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MEErKAT
MEsenteric Excision and Kono-S Anastomosis Trial

MEsenteric Excision and Kono-S Anastomosis Trial

RESEARCH PROTOCOL

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Sheffield Clinical Trials Research Unit (CTRU)

The MEErKAT trial: MEsenteric Excision and Kono-s Anastomosis Trial

This document describes a clinical trial, and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

Contents

Abbreviations

Definition of terms

ACPGBI	Association of Coloproctology of Great Britain and Ireland
AE	Adverse Event
BSG	British Society of Gastroenterology
CCC	Confirmation of Capacity and Capability
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CI	Chief Investigator
CRF	Case Report Form
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
EME	Efficacy and Mechanism Evaluation
ER	Endoscopic recurrence
GCP	Good Clinical Practice
HR	Hazzard Ratio
IBD	Inflammatory Bowel Disease
ICC	Intraclass Correlation
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials
ITT	Intention to Treat
NHS R&D	National Health Service Research & Development
PCR	Polymerase Chain Reaction
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

ScHARR	Sheffield School for Health and Related Research
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
STH	Sheffield Teaching Hospital
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

Agreement Page

The clinical study as detailed within this research protocol (Version 1, dated 15th December 2021), or any subsequent amendments, will be conducted in accordance with the UK Policy Framework for Health & Social Care (2017), the World Medical Association Declaration of Helsinki (1996) and the Principles of ICH-GCP and any subsequent amendments of the clinical trial regulations.

Lead Chief Investigator Name: Professor Steven Brown

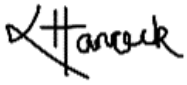
Lead Chief Investigator Site: Sheffield Teaching Hospitals NHS Foundation Trust

Signature and Date:  **28 June 2023**

Print name: Steven Brown

Co-Chief Investigator Name: Ms Laura Hancock

Co-Chief Investigator Site Manchester University NHS Foundation Trust

Signature and Date:  **28 June 2023**

Print name: Laura Hancock

Sponsor Organisation: Sheffield Teaching Hospitals NHS Foundation Trust

Signature and Date:  **28 June 2023**

Print name: Dipak Patel

Senior Statistician Name: Professor Stephen J Walters

Organisation: University of Sheffield

Signature and Date:  **28 June 2023**

Print name: Professor Stephen J Walters

1. Key Contacts

1.1 Investigator details

Lead Chief Investigator:

Prof Steven Brown
Professor/Honorary Consultant Colorectal Surgeon
Sheffield Teaching Hospitals NHS Foundation Trust
Royal Hallamshire Hospital,
Sheffield
S10 2JF

Email: steven.brown13@nhs.net
Tel: 0114 226 6292

Co-Chief Investigator:

Ms Laura Hancock
Consultant General & Colorectal Surgeon
Central Manchester University Hospitals NHS Foundation Trust
Wythenshawe Hospital
Manchester
M23 9LT

Email: laurahancock@doctors.org.uk
Tel: 0161 291 6123

Other Co- applicants:

Professor Stephen Walters
Senior Statistician
The University of Sheffield

Professor Mark Travis
Professor of Immunology
The University of Manchester

Professor Alan Lobo
Consultant Gastroenterologist
The University of Sheffield

Professor Daniel Hind
Professor of Evaluation
The University of Sheffield

Mr William Waterworth
PPI representative

Ms Lucy Sibbald
PPI representative

1.2 Clinical Trials Research Unit

CTRU oversight:
Name: Daniel Hind
Email: d.hind@sheffield.ac.uk
Tel: 0114 222 0707

Senior Statistician:
Name: Stephen Walters
Email: s.j.walters@sheffield.ac.uk
Tel: 0114 222 0730

Statistician:
Name: Esther Herbert
Email: e.herbert@sheffield.ac.uk
Tel: 0114 215 9428

Trial Manager:
Name: Jamie Hall
Email: jamie.hall@sheffield.ac.uk
Tel: 0114 222 2963

Research Assistant:
Name: Liv Hawksworth
Email: o.hawksworth@sheffield.ac.uk
Tel: 0114 222 0868

Clinical Trials Research Unit, ScHARR
The University of Sheffield
Innovation Centre
c/o 30 Regent Street
Sheffield, S1 4DA
Fax: 0114 222 0870

1.3 Sponsor details

Clinical Research & Innovation Office
Sheffield Teaching Hospitals NHS Foundation Trust
Room D49, D Floor,
Royal Hallamshire Hospital,
Sheffield, S10 2JF

Sponsor Representative: Name: Modhumita Harris
Email: modhumita.harris@nhs.net
Tel: 0114 2713570

1.4 Trial Steering Committee members

Professor Christopher Probert Professor of Gastroenterology University of Liverpool (Chair)	Mr Aidan Armstrong Surgeon Belfast Health and Social Care Trust
Miss Katherine Grant Consultant Colorectal Surgeon County Durham and Darlington NHS Foundation Trust	Dr Neil Walker Senior Statistician Queen Mary University
Ms Kathleen Bone PPI Representative	Ms Louise Walker PPI Representative

1.5 Data Monitoring and Ethics Committee members

Mr Justin Davies (Chair) Consultant Colorectal & Laparoscopic Surgeon Cambridge University Hospitals NHS Foundation Trust	Dr Catriona Keerie Senior Statistician The University of Edinburgh
Dr Miles Parkes Consultant Gastroenterologist Addenbrooke's Hospital, Cambridge	

1.6 Funder

This project (NIHR131988) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The views expressed in this protocol are those of the authors and not necessarily those of the MRC, NIHR or the Department of Health and Social Care. The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication. The funder has approved the selection of members for oversight committees.

1.7 Protocol amendments

Version	Amendment detail
1.0	N/A – first version

2.0	Updates include:
	- Header and front page – Updated the Sheffield CTRU logo
	- Clarified the identity of the Lead Chief Investigator and Co-Chief Investigator
	- Amended the Study Manager from Marie Hyslop to Jamie Hall
	- Amended the Research Assistant from Jamie Hall to Liv Hawksworth
	- Amended the Statistician to Esther Herbert
	- Amended 'radical mesenteric excision' to 'extended mesenteric excision' throughout in line with literature terminology
	- Trial Summary section
	  ○ Added the ISRCTN
	  ○ Corrected the 6 month to three year endoscopic recurrence window to up to three years
	  ○ Added the EQ-5D-5L
	  ○ Clarified the follow up duration
	  ○ Corrected the definition of the end of trial to be based on randomisation rather than surgery
	- Section 1.4 - Updated the TSC membership
	- Section 3.1 - Clarified the data collection range for the clinical objectives
	- Section 4 - Clarified the follow up duration
	- Section 5.2
	  ○ Added clarification on participants who become pregnant
	  ○ Added "proximal to the anastomosis" to the stoma exclusion criteria as patients whose anastomosis can still be inspected by colonoscopy for the primary endpoint assessment are elgibile.
	- Section 8
	  ○ Primary outcomes - Clarified the follow up duration
	  ○ Secondary outcomes - Removed the 'time to endoscopic recurrence' as this was a repeat of the primary outcome
	  ○ Secondary outcomes – Removed 'Mesenteric Disease Activity Index' as this is only collected at baseline for analysis and is not an outcome measure
	- Section 9.2 - Added collection of colonoscopy data by note review to the up to three year column of the assessments schedule
	- Section 9.3 - Added the option to lay out the excised specimen next to a reference object
	- Section 10
	  ○ Removed the statement 'Unrelated AEs will not be recorded' from Section 10 as this is not accurate (all AEs will be recorded so relatedness can be assessed)
	  ○ Clarification of the (Serious) Adverse Event reporting process
	- Section 11.2
	  ○ Clarified the primary outcome timing
	  ○ Removed complier average causal effects (CACE) analysis and replaced with per-protocol analysis
	- Added the option to take consent remotely via post or online
	- Correction of typographical errors throughout

Trial Summary

Study title	MEsenteric Excision and Kono-S Anastomosis Trial (MEErKAT).
Sponsor	Sheffield Teaching Hospitals NHS Foundation Trust
Funder	Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership (NIHR131988)
ISRCTN	ISRCTN16900055
Project start date	1st September 2021
Project end date	30th April 2026
Hypothesis	How and why should surgeons consider the mesentery and anastomotic technique in Crohn's disease?
Aim	Compare recurrence after different mesenteric excision and anastomosis techniques.
Trial design	A multicentre, 2 × 2 factorial, randomised controlled, open-label superiority trial.
Internal pilot/feasibility criteria	Internal red, amber or green stop/go pilot feasibility criteria, based on participants consented after 12 months from start of recruitment, will recommend: 1. Absolute Recruitment Numbers 2. Eligible to Consent Rate 3. Equipoise
Setting	Surgeons will recruit adults undergoing ileocaecal resection for primary/recurrent Crohn's disease where an anastomosis is carried out, excluding those with inflammation affecting the vascular root of the mesentery, undergoing stoma formation

	proximal to the anastomosis, or with contraindication to colonoscopy.
Participants	308 patients undergoing ileocaecal resection for primary/recurrent Crohn's disease.
Intervention & control groups	Participants will be centrally randomised (1:1:1:1) to: (1) Kono-S + extended mesenteric resection; (2) Kono-S + close mesenteric resection; (3) Standard anastomosis + extended mesenteric resection; (4) Standard anastomosis + close mesenteric resection. Randomisation will occur at the time of (or during) surgery.
Primary outcome	Primary outcome: time to endoscopic recurrence (ER) post-randomisation (up to 3 years follow up)
Secondary outcomes	Secondary outcomes: severe endoscopic recurrence, symptomatic recurrence, surgical recurrence, complications and mesenteric disease activity.
Mechanistic outcomes	The degree and anastomotic locality of different immune cells and fibrocytes, focussing on mucosal T cell clonality and exhaustion, especially CD8+ T cells, will be compared before and after each intervention utilising flow cytometry, multiplex PCR and sequencing and qPCR.
Duration of recruitment period and first enrolment date	30 months (first enrolment planned May 2022)
Duration of follow-up	The final protocol stipulated face-to-face assessment is at one year (window -6 months/ + 3 months). All patient notes will be reviewed for relevant endpoints at the end of the trial. This means that participants randomised earlier in the

	trial will get a longer follow up (up the three years) than those recruited later.
Target sample size	308 patients (77 per group; 154 per group for the factorial design)
Definition of end of trial	The end of the trial is defined as the date of the last recruited participant's 1 year (window -6 months/+3 months) post-randomisation follow up visit. Sites will be closed once data cleaning is completed and the regulatory authority and ethics committee will be informed.

2. Introduction

2.1 Background

Crohn's disease is an inflammatory condition of the gastrointestinal tract affecting 300 per 100,000 population (200,000 in the UK) (Latella and Papi 2012). It follows a chronically relapsing pattern despite advances in medical therapy. Almost all patients eventually require resection of diseased bowel. Even after surgery over one third of patients need further surgery within 10 years (Cullen, O'Toole et al. 2007). Animal models and pathological specimens suggest recurrence after surgery is initiated at the mesenteric border of the surgical join in the bowel (the anastomosis)(Anthony, Dhillon et al. 1997, Anthony, Dhillon et al. 1999, Anthony, Pounder et al. 2000). Some hypothesise the underlying mechanisms to involve faecal stasis and microbiome changes (Caprilli, Corrao et al. 1996). Others point to the mesenteric vascular anatomy: the mesenteric border of the bowel is supplied by end arteries whereas the antimesenteric border has collateral supply. Disease in the mesentery would tend to disrupt the blood supply to the mesenteric border of the bowel before the antimesenteric border and cause the pattern of ischaemic type changes (ulceration) that are seen (Hultén, Lindhagen et al. 1977, Thornton and Solomon 2002). Further evidence for this theory comes from studies that have examined a specific type of operation known as a strictureplasty. This intervention does not resect bowel; instead the antimesenteric border of the bowel is opened longitudinally and closed transversely, thereby increasing the luminal diameter. A systematic review of this procedure suggests a very low site specific surgical recurrence rate despite leaving diseased bowel and mesentery behind (Yamamoto, Fazio et al. 2007). Others suggest the mesentery as the focus of the disease, with high visceral fat content, increased lymphatic vascular density at the resection margin and granulomata in the mesenteric lymph nodes associated with recurrence (Li, Zhu et al. 2015, Li, Zhu et al. 2016, Li, Ge et al. 2018) and extended resection as the only way of removing the disease focus.

These competing theories of recurrence have led surgeons to contemplate whether the techniques of resection and anastomosis can affect recurrence. Various anastomotic configurations have been trialled, with conflicting results (Choy, Bissett et al. 2011, He, Chen et al. 2014). Current consensus supports a wide lumen configuration, accomplished with a stapled side-to-side technique (Simillis, Purkayastha et al. 2007, Dignass, Van Assche et al. 2010). Two techniques have gained traction based on poor evidence but apparent spectacular reduction in recurrence (Alshantti, Hind et al. 2021). The Kono-S anastomosis takes into account the predisposition for mesenteric border recurrence by proposing an antimesenteric anastomosis. High quality data is needed to establish whether this technique is as effective as suggested; some comparative studies are ongoing (Nct 2014). An interesting component of the technique is the proposal that the mesentery is essentially preserved. The other school of thought proposes

the mesentery as the driver of disease, requiring a more radical resection of diseased mesentery, with the anastomosis irrelevant to recurrence (Coffey and O'Leary 2016, Coffey and O'Leary D 2017). Evidence for this technique is poor but comparative studies are ongoing (Li, Mohan et al. 2020). Despite the contrasting techniques, there may be commonalities that explain why both are effective. Both aim to isolate the anastomosis from diseased mesentery. Kono-S does this by a totally antimesenteric anastomosis as far away as possible from the mesentery; extended mesenteric resection by removing the theoretical disease driver. A combination of techniques is possible and may increase efficacy. A multicentre, superiority, 2 × 2 factorial, randomized, open-label trial comparing combinations of extended mesenteric excision or preservation, Kono-S and conventional anastomosis would efficiently assess not only the efficacy of each intervention compared with standard surgery but also any additive effect.

If one or both interventions result in reduced recurrence, the underlying mechanism of action remains a key question within the EME's remit. The beneficial effect of the anastomosis on the antimesenteric border can be easily explored in vivo by examining the locality of any mucosal recurrence. Current thinking suggests Crohn's disease occurs due to interaction of genetic heritable traits and environmental factors (such as the microbiota) leading to innate and adaptive immune cell-mediated inflammation (Ha, Martin et al. 2020). Analysis of immune cell phenotype in the mucosa (Camus, Esses et al. 2014, Chapman, Yamaguchi et al. 2016, Doorenspleet, Westera et al. 2017), in the different combinations of resection and anastomosis: 1) mesentery wholly excised; 2) mesentery somewhat retained; 3) either option with or 4) without isolation from the anastomosis will give insight into whether each intervention has different effects on the mechanism of inflammation. Visceral fat area, fibrocyte levels and investigation of immune activation, with a focus on T cell clonality and exhaustion will enable us to explore potential underlying mechanisms of action. This includes investigation of antigen presentation - a key potential mechanistic role for the mesentery.

2.2 Why is this research needed now?

The James Lind Alliance ranked identifying the optimal treatment strategy including surgical efficacy and safety a top research priority (James-Lind-Alliance 2020). Surgery for CD was listed in the top 10 non-cancer research priorities by the Association of Coloproctology (McNair, Heywood et al. 2017). People with CD have a severely compromised quality of life. They are usually young and profoundly affected by sick-leave and social marginalization (Love, Irvine et al. 1992, Delaney, Kiran et al. 2003). Decision-making is difficult: many persist with pharmacotherapy as long as possible, but over a quarter wish they had had surgery earlier (Tang, Ge et al. 2019). As newer medications are marketed, the cost of treatment is escalating. Early surgical intervention in Crohn's disease often dominates (higher efficacy, less cost) medical therapy in health economic terms (Broide, Eindor-Abarbanel et al. 2020, Ryan, Orsi et al. 2020). If surgery reduced recurrence or negated the need for adjuvant medical therapy, patients might

opt for surgery earlier, reducing decision regret, with significant cost savings for the NHS. From a clinician point of view a low recurrence rate after surgery would fundamentally change practice with early surgery becoming the norm rather than the last resort.

The microcellular pathway leading to Crohn's recurrence after surgery is poorly understood. Exploration of *in vivo* locality of recurrence and changes to immunological profiles will improve our understanding of CD, allow stratification of patients for concomitant medical therapy and focus future research. This research offers a unique opportunity to study the effect of the mesentery on immune activation.

2.3 What is the knowledge gap this research will address?

Reported substantial reductions in otherwise very high recurrence rates from two novel surgical innovations - the Kono-S anastomosis and extended mesenteric excision - demands robust study of their individual efficacy and additive effect. Efficient mechanistic investigation will tell us if recurrence is initiated on the mesenteric border of the bowel and if that is affected by surgical strategy. What we learn about the local tissue immune response will improve understanding of the disease process and of which patients are more likely to recur.

2.4 Recent and ongoing trials and proof of concept

Our trial brings together empirical and theoretical research traditions on: (1) the Kono-S anastomosis; (2) extended mesenteric excision; (3) the locality of recurrence after surgery; and (4) local tissue immune response and its association with surgical recurrence. A systematic review of the Kono-S anastomosis found several low quality studies and 1 high quality RCT confirming the safety of Kono-S and suggesting a 65% reduction in endoscopic recurrence after 6 months (22.2% Kono-S group vs. 62.8%) (Alshantti, Hind et al. 2021). If recurrence rates are reduced by this magnitude, Kono-S should have profound implications for management. An ongoing trial comparing the technique with standard anastomosis was registered 6 years ago and progress is unknown (Nct 2014). It has no mechanistic component and does not take into account the degree of mesenteric resection. Empirical data supporting the theory of the mesentery as the driver of disease recurrence and the necessity of extended resection is poor (Coffey, Kiernan et al. 2018, de Groof, van der Meer et al. 2019). One RCT comparing extended mesenteric excision with standard excision is ongoing and has no mechanistic component (Li, Mohan et al. 2020). As it does not take into account novel types of anastomosis, it is not future-proofed. A large cohort study, awaiting publication (Coffey *pers. comm.*), also indicates extended mesenteric resection reduces recurrence. Literature reporting initial recurrence being confined to the mesenteric border of the bowel is only from animal models and pathological specimens (Anthony, Dhillon et al. 1997, Anthony, Dhillon et al. 1999, Anthony, Pounder et al. 2000) with no in vivo studies to confirm this pattern of recurrence, which is easy to confirm within normal

clinical care pathways. The mesentery is a key site for immune key immune pathways in Crohn's disease (Sakuraba, Sato et al. 2009, da Silva, Pascoal et al. 2020). Alterations in T cell receptor repertoire in CD have been observed for many years (Probert, Chott et al. 1996, Matsuda, Gapin et al. 2000, Probert, Saubermann et al. 2007, Camus, Esses et al. 2014, Chapman, Yamaguchi et al. 2016, Doorenspleet, Westera et al. 2017). Recent observations suggest patients with persistent high clonality of CD8+ T cells (i.e. less T cell receptor diversity) have a poorer prognosis, and that gene expression profiling after resection predicts recurrence (Lee, Lyons et al. 2011). In addition, enhanced T cell exhaustion has been associated with improved disease outcome (Tang, Ge et al. 2019). The effect of the mesentery and type of anastomosis on recurrence has not been explored. Visceral fat area and fibrocyte proportion in peripheral blood also correlate with inflammation and recurrence (Probert, Chott et al. 1996, Li, Zhu et al. 2016).

The study will be conducted in accordance with the protocol and ICH GCP.

3. Aims and objectives

3.1 Aims

The main aim of the study is to compare recurrence after standard mesenteric excision or extended excision and standard anastomosis or Kono-S anastomosis (with or without extended mesenteric excision).

3.1 Objectives

Feasibility objectives:

To undertake an internal pilot trial to determine the feasibility of a full-scale trial, in terms of:

- Recruitment
- Eligible to consent rate
- Equipoise

Clinical objectives

- Assessment of endoscopic recurrence (Modified Rutgeerts score ≥i2) and severe endoscopic recurrence (Modified Rutgeerts score ≥i3) for up to three years from randomisation.
- Assessment of symptomatic recurrence after at least 6 months and assess the time to recurrence using IBD Control (Bodger, Ormerod et al. 2014) and Crohn's Disease Activity Index (Best, Becktel et al. 1976).
- Assessment of surgical recurrence
- Assessment of complications for each intervention
- Assessment of need for escalating medical therapy

Mechanistic objectives

- Investigate the locality of endoscopic recurrence in relation to the mesenteric border.
- Investigate the degree and anastomotic locality of mucosal T cell clonality and exhaustion, especially CD8+ T cells and fibrocyte alterations
- Investigate changes in antigen presentation in the mesentery, blood and mucosa.

Endoscopic recurrence is an appropriate and sensitive primary efficacy/mechanistic outcome that is routinely collected. Informed consent and routine data will allow follow-on studies to assess longer-term surgical recurrence for all patients. A survey of 34 surgeons shows 95% are satisfied with endoscopic recurrence as a primary outcome for this comparison. Patients will be blinded. Endoscopists - who cannot be blinded as each anastomosis has a unique colonoscopic configuration will be independent of the study team. Photographs will be taken (with open biopsy forceps for definition of scale) for sourced data verification.

4. Trial Design

The study is a UK multicentre, superiority, 2 × 2 factorial, randomised, open-label trial with a one-year follow-up (-6 months/+3 months). Participants will be randomised (1:1:1:1) to one of four groups:

(1) Kono-S + extended mesenteric resection;

(2) Kono-S + close mesenteric resection;

(3) Standard anastomosis + extended mesenteric resection;

(4) Standard anastomosis + close mesenteric resection.

Endoscopic recurrence will be evaluated at the post-surgery/randomisation endoscopic follow up visit. The locality of recurrence will be investigated using colonoscopic assessment of mucosa relative to mucosal tattoos placed at the time of operation. A mechanistic component will determine in those that develop endoscopic recurrence, the locality of that recurrence. All patient notes will be reviewed for relevant endpoints at the end of the trial. This means that participants randomised earlier in the trial will get a longer follow up (up the three years) than those recruited later.

Extended mesenteric resection: mesenteric resection resecting all macroscopically abnormal tissue and dividing the mesentery up to the origin of the ileocolic trunk (Li, Mohan et al. 2020, van der Does de Willebois, Buskens et al. 2021) with preservation of the main ileocolic vessels.

Close mesenteric resection: the mesentery is resected within 3 cm of the border of the bowel, leaving most of the mesentery in situ.

Kono-S: Resected bowel stapled perpendicular to the mesentery and the stapled ends sutured together. 7cm antimesenteric enterotomies are made 1-1.5cm from the stapled resection margin and a side to side anastomosis created by suturing the enterotomies together.

4.1 Blinding

As there is no difference between the interventions in abdominal access or closure it is easy to blind the participant. Those assessing the 12 month (window -6 months/+3 months) endoscopic outcomes will be blinded to the allocation. Colonoscopists may recognise the Kono-S anastomosis in the bowel configuration, but will not be directly involved in the study. The degree of mesenteric excision will not be apparent during colonoscopy.

5. Selection of participants

The study will recruit patients aged over 18 years undergoing ileocaecal resection for primary/recurrent Crohn's disease where an anastomosis is carried out. The study will be run nationally within the UK across up to twenty centres, recruiting one participant per month over a maximum of 30 months. Post-operative medical treatment will be in line with the recommendations from the BSG guidelines (Lamb, Kennedy et al. 2019).

5.1 Inclusion criteria

- Patients aged 18 years and over
- Patients undergoing ileocaecal resection for primary/recurrent Crohn's disease where an anastomosis is carried out.

5.2 Exclusion criteria

- Patients with markedly extensive inflammation affecting the vascular root of the mesentery seen on imaging or at operation
- Patients undergoing stoma formation proximal to the anastomosis
- Patients who have contraindication to subsequent colonoscopy
- Patients unable to give full informed consent

- Patients who are pregnant* (as ascertained by standard pregnancy tests undertaken at pre-operative visits/ as per standard clinical care)
- Patients who, in the opinion of the principle investigator, do not meet the criteria for relevant surgery

**Participants who become pregnant following their surgery do not have to be withdrawn from the trial*

In a very small subset of patients, it may be the case that extensive mesenteric inflammation (an exclusion criteria) is only seen once undergoing surgery. Usually, this degree of inflammation would be picked up prior to surgery via relevant scans. In the case when it is only found at operation and the surgeon is unwilling to do an extended mesenteric excision, the patient would not be eligible for the trial. This decision is based on the surgeon's usual practice and standard of care. Participants should therefore not undergo randomisation until such time as the diseased area can be visually assessed at operation.

5.3 Participant identification and Target Population

The trial follows the standard pathway for ileocaecal Crohn's. Participants are recruited when surgery is deemed appropriate. Potential participants will be discussed at MDT meetings and identified at the time of pre-operative assessment before the day of surgery. Surgeons, research nurses and trainees will also check waiting lists for those listed for ileocaecal resection for primary or recurrent Crohn's disease.

5.4 Informed consent process

A member of the patient's care team will identify eligible participants. Potential participants will receive an approved Participant Information Sheet (PIS) and given the opportunity to ask questions from both the surgical and research team. The PIS may also be posted to potential participants prior to their clinic visit, for those that are identified by the local care team as potentially eligible for the trial. Potential participants will be approached either at their clinic visit prior to surgery or pre-operative assessment.

An appropriately trained member of the site research team who has been delegated to take informed consent may obtain consent from participants and enter them into the study. Consent may be obtained in person at a pre-operative assessment clinic or other face to face appointment. Consent may also be obtained remotely by post, or using an electronic system, Qualtrics.

For postal consent, the potential participant will be given, or sent a consent form. They will complete the consent form during a 'visit' with an appropriate member of the site study team

during a call. The participant will then post the completed form to the site study team for signature by the member of the team who conducted the call.

For electronic consent, an appropriate member of the study team will enter the participants details into the Qualtrics system, which will automatically email a link to the participant to complete the consent form. The participant will complete the form during a call with an appropriate member of the site study team. Once complete, the site study team will send the completed form to the member of the site study team who took consent for signature.

Consent should be obtained at least 7 days prior to a patient's day of surgery to ensure correct completion of the daily symptom diary of the CDAI questionnaire. The research team should reconfirm the patient is content to continue with the study at their surgery visit. No study related procedures will occur before the approved consent form is signed, other than initial case note review for eligibility.

For each participant, the original copies of the signed consent forms will be retained by the investigator in the site file but must be made available for inspection by the study monitor. Patients will also receive a copy of the PIS and their signed consent form to keep, and a copy will be filed in their medical notes. A copy of the consent form should also be sent to the central MEErKAT study team via the study NHS email address. Consent will be verbally reconfirmed at each study visit, as recommended by Good Clinical Practice Guidelines.

A screening log will be maintained for each site, to document all potential participants screened, whether they were recruited, and any reasons for non-recruitment where this information is available. Screening logs will be requested and reviewed by CTRU on a regular basis.

5.5 Co-enrolment guidelines

The MEErKAT study attempts to follow standard care pathways as much as possible e.g. post-surgery endoscopic follow up visit is what a patient would undertake as per their standard of care, regardless of the trial. It is hoped the trial puts minimal burden on patients, and thus co-enrolment in other studies is permitted on a trial by trial basis. Concurrent participation in any other clinical trial is allowed provided the following:

- The TSCs of both trials approve it
- There is no risk to either study in terms of delivery
- The patient burden is not excessive (in some cases this can be managed through data sharing).

6. Trial treatment

There are 2 groups of mesenteric excision and 2 groups of anastomosis

Mesenteric excision

Extended Mesenteric Excision

The mesentery is resected up to the origin of the ileocolic trunk but preserving the ileocolic vessels (van der Does de Willebois, Buskens et al. 2021) as shown in video (https://www.youtube.com/watch?v=KjVa76Db4yM). In participants who have markedly extensive inflammation affecting the vascular root of the mesentery seen on imaging or at operation these should not undergo extended resection due to the risk of vascular injury and should be excluded from the trial.

Close Mesenteric Excision

The mesentery is resected within 3 cm of the border of the bowel, leaving most of the mesentery in situ. For all cases the mode of access (laparoscopic or open), closure technique and post-operative care is according to usual practice for that participating centre.

Anastomosis groups

Patients randomised to Kono-S

For this anastomosis the resected bowel is stapled perpendicular to the mesentery and the stapled ends sutured together to form the supporting column. 7cm antimesenteric enterotomies are made 1-1.5 cm from the stapled resection margin and a side to side anastomosis created by suturing the enterotomies together.

Patients randomised to Standard of Care

Standard care is essentially surgeons' preference of anastomosis. Anastomosis may utilise staples or sutures and have a configuration of either end to end, functional end to end, or end to side.

Essentially patients will be randomised onto one of 4 combinations
-Close mesenteric excision and Kono-S anastomosis
-Extended Mesenteric excision and Kono-S anastomosis
-Close mesenteric excision and 'standard' anastomosis
-Extended Mesenteric excision and 'standard' anastomosis

For all cases the mode of access (laparoscopic or open), closure technique and post-operative care is according to usual practice for that participating centre.

For all groups the mesenteric incision will be made proximal to the mesenteric transition zone (Coffey, Kiernan et al. 2018), while the distal incision will be placed where both the mesentery and intestine are macroscopically normal immediately distal to the region of disease. Each technique consists of components familiar to bowel surgeons. The extended mesenteric excision technique is described in reference (van der Does de Willebois, Buskens et al. 2021) and in video form (https://www.youtube.com/watch?v=KjVa76Db4yM).

Every participating surgeon will have been mentored for the Kono-S anastomosis and will have carried out at least 2 procedures outside the trial. A video of each technique will be created and distributed to all surgeons. Localisation of recurrence will be aided by a tattoo of the mesenteric border of the anastomosis at the time of surgery using carbon black which is commercially available, widely used in colonoscopy and approved by the US Food and Drug Administration in various formulations. This safe and easy-to-use technique involves minimal time/cost. It is standard practice for patients to routinely undergo colonoscopy 6-12 months after surgery allowing assessment of any recurrence in relation to the tattoo marking. Post-operative follow up and colonoscopic assessment are standard (Probert, Saubermann et al. 2007). Colonoscopic assessment and biopsy take a few minutes. Some additional blood tests for those patients in the optional mechanistic sub-study are planned over and above standard care (see section 8.3).

Participants will undergo standard supportive care for surgical interventions as per local procedures. This will usually be in the form of available clinical contact for any concerns as well as access to clinicians responsible for the participant care if appropriate.

7. Randomisation and enrolment

Once consent has been obtained, baseline data recorded and eligibility confirmed, participants will be centrally randomised using the CTRU online randomisation system (SCRAM). Randomisation should be undertaken at the time of surgery, this is to ensure patients do not meet any of the exclusion criteria which can only be correctly ascertained at surgery. The doctor or research nurse will access the web-based randomisation system, patient demographic details (ID, date of birth) will be entered and the treatment allocation will be returned. Participants will be randomly allocated to (1) Kono-S + extended mesenteric resection; (2) Kono-S + close mesenteric resection; (3) Standard anastomosis + extended mesenteric resection; (4) Standard anastomosis + close mesenteric resection or surgeons' choice, in the ratio 1:1:1:1

Participants will be allocated using a computer generated pseudo-random list, stratified by centre, with random permuted blocks of varying sizes. The sequence will be restricted by

authorisation until analyses are complete. As there is no difference between the interventions in abdominal access or closure it is easy to blind the participant. Those assessing 12 month (-6 months/+3 months) endoscopic outcomes will be independent of the study and blinded to the allocation. Endoscopists may recognise the Kono-S anastomosis in the bowel configuration, so will not be directly involved in the study. However, they will be provided with clear instructions about grading the severity of disease (as per standard practice and utilizing the Modified Rutgeert's score), the need for localization of the recurrence in relation to any tattoo (see section 8.3) and the number and location of any mucosal biopsies (see section 9.3). The degree of mesenteric excision will not be apparent during colonoscopy.

8. Outcomes

8.1 Primary outcome

The primary outcome is time to endoscopic recurrence of disease (up to three years follow-up) from the date of randomisation using the Modified Rutgeerts score (≥i2)(Rutgeerts, Geboes et al. 1990, McLeod, Wolff et al. 2009).

8.2 Secondary outcomes

Secondary outcomes are:

- incidence of severe endoscopic recurrence (Modified Rutgeerts score ≥i3);
- clinician and patient-reported symptomatic recurrence (Best, Becktel et al. 1976, Bodger, Ormerod et al. 2014);
- quality of life (EQ-5D-5L)(Herdman, Gudex et al. 2011);
- surgical recurrence up to three years (clinician and patient reported);
- radiological and surgical anastomotic leak as defined by the latest consensus (van Helsdingen, Jongen et al. 2020); other complications for each intervention;

The definition of symptomatic recurrence will be:

- self-reported recurrence in combination with endoscopic ally confirmed recurrence; **OR**,
- surgical re-intervention in combination with histological confirmation of recurrence; **OR**,
- change of medical strategy for reasons other than safety/tolerability; **OR,**
- IBD Control >13; OR, CDAI >220. These measures are only collected for this trial endpoint at the 6-15 month follow up

The definition of a radiological anastomotic leak will be:

- extravasation of endoluminal-administered contrast;
- collection around the anastomosis;
- perianastomotic air;
- free intra-abdominal air (depending on the number of post-operative days).

The definition of a surgical leak will be;

- necrosis of the anastomosis
- signs of peritonitis
- dehiscence of the anastomosis

Justification for the nature and timing of primary and key secondary outcomes

An ideal primary outcome would be surgical recurrence at 5 years. Using such an outcome would require a 9-10-year study. This is not realistic within a reasonable funding envelope. Endoscopic recurrence is an early surrogate for surgical recurrence, and is frequently used as a primary outcome in related previous (Luglio, Rispo et al. 2020) and ongoing trials (Li, Mohan et al. 2020). A survey of 34 surgeons showed 95% are satisfied with endoscopic recurrence as a primary outcome for this comparison. Participant consent and routine data will allow a separately-funded follow-on study to assess surgical recurrence with a minimum follow-up of five years.

8.3 Mechanistic Outcomes

All patients will undergo tattooing of the mesenteric border around the anastomosis using carbon black. Subsequent standard follow up involves an assessment for endoscopic recurrence at around 12 months (De Cruz, Kamm et al. 2015). This will allow localisation of any recurrence in relation to the tattoo. Endoscopic recurrence will be noted as: consistent with the hypothesis (confined to the tattooed mesenteric border only; confined to sites including the tattooed mesenteric border but more severe at the mesenteric border); refutes hypothesis (recurrence seen more than 2cm from the tattoo with the tattooed mesenteric border being recurrence free; confined to sites including the tattooed mesenteric border but less severe recurrence seen within 2cm of the tattoo); or, confined to sites including the tattooed mesenteric border of equivalent severity. To understand the mechanistic basis of intervention efficacy we will assess the sequential events between surgery and colonoscopic follow up. Visceral fat area will be assessed radiologically or at operation and correlated with recurrence (using methods described in (Probert, Chott et al. 1996, Li, Zhu et al. 2016)).

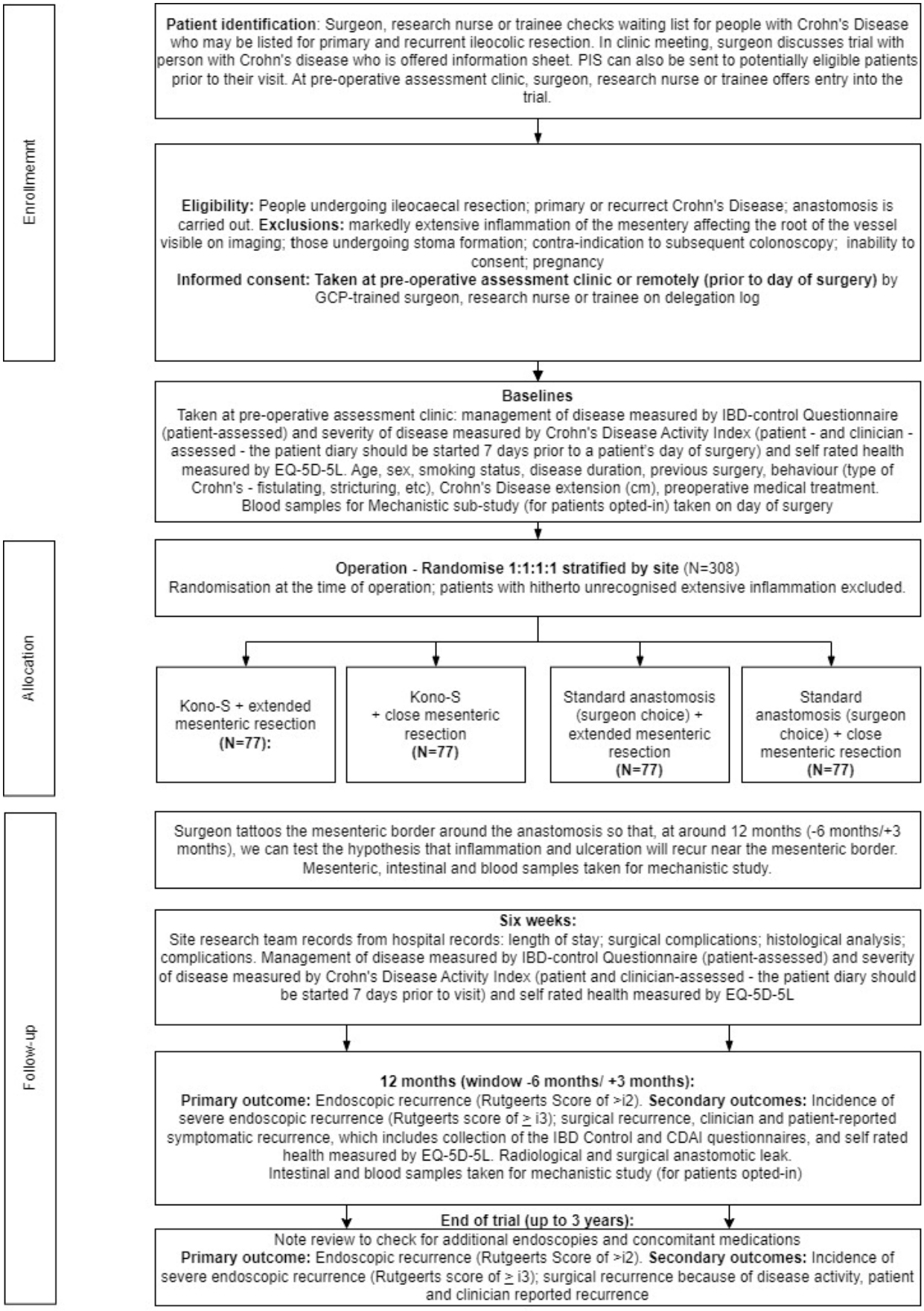
For around a minimum of 140 patients fibrocytes will be measured in peripheral blood taken pre-operatively and at colonoscopic assessment around 12 months (using methods described in (Probert, Chott et al. 1996)). Samples of mucosa will be taken at the time of operation from both the mesenteric and antimesenteric borders of the resected specimen. These will be analysed using flow cytometry for general immune activation profile, multiplex PCR and sequencing for T cell repertoire analysis and qPCR for T cell exhaustion markers (using an established 17 gene profile (Biasci, Lee et al. 2019)). Further samples will be taken at the follow up colonoscopy from the small bowel mesenteric and antimesenteric borders.

In this subset of a minimum of 140 patients peripheral blood fibrocyte levels, visceral fat area, general immune activation, and T cell clonality and exhaustion and antigen presentation will be assessed pre-operatively and compared with post-operative recurrence in order to confirm the previous literature indicating elevated fibrocytes, high visceral fat, enhanced CD8+ T cell clonality and lower T cell exhaustion are poor prognostic markers regardless of surgical intervention. Changes will be assessed after each intervention to examine 3 potential scenarios:
(1) there is no change in peripheral blood fibrocytes, mucosal immune activation/clonality/exhaustion after each intervention;
(2) there is a reduction in fibrocytes, immune activation/clonality/exhaustion with one or both interventions and not in the control group suggesting the intervention(s) alter(s) the immune pathway;
(3) there are changes in locality of activated immune cells, clonal and exhausted T cells with changes on the mesenteric border suggesting a mechanism whereby an antimesenteric anastomosis may influence outcome.

9. Assessments and procedures

9.1 Study Flow Chart

9.2 Study assessments schedule



Baseline data will be collected by a research nurse or clinician (Table 1). Operative details will be recorded by the operating surgeon. Six-week and 6-12-month follow up data will be collected by a research team member who is blind to allocation. Standard colonoscopic follow-up will be collected by a colonoscopist not involved in the trial. Colonoscopists will collect mucosal biopsies and recurrence data, relative to the small bowel mesenteric tattoo, at colonoscopic follow-up. At the end of the study (12 to 42 months after surgery) further data will be collected by a team member who is blind to allocation.

Table 1 – Assessments during study

	Baseline	Operation	6 wks.	12 months (-6 to + 3 months	Study end (up to 3 years)
Eligibility Assessment	X[1]	X[1]			
Consent	X				
Medical History	X				
Concomitant Medications	X		X	X	X
Demographics	X				
IBD-Control	X		X	X	
CDAI	X[2]		X	X	
EQ-5D	X		X	X	
Randomisation		X			
Mesenteric disease activity index		X			
Adverse Events		X	X	X	
Colonoscopy				X	X[3] (via note review)
Blood samples	X[4]			X[4]	

Mucosal/mesenteric biopsies		X[5]		X[5]	
Surgical recurrence				X	X (via note review)

[1] *General eligibility assessment will be done at baseline to assess patient is suitable for trial; however, formal eligibility assessment can only be carried out at surgery when surgeon physically observes the gut (see section 5.2).*

[2] *CDAI patient diary should be started 7 days prior to a patient's day of surgery*

[3] *Data will be collected on any additional colonoscopies participants receive as part of their standard care*

[4] *Patients in (optional) mechanistic sub-study only (see section 9.3).*

[5] *Biopsies should be as per standard care for main trial patients. Patients in (optional) mechanistic sub-study will have extra samples taken (see section 9.3).*

9.3 Procedures for assessing efficacy

Baseline data is collected as close as possible to the surgery. Blood samples are taken according to section 9.2. Intraoperative data will include the mode of access, the type of resection and anastomosis, any intra-abdominal complications and the mesenteric disease activity index (Coffey, Kiernan et al. 2018).

Mesenteric disease	Score
Fat wrapping minimal, mesenteric thickening minimal	1
Fat wrapping <25%circumference of bowel, thickening of vascular pedicle only	2
Fat wrapping <25%circumference of bowel, pan mesenteric thickening	4
Fat wrapping >25%circumference of bowel, pan mesenteric thickening	6

To quality assure the surgery, surgeons will be asked to pin or lay out the specimen after operation next to a ruler or another reference object and take a digital photograph. A digital camera will be supplied to each centre (if required) and the photographs will be anonymised. The photographs will be assessed centrally to assess the adequacy of the mesenteric resection according to the degree of mesentery (adequate or not adequate). If not deemed to be adequate this will be fed back to the operator. The central assessors will be the Chief Investigators.

Postoperative medications (e.g. metronidazole) will be according to usual practice for the participating centre but will be recorded at the 6 week follow up along with any complications.

Current guidelines suggest a colonoscopy at 6-12 months post-surgery. Participating centres will be encouraged to carry out colonoscopy closer to 12 months post-surgery if clinically possible but the protocol allows for colonoscopic assessment at an earlier (or later) date (window -6 months/+3 months).

At colonoscopic follow up, details of the severity and location of recurrence in relation to the small bowel mucosal tattoo will be assessed by a colonoscopist independent to the study and blinded to the intervention. Recurrence will be graded according to the Modified Rutgeerts' score (Rutgeerts, Geboes et al. 1990, McLeod, Wolff et al. 2009). The endoscopist will be asked to take pictures of the anastomosis and areas of supposed recurrence which will be assessed centrally for subgroup analysis (see section11.2). The central assessors will be the Chief Investigators and will be blinded to the intervention.

Modified Rutgeerts' Score	**Endoscopic description of findings**
i0	no lesions in distal ileum
i1	≤ 5 aphthous lesions
i2	> 5 aphthous with normal mucosa between the lesions
i3	deep aphthous ileitis with diffusely inflamed mucosa
i4	diffuse inflammation with already large ulcers, nodules and/or narrowing

For a subset of around 140 patients mesenteric and antimesenteric mucosal biopsies will be taken along with blood samples. Specifically;

- Immediately before surgery
  - Blood samples (5-10ml) in an EDTA tube
- At operation
  - Tissue samples 5-10mm in size will be taken from the mesenteric and antimesenteric small bowel (at the edge of the resection specimen where macroscopically normal mucosa will be present)
  - A tissue sample of 5-10mm of small bowel mesentery from the edge of the resected specimen.
- At endoscopic follow up
  - 2-4 mucosal biopsies will be taken from within 1cm of the mesenteric border tattoo and 2 from the opposite side of the small bowel (the antimesenteric border)

- Blood samples (5-10ml) in an EDTA tube

9.4 Procedure for assessing safety

The definition of leak is detailed in section 8.2. Other complications of surgery may include: haemorrhage; ileus/bowel obstruction; wound infection; urinary tract infection; cardiac events; pulmonary embolism (PE)/ deep vein thrombosis (DVT); and, respiratory insufficiency/pneumonia. Late postoperative complications may include: trocar-site and incisional hernia; ureteral stenosis (retroperitoneal fibrosis). We will collect data on the Adverse Events (AEs) which are considered related to the study treatment including but not limited to those listed above as expected events on the CRFs. Complications occurring following surgery will be identified on the 'procedure details' CRF; others may be identified at the six-week clinic visit and at the 12-month follow-up. Where these are/become Serious Adverse Events (SAEs) they will be reported in accordance with the CTRU's Standard Operating Procedures (SOPs). Unrelated AEs and SAEs will not be recorded. Site staff will be responsible for reporting related SAEs on identification, completing an SAE form, sending it to the CTRU and informing the local principal investigator.

9.5 Participant withdrawals

Participants may withdraw their consent for the study at any time, without providing a reason for this. If this occurs, this will be documented on a study completion/ discontinuation form and the patient notes, and no further data will be collected for this participant for the study. Although the participant is not required to give a reason for discontinuing their study treatment, a reasonable effort will be made to establish this reason while fully respecting the participants' rights. Any data collected up to the point of the participant's withdrawal will be retained, and used in the final analysis, and this is made clear to the patient at the time of consent.

Excessive participant withdrawal from follow-up has a negative impact on a study. Centres will explain the importance of remaining on study follow-up to participants, and that changes to planned treatment need not imply withdrawal from the study. Nevertheless, if participants do not wish to remain in the study their decision must be respected. If the participant explicitly states their wish not to contribute further data to the study, this will be recorded.

Participant-requested withdrawals from the intervention only are not expected, as randomisation takes place during the surgery, when participants are under general anaesthetic. It is anticipated that once surgeons have confirmed eligibility and randomised participants during their surgery, it will only rarely be clinically necessary to deviate from the assigned surgical procedures.

9.6 Unscheduled visits

Participants' local care team may also be part of the research team. Therefore, participants may be seen at additional visits outside those scheduled for the study, but these visits would be part of usual care. Any adverse events identified at additional usual care visits, will be documented in the CRF.

9.7 Loss to follow-up

Participants will be defined as lost to follow up if they do not have an endoscopic assessment by study end. If a participant is lost to follow up, this will be recorded in the CRF using the study completion/discontinuation form. In this case for the analysis of the primary outcome (ER) the patient will be censored at the date of last known follow-up.

10. Safety Reporting

ICH-GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events in clinical studies. These procedures are described in this section.

We will collect data on the Adverse Events (AEs) which are considered related to the study treatments including but not limited to those listed below as expected events on the CRFs. Any complications that occur following the interventions will be identified at the 6 week and around 12 month follow up. Where these related events become Serious Adverse Events they will be reported in accordance with the CTRU's and the sponsor's Standard Operating Procedures (SOPs). These SOPs have been developed to comply with guidance from the National Research Ethics Service, which is a subdivision of the National Patient Safety Agency, and Good Clinical Practice (GCP). Site staff will be responsible for reporting all related SAEs; on identification they will complete an SAE form and send it to the CTRU and ensure that the local Principal Investigator has been informed. SAEs which are related and unexpected will be reported to the sponsor and we will expedite these to the REC within 15 days of becoming aware.

We will record the occurrence of the following complications that are associated with the four interventions;

- Anastomotic leak. See section 8.2

Other complications of surgery may include:

- haemorrhage; ileus/bowel obstruction; wound infection;
- urinary tract infection;
- cardiac events;
- pulmonary embolism (PE)/ deep vein thrombosis (DVT); and,
- respiratory insufficiency/pneumonia.

Late postoperative complications may include:

- trocar-site and incisional hernia;
- ureteral stenosis (retroperitoneal fibrosis).

Additionally, occurrences of the following complications of anaesthesia will be recorded: nausea, vomiting, sore throat, dizziness, blurred vision, headaches, bladder problems, damage to lips or tongue, itching, aches and pains, pain during injection for drugs, bruising and soreness, confusion, memory loss, chest infection, muscle pains, slow breathing, damage to teeth, worsening of existing medical conditions, damage to the eyes, heart attack or stroke, serious allergy to drugs, nerve damage, equipment failure and death.

10.1 Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a study participant.
Unexpected AE/SAE	An adverse event or serious adverse event which has not been pre-specified as expected.
Serious Adverse Event (SAE)	An AE which is serious, defined as any untoward medical occurrence or effect that : ● Results in death ● Is life-threatening* ● Requires hospitalisation or prolongation of existing inpatients' hospitalisation** ● Results in persistent or significant disability or incapacity ● Is a congenital anomaly/birth defect ● Is otherwise considered medically significant by the investigator***
Related AE/SAE	An AE or SAE which is related to a research procedure
Notable Event	An event of particular interest that does not necessarily meet the criteria for seriousness but requires expedited reporting as per the protocol.

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Recording and reporting

All Adverse Events (AEs) will be recorded on the adverse event report form, within the participant CRF, including those that fulfil the criteria for being serious (see section 10.1). Sites are asked to enter all available information onto the study database as soon as possible after the site becomes aware of the event.

We will collect data on all AEs, including but not limited to those listed below as expected events on the CRFs. Complications such as myocardial infarction, pulmonary embolism and others may be identified during surgery Intra-operative complications will be identified on the 'Surgery details CRF'; others may be identified at the six-week clinic visit and at the 12-month follow-up. Any complications that occur following the interventions will be identified at the 6 week and around 12 month follow up.

We will record the occurrence of the following complications that are associated with the four interventions:

- Anastomotic leak. See section 8.2

Other complications of surgery may include:

- haemorrhage; ileus/bowel obstruction; wound infection;
- urinary tract infection;
- cardiac events;
- pulmonary embolism (PE)/ deep vein thrombosis (DVT); and,
- respiratory insufficiency/pneumonia.

Late postoperative complications may include:

- trocar-site and incisional hernia;
- ureteral stenosis (retroperitoneal fibrosis).

Additionally, occurrences of the following complications of anaesthesia will be recorded: nausea, vomiting, sore throat, dizziness, blurred vision, headaches, bladder problems, damage to lips or tongue, itching, aches and pains, pain during injection for drugs, bruising and soreness, confusion, memory loss, chest infection, muscle pains, slow breathing, damage to teeth,

worsening of existing medical conditions, damage to the eyes, heart attack or stroke, serious allergy to drugs, nerve damage, equipment failure and death.

Where these related events become Serious Adverse Events they will be reported in accordance with the CTRU's and the sponsor's Standard Operating Procedures (SOPs). These SOPs have been developed to comply with guidance from the National Research Ethics Service, which is a subdivision of the National Patient Safety Agency, and Good Clinical Practice (GCP). Site staff will be responsible for reporting all related SAEs. On identification they will complete an SAE form and send it to the CTRU and ensure that the local Principal Investigator has been informed. SAEs will require more detailed information to be recorded. In such cases, the event must also be reported to the Sheffield CTRU within 24 hours of the site becoming aware of the event. SAEs which are related and unexpected will be reported to the sponsor and we will expedite these to the REC within 15 days of becoming aware.

10.3 Study specific exemptions

There are no study specific exemptions.

10.4 SAE notification procedure

Site staff will be responsible for reporting all SAEs. Once an SAE has been identified, a member of the site research team will complete an SAE form, notifying the site's PI and send this to the CTRU.

All SAE forms must be sent by email to ctru-saes-group@sheffield.ac.uk. Receipt of the initial report should be confirmed within one working day. The site research team should contact the study team at CTRU if confirmation of receipt is not received within one working day.

SAEs which are related and unexpected will be reported to the sponsor and we will expedite these to the Research Ethics Committee (REC) within 15 days of becoming aware.

10.5 CTRU responsibilities

The Sponsor usually delegates CTRU responsibility for the reporting of SAEs to the regulatory authorities and the research ethics committee, as appropriate. CTRU will also keep all investigators informed of any safety issues that arise during the course of the study.

10.6 SAE additional reporting

The DMEC and TSC will also receive information on all AEs and SAEs, at a frequency agreed with each committee and documented in the appropriate charter/terms of reference.

11. Statistics

11.1 Sample size

The primary outcome will be the time to endoscopic recurrence (ER) post-randomisation (Modified Rutgeerts score >= i2). All participants will be followed up for a minimum of 6 months post-randomisation and up to a maximum of three years. The best existing data indicates ER rates of approximately 65% on conventional surgery and 24% on Kono-S surgery at 12 months (Rispo, Imperatore et al. 2018). Other published data on the rate of endoscopic recurrence after conventional surgery varies from 58-93% (Rutgeerts, Geboes et al. 1984, Rutgeerts, Geboes et al. 1990, Olaison, Smedh et al. 1992, Pascua, Su et al. 2008, De Cruz, Kamm et al. 2015). The systematic review unfortunately found no published data on the ER rates after close or extended mesenteric resection (Alshantti, Hind et al. 2021). In a survey of 34 surgeons, 71% were persuaded to change practice based on a reduction in endoscopic recurrence to 30% or less after 12 months.

The sample size calculation for the 2 x 2 factorial design assumes: 90% power; 5% (two-sided) significance level; and estimated 1-year endoscopic recurrence rates of 65% in the standard anastomosis/close mesenteric resection group; 40% in the standard anastomosis and extended mesenteric resection group (for a combined ER rate of 52.5% on standard anastomosis) ; 40% in the Kono-S and close mesenteric resection group and a 25% recurrence rate in the Kono-S and extended mesenteric resection group (estimated assuming no interaction) for a combined ER rate of 32.5% on Kono-S. Based on a reduction in the 1-year ER rate from 52.5% to 32.5%, equivalent to a hazard ratio of 0.528, a total of 112 recurrences are required (using the Freedman method) or a sample size of 130 patients per group (260 in total) of Kono-S versus standard anastomosis (or extended mesenteric resection vs close resection).

To account for surgeon effects we assume each of 12 sites would have 2 surgeons and an ICC of 0.01 (surgical procedures are well-developed, standardized and performed by experienced surgeons; the ICC from HubBLe was <0.0001 (Brown, Tiernan et al. 2016)) and 15 patients per surgeon (equivalent to design effect of 1.14), the number was increased to 149 per group. Based on a further 3% attrition we require 308 patients (77 per group; 154 per group for the factorial design). We are assuming there is no interaction between the two treatments (i.e. extended resection of the mesentery in addition to Kono-S surgery does not change the effect of Kono-S surgery and vice versa). The trial is not powered to assess any observed interaction, which would require a fourfold increase in size to N~1200, not achievable in a reasonable time scale or resource envelope.

Table 2: Estimated 1-year post randomisation endoscopic recurrence rates for 2 x 2 factorial design

	Factor B		
Factor A	**Extended mesenteric resection**	**Close mesenteric resection**	***Total***
Kono-S	25%	40%	*32.5%*
Standard anastomosis	40%	65%	*52.5%*
Total	*32.5%*	*52.5%*	

estimated assuming no interaction, that is additive independent effects.

11.2 Statistical Analysis

The primary outcome is the time to endoscopic recurrence (ER), over a follow-up of up to three years defined as a Modified Rutgeerts score [≥i2]. Patients without a reported ER will be censored at their last known date of not having had ER. The primary effectiveness analysis, on the intention-to-treat (ITT) sample, will compare the time to ER, between the two factors (Kono-S vs standard anastomosis surgery; extended mesenteric resection vs close mesenteric resection) using a mixed-effects parametric survival model with random effects for centre and surgeon and fixed effects for the two factors.

The initial statistical model will include an interaction (Kono-S (yes or no) vs extended mesenteric resection (yes or no)) term between the two factors. We will report the estimate of the interaction term and its associated 95% confidence interval (CI). If the CI for the HR for the interaction term includes one (no evidence of an interaction) then we will analyse the data, without the interaction term, using the simpler factorial design with the two main factors. The CIs for the Hazard Ratios for the Kono-S vs standard anastomosis contrast and extended mesenteric resection vs close resection contrasts will be reported from this simpler model. If the CI for the HR for the interaction term excludes one (i.e. evidence of an interaction) then we will analyse the data using the four randomised groups (1. Kono-S + extended mesenteric resection; 2. Kono-S + close mesenteric resection; 3. Standard anastomosis + extended mesenteric resection; 4. Standard anastomosis + close mesenteric resection) separately with standard anastomosis and close mesenteric resection as the reference treatment. The treatment effects and corresponding 95% CIs will be presented for all relevant comparisons.

We will complement the ITT analysis of the primary outcome with a number of sensitivity analyses, including the following analyses. A per protocol analysis will estimate the efficacy of the Kono-S vs standard anastomosis and extended vs close mesenteric resection in Crohn's disease in participants who adhere to the main aspects of the protocol. Missing data will be imputed through best- and worst-case scenarios to investigate the impact of assuming informative missingness (missing not at random assumptions).

Secondary endpoints will be analysed as follows: Time-to-event outcomes will be analysed as per the primary outcome. Binary outcomes will be compared between the two factors (1: Kono-S vs standard anastomosis and 2: extended vs close mesenteric resection) using a multi-level mixed effects logistic regression model with adjustment for baseline covariates, with associated ORs and 95% CIs. Absolute risk differences with 95% Cis will also be presented for binary outcomes. Continuous outcomes will be analysed using multi-level mixed effects regression model with adjustment for baseline covariates. The number of participants with at least one serious adverse event (SAE) rates for the up to 12 month (-6/+3 months) post-randomisation period will be compared between the four randomised groups using a chi-squared test and 95% CIs for each of the four randomised groups. We will also count the total number of SAEs experienced by each patient, and compare counts using a Poisson generalised linear model (GLM) and reporting the risk ratio and associated 95% CIs.

Regardless of the statistical significance of the overall effect, exploratory subgroup analyses will be carried out for the primary outcome (ER). We will carry out subgroup analyses to examine if treatment effects differ between subgroups based on patient demographics (e.g. smoking status, family history), disease features (e.g. penetrating, recurrent, presence of perianal disease, resection margin positivity, presence of granulomas, extensive small bowel disease, degree of visceral fat) and medical treatment history. As recent literature has questioned the validity of Rutgeert's score, suggesting recurrence is over staged when there is a stapled anastomosis compared with a hand sewn, we will do a subgroup analysis on recurrence compared with each anastomotic technique (handsewn vs stapled). We will use an interaction test between the intervention and subgroup to examine the strength of evidence for the treatment difference between the treatment groups varying between subgroups, and present results graphically (forest plots). As this trial is not formally powered for subgroup analyses, all subgroup effects will be considered exploratory, and p-values will not be presented.

A secondary mediation analysis will investigate putative mediation factors (i.e. peripheral blood fibrocyte levels, visceral fat area, general immune activation, T cell clonality and exhaustion and antigen presentation) using Direct Acyclic Graphs (DAGs) and Structural Equation Models to test for mediation of surgical treatment on treatment outcome (endoscopic recurrence) through the

factors. Analyses will adjust for baseline measures of the factor and possible measured confounders/moderators (e.g. age, sex). We will test for possible mediation factors by testing interactions between baseline factors and treatment on treatment response and safety outcomes.

12. Trial supervision

12.1 Trial Steering Committee

The TSC will consist of an independent chair, professionals with relevant clinical and academic experience and two patient representatives. The role of the TSC is to provide supervision of the protocol, and statistical analysis plan, to provide advice on and monitor the study, to review information from other sources and consider recommendations from the DMEC. The TSC will meet at regular intervals, typically every 6 months, as defined in the TSC terms of reference.

12.2 Data Monitoring and Ethics Committee

The DMEC will review reports provided by the CTRU to assess the progress of the study, the safety data and the critical endpoint data as required. The DMEC will meet at regular intervals, typically every 6 months, as defined by the DMEC charter. The DMEC will consist of an independent statistician, and at least two independent physicians with research experience. There will be no interim analyses (other than for the purposes of the blinded internal pilot) or definitive stopping guidelines, but the DMEC may request unblinded data or study termination on grounds of safety/futility.

12.3 Trial Management Group

The Trial Management Group (TMG) is comprised of the CI, trial manager, statistician, data manager and grant co-applicants. PIs will also be invited to represent sites. The CI will chair monthly meetings with the TMG to discuss the day-to-day implementation of the study.

13. Data handling and record keeping

Participant confidentiality will be respected at all times and the principles of the UK Data Protection Act (DPA) will be followed. The investigator will ensure that identifiable data is kept securely and protected from unauthorised parties.

Data management will be provided by the University of Sheffield Clinical Trials Research Unit (CTRU) who adhere to their own Standard Operating Procedures (SOPs) relating to all aspects

of data management, including data protection and archiving. A separate data management plan (DMP) will detail data management activities for the study in accordance with SOP (Shef/CTRU/DM009).

The investigator or delegate at each site will maintain comprehensive and accurate source documents to record all relevant study information regarding each participant. All participants will be assigned a unique study ID number at screening that will link all of the clinical information collected for them on the study database. It will also be used in all correspondence between CTRU and participating centres. All CRFs will only identify the participant by their study ID number

Study records, including source data, will be stored for 10 years after the completion of the study by participating sites, before being destroyed. Each investigator is responsible for ensuring records are retained and securely archived during the retention period and information supplied to the Chief Investigator and Sponsor. Where trial related information is documented in the medical records, those records will be retained for at least 10 years after the last patient last visit. Access will be restricted to authorised individuals.

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (CTRU SOP PM012) for 10 years following completion. Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for a minimum of 10 years to ensure that access is future-proofed against changes in technology. Electronic data may also be stored (e.g. on a compact disc or USB flash drive) with the paper files. Archived documents will be transferred to the Sponsor before destruction.

13.1 Archiving

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (*SOP PM012 Archiving*). Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for the period stated above.

14. Data access and quality assurance

The study will use the CTRU's in-house data management system (Prospect) for the capture and storage of study specific participant data. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive access management feature will be used to

ensure that users have access to only the minimum amount of data required to complete tasks relevant to their study role. This feature can also be used to restrict access to personal identifiable data.

The research staff at each site will enter data from source documents into the study specific Prospect database when available. After data has been entered, electronic validation rules are applied to the database on a regular basis; discrepancies are tracked and resolved through the Prospect database. All entries and corrections are logged with the person, date and time captured within the electronic audit trail.

Participant confidentiality will be respected at all times. All research data will be anonymised, and will only be identifiable by the participant's study ID number. No patient identifiable data will be transferred from the database to the statistician. Participating investigators shall agree to allow study-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this will be obtained as part of the consent process.

14.1 Site assessment

Throughout this protocol, the trial 'site' refers to the hospital at which trial-related activities are conducted. Participating sites must be able to comply with:

- Trial treatments, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research
- Data collection requirements

All site staff, including research staff, must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. CVs for all staff must be kept up to date, and copies held in the Investigator Site File (ISF), and the Trial Master File (TMF).

Before each site is activated, capability to conduct the trial will be assessed and documented. The CTRU will arrange a site initiation visit with each site or carry this out remotely. Site staff will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Once all the required documentation is in order and site staff have been trained, CTRU will formally activate the site to start recruitment. Sites should not open to recruitment until CTRU have provided this confirmation of activation.

14.2 Risk assessment

A risk assessment has been performed by the CTRU, in accordance with Sheffield CTRU Standard Operating Procedures.

Central and/or on-site monitoring will be undertaken at a level appropriate to the detailed risk assessment. The level of risk will be agreed with the Sponsor. Central and on-site monitoring will be undertaken at a level appropriate to the detailed risk assessment, and will be documented in the Trial Monitoring Plan (TMP). This will include (at a minimum):

- Source Data Verification (SDV)
- SAEs/SUSARs – reported to the Sponsor and followed up to resolution
- Resolution of data queries
- Investigator site file maintenance
- Training records for site staff (trial specific and GCP) and appropriate delegation of duties
- Patient consent procedures
- Reporting of protocol non-compliances

14.3 Reporting serious breaches and non-compliances

A “serious breach” is a breach of either: the conditions and principles of GCP in connection with the trial or; the protocol relating to the trial; which is likely to effect to a significant degree –

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition may apply during the trial conduct phase. The sponsor of a clinical trial will notify the REC and, for CTIMPs, the MHRA in writing within 7 days of becoming aware of a serious breach.
All serious breaches and protocol non-compliances should be reported to CTRU within 24 hours of site staff becoming aware.

14.4 On-site monitoring

On-site or remote monitoring will be performed according to the monitoring plan and in line with the Sheffield CTRU Site Monitoring SOP.

A site initiation visit will be performed or carried out remotely at/for each participating site before each site recruits their first participant. During this visit/remote contact, the Monitor will review with site staff the protocol, study requirements and their responsibilities to satisfy regulatory, ethical and Sponsor requirements.

Regular site monitoring visits will occur throughout the study as specified in the Site Monitoring Plan and additional visits will be undertaken where required. At these visits, the Monitor will review activity to verify that the:

1. Data are authentic, accurate and complete.
2. Safety and rights of the patient are being protected and
3. Study is conducted in accordance with the approved protocol and study agreements, GCP and all applicable regulatory requirements.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against Investigator's records by the Study Monitor (source document verification) (see section 13 for further details on data collection). Study Monitor will contact and visit sites regularly to inspect CRFs throughout the study, to verify adherence to the protocol and completeness, consistency and accuracy of the data being entered on the CRFs.

A close-out visit will be performed after the last patient last visit at each site. Further close-out activities may be carried out remotely after this time, up to database freeze.

14.5 Central monitoring

CTRU staff will review entered data for possible errors and missing data points. A central review of consent forms will also be completed, and sites will be requested to post consent forms to CTRU on an ongoing basis. This will be made clear to the participant prior to their consent to the trial.

15. Publication

Results of the study will be disseminated through peer reviewed scientific journals and at clinical and academic conferences, as well as submission of a final report to the funder, which will be made available online.

Details of the study will also be made available on the Sheffield CTRU website. Summaries of the research will be updated periodically to inform readers of ongoing progress.

We aim to change policy and practice, giving patients greater understanding of available options and the trade-offs involved. Open access publication will ensure findings are widely available. We will present results in high-impact journals and at international conferences. The Association of Coloproctology of Great Britain and Ireland (ACPGBI), which promotes care of patients with bowel disease, will communicate study findings. International audiences will be targeted through the European Society of Coloproctology. We will provide specific reports for the Department of Health, Royal College of Surgeons and NHS Trusts. Formal ACPGBI adoption of the will be

sought, enabling dissemination through regular news emails from affiliated bodies reaching over 1000 UK specialty surgeons. We will advise NICE on our findings and recommend implementation pathways. Plain language summaries will communicate findings to the public over a range of media platforms.

PPI members (Lucy and William) and existing relationships with Crohn's and Colitis UK, will ensure dissemination to people with Crohn's Disease. We will employ a knowledge transfer strategy that communicates a recognisable branding that we have built during trial development. In partnership with our participating hospitals and PPI representatives, our findings will be made available to front line NHS staff, across all care disciplines. Open access publication will ensure the implications of our research findings are rapidly available, as widely as possible. Lay members of the study group will facilitate sharing information with groups representing the interests of haemorrhoid populations and their carers at a local, regional and national level.

We will engage the media as is appropriate to the research findings, for example publishing a summary video on popular media streaming sites such as YouTube, engaging in radio interviews and submitting press releases. Our PPI representatives have the capacity to act as ambassadors for the trial and will have the opportunity to transfer knowledge on to peers in other PPI forums and also on to the wider public over the course of the trial.

The results will be published on a freely accessible database within one year of completion of the trial.

Full details, including guidance on authorship, are documented in the Publication and Dissemination Plan.

16. Finance

This project (NIHR131988) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership and details have been drawn up in a separate agreement. Further details are included in the collaborator agreement.

17. Ethics approval & regulatory compliance

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and Sheffield CTRU standard operating procedures. All clinicians responsible for recruiting patients to the trial will be trained in Good Clinical Practice (GCP). A Trial Steering

Committee (TSC), a Data Monitoring and Ethics Committee (DMEC) and a Trial Management Group (TMG) will be established. The Trial Manager will be jointly supervised by the CI (SB) and the Sheffield CTRU Lead (DH), meeting at weekly intervals, and will liaise with the team. Central and site monitoring will be undertaken at a level appropriate to a risk assessment approved by the sponsor.

Before initiation of the study at the participating site, the protocol, informed consent forms and information materials to be given to the participants will be submitted to the REC and the HRA. Any further amendments will be submitted and approved by the HRA and REC committee. Recruitment will commence after REC favourable opinion and HRA approval have been issued. Sheffield CTRU will communicate amendments approved by the funder and HRA to study personnel.

18. Sponsor and site approval

Before initiation of the study at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will require sponsor approval.

Sheffield Teaching Hospitals (STH) NHS Foundation Trust will be the Sponsor. A site agreement between the Sponsor, participating sites and Sheffield CTRU outlines responsibilities of all parties and is to be signed prior to commencement of recruitment at sites. Recruitment of study participants will not commence at a site until a letter local R&D of Confirmation of Capacity and Capability (CCC) has been issued.

18.1 Expertise

Ms Laura Hancock, Co-Chief Investigator, is a consultant surgeon, and has extensive experience in recruiting and running trials and surgical expertise in IBD. Professor Steven Brown, Co-Chief Investigator, is Professor of Surgery, an NIHR chief investigator (10/57/46; 17/17/02) and co-applicant (12/35/07; 08/24/02). He has experience in recruiting and running trials and surgical expertise in IBD. William Waterworth and Lucy Sibbald, people with lived experience of Crohn's disease and the surgical techniques under evaluation, will be our PPI leads. Professor Alan Lobo is Professor of Gastroenterology, with an interest in IBD, experience in recruiting and running trials. Professor Daniel Hind is Assistant Director of Sheffield CTRU. He will oversee the implementation and write-up of the trial. Professor Stephen J Walters is Professor of Medical Statistics and Clinical Trials and an NIHR Senior Investigator, who will oversee statistical design, conduct, analysis and reporting of the trial. Professor Mark Travis, Professor of Immunology at the University of Manchester, has experience in performing mechanistic studies focussed on the

immune system and its dysregulation in IBD patients; and will oversee the implementation and analysis of the mechanistic components.

19. Trial Organisation and Responsibilities

19.1 Principal Investigators

Each site will have a local Principal Investigator (PI) who will be delegated responsibility for the conduct of research at their centre and must sign a declaration to acknowledge these responsibilities. The local PI should ensure that all relevant staff involved are well informed about the trial and trained in study procedures, including obtaining informed consent and conduct of the trial according to GCP. The local PI will liaise with the Trial Manager on logistic and administrative matters connected with the trial.

19.2 Sheffield Clinical Trials Research Unit (CTRU)

The Sheffield CTRU at Sheffield University will provide set-up and monitoring of the trial conduct to CTRU SOPs and the GCP conditions and principles as detailed in the UK Policy Framework for Health and Social Care Research 2017. CTRU responsibilities include randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support the main REC, HRA and site-specific submissions, clinical set-up, ongoing management including training, monitoring reports and promotion of the trial.

The CTRU Trial Manager or delegate will be responsible for supplying investigator site files to each collaborating centre after relevant ethics committee approval and local R&D Confirmation of Capacity and Capability (CCC) has been obtained. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses. The CTRU will develop the site monitoring plan and data management plan and will assist the CI to resolve any local problems that may be encountered during the trial including any issues of noncompliance.

20. Patient & Public Involvement (PPI)

Our PPI representatives have lived experience of IBD and surgery. The aim of their involvement is to make the study more attractive to eligible patients, procedures more acceptable to participants and outputs more useful to everybody. PPI representatives will guide planning through the set-up period, implementation through the accrual period and the drafting of plain language and scientific summaries through the dissemination period. If funded we will convene

a patient panel on a quarterly basis to instruct the trial team, with two or more PPI representatives attending trial management group meetings in between.

21. Indemnity / Compensation / Insurance

The University of Sheffield has in place clinical trials insurance against liabilities for which it may be legally liable and this cover includes any such liabilities arising out of this clinical study. Standard NHS indemnity operates in respect of the clinical treatment that is provided.

22. References

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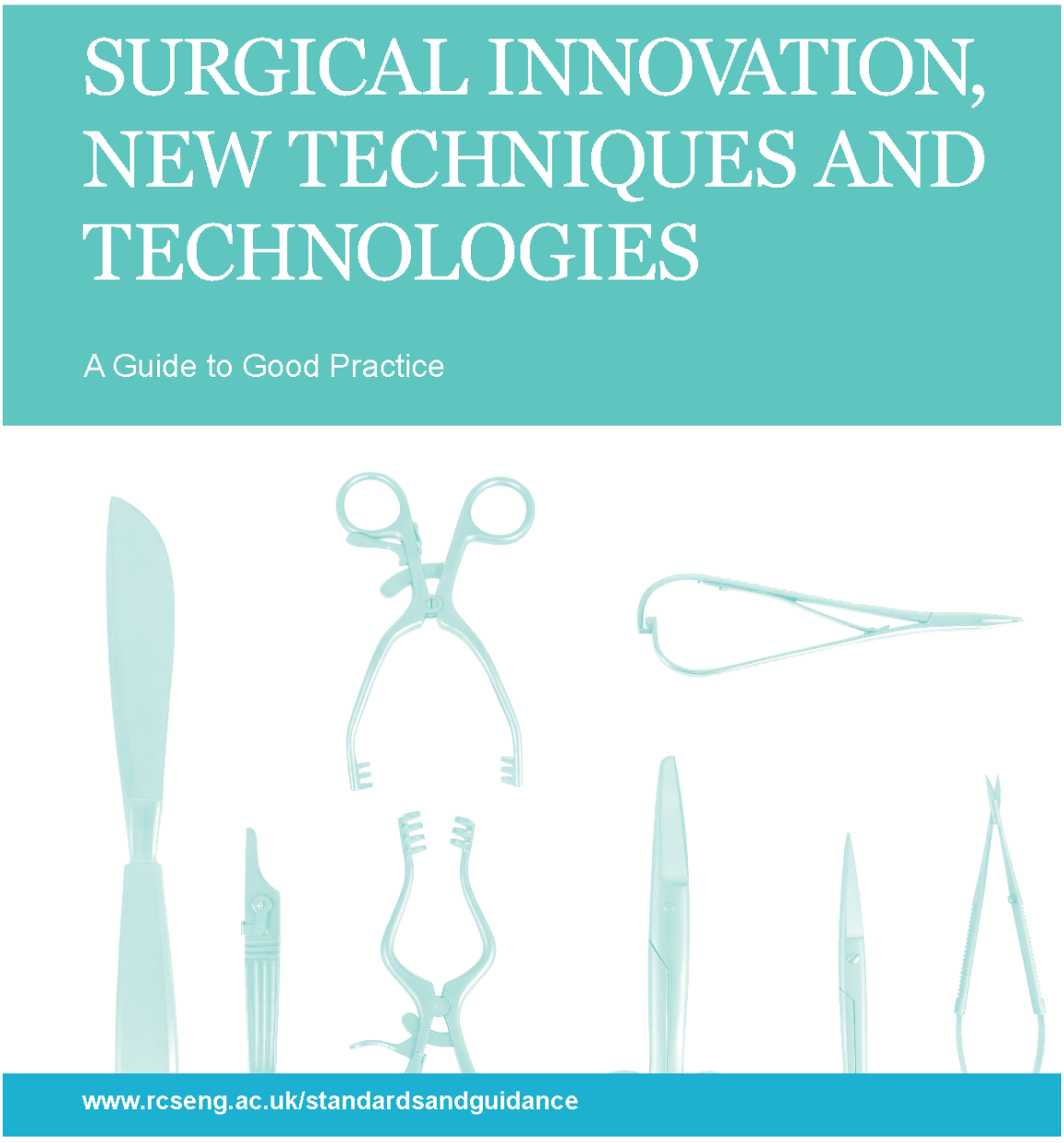
Appendices

Appendix 1: Surgical Innovation, New Techniques and Technologies – A Guide to Good Practice

Some sections or statements have been highlighted by the study team for emphasis.

SURGICAL INNOVATION, NEW TECHNIQUES AND TECHNOLOGIES

Royal College of Surgeons
ADVANCING SURGICAL CARE



RCS Professional Standards

February 2019

inQuisit was commissioned by The Royal College of Surgeons of England to prepare this guide. The RCS would like to thank Sally Williams for drafting the report"

Contents

1. Introduction

Surgeons are innovators. The advancement of surgery is set against a backdrop of continuous development and, in the past 50 years, surgical innovations have transformed the way clinical care is delivered. Procedures that were unthinkable only a few decades ago are now common practice. Surgical innovations have improved patient outcomes, reduced complication rates and length of hospital stay, and have decreased morbidity and mortality.

The introduction of minimally invasive surgery, for example, has transformed patient outcomes across many different surgical specialties. The use of smaller incisions has reduced surgical trauma, improved postoperative pain and shortened recovery times. For surgeons, it has meant a shift in the way they physically operate, with a move away from seeing, feeling and manipulating organs and tissues with their own eyes and hands. The technology has also opened the door to the increasing use of robotics in surgery, allowing increased surgical precision within confined spaces and introducing the prospect of remote operating.[1]

The pace of surgical innovation shows no sign of slowing, from developments in three-dimensional printing, artificial intelligence and nanotechnology to advances in regenerative medicine and the ability to grow organs and tissues in the laboratory. Such innovations will have fundamental consequences for surgical decision making and the way surgeons treat patients.

As exciting as these innovations are in terms of their potential, there are significant risks in allowing innovation to occur in the absence of a clear guiding framework. Surgical innovations can be risky. Without proper evaluation, regulation and training in their use, innovations have the potential to harm patients rather than benefit them.

Historically, the development of new techniques has often taken place in the absence of the rigour associated with the development of new medicines or devices. Surgical innovation is frequently driven by one clinician's desire to improve care for an individual patient. The onus has been on the individual surgeon to use his or her clinical judgement and professionalism to decide on a new technique, identify which patients might benefit and to know and recognise the surgical limitations despite their personal enthusiasm for the innovation. There then arises the need to communicate all of this clearly to the patient so that they are in a position to give informed consent. The recent notorious case of a breast surgeon single-handedly creating and applying a novel surgical procedure, the so-called 'cleavage-sparing mastectomy', outside the parameters of peer review or a strong clinical governance framework, demonstrates the harm that can be done to large numbers of patients without proper oversight of new procedures.

Most surgery now takes place in teams, and effective surgical teamworking results in better outcomes for patient safety.[2,3] Even so, there remain issues about:

- the processes by which a surgeon (and the surgical team) train in a new approach
- the oversight and quality assurance underpinning the training
- how patients are selected
- how consent is obtained
- how the outcomes of the new approach are audited.[4]

Surgeons, clinical leaders in hospitals (including medical and clinical directors), commissioners and health system leaders need to be cognisant of the challenges associated with innovations and not just the opportunities they offer. It is incumbent upon the surgical profession to ensure that surgical innovation takes place with great care, with the consensus of other surgeons and clinicians and is underpinned by rigorous clinical governance processes, appropriate training and close oversight of outcomes.

1.1 ABOUT THIS GUIDE

This guide seeks to provide surgeons with up-to-date thinking on the development, implementation and dissemination of surgical innovation. A strong framework is needed to ensure that the development of new techniques is driven by altruistic motives and that both patient safety and the best interests of patients always come first.

This guide highlights the challenges commonly faced by surgeon innovators and signposts sources of assistance. It is also written for those medical and clinical directors charged with providing oversight of surgical activity within their organisations.

The RCS has launched an independent commission to explore the future of surgery in the next 20 years. For further details see www.rcseng.ac.uk/standards-and-research/future-of-surgery.

2. Developing a new technique

2.1 WHAT IS A NEW TECHNIQUE?

There is no consensus on what constitutes a 'surgical innovation'. Surgical innovation tends to fall somewhere between commonly undertaken variations (or minor modifications) of procedures and surgical research. A surgeon might adapt techniques taken from two or more different procedures to deal with a particular patient situation, without feeling that they have introduced a truly innovative procedure. Surgical research, on the other hand, might develop innovations that need much further research and evaluation before they are suitable to be introduced into patient care.

This guide uses the definition for surgical innovation offered by the IDEAL (idea, development, exploration, assessment, long-term follow-up, improving the quality of research in surgery) framework: 'surgical innovations comprise new techniques, modified strategies, or innovative instruments'.[5] Under this definition, new techniques are one type of surgical innovation, although it remains unclear how and when a variation is distinguished from an innovation.

Researchers at Macquarie University in Australia distinguish between two types of innovation: those that involve new techniques and those that involve a new device (see Appendix 1). Each of these may be new in three different ways. They may be altogether new, new to an anatomical location or new to a certain patient group.[6] This distinction does not include considerations such as 'new to the hospital' or 'new in the hands of the surgeon', which can equally apply to long-established and new procedures and are features of introduction rather than innovation.

In practice, new techniques are often introduced in conjunction with new devices. The Macquarie researchers identified three key questions that seek to clarify the degree of change and the potential risks:

1. Are the likely outcomes of the change unknown or have they been described previously?
2. Are the outcomes likely to be publishable or suitable for uptake more generally?
3. Should special preparation be undertaken by the surgeon and/or the surgical team?

Designed to be used alongside these questions is the Macquarie Surgical Innovation Identification Tool (Appendix 2). The tool is a checklist designed as a practical tool for hospitals to identify planned surgical innovations.[7] It asks whether the techniques, instruments or devices have been used before, either in the hospital or by the surgeon. Hospitals may want to provide the same level of support for the local introduction of established techniques or technologies as they do for truly innovative procedures.

2.2 WHAT TO CONSIDER WHEN DEVELOPING A NEW TECHNIQUE

Surgeons working in the NHS are encouraged to innovate.[8] Technological change has been identified as the most important determinant of improvements in health care and hospital productivity.[9] These benefits are only likely to be realised if surgical innovation happens in a structured way that has evaluation at its centre.

The Medical Research Council (MRC) recommends that those planning to develop a complex intervention should ask themselves the following questions:[10]

1. Are you clear about what you are trying to do? What outcome are you aiming for and how will you bring about change?
2. Does your intervention have a coherent theoretical basis? Have you used this theory systematically to develop the intervention?
3. Can you describe the intervention fully, so that it can be implemented properly for the purposes of your evaluation and replicated by others?
4. Does the existing evidence (ideally collated in a systematic review) suggest that it is likely to be effective or cost effective?
5. Can it be implemented in a research setting and is it likely to be widely implementable if the results are favourable?

If there is uncertainty about the answers to these questions, further development work is needed before an evaluation can begin. The MRC further distinguishes between five stages of investigation in the evaluation of a complex intervention, with objectives to be met at each stage before moving to the next (see Appendix 3).

The IDEAL framework describes the stages of innovation in surgery as: idea, development, exploration, assessment and long-term study. Proponents of this framework argue that surgery has a specific combination of attributes that create additional problems.[11] These attributes add complexity

because they include dependence of the outcome on the operator, the surgical team, the setting and other quality variations. The IDEAL framework therefore takes the MRC recommendations and tailors them to the surgical setting to avoid hindering surgical innovation with overly-demanding requirements. There are still five stages of progression, but at the heart of the IDEAL framework is a conviction that surgical innovation and evaluation should evolve together in an ordered manner from concept, through exploration, to validation by randomised trials. The different stages of the IDEAL framework are shown in Table 1.

Traditionally, research into surgery and new surgical techniques has been poorly funded in comparison with research into basic medical sciences and new medicines. The Royal College of Surgeons of England (RCS) has worked with the National Institute of Health Research and others, to establish a national network of surgical trial centres to develop and expand clinical trials in surgery, raise surgical standards and transform the quality of patient care across a number of conditions.[12] This initiative has significantly increased funding for clinical research in surgery, with many more patients being entered into well-designed and properly supervised clinical trials across the UK.

2.3 THE COST IMPLICATIONS OF DEVELOPING A NEW TECHNIQUE

Surgeon innovators should assess the cost implications of a new procedure before embarking upon its development. The assessment will often require an understanding of the costs before data are available on safety and efficacy or long-term outcomes. This understanding is necessary to establish whether the investment costs in equipment and/or personnel needed to support introduction of the procedure are justified and to understand the financial implications of rolling out the procedure within the organisation.

New techniques often rely on new technology, which is almost always more expensive than traditional techniques.[13] Other costs include the operating time (new procedures often take longer, at least while the surgeon is getting familiar with the technique) and the costs associated with training in the new technique for the surgeon or the surgical team.[14] These costs will influence which and how many patients may be able to receive the new procedure.

Not all surgical innovations have to be costly. The Royal Academy of Engineering highlights the potential of 'frugal innovation' in medical technologies. Re-engineering devices, such as adapting a mobile phone to incorporate diagnostic sensors, is one example.[15] Some innovations can reduce costs if resources are fully released from displacing older technologies and, as innovations mature, their cost effectiveness often improves.[9]

Surgeons who innovate need to be prepared to pitch for investment to support the development of their innovation, as do surgeons who wish to introduce more costly new technologies to their hospital in the face of organisational financial constraint. This is an area where surgeons may need to gain specific skills to win support within their organisation or externally with financiers, such as how to create a credible business plan.

Securing early-stage investment can be a challenge. Key factors to be taken into account are:

- a well-designed early stage surgical innovation or technology
- clear and transparent evidence of clinical benefit
- adequate scientific evaluation and peer review
- well-designed surgical databases, registries and reporting systems.

Good Surgical Practice expects surgeons to be open and transparent about the sources of funding for the development of any new technique.[2]

2.4 REGULATORY REQUIREMENTS

There are few regulatory requirements for surgery in terms of introducing innovative surgical techniques. The General Medical Council reminds doctors to take account of the clinical guidelines published by the National Institute for Health and Care Excellence (NICE) and equivalent bodies, in addition to the medical royal colleges.[16] *Good Surgical Practice* also advises surgeons to contact the interventional procedures programme at NICE to learn the status of the procedure and/or register it and liaise with the relevant surgical specialty association.[2] Surgeons are reminded to ensure that any new device complies with European standards and is certified by the competent body, such as the Medicines and Healthcare Products Regulatory Agency in the UK.

The NHS is legally obliged to fund and resource medicines and treatments recommended by NICE's technology appraisals (see Appendix 4) and the NHS Constitution gives patients the right to drugs and treatments that have been recommended by NICE for use in the NHS, if their doctor believes that they are clinically appropriate.[17] In practice, many surgical interventions are not subject to NICE guidance as the evidence available is often sparse.[18] Guidance on surgical interventions tends to be more advisory in nature, offering advice on safety and efficacy rather than cost effectiveness.

NICE states that where it has not published interventional procedures guidance for the procedure, a surgeon's organisation can still approve it as long as the clinician has appropriate training and experience, patients are made aware and give their consent and arrangements are made for data collection and audit (all addressed in other sections of this guidance).

2.5 WHERE TO START?

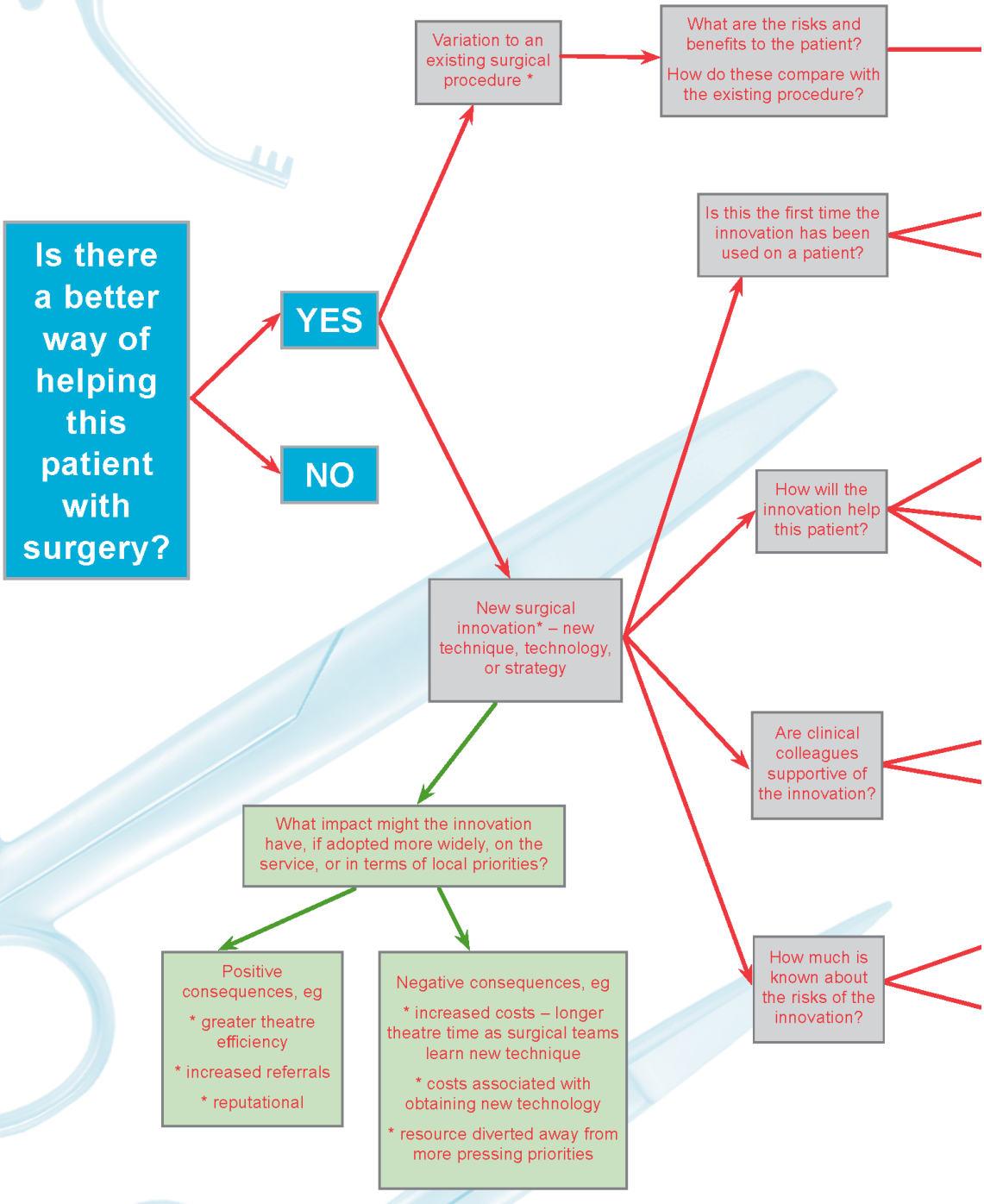
The decision tree shown in Figure 1 seeks to help surgeons at the stage of inception of an idea to innovate. The emphasis throughout this decision tree is on involving and discussing the innovation with other surgeons and agreeing appropriate mechanisms for oversight and reporting of outcomes.

Table 1: Stages of surgical innovation (source: McCulloch *et al. Lancet* 2009; **374**: 1,105–1,112)

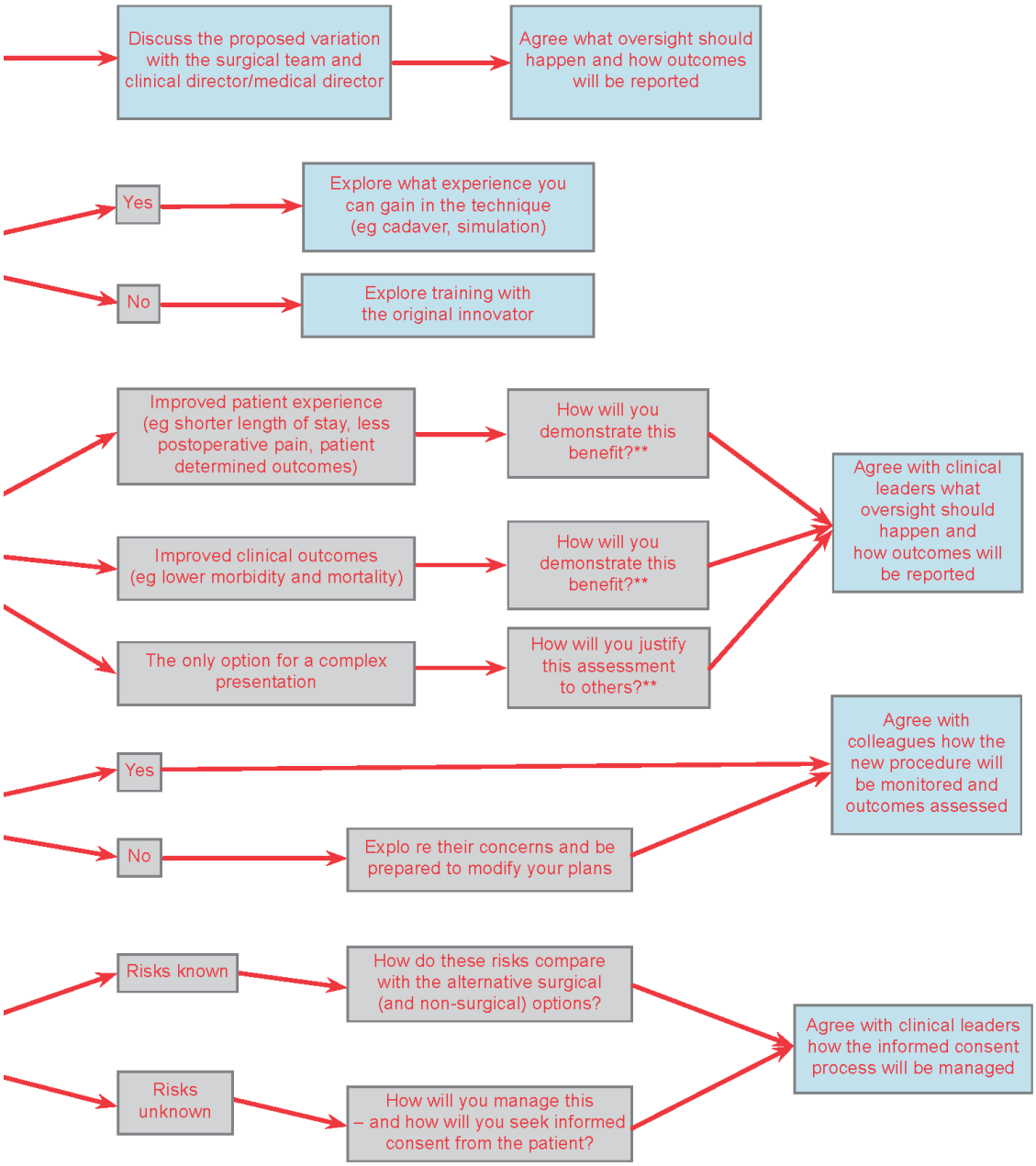
	1a Proof of concept	2a Development	2b Learning	3 Assessment	4 Long-term study
Purpose	Proof of concept	Development	Learning	Assessment	Surveillance
Number and types of patients	Very few; innovators	Few; selected	Many; may expand to mixed; broadening indication	Many; expanded indications (well defined)	All eligible
Number and types of surgeons	Very few; innovators	Few; innovators and some early adopters	Many; innovators, early adopters, early majority	Many; early majority	All eligible
Output	Description	Description	Measurement, comparison	Comparison; complete information for non-RCT participants	Description; audit, regional variation; quality assurance; risk adjustment
Intervention	Evolving; procedure inception	Evolving; procedure development	Evolving; procedure refinement; community learning	Stable	Stable
Method	Structured case reports	Prospective development studies	Research database; explanatory or feasibility RCT (efficacy trial); disease based (diagnostic)	RCT with or without additions/ modifications; alternative designs	Registry; routine database (eg SCOAP, STS, NSQIP); rare-case reports
Outcomes	Proof of concept; technical achievement; disasters; dramatic successes	Mainly safety; technical and procedural success	Safety; clinical outcomes (specific and graded); short-term outcomes; patient-centred (reported) outcomes; feasibility outcomes	Clinical outcomes (specific and graded); middle- and long-term outcomes; patient-centred (reported) outcomes; cost effectiveness	Rare events; long-term outcomes; quality assurance
Ethical approval	Sometimes	Yes	Yes	Yes	No
Examples	NOTES video[6]	Tissue engineered vessels[7]	Italian D2 gastrectomy study[8]	Swedish obesity study[9]	UK national adult cardiac surgical database[10]

NSQIP, National Surgical Quality Improvement Programme; NOTES, natural orifice translumenal endoscopic surgery; RCT, randomised controlled trial; SCOAP, Surgical Clinical Outcomes Assessment Programme; STS, Society of Thoracic Surgeons.

Figure 1 Decision tree for surgeons at the



stage of inception of an idea to innovate



* The Macquarie Surgical Innovation tool is designed to help identify new procedures

** The IDEAL framework supports the assessment and reporting of new surgical innovations

7

3 Demonstrating safety and effectiveness

The risks faced by patients from innovative new techniques can be substantial and surgeon innovators and their organisations cannot understand these risks without conducting an evaluation of the innovation in terms of clinical outcomes and other effects. Gathering an evidence base should not only help to establish safety and effectiveness but may also change the way in which the surgical innovation is undertaken and widen the pool of patients who could benefit.

The RCS has identified the enablers necessary to create a virtuous circle, which in turn leads to greater uptake and the development of stronger evidence, as set out in Figure 2.

3.1 CHALLENGES IN SURGICAL RESEARCH

Historically, surgical innovations have often been adopted without adequate supporting evidence of efficacy and safety. The RCS has found that undertaking surgical research in the area of new surgical techniques and technologies has been 'somewhat limited in extent, scope and ambition when compared with other forms of research'.[18] While randomised controlled trials (RCTs) are considered the gold standard for establishing safety and efficacy of an intervention, high quality RCTs have often proved difficult to undertake in surgery. Challenges include a perceived lack of equipoise, problems with double-blinded design, 'surgical exceptionalism' and the unique nature of surgery and the difficulties of gaining statistical significance from often small patient populations.[19] Other factors that may make surgical trials more difficult include a lesser tolerance (than physicians) of uncertainty about the effectiveness of alternative treatments and issues with timing the randomisation close to the intervention.[20]

The following questions may assist surgeon-innovators during the design of surgical RCTs, as suggested by Hirst *et al*:[21]

1. Does the RCT involved a surgical intervention?
2. What is/are the surgical intervention(s) under evaluation?
3. What is/are the co-interventions accompanying the surgical intervention?
4. How will the intervention(s) be standardised in the RCT?
5. How will delivery of the intervention(s) be monitored?
6. Who will deliver the intervention(s)?
7. Where will the intervention(s) be delivered?

It is not in keeping with modern surgical practice to adopt surgical innovations without evidence of safety and effectiveness, and there is reason for optimism that the challenges associated with providing a robust evidence-base are being overcome. Pinkney and Morton report that:[22]

- Clinical research activity in surgery in the UK is at a record high, supported by engagement between the National Institute of Health Research, RCS and major charitable funders to develop multicentre clinical trials.
- There are now national research leads in all major surgical specialties and dedicated surgical clinical trials units have been created nationally.
- Trainee-led collaboratives exist across the country in both general and subspecialist branches of surgery.
- Multi-arm, multi-stage trials are starting to emerge in surgery, which allow for multiple similar interventions to be evaluated in tandem.

3.2 THE IDEAL FRAMEWORK

The IDEAL framework provides a pathway for the assessment and reporting of surgical innovations. It is based on the assumption that surgical innovation and evaluation can and should evolve together in an ordered manner from concept through exploration to validation by randomised trials.[5] It places emphasis on improving transparency in reporting surgical research, including mandatory registration of procedures thought to be first in-man and confidential reporting of adverse outcomes and registries for surveillance.[23]

Two summary tables have been developed by the IDEAL Collaboration to help surgeon innovators identify the stage their own surgical research sits and to help guide the design of the study (Appendix V).

Figure 2 The cycle of innovation

4. Clinical governance and oversight

The interests of patients must always be paramount in introducing new techniques. *Good Surgical Practice* is clear that any new clinical interventions or surgical techniques (including equipment) that deviate significantly from established practice and are not part of an NHS local ethics committee research programme, must be underpinned by rigorous clinical governance processes.[2]

Surgeons must:

- discuss the technique with colleagues who have relevant specialist experience
- seek formal approval from their hospital's medical director
- follow local protocols for obtaining approval by the local ethics committee or the local clinical governance committee.

Local arrangements should include provision of evidence that the new technique is safe and that all clinical staff who plan to use the new technique will undertake relevant training, mentorship and assessment.[2] Deciding what constitutes relevant training may not be straightforward – see Section 5. Healthcare providers should record the use of new procedures to support the monitoring of implementation and the impact they have.[12]

This guidance is echoed by NICE, which expects provider organisations to have a process in place for introducing a new procedure and for healthcare professionals planning to perform a new interventional procedure in the NHS to obtain approval using the appropriate governance structures of the organisation in which the procedure will be performed.[24] The medical director (or nominated deputy) should ensure that any new procedure falling within scope of the interventional procedures programme at NICE (see Appendix 4) is notified to NICE, unless the procedure is being used solely within a protocol approved by a research ethics committee. The use of a new surgical device or a clinical study using new devices also needs to be reported to the Medicines and Healthcare Products Regulatory Agency.

It should go without saying that any failure by a surgeon to comply with the above governance requirements in their local hospital when introducing new techniques or technologies demonstrates a lack of probity, subject to appropriate disciplinary procedures.

4.1 INNOVATIONS COMMITTEES

Often, ethics committees within healthcare organisations will provide oversight to surgical innovation. Where possible, it is recommended that dedicated surgical innovation committees are established, to carefully evaluate proposed surgical innovations.

The Macquarie Surgical Innovation Identification Tool can help committees identify planned surgical innovations (see Appendix 2), as well as guiding surgeons (and patients) through the process of informed consent, managing conflicts of interest and evaluating the outcomes. The committee should consider what type of training is needed and any other preparatory work needed to ensure the safety of the technique. Another task for the committee is to consider patients' rights of access to new techniques.

The composition of an oversight committee will vary according to the local context and the nature of the surgical innovation. It should at least include surgeons with an understanding of the proposed new technique, plus others able to represent the interests of patients. The committee will need to balance the need for caution when introducing innovations against the potential to improve patient outcomes.

Certain new techniques may benefit from oversight provided at regional or national level. This oversight is needed where the necessary specialist expertise is not available locally or where the innovation is being performed in several centres, making a centralised and standardised approach useful. National oversight can also provide monitoring of long-term outcomes.

Key questions an oversight committee should ask:

- Why is this new technique being proposed?
- Which patient groups could benefit?
- Has the innovation been performed elsewhere? If so, what is known about this?
- What is known of the risks associated with the new technique?
- What training/mentoring will the surgeon and/or surgical team have to make the technique as safe as possible?
- How will patients be informed before undergoing this new technique? What information will be included on the consent form they are asked to sign?
- How are the outcomes to be monitored and evaluated? Should these outcomes be shared with regional or national committees or registries?
- What ethical questions do we need to consider in deciding on the introduction of this new technique?

4.2 CLINICAL AUDIT

Clinical audit of new techniques should be built into the processes for introducing and overseeing surgical innovations. Clinical audit can have an important role in research by, for example:

- evaluating the efficacy of different techniques
- analysing variations in care
- facilitating further research into patterns of care.[18]

Clinical audits can also support improvements in outcomes by assessing variations in clinical practice, processes, patient outcomes, productivity and costs. Where more than one hospital is involved in the introduction of a new technique or device, it is important to ensure that the results of individual audits are collated in order to provide the most robust information possible through strength of numbers. Ideally, participating centres should be submitting data to a national audit, whether run as part of the evaluation process or sponsored by the relevant surgical specialty association. The outcomes of such audits should be transparent and readily available to both the participants and to those who might seek to adopt the innovation in their own hospital. Surgeons should be wary of commercial companies that restrict dissemination of preliminary data on novel devices under the cloak of commercial sensitivity, as such data may also conceal adverse outcomes.

In the case of surgical implants such as stents or joint prostheses, the RCS position is that all implants should be recorded on a national registry. While this requirement is not universally applied at present, it should certainly be mandatory for newly developed implants.

5 Training in new techniques

New techniques often require the development of new skills for which training is necessary. Where a technique is being undertaken for the first time, training may involve practising the technique on a cadaver or in a simulation lab. When the technique has been performed previously by others, training might comprise:

- hands-on experience of the procedure under supervision
- scrubbing in to observe another surgeon operate
- undertaking a fellowship
- participating in a formal training programme
- performing the procedure under mentorship from a trained surgeon.

The surgeon should have a surgical mentor experienced in the technique to allow oversight for a defined number of initial procedures, sufficient to ensure proficiency before operating independently. The mentor must be approved by the hospital authorities to intervene during the procedure, if necessary.

The amount of training required will depend on the surgeon's experience and expertise. The underlying principle is that training must be delivered on the right scale and at the right pace to assure the quality, safety and efficiency of a new technique. The quality of delivery and the safety of many techniques requires the surgeon to undertake appropriate volumes of procedures.[12]

One of the factors that influences whether an innovation spreads is the establishment of training programmes to ensure that qualified surgeons are able to undertake new techniques to a high standard of quality and safety.[18] Training has played a critical role in ensuring the roll-out of techniques such as endovascular aneurysm repair, laparoscopic bowel surgery and sentinel node biopsy, for the benefit and safety of patients. Some practical solutions to support training in new techniques include treating national training programmes as part of the research implementation process and allocating a dedicated training uplift to the tariff for new techniques for an interim period.

A surgeon's experience and outcomes with the new technique should be shared across the surgical community, including negative outcomes.

A system of accreditation for performing a novel procedure is one approach to ensuring that surgeons are properly trained in a new surgical technique.[19] Suppliers of new surgical devices may insist on appropriate training and mentorship before they will supply a surgeon with the new technology, a requirement often driven by their legal and financial liability if things go wrong.

5.1 THE LEARNING CURVE

The 'learning curve' refers to the increased risks to patients during the time that a surgeon or surgical team gain competency in a new procedure.[25] It applies where the original innovator is gaining experience in the new technique but also where the technique is performed in different hospitals by other surgeons.

One of the problems associated with the learning curve is that it may not be apparent to the surgeon or surgical team that they are in the steepest arc of the curve until after they have moved beyond it. This creates an ethical challenge as 'it becomes very difficult to disclose the risks of the learning curve to patients when those risks may be unknown'.[13] Informing the patient of a surgeon's experience with an innovative procedure should be a core element of the informed consent process. Training, whether hands-on, simulated or apprenticeship, may not only improve the surgeon's confidence in performing the new technique but also accelerate the learning curve.

5.2 TRAINING IN ENTREPRENEURSHIP

Surgeons often demonstrate innovative tendencies, yet education on entrepreneurship tends not to be a component of surgical training programmes, which naturally concentrate on preparing surgeons for clinical roles.

For the next generation of surgeons, the NHS England Clinical Entrepreneur Training Programme offers opportunities for junior doctors and other health professionals to develop their entrepreneurial skills during their clinical training period. The programme offers time for entrepreneurial activity, mentoring, coaching, entrepreneurial placements and internships, and it also facilitates relationships with commercial organisations to develop business and procurement acumen (NHS England).[26]

6 Seeking patient consent

Gaining the patient's consent for a surgical procedure can be a challenging process at the best of times, relying as it does on the surgeon tailoring the discussion to the individual patient, to ensure that they are aware of any risks that are material to them and any available alternatives.[27] These difficulties are amplified when it comes to a new technique, particularly where there may be only a limited understanding of the potential risks and benefits at the early stages of innovation. Key challenges include a limited collective experience with the new approach and a lack of information on long-term results.[28]

Surgeons have a duty to have full and frank discussions with patients regarding proposed surgical procedures. But how do we do this when the surgeon is learning the new technique and the extent of the risks are unknown?

6.1 WHAT TO TELL PATIENTS

The College's guide *Consent: Supported Decision-Making* sets out the information that surgeons should provide to patients as part of the consent process.[27] This includes the purpose and expected benefit of the treatment, what it involves, the likelihood of success, the material risks of the procedure and the alternative options. If the recommended treatment is not in keeping with current guidelines (such as NICE or the Scottish Intercollegiate Guidelines Network), the surgeon must explain the reason for not following standard guidelines. Surgeons should also ensure that options are presented 'side by side' and that the relative risks and benefits of the different options for treatment are discussed.[27]

It is essential that patients understand that a technique is new and they must be given this information during the consent process. A systematic review of studies looking at consent and innovations by Broekman *et al* found that the information that should be provided to patients should include:[19]

- the innovative nature of the procedure
- the surgeon's learning curve (see Section 5.1 for more on this) and his or her experience with the procedure
- the risks and benefits of the procedure, including possible unforeseeable or unknown risks or outcomes due to the 'experimental and unvalidated nature of the procedure'
- the evidence (or lack thereof)
- alternatives to the innovative procedure.

This review found that a majority of patients consider the technical details of the procedure to be essential information informing their decision to undergo an innovative operation, even though only 20% of the surgeons thought so.

Char *et al* explored what information patients and surgeons consider essential to disclose before an innovative surgical procedure.[29] They found that, compared with surgeons, patients placed greater importance on nearly all types of information, particularly volumes and outcomes. For three techniques, around 80% of patients indicated that they could not decide on surgery without being told whether it would be the surgeon's first time doing the procedure. When considering innovative robotic surgery, a clear majority of both patients and surgeons agreed that it was essential to disclose the procedure's novel nature, potential unknown risks and benefits and whether it would be the surgeon's first time performing the procedure. When accurate volumes and outcome data are available, surgeons should also discuss these with patients.

Following the Montgomery ruling on consent, what to tell the patient will also depend on assessing what impact the new technology might have on them, on the basis of what a reasonable person in the patient's position would attach significance to when deciding consent. The burden of disclosure rests with the surgeon even though the surgeon rarely owns the new technology, because it is the surgeon who decides whether to offer this new technology to the patient.

The discussion about consent should include details of alternatives to the innovative procedure, which will generally be the traditional procedure or the choice of no procedure.

It is the surgeon's responsibility to ensure that the patient understands the information they are given well enough to allow them to objectively weigh the risks and benefits of a new procedure. Suggestions to support this process include the presence of a third-party communicator, the use of a patient advocate or the use of a multimedia presentation to explain the procedure to the patient.[19]

6.2 OPTIMISM BIAS

Both surgeon and patient bring inherent bias to discussions about consent, which may be increased when a new technique is being offered. There is often a tendency for patients to believe that what is new is improved and surgeons may be overly optimistic about an innovative procedure. The informed consent process is at risk of excluding a balanced discussion of the potential and unknown risks of the procedure, which fade into the background while both surgeon and patient focus on the potential benefits.

One way of tempering a patient's optimism bias is to impose a mandatory 'cooling off' period after the initial discussion and to require a second visit at which informed consent is formally obtained. The involvement of a patient advocate or other third party could also help to dampen any optimism bias and ensure that the patient's interests are properly served.

The surgeon's optimism bias should be robustly explored in the multidisciplinary team meeting setting, where consensus from colleagues should be obtained to offer the new procedure on a patient by patient basis.

7 Managing conflicts of interest

Surgeons must be open about any conflict of interest and provider organisations should make sure that they are aware of any conflicts arising for both the surgeon and for the organisation.

Potential conflict of interest can arise for the surgeon from their relationship with the companies that manufacture the innovative technology, particularly where this leads to significant financial or reputational gain. Surgeons should disclose to their organisations and to patients any ties with companies that manufacture technology used as part of a new technique.

Conflicts may also arise where the patient has been referred to or has specifically asked to see a particular surgeon because they are known to undertake an innovative procedure, placing pressure on the surgeon to undertake the procedure even though an alternative might be more suitable for that particular patient. There may be financial incentives for both the surgeon and for healthcare providers to offer an innovative procedure, in terms of the fees paid. In these situations, conflicts can arise for both the surgeon and the organisation.

Oversight mechanisms for the surgical innovation (see Section 4) must be aware of and exclude any temptation to encourage patients to undergo a new technique over an existing procedure or any over-statement of its benefits. Miller *et al* warn that the natural desire to obtain positive outcomes when implementing an innovation that is believed to be beneficial may lead to bias in patient management decisions and data collection and reporting.'[4] The authors argue: 'The surgeon-innovator must preserve the best interests of the patient, rather than his or her own self-interest, and uphold ethical standards when making decisions about the application and dissemination of a new procedure or technique.'

8 Translating a new technique into wider practice

The barriers to implementation of surgical innovation are various. One of the main challenges lies in establishing the evidence-base and difficulties in getting funding to produce the evidence.[18] Other common issues include:

- the need for new skills and training
- the need for new equipment, working arrangements or configuration of services, requiring capital investment as well as service redesign
- clinical and patient demand, which will require the provision of patient information on benefits and risks.[12]

More complex types of innovations that require engagement of teams from across different organisations, such as new models of care or pathways, have been found to make slower progress in scaling.[30] Other barriers are incompatibility of information technology systems, difficulties in navigating commissioning structures and identifying patients who can benefit from the innovation.

The RCS has identified six common factors that help to overcome these issues and encourage the spread of innovation:[12]

1. Early identification of the potential benefits of an innovation.
2. Leadership to champion and advocate its adoption.
3. Establishing the infrastructure to enable its use.
4. Defining what should be implemented and how its impact will be measured.
5. Developing levers and incentives to encourage appropriate adoption.
6. Providing information to support clinical adoption and patient choice.

Other factors that are key in influencing the spread of an innovation include:

- the availability of national guidance detailing appropriate use
- the establishment of training programmes to ensure that qualified surgeons are able to undertake the new techniques to a high standard of quality and safety
- the availability of readily accessible information on trials and studies in progress.[18]

8.1 SURGICAL LEADERSHIP

Surgeon preference is crucial in determining the adoption of a new surgical innovation. If surgeons are unconvinced of the benefits or prefer their familiarity with established techniques, they are unlikely to adopt the innovation into their own practice.

The perceived lack of robust evidence was an initial barrier to the timely adoption of sentinel lymph node biopsy in the UK. Clinicians who advocated change often met with resistance from surgical colleagues and managers who were reluctant to support a new technique that was being practised on a relatively small scale. The value of surgical leadership was demonstrated by the important role played by clinical champions in convincing the Department of Health to implement a national training programme and in driving participation in training across England. Strong clinical leadership was also key in pioneering the enhanced recovery pathway, in securing action and funding to provide training in laparoscopic colorectal surgery via the national Lapco programme and in pushing the implementation of total mesorectal excision.[12]

A key source of help for surgeon innovators looking to drive wider adoption of a new technique is the relevant surgical specialty association. The RCS has recommended that surgical specialty associations develop good practice guidance to support clinical teams to work together at a local level to deliver an effective business case and drive organisational change.[12]

Strategic clinical networks are another important resource. These networks support commissioners to improve services for particular conditions (eg cancer or cardiovascular conditions).[31] Among other things, these networks seek to encourage innovation in service provision and the RCS has

called for them to be required to review and advise on the roll-out of innovative surgical procedures at a regional level.[12]

8.2 INCENTIVES TO SUPPORT 'SCALING UP'

For those innovations with demonstrable value there are financial incentives to encourage their wider adoption. These include:

- **The NHS Innovation and Technology Payment** This payment builds on the Innovation and Technology Tariff (ITT) and aims to support the NHS in adopting innovation by removing financial or procurement barriers.[32] There is a competitive process to identify innovations and technologies that will offer the greatest quality and efficiency benefits with wider adoption. Successful innovations include 'Plus Sutures', a new type of surgical suture that reduces the rate of surgical site infection through the use of antimicrobial suture packs, and also 'Endocuff Vision', a new type of bowel scope that improves colorectal examination for patients undergoing bowel cancer tests.
- **The NHS Innovation Challenge Prize** may help individual surgeons gain support for an innovation. The prizes seek to encourage, recognise and reward front-line innovation and drive adoption of these innovations across the NHS.[33]
- **The Innovation Scorecard** seeks to reduce variation and strengthen compliance of the uptake of NICE Technology Appraisals, including those for surgical procedures, which the NHS is legally obliged to fund and resource. It does this by enabling benchmarking and increasing transparency to patients and the public. The scorecard is produced quarterly by the Health and Social Care Information Centre.[34]

Other levers to encourage appropriate uptake of surgical innovations, include:

- providing written information to patients to help them make an informed decision about the most appropriate treatment option, including newer technologies
- disseminating information on new techniques to clinicians
- incentivising the uptake of new technologies through schemes such as commissioning for quality and innovation
- creating best practice tariffs where a clinically superior intervention is available that may not otherwise be used (and may require upfront investment)
- ensuring that appropriate use of interventions is considered as part of the revalidation process for surgeons.

The decommissioning of practices that have no added value, or have been replaced by something new or better, is just as important as the implementation of innovations that do have value. This process is sometimes referred to as 'reverse innovation'. The never-events regimen may in future be extended to actively drive 'old practice' out of the system, especially where it is found to be unsafe.[8]

9 Measuring long-term outcomes

Once a surgical innovation is introduced into routine practice, there need to be mechanisms in place to monitor the long-term impact. The MRC recommends that monitoring should be undertaken to detect adverse events or long-term outcomes that could not be observed directly in the original evaluation or to assess whether the effects observed in earlier evaluation are replicated in routine practice.[35]

The full risks of a new technique may not be known at the time of implementation. Miller *et al* highlight the example of laparoscopic cholecystectomy, after it was widely adopted in the United States.[14] It was only after a registry of operative complications was published that it was understood that the low incidence of common bile duct injury in open cholecystectomy was increased 15-fold in laparoscopic cholecystectomy. It can take many years' worth of outcomes data to discover the true incidence of complications. It is therefore important to demonstrate the long-term outcomes of a surgical innovation and how they compare with the procedure that would otherwise have been performed.

Other risks that show themselves over time may be related to new equipment or technology that accompany the new technique, such as the risk of burns from fires caused by fibreoptic cables. There are also the risks associated with the learning curve (see Section 5.1) as dissemination of the innovation emerges and more surgeons begin to gain experience in performing the new technique.

The mechanisms for providing oversight when a surgical innovation is first introduced should also scrutinise the longer-term impact of the innovation at 12 months, 24 months, 5 years and beyond. Innovations committees should ensure that an innovation that initially shows promise and is beneficial in the first few years of implementation, continues to demonstrate value and that any unintended consequences are fully understood.

In some cases, the innovative procedure may demonstrate no more than equivalence with the traditional procedure that would otherwise have been performed. Mayer and Darzi observe that trials that show equivalence for an innovation are sometimes interpreted as supporting a return to existing practice, including re-diverting the training of a generation of surgeons who might have followed the innovation's evolution.[36] However, equivalence and non-inferiority could also be seen as positive, showing that the innovation has preserved the intended and well-established purpose of surgical intervention, such as good oncological outcomes balanced against acceptable functional adverse effects.

9.1 DATABASES AND REGISTRIES

Surgeons should keep an accurate and accessible record of all their surgical activity and submit activity data to national audits, registries and databases relevant to their practice. Surgeons should also present the results at appraisal for review against the national benchmark. Benchmarking data are unlikely to be available for a surgical innovation until its dissemination has had sufficient reach and depending on the numbers of patients eligible for the new technique. Work being undertaken by the surgical specialties to identify 'indicator' operations that would give a sound judgement of skill,[36] may assist in providing comparators against which the equivalence of new techniques can be measured.

Good Surgical Practice expects surgeons to contribute to the evaluation of a new procedure by auditing outcomes and reviewing progress with a peer group, and by complying with guidelines by NICE or the Scottish Intercollegiate Guidelines Network.[2]

IDEAL recommends the widespread use of prospective databases and registries, and for reports of new techniques to be registered as a professional duty, anonymously if necessary when outcomes are adverse. Stage 4 of the IDEAL framework focuses upon long-term study, to assess innovations for 'rare and long-term outcomes, and for variations in outcome', which may reveal differences in the quality of surgery or aftercare.[11] The IDEAL proponents argue that only key outcomes and relevant information should be obtained to encourage complete data entry. Depending on the frequency of the procedure, it may be possible to investigate outcome variations among subgroups.

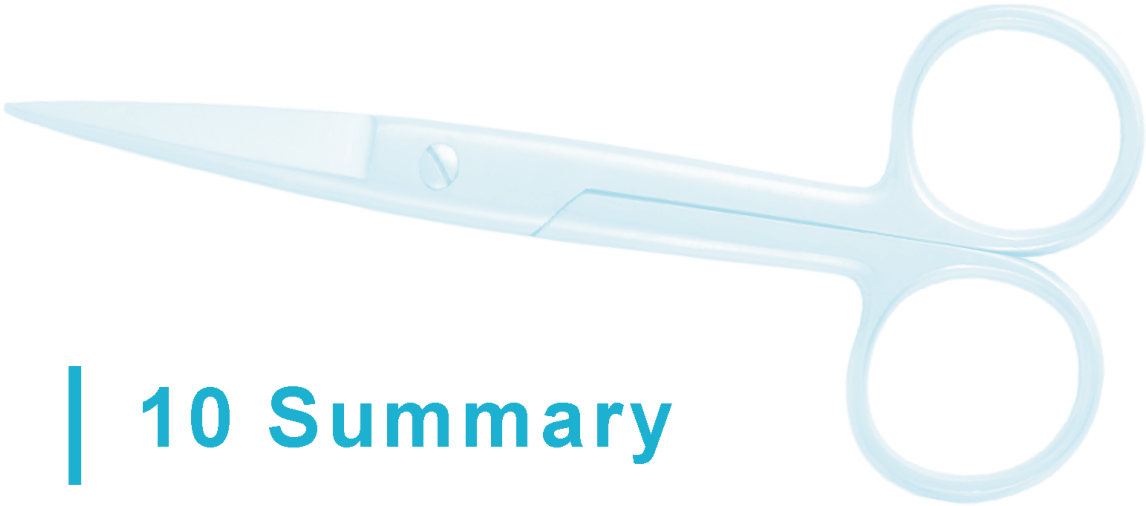
9.2 PATIENT-REPORTED OUTCOMES

Since surgical innovation is often motivated by a desire to improve patient care, it is right that measurement of the impact of the innovation reflects

patient-defined benefits in addition to clinical analysis. In some situations, patient-defined outcomes are more important than clinical outcomes (for example, palliative surgery, and functional outcomes after joint replacement surgery).

The RCS has led the way in piloting a system of patient-reported outcome measures and, since 2008, these measures have been gathered for patients undergoing hip, joint, hernia and varicose vein operations.[37]

The RCS is also working to improve systems of measuring outcomes, to ensure greater public transparency and accountability, enable surgeons to have a better basis for judging and improving their practice, and to offer improved patient choice, service improvement and quality assurance of operations.[37] The intention is to have a system for outcome measurement that will combine existing statistics and audits, new clinical registries and patient attitudes to the results of their operation. These developments should be of value in measuring outcomes for surgical innovations, as well as for established procedures.



10 Summary

The introduction of new technology or new techniques in surgery has no place for the maverick surgeon who proceeds without appropriate peer review or training. All surgeons have a duty to consider carefully whether or not the innovation has a real patient benefit at an affordable cost, both in terms of morbidity and mortality and of cost effectiveness compared with established procedures. Such considerations should include widespread dissemination and debate of preliminary studies among peer groups to establish a consensus for the adoption of the innovation. Innovations should be the subject of clinical trials comparing them with established procedures to help inform these discussions and debate. Surgeons must be wary of the risks of optimism bias and conflict of interest when explaining the procedure and consenting their patients. No surgeon should attempt a novel procedure without appropriate institutional support, preliminary training and mentorship. Outcomes should be carefully monitored and audited, both locally and nationally, with open and transparent dissemination of results. It is also important to ensure that long-term outcomes are monitored through the use of databases and registries, to ensure that any innovation not only improves patient outcomes but is also durable when compared with established procedures.

Appendix 1:A definition of innovative surgery

An innovative surgical procedure is any procedure that meets one or more of the following criteria:

1. **Innovative technique**: the technique used is new or differs from the standard technique in one or more of the following ways:
   - 1a altogether new (eg pioneering transplant surgery: first face transplant)
   - 1b new to anatomical location (eg use of established anastomotic techniques in new locations)[a]
   - 1c new to patient group eg expansion of indications to groups whose surgical outcomes may be different, such as children.

Examples of innovative techniques: different incision position or size; combination of two procedures such as mastectomy and reconstruction; extension of microsurgical techniques.

Or

2. **Innovative device**: the tools or devices used are new, or the use differs from standard use in one of the following ways described:
   - 2a altogether new (eg first use of laparoscope)
   - 2b new to anatomical location (eg application of laparoscope to new organ/cavity)[a]
   - 2c new to patient group (eg use of device on people with comorbidities likely to influence surgical outcomes).

   Examples of innovative devices: surgical robot; new hip prosthesis; implant made from new material; use of laparoscope to perform procedure usually done without one.

[a] Excludes procedures, such as fixation of fractures, which are not standardised to a particular part of the body.

Source: Hutchinson *et al.*[6]

Appendix 2: Macquarie Surgical Innovation Identification Tool

1. The **techniques, instruments and/or devices** to be used in the operation for which the patient has consented:
   - 1a. Have all been used before in this **hospital** • yes • no
   - 1b. Have all been used before by this **surgeon** • yes • no

   A 'no' response for either of these items identified the first performance of the intervention by the surgeon or introduction of the intervention to the institution. This may flag innovation if the intervention has never been performed elsewhere. Further details should be requested regarding requirements for training and supervision, change in resources, extent of patient communication and prior experience of the intervention elsewhere.

2. The conditions under which this operation will take place do not depart from those under which such a procedure would usually occur, for example the **techniques, instruments and/or devices** to be used in the operation for which the patient has consented are routinely used:
   - 2a. For this indication • yes • no
   - 2b. In patients of this sex (where sex differences relevant) • yes • no
   - 2c. In patients of this age (c.f. paediatric and elderly patients) • yes • no
   - 2d. In patients with this comorbidity • N/A • yes • no

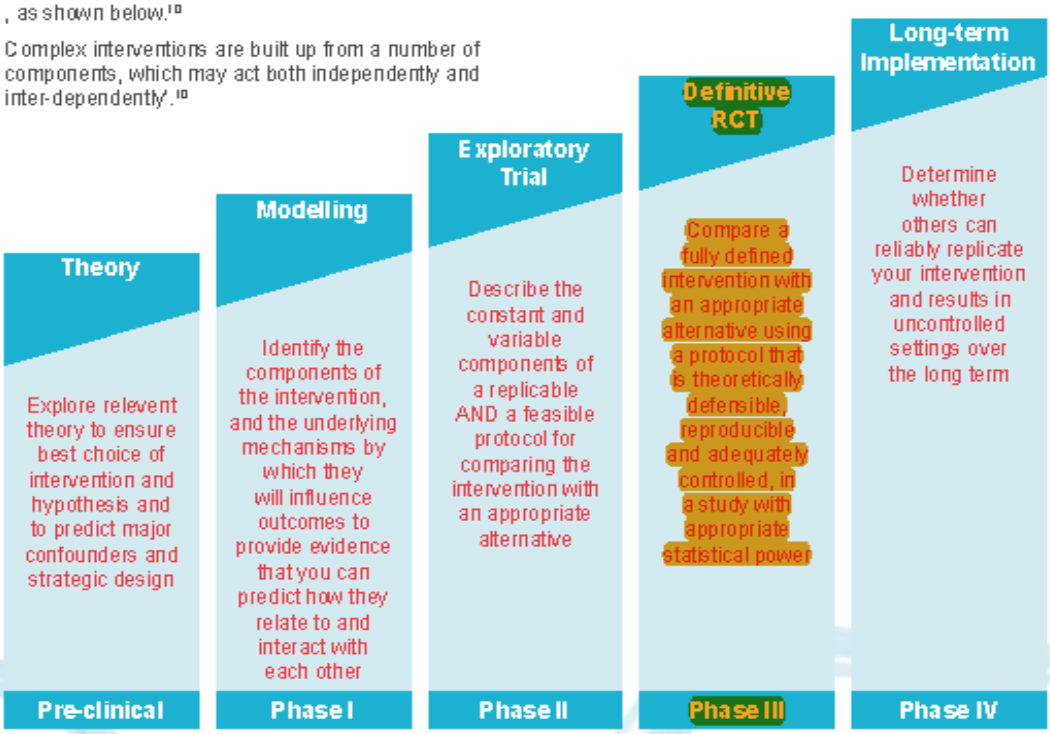
   A 'no' response for either of these items suggests that innovation may be occurring. Further details should be requested regarding the surgeon's knowledge of the likely outcomes of the procedure, whether the outcomes of the surgery are likely to be of interest to surgical peers (eg publishable) and whether special preparation are needed (such as training or special instructions to the anaesthetist or the preoperative, perioperative or postoperative teams.

Source: Blakely *et al.*[7] Also found in Hutchinson *et al.*[6]

Appendix 3: Medical Research Council stages of investigation and evaluation

The MRC distinguishes between five stages of investigation in the evaluation of a complex intervention , as shown below.[10]

Complex interventions are built up from a number of components, which may act both independently and inter-dependently'.[10]



The MRC's framework sets the objectives to be met at each stage before moving to the next. Updated MRC guidance refers to the development-evaluation-implementation process.[35]

Appendix 4: National Institute for Health and Care Excellence requirements

Interventional procedures guidance: NICE defines an interventional procedure as one that is used for diagnosis or for treatment that involves:

- making a cut or a hole to gain access to the inside of a patient's body (eg carrying out an operation on inserting a tube into a blood vessel)
- gaining access to a body cavity without cutting (eg carrying out treatment inside the stomach using an instrument inserted via the mouth)
- using electromagnetic radio (eg using a laser to treat eye problems).[23]

NICE states that where it has not published interventional procedures guidance for the procedure, a surgeon's organisation can still approve it as long as the clinician has appropriate training and experience, patients are made aware and give their consent and arrangements are made for data collection and audit (all addressed in other sections of this guidance).

Technology appraisals: NICE undertakes technology appraisals of existing and new medicines and treatments, including medical devices, diagnostic techniques and surgical procedures. The guidance is based on a review of clinical evidence (to show how well the medicine or treatment works) and economic evidence (to show how well it works in relation to how much it costs the NHS).

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Appendix 5: The IDEAL framework

Defining characteristics of IDEAL framework phases

Phase 1	Phase 2a	Phase 2b	Phase 3	Phase 4
IDEA	DEVELOPMENT	EXPLORATION	ASSESSMENT	LONG-TERM MONITORING
Initial report	Tinkering (rapid iterative modification of technique and indications)	Technique now more stable	Gaining wide acceptance	Monitoring late and rare problems, changes in use
Innovation may be planned, accidental or force	Small experience from once centre	Replication by others	Considered as possible replacement for current treatment	
Focus on explanation and description	Focus on technical details and feasibility	Focus on adverse effects and potential benefits	Comparison against current best practice	
		Learning curves important		
		Definitions and quality parameters developed		

Key recommendations for research design at each IDEAL phase

IDEA	DEVELOPMENT	EXPLORATION	ASSESSMENT	LONG-TERM MONITORING
Professional innovation database	Prospective development studies	Phase IIS studya	Surgical RCT	Prospective registries
Compulsory reporting of all new innovations	Detailed description of selection criteria	To evaluate technique prospectively and cooperatively	RCT – question agreed in phase IIS	Should monitor indications as well as outcomes
Confidential entry allowed to encourage reporting of failed innovations	Detailed technical description	To develop a consensus over definition of the procedure, quality standards and indications	Use power calculations from phase IIS	Statistical process control used for quality control (Shewart charts, CUSUM, VLAD)
Hospital or institution to be informed separately as a professional duty	Prospective account of ALL cases consecutively, including those NOT treated with new technique/device	To gather data for *power calculations*	Use learning curve data to decide entry points for clinicians	
	Clear STANDARDISED definitions or outcomes reported	To evaluate and monitor *learning curves*	Use phase IIS consensus to define operation, quality control AND outcome measures	
	Descriptions of ALL modifications and when they were made during the series	To achieve consensus on the *trial question*	Use modified RCTs or recognised alternative if RCT not feasible	
	Registration of PROTOCOL before study starts	To develop a multicentre *randomised trial (RCT)*	Feasibility RCT, expertise-based RCT, cohort multiple RCT, step-wedge design, controlled interrupted time series	
	Use of statistical process control methods to evaluate progress			

[a] Prospective collaborative studies.
CUSUM, cumulative sum control chart; RCT, randomised controlled trial; VLAD, variable life adjusted display.
Source: The IDEAL Collaboration

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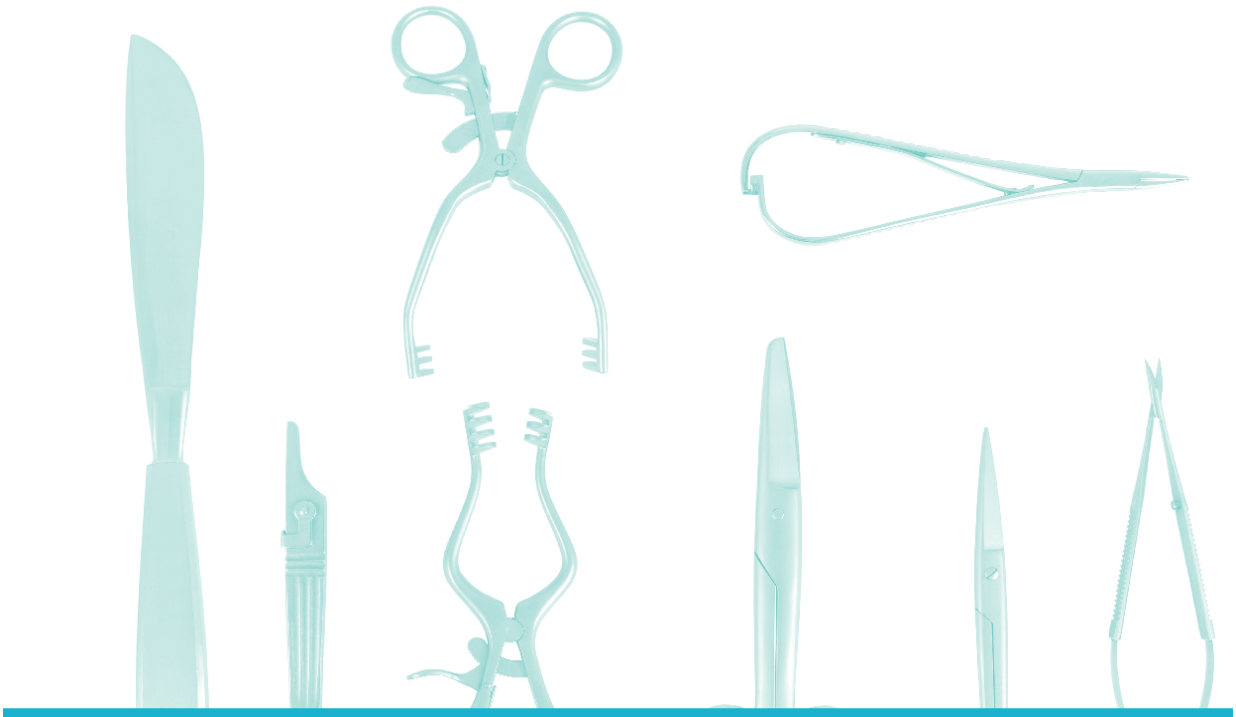

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