Research Update – IA Information Day
May 2024

Professor Thomas Pinkney

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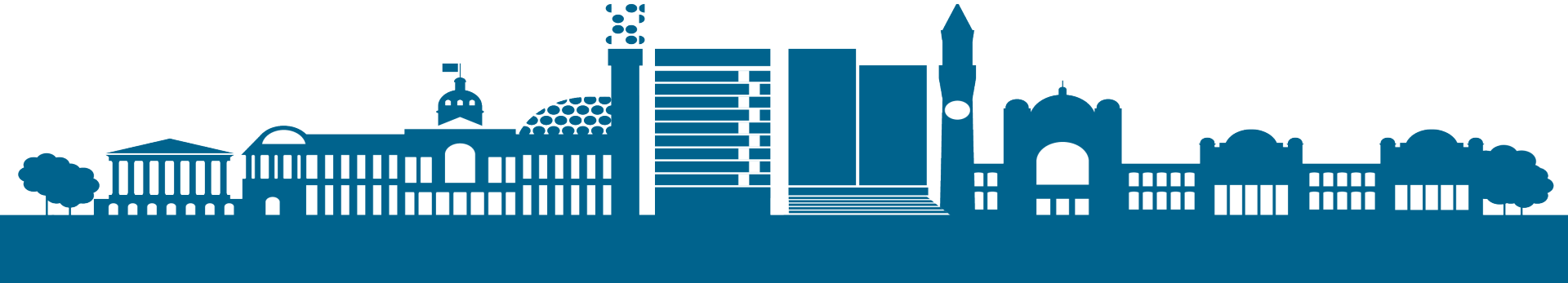
Consultant Colorectal/IBD Surgeon, Queen Elizabeth Hospital Birmingham



The plan:

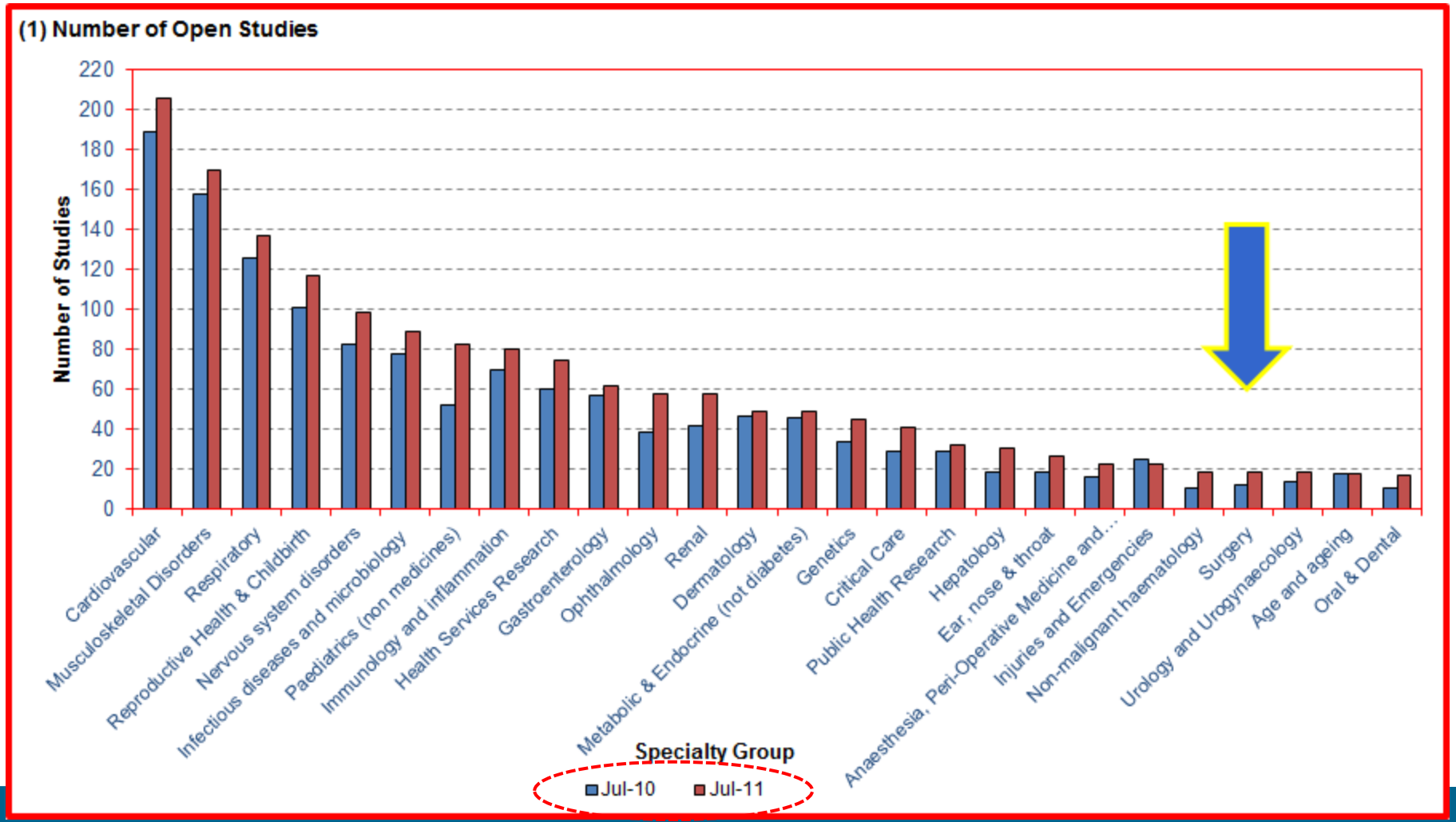
- Why research is important
- Why research can be difficult in surgery
- How research might fit into the surgical pathway
- New types of research
- Opportunities to get involved

- ACCURE-UK 2
- OCEAN
- MEErKAT
- PROPHER
- ROSSINI 2
- PROMISE-IBD

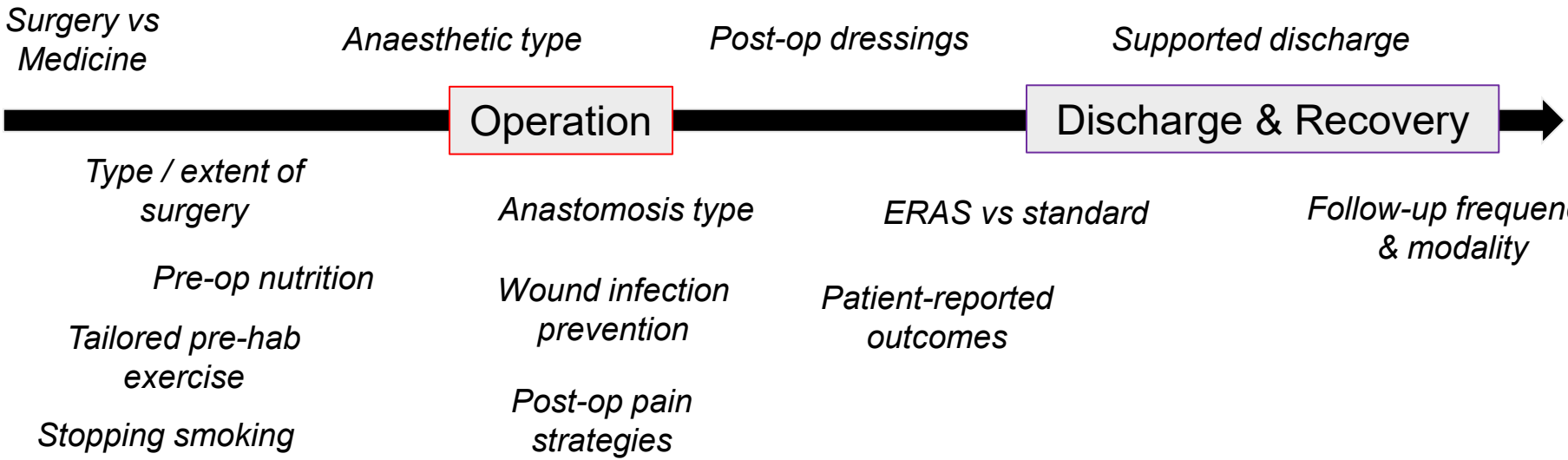
- ACCURE-UK 2 *- results!*
- OCEAN *- just opening*
- MEErKAT *- ongoing*
- PROPHER *- ongoing and great*
- ROSSINI 2 *- update on progress & extension*
- PROMISE-IBD *- starting later in 2024*

- Average UK adult: 4-5 operations in their life
- 40-45% of NHS annual budget on surgery

- 7.7M operations currently waiting to be done


(1) Number of Open Studies
Number of Studies
220
200
180
160
140
120
100
80
60
40
20
0
Cardiovascular
Musculoskeletal Disorders
Respiratory
Reproductive Health & Childbirth
Nervous system disorders
Infectious diseases and microbiology
Paediatrics (non medicines)
Immunology and inflammation
Health Services Research
Gastroenterology
Ophthalmology
Renal
Dermatology
Metabolic & Endocrine (not diabetes)
Genetics
Critical Care
Public Health Research
Hepatology
Ear, nose & throat
Anaesthesia, Peri-Operative Medicine and…
Injuries and Emergencies
Non-malignant haematology
Surgery
Urology and Urogynaecology
Age and ageing
Oral & Dental
Specialty Group
Jul-10
Jul-11


Operation
Discharge & Recovery

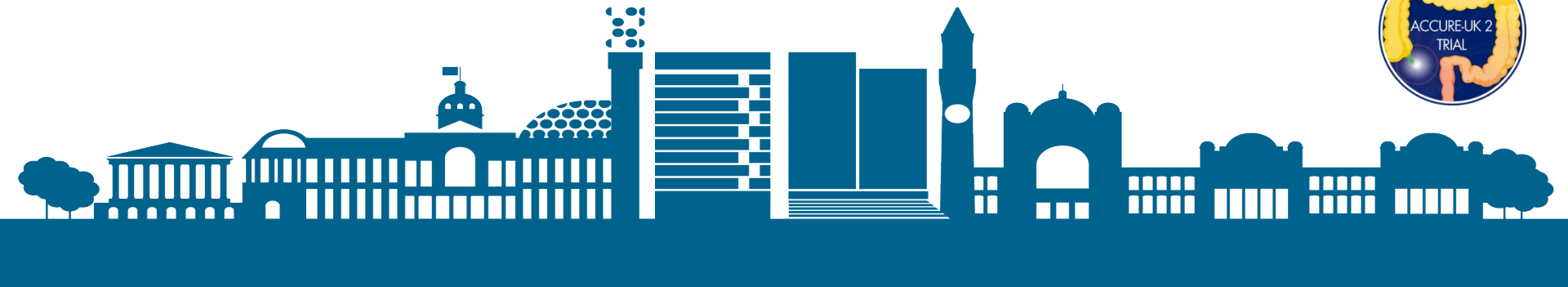

Surgery vs Medicine
Anaesthetic type
Post-op dressings
Supported discharge
Operation
Discharge & Recovery
Type / extent of surgery
Pre-op nutrition
Tailored pre-hab exercise
Stopping smoking
Anastomosis type
Wound infection prevention
Post-op pain strategies
ERAS vs standard
Patient-reported outcomes
Follow-up frequency & modality

The Appendix in UC – finally some results!

Prof Thomas Pinkney

University of Birmingham, UK

ACCURE-trial

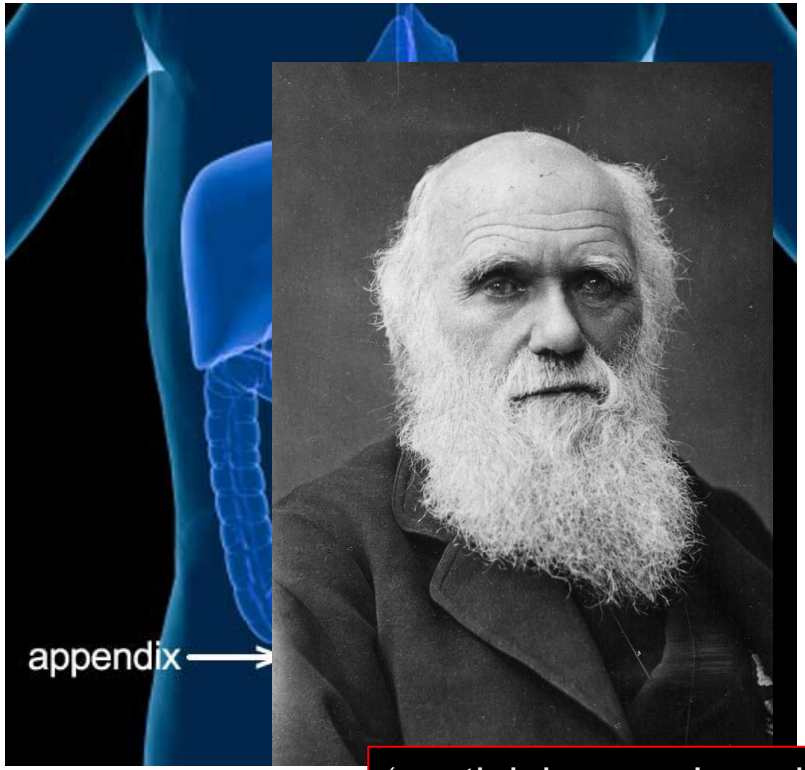


ACCURE-trial

Amsterdam UMC
Universitair Medische Centra

Eva Visser

The appendix



THE

DESCENT OF MAN,

AND

SELECTION IN RELATION TO SEX.

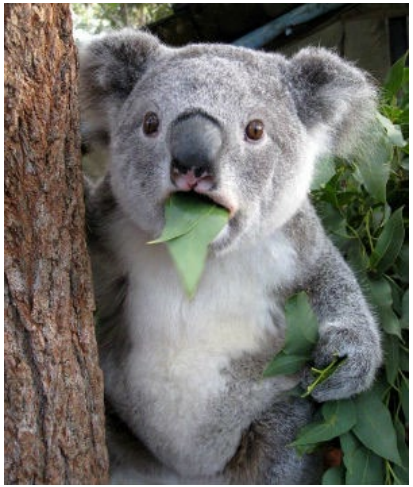
By CHARLES DARWIN, M.A., F.R.S., &c.

IN TWO VOLUMES.—Vol. I.

WITH ILLUSTRATIONS.

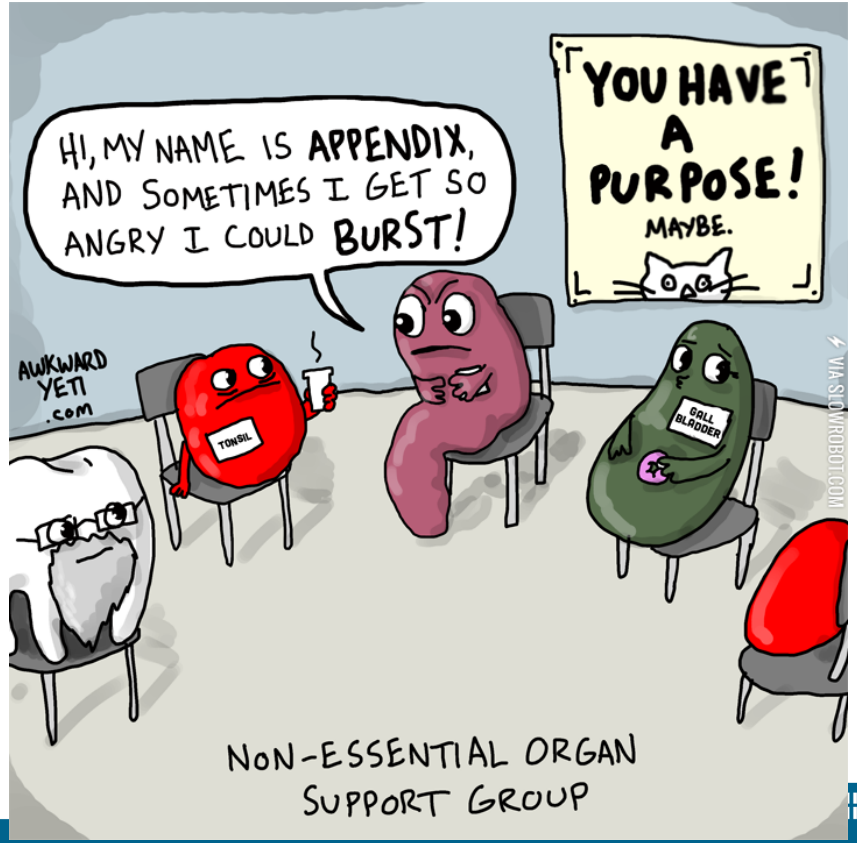
LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1871.

[The right of Translation is reserved.]



‘vestigial organs’ = evidence for evolution

The role of the appendix in humans?



Appendicectomy and the development of UC

Appendectomy Protects against Ulcerative Colitis

Appendicectomy as a child results in

⇩⇩ lifetime risk of *developing* UC in the future

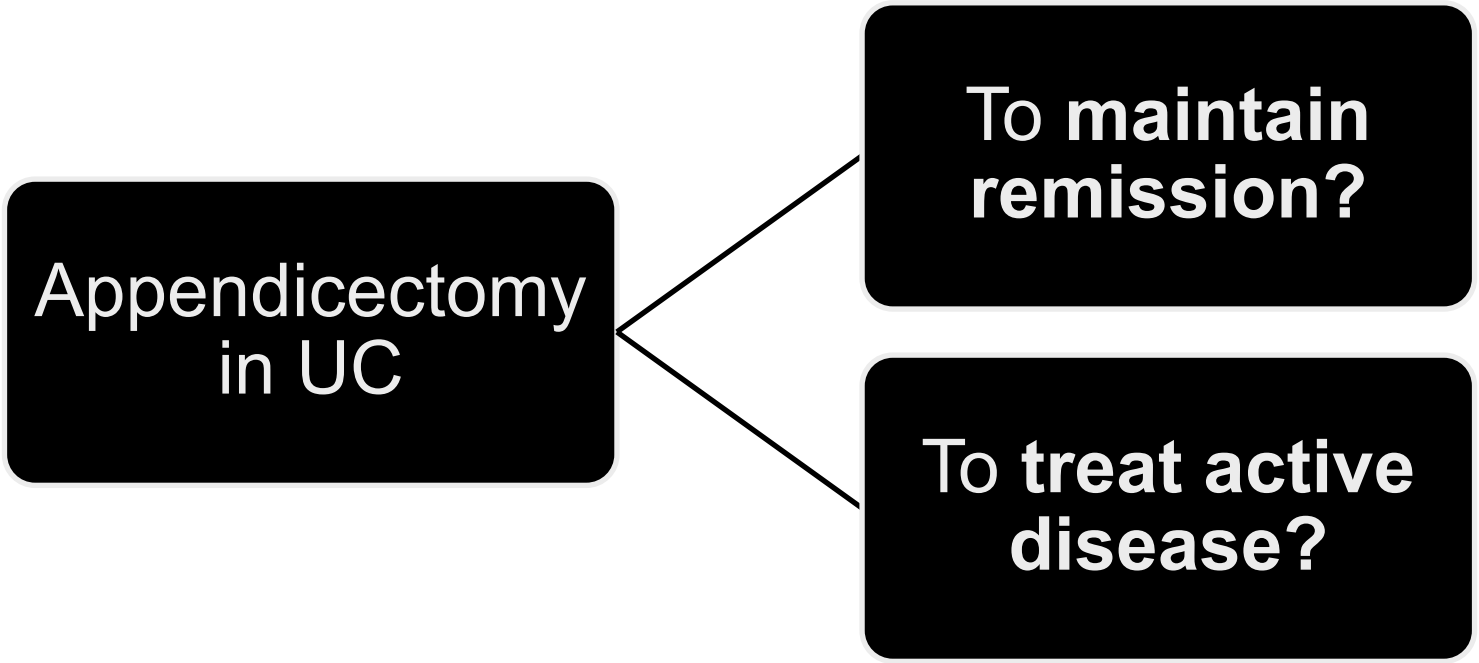
Case reports – emergency appendicectomy for **appendicitis** in UC patients

- Lifetime population risk of developing appendicitis is around 9%

- Patients with UC developed appendicitis, had appendicectomy and **noticed symptoms of UC seemed to improve**

Deliberate **therapeutic** appendicectomy in UC pts

Author	Year	n =	Inclusion	Findings/success rate
Bolin	2009	30	**Active ulcerative proctitis with unremitting symptoms despite medical therapy**	Improvement in CAI in 27 of 30 (90%). 12 of 30 (40%) had full resolution of symptoms and came off medication
Radford-Smith	2003	15	**Refractory UC**	“Significant improvements in CAI (P=0.015), endoscopic activity (P=0.02) and need for medication (P=0.02) at 12mths”
Okazaki	2000	1	**Distal active UC**	Asymptomatic at 3yrs (100%)
Kim	2006	1	**Severe pancolitis**	No relapse at 1yr; came off medication (100%)
Jarnerot	2001	6	**UC refractory to standard treatment in whom proctocolectomy was being considered.**	Unclear. Not reported - most patients (5 of 6) got better; but they could find other possible ‘reasons’ for this improvement (eg restarting smoking, change of maintenance medication)
Bageacu	2011	8	**Refractory ulcerative proctitis**	All patients had mucosal healing. 4 patients (50%) experienced only one flare-up post-appendectomy then nil further.


Appendicectomy in UC
To **maintain remission?**
To **treat active disease?**

Aim

To evaluate the efficacy of appendicectomy in maintaining remission in UC patients

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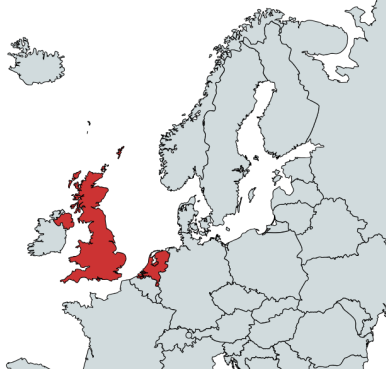
Methods



Trial design
Multicenter, randomized controlled superiority trial (1:1)
Stratification by disease extent

Study population
UC patients **in complete remission** (clinically and endoscopically) after being medically treated for disease relapse within the past 12 months

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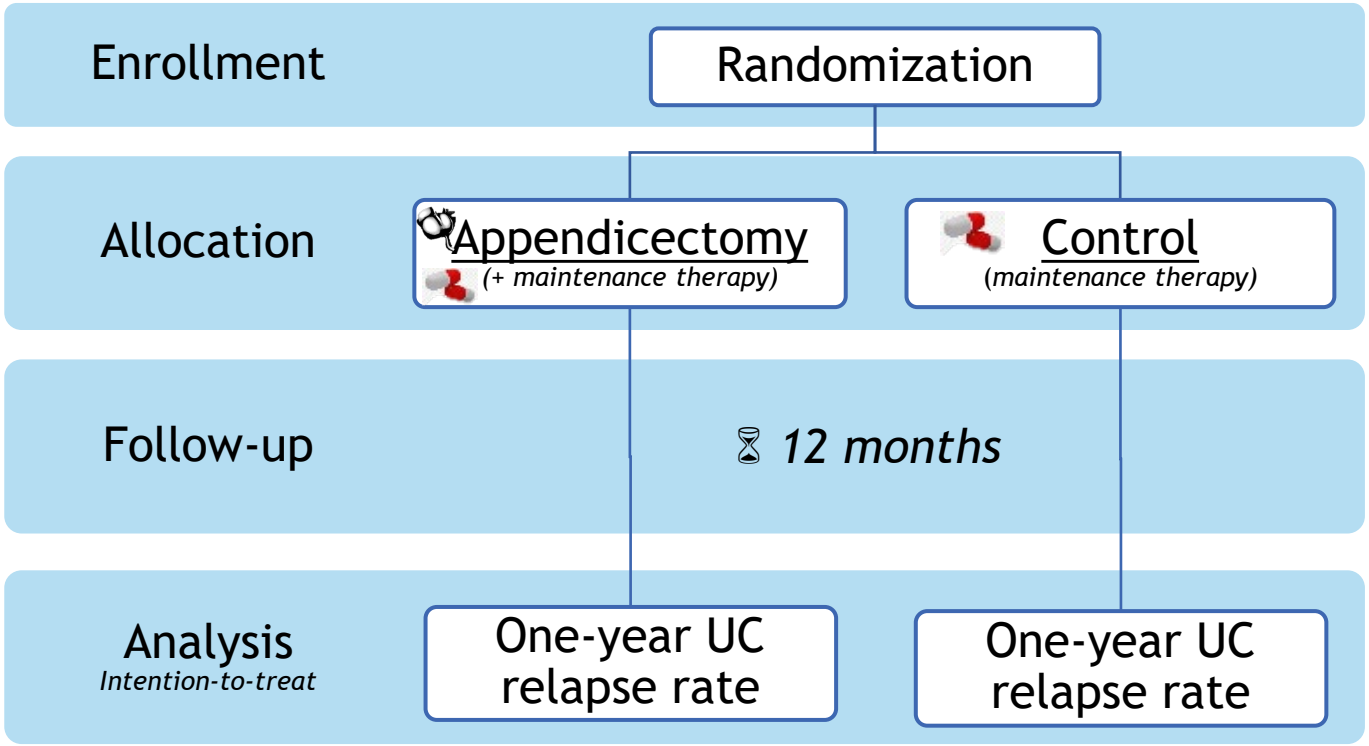
IBD Center Amsterdam

Methods


Enrollment
Randomization
Allocation
Appendicectomy
(+ maintenance therapy)
Control
(maintenance therapy)
Follow-up
12 months
Analysis
Intention-to-treat
One-year UC relapse rate
One-year UC relapse rate

Methods

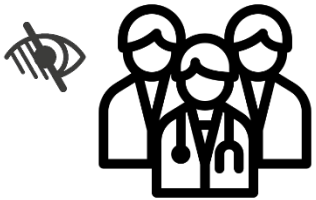
Primary outcome
One-year UC relapse rate

- Total Mayo-score ≥5 with endoscopic subscore of 2 or 3
- Clinical *(exacerbation of symptoms + rectal bleeding / FCP>150 / intensified therapy)*

TOILET

ENDOSCOPY

CLINICAL SUSPECTED RELAPSE



CRITICAL EVENT COMMITTEE

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Methods

Secondary outcomes

- Number of relapses per patient
- Time to first relapse
- Disease activity
- Number of colectomies
- Medication usage
- Health-related quality of life

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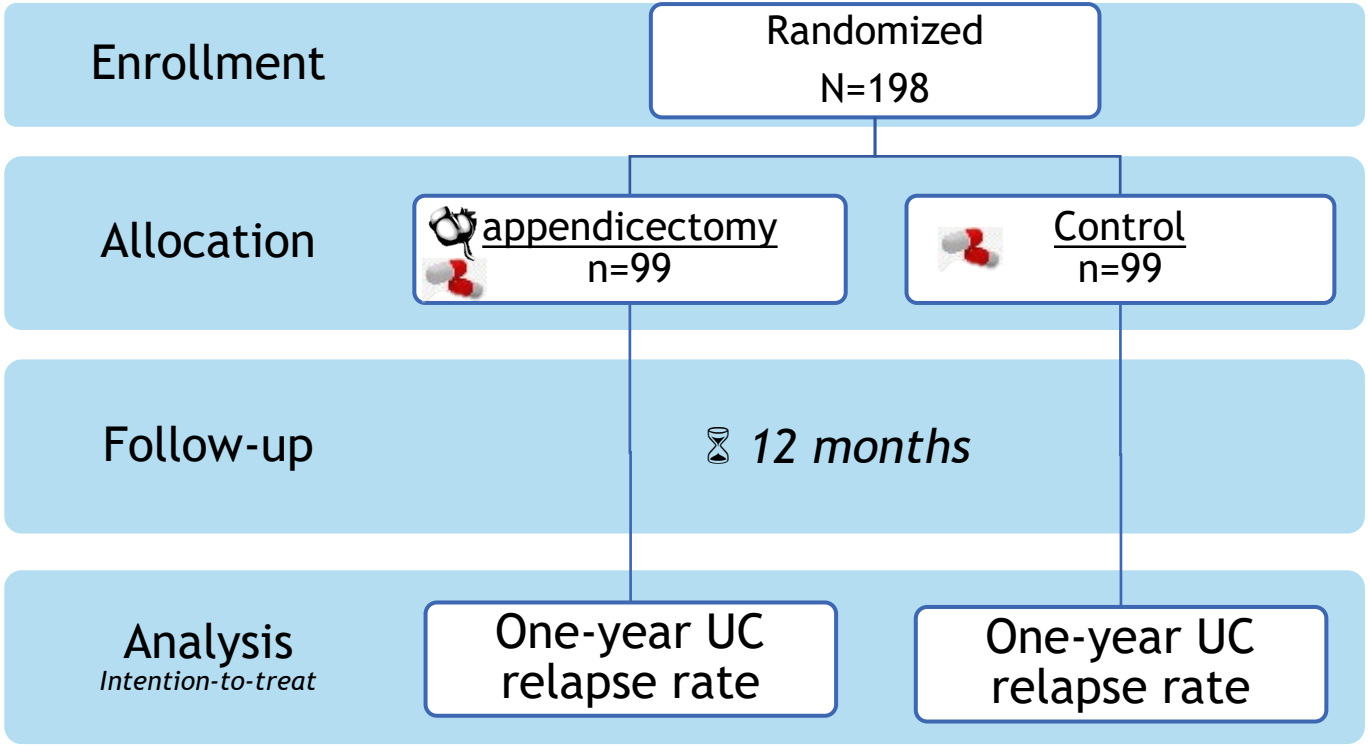
Results



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Results

Start 2012 (n=168)

Start 2019 (n=30)

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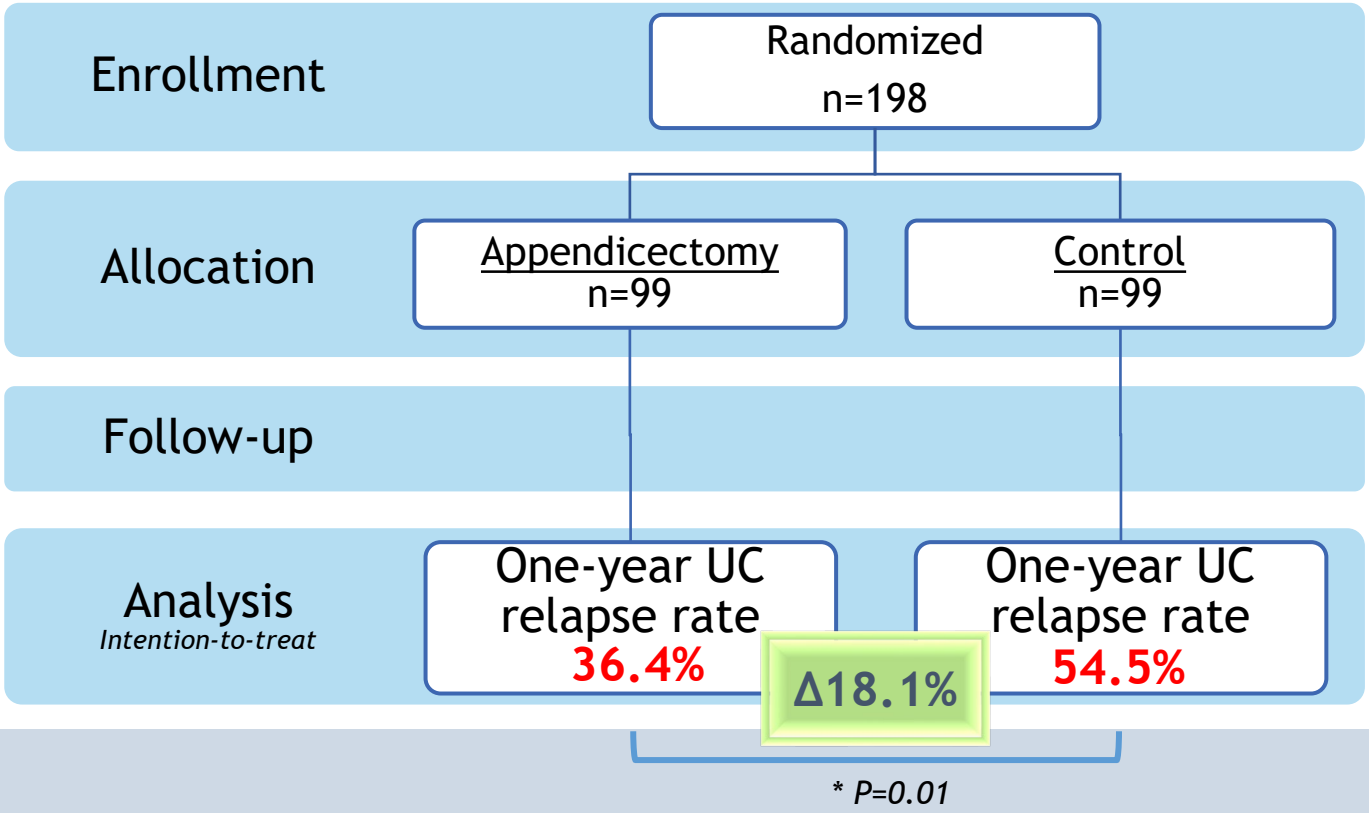
Table 1. Baseline characteristics of the patients included in the trial (n=198)

	Appendicectomy (n=99)	Control (n=99)
Median age (IQR) – years	41 (32-49)	41 (34-45)
Female sex	57.6%	57.6%
Median disease duration (IQR) – years	5 (2-12)	5 (2-11)
Former smoker	38.4%	47.5%
PSC	1.4%	-
Family history of IBD	25.5%	31.3%
Medication at inclusion		
5-ASA	74.7%	81.6%
Immunomodulators	6.1%	12.2%
Extent of disease		
Proctitis	38.4%	39.4%
Left-sided colitis	34.3%	36.4%
Pancolitis	27.3%	24.2%
Median time from start most recent exacerbation to randomization (IQR) – weeks	26 (17-42)	28 (16-44)

Abbreviations: IQR: interquartile range; PSC: primary sclerosing cholangitis; IBD: inflammatory bowel disease; 5-ASA: 5-aminosalicylic acid.

Results


Enrollment
Randomized
n=198
Allocation
Appendicectomy
n=99
Control
n=99
Follow-up
Analysis
Intention-to-treat
One-year UC relapse rate
36.4%
Δ18.1%
One-year UC relapse rate
54.5%
* P=0.01

Results

Secondary outcomes

- Number of relapses per patient
  - Appendicectomy: n=1 (80.6%) n=2 (19.4%) *p=0.207*
  - Control: n=1 (69.8%) n=2 (22.6%) n=3 (7.5%)
- Time to first relapse
  - Appendicectomy: 26 (IQR 11—49) weeks *p=0.189*
  - Control: 16 (IQR 6-35) weeks
- Number of colectomies
  - One-year: none
  - 5-year: appendicectomy: none, control: n=3 (therapy-refractory UC)

Medication usage

Table 4. Preliminary mediation usage

	Baseline		12 months	
	A N=99	C N=99	A N=93	C N=93
No medication	12.1%	4.1%	22.6%	7.7%
5-ASA	74.7%	81.6%	61.3%	38.7%
Systemic steroids	1.0%	1.0%	2.2%	5.5%
Immunomodulators	6.1%	12.2%	6.5%	13.2%
Biologicals	-	-	3.2%	5.5%

Abbreviations: A: appendicectomy; C: control; 5-ASA: 5-aminosalicylic acid

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Safety

Appendicectomy (n=99)

3 SAEs
- 2 Surgical reintervention
- 1 Hospitalization (Clostridium)

Control (n=99)

1 SAE (acute appendicitis)

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Colectomy during long-term follow-up

No colectomies in appendicectomy group

3 colectomies in the control group (3.6%) for therapy refractory UC

Conclusion

Appendicectomy in UC patients showed a significant **reduction (Δ18.1%)** in the one-year relapse rate.

Patients in the appendicectomy group also had **significantly less medication use** after one year.

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Appendectomy to treat active UC

Refractory ulcerative proctitis (n=30)

- 90% improvement in clinical colitis activity index
- 40% complete remission

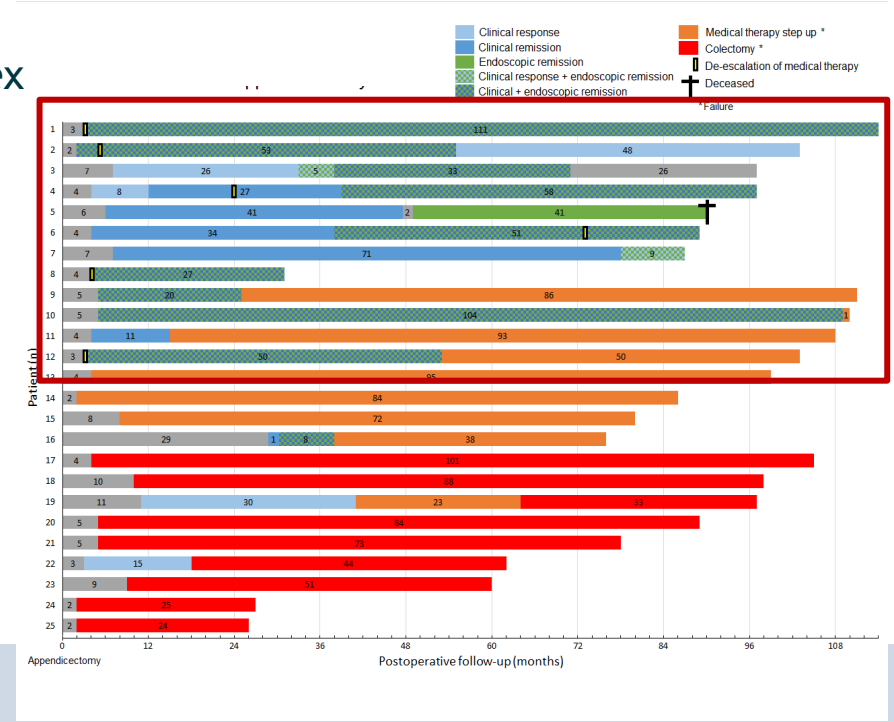
PASSION study (refractory UC, n=30, FU 7y)

- Endoscopic remission: 48%

  median duration: 42 months

- Clinical remission: 60%

  median duration: 80 months



Bolin. Am J Gastroenterol 2015, Stellingwerf. Br J Surg 2019

Should people with UC be having their appendix removed now…?

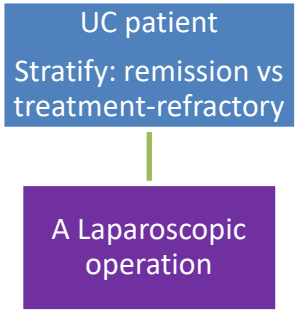
What about the placebo effect?

Sham/placebo appendicectomy…?

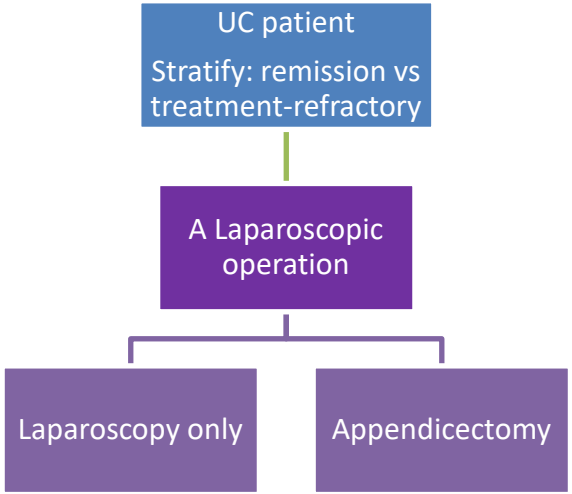
- Overcome selective reporting; subjectivity
- Undertake standard 3-port laparoscopy but randomise some patients to miss out the *critical surgical element* (appendicectomy)

UC patient

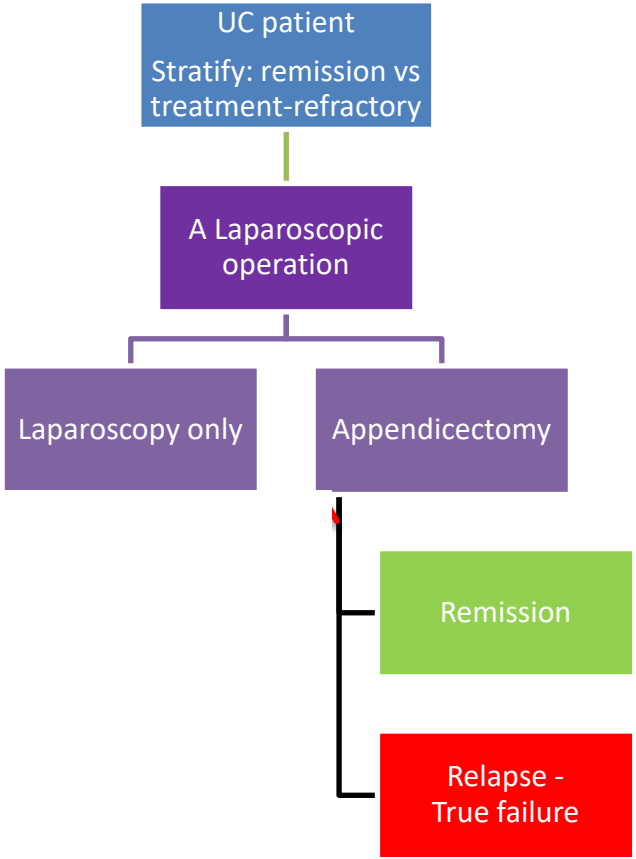
Stratify: remission vs treatment-refractory


UC patient
Stratify: remission vs treatment-refractory
A Laparoscopic operation

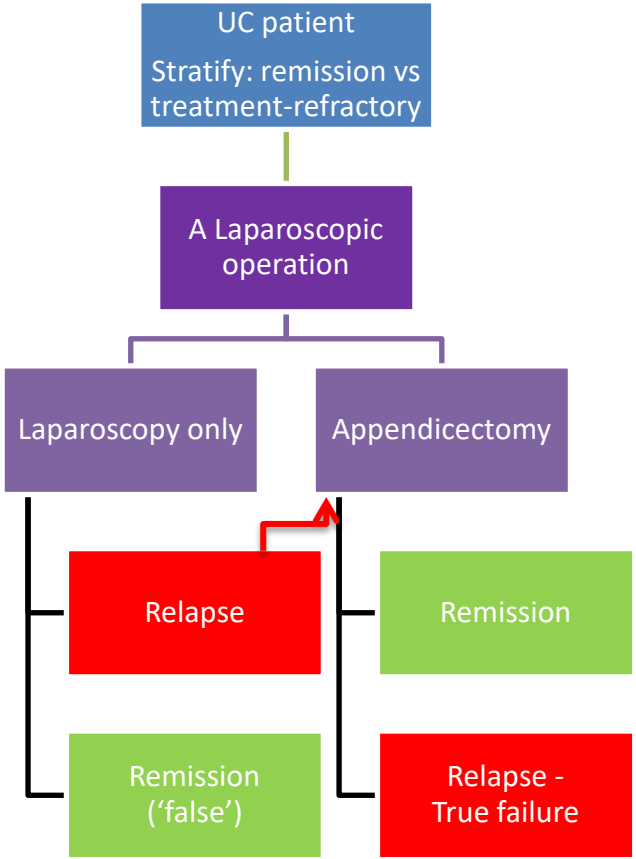
Randomisation (in theatre)



Randomisation
(in theatre)



Randomisation
(in theatre)



Considerations and methods for pla trials (ASPIRE guidelines)

David J Beard, Marion K Campbell, Jane M Blazeby, Andrew J Carr, Charles Weijer, Brian
Felicity L Bishop, Jonathan Pugh, Sian Cousins, Ian A Harris, L Stefan Lohmander, Nata
Andrew Cook, Dair Farrar-Hockley, Julian Savulescu, Richard Huxtable, Amar Rangan,
Jon Nicholl, Barnaby C Reeves, Freddie Hamdy, Samuel CS Rowley, Jonathan A Cook

Lancet 2020; 395: 828–38

Placebo comparisons are increasingly being considered for rando

Panel 2: Stages of the Deconstruct, Identify, Take out, Think risk, Optimise framework (known as DITTO)

Stage one: Deconstruct
Deconstruct the treatment intervention, including the co-interventions. The updated typology is used to deconstruct the treatment intervention, resulting in a comprehensive list of treatment components and steps, including co-interventions.

Stage two: Identify
Identify the essential surgical element, which could be one or more components or steps in the surgical intervention, and identify which treatment components and steps are included or not in the placebo intervention.

Stage three: Take out
Omit the essential surgical element from the proposed placebo intervention.

Stage four: Think risk
Consider the potential risk to patients, feasibility, and the role of the placebo intervention within the randomised controlled trial (eg, as a control intervention to elucidate treatment mechanism). This stage might result in further components or steps being omitted from the placebo intervention.

Stage five: Optimise
Optimise the placebo throughout the design process (eg, sensory masking).

The NEW ENGLAND JOURNAL of MEDICINE

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ORIGINAL ARTICLE

A Controlled Trial of Arthroscopic Surgery for Osteoarthritis of the Knee

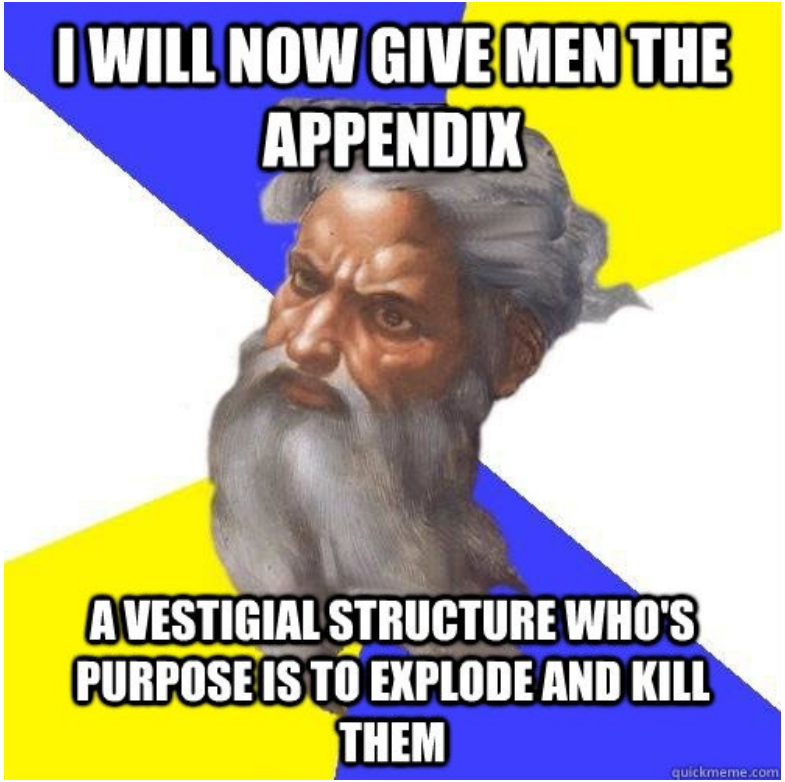
J. Bruce Moseley, M.D., Kimberly O'Malley, Ph.D., Nancy J. Petersen, Ph.D., Terri J. Menke, Ph.D., Baruch A. Brody, Ph.D., David H. Kuykendall, Ph.D., John C. Hollingsworth, Dr.P.H., Carol M. Ashton, M.D., M.P.H., and Nelda P. Wray, M.D., M.P.H.

N Engl J Med 2002; 347:81-88 | July 11, 2002 | DOI: 10.1056/NEJMoa013259

LUNA Trial

CSAW
CAN SHOULDER ARTHROSCOPY WORK?

Conclusions



Conclusions

- The appendix and UC are linked
- Appendicectomy is effective as a treatment in **both:**
  - UC in remission to reduce relapses
  - Active/treatment-refractory UC to prevent colectomy
- Do we now need a placebo-controlled trial?

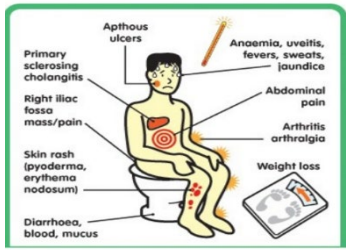
OCEAN

The role of pre-operative Exclusive Enteral Nutrition (EEN) in Crohn's Disease

Exclusive Enteral Nutrition (EEN):

EEN is an extremely effective treatment (in children)

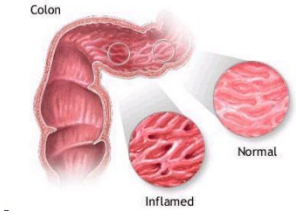
Makes people feel better (>80%)



Works at least as well as oral steroids

Improves blood disease markers

Induces mucosal healing better than steroids



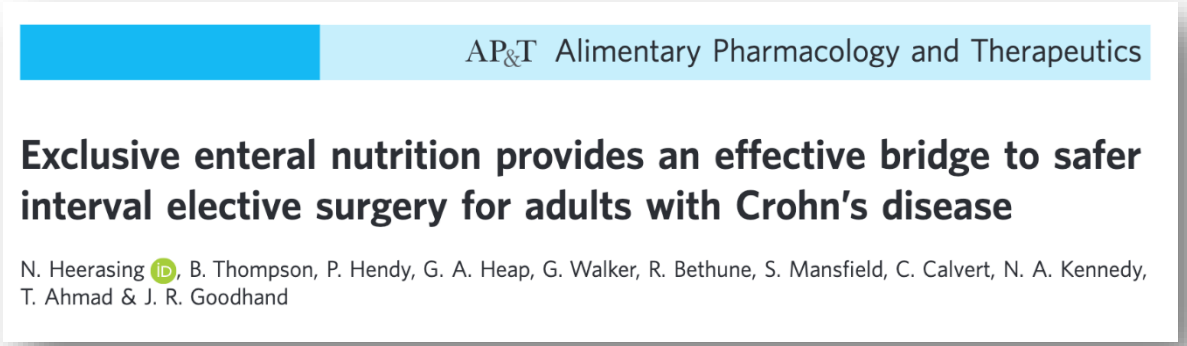
Replenish nutritional deficits and build muscles

Gerasimidis et at, IBD 2013; Gerasimidis et al, JCG 2011; Cameron et al, APT 2013; Buchanan et al, APT 2009; Gerasimidis et at, IBD 2012; Duncan et al BMC Gastro, 2014; Logan et al APT 2019; Borrelli et al Clin Gastro 2006

Evidence supporting pre-op EEN in adults

- Multiple small studies; mostly single centre & retrospective

- EEN appears to..
  - Improve **BMI**
  - Improve **albumin** levels, **haemoglobin** levels, reduce **CRP**
  - Allow **time to get off steroids**
  - Allow time to **stop smoking**
  - Reduce **complication** rates
  - Reduce **stoma** rates



AP&T Alimentary Pharmacology and Therapeutics

Exclusive enteral nutrition provides an effective bridge to safer interval elective surgery for adults with Crohn's disease

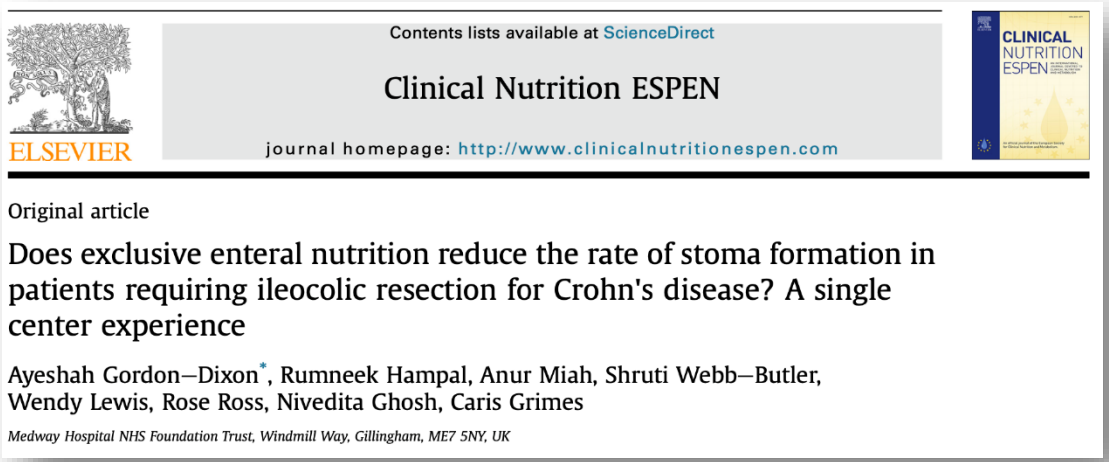
N. Heerasing, B. Thompson, P. Hendy, G. A. Heap, G. Walker, R. Bethune, S. Mansfield, C. Calvert, N. A. Kennedy, T. Ahmad & J. R. Goodhand

EXETER, UK

- 51 pts
- Reduction in CRP at surgery
- Op durations shorter
- Complications much lower
- 13 (25%) avoided surgery completely

MEDWAY, UK

- 24 pts
- Reduction in CRP at surgery
- Increase in albumin at surgery
- Only 3 needed a stoma
- Low complication rates



Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

ELSEVIER

CLINICAL NUTRITION ESPEN

Original article

Does exclusive enteral nutrition reduce the rate of stoma formation in patients requiring ileocolic resection for Crohn's disease? A single center experience

Ayeshah Gordon–Dixon*, Rumneek Hampal, Anur Miah, Shruti Webb–Butler, Wendy Lewis, Rose Ross, Nivedita Ghosh, Caris Grimes

Medway Hospital NHS Foundation Trust, Windmill Way, Gillingham, ME7 5NY, UK

NIHR | National Institute for Health and Care Research

Health and Care Professionals | Researchers | Patients and the Public

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HTA commissioned call

20/133 Pre-operative exclusive enteral nutrition for Crohn's disease

OCEAN TRIAL

FUNDED BY
NIHR | National Institute for Health and Care Research

- Elective Crohn's surgery (small bowel +/- colonic)
- Re-do surgery included; stricturoplasty included
- Randomised to 6 weeks of pre-operative Exclusive Enteral Nutrition (EEN) vs standard care
- 40 units; n = 618 patients
- Will interlink with Crohn's *surgical technique* RCT
- Co-leads: Gastroenterology and Surgery
- Birmingham Clinical Trials Unit

EEnKAT

BIRMINGHAM SURGICAL TRIALS CONSORTIUM BiSTC

Optimisation before Crohn's surgery using Exclusive enteral Nutrition (OCEaN) Trial Schema and Flowchart

FUNDED BY
NIHR | National Institute for Health and Care Research

Population

Adult patients having elective surgery for luminal small bowel and/or colonic Crohn's Disease (CD) – including primary or re-do surgery - identified as potentially eligible for trial during acute hospital admission, MDT discussion or outpatient clinic.

Eligibility

Eligibility criteria:

- Proven Crohn's disease requiring resectional surgery or stricturoplasty
- Willingness to go on EEN for the duration of the intervention period
- >18 years of age and able and willing to give informed consent

st 8 months.
tervention as well as in-depth
ds for patients in both arms.

Dual Primary outcomes at 6 weeks post operation:

Patient reported Crohn's Life Impact Questionnaire (CLIQ) - assessing the impact of Crohn's disease on the patient

Comprehensive Complication Index (CCI) - a measure of post-operative complications

Randomisation

Baseline parameters measured and recorded
n = 618 patients randomised

RANDOMISATION
(1:1)

Treatment Allocation

INTERVENTION ARM **n = 309 pts**
EEN for 6 weeks pre-op

CONTROL ARM **n = 309 pts**

SURGERY

SURGERY

Follow-up

Follow-up at 6 weeks, 6 and 12 months post-surgery at surgical, IBD or research clinic.
Surveillance colonoscopy 6 - 12 months post-operatively.

Internal pilot with embedded qualitative
In-depth qualitative data concerning the acceptability of EEN
understanding of the comparative experience of pre- and

Will also assess:

- QoR score
- EEN Compliance
- Cost Effectiveness
- Proportion avoiding surgery
- Disease recurrence rates

Advanced Coloproctology Course

- First sites opened last week
- First patient recruited (at Russells Hall Hospital) on Tuesday
- *If you or someone you know is undergoing an operation for Crohn's you should ask about it*

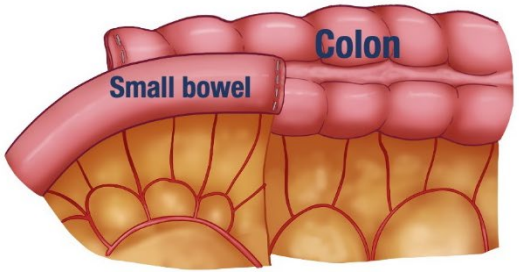
MEErKAT
MEsenteric Excision and Kono-S Anastomosis Trial

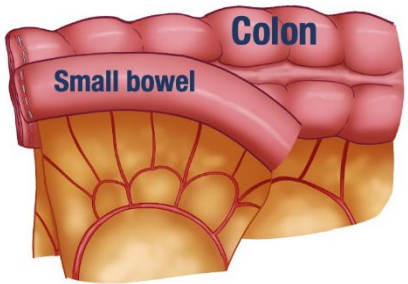
Steve Brown & Laura Hancock

Sheffield CTU

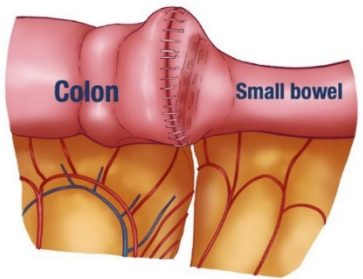
Background - Kono-S

- It is an alternative method of joining the small bowel and colon
- This results in the join being positioned away from the mesentery
- Limited evidence suggests this reduces recurrence





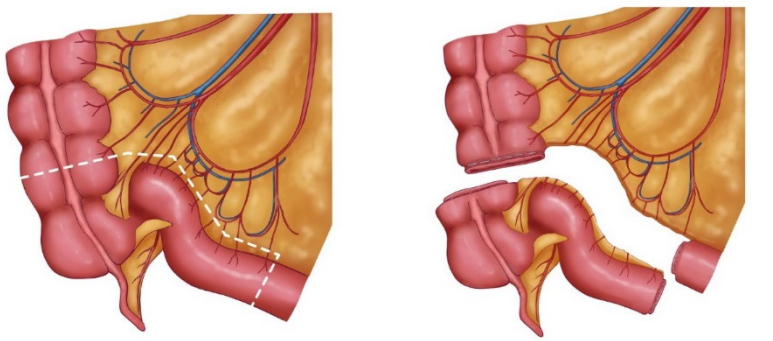
Examples of standard bowel joins after ileocecal resection



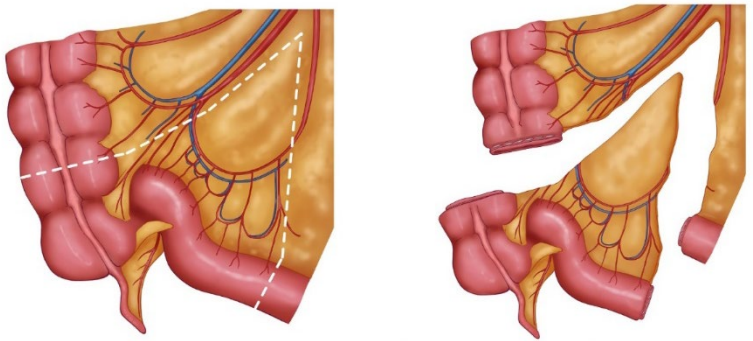
Bowel join after Kono-S resection

Background – Mesenteric excision

- Some clinicians believe that removing more of the mesentery results in a lower recurrence of disease
- So far evidence of this is lacking

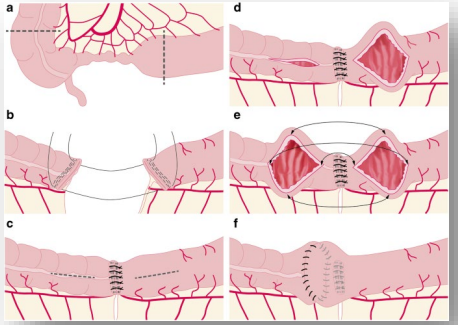


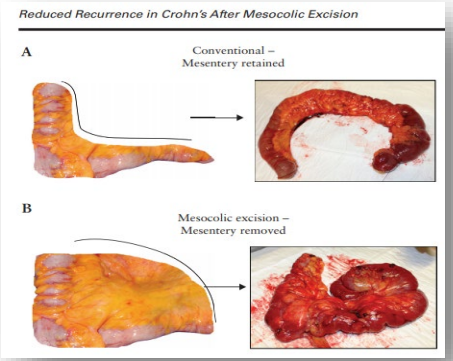
Close mesenteric excision



Extended (Radical) mesenteric excision

MEErKAT
MEsenteric Excision and Kono-S Anastomosis Trial





- Crohn's ileocaecal resections
- 2x2 design: Kono-S & wide mesenteric resection

Mesentery: Normal **Anastomosis: Close**	**Mesentery: Normal** **Anastomosis: RADICAL**
Mesentery: KONO-S **Anastomosis: Close**	**Mesentery: KONO-S** **Anastomosis: RADICAL**

- Open now across UK – 127 pts recruited

Patient Reported Outcomes

‘A PRO is any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else.’

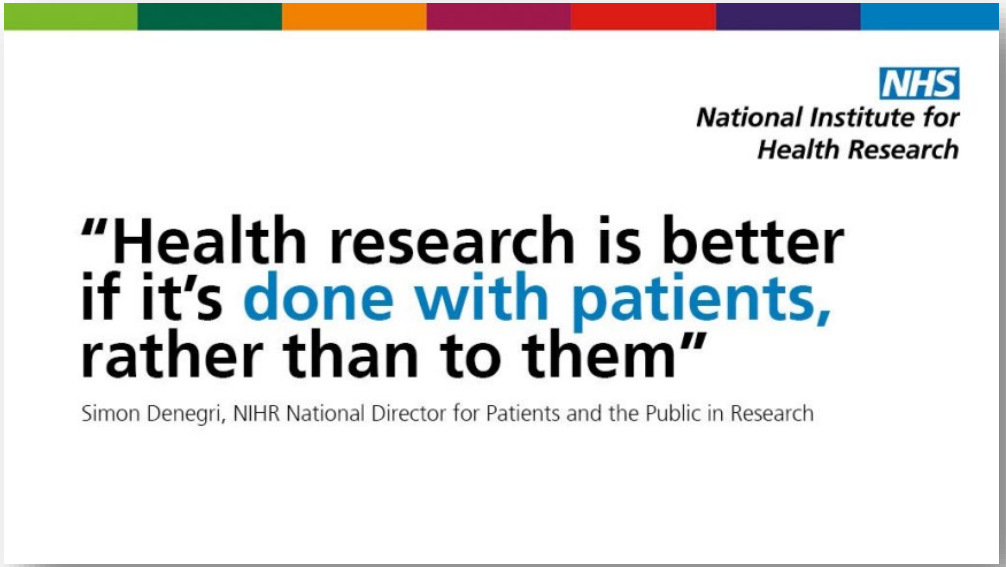
FDA guidance: Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009

Why assess PROMs in a trial?

- Inform future patient choice and consent
- Particularly when
  - minimal differences in survival
  - treatments have different side effects
- Feed into health economic evaluation and health policy

Is it harder to use PROMS in surgical trials?

- Perhaps PROMs are <u>easier</u> in surgery (compared to other settings)
  - Surgery is a discrete event
  - Several specific post-operative outcomes that can **only** be reported by patients:
    - Pain
    - Quality of recovery
    - Return to normal function
    - Satisfaction / *did it actually work ?*
  - Remember, surgery is a complex intervention


NHS
National Institute for
Health Research
"Health research is better if it's done with patients, rather than to them"
Simon Denegri, NIHR National Director for Patients and the Public in Research

Patient Reported Outcomes after Parastomal HErnia tReatment

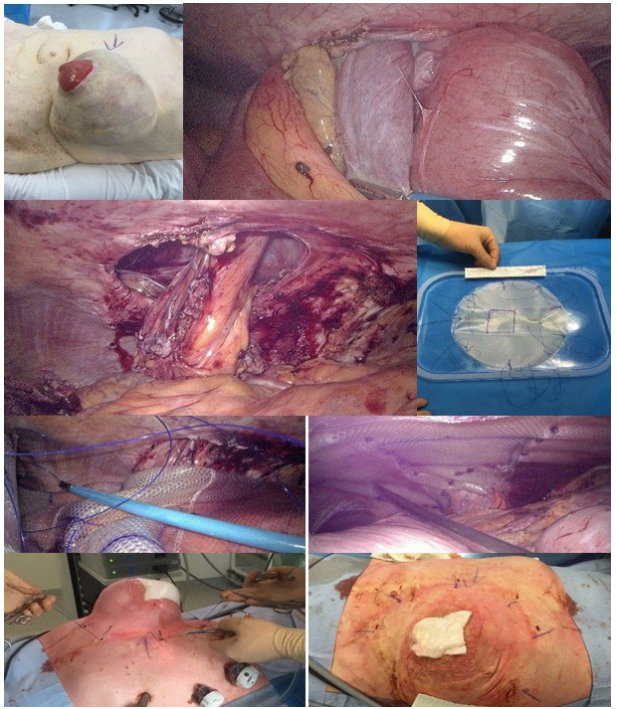
Professor Thomas Pinkney, *University of Birmingham*
&
Miss Sue Blackwell, *Patient co-chief Investigator*

@PropherStudy

TRIPARTITE COLORECTAL MEETING 2020

Management of parastomal hernia

VS



EHS Guidelines on Prevention and Treatment of Parastomal Hernia 2017

What we know

Watchful waiting - commonest strategy

- Risk vs benefit unknown
- Increase in size over time?
- More complex surgery if left?
- When to operate?

Surgical Repair

- That we don't know the best way to repair a parastomal hernia!

Statement: *There is no evidence on the comparative outcome of the benefit of watchful waiting versus surgery for patients with a parastomal hernia.*
Recommendation: *No recommendation can be made on the policy of watchful waiting for patients with a non-incarcerated parastomal hernia.*
Quality of evidence: ☒☐☐☐
Strength of recommendation: *No*

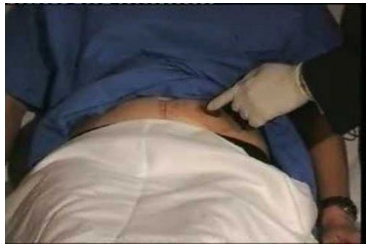
Statements: *There is insufficient evidence on the risk of recurrence following laparoscopic versus open parastomal hernia repair with a mesh.*
There is insufficient evidence on the morbidity following laparoscopic versus open parastomal hernia repair with a mesh.
Recommendation: *No recommendation can be made in favor of laparoscopic or open parastomal hernia repair with a mesh in elective surgery.*
Quality of evidence: ☒☐☐☐
Strength of recommendation: *No*

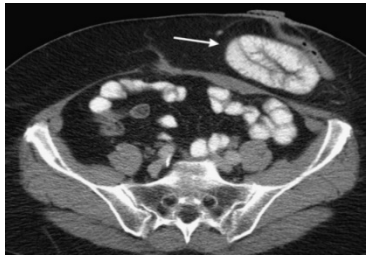
Statements: *There is insufficient evidence on the most effective mesh for parastomal hernia repair with regard to recurrence or morbidity.*
There is no evidence supporting superiority of biological over synthetic meshes with regard to recurrence or morbidity.
Recommendation: *No recommendation can be made on the use of specific mesh material for parastomal hernia repair.*
Quality of evidence: ☒☐☐☐
Strength of recommendation: *No*

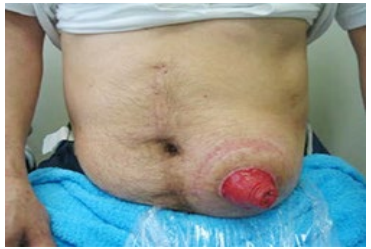
Assessing outcomes of PSH treatment

Outcome reporting – who to believe?

- Surgeon's assessment of stoma site?
- Radiological investigation?
- Patient-reported?







- Largest study of parastomal hernia management
- First time patient reported outcomes have been a primary outcome measure in parastomal hernia research
- Largest prospective evaluation of Quality of Life and parastomal hernia repair
- Use of novel technology to report PROMS

Who

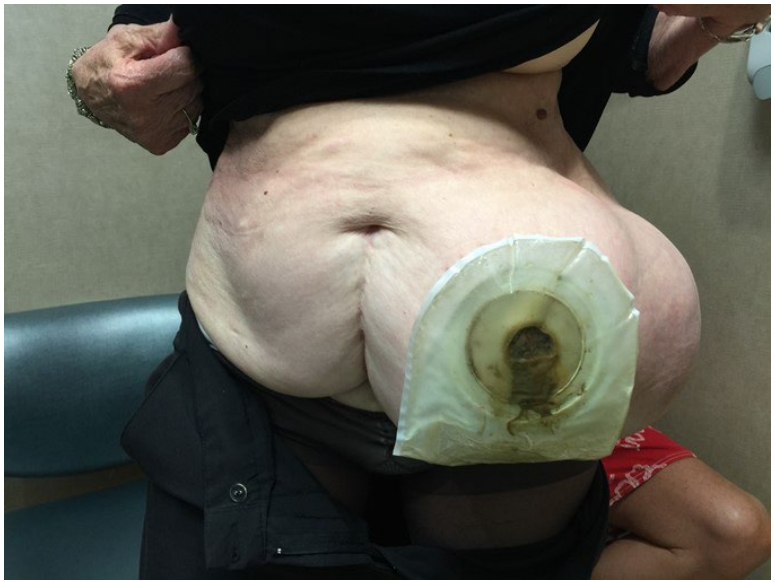
Any patient with PSH having active management

- Stoma Care Nurse or Surgeon recruitment
- > 18 years
- Bowel stoma

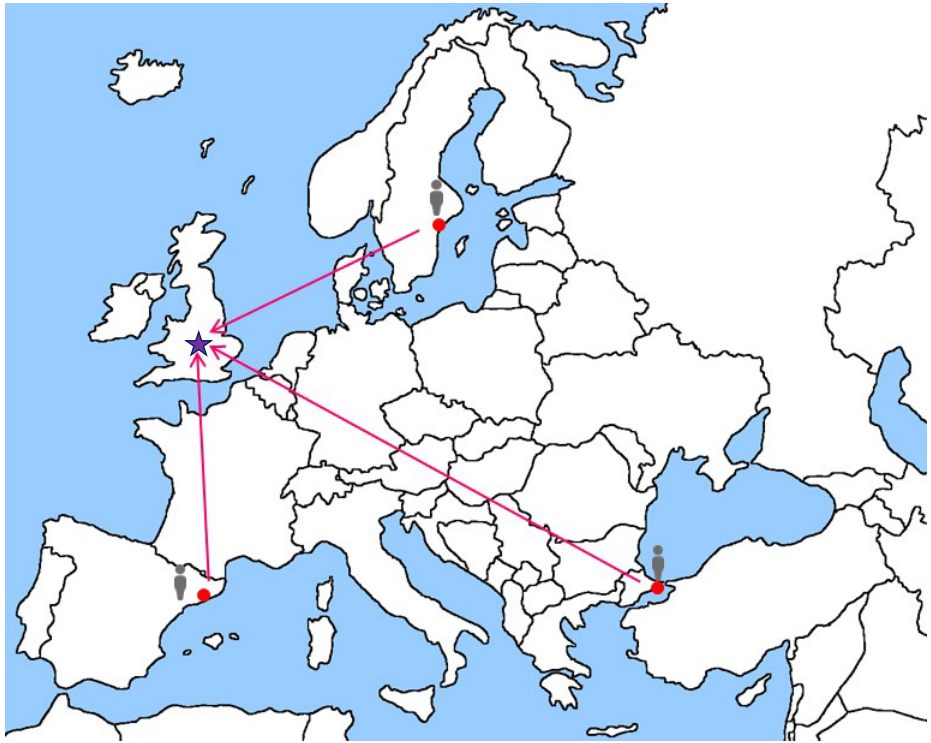
Watchful waiting

or

Operative intervention



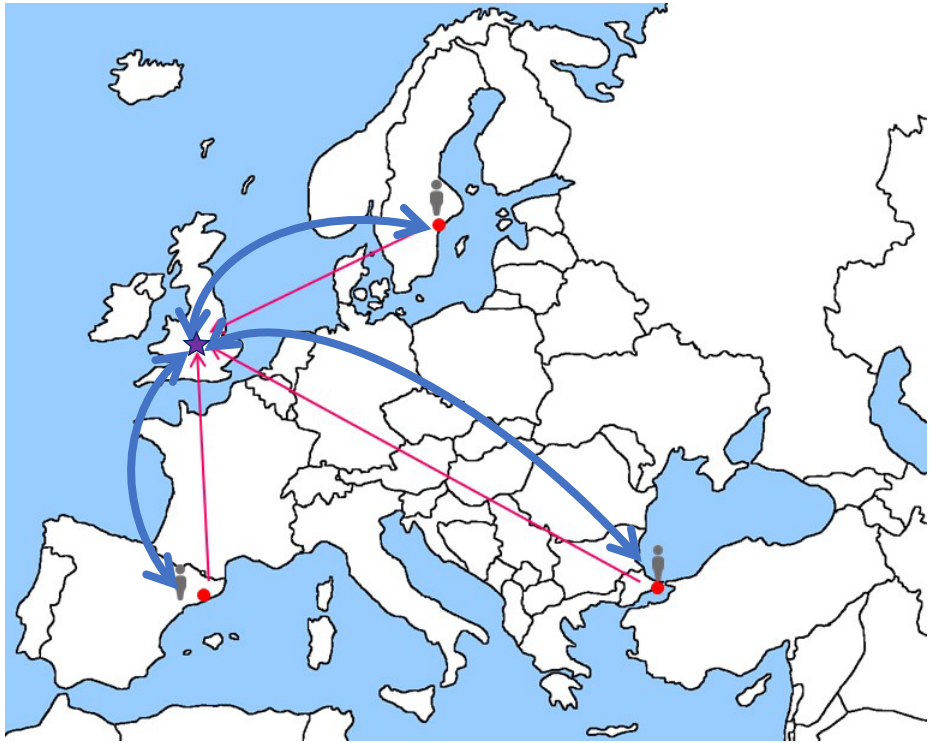
How



CLINICIAN: Patient demographics; operation technique and short-term (30 day) outcomes

REDCap
Research Electronic Data Capture

How



CLINICIAN: Patient demographics; operation technique and short-term (30 day) outcomes

REDCap
Research Electronic Data Capture

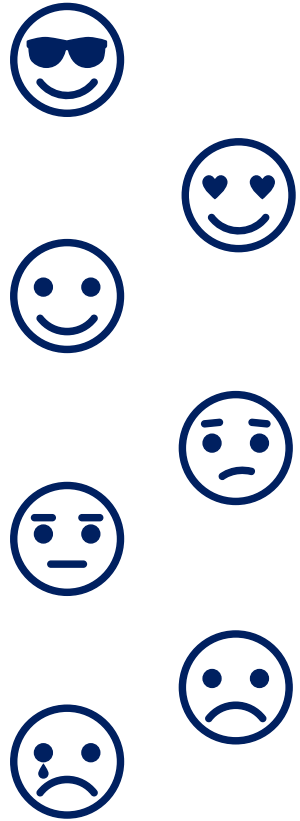
PATIENT: Long term outcomes, satisfaction, QOL up to 12 months

REDCap
Research Electronic Data Capture


PROPHER
PROPHER
Hi Sue
It's time to complete
your twelve month
follow up questionaires
for the PROPHER study

Patient reported outcomes

- HR QOL
- Stoma Impact Score
- Measure Yourself Medical Outcomes Profile (MYMOP)
- Decisional Regret



*** MYMOP2 ***

Full name ..... Date of birth .....

Address and postcode.....

.....

Today' s date ..... Practitioner seen .....

Choose one or two symptoms (physical or mental) which bother you the most. Write them on the lines.
Now consider how bad each symptom is, over the last week, and score it by circling your chosen number.

SYMPTOM 1:	0	1	2	3	4	5	6
.....	As good as it could be						As bad as it could be
SYMPTOM 2:	0	1	2	3	4	5	6
.....	As good as it could be						As bad as it could be

Now choose one activity (physical, social or mental) that is important to you, and that your problem makes difficult or prevents you doing. Score how bad it has been in the last week.

ACTIVITY:	0	1	2	3	4	5	6
.....	As good as it could be						As bad as it could be

Lastly how would you rate your general feeling of wellbeing during the last week?

0	1	2	3	4	5	6
As good as it could be						As bad as it could be

How long have you had Symptom 1, either all the time or on and off? Please circle:

0 - 4 weeks 4 - 12 weeks 3 months - 1 year 1 - 5 years over 5 years

Are you taking any medication FOR THIS PROBLEM ? Please circle: YES/NO

IF YES:

1. Please write in name of medication, and how much a day/week

.....

2. Is cutting down this medication: Please circle:

Not important a bit important very important not applicable

IF NO:

Is avoiding medication for this problem:

Not important a bit important very important not applicable

Decision Regret Scale

Please think about the decision you made about _____ after talking to your [doctor, surgeon, nurse, health professional, etc.]. Please show how you feel about these statements by circling a number from 1 (strongly agree) to 5 (strongly disagree).

1. It was the right decision	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree
2. I regret the choice that was made	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree
3. I would go for the same choice if I had to do it over again	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree
4. The choice did me a lot of harm	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree
5. The decision was a wise one	1 Strongly Agree	2 Agree	3 Neither Agree Nor Disagree	4 Disagree	5 Strongly Disagree

	Site	Date opened	Screened	Eligible	Consented
1	**QE Birmingham**	21-Aug-23	43	42	**31**
2	Royal Devon & Exeter	18-Sep-23	42	41	**20**
3	**Warwick Hospital**	18-Oct-23	6	6	**1**
4	Royal Victoria Infirmary	02-Nov-23	46	26	**13**
5	Bedford Hospital	20-Nov-23	10	8	**8**
6	Broomfield Hospital	27-Nov-23	2	2	**1**
7	Northern General Hospital	28-Nov-23	5	5	**1**
8	Salisbury District Hospital	29-Nov-23	8	5	**3**
9	Darent Valley Hospital	22-Jan-24	11	11	**5**
10	Leicester Royal Infirmary	30-Jan-24			
11	Royal Cornwall Hospital	06-Feb-24	7	7	**2**
12	Scarborough General Hospital	19-Feb-24			
13	York Teaching Hospital	19-Feb-24	3	3	**2**
14	Wycombe General & Stoke Mandeville Hospitals	19-Mar-24	2	2	**1**
15	**Russells Hall Hospital**	17-Apr-24			
16	Maidstone Hospital	25-Apr-24			
17	Salford Royal Hospital	30-Apr-24			
		Total	185	158	**88**

@PropherStudy

UNIVERSITY OF BIRMINGHAM

WM RESEARCH COLLABORATIVE

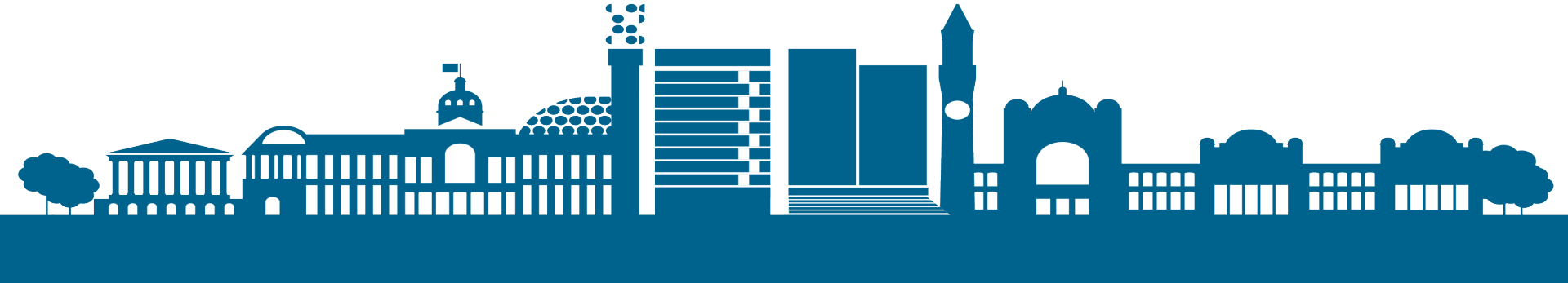
MRC Clinical Trials Unit

BIRMINGHAM SURGICAL TRIALS CONSORTIUM BiSTC

NIHR | National Institute for Health Research

ROSSINI 2

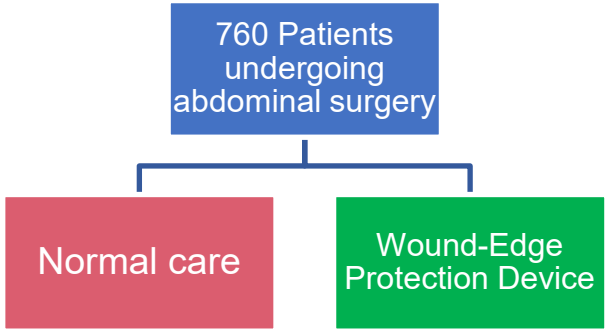
A multi-arm, multistage RCT of intra-operative interventions to reduce surgical site infection

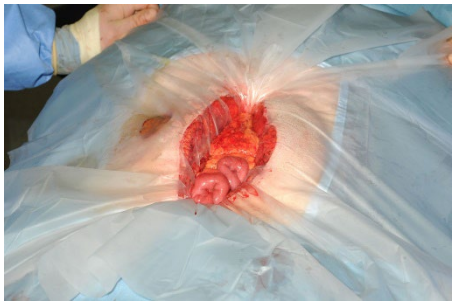


Surgical site infection (SSI) – Background

- SSI:
  - Commonest post-operative complication
  - up to 25% (30%) of abdominal operations
- Significant ↑ morbidity, ↑ Mortality, ↑ costs
  - Doubles length of stay
  - Increased cost approx. £4000 per abdominal SSI
- Many interventions; most have poor evidence
- Likely to be multi-factorial in aetiology
- PROBABLY PREVENTABLE

Planning a follow-on study to ROSSINI…





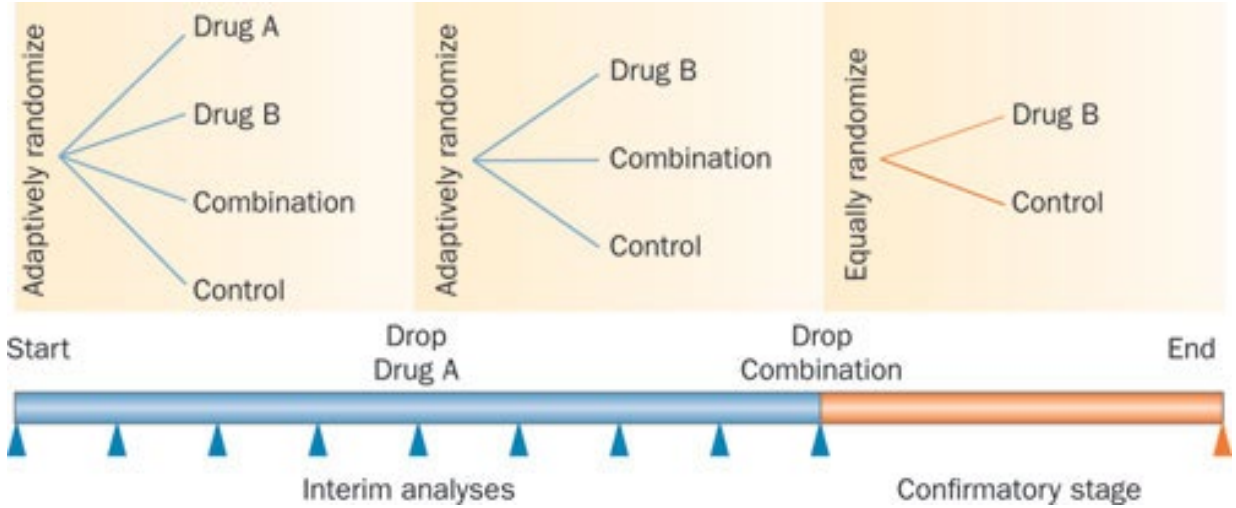
Primary outcome of SSI is available,

by definition,

*at **30 days** after surgery / randomisation*

Multiarm, Multistage (MAMS) design

exploits 30d outcome measure



ROSSINI II – Peri-theatre interventions which may reduce SSI rate…

~60 options

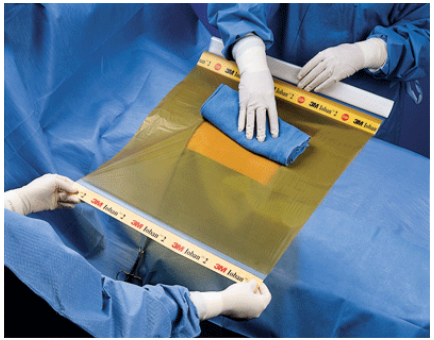
- Variably used in NHS practice
- Cost effective (potentially)
- Biologically plausible
- Explore interactions

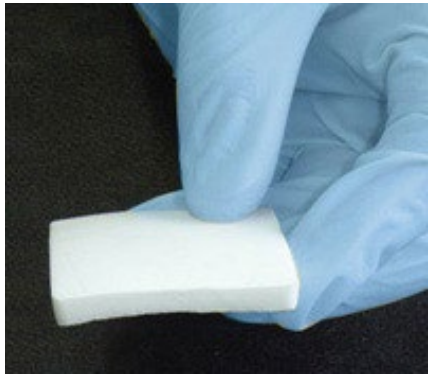
A] Chlorhexidine 2% alcoholic skin prep

[versus any other standard wound prep agent of surgeon's choice]

B] loban-impregnated incise drapes

[versus no drape]

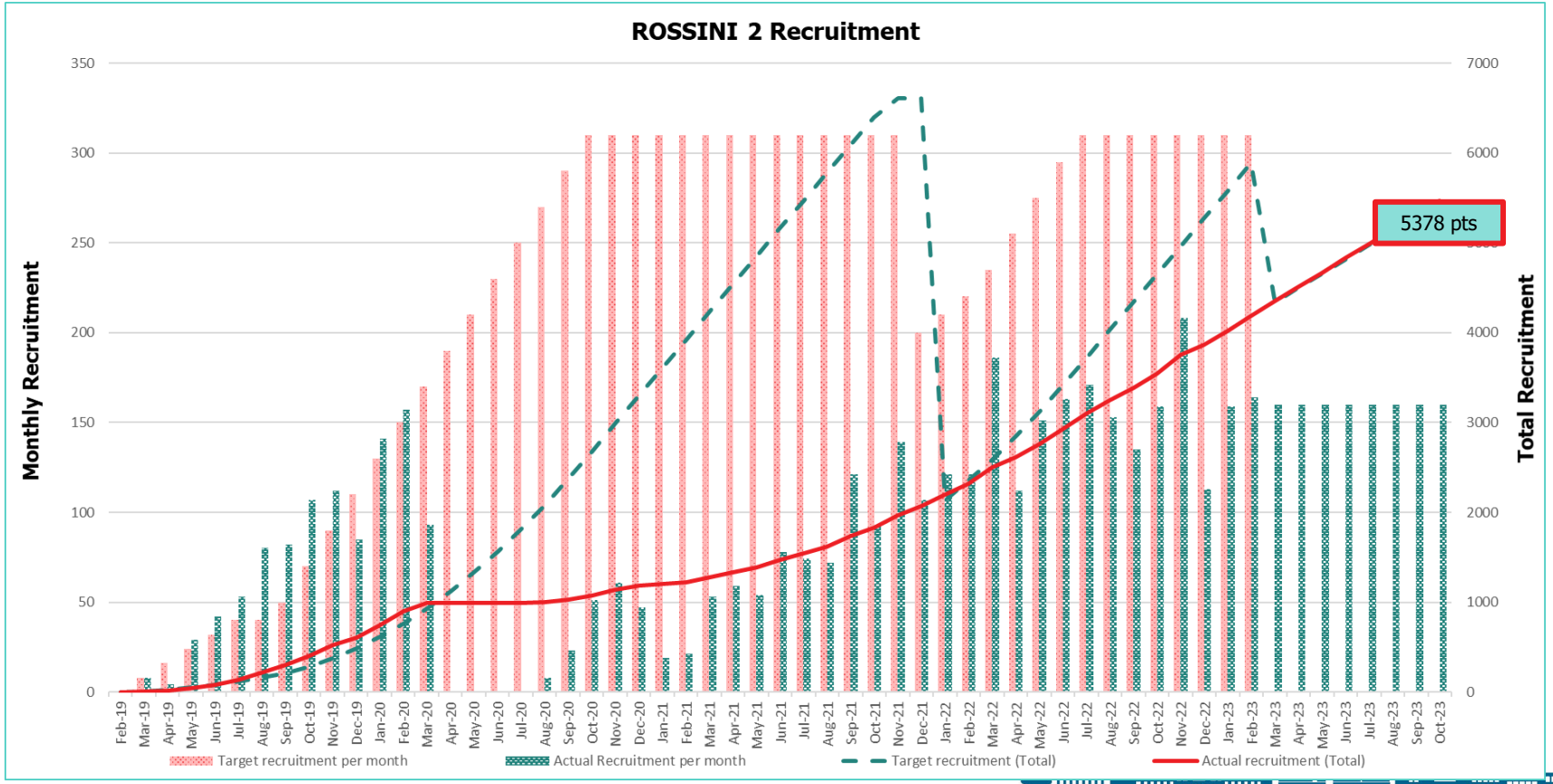


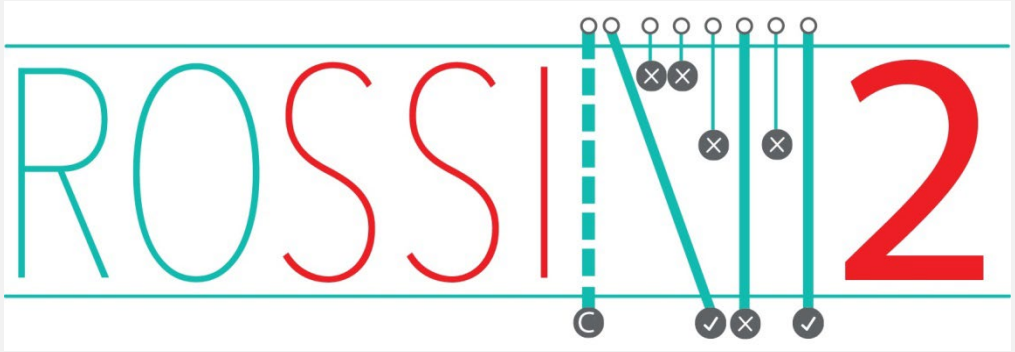


C] Gentamicin-impregnated collagen sponge

[versus no sponge]

Trial Update



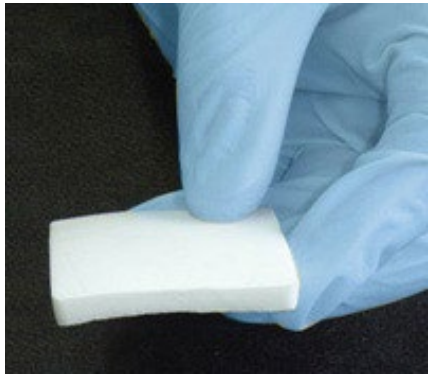


Reduction **O**f **S**urgical **S**ite **I**nfection using several **N**ovel **I**nterventions

First Interim Analysis

A] Chlorhexidine 2% alcoholic skin prep
[versus any other standard wound prep agent of surgeon's choice]

B] Ioban-impregnated incise drapes
[versus no drape]

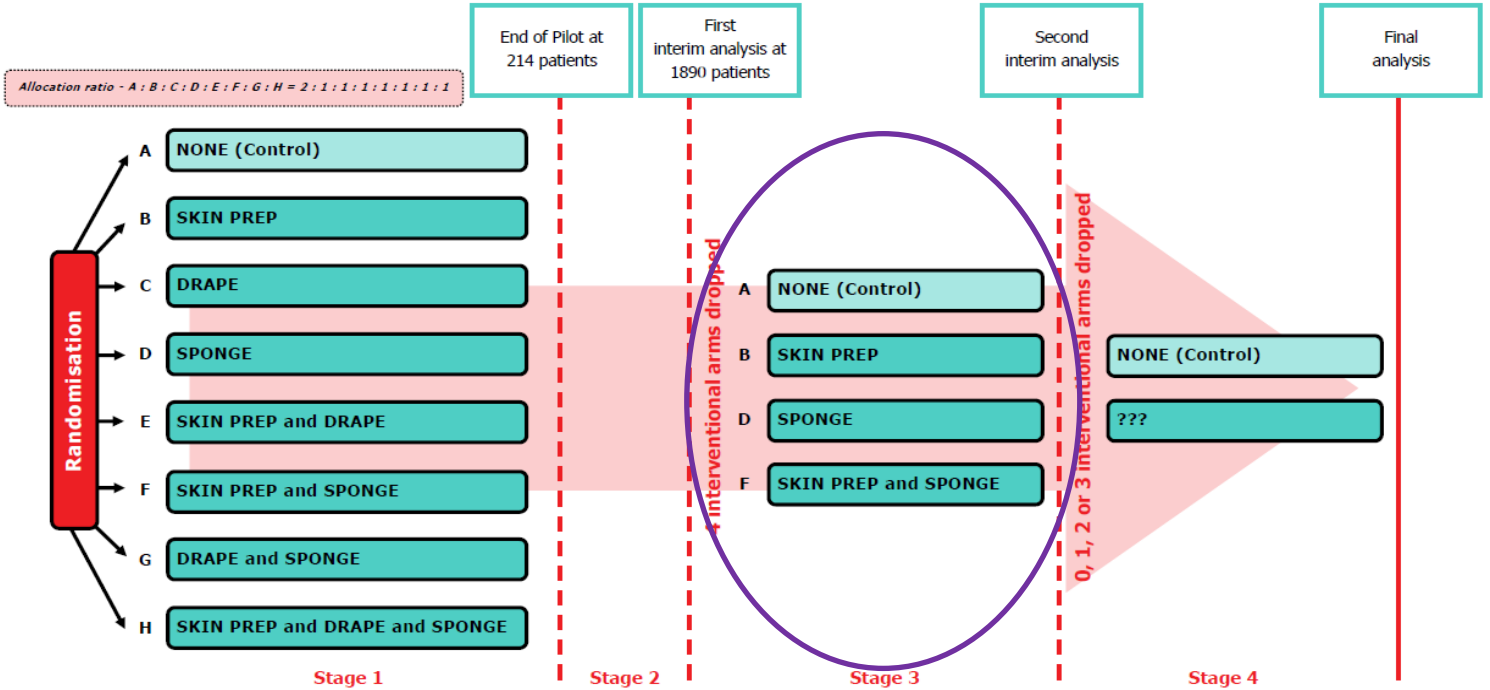


C] Gentamicin-impregnated collagen sponge
[versus no sponge]

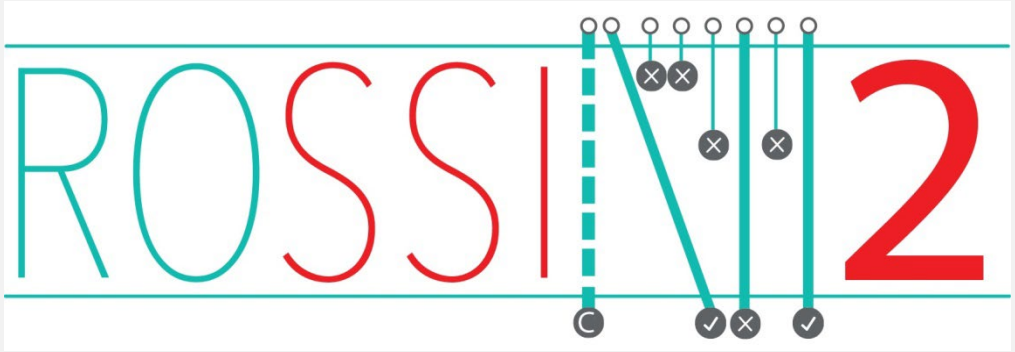
Intervention 1 - 2% alcoholic chlorhexidine skin preparation [SKIN PREP]

Intervention 2 - Iodophor-impregnated incise drape [DRAPE]

Intervention 3 - Gentamicin-impregnated collagen sponge [SPONGE]



Randomisation will cease to arms demonstrating a lack of effectiveness or lack of benefit compared to the control arm.



Reduction **O**f **S**urgical **S**ite **I**nfection using several **N**ovel **I**nterventions

Second Interim Analysis

A] Chlorhexidine 2% alcoholic skin prep

[versus any other standard wound prep agent of surgeon's choice]

B] Ioban-impregnated incise drapes

[versus no drape]

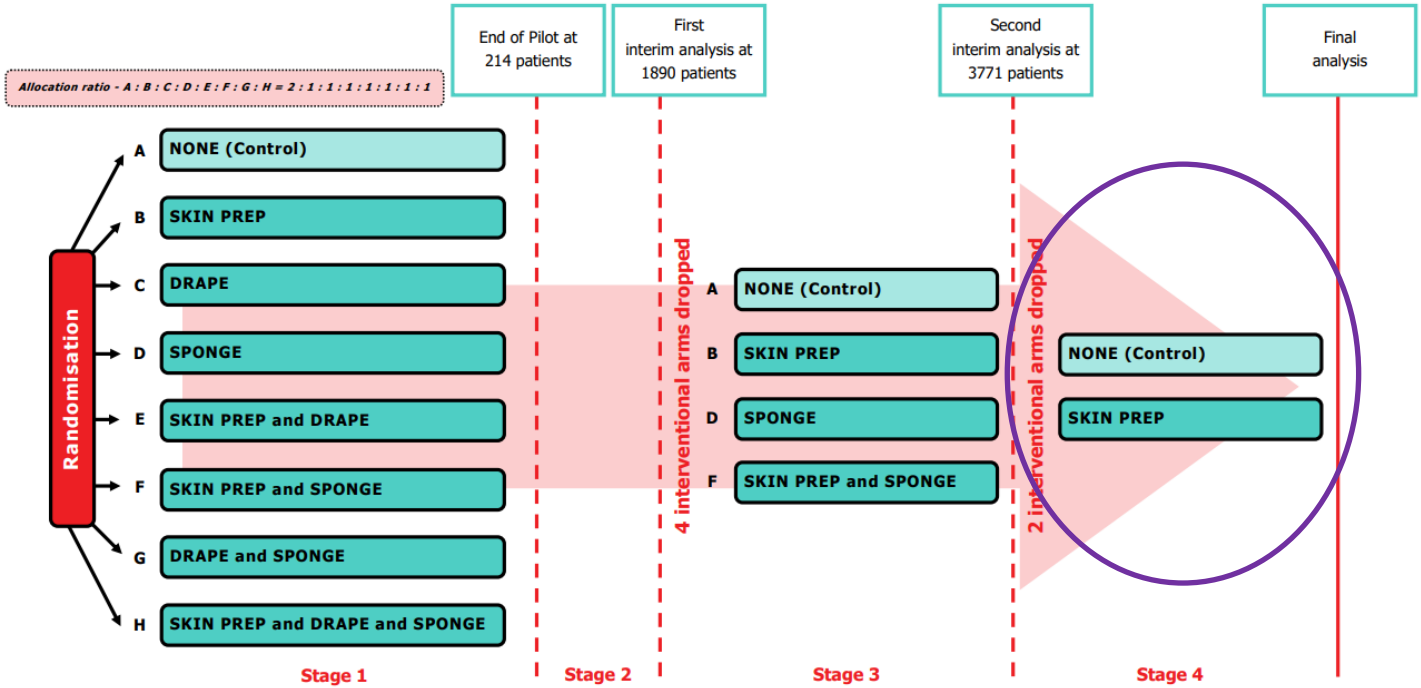
C] Gentamicin-impregnated collagen sponge

[versus no sponge]

Intervention 1 - 2% alcoholic chlorhexidine skin preparation [SKIN PREP]

Intervention 2 - Iodophor-impregnated incise drape [DRAPE]

Intervention 3 - Gentamicin-impregnated collagen sponge [SPONGE]



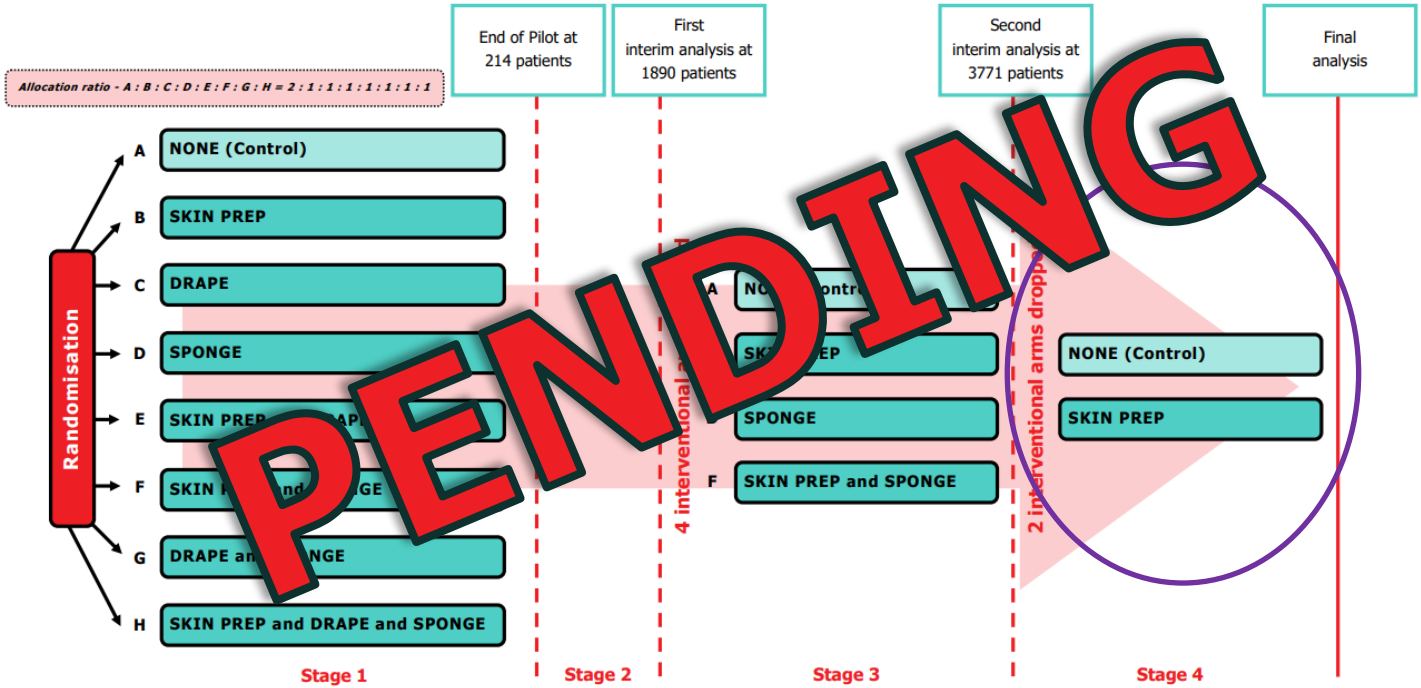
Randomisation will cease to arms demonstrating a lack of effectiveness or lack of benefit compared to the control arm.

Final Analysis results

Intervention 1 - 2% alcoholic chlorhexidine skin preparation [SKIN PREP]

Intervention 2 - Iodophor-impregnated incise drape [DRAPE]

Intervention 3 - Gentamicin-impregnated collagen sponge [SPONGE]



Randomisation will cease to arms demonstrating a lack of effectiveness or lack of benefit compared to the control arm.

ROSSINI 2 - Key Figures (mid-2023)

In the first 4000 patients:

- Control arm SSI rate = **20.3%**
- 96% were elective operations
- 62% were laparoscopic or lap-assisted operations

So…..what about adding new intervention(s)?

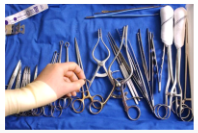
CHEETAH CLUSTER RCT | NIHR Global Health Research Unit on Global Surgery

Cluster randomised trial of sterile glove and instrument change at wound closure to reduce surgical site infection

On behalf of NIHR Unit on Global Surgery
University of Birmingham (UK)

CHEETAH Primary objective

Does **change of gloves and separate sterile instruments** before closing the abdominal wall reduce Surgical Site Infection (SSI) in clean-contaminated, contaminated, or dirty **abdominal surgery**



CHEETAH CLUSTER RCT | NIHR Global Health Research Unit on Global Surgery

Articles

Routine sterile glove and instrument change at the time of abdominal wound closure to prevent surgical site infection (ChEETAh): a pragmatic, cluster-randomised trial in seven low-income and middle-income countries

*NIHR Global Research Health Unit on Global Surgery**

Summary

Background Surgical site infection (SSI) remains the most common complication of surgery around the world. WHO does not make recommendations for changing gloves and instruments before wound closure owing to a lack of evidence. This study aimed to test whether a routine change of gloves and instruments before wound closure reduced abdominal SSI.

Lancet 2022; 400: 1767–76
Published Online October 31, 2022
https://doi.org/10.1016/S0140-6736(22)01884-0

	SSI rate	Adjusted risk ratio (95% CI)	p value
Primary analysis			0·0032
Current practice group	1280/6768 (18·9%)	reference	
Intervention group	931/5789 (16·1%)	0·87 (0·79–0·95)	
Sensitivity—per protocol			0·0010
Current practice group	1280/6768 (18·9%)	reference	
Intervention group	919/5693 (16·1%)	0·84 (0·76–0·93)	
Sensitivity—best case scenario			0·0009
Current practice group	1280/6848 (18·7%)	reference	
Intervention group	931/5831 (16·0%)	0·81 (0·72–0·92)	
Sensitivity—worst case scenario			0·0059
Current practice group	1360/6848 (19·9%)	reference	
Intervention group	973/5831 (16·7%)	0·86 (0·78–0·95)	
Sensitivity—target reached – 200			0·0004
Current practice group	1050/5313 (19·8%)	reference	
Intervention group	684/4127 (16·6%)	0·82 (0·74–0·91)	
Sensitivity—50% target reached			0·0002
Current practice group	1200/5241 (19·2%)	reference	
Intervention group	831/5145 (16·2%)	0·84 (0·77–0·93)	
Sensitivity—minimisation adjusted only			<0·0001
Current practice group	1280/6768 (18·9%)	reference	
Intervention group	931/5789 (16·1%)	0·66 (0·60–0·73)	

0·25 0·50 1·00 2·00

Figure 3: **Primary and sensitivity analyses of the primary outcome**
Intraclass correlation coefficient for primary analysis model=0·06 (95% CI 0·05–0·07). SSI=surgical site infection.

Interpretation This trial showed a robust benefit to routinely changing gloves and instruments before abdominal wound closure. We suggest that it should be widely implemented into surgical practice around the world.

NICE National Institute for Health and Care Excellence

Technology

2.1 Leukomed Sorbact (Essity), is a sterile, single-use, bacteria-binding, adhesive-bordered wound dressing. It is used to prevent surgical site infection (SSI) in closed surgical wounds that have low to moderate exudate.

2.2 The dressing comprises an absorbent non-woven wound contact pad and an outer transparent adhesive polyurethane film. The pad is made of a white viscose polypropylene and polyester mesh that is coated with the proprietary compound dialkylcarbamoyl chloride (DACC). DACC is hydrophobic, meaning that it does not mix with water and tends to bind to itself or other hydrophobic materials if water is present. In a moist wound, DACC binds to hydrophobic bacteria and fungi that cause SSI. These bound microorganisms are then removed from the wound site when the dressing is changed. Binding to DACC does not cause bacteria to be lysed (broken open), which avoids causing inflammation at the wound site. The polyurethane film is designed to contamination. The dressing

1 Recommendations

1.1 Evidence supports the case for adopting Leukomed Sorbact for closed surgical wounds after caesarean section and vascular surgery.

1.2 Leukomed Sorbact should be considered as an option for people with wounds that are expected to have low to moderate exudate after caesarean section and vascular surgery. It should be used as part of usual measures to help reduce the risk of surgical site infection. More evidence is needed on the use of Leukomed Sorbact on wounds after other types of surgery.

1.3 Cost modelling shows that the reduced rate of surgical site infection with Leukomed Sorbact compared with standard surgical dressings leads to savings of:

- £107 per person after caesarean section
- £18 per person after vascular surgery.

By adopting this technology, the NHS may save up to £5.3 million per year for caesarean section and up to £1.2 million per year for vascular surgery. Cost savings are expected because fewer people will need to stay in hospital for treatment of surgical site infection. For more details, see the NICE resource impact report.

Dressing is CE-marked and already available on UK market

What's Next?

"The delivery of most clinical trials is incredibly inefficient - it's like building a new stadium for every football game"

Munya Dimairo[1], Sheffield Clinical Trials Research Unit

Dear Professor Pinkney

HTA Project: NIHR160509 – ROSSINI 2 EXTENSION - A Phase 3, multi-arm, multi-stage (MAMS), pragmatic, blinded multicentre RCT to evaluate the use of in-theatre interventions, alone or in combination, to reduce SSI rates in patients undergoing abdominal surgery.

Thank you for responding to the concerns raised by the Funding Committee. Following consideration of your revised application dated 22 November 2023, I am pleased to inform you that your above-titled proposal has been recommended for funding. Please would you inform your co-applicants of the decision.

ROSSINI 2 Extension Phase [Stage 5]

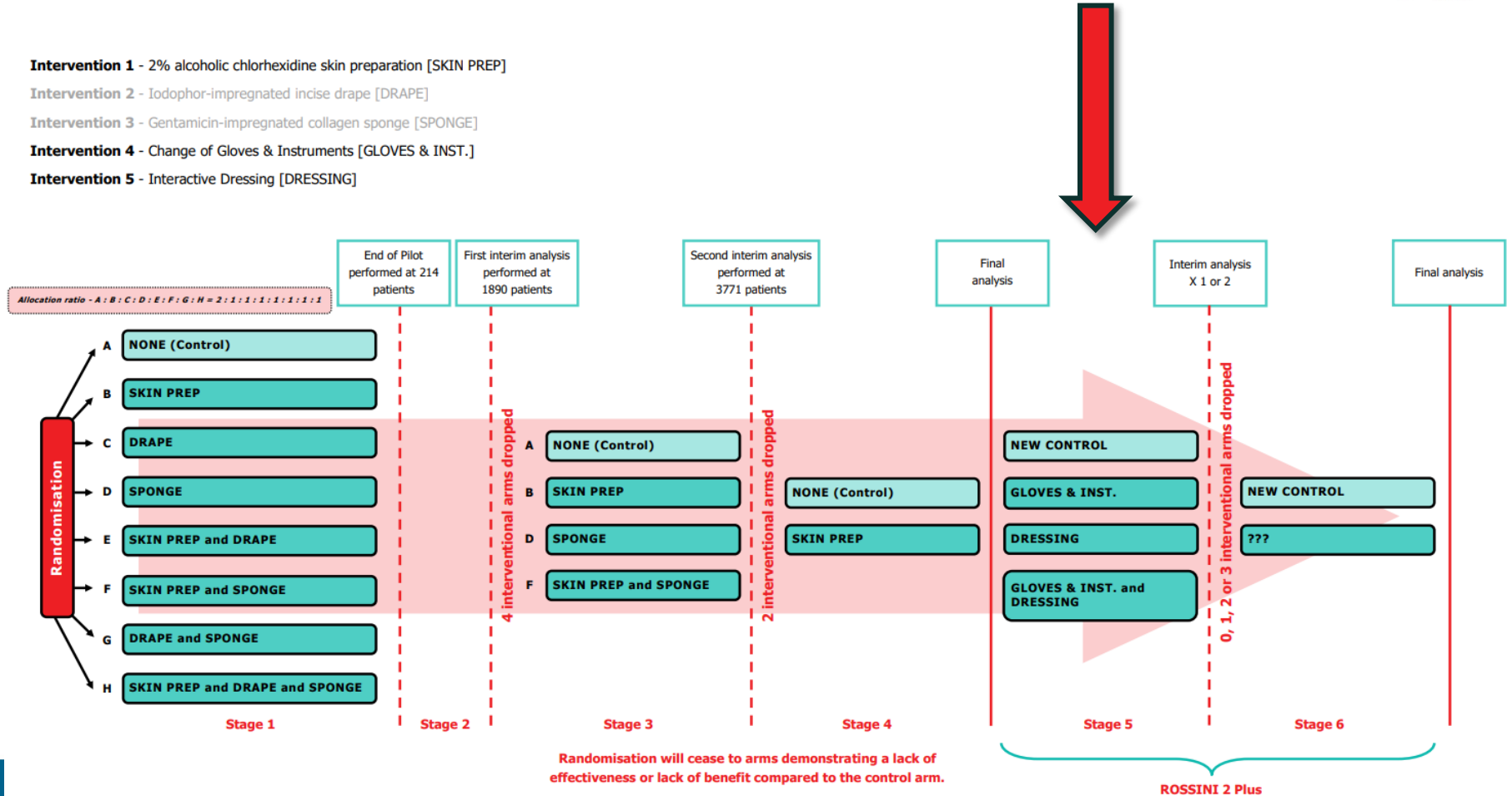
Intervention 1 - 2% alcoholic chlorhexidine skin preparation [SKIN PREP]

Intervention 2 - Iodophor-impregnated incise drape [DRAPE]

Intervention 3 - Gentamicin-impregnated collagen sponge [SPONGE]

Intervention 4 - Change of Gloves & Instruments [GLOVES & INST.]

Intervention 5 - Interactive Dressing [DRESSING]



ROSSINI-**Platform**….

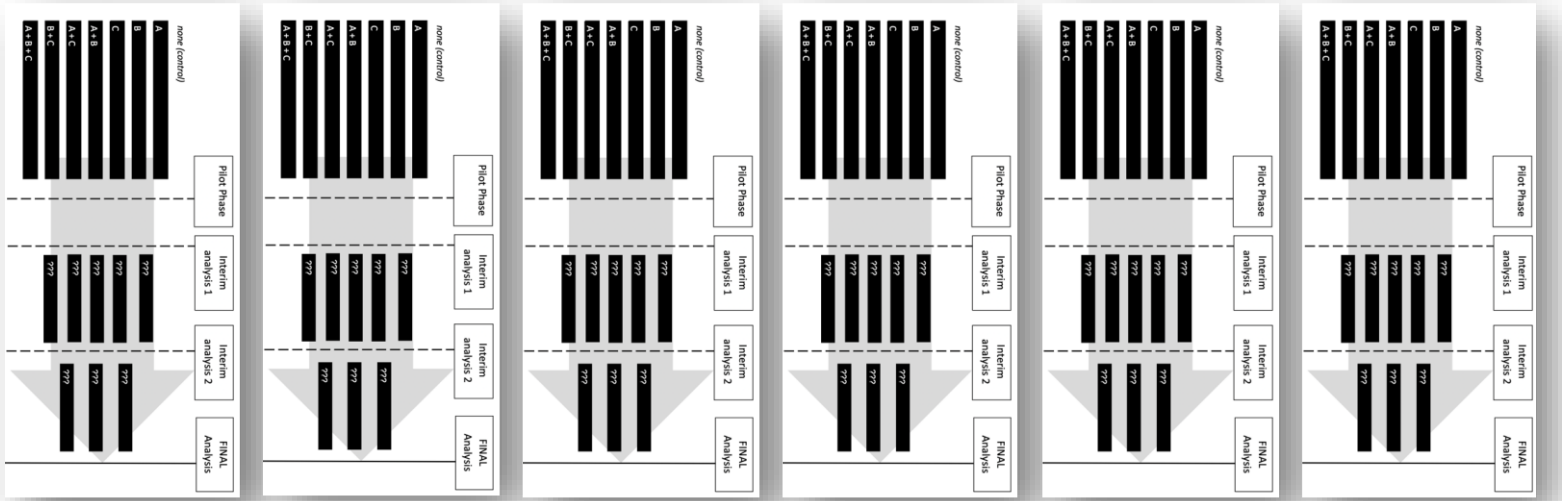
- SSI is a preventable complication across the *whole* of surgery
- Current guidelines/behaviours too generalised
- Different aetiological mechanisms/causative pathogens across the panoply of surgery
- An opportunity for evidence-driven stratification according to the **specific procedure** a patient is undergoing

ROSSINI-Platform – Proposed schematic for full trial

EXECUTIVE TRIAL MANAGEMENT GROUP

Oversees generic trial processes and oversight of overall activity and outcomes within the separate pillar RCTs. Makes decisions about inter-pillar arm transfer, including adaptive randomisation decisions

BREAST Pillar	Vasc. GROINS Pillar	CARDIAC Pillar	NEUROSURGERY Pillar	AMPUTATIONS Pillar	THORACIC Pillar
CI: Potter	CI: Wall	CI: Vaja	CI: Edlmann	CI: Bosanquet	CI: Surendrakumar
Co-CI: McIntosh	Co-CI: Chetter	Co-CI: Murphy	Co-CI: Jenkinson	Co-CI: Chetter	Co-CI: Naidu
Run by Breast TMG	Run by Groins TMG	Run by Cardiac TMG	Neurosurgery TMG	Amputations TMG	Run by Thoracic TMG



Arms (single intervention or a combination of interventions) found to be effective within one pillar can be transferred into vacated slots within other pillars for rapid testing

ADAPTIVE RANDOMISATION may be utilised to more rapidly prove effectiveness of an arm (e.g. it has been shown to work within one of the other pillars), or to more rapidly drop an arm if a signal of potential non-effectiveness has been observed at interim analysis

PROMISE IBD

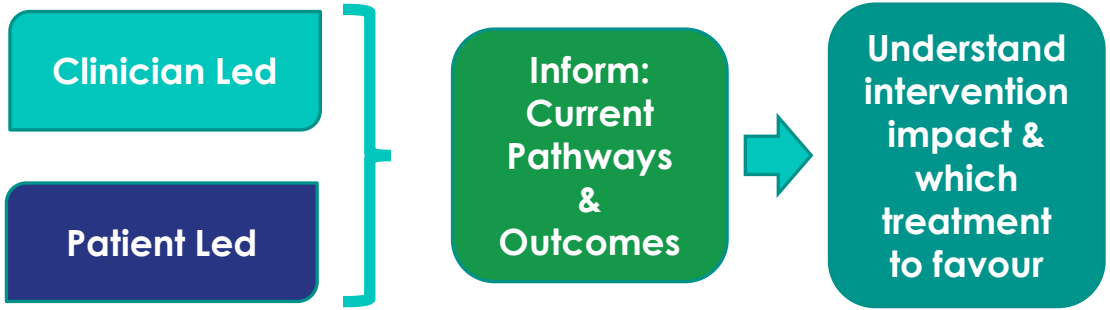
Abi Patel, Katie Adams and ACPGBI IBD Subcommittee & PROMISE IBD Steering Group

The Association of Coloproctology of Great Britain & Ireland

BiCOPS Birmingham Centre for Observational and Prospective Studies

Overview

- Prospective national cohort study of IBD Surgery in the UK
- Collaboration between IBD clinicians and patients with IBD to collate information:
  - Individual treatment
  - Surgical Short Term outcomes
  - Medium Term outcomes
  - Long Term outcomes



PROMISE IBD

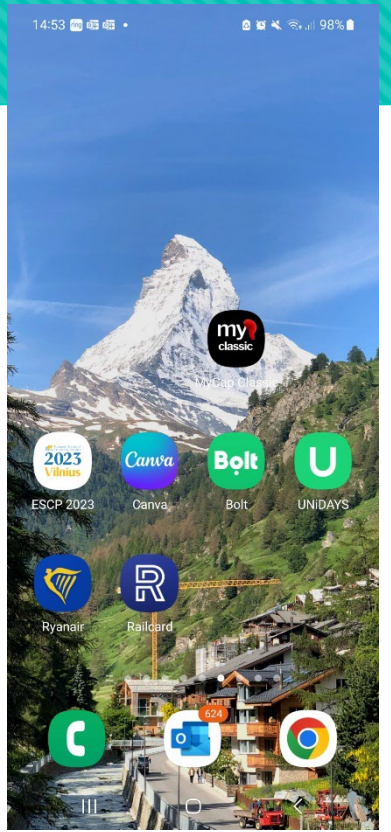
- UK wide multi-centre prospective cohort study
- Internal pilot phase: At least 10 hospitals, 100 patients
- Main study: Up to 100 hospitals across the UK, 1500-2000 patients
- Includes PROMS as a primary outcome
- PPI oversight group

Eligibility

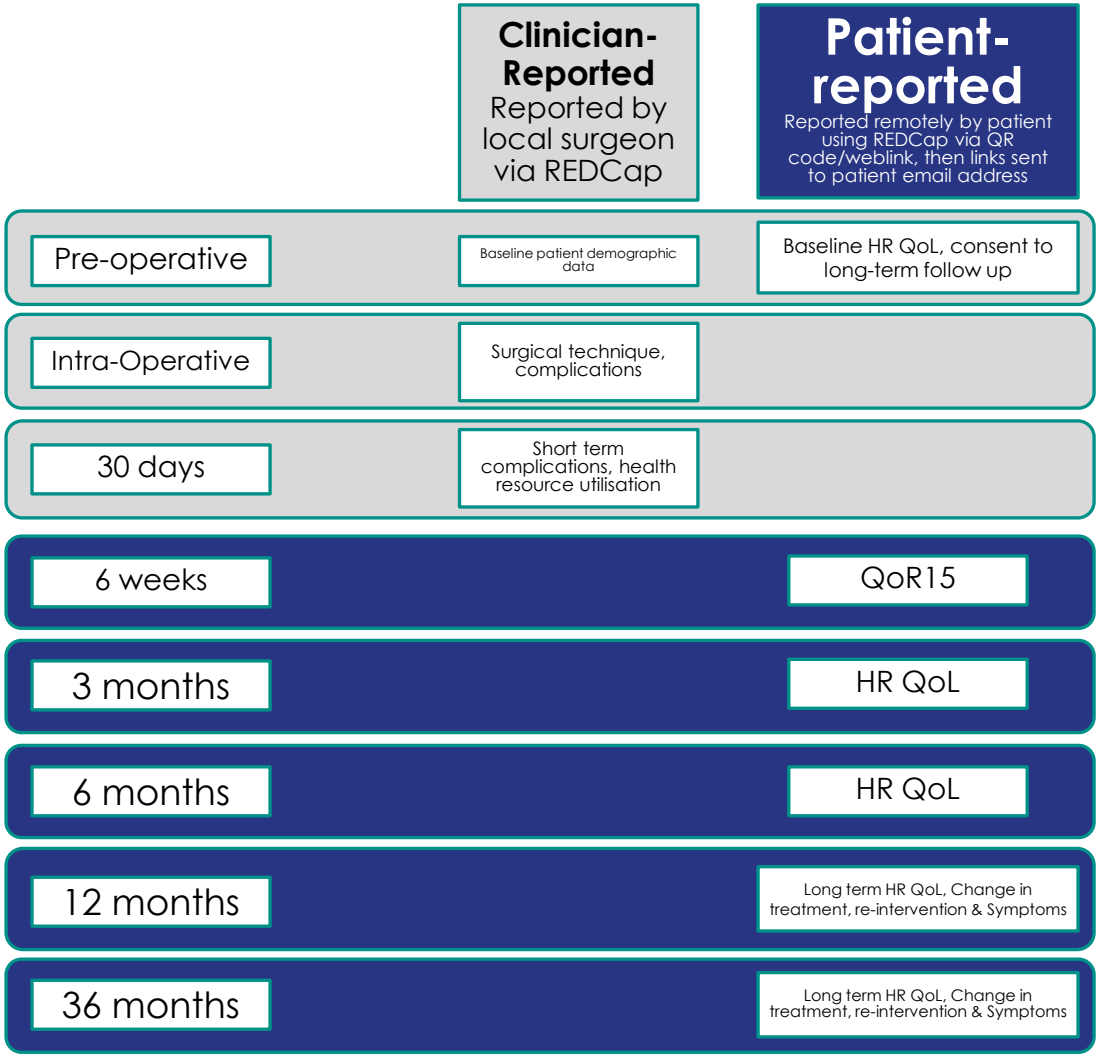
- Patients over the age of 16
- Undergoing abdominal surgery for IBD (proven or suspected)
- Any abdominal operation, including stoma reversal
- Elective and emergency presentations

Patient Reported Outcomes

- Using validated PROMS to collect outcome data that matters to patients
- PROM selection in consultation with patients
- Will include quality of recovery, overall quality of life, bowel function, return to normal activities, decisional regret
- Collected via MyCap - directly from the patient
- Option for Patient self-enrollment



Study Design



Patient directed research

- PPI Group involvement in full trial design
- HR QoL will vary depending on
  - IBD diagnosis
  - Treatment choice

Patient Group Results & Feedback

- Questionnaire shared by CCUK – 80 responses!
- 90% - PROMS as primary outcome very important
- Want PROMS that cover items such as: bowel function, QoL, return to normal activities, fatigue, quality of recovery, mental health, and pain
- Happy to complete multiple PROMS at each time point if done via app on phone
- 51 volunteers for the PPI Group!

Launching in Summer 2024

The (ongoing) future of surgical research

Bigger, Better, More Impactful

- Even more collaborative
- Even more international
- Even more accessible

For the benefit of all of our patients

For Clinical Research in Surgery