



Leeds Surgical Trials Centre
Leeds Institute of Clinical Trials Research



@leeds_stc
@LeedsCTRU



UNIVERSITY OF LEEDS

Surgical Trials Methodology: a Bright Future

Professor Deborah D Stocken PhD Cstat
NIHR Research Professor

UKCRC
Registered
Clinical
Trials Units



FUNDED BY

NIHR

National Institute for
Health and Care Research



Core Values: Collaboration, Innovation, Excellence

CTRU Overview: International Leader in Clinical Trials Research

- ❖ Large UK CTU ~ 220 staff across 4 Research Divisions
- ❖ International and National Trials Portfolio
- ❖ Early and Late Phase Trials Portfolio
- ❖ Expertise in innovative trials methodology, dedicated Methodology Division
- ❖ Academic partnership and leadership in research conduct and dissemination

CTRU: Interventions

- ❖ Surgery
- ❖ Medical devices
- ❖ Imaging
- ❖ Diagnostics
- ❖ CTIMPs (phase 1-4)
- ❖ Radiotherapy
- ❖ Complex interventions
- ❖ Rehabilitation

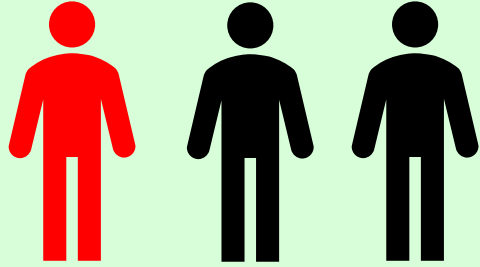
Challenges in Clinical Trial Design

- **P**opulation: variability in types and stage, generalisability
- **I**nterventions: systemic, surgery, ablation, RT, watchful wait
- **C**ontrol: variable SOC
- **O**utcomes: morbidity, pain, safety, surgical success, response
- **S**tatistical Design: ensuring quality evidence and conclusions
 - Hypothesis – superiority / non-inferiority
 - Phase – specific to hypothesis/ outcomes, position in research pathway
 - Design – prospective cohort/ RCT/ adaptive, specific to phase
 - SAP – specific to hypothesis, phase, design, intervention
 - Sample size – specific to SAP

**“Challenges are one of the best ways to spark innovation.
Test your mettle. Change the world”
Richard Branson**



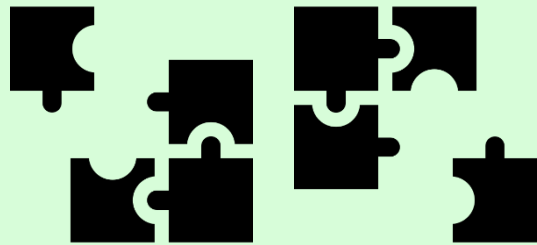
Mettle: [noun] a person's ability to cope well with challenges; spirit and resilience; strength of will and determination
e.g. the [trials] team proved its real mettle in the final [funding] round!



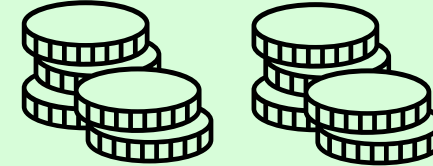
1 in 3 hospital admissions involve surgical care ~4.7million



Surgical innovations introduced without evidence



Complex, expensive, longer



<5% medical research budget
~ 4% NIHR portfolio studies

Characteristics of Randomized Clinical Trials in Surgery From 2008 to 2020

A Systematic Review *Robinson, JAMA Open 2021*

Table 2. Trial Design of 388 Included Trials

Variable	Frequency, No. (%)	
Registration in trials registry	242 (62.4)	
Discrepancy between registered and primary outcome	81 (33.5)	←
Superiority design	329 (84.8)	
Estimated relative treatment effect, median (IQR), %	50.0 (24.7-63.3)	←
Sample size, median (IQR)		
Projected	144 (86-299)	
Final	122 (70-245)	←
Control for surgeons' experience		
None	303 (78.1)	←
Surgeons' experience cut-off	60 (15.5)	
Pretrial training	25 (6.4)	
Monitoring of the intervention		
None	371 (95.6)	←
Details of the experimental procedure		
None	41 (10.6)	
Limited	226 (58.2)	
Detailed	121 (31.2)	←
Risk of bias assessment		
Low risk	86 (22.2)	←
Some concerns	211 (54.4)	
High risk	91 (23.5)	

388 RCTs over 12 years

“Improvements in design, implementation and reporting of RCTs in surgery are warranted”

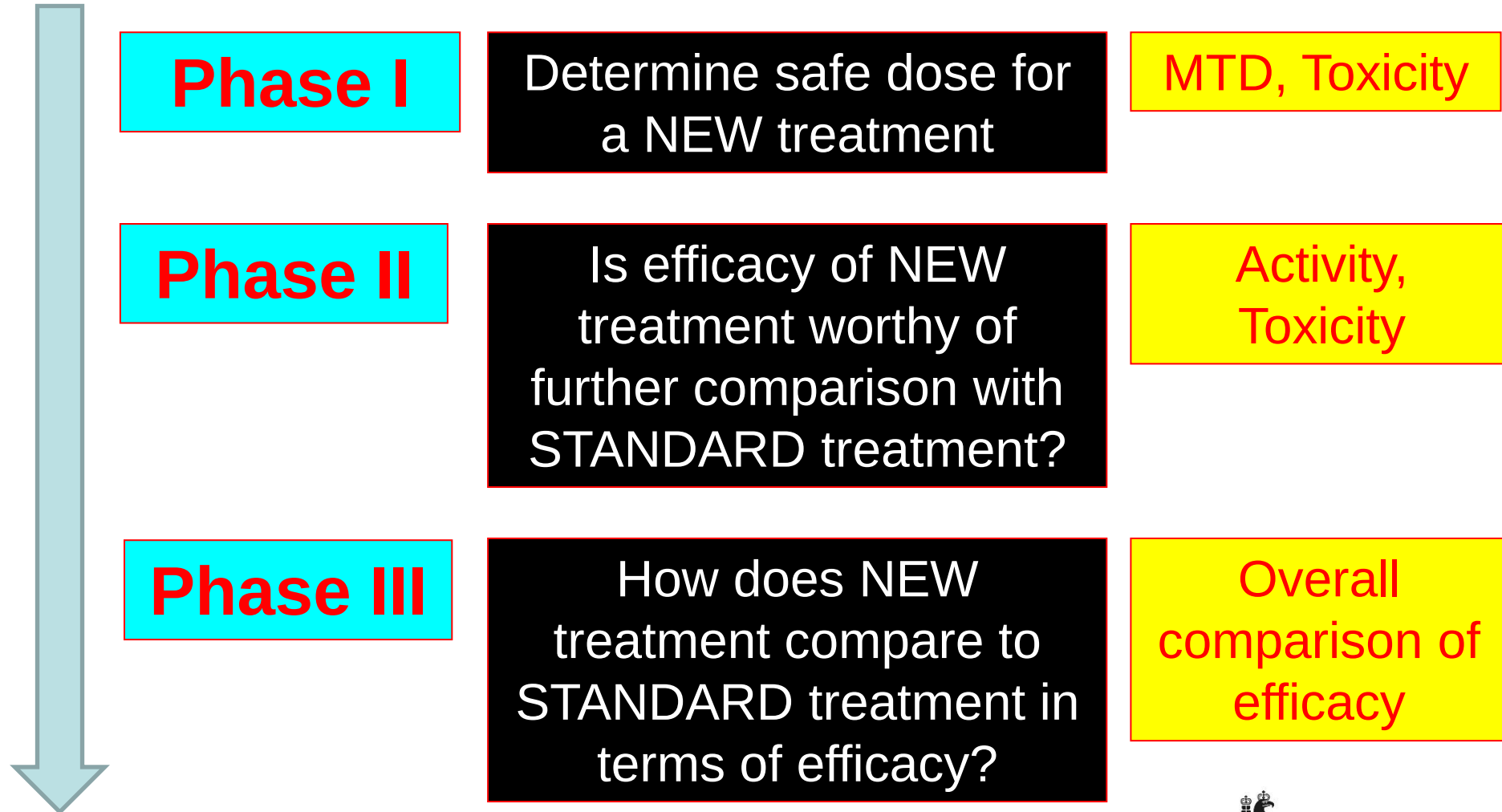
Why are Surgical Trials Difficult/ Different?

- Complex clinical environment
 - Understanding “buy-in”
 - Understanding behaviour change
- Research environment
 - Less well developed
- Individualised / tailored interventions
 - Multi-factorial structure with interacting components
 - Clustering effects of interventions and surgeons
 - Learning the intervention
 - Complex Interventions (MRC 2000, 2008, 2021)



Phases of Drug Evaluation

Pre-Clinical Studies: Lethal Dose



Phase IV: Surveillance of long-term effects

A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance

Skivington, 2021 BMJ [Campbell 2000, Craig 2008]

Interventions become more complex in line with increasing the:¹

- number of intervention components and the interactions between them
- range of behaviours, expertise and skills (e.g. particular techniques and communication) required by those delivering or receiving the intervention
- number of groups, organisational levels or settings that are targeted by the intervention
- level of flexibility or tailoring of the intervention or its components that is permitted (i.e. how dynamic or adaptive the intervention is).

Surgical specific challenges:

i) Multi-factorial structure, ii) Individualised interventions, iii) Clustering effects

No surgical innovation without evaluation: the IDEAL recommendations

Peter McCulloch, Douglas G Altman, W Bruce Campbell, David R Flum, Paul Glasziou, John C Marshall, Jon Nicholl, for the Balliol Collaboration*

IDEAL Framework

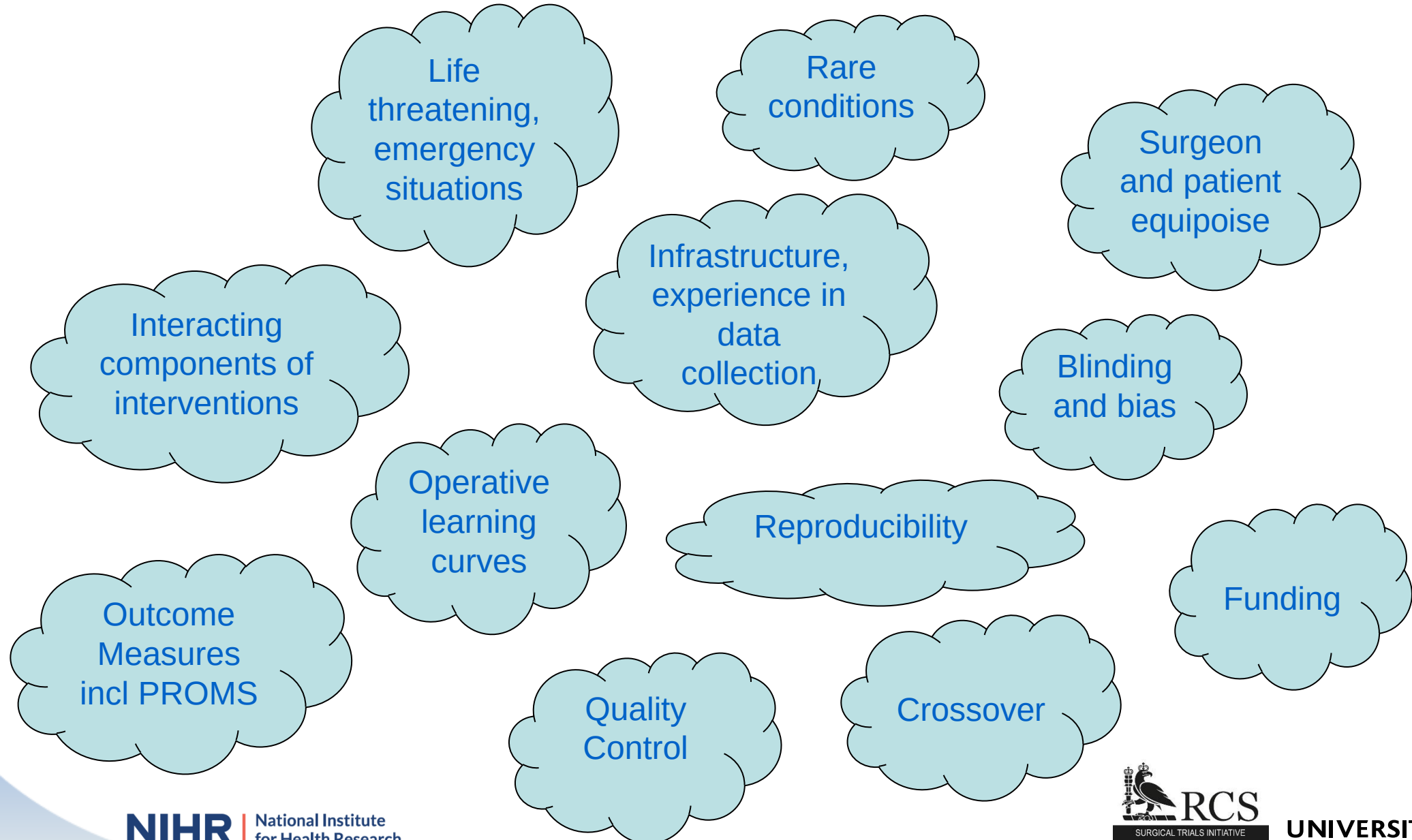
Lancet 2009, Annals Surg 2019

	1 Idea	2a Development	2b Exploration	3 Assessment	4 Long-term study
Purpose	Proof of concept	Development	Learning	Assessment	Surveillance
Number and types of patients	Single digit; highly selected	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-term 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 obese patients study ⁹	UK national adult cardiac surgical database ¹⁰

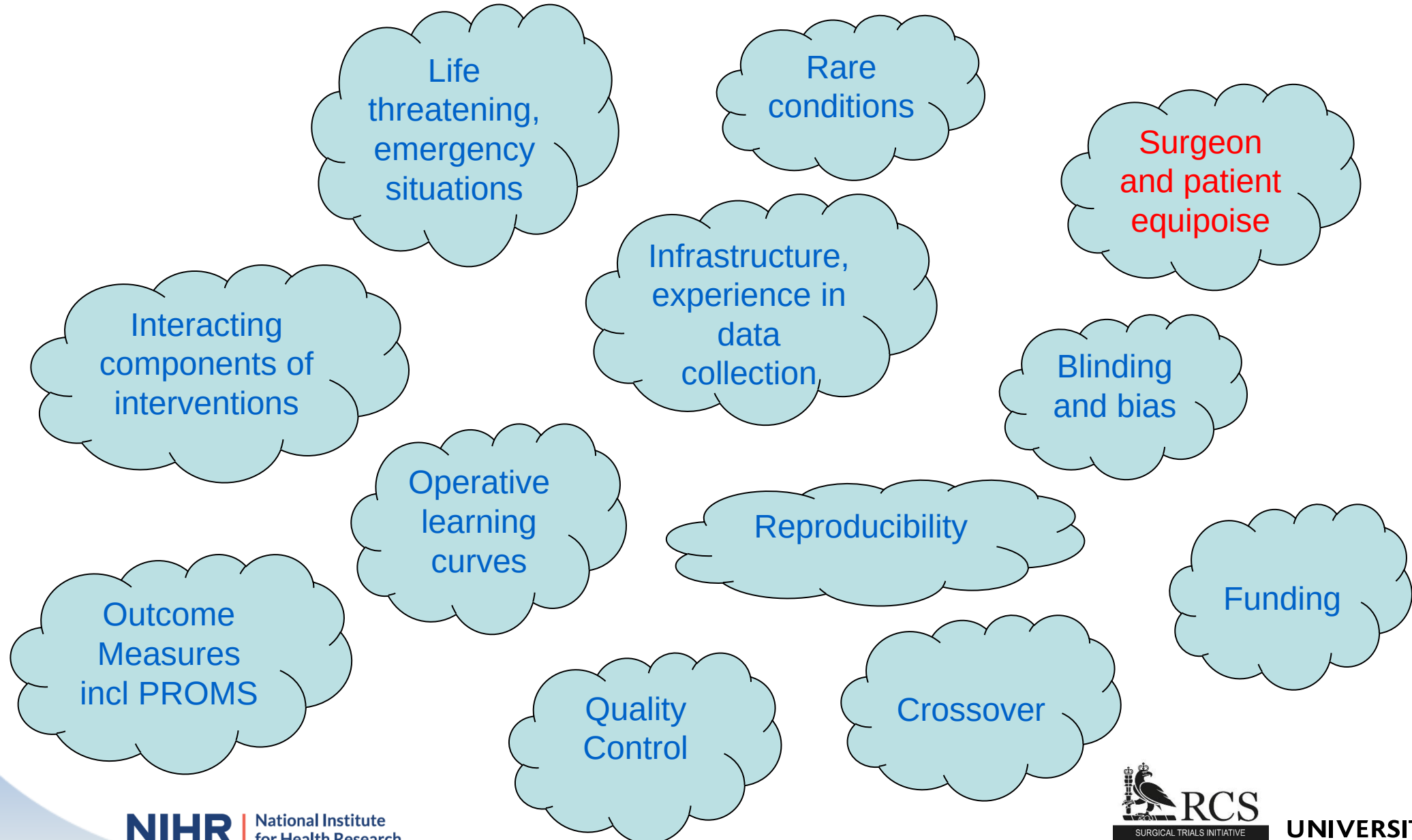
RCT=randomised controlled trial. SCOAP=Surgical Clinical Outcomes Assessment Programme. STS=Society of Thoracic Surgeons. NSQIP=National Surgical Quality Improvement Program. NOTES=natural orifice transluminal endoscopic surgery.

Table: Stages of surgical innovation

Challenges in Surgical Trial Design and Delivery



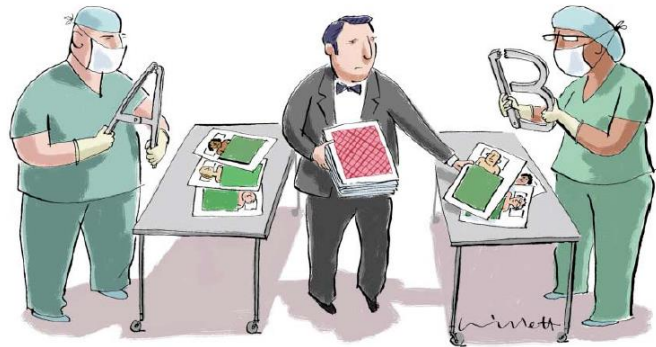
Challenges in Surgical Trial Design and Delivery



Individual vs Community Equipoise

Lilford, 1995

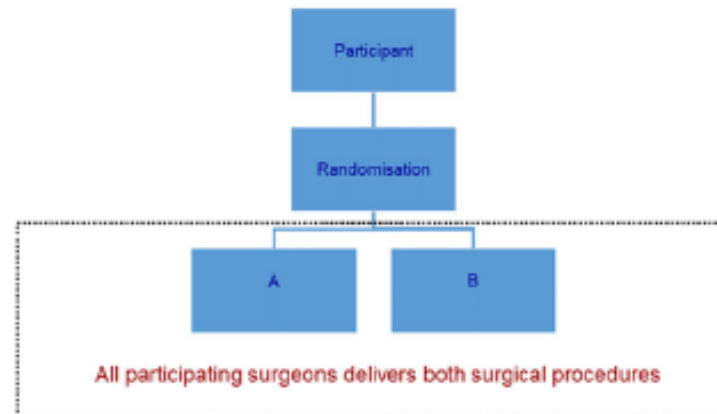
- Individual investigators are allowed to NOT sit on the fence
- Best practice is derived from community of experts who MUST be in equipoise



Need for expertise based randomised controlled trials *BMJ 2005*

P J Devereaux, Mohit Bhandari, Mike Clarke, Victor M Montori, Deborah J Cook, Salim Yusuf, David L Sackett, Claudio S Cinà, S D Walter, Brian Haynes, Holger J Schünemann, Geoffrey R Norman, Gordon H Guyatt

Standard (within-surgeon) trial design



Expertise-based trial design

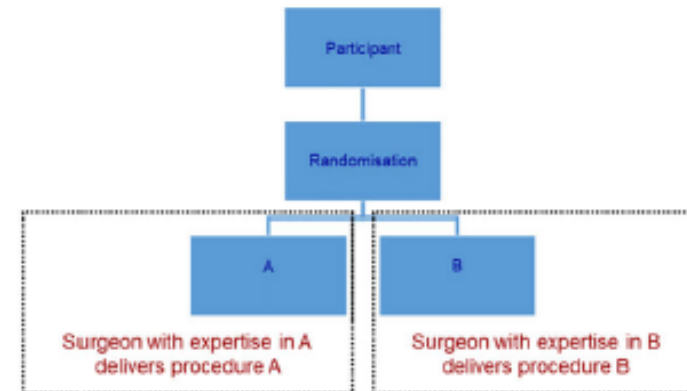


Fig. 1 Standard and expertise-based two-arm trial designs

Expertise-Based Designs

- “Both surgeons and methodologists saw potential advantages in the expertise-based design.....”
- “Several logistical and methodological concerns remain to be addressed before being more widely adopted.”



RESEARCH

Open Access

Surgeons' and methodologists' perceptions of utilising an expertise-based randomised controlled trial design: a qualitative study



Jonathan A. Cook^{1,2*} , Marion K. Campbell³, Katie Gillies³ and Zoë Skea³

Table 1 Participants' perceived potential advantages and disadvantages of an expertise-based versus a standard trial design

Expertise-based versus standard trial design

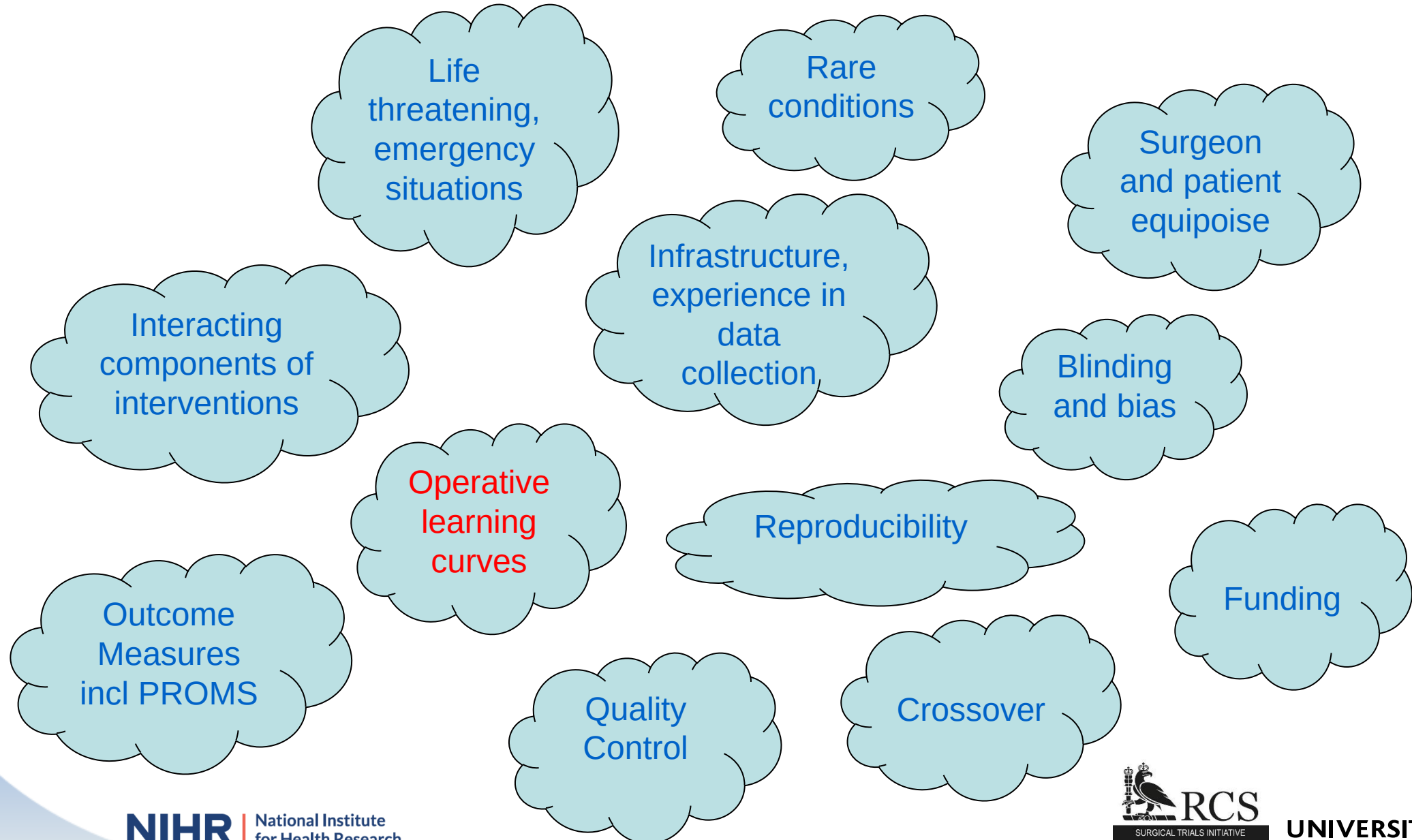
Advantages

- Greater accommodation of surgeons' treatment preferences
- Treatments performed in their 'best light'
- More appealing to patients
- Better suited to some clinical settings

Disadvantages

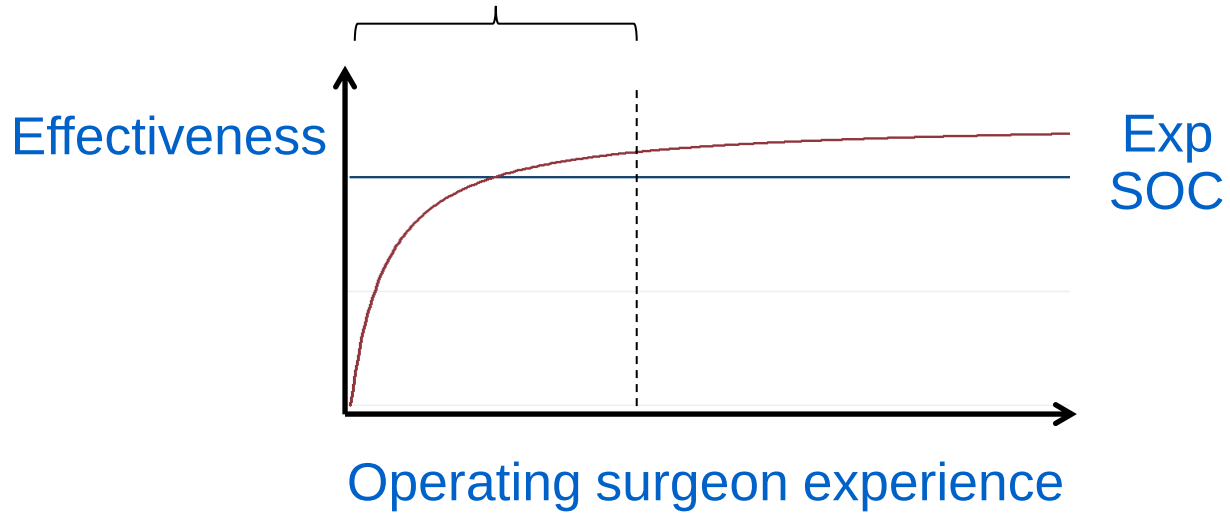
- Added complexity in terms of site set and administration, including greater co-ordination between surgeons required
- Design specific challenges which need to be addressed (e.g. defining an expert)
- Impact upon the patient-surgeon relationship
- Relation to clinical practice
- Perception of stakeholders

Challenges in Surgical Trial Design and Delivery



Learning Curve Effect

Learning curve effect: an improvement in performance over time



Ramsey, 2000

“Statistical methods used are weak”

“...need for methods that can estimate the rate and length of learning...”

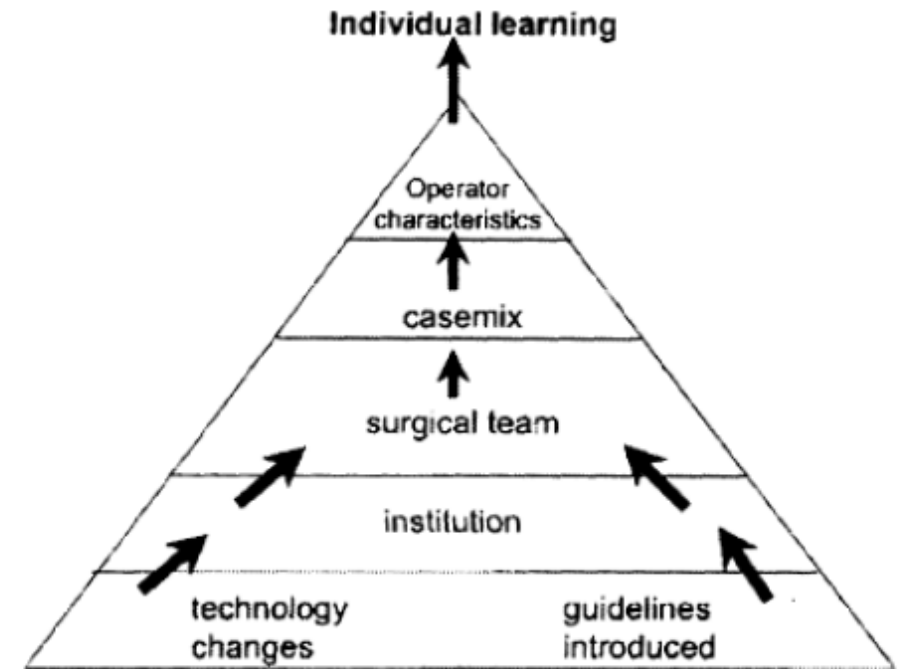


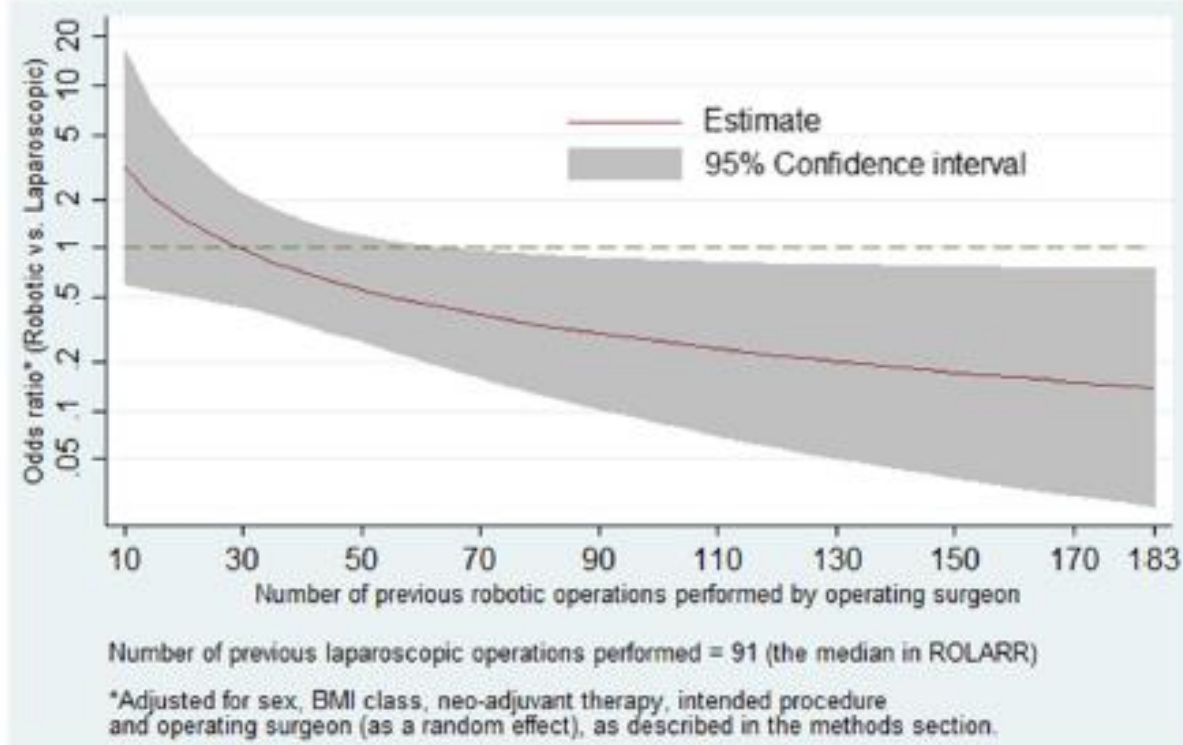
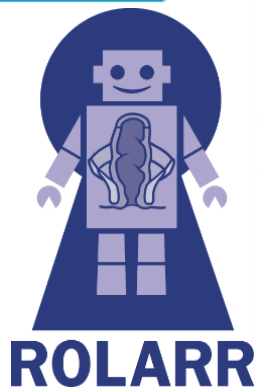
Figure 1 Hierarchical factors that influence learning.

RESEARCH

Open Access

Exploring and adjusting for potential learning effects in ROLARR: a randomised controlled trial comparing robotic-assisted vs. standard laparoscopic surgery for rectal cancer resection

Neil Corrigan^{1*} , Helen Marshall¹, Julie Croft¹, Joanne Copeland¹, David Jayne² and Julia Brown¹

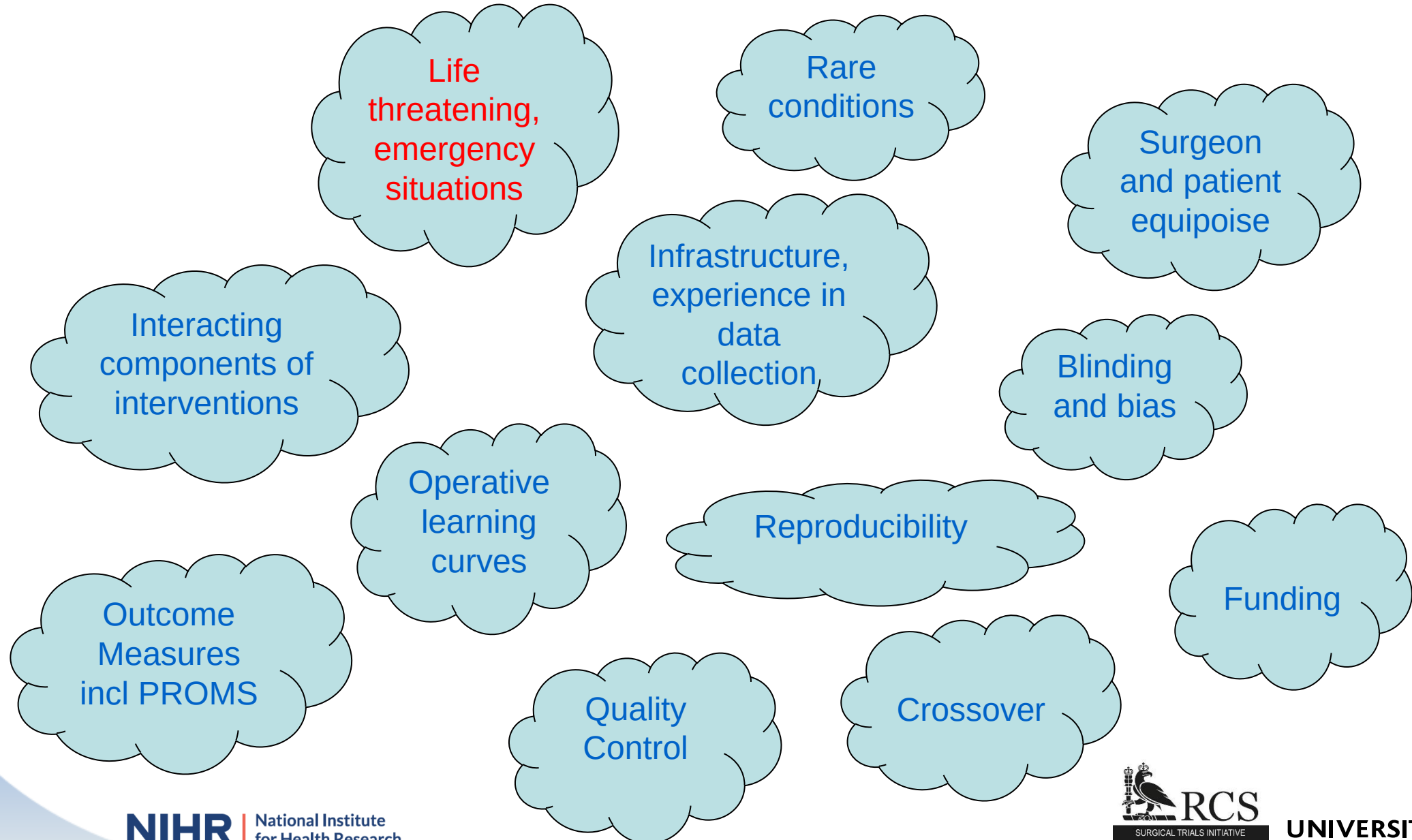


Managing clustering effects and learning effects in the design and analysis of randomised surgical trials: a review of existing guidance

Elizabeth J. Conroy^{1,2*} , Jane M. Blazeby³ , Girvan Burnside¹ , Jonathan A. Cook²  and Carrol Gamble¹ 

- 2/3 target design, 1/3 analysis
- Clustering by surgeon less documented
- Guidance on reporting restricted to early phase

Challenges in Surgical Trial Design and Delivery

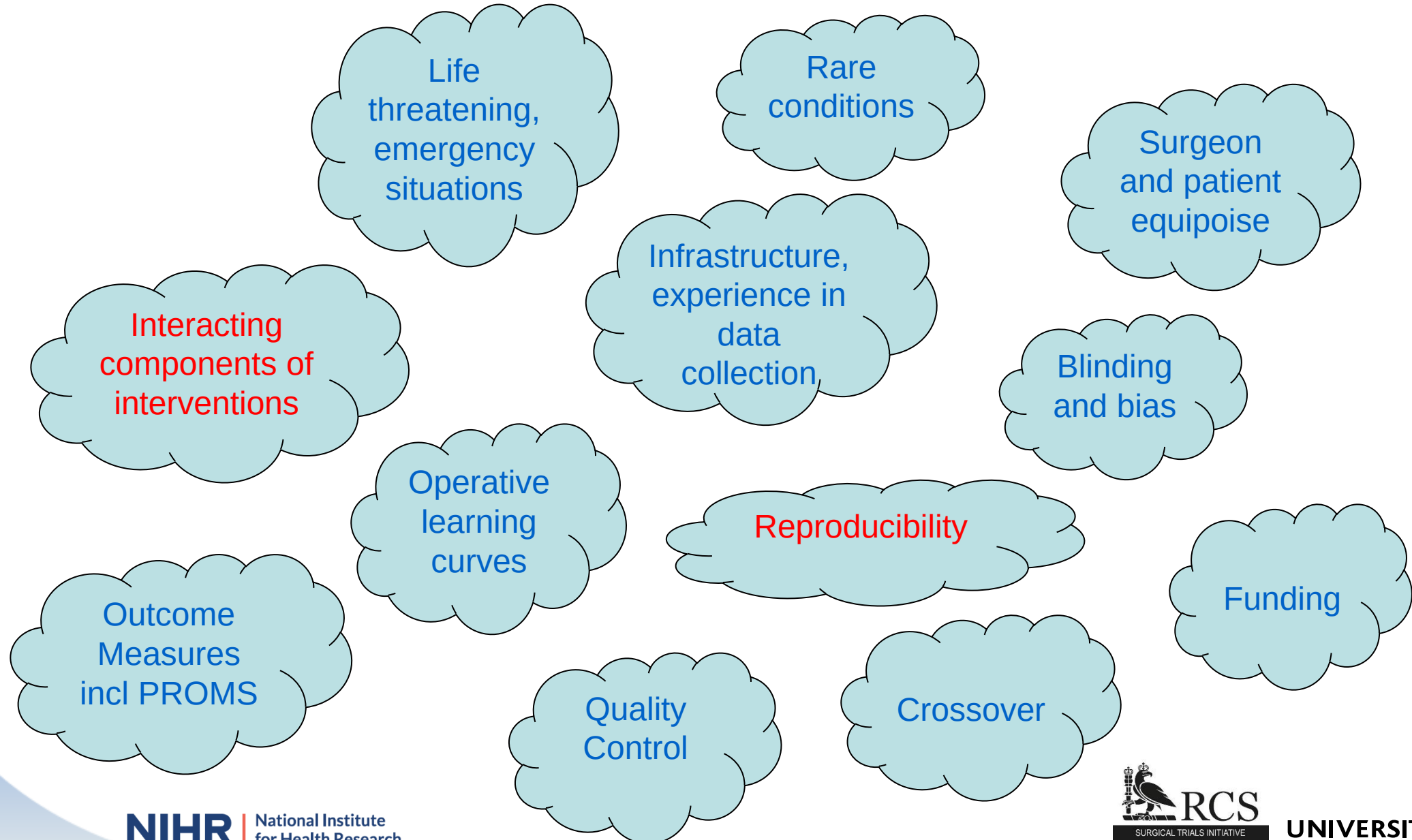


Emergency Surgery

- Regulatory
 - Patient information and consent
- Deliverability
 - Pre-randomisation assessments: PROMS
- Surgical availability
 - On call surgeons
- Methodological
 - Confounded outcomes: multi-morbidities



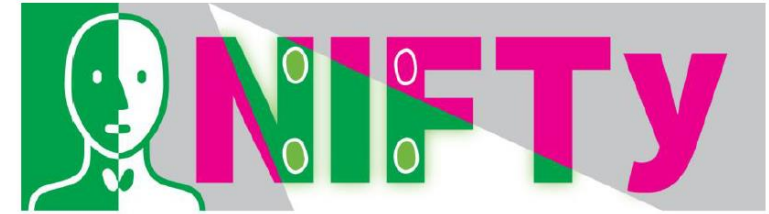
Challenges in Surgical Trial Design and Delivery



Intervention Development and Reproducibility

- Framework for Identifying Intervention Components *BJS 2016*

Standardizing and monitoring the delivery of surgical interventions in randomized clinical trials



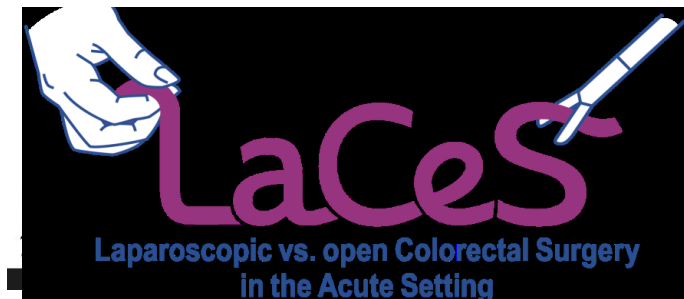
N. S. Blencowe^{1,3}, N. Mills¹, J. A. Cook⁴, J. L. Donovan¹, C. A. Rogers^{1,2}, P. Whiting¹,
J. M. Blazeby^{1,3}

Near Infrared Fluorescence imaging to prevent post-surgical hypoparathyroidism after Thyroid surgery

- Pre-trial work to optimise definitive surgical studies *BJS 2019*

Value of surgical pilot and feasibility study protocols

K. Fairhurst¹ , J. M. Blazeby¹ , S. Potter¹ , C. Gamble², C. Rowlands¹ and K. N. L. Avery¹



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Table: Stages of surgical innovation

Feasibility

? What is Feasibility?

- NIHR: “whether something can be done”
- E.g. intervention delivery, data collection, trial recruitment

? What about “activity”

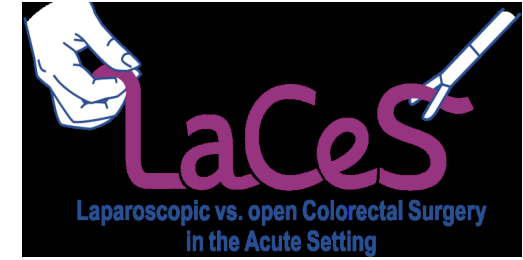
Considerations

? What to measure

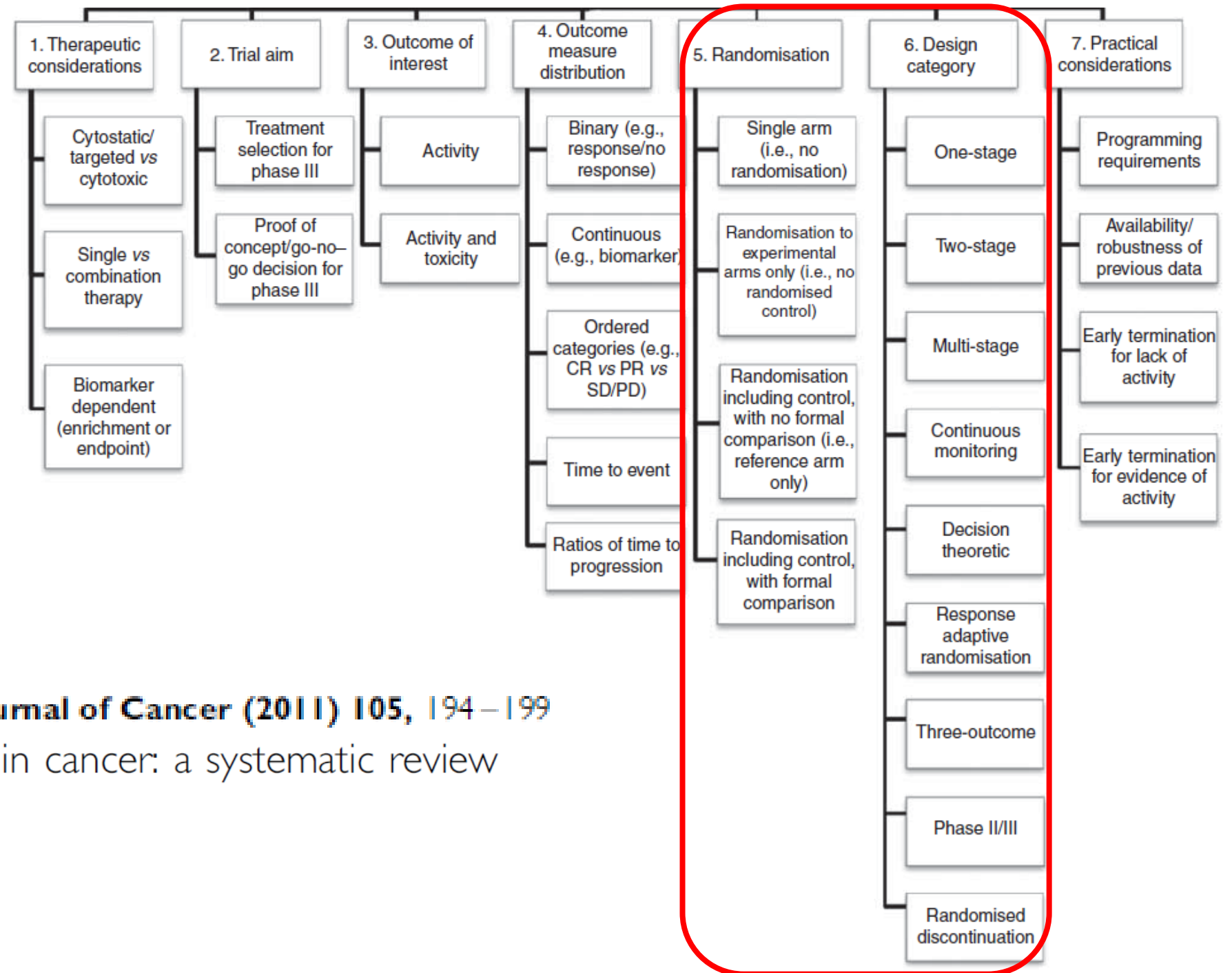
“Response” = surgical success, complications, mechanistic

? What if “response” > benchmark due to patient populations?

Do we need a control arm?



Early Phase Designs



SR Brown^{*,1} British Journal of Cancer (2011) 105, 194–199

Designing phase II trials in cancer: a systematic review and guidance

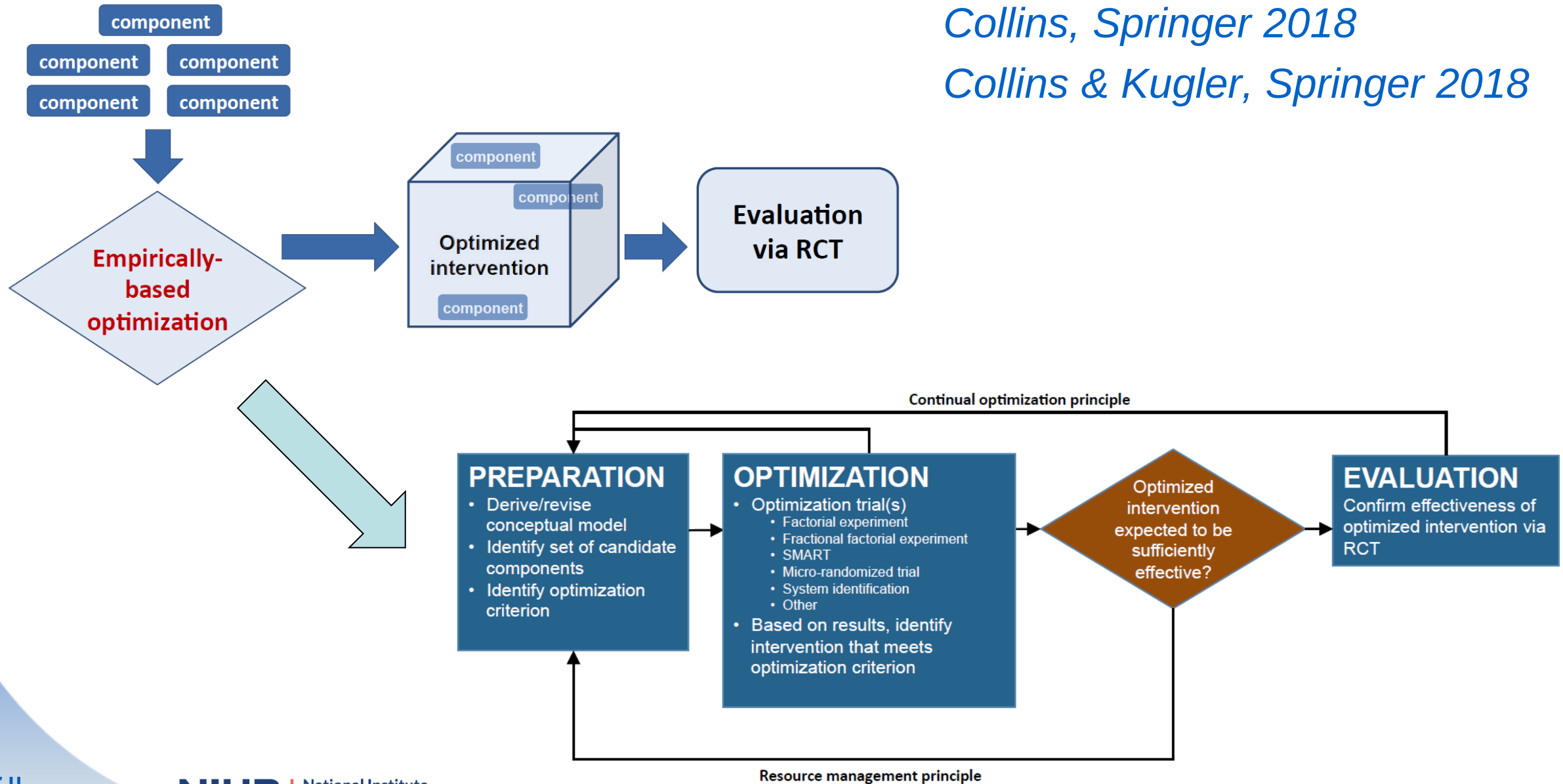
Early Phase Designs

- IDEAL2: Feasibility OR Smaller 'screening' studies
- Clinical aim
 - assess whether a new intervention is good enough to investigate further
- Statistical aim
 - identify probability of 'activity/ response' worthy of further investigation
- IDEAL-2a:
 - Single stage, two-stage, randomised
 - Shorter term surrogate outcomes - surgical success, complications
- IDEAL 2b:
 - Randomised - shorter term surgical success
 - Seamless: short term surgical success and longer term functioning

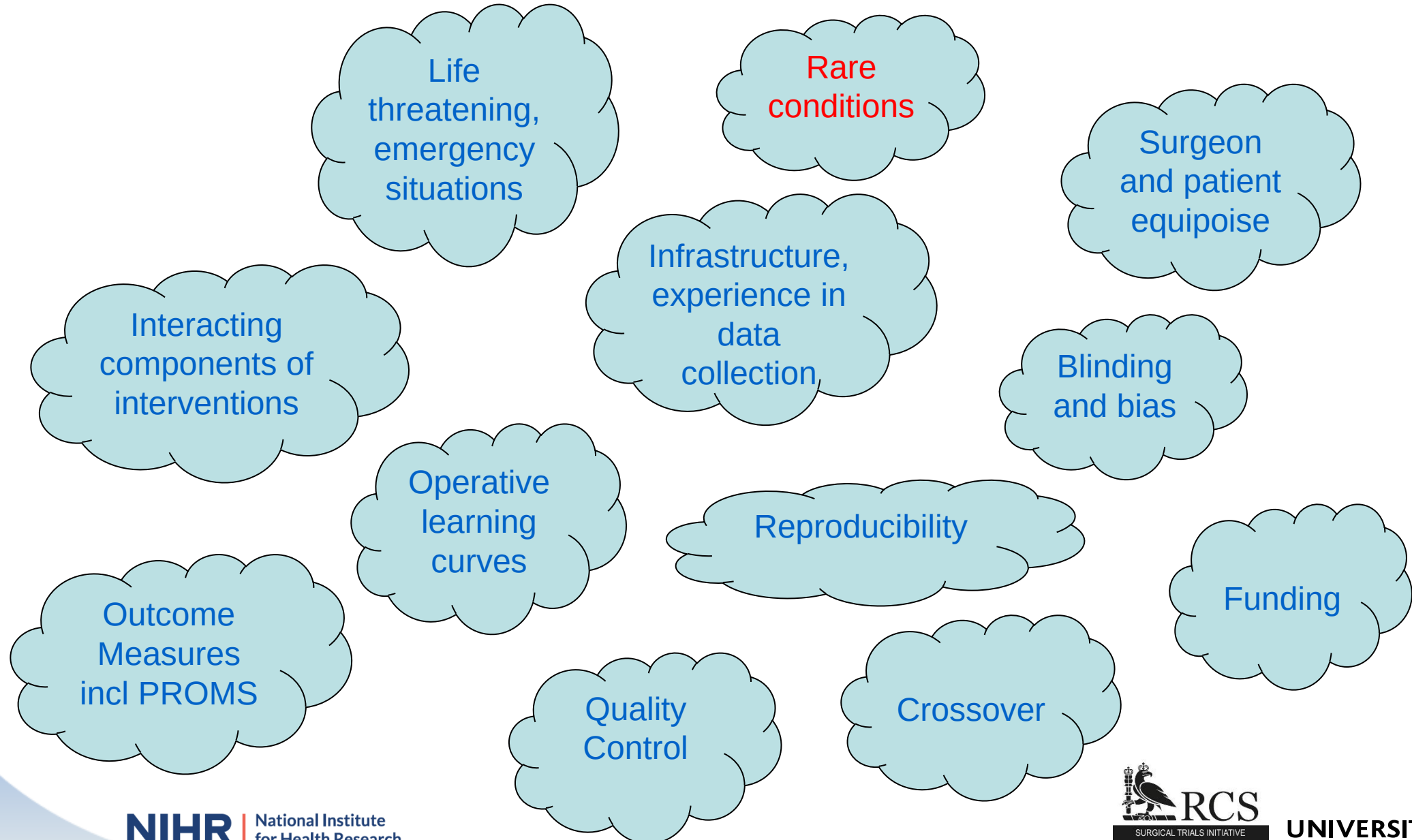
MOST: Multiphase Optimisation Strategy

Collins, Springer 2018

Collins & Kugler, Springer 2018



Challenges in Surgical Trial Design and Delivery

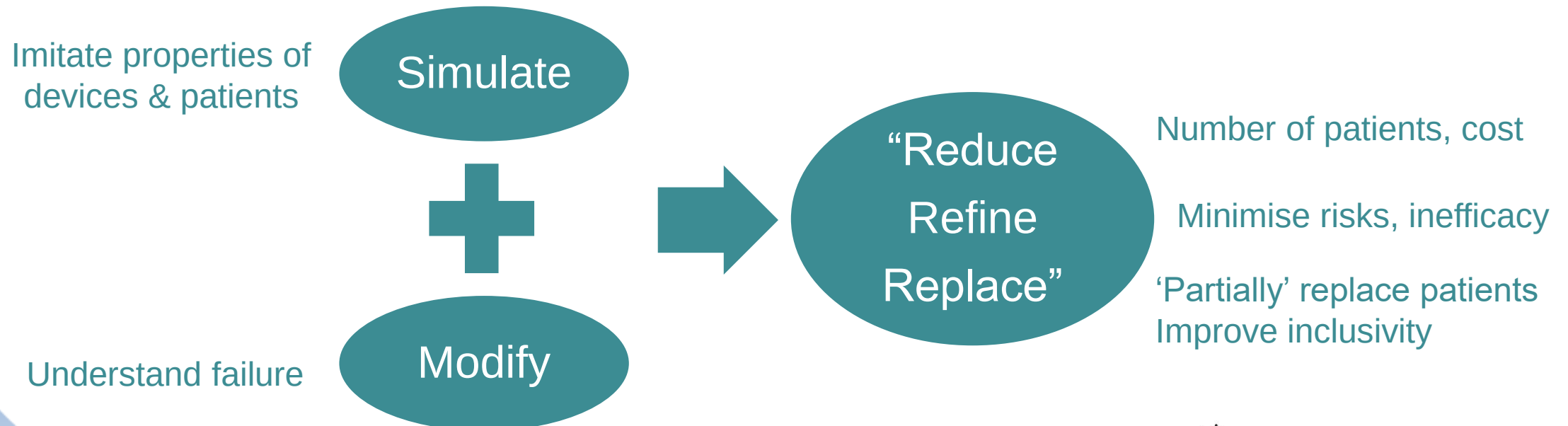


In Silico Clinical Trials

“The use of individualised computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention.”

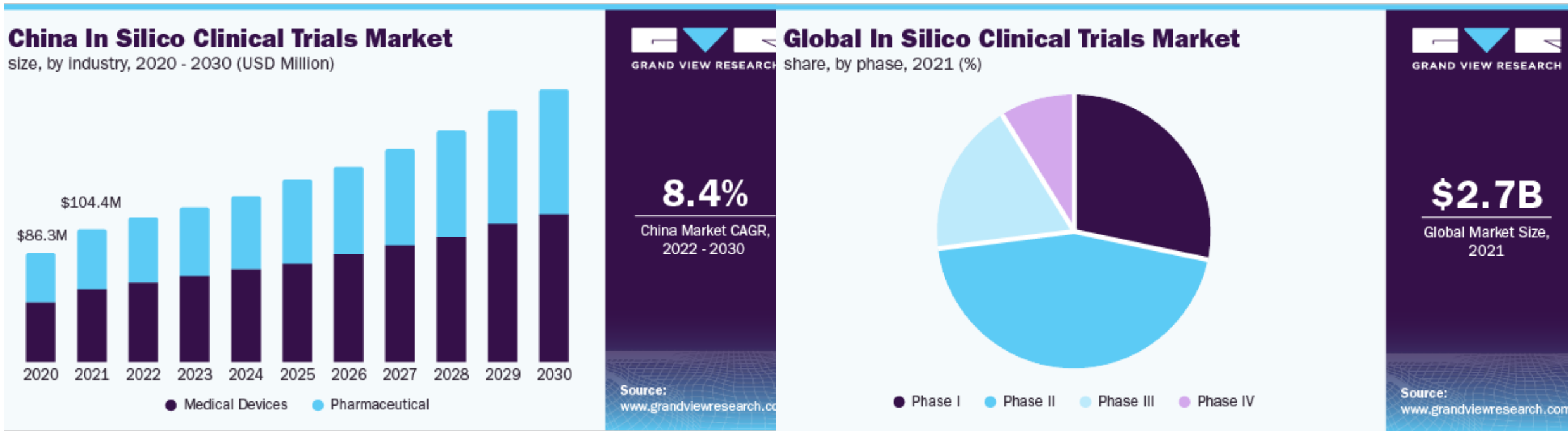
Viceconti, Int J Clin Trials 2016

Aim



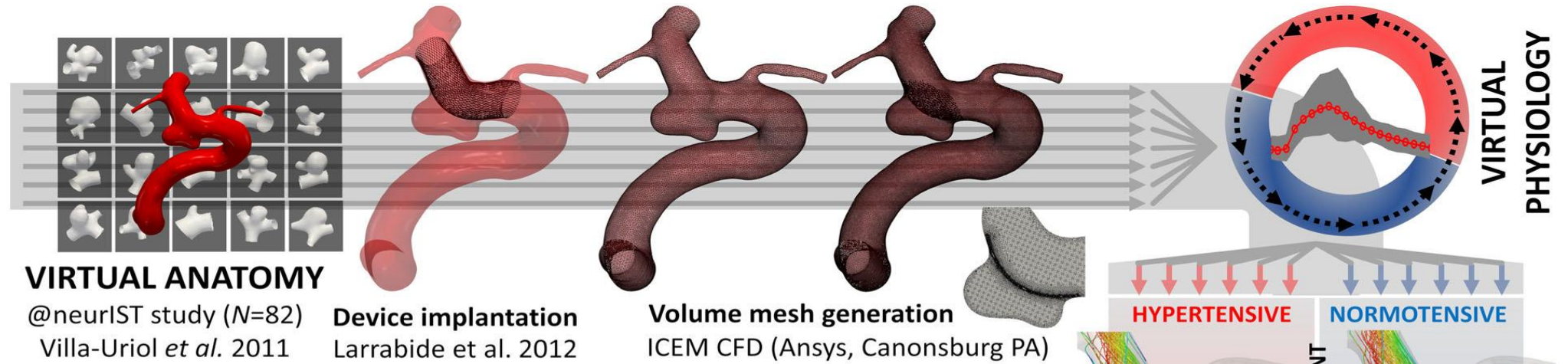
Explosion

"The utilization of computer simulations in healthcare is only going to increase..." Badano, 2021



In Silico Clinical Trials Market Size, Share & Trends Analysis Report By Therapeutic Area (Oncology, Infectious Diseases), By Phase (Phase I, II, III), By Industry (Medical Devices, Pharmaceutical), And Segment Forecasts, 2022 – 2030. Report ID: GVR-4-68039-914-9

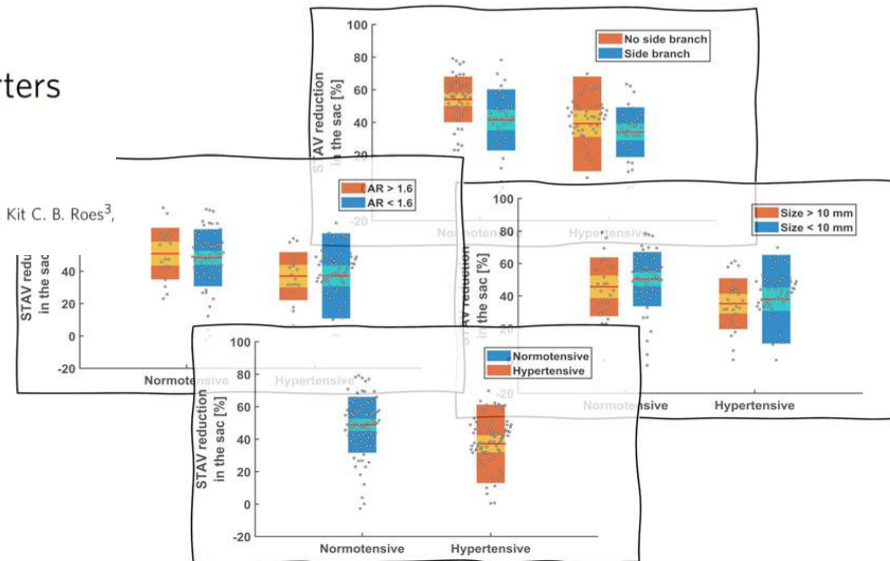
Example: FD-PASS



<https://doi.org/10.1038/s41467-021-23998-w> OPEN

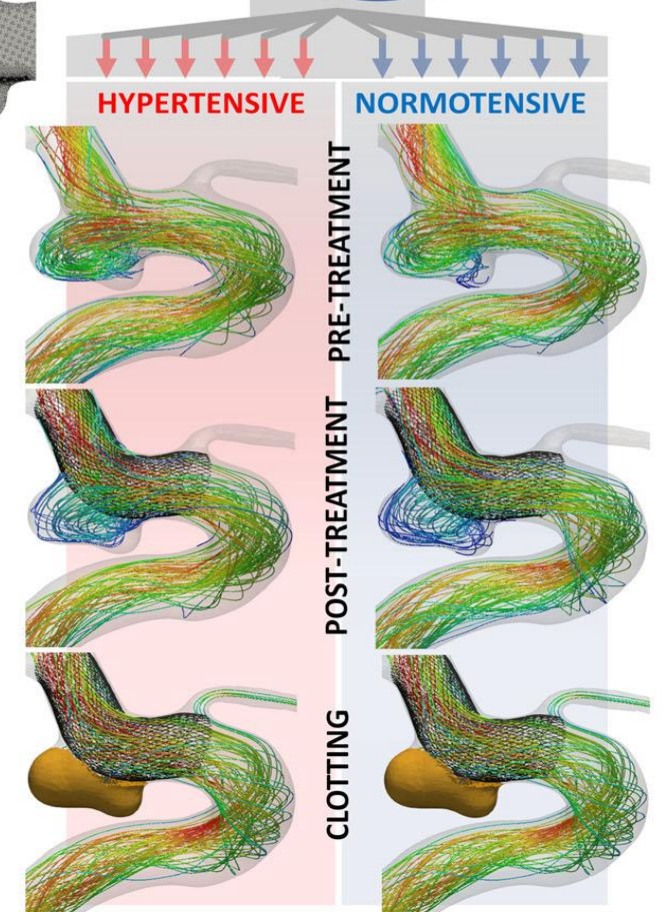
In-silico trial of intracranial flow diverters replicates and expands insights from conventional clinical trials

Ali Sarrami-Foroushani^{1,2}, Toni Lassila¹, Michael MacRaid¹, Joshua Asquith¹, Kit C. B. Roes³, James V. Byrne⁴ & Alejandro F. Frangi^{1,2,5,6}



Statistical analysis of device performance

Flow reduction -related endpoint (AMVR) acts as surrogate for complete occlusion (clinical endpoint)



Lassila et al. 2019 (N=164)

CFD modelling & simulation

Sarrami-Foroushani et al. 2019

Example: VICTRE

Badano *Trials* (2021) 22:64
<https://doi.org/10.1186/s13063-020-05002-w>

COMMENTARY

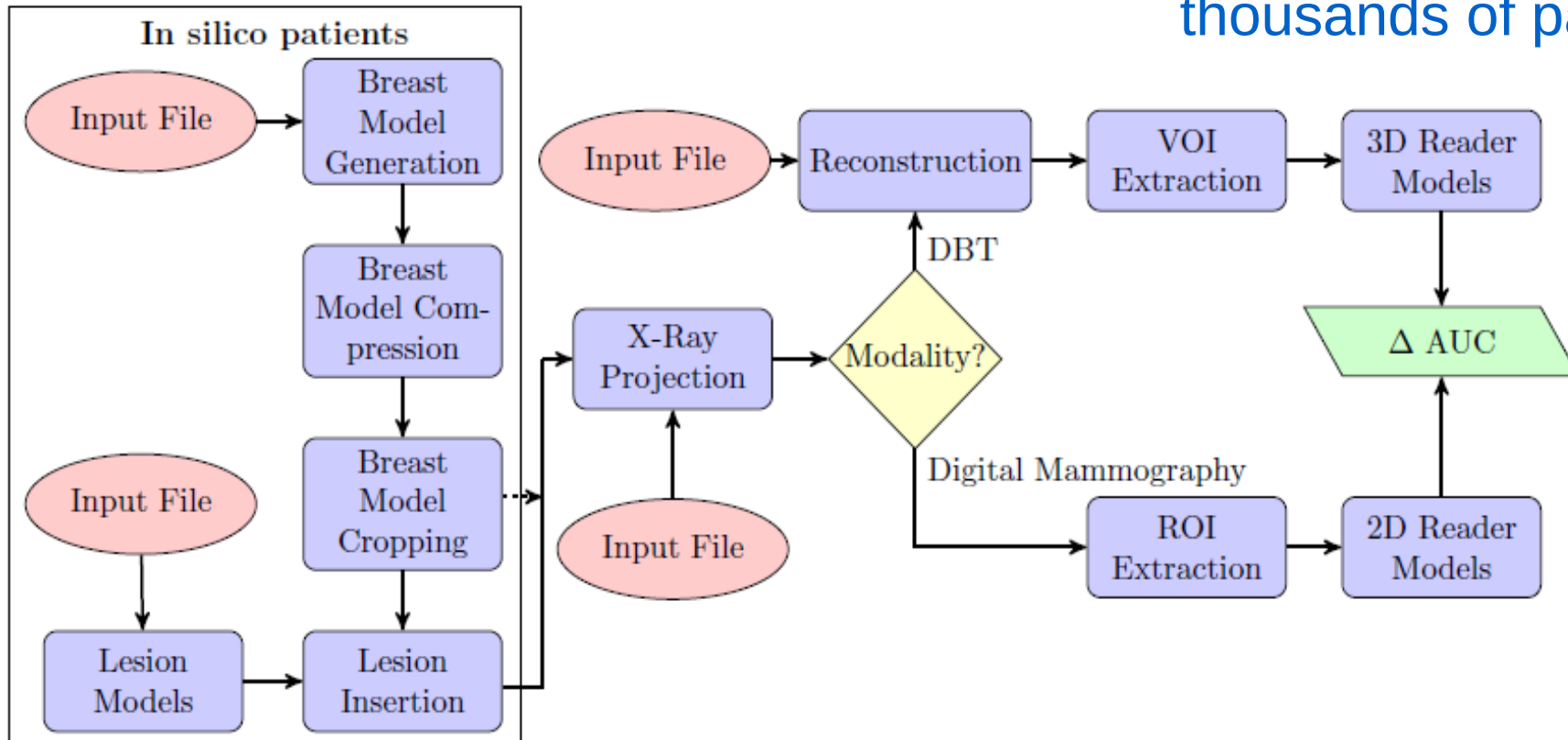
Open Access

In silico imaging clinical trials: cheaper, faster, better, safer, and more scalable

Aldo Badano 

Trials

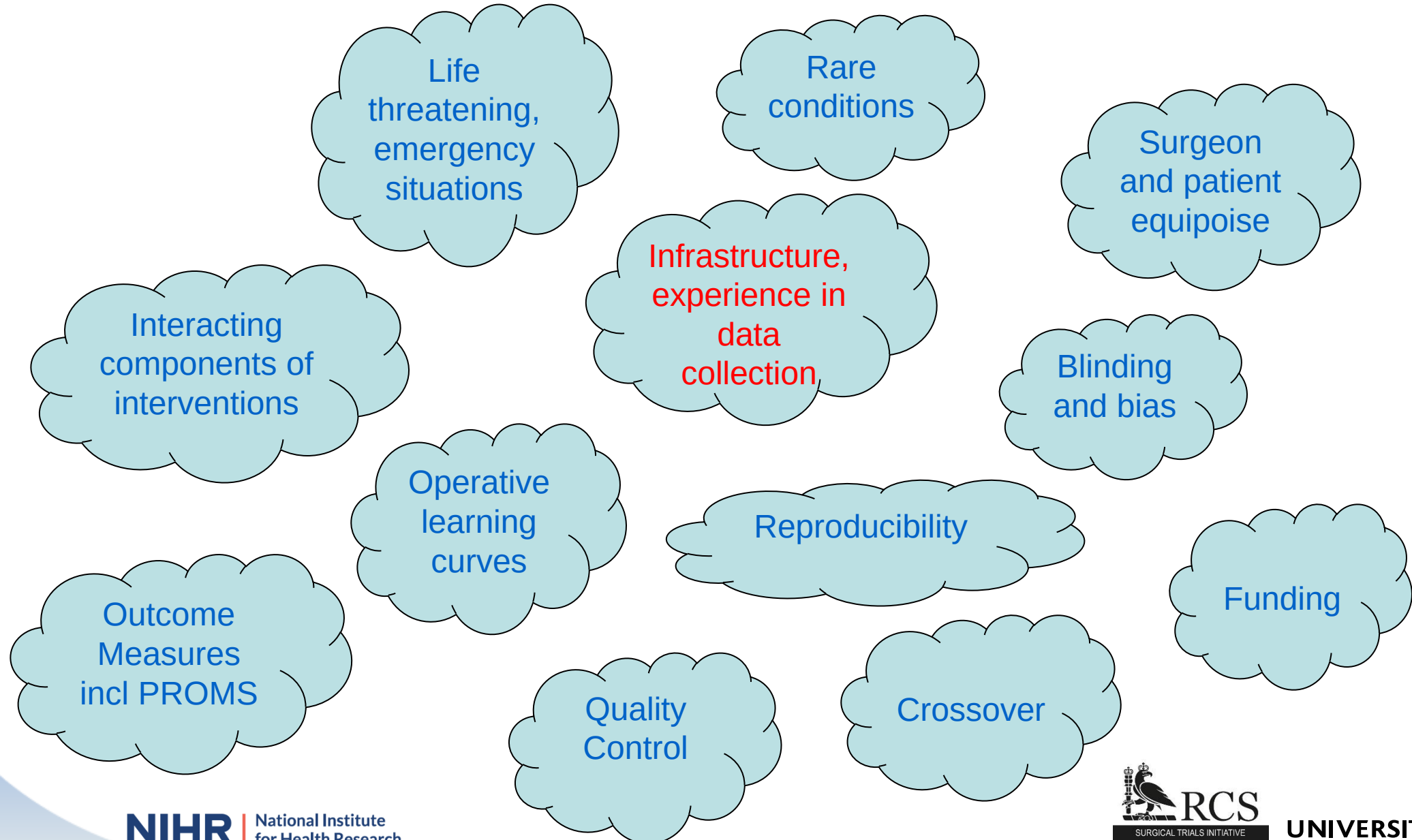
- 1st all-in silico virtual imaging clinical trial for regulatory evaluation
- “In silico imaging” simulates an entire imaging system
- Ability to execute a complete trial with thousands of patients in a day



“potentially minimises the need for clinical trials”

“much to be understood about robustness”

Challenges in Surgical Trial Design and Delivery



UK implements national programme for surgical trials

A clinical research programme is being developed by the UK's Royal College of Surgeons that puts new surgical devices and techniques through randomised clinical trials. Becky McCall reports.



Rosetrees Trust

Supporting the best in medical research

- RCSEng Rosetrees Surgical Trials Initiative 2018
 - 9 Surgical Trials Centres
 - 9 Chairs, 25 Surgical Specialty Leads - across all disciplines
- Collaborative research between academia and surgeons
- Impact
 - 3-fold increase with doubling of recruitment in surgical-led trials
- Trainee involvement key to portfolio development and delivery

Making large-scale surgical trials possible: collaboration and the role of surgical trainees *Jepson, Trials 2021*

- Key role assisting consultants, RN
 - Screening, identifying, consenting pts
- More engaged personnel
 - Trials recruit more quickly
- Career development
 - Research skills and experience
 - Potential to publish
 - Potential to change practice
- NIHR API formal framework



International Trials Toolkit



Sponsorship



Finance



Contracts



Insurance



Research
Governance



Protocol



Monitoring



Trial Supplies



Data
Collection



Sample
Collection



Health
Economics



Data
Ownership &
Access

<https://internationaltrialstoolkit.co.uk/>

Resource to guide efficient set-up and conduct of international surgical trials

- Collaboration across STCs
- Experiences, obstacles and solutions
- Data protection, regulation, sponsorship

A Substantial Unmet Need

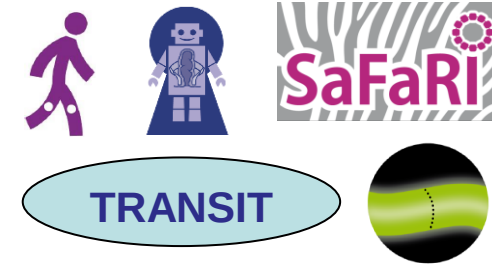
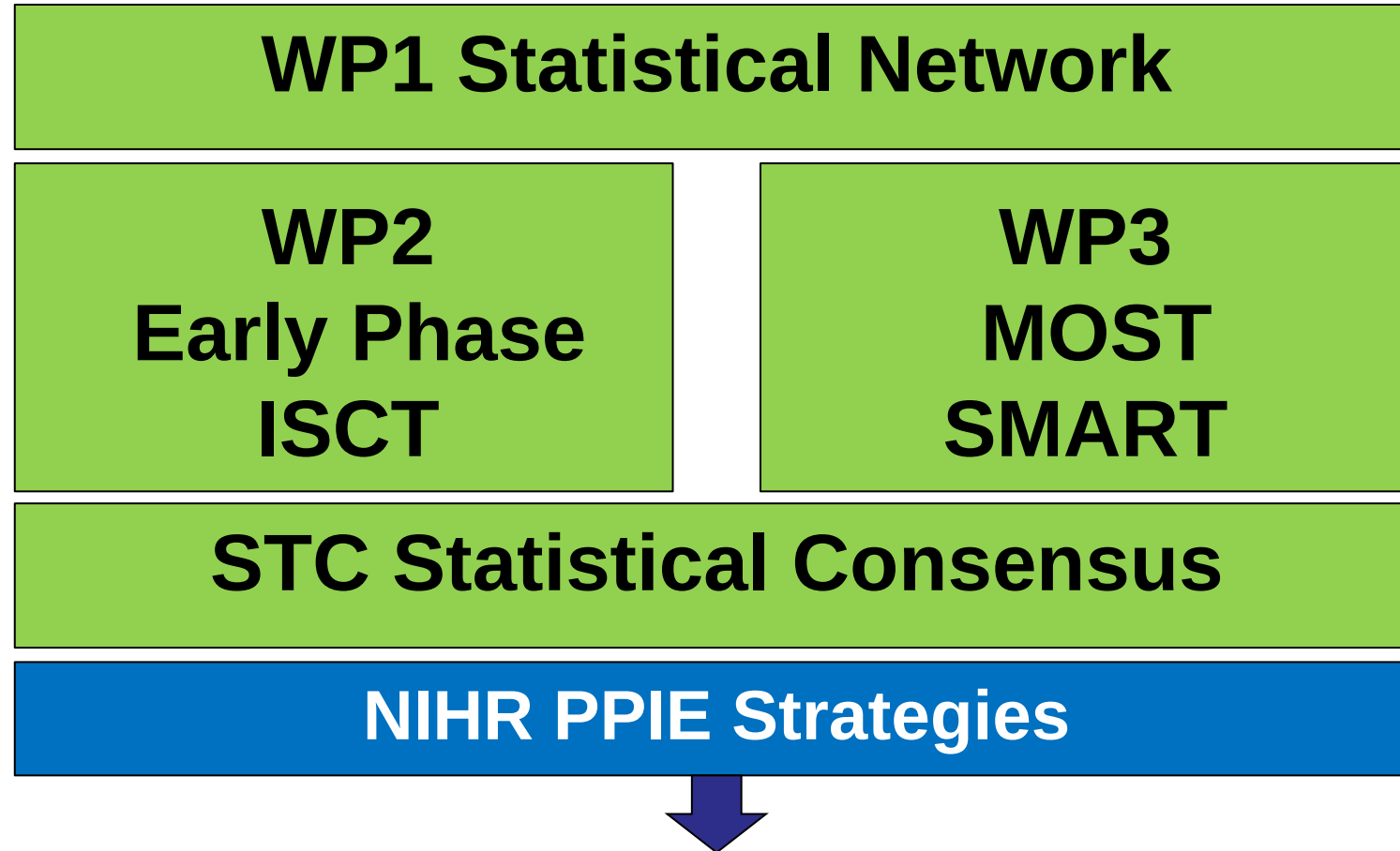
“single most important way to improve healthcare [is] through increasing use of innovative research designs”

2021 Dept Health & Social Care strategy



Currently, there is no aligned statistical framework for the statistical underpinning of trial designs in IDEAL

SIGMA-S: Statistical Innovation and Guidance on Methods and Analysis in Surgery



Safe Translation of Surgical Innovations for Patient Benefit

Improve
quality and
quantity of
surgical trials

Embed novel
and efficient
statistical
designs

Create an
international
community
for adoption

UKCRC
Registered
Clinical
Trials Units



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SURGICAL TRIALS INITIATIVE

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Surgical Trials Methodology: a Bright Future

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