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Linkage with clinical data

John Robson, Charles Knowles, Cecilia Okusi

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Linkage methods

- 50 patients undergoing general surgical operations in 2016
- Taken from logbook (tertiary avoided)
- Linkage via NHS number in *OpenPseudonymiser*
- 37 found in EMIS
- Prototype variables tested by data availability expressed as proportion of 37 patients

Linkage: results 1

Variable	Number with linkage	Notes
Demographic		
Age	37/37	Latest recording. Age at search date calculated from year of birth.
Sex	37/37	Latest recording.
Ethnic group	35/37	Latest recording. Columns: code, date, term.
Index of m. deprivation	37/37	Latest recording. LSOA (lower super output area) mapped to IMD quintile.

Linkage: results 2

Comorbidities		
Cardiovascular		
Myocardial Infarction	1/37	Earliest recording and latest recording. Columns: code, term, date.
Ischaemic heart disease	1/37	Earliest recording and latest recording. Columns: code, term, date.
Stroke/TIA	0/37	Earliest recording and latest recording. Columns: code, term, date.
Heart failure	1/37	Earliest recording and latest recording. Columns: code, term, date.
Atrial fibrillation	2/37	Earliest recording and latest recording. Columns: code, term, date.
Peripheral arterial disease	0/37	Earliest recording and latest recording. Columns: code, term, date.
Hypertension (and BP >140/90)	4/37	Earliest recording and latest recording. Columns: code, term, date.
Venous or arterial leg ulcer	1/37	Earliest recording and latest recording. Columns: code, term, date.
Use of anticoagulant	0/37	Information collected in prescribing.

Linkage: results 2

Comorbidities		
Cardiovascular		
Myocardial Infarction	1/37	Earliest recording and latest recording. Columns: code, term, date.
Ischaemic heart disease	1/37	Earliest recording and latest recording. Columns: code, term, date.
Stroke/TIA	0/37	Earliest recording and latest recording. Columns: code, term, date.
Heart failure	1/37	Earliest recording and latest recording. Columns: code, term, date.
Atrial fibrillation	2/37	Earliest recording and latest recording. Columns: code, term, date.
Peripheral arterial disease	0/37	Earliest recording and latest recording. Columns: code, term, date.
Hypertension (and BP >140/90)	4/37	Earliest recording and latest recording. Columns: code, term, date.
Venous or arterial leg ulcer	1/37	Earliest recording and latest recording. Columns: code, term, date.
Use of anticoagulant	0/37	Information collected in prescribing.
Respiratory disease		
Asthma	6/37	Earliest recording and latest recording. Columns: code, term, date.
COPD	1/37	Earliest recording and latest recording. Columns: code, term, date.

Linkage: results 3

GI disease		
Gastroenteritis	2/37	Earliest recording and latest recording. Columns: code, term, date.
Liver disease	1/37	Fatty liver. Earliest recording and latest recording. Columns: code, term, date.
Hep B, C	0/37	Earliest recording and latest recording. Columns: code, term, date.
Cirrhosis	0/37	Earliest recording and latest recording. Columns: code, term, date.
Portal hypertension	0/37	Earliest recording and latest recording. Columns: code, term, date.
Bleeding varices	Not included in data collection	
IBD: Crohn's disease	6/37	Earliest recording and latest recording. Columns: code, term, date.
IBD: ulcerative colitis	1/37	Earliest recording and latest recording. Columns: code, term, date.
Gastric or duodenal ulceration	2/37	Earliest recording and latest recording. Columns: code, term, date.

Linkage: results 4

Metabolism / Endocrine		
Diabetes T1/2	4/37	Earliest recording and latest recording. Columns: code, term, date.
Chronic renal impairment eGFR <60	2/37	Earliest recording and latest recording. Columns: code, term, date.
Chronic renal impairment eGFR <30	0/37	Earliest recording and latest recording. Columns: code, term, date.
Autoimmune		
Rheumatoid	0/37	Earliest recording and latest recording. Columns: code, term, date.
SLE	0/37	Earliest recording and latest recording. Columns: code, term, date.
Sjorgrens	0/37	Earliest recording and latest recording. Columns: code, term, date.
Sarcoid	0/37	Earliest recording and latest recording. Columns: code, term, date.
Polymyalgia	0/37	Earliest recording and latest recording. Columns: code, term, date.
Vasculitis	0/37	Earliest recording and latest recording. Columns: code, term, date.

Linkage: results 5

Neurological		
Dementia	0/37	Earliest recording and latest recording. Columns: code, term, date.
Parkinson's disease	0/37	Earliest recording and latest recording. Columns: code, term, date.
Multiple sclerosis	0/37	Earliest recording and latest recording. Columns: code, term, date.
Serious mental illness	7/37	Earliest recording and latest recording. Columns: code, term, date.
Depression	12/37	Earliest recording and latest recording. Columns: code, term, date.
Epilepsy	0/37	Earliest recording and latest recording. Columns: code, term, date.
Learning disability	0/37	Earliest recording and latest recording. Columns: code, term, date.

Linkage: results 6

Cancer-related		
Colorectal	0/37	Earliest recording and latest recording. Columns: code, term, date.
Anal	0/37	Earliest recording and latest recording. Columns: code, term, date.
Uterine	0/37	Earliest recording and latest recording. Columns: code, term, date.
Cervical	0/37	Earliest recording and latest recording. Columns: code, term, date.
Prostate	0/37	Earliest recording and latest recording. Columns: code, term, date.
Bladder	0/37	Earliest recording and latest recording. Columns: code, term, date.
Lung	1/37	Earliest recording and latest recording. Columns: code, term, date.
HIV positive	0/37	Earliest recording and latest recording. Columns: code, term, date.
Palliative care	0/37	Earliest recording and latest recording. Columns: code, term, date.

Linkage: results 7

Exposures		
Smoking status	37/37	Earliest recording and latest recording. Columns: category, code, term, date.
Alcohol intake	33/37	Earliest recording and latest recording. Columns: code, date, value, units.
Major Substance misuse	0/37	Earliest recording and latest recording. Columns: code, term, date.
Scores		
Charlson comorbidity score	37/37	Earliest recording and latest recording for 21 conditions. Each condition is assigned a weight. Sum of weights = Charlson comorbidity score.
Frailty score	1/37	Earliest recording and latest recording. Columns: code, date, value.

Linkage: results 8

Measurement		
Systolic/diastolic BP last recorded	34/37	Earliest recording and latest recording. Columns: code, date, value, units.
Weight	35/37	Earliest recording and latest recording. Columns: code, date, value, units, age at event.
Height	34/37	Earliest recording and latest recording. Columns: code, date, value, units, age at event.
BMI	31/37	Earliest recording and latest recording. Columns: code, date, value, units, age at event.
eGFR	28/37	Earliest recording and latest recording. Columns: code, date, value, units.
Hb	30/37	Earliest recording and latest recording. Columns: code, date, value, units.
HbA1c	24/37	Earliest recording and latest recording. Columns: code, date, value, units.
ALT	29/37	Earliest recording and latest recording. Columns: code, date, value, units.

Linkage: results 9

Prescribing		
Anticholinergics	0/37	Latest recording within 6 months. Columns: BNF chapter, BNF chapter heading, term, issue date, quantity, units.
Acetylcholinesterase inhibitors	Not included in data collection	
Hypnotics	1/37	Latest recording within 6 months. Columns: BNF chapter, BNF chapter heading, term, issue date, quantity, units.
Axiolytics	0/37	Latest recording within 6 months. Columns: BNF chapter, BNF chapter heading, term, issue date, quantity, units.
Antipsychotics	0/37	Latest recording within 6 months. Columns: BNF chapter, BNF chapter heading, term, issue date, quantity, units.
Tricyclic antidepressants	2/37	Latest recording within 6 months. Columns: BNF chapter, BNF chapter heading, term, issue date, quantity, units.
MAOIs	0/37	Latest recording within 6 months. Columns: BNF chapter, BNF chapter heading, term, issue date, quantity, units.
SSRIs	3/37	Latest recording within 6 months. Columns: BNF chapter, BNF chapter heading, term, issue date, quantity, units.
Calcium channel blockers	1/37	Latest recording within 6 months. Columns: BNF chapter, BNF chapter heading, term, issue date, quantity, units.
Anticoagulants	0/37	Latest recording within 6 months. Columns: BNF chapter, BNF chapter heading, term, issue date, quantity, units.
NSAIDs	2/37	Latest recording within 6 months. Columns: BNF chapter, BNF chapter heading, term, issue date, quantity, units.
Opioid containing analgesics [weak, strong – some basic classification]	7/37	Latest recording within 6 months. Columns: BNF chapter, BNF chapter heading, term, issue date, quantity, units.
Stoma appliances	Not included in data collection	

Previous surgery		
Hysterectomy +/- oophorectomy	Not included in data collection	
Colorectal surgery	Not included in data collection	
Other abdominal surgery	12/37	Endoscopy. Earliest recording and latest recording. Columns: code, date, term.
Primary HC utilisation		
Total GP attendances	Not included in data collection	
Total home visits	Not included in data collection	
GP attendances: abdominal / pelvic pain	Not included in data collection	
GP attendances: constipation	Not included in data collection	
GP attendances: rectal or uterine prolapse	Not included in data collection	
GP attendances: faecal or urinary incontinence	Not included in data collection	
GP attendances: rectal bleeding	Not included in data collection	

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Next steps in applied research

Prof. Charles Knowles

Blizard Inst.

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Summary

- Introduction
- Examples of future studies

Introduction

Typical UK NIHR RCT

- Average duration ~4 years
- Costs ~£1.5million
- 45% fail to achieve target sample size despite longer recruitment periods [1] (and surgery has worse performance: CRN data)
- Impact on internal and external validity
- Impact on cost – fewer trials funded
- Impact on patient care

Contracts
Regulation (esp. devices)
Governance and data protection (esp. EU)
UK: fighting with NHS support and excess treatment costs

Sully BG *et al.*, Trials 2013: 14: 166.

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Surgical RCT: challenges (1)

Completing the trial

- Valid comparator esp. placebo / sham
- Blinding
- Recruitment
  - surgeon equipoise
  - patient preference
- Performance
  - fidelity of standardised intervention
  - technical evolution
  - control convergence (Hawthorne effect)

Barkun *et al*., Lancet 2009; 374: 1089-1096.
Ergina *et al*., Lancet 2009; 374: 1089-1103.

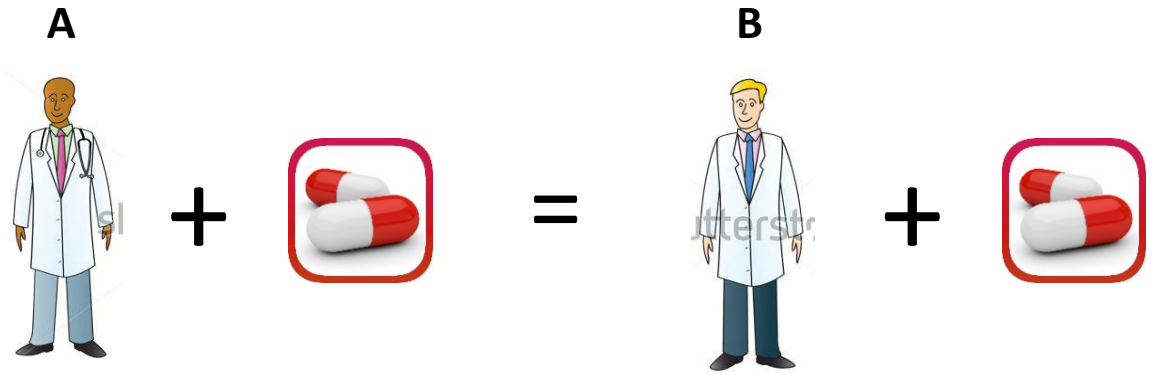
Surgical RCT: challenges (2)

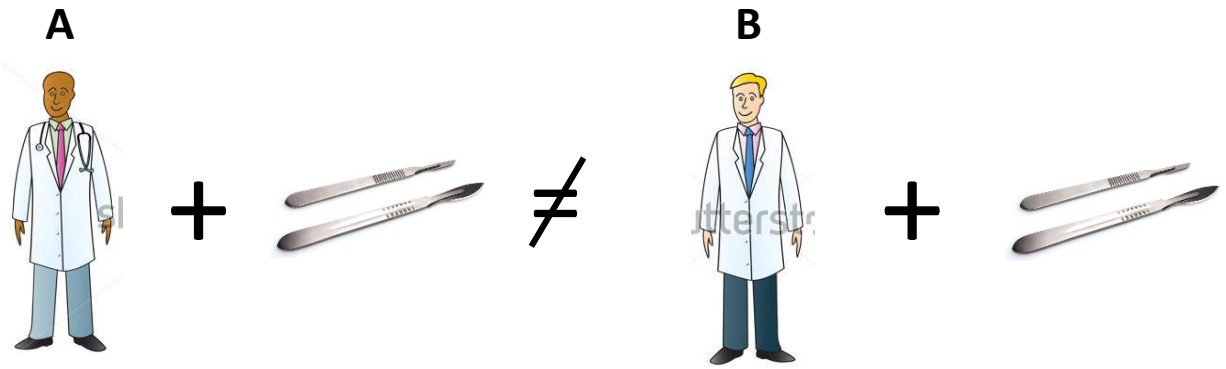
Relevance and external validity

- Unmeasured rare or distant (future) harms
- Buxton's law (too early and then too late)
- Selection bias (the perfect patient for the 'new' intervention)
- Surgeon-intervention-interaction

Barkun *et al*., Lancet 2009; 374: 1089-1096.
Ergina *et al*., Lancet 2009; 374: 1089-1103.

Surgeon-intervention-interaction





Cleveland Clinic
Digestive Disease Institute

DDI WEEK 2017

February 14 – 18, 2017

ca Raton, Florida

28th Jagelman/38th T

International C sium

February 14 – 18, 2017

11th Annual

Transanal Surgery Work

February 14, 2017

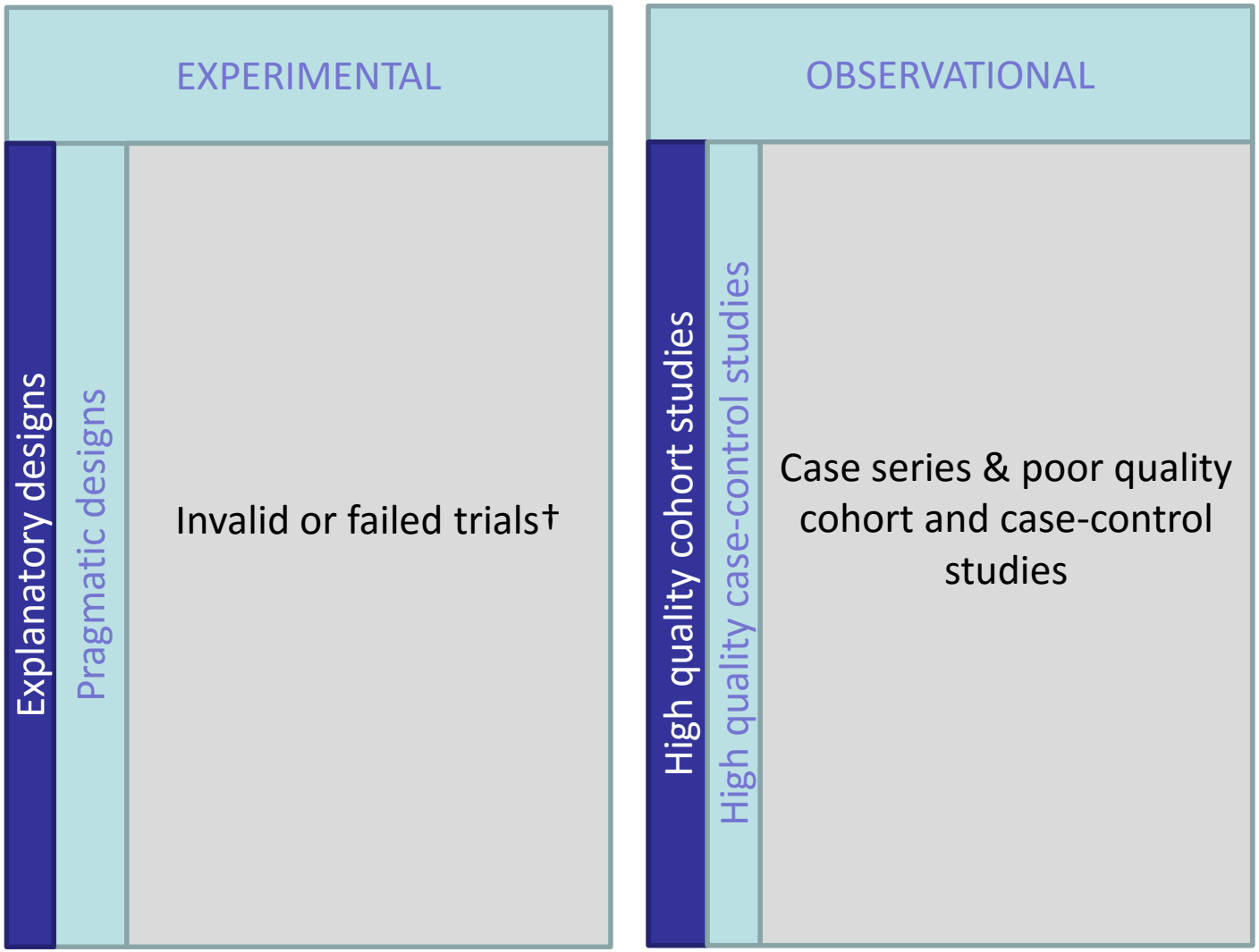
Rectal Cancer: The Experts Debate

Moderator: S. Wexner

The Best Technique Is:

7:15 am	Open I. Lavery
7:30 am	Laparoscopic W. Law
7:45 am	Robotic A. Pigazzi
8:00 am	TaTME A. Lacy
8:15 am	Extralevator APR A. Habr-Gama
8:30 am	Standard Cylindrical APR S. Steele
8:45 am	No Surgery after a Complete Response J. Marcet
9:00 am	Panel Discussion / Q & A
9:35 am	Break

Clinical study designs: surgery



* Oxford CEBM. BMJ
† not 'negative' trials

CapaCiTY

The Pelvic Floor Society

NHS England

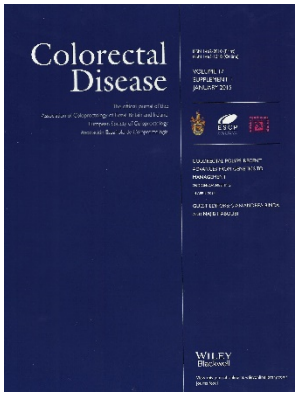
The Association of Coloproctology of Great Britain and Ireland

NHS National Institute for Health Research

ESCP European Society of COLOPROCTOLOGY

Procedure	Number of reviewed studies by evidence level				
	1b	2b	3b	4	Total
Colonic resection	0	1	0	39	40
Suspension procedures	0	2	0	16	18
Excisional procedures	3	26	0	18	47
Reinforcement procedures	2	9	0	35	46
Sacral neuromodulation	0	0	0	8	8
ALL	5	38	0	115	148

115/148 (77.8%) level 4



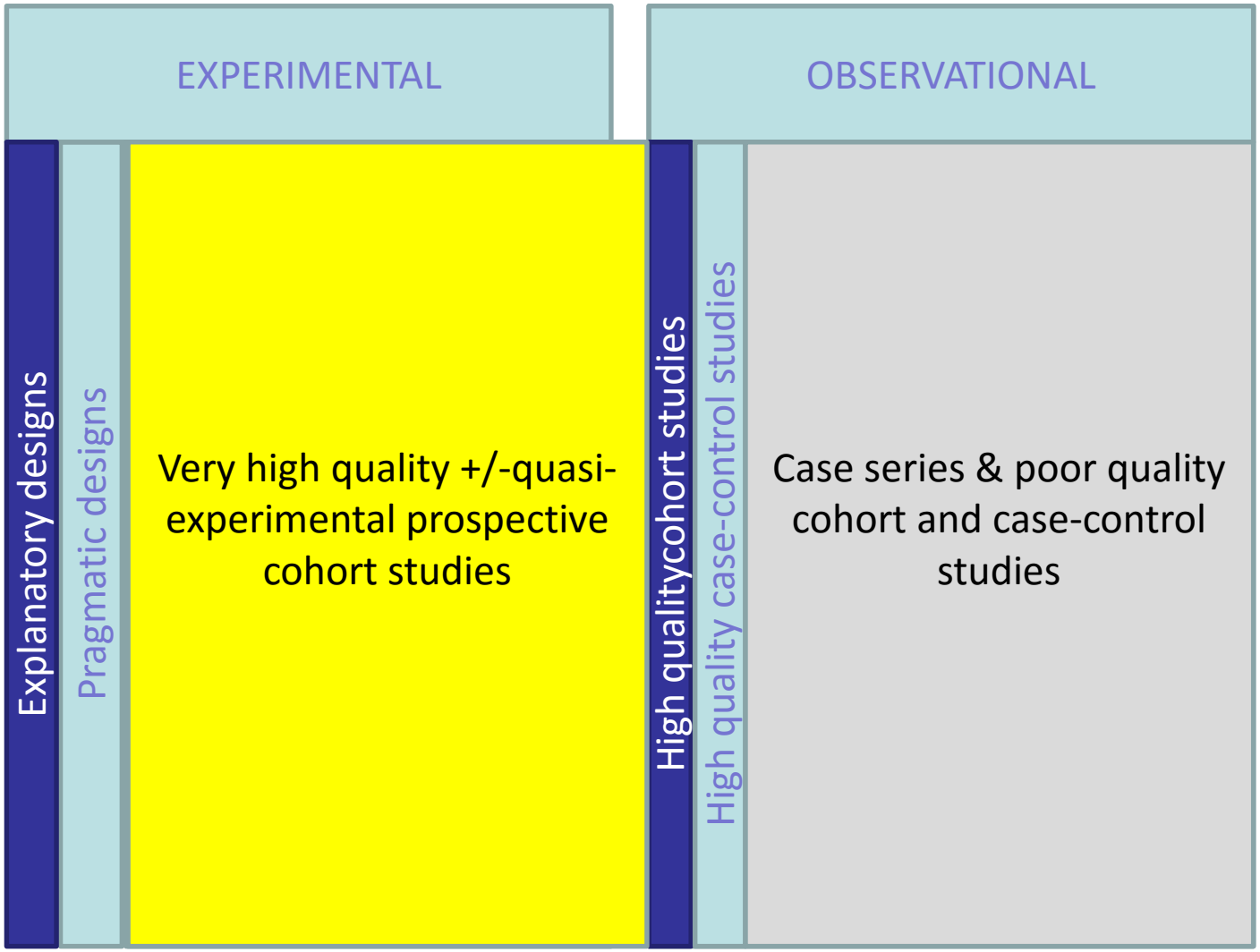
7 papers
Open access

Observational studies in surgery: bias

- Every bias possible from selection to publication

"observational studies are not fundamentally bad, we (surgeons) just do them very badly"

Clinical study designs: surgery (the future)



* Oxford CEBM. BMJ

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IDEAL framework
Ergina *BMJ* 2013;346:f3011

Stage 3: assessment

"Any observational study conducted as an alternative to a high quality, randomised controlled trial should have as many positive design features of such a trial as possible."

VHQ prospective cohort studies

Embody ALL possible positive features of a high quality RCT other than experimental allocation

- Prospectively designed and powered to test a specific hypothesis
- Optimally designed for efficiency
- Robust inclusion and exclusion criteria and informed consent
- Managed by registered CTU (or equivalent) to ensure:
  - QA and governance
  - Data: entry validation, protection, cleaning, lockdown
  - Data analysis using predefined plan and with professional statistical support
  - Funded accordingly
- Observer-blinded (third party - independent) outcome data collection and analysis

Proximity (car park) effect

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Patient Reported Outcome MeasureS using Electronic informed consent and data capture – developing methods and infrastructure

NHS National Institute for Health Research

PCTU

+

Imperial

Birmingham

Edinburgh CTU

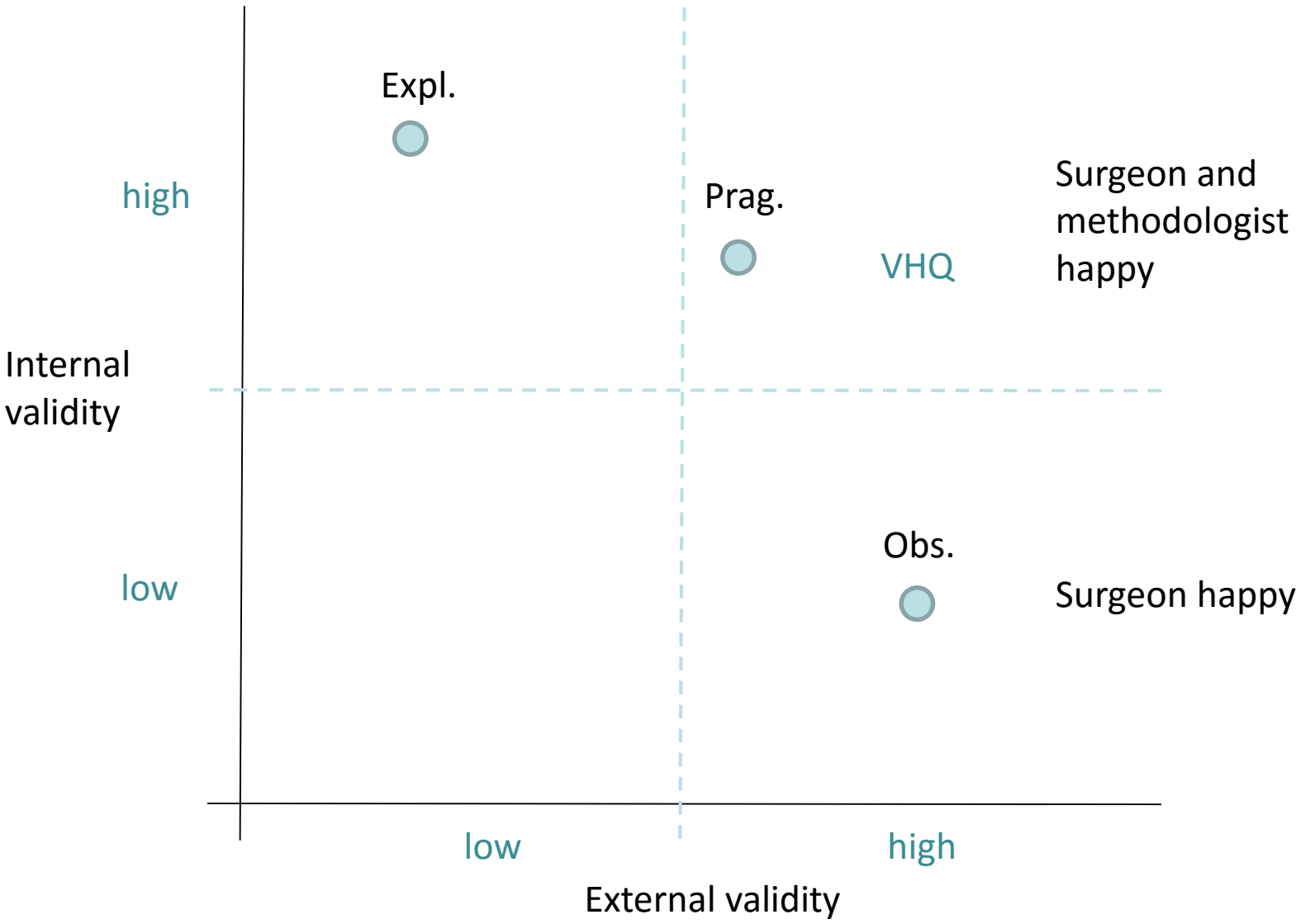
Patient Identifiable Information and Consent

NHS Direct Care Teams

FIREWALL

Pseudonymised Patient Reported Outcome Measures

Research Centre Hub


Expl.
Prag.
VHQ
Obs.
Surgeon and methodologist happy
Surgeon happy
high
low
Internal validity
low
high
External validity

Applied surgical research: examples

PRoSECCO

Prolapsed Rectum Surgery EnhanCed COhort Study

Rectal prolapse: impact

- Not very common but miserable condition
- Increasing with older population
- ACPGBI: Delphi exercise top benign condition
- Only treatment is surgery

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Rectal prolapse: need for a cohort study

- Several competing operations
- Cochrane review: poor evidence base
- Spectacular failure of previous RCT attempts e.g. PROSPER
  - 10 years
  - 30/80 centres recruited
  - 293/950 target
- Previous funding attempts at new pragmatic RCTs not funded by HTA (DeliVar and RAPPORt)
- Media focussed on mesh (used during current gold standard operation: lap VMR)

Laparoscopic ventral mesh rectopexy

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PRoSECCO: primary objective

- To determine whether well-established procedures for external rectal prolapse (posterior rectopexy or perineal procedures) are non-inferior to lap VMR based on a margin of 0.1 using EQ-5D at one year
- Interpretation:
  - rejection of null hypothesis: lap VMR is justified over perhaps safer and less expensive procedures;
  - acceptance: supports renewed use of other procedures (esp. considering media attention).

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Selection = WL for ext. rectal prolapse

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NHS Direct Care Teams		Research Centre Hub

CRFs

- Baseline state and trait characteristics e.g. frailty
- Perioperative data to 30 days

Health Economics

- HES data
- -1 year to end epoch

Serial stepped (2 monthly)

- EQ5D
- Patient-reported prolapse 'recurrence'

6 monthly

- PAC-SYM

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PRoSECCO: analysis

- Effective prolapse surgery improves EQ-5D by 0.2 points (PROSPER)
- For non-inferiority we take 50% this effect size = 0.1 points
- SD = 0.59 points (PROSPER)
- Ratio anticipated 25: 42: 33
- 90% power
- Sample size = 388 (10% drop out) = 430 patients

PRoSECCO: risks

- *Lap VMR banned*
  - No problem – compare next best with next 2 available
- *Elderly unable to use PROMiSE platform*
  - Results thus far do not support this
- *Long waiters not the same as short waiters (systematic bias)*
  - Initial results of WAITER encouraging

Medical Research

- Our Research Priorities
- Progress Reports
- **Ongoing projects**
- Grant applications
- Research Trial Recruiters
- Research & Audit Committee

Designing a study to find the optimum surgical technique for treating rectal prolapse

Posted in Delphi grants - round 1

Lead investigator

Steven Brown - Consultant surgeon

Research team

Danny Hind, Mathew Lee, Charlie Knowles, Jon Lacy-Colson, Adam Farquarson

Institution

Sheffield School of Health and Related Research

The Association of Coloproctology
of Great Britain and Ireland

Diverticular Abscess Management Single Blinded Cohort Study

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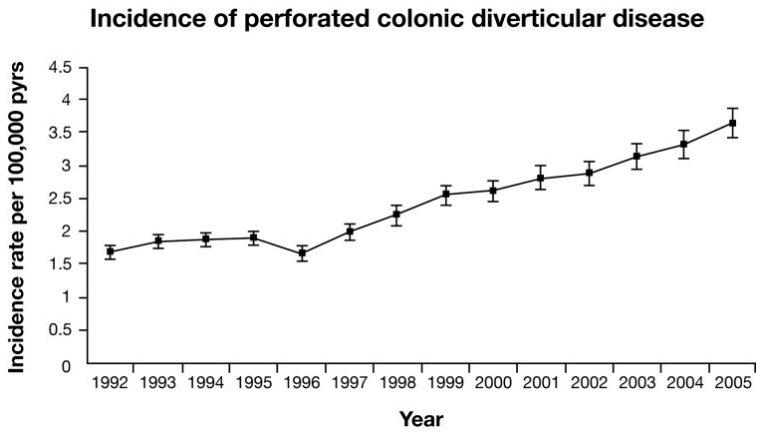
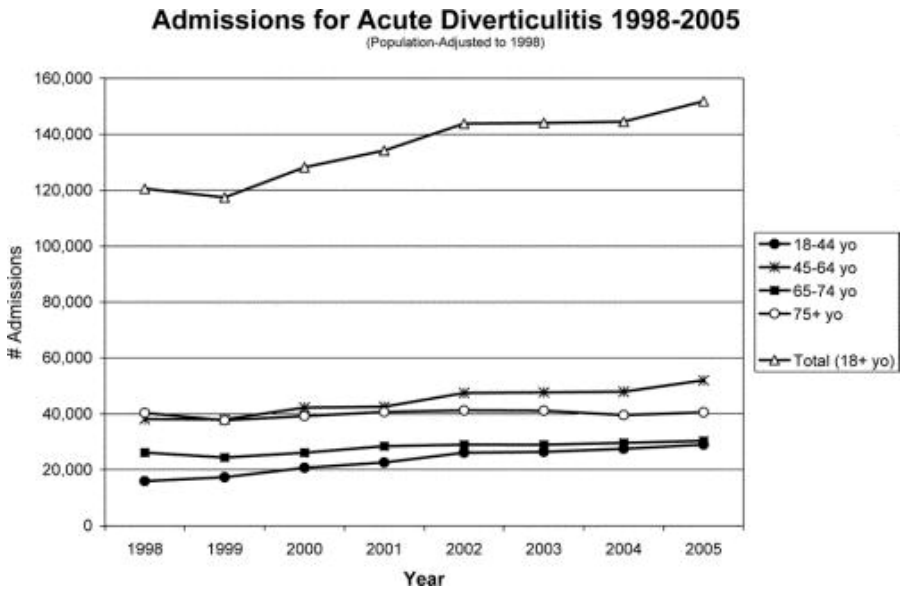
NHS Countess of Chester Hospital NHS Foundation Trust

Diverticular disease: impact

- 5th most important GI disease in the western world based on direct and indirect costs
- US 2004 national audit data
  - 312,000 admissions
  - 1.5 million inpatient days
  - $2.6 billion
- UK 2005 NHS data
  - 217,000 bed days (more than UC and CD combined!)
  - 2000 deaths (vs. 300 for UC and CD combined)

Diverticular disease complications: epidemiology





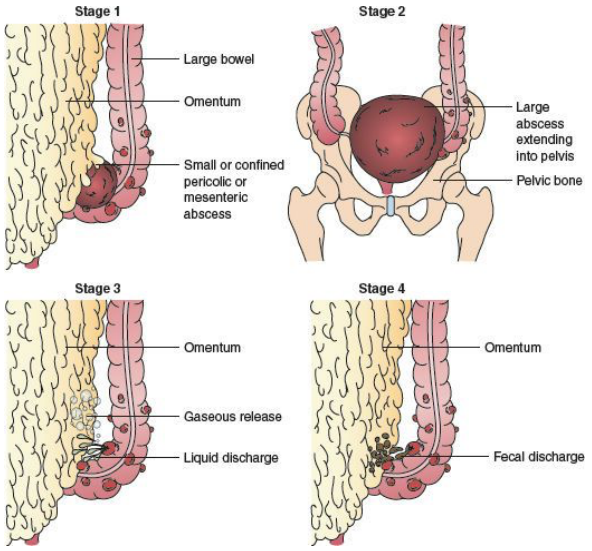
Humes *et al*, *Gastroenterology* 2009; 136: 1198-1205.
Etzioni *et al*, *Ann Surg* 2009; 249: 210-217.

Diverticular disease: Hinchey Classification

- Hinchey 0: mild clinical diverticulitis
- Hinchey Ia: confined pericolic inflammation, phlegmon
- Hinchey Ib: confined pericolic abscess
- Hinchey II: pelvic, distant intra-abdominal abscess
- Hinchey III: generalised purulent peritonitis
- Hinchey IV: faecal peritonitis

Treatment of perforated diverticular disease of the colon.
E J Hinchey, P G Schaal, G K Richards.
Adv Surg 1978;12:85-109.

Dr. Gerald Fried (right) presents Dr. John Hinchey with his Honourary member certificate.



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NHS
Countess of Chester Hospital
NHS Foundation Trust

Diverticular disease: management evidence base

- Hinchey 0: mild clinical diverticulitis
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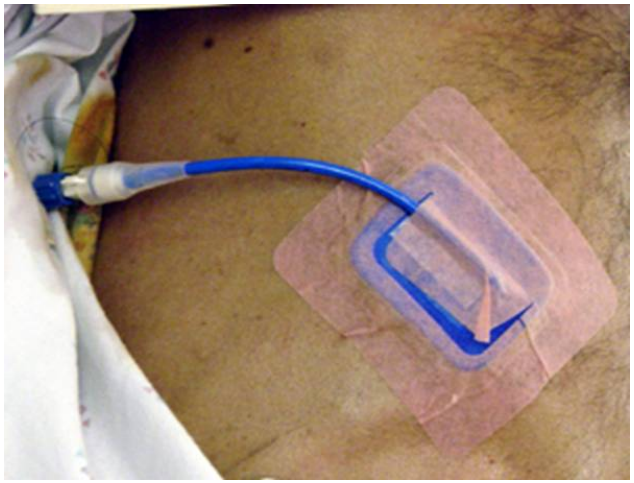
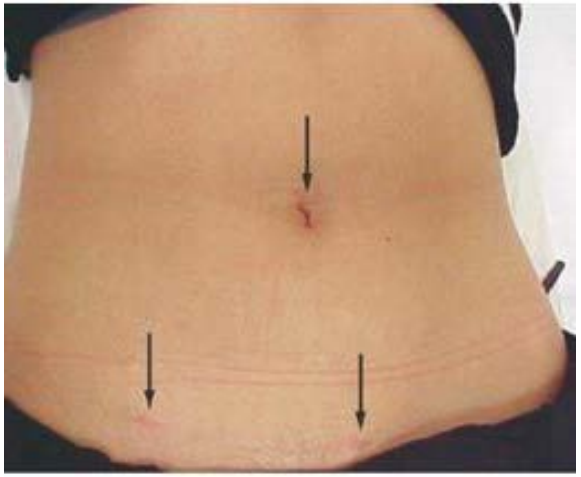


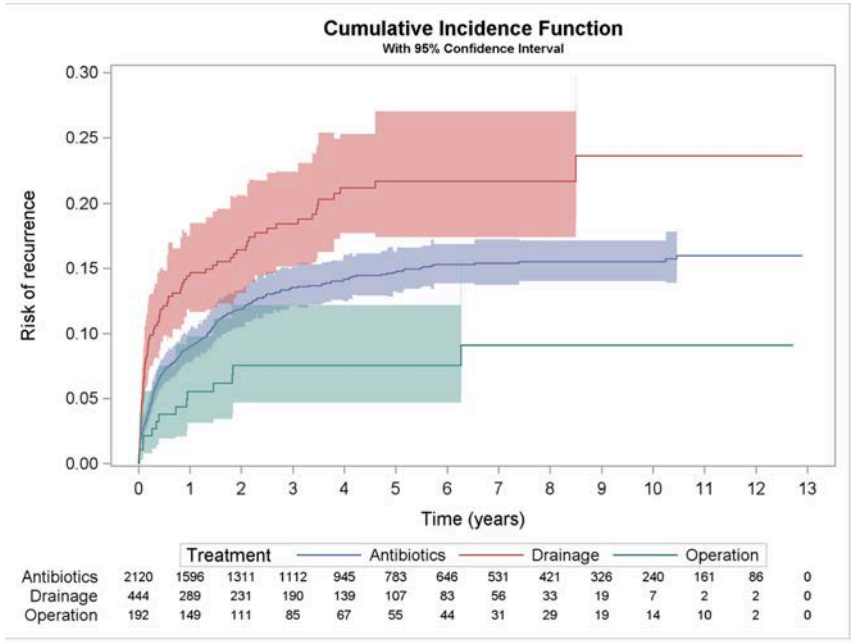


VS.

OR

Diverticular abscess: variation

Year	Authors	Type	No.	Failure rate	Colectomy rate	Recurrence rate
2008	Singh et al.	Retrospective	26	38%	31%	
2013	Gaetner et al.	Retrospective	218		85%	
2014	Lamb et al.	Sys review	1050	61%	72%	
2015	Elagili et al.	Retrospective	114			
2016	Gregersen et al.	Retrospective	8766	20%		25%
2016	Deveraj et al.	Retrospective	65		59%	74%
2016	Buchwald et al.	Retrospective	107			27%
2018	Gregersen et al.	Retrospective	3148			23.6%
2018	You at al.	Prospective	81		0%	32%



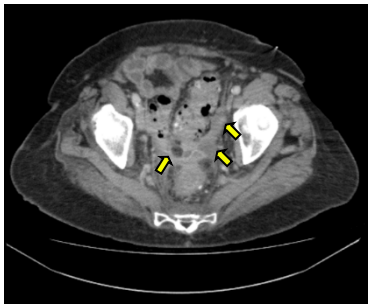
Gregersen R *et al. Int J Colorectal Dis.* 2018; 33: 431-440.

2020 VISION: small numbers=BIG study

DAMASCuS: co-primary objectives

1. Record national and international variation in initial management (at index admission).
2. To determine the effectiveness of surgery (vs. non-surgical management) in patients with diverticular abscesses based on a superiority margin of 0.1 using EQ-5D-5L index

Selection = diverticular abscess



Patient Identifiable Information and Consent

NHS Direct Care Teams

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Pseudonymised Patient Reported Outcome Measures

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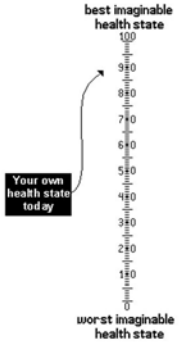
Serial stepped (3 monthly) measurement

Paper CRFs

- Baseline disease and patient factors
- Management data inc. surgical (if performed)
- LOS
- 30 day complications inc. death



EQ-5D

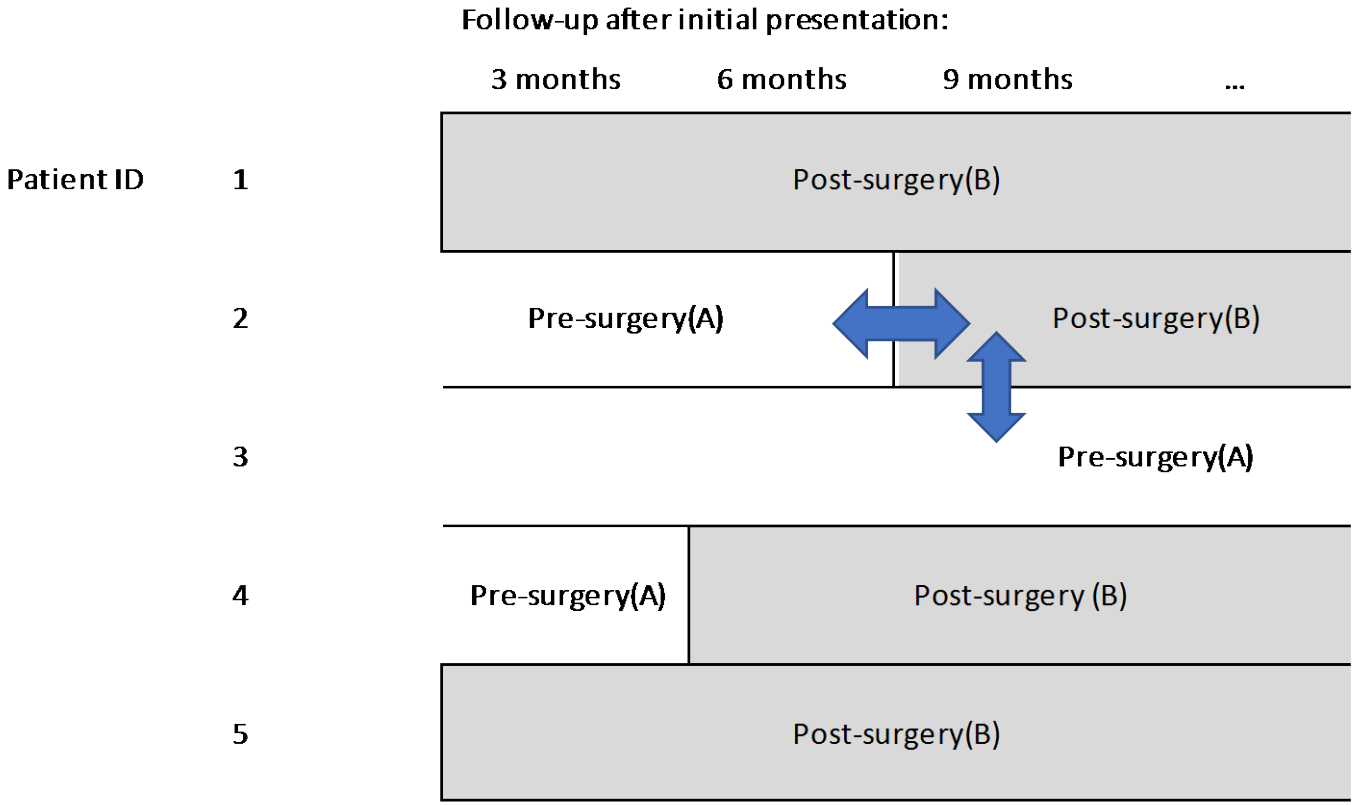
- MOBILITY
  - I have no problems in walking about
  - I have some problems in walking about
  - I am confined to bed
- SELF-CARE
  - I have no problems with self-care
  - I have some problems washing or dressing myself
  - I am unable to wash or dress myself
- USUAL ACTIVITIES (e.g. work, study, housework family or leisure activities)
  - I have no problems with performing my usual activities
  - I have some problems with performing my usual activities
  - I am unable to perform my usual activities
- PAIN/DISCOMFORT
  - I have no pain or discomfort
  - I have moderate pain or discomfort
  - I have extreme pain or discomfort
- ANXIETY/DEPRESSION
  - I am not anxious or depressed
  - I am moderately anxious or depressed
  - I am extremely anxious or depressed

2

Objective 1

Objective 2

DAMASCuS: analysis



- Is state B superior to state A based on QoL?
- Is an early switch from A to B superior to later switch

DAMASCuS: risks

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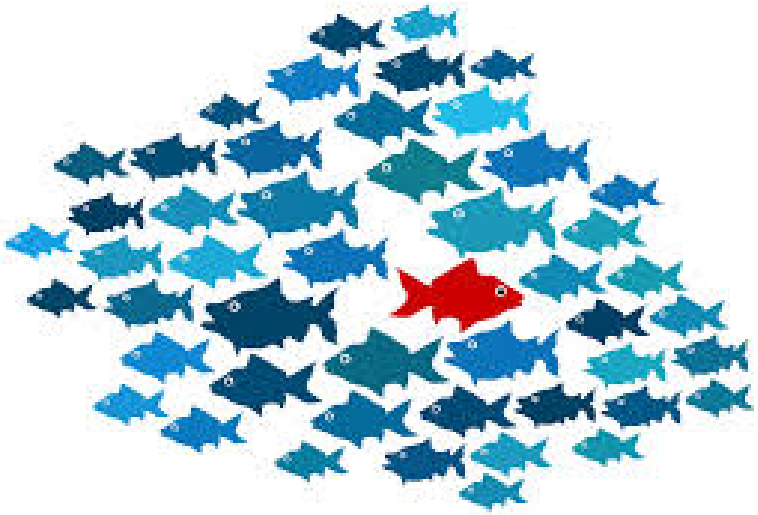
NHS Direct Care Teams		Research Centre Hub

Surgeon acceptability (CRF filling)

Data linkage unlikely

Patient acceptability and platform



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COHORT STUDIES & AUDITS

Thus far, the ESCP has adopted a strategy of promoting short duration, high volume prospective audits (termed snap-shot audits) and these have been hugely successful (see below).

It is, however, an ambition of the research committee that before 2020, the ESCP will identify and promote at least two major prospective cohort studies with sufficient patient-level follow up to derive meaningful functional outcomes for colorectal interventions with uncertain (inadequate or contradictory) clinical effectiveness. Such outcomes will ideally cross-reference to ESCP development work in core outcome sets, especially patient-reported outcome measures (PROMS).

PROMISE

PCTU

Summary

- The RCT is not the only valid method for developing clinical evidence and has particular issues (of both internal and external validity) in surgical research
- Observational designs are not bad, we (surgeons) just do them badly
- High-quality and quasi-experimental observational studies are possible and represent a major opportunity for evidence generation in surgery
- Applications in process