARITY study. The study will be conducted in compliance with the approved protocol, the General Data Protection Regulation (GDPR) and subsequent amendments, 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.	

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Dale Vimalachandran	Consultant surgeon

CHIEF INVESTIGATOR AND DECLARATION

The undersigned confirm that the following protocol has been agreed and accepted and that the chief investigators agree to conduct the study in compliance with the approved protocol.

<table>
<tr><td colspan="4">The undersigned confirm that the following protocol has been agreed and accepted and that the chief investigators agree to conduct the study in compliance with the approved protocol.

We, the undersigned, 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. We also confirm that we will make the findings of the study publicly 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.

This protocol has been approved by:</td></tr>
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STUDY SUMMARY

Research question: Can implementation of an evidence based educational intervention, focussed on accurate diagnosis of appendicitis, safely reduce unnecessary admissions to hospital in patients with suspected appendicitis?

Background: Acute appendicitis is one of the most common surgical emergencies. Over 55,000 operations for appendicitis are performed each year in the UK. However, a significant proportion of patients with right iliac fossa (RIF) pain are misdiagnosed and placed on incorrect care pathways. Most of these patients receive unnecessary hospital admissions for monitoring and do not undergo an intervention. Some admissions result in patients receiving a negative appendicectomy, exposing them to unnecessary pain and complications. Furthermore, this leads to delayed treatment for the underlying condition they initially presented to hospital with.

Aim: To improve right iliac fossa care pathways by reducing unnecessary admissions to hospital.

Design: Multicentre, parallel cluster randomised controlled trial with an effectiveness-implementation design. This type of trial combines elements of both implementation and effectiveness research to address the real-world effectiveness of an intervention while also considering how well it can be implemented in practice. Each cluster corresponds to an acute care hospital.

Eligibility: Any hospital in the UK providing an acute general surgery service. Additionally, the hospital must have the ability to admit patients overnight and to schedule follow up in the surgical admissions unit or ambulatory clinic.

Participants: Members of the acute surgical team involved in the assessment of patients with RIF pain and suspected appendicitis.

Population: Data from hospital notes will be collected from consecutive patients aged 16 to 39 years old (inclusive) attending hospital with right iliac fossa pain over an 8-week period.

Intervention: The intervention is the CLARITY accurate diagnosis package, which is made up of three components: the evidence based education programme (EBP), an implementation checklist and local implementation strategies. The EBP is considered the main component of our intervention and will be delivered using a digital education platform to intervention sites.

Comparison: Routine clinical care (sites without CLARITY EBP).

Primary Outcome: Non-operative admission rate (NOAR) - defined as unnecessary overnight admission.

Secondary Outcomes: Safety (including negative appendicectomy, postoperative complication rate, readmission, missed disease).

Sample size: 40 clusters (20 per arm) of 120 patients would be required to detect a 25% reduction in non-operative admission rate (4800 patients in total, power = 0.90, α = 0.05).

Randomisation: Hospitals will be categorised by bed size (<400 or >400 beds) and randomised using a 1:1 minimisation algorithm.

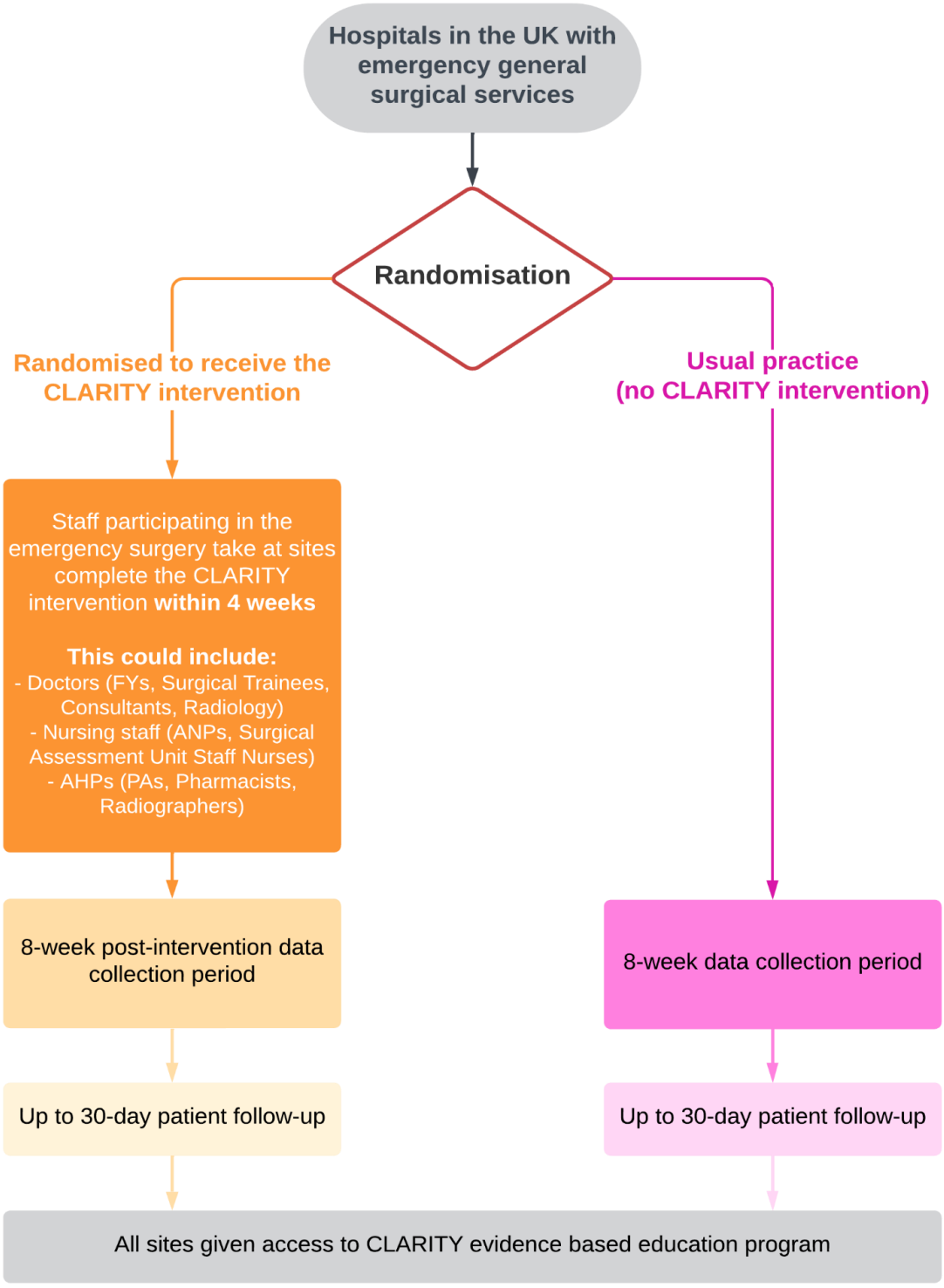
Follow up: This will be carried out by reviewing hospital notes 30 days after attendance/admission.

Analysis: Intention to treat, including implementation analyses.

Potential Impact:

1. Improved patient care, with a reduction in unnecessary admissions and negative appendectomies.
2. Reduction in healthcare costs by preventing unnecessary surgeries.
3. More efficient allocation of emergency resources, reducing hospital stays and admissions.

Figure 1: CLARITY trial design



PLAIN LANGUAGE SUMMARY

Appendicitis is a common condition, it is caused by inflammation of a small part of the bowel called the appendix. It does not usually get better by itself and the main treatment is to remove the appendix with an operation. This can then be studied by doctors under the microscope to confirm the diagnosis.

Appendicitis can be challenging to diagnose, as many other conditions can cause similar symptoms. To help make a diagnosis doctors can use blood tests and scans, but how these are used and the decisions made based on results is different across the country. This has led to many patients receiving an incorrect diagnosis and treatment. Often many patients are admitted to hospital for suspected appendicitis but are monitored and do not receive any treatment before they are discharged. Furthermore, some of those admitted go on to have an unnecessary surgery to remove a healthy appendix. In the UK, around 20% of patients who have an operation to remove an inflamed appendix are found not to have appendicitis. Therefore, these people will have undergone an operation that they did not require. This rate of unnecessary operations is three times higher than other European Countries.

CLARITY is a study which aims to improve patient care pathways and to ensure that patients with suspected appendicitis receive the appropriate care that they need. We will do this by trying to reduce unnecessary admissions for appendicitis in the United Kingdom. CLARITY will test whether educating doctors who diagnose and treat appendicitis prompts them to use the best evidence strategies to diagnose appendicitis correctly. In turn this may enable doctors to reach the correct diagnosis earlier and to use admissions or surgery in patients that require them. As this trial is testing an intervention on doctors, rather than individuals with appendicitis, there will be no change to the care received and no extra appointments or surveys to complete for most people included in the study. The CLARITY trial is being funded by the University of Birmingham. We will share the results with patients and doctors through social media communications, presentations at scientific conferences and publishing our work.

BACKGROUND AND RATIONALE

Need for research in acute appendicitis

Acute appendicitis is one of the most common surgical emergencies managed by general surgical departments worldwide. In the UK, approximately 50,000 appendicectomies are performed every year.[1] It is generally considered the gold standard for the treatment of appendicitis. However, there is growing concern that a significant proportion of patients who are admitted to hospital or undergo surgery for appendicitis have a histologically normal appendix.

This is because appendicitis is often difficult to diagnose accurately. Typically, an individual with appendicitis presents with abdominal pain that localises to the right iliac fossa. However, some patients may have an atypical presentation or symptoms that overlap with an alternate diagnosis (for example, a ureteric stone, a urinary tract infection or problems affecting the fallopian tubes or ovaries).

Unnecessary admissions and operations are accompanied with significant risks and costs for the health service. Around 60% of patients admitted for suspected appendicitis are monitored and do not receive an intervention.[2-3] This signifies suboptimal care and places a significant burden on the health service. It is thought that improved diagnostic processes, such as risk stratification, imaging and redirection through ambulatory services, could improve right iliac fossa care pathways.

A particular concern with unnecessary admissions is that a proportion of patients, particularly those with longer hospital stays, undergo a negative appendicectomy.[3] An unnecessary appendicectomy carries the same rate of complications as surgery for true appendicitis.[4] Complications include wound infections, port site hernias, pain and unnecessary time away from their usual activities, such as work, education and caring.[2,5-6] In the UK, the negative appendicectomy rate (NAR) has consistently been found to be around 20%. This suggests there are up to 15,000 appendicectomies being performed annually for patients with a normal appendix. Hence, a large number of patients are exposed to harm from postoperative complications (7% of women and 23% of men).[2] In comparison to other European countries, the UK has a three-fold higher rate of unnecessary operations for appendicitis.[2]

Standardisation of pathways in right iliac fossa pain

There is significant variation in UK practice in the management of RIF pain, which leads to inappropriate selection of patients for imaging and surgery and results in suboptimal patient outcomes.[2-3] Our goal is to use education to standardise practice and encourage risk stratification and selective imaging in RIF pain. Evidence-based recommendations for diagnosing appendicitis exist but many healthcare professionals are not aware of them and they are rarely implemented in practice. Our primary intervention is an evidence-based programme to improve diagnostic assessment in suspected appendicitis. We also assess the effectiveness of the CLARITY implementation strategies in the emergency setting.

The variation in diagnostic practices in the UK may help explain the differences in patient outcomes, particularly when compared to other high income countries. Increasing use of cross-sectional imaging in other countries has been associated with a reduction in unnecessary operations for appendicitis. In the United States, one study showed that the percentage of appendicectomy patients receiving a preoperative CT scan increased from 1% to 97.5% over an 18-year period. Over the same time period, the NAR was found to drop from 23% to 1.7%.[7] Additionally, a comparison between the UK and Netherlands showed that only 32.5% of patients having an appendicectomy in the UK had any preoperative imaging, with an NAR of 20%. This compares to the 99.5% of patients who had preoperative imaging in the Netherlands, where the NAR is approximately 3%.[8]

However, there is a concern over the radiation exposure associated with standard CT and evidence suggests its use significantly increased during the COVID pandemic.[9] There are currently no mechanisms in place to ensure that ionising imaging is used selectively and at the lowest radiation levels necessary. Ultrasound scans are commonly conducted in patients with RIF pain but appear to have a low sensitivity and specificity for appendicitis.[2] Equally, use of magnetic resonance imaging in such a common condition would not be feasible due to the lack of infrastructure. The use of low dose CT (equivalent to 3 abdominal x-rays) has been recommended in suspected appendicitis in guidelines and Cochrane reviews.[10-11]

Furthermore, in cases where there is diagnostic uncertainty, surgical teams may opt for surgery or observation due to concerns over missed diagnoses or delaying the treatment of patients with appendicitis. However, in practice, missed diagnoses are rare (<1%) and there is increasing evidence that delayed treatment (<24 hours) does not result in adverse patient outcomes or increased disease severity.[12]

Pre-operative risk stratification has been shown to reduce the need for imaging and to reduce the NAR. In our previous study, we validated appendicitis risk scores in over 5300 patients in the UK (<5% error rate). These tools could reassure surgical teams and allow patients to be discharged rather than being admitted for observation.[2]

Need for implementation research in surgery

There is a significant gap between the publication of research and its widespread integration into practice. Although the efficacy of many interventions in perioperative and surgical care are well-established, there is a difficulty in translating these interventions into the emergency setting. Although many pragmatic trials looking at intervention effectiveness have had promising results, they continue to be met with significant environmental and organisational barriers.

In this trial, we already know what the best evidence based practice for the diagnosis of appendicitis is. The main barrier to improving care is identifying methods of effectively implementing the evidence into practice, which this trial aims to do. We will assess the effectiveness of our intervention but also measure how effective implementation strategies are for facilitating its adoption. Currently, there are very few studies which have assessed implementation factors in the perioperative or surgical setting.

Therefore, there is a clear need for research into how we can implement best clinical practice effectively into the National Health Service (NHS) for patients with suspected appendicitis, with the aim of minimising unnecessary hospital admissions and unnecessary surgery.

Justification of patient population

We will include all consecutive patients aged between 16 to 39 (inclusive) years old who present with right iliac fossa pain to participating hospitals over a given 8-week period. This age group are at highest risk of developing acute appendicitis and being admitted to hospital unnecessarily. Other diagnoses are more important in patients aged 40 and over, namely right sided colorectal cancer. These patients should routinely receive standard CT scans and are at a much lower risk of receiving unnecessary admissions or operations since CT is very accurate for diagnosing acute appendicitis.

We will not include patients who have already had their appendix removed as they cannot develop appendicitis. We will also not include pregnant people in this study, as they should be cared for by obstetricians, rather than the emergency general surgery team.

Rationale for study design

CLARITY is a multicentre, parallel cluster randomised controlled trial with a hybrid type II effectiveness-implementation design. This will assess both the implementation and effectiveness of our intervention. Our primary intervention is the evidence-based programme to improve diagnostic assessment in suspected appendicitis. However, we also assess the effectiveness of the CLARITY implementation strategies. Studying implementation strategies tailored to acute surgical teams is crucial to increasing the adoption of practice-changing interventions in emergency surgery.

CLARITY involves healthcare staff at the level of the hospital, not individual patients. Therefore, a cluster randomised trial is the most appropriate design (figure 1). We will study whether undertaking the CLARITY intervention increases the adoption of best-practice recommendations and whether this leads to an improvement in patient outcomes.

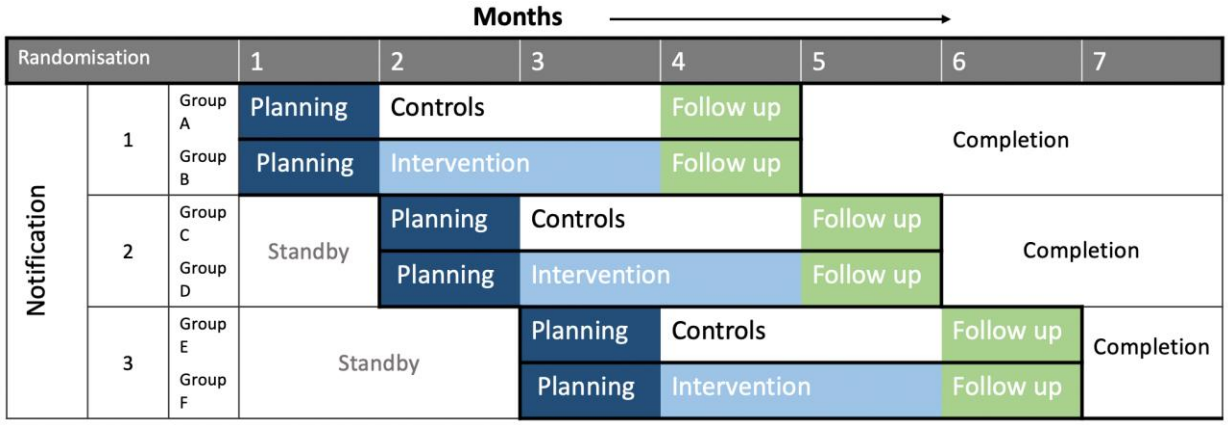
RESEARCH QUESTION

Can implementation of an evidence-based educational intervention, focused on the accurate diagnosis of acute appendicitis, safely reduce unnecessary admissions to hospital in patients with suspected appendicitis?

Trial design

The CLARITY trial is a multicentre, cluster randomised controlled trial using a hybrid type II implementation effectiveness design. Sites will be randomised using a 1:1 minimisation algorithm into three batches with a staggered start (see figure 2). CLARITY includes an internal pilot study.

Figure 2: Parallel cluster randomisation with staggering of sites across three start dates. Groups A+B are part of the internal pilot and include roughly 10 sites. The remaining groups will contain at least another 30 sites between them.



TRIAL OBJECTIVES

Pilot study objectives

We aim to conduct a pilot study assessing the feasibility of a full phase trial, measured by site recruitment, uptake of our intervention and collection of primary outcome data. This includes the following objectives:

- Open at least 9 sites, with a mix of rural, district general and tertiary centres
- Accrual of data from a minimum of 100 patients over 8 weeks
- Sufficient uptake of the intervention by local participants

Main trial objectives

- To determine whether implementation of the CLARITY evidence-based programme can reduce non-operative admission rates

Secondary objectives

- To determine whether implementation of the CLARITY evidence-based programme can reduce unnecessary surgeries and improve patient outcomes
- To assess the effectiveness of the CLARITY implementation strategy on increasing uptake of the intervention and adherence to evidence-based recommendations in the emergency surgery setting

ELIGIBILITY

Hospital inclusion criteria

- Any hospital in the UK providing emergency general surgical services
- The ability to schedule patients for a follow up assessment in the surgical admission unit or ambulatory/hot clinic service

Participant inclusion criteria

- Doctors and clinicians assessing patients with RIF pain, within the acute surgical team
- This includes consultants, specialty doctors, registrars, senior house officers, foundation doctors, surgical nurse practitioner and physicians associates

Patient inclusion criteria

- All patients aged 16 to 39 (inclusive) years old attending hospital with right iliac fossa pain

- AND under the care of the general surgery team, including in the emergency department, surgical admissions unit, or paediatrics ward.

Patient exclusion criteria

- Previous appendicectomy
- Current pregnancy
- Patients with RIF pain under the care of secondary teams

Each patient should only be included in CLARITY once. Following the index assessment included in CLARITY, patients undergoing additional assessments within the study window should not be included for a second time. Readmission is captured as a study outcome.

If patients with right iliac fossa pain are subsequently found to have an alternative diagnosis or pathology causing the pain, they must still be included in the study and followed up.

Selection bias

Selection bias will be closely monitored by the Study Management Group. CLARITY trial coordinators will regularly liaise with site Principal Investigators to ensure that all eligible patients are entered. Recruitment rates will be monitored across individual sites and clarification will be sought in case of a drop in recruitment which might indicate that eligible patients are not being included. An independent validation process will monitor case ascertainment (see *Monitoring* and *Data Validation*).

PATIENT IDENTIFICATION

Each hospital will decide how best to identify eligible patients in their own patient pathways.

As guidance, it is anticipated that patients may be identified from any of the following settings, as long as their attendance or admission start date falls within the trial data collection period:

- At time of attendance to hospital: Referrals made to the surgical team and/or emergency surgical admissions

- During admission: By the emergency surgical team or research team

Patients will be identified by a suitable person who may include:

- Any doctor involved in the patient's care (e.g. surgeon in training)
- Nurse practitioner or research nurse or members of the extended surgical team
- Medical students

Patients do not need to stay overnight or to be admitted to hospital to be eligible for inclusion in the study.

STUDY INTERVENTION

We will be delivering the CLARITY accurate diagnosis package across sites in the UK. Within this, *our main intervention* is the evidence-based programme to improve diagnostic assessment in suspected appendicitis. We will also assess the effectiveness of the CLARITY implementation strategies and access to tools and checklists.

The CLARITY accurate diagnosis package

The CLARITY accurate diagnosis package consists of an evidence-based education programme, an implementation checklist and implementation strategies. The package combines education with implementation science. It aims to provide an evidence-based learning programme around how to diagnose and manage appendicitis in a safe way which minimises unnecessary admission and surgery, whilst ensuring people with appendicitis receive prompt treatment. The content of the EBP is based on the latest evidence and provides education on how to provide 'gold-standard' care for patients with appendicitis. It does not involve any new interventions which would not be regarded as routine clinical care. The following describes the three components of CLARITY accurate diagnosis package in greater detail:

- Evidence-based education programme: aimed at increasing the adoption of evidence based practice and reducing misdiagnosis, unnecessary admission and negative appendicectomy in suspected appendicitis. This intervention provides accessible information on how to calculate

the risk of acute appendicitis in people with right iliac fossa pain and choosing the best diagnostic imaging modality.

- Implementation checklist: A summary of EBP recommendations and access to tools such as prompts or checklists for participants to consider implementing within their practice. We will capture data on whether these tools are useful or used in clinical practice.
- Local implementation strategies: a guide for local facilitators that focuses on environmental implementation strategies. It was developed using results of a national survey of acute surgical teams. It includes a graded strategy system to promote uptake of the education package and to support implementation of its evidence-based recommendations. All participating sites will be asked to report the level of implementation of the proposed strategies.

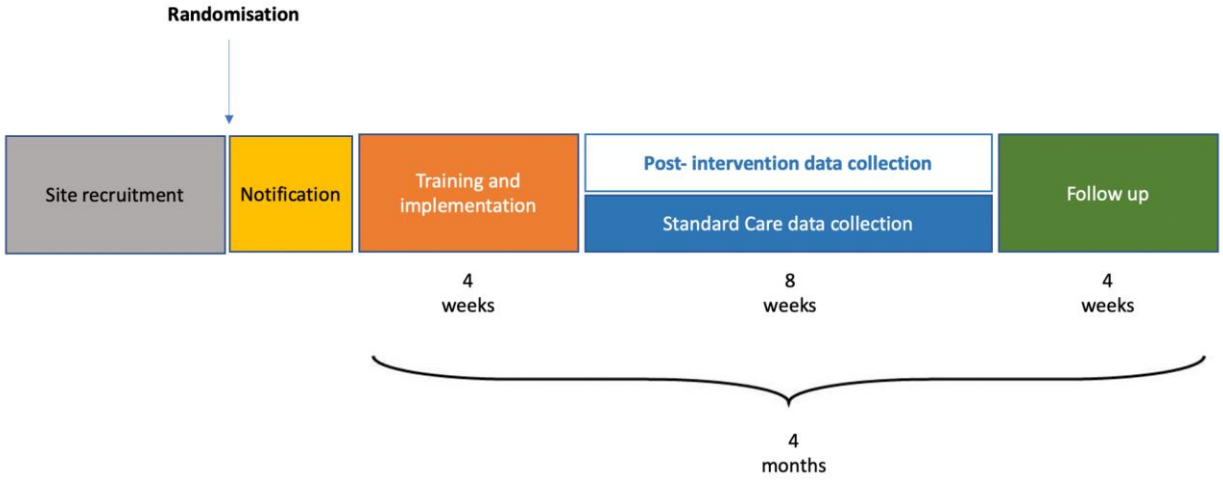
The CLARITY evidence-based education programme

The EBP is an online educational intervention containing six modules:

1. Introduction to the anatomy and pathophysiology of appendicitis and how to manage risk which evolves over time
2. Discussion on the meaning of evidence and how to use it in clinical practice
3. Patient-level risk stratification of appendicitis for RIF pain, focusing on the management of low-risk patients
4. Patient-level risk stratification of appendicitis for RIF pain, focusing on the management of medium- and high-risk patients
5. Communication with patients and colleagues (implementation)
6. Summary of the EBP

Intervention timing

Figure 3: Illustrates the timeline for site recruitment and participation.



Sites will be randomised to either receive the CLARITY intervention or usual care once all site approvals have been confirmed. A minimisation algorithm will be used which will allow for sites to be sequentially randomised once ready. The data collection window will take into account changeover in clinical placements for doctors. If the trial is not completed within a single rotation, doctors who have received the CLARITY package could move from sites which received the intervention to sites which did not receive the intervention, thereby contaminating the results. We will monitor and try to minimise this effect as much as possible.

To ensure that the study is attractive for potential collaborators to participate, all hospitals will have access to the CLARITY accurate-diagnosis package at the end of the trial.

Training platform

The EBP will be delivered on an e-learning platform, accessible to all participating sites through an internet connection. The uptake and completion rate of the EBP will be monitored on a site-by-site basis. It is intended that this educational module will be completed by any providers of acute surgical care (including consultant surgeons, trainee/resident surgeons, and surgical care practitioners/allied healthcare professionals in surgery/physician associates) in the 4-week implementation period. A dedicated implementation package for acute surgical assessment units will also be provided.

Validation of learning platform

The training programme has been reviewed by the West Midlands Deanery Postgraduate School of Surgery and the European Society of Coloproctology. It has also been beta-tested by 20 external doctors.

TRIAL STAGES

We will run the trial in two stages — a pilot stage to test feasibility and how well the operational aspects of the trial run, followed by a main trial expanded across more sites. The pilot and main trial will share many similarities, but for simplicity we have split the protocol into two sections to outline each stage.

PILOT TRIAL

A review of the pilot will be performed and a STOP-GO decision made to proceed to the main trial phase. This will enable identification of key issues and allow appropriate measures to be put in place to ensure the main trial phase runs smoothly.

Pilot study STOP-GO criteria

We will use the internal pilot to assess whether the study can be feasibly scaled to the required number of centres (clusters) for phase 2. We have set criteria according to the number of sites set up and the rate of participation per site. The following areas will be assessed in the STOP-GO assessment of the pilot study:

- Can 9 sites be opened to the study?
- Did 50% of participants in the intervention arm complete the CLARITY evidence-based education programme within 4 weeks?

Each area will be given a rating on a traffic light scale — GREEN (no difficulties encountered — proceed), AMBER (some difficulties encountered — proceed with no change to study design but amend administrative processes) or RED (difficulties encountered requiring alteration to proposed study design).

Finally, a decision will be made on these two areas according to the following criteria:

- All GREEN — proceed to the main phase of the study

- Any AMBER — revise study administration procedures and proceed to the main phase of the study
- Any RED — consider delaying the main phase, fully assess feasibility and revise trial procedures

Pilot Trial Design

CLARITY is a multicentre, cluster randomised controlled trial using a hybrid type II implementation effectiveness design. Sites will be randomised using a 1:1 minimisation algorithm.

Pilot Trial Setting

The study will take place in NHS trusts across the UK with emergency surgery services. The evidence-based programme will be delivered at the hospital-level, with outcomes assessed at the individual patient-level.

Pilot Trial Time Frame

Each participating hospital will collect data on consecutive patients for 8 weeks. Centres randomised to the intervention arm should aim to have staff trained in the CLARITY EBP, any changes implemented and running within 4 weeks, prior to the launch of data collection. Data on patients presenting or referred with right iliac fossa pain (suspected appendicitis) will then be collected for 8 weeks and used to measure the impact of implementing the CLARITY EBP.

These timeframes have been selected to allow recruitment and data collection to be completed within a single placement rotation of medical staff. This minimises the risk that staff who had completed the CLARITY intervention move to hospitals that have been randomised not to receive the intervention and vice-versa.

Pilot Trial Cluster Randomisation

Cluster randomisation will be performed at the hospital-level (one hospital is defined as one cluster). The CLARITY package is targeted at healthcare professionals, therefore individual patient-level randomisation would not be appropriate.

A minimisation algorithm will be used at the time of randomisation to ensure that the two groups are balanced for size of hospital and other factors which may influence outcomes (e.g. availability of imaging out of hours). In terms of hospital size, we will minimise based on the total number of beds. A large hospital will be deemed to be 400 beds and over, whereas a small hospital is under 400 beds.

The randomisation will be performed by a statistician and checked prior to implementation. Centre approvals will be checked and finalised before centres are randomised. A minimisation algorithm has been chosen as it allows for sequential allocation of centres as and when they are ready to be randomised. The method will allow for a 1:1 allocation and include a stochastic element to prevent lack of allocation concealment and prevent predictability of upcoming assignment.

Pilot Trial Outcomes

The outcomes of the pilot trial are:

1. The number of sites opened to recruitment within the first four month study period.
2. The proportion of patients with complete data collection by the end of the first 4 month study period.
3. The proportion of participants completing the CLARITY EBP within the first 4 week training and implementation period.

MAIN TRIAL

Main Trial Design

The CLARITY trial is a multicentre, cluster randomised controlled trial using a hybrid type II implementation effectiveness design. Sites will be randomised using a 1:1 minimisation algorithm.

Main Trial Setting

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Main Trial Time Frame

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Main Trial Primary Outcome Measure

The primary outcome measure is the proportion of people admitted overnight with right iliac fossa pain, who do not undergo an operation. This is known as the non-operative admission rate (NOAR). A small minority of non-operative admissions on the suspected appendicitis pathways will be due to other acute GI pathologies treated by the general surgical team (e.g. diverticulitis, colitis, hepatobiliary, tumours of the appendix, small bowel or colon etc.). Furthermore, a few patients with simple appendicitis may be managed nonoperatively. According to RIFT study, these groups constitute around 3% of all RIF pain referrals. Our objective is to reduce the NOAR while accepting that a very small number of nonoperative admissions will remain necessary. We will measure the contribution of these groups to non-operative admissions.

Main Trial Secondary Outcome Measure

The secondary outcomes will describe the efficacy and safety of the CLARITY package. Of primary concern is safety, as the CLARITY trial seeks to test whether the EBP can reduce unnecessary appendicectomy, whilst maintaining safety. All outcomes in the main study should be measured up to 30 days from attendance/admission, with day 0 being the first day of attendance/admission.

The secondary safety outcomes will include:

- Proportion of patients that were not correctly diagnosed with appendicitis on their first hospital attendance and review by the surgical team (missed or delayed diagnosis)
- The proportion of patients with complicated appendicitis (phlegmon, abscess or perforation)

- Days alive and out of hospital
- Readmission or re-attendance to hospital (including discharge from assessment unit and subsequent reattendance for appendicitis i.e. 'missed appendicitis')
- Radiological, percutaneous or endoscopic drainage
- Unplanned admission to critical care (Level 2/3 care)
- Mortality (both inpatient and in the community from any cause)

The secondary safety outcomes for patients who received an operation are:

- Proportion of patients with a negative appendicectomy (appendix normal on histopathological examination)
- Time from symptom onset to decision to operate and to skin incision (in hours)
- Surgical site infection, as defined by the Centers for Disease Control criteria
- Surgical complications, as measured using the Clavien-Dindo classification system
- Reoperation for any cause

CLARITY CHAMPIONS AND TRAINING

The CLARITY champions at each site include the principal investigator and two associate principal investigators.

CLARITY will be led at each site by a surgeon principal investigator (PI). These will be consultants who are responsible for the overall conduct of the study. In addition, they will recruit associate principal investigators who will also act as *'CLARITY Champions'* in their centre. The two associate PIs must include one surgical trainee and one staff nurse/nurse practitioner. An additional radiology associate PI is also recommended where possible. These site champions will oversee dissemination of training to doctors and clinicians at their site, implementation of evidence-based practice and sustainability of implementation. The *'CLARITY Champions'* will be asked to coordinate training days at their local centre, encourage completion of the online educational module by all members of the surgical team (e.g. local presentations to research and/or governance meetings, discussion and presentations at radiology

meetings, announcements at handover) and encourage behaviour change within their hospital or department.

All trainees, surgeons and allied health professionals who care for acute general surgical patients in the CLARITY intervention arm will be invited to complete the online educational module. The training modules will be password protected to monitor compliance within the experimental arm and centre-level completion rates monitored. Once the randomisation sequence requires implementation of the intervention, this will be introduced over an implementation period of four weeks before post-implementation data collection is commenced.

STUDY TEAMS

The study teams will consist of at least four collaborators that are staff members and one medical student as the acting STARSURG regional lead.

Care of the emergency general surgical patient involves a multidisciplinary team, including surgical specialties, anaesthetics, radiology, nursing and allied healthcare professionals. Many of the best practice learning points within the CLARITY educational intervention will relate to these different specialties and professionals. To best implement the educational intervention, the CLARITY study team must include two consultant surgeons, at least one surgical trainee and at least one radiologist, anaesthetist or nurse practitioner. The team can include any number of members beyond this from any profession, including students. This may include radiographers, physician associates and clinical support workers who work in surgical emergency / surgical assessment centres.

Each centre will also have a medical student Regional Lead selected through a competitive process by the STARSurg Steering Committee. The Regional Leads will be an invaluable resource in the research team, allowing for timely study progression, clarification of minor questions or issues, independent data collection and medical student collaborator recruitment. Medical students will be integral in collecting

data in two phases using the REDCap software. They will be expected to fill out patient case report forms after admission, including data on presentation, investigations and management. Additionally, they will follow patients up 30 days after admission and collate this data on REDCap for data completeness. Their contributions will be recognised in future publications based on the authorship rules described in this protocol. Contact details of the Regional Leads are listed here: https://starsurg.org/our-2023-24-representatives/.

All members of the CLARITY study team at each site are eligible for inclusion in co-authorship on any arising publications, provided they have materially contributed to at least one of the following:

- Gaining research and development / Caldicott guardian approvals.
- Implementing the educational intervention at the site (i.e. arranging for departmental teaching within surgical and radiology departments).
- Capturing data (entered under their login into REDCap).
- Data validation (validating the data or being an independent consultant for verifying this data).

THE REMAINING PROTOCOL SECTIONS COVER BOTH TRIAL PHASES

ETHICS AND CONSENT

This study would not be feasible with individual patient randomisation due to a high risk of bias and contamination between study arms. A cluster randomised trial is the most appropriate study design due to the intervention being implemented at hospital-level. Once the emergency surgical teams have completed the educational module, they will implement a change in practice for all subsequent patients they see.

Individual patient consent for the intervention is not possible, as the intervention is being implemented at hospital-level. Moreover, the intervention is low-risk with no specific risks anticipated. Importantly, in this pragmatic study, the educational e-modules are intended to inform clinical practice and harmonise

care according to current best clinical practice. Patients in sites allocated to the intervention arm will receive what is deemed to best evidence based care, with no new approaches tested.

Only routinely collected data will be collected in the CLARITY trial. Patients will not undergo any additional investigations for the purposes of this study. Clinical follow-up will be limited to review of health records up to a maximum of 30 days following attendance/admission to hospital. There will be no additional patient contact (telephone or in-person) beyond what is normal clinical practice at each centre. As such, if a patient is discharged from hospital before day 30, and no further routine contact with medical services is made, follow-up will be limited to inpatient care.

We anticipate that most ethics review boards will waive the requirement for patient consent, as only anonymised audit data will be collected. Each centre must, however, gain written approval from their research and development department.

BLINDING

The patient will be blinded to their hospital's randomised allocation. While individual patients will be fully informed of the details of their clinical care, they will not be aware whether the CLARITY intervention has been implemented at their hospital. This reflects routine clinical practice in which patients would not typically be aware of specific details of ongoing surgical training or guidelines. It is not possible to blind the emergency surgical team or outcome assessor since the hospital allocation will be known to all members of the clinical team prior to patient recruitment. However, since there are objective endpoints, assessors will be trained to collect these data in a standardised manner. Analysis will be performed blind to allocation sequence.

PATIENT ENTRY

Once a patient's eligibility is confirmed, the case report form (CRF) should be completed. When the data are uploaded onto the CLARITY Research Electronic Data Capture (REDCap) database, a unique REDCap identifier will be allocated to the patient. The REDCap identifier should be recorded on the CRF. This unique study number will be used in all correspondence between the CLARITY study office and the site.

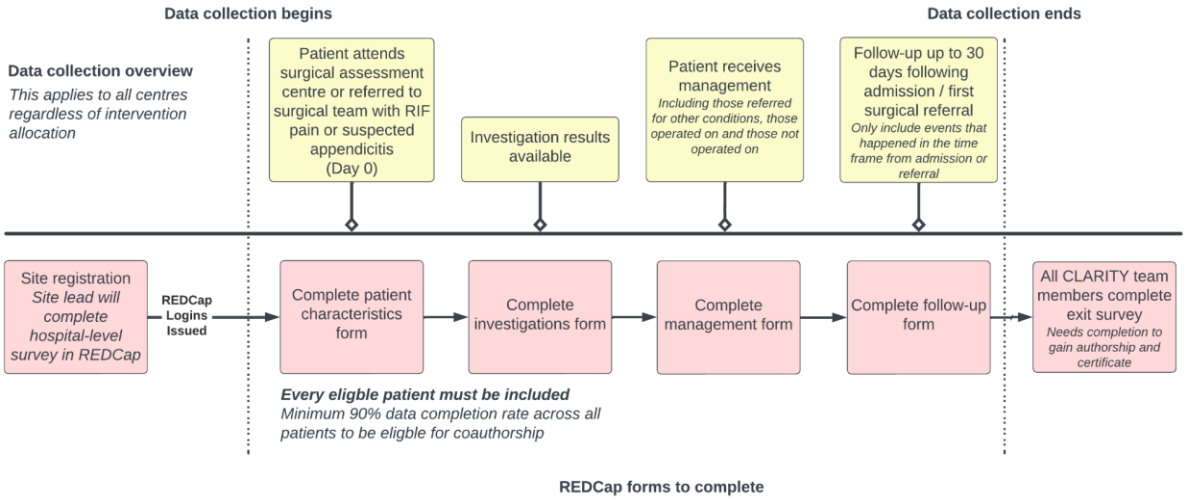
DATA COLLECTION AND FOLLOW-UP

Data will be collected in two phases. Figure 4 shows the data collection forms which need to be completed for patients in the main CLARITY trial. During the index attendance or admission, data on clinical presentation, investigations and management will be collected. If the patient undergoes an operation, intraoperative data will also be collected. Local Principal Investigators will establish pathways in their hospitals to ensure robust data collection. For example, clinical presentation data could be collected on admission, with intra-operative data fields completed in theatre immediately following completion of the procedure. Alternatively, all data could be collected on the ward for those who are admitted.

In the latter phase of data collection, patients who attended or were admitted to hospital with right iliac fossa pain, including those who did not undergo appendicectomy or were found to have alternative cause for their right iliac fossa pain, will be followed up to a maximum of 30 days (with day 0 being the day of attendance/admission) by a review of their inpatient health records, routine clinic visit letters, and reports for postoperative radiological investigations arranged as part of normal patient care. There will be no additional patient contact (telephone or in-person) beyond what is normal clinical practice at each centre. The study is designed so that existing patient follow-up pathways and health records can be used efficiently, with only data that is routinely collected as part of normal clinical care being captured. Appendicitis is unlikely to spontaneously resolve or recur without treatment (surgery or antibiotics), so 30 days should provide an adequate time frame to capture any complications or readmissions.

The CRF on REDCap has been designed to be straightforward and focuses on pertinent data points. In order to ensure the trial has validity, a minimum threshold of 90% data completion across all included patients will be used. Centres who have 90% or higher data completion rates will be included in the trial analysis and all CLARITY team members will be eligible for co-authorship. Centres with data completion below 90% will not be eligible for co-authorship.

Figure 4: Overview of REDCap data collection forms to be completed for the main CLARITY study.



SAMPLE SIZE

To detect a 25% reduction in the non-operative admission rate, assuming an intra-cluster correlation (ICC) of 0.06 and an α of 0.05, 40 clusters (20 per arm) of 120 patients would be required — 4800 patients in total. This sample size would provide a power of 0.90. We have been conservative in these estimates and factored in a cluster size variation of 50%.

PROJECTED ACCRUAL

Assuming each of the 40 centres sees 20 patients per week with right iliac fossa pain or suspected appendicitis, each centre should have accrued adequate data within 6 weeks of data collection commencing. The data collection period should run for 8 weeks, so there will be adequate time for centres to accrue cases and achieve the expected sample size.

STATISTICAL ANALYSIS PLAN

Analyses will be conducted on an intention-to-treat basis (i.e. all patients recorded in the database during the scheduled 8-week recruitment periods will be included). We will compile a full statistical analysis plan prior to data analysis. This trial will be reported according to the CONSORT guidelines, the CONSORT cluster RCT extension and the Standards for Reporting Implementation Studies (StaRI) statement.

Statistical analysis

All analyses will be performed with respect to the clustered nature of the data. Summary data will be tabulated using simple counts and percentages for categorical data. Where continuous data are normally distributed, the mean average will be presented alongside the standard deviation. Where data are not normally distributed, the median average will be presented alongside the 25th and 75th percentiles. Given randomisation, we will not formally test for differences in the characteristics of patients included in different clusters.

All data will be checked and data quality rules will be implemented to ensure data included in analyses are accurate. Missing covariate data will be fully reported and the reason for missingness established. Where possible, centres will be asked to supply the missing data, however, if this is not possible, we will perform multiple imputation when there is a significant amount of missing data (>10%). For missing outcome data, we will perform a best/worst case scenario analysis by imputing missing values with extreme values to assess whether missing outcome data is likely to impact our findings.

For binary outcome measures, we will report the absolute and relative treatment effects, alongside the corresponding 95% confidence intervals. Where an outcome measure is a continuous scale, we will report the mean difference with the corresponding 95% confidence interval. In the primary analysis, the primary outcome will be compared across treatment groups using mixed effects logistic regression with random cluster (hospital) effects allowing inclusion of baseline risk factors and adjustment for a fixed time effect between time periods. Treatment effects will be estimated using restricted maximum likelihood and generalised mixed linear models, with relevant small sample corrections. For rare events, we will use methods that maximise the likelihood of model convergence, such as propensity score matching. We will match patients using pre-specified clinically relevant covariates, including those used within the minimisation algorithm. For matched comparisons, we will also present a secondary covariate adjusted analysis.

Planned subgroup analyses

Pre-planned exploratory subgroup analyses of the primary outcome will be performed in the following groups:

At the cluster (hospital) level:

- Number of beds (<400 versus ≥400 total hospital beds)
- Trial phase (pilot trial versus main trial entrants)
- Availability of cross sectional imaging and diagnostic tests (limited blood testing only [only one available from haematology, biochemistry, point of care blood gas testing], comprehensive blood testing [haematology and biochemistry, but no cross sectional imaging], cross sectional imaging available — non-resident radiographer, cross sectional imaging available - resident radiographer)

- Proportion of clinicians (doctors and specially trained nurses or physicians associates on the acute general surgical team) in each centre completing the online training modules prior to post-implementation data collection (high [≥80%], intermediate [50-79%], low [<50%])

At the patient level:

- Patient age
- Patient sex
- Operative approach (open versus laparoscopic)
- Previous surgery
- Primary operating surgeon experience as reported (trainee versus consultant)
- For people who had appendix removed, the features of inflammation on histological reports to ensure the primary outcome is robust and measured consistently across sites

Reverse analysis will also be undertaken to explore the characteristics of hospitals with a large versus no changes in outcomes.

DATA HANDLING AND RECORD KEEPING

Source Data

Source data within the CLARITY study will be kept as part of the participants' medical notes generated and maintained at each site. As all data collected and analysed within the CLARITY study are routinely collected, source data will only be within the medical notes or linkage to routinely captured administrative datasets.

Data Management

Information will be collected at the following times:

- During the index hospital admission or attendance

- Up to 30 days after the hospital admission or attendance

Data will be entered directly onto the secure electronic CLARITY REDCap database by study collaborators at the participating hospital sites.

Site study collaborators will be provided with a paper copy of the eCRF to facilitate data collection. If this is used, they should transfer data from the paper CRF into the online CLARITY database (**https://www.bistc.redcap.bham.ac.uk**). CLARITY data management staff will check all incoming data CRFs for completeness, data consistency and compliance with the protocol. If discrepancies or missing data are identified, the CLARITY data management staff will raise queries with the research team at the participating hospital via the CLARITY REDCap database.

Data Security and Data Protection

The security of the Study Database System is governed by the policies of the University of Birmingham. The CLARITY study database will be hosted on the REDCap system managed and maintained by the BiSTC.

Data management and data security within the BiSTC will abide by the requirements of the General Data Protection Regulations (GDPR) and any subsequent amendments. The study will be conducted at collaborating sites in accordance with the country-specific data protection requirements. Data will be acquired and stored on the REDCap platform. Access to data will be restricted with usernames and passwords. Each participant will be allocated a unique study number at entry. All communication will use this as the identifier. All data will be analysed and reported in summary format. No individual will be identifiable in any summary data statistics. Linked data will be analysed within a trusted research environment. In all analyses, patients will remain anonymous.

QUALITY CONTROL AND QUALITY ASSURANCE

Site set-up and initiation

Study collaborators at participating hospitals will undergo a detailed, standardised site set-up training package. The package is formed of multiple components and covers the following areas:

- Training modules

  These will include modules on the intervention, study set-up, study delivery, and follow-up. Study-specific GCP training will be incorporated throughout these modules. Training will be CPD-accredited to encourage uptake. Site training is mandatory and completion of each module by the relevant staff is a prerequisite to site opening to recruitment. The monitoring of completion of training will be undertaken by staff at the CLARITY Study Office.

- Site initiation visit

  Once a site has completed all set-up processes, all team site team members will be invited to attend a teleconference with a CLARITY Coordinator and/or Operations Committee member. This teleconference will cover details regarding the intervention, study delivery, and follow up.

- Ongoing support

  Each local Principal Investigator will have ongoing support from an assigned CLARITY Coordinator with at least weekly teleconference or email contact. As the study proceeds, CLARITY Coordinators will tailor the content of these weekly contacts to the specific study processes that are relevant at that time.

Prior to opening, all participating local Principal Investigators will sign an Investigator's Agreement with the University of Birmingham to document acceptance of the responsibilities of the PI at the site.

Monitoring

Due to the nature of CLARITY, monitoring will be employed to ensure the credibility of the data. Monitoring will be undertaken centrally and will include, but will not be limited to, monitoring of: protocol adherence; patient selection and minimisation of selection bias; and review of data relating to the primary and secondary outcomes. Monitoring will be via data validation and range checks built into the REDCap database used to collect and manage the data; statistical monitoring techniques will be used

to compare data from different sites to identify sites that may warrant further investigation, site monitoring and/or support and training. Review by the study oversight committees (SSC, DMOC, SMG) will also include the review of completion of primary and secondary outcomes, adherence to protocol, and selection bias.

CLARITY study staff from the University of Birmingham will be in regular contact with the site research teams to check on progress and address any queries that they may have. The CLARITY Data Management Committee will check submitted CRFs from the participating hospitals for compliance with the protocol, data consistency and missing data. They will send participating hospitals data queries for missing data or clarification of inconsistencies or discrepancies.

Data validation

Validation of case ascertainment (the proportion of eligible cases that were included within the CLARITY study) will be undertaken in a random sample of 10% of centres. In those centres, data validation will be led by a member of the emergency general surgical team or medical student who was not involved in the initial data collection (known as the 'data validator'). They will review attendance, admission and theatre records to identify any potential patients which have been missed. The data validator will confirm these patients' eligibility through consultation with an independent surgeon who has not been involved in the initial data collection at that site. The total number of eligible cases at each site will be submitted to the CLARITY Coordinating Office. The total number of eligible cases and cases actually submitted to REDCap will be pooled across centres participating in the validation exercise, and the case ascertainment rate will be calculated.

STUDY ORGANISATIONAL STRUCTURE

The CLARITY Study Office

The coordinating centre for CLARITY is based at the University of Birmingham through the Birmingham Surgical Trials Consortium (BiSTC). Each site will appoint a Principal Investigator (PI) who will take responsibility for the study at site. This will be a consultant surgeon who is responsible for the overall

conduct of the study. In addition, they will recruit co-principal investigators ('site-leads'); this must include at least one surgical trainee, at least one radiologist and at least one nurse practitioner or staff nurse. The rest of the research team at the site can comprise any profession involved in the surgical care of emergency general surgical patients, including allied health professionals and students. All members of the research team are eligible for inclusion as co-authors on any arising publications under the corporate author byline 'CLARITY Trial Collaborators'. Each site will be mentored by a member of the CLARITY Study Management team, who will provide guidance, oversight and support directly to that site on behalf of the Study Management Group (SMG).

Sponsor

The University of Birmingham is the sponsor of the CLARITY study in all collaborating countries. Sponsorship will be provided by the University of Birmingham upon signing of the Study Agreement with each site.

CLARITY Study Management Group

The CLARITY Study Management Group includes those individuals responsible for the day-to-day management of the study. This will include the Chief Investigator, CLARITY operations staff, statisticians, and lead clinicians. The group will meet every six weeks to review ongoing progress. The role of the SMG is to monitor all aspects of the conduct and progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard the quality of the study itself.

CLARITY Operations Committee

The CLARITY Operations Committee is chaired by the Chief Investigator. It includes the surgical coordinators responsible for the delivery of the study at sites and CLARITY operations staff. The group will initially meet on a weekly basis at the start of the study and then two-weekly or monthly as the study progresses, depending on the needs of the project. The role of the operations group is to recruit investigators and hospitals to the study, and to support study set-up at individual hospitals. The

Operations Committee will have weekly contact with all participating centres either by teleconferencing or email to ensure adherence to the study protocol. In view of the large size of the study, the Operations Committee will be supported by a wider pool of CLARITY Coordinators who will act as an interface between local Principal Investigators and the Operations Committee.

CLARITY Data Committee

The CLARITY Data Committee includes the study statistician and CLARITY operations staff. Access to study databases is restricted to the members of the Data Committee. The Data Committee will liaise closely with the Operations Committee to manage and monitor database access.

Study Steering Committee

The remit of the Study Steering Committee (SSC) is to provide overall supervision of the study and ensure that it is being conducted in accordance with the principles of Good Clinical Practice and other relevant regulations.

The SSC will meet face-to-face or via teleconferencing every three months, or more often if required.

The specific tasks of the SSC are:

- To approve and sign off the study protocol and any protocol amendments.
- To resolve problems brought to it by the CLARITY study management team
- To provide advice to the investigators on all aspects of the study.
- To review recommendations from the DMOC, and help with the decision-making that follows on from the recommendations of the DMOC.

Data Monitoring Oversight Committee

The DMOC is scheduled to meet prior to the study commencing every three months thereafter until the study closes to recruitment. Additional meetings may be called if recruitment is much faster than anticipated and the DMOC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if required. The

DMOC will review data completeness, recruitment per-site, recruitment overall, and protocol deviations. The DMOC will make recommendations to the SSC. Data monitoring will be undertaken according to a separate, pre-specified plan.

CONFIDENTIALITY AND DATA PROTECTION

Patient identifiable information will not be collected in this study (i.e. names or dates of birth). All data for analysis at the University of Birmingham will be anonymised. All data collected about participants will be identified using only a unique CLARITY study number. This number will be automatically allocated via REDCap once a new patient record is created in the CLARITY REDCap database. Any correspondence between the CLARITY study office and hospital sites will use the CLARITY study number only. The linkage between REDCap study ID and participants will be maintained in strict confidence at participating sites. This data will not be submitted to the CLARITY study office and will not be sent outside of the participating site. Confidentiality of all participant's data will be maintained and there will be no disclosure of information by which participants may be identified to any third party other than those directly involved in the treatment of the participant.

INSURANCE AND INDEMNITY

The University of Birmingham has in place Clinical Trials indemnity coverage for this study 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 study.

The risk of the trial is no greater than the risk of the standard clinical care. Responsibility for the participants at sites remains with the organisation responsible for the clinical site and it is therefore indemnified through their normal arrangements.

AUTHORSHIP

The output from this research will be published under a single corporate authorship group: "CLARITY Trial Collaborators". The following roles will be recognised within the collaborating authorship list: Writing group, Protocol group, CLARITY Study Management Group, CLARITY Operations Committee, CLARITY Education Committee, CLARITY Data Management Committee, Study Steering Committee, Data Monitoring Committee, Statistical Analysis, CLARITY co-ordinators, Principal Investigators, co-Principal Investigators, Collaborators.

Each participating hospital may include any number of collaborators, so far that is reasonable. Numbers of collaborators will be monitored at each site and should be proportional to the amount of emergency general surgery activity at that site. All co-authors will be asked to attest their contribution. To ensure co-authorship is fairly attributed across all sites, the CLARITY coordination team reserves the right to request evidence of the claimed contribution. All co-authors will be PubMed searchable and citable.

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APPENDIX 1. CLARITY Case Report Form