UNIVERSITY OF BIRMINGHAM

WM RESEARCH COLLABORATIVE

MRC Clinical Trials Unit

BIRMINGHAM SURGICAL TRIALS CONSORTIUM BiSTC

NIHR | National Institute for Health Research

ROSSINI 2

Reduction Of Surgical Site Infection using several Novel Interventions

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

Trial Overview

- Phase III
- Multi-arm, Multi-stage (MAMS)
- Pragmatic
- Blinded (patient and outcome assessor)
- Multicentre
- Randomised controlled trial (RCT)
- With an Internal Pilot Phase
- Evaluating the use of three in-theatre interventions, used alone or in combination
- Reduce SSI rates in patients undergoing abdominal surgery

What is an adaptive design?

'… A study design is called 'adaptive' if statistical methodology allows the modification of a design element (e.g. sample-size, randomisation ratio, number of treatment arms) at an interim analysis...'

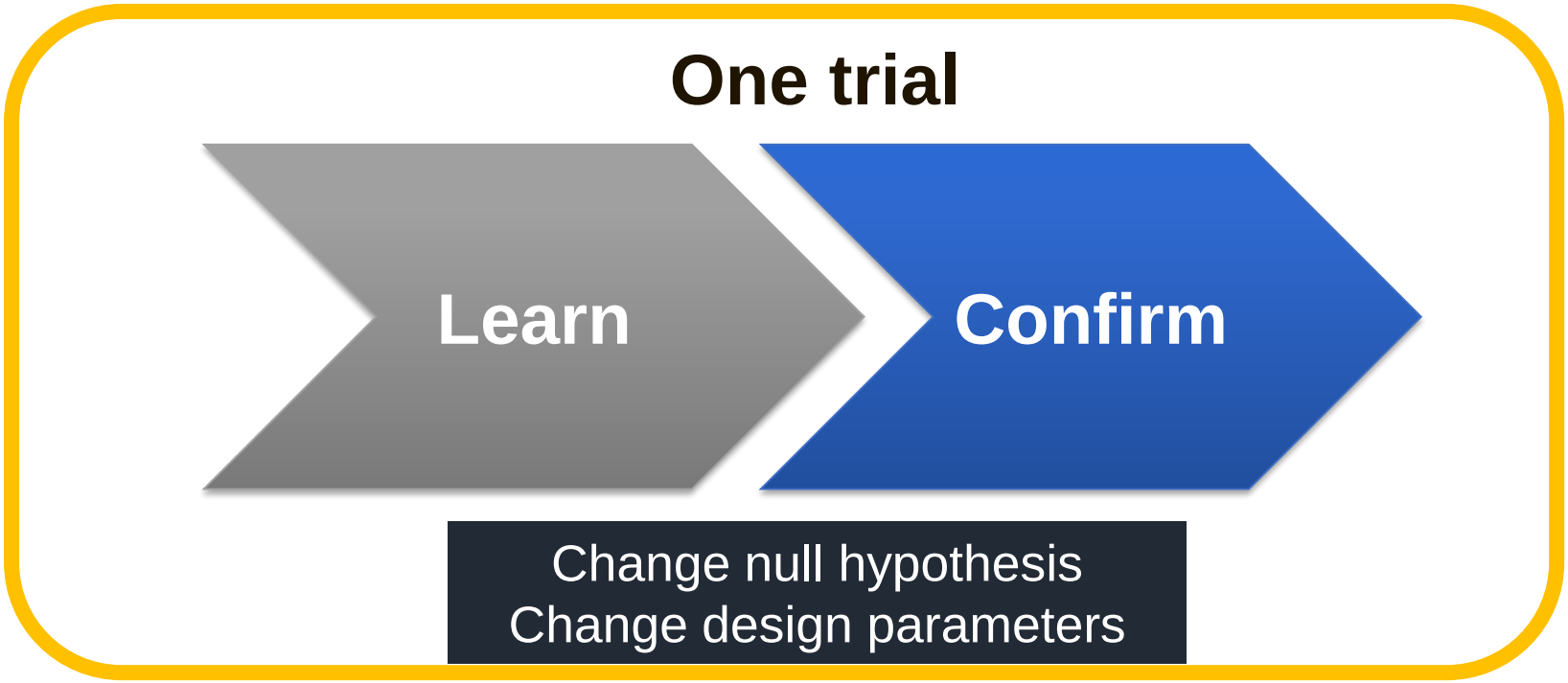
Several possible approaches

- Modifications of
  - study eligibility criteria
  - study sample size or study objective to maintain overall power
  - treatment arm
  - analysis plan
- Early stopping rules for futility or efficacy (group sequential designs)
- Drop treatment arm(s) / ‘pick the winner’ designs
- Enrichment designs
- Adaptive randomisation

Well understood

Less well understood

Most adaptive designs come down to…

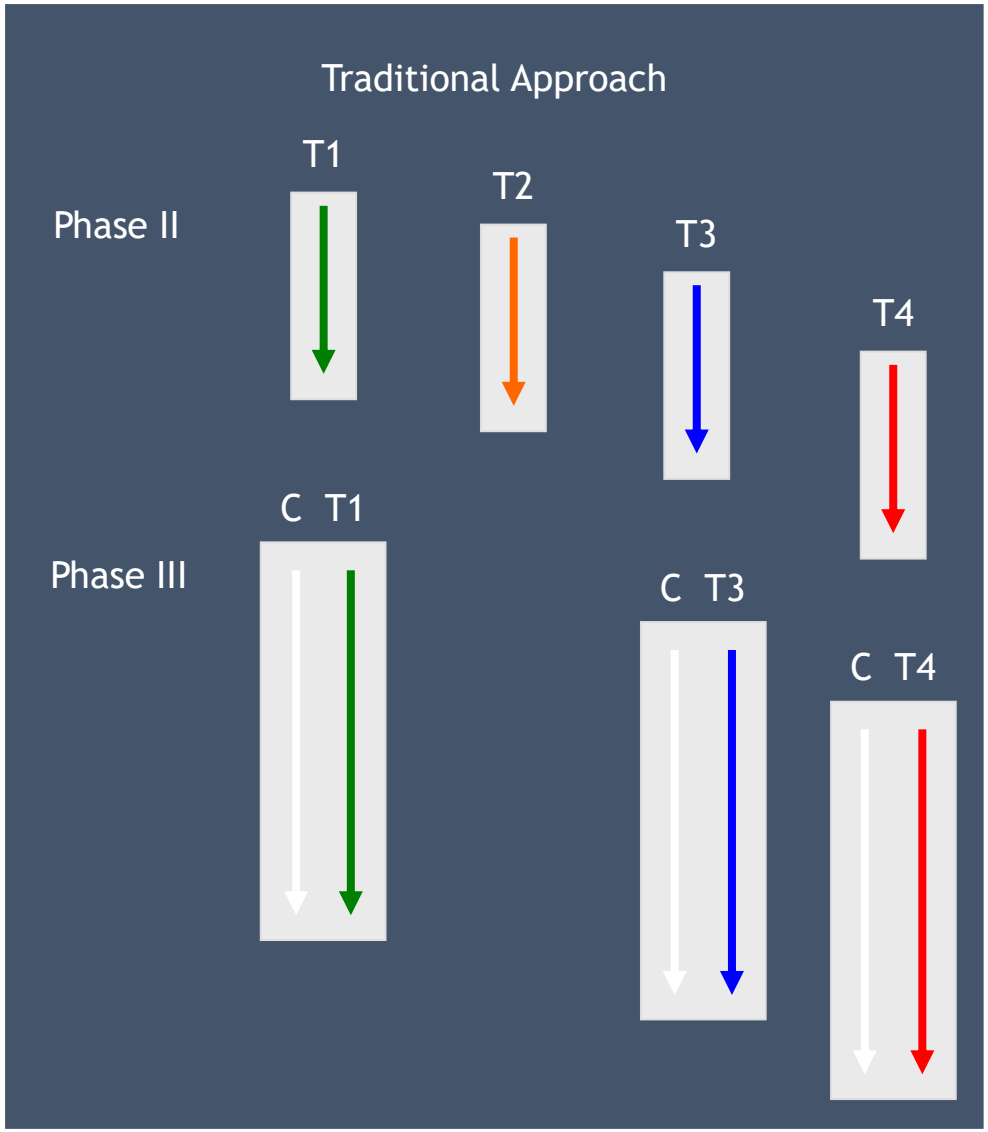


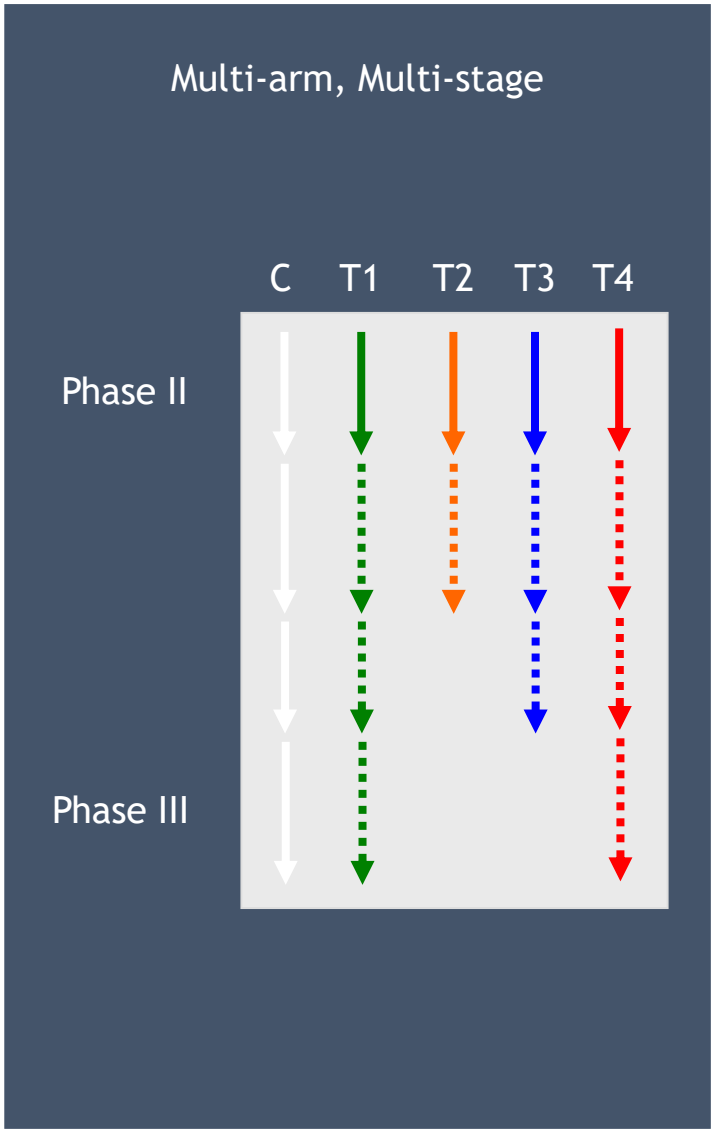
The need for speed and change

- Development and testing process too slow (>10 years)
- Too often shows new is not better than standard
- In some diseases number of new therapies demanding evaluation is large
- Process of developing and starting a new trial is very time consuming – often a long gap between trials

Principles underlying solutions

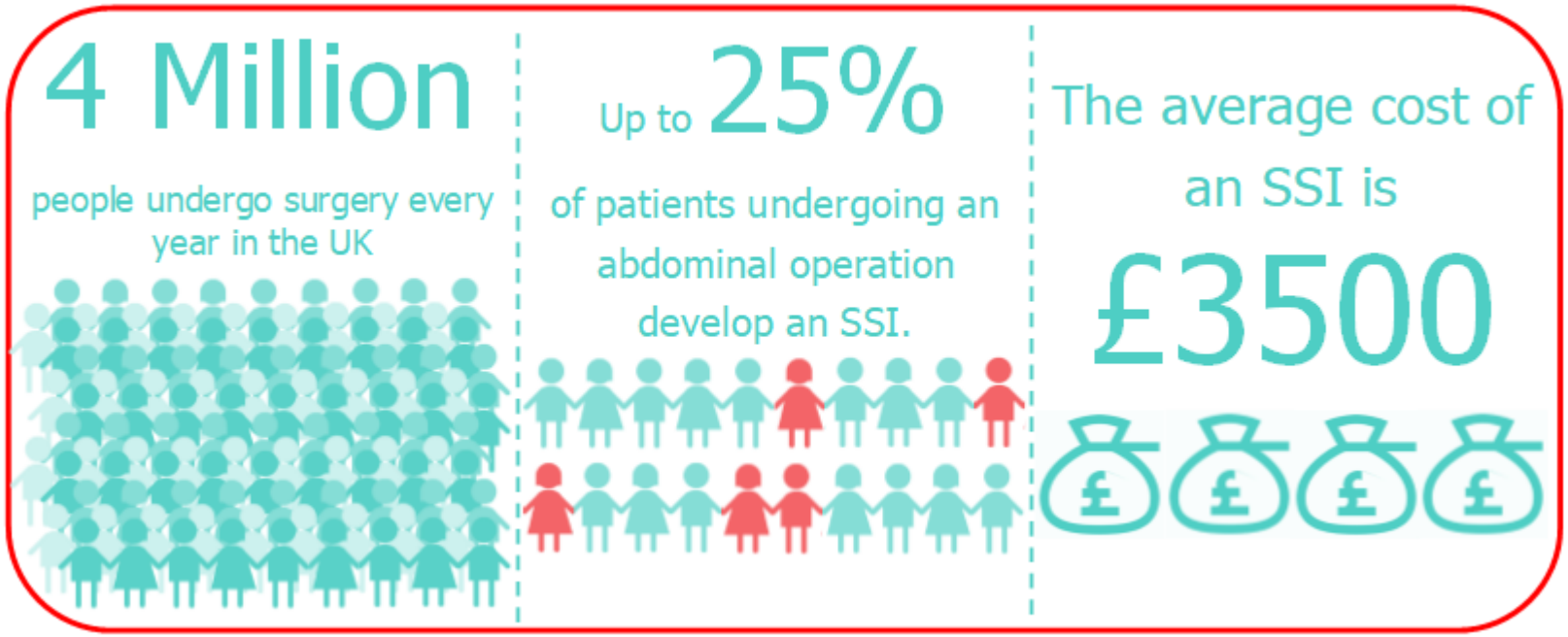
- Evaluate many primary hypotheses/treatments in the same protocol
- If there is a pilot/feasibility/phase II
  - seamless run through to the phase III and
  - include all phase II information in the phase III
- Conduct an adaptive trial, with only major adaptations, e.g.
  - Dropping arms
  - Adding arms


Traditional Approach
Phase II
T1
T2
T3
T4
Phase III
C T1
C T3
C T4


Multi-arm, Multi-stage
C T1 T2 T3 T4
Phase II
Phase III

BACKGROUND

- **Surgical Site Infection after abdominal surgery**
  - Surgical site infection (SSI) is a significant problem for patients and the health service, but is potentially preventable.



BACKGROUND

❖ Impact of surgical site infection

- There is a significant health need for research to address the problem of SSI, with benefit for both patients and the NHS.

SSI is associated with:

- considerable morbidity

- a reduction in quality of life

- increased healthcare costs.

Development of an SSI significantly increases patient hospitalisation, additional nursing care and drug treatment costs.

- There is an additional societal burden of SSI, delaying return to work or normal activity and increasing care burden.

Planning a follow-on study to Rossini…

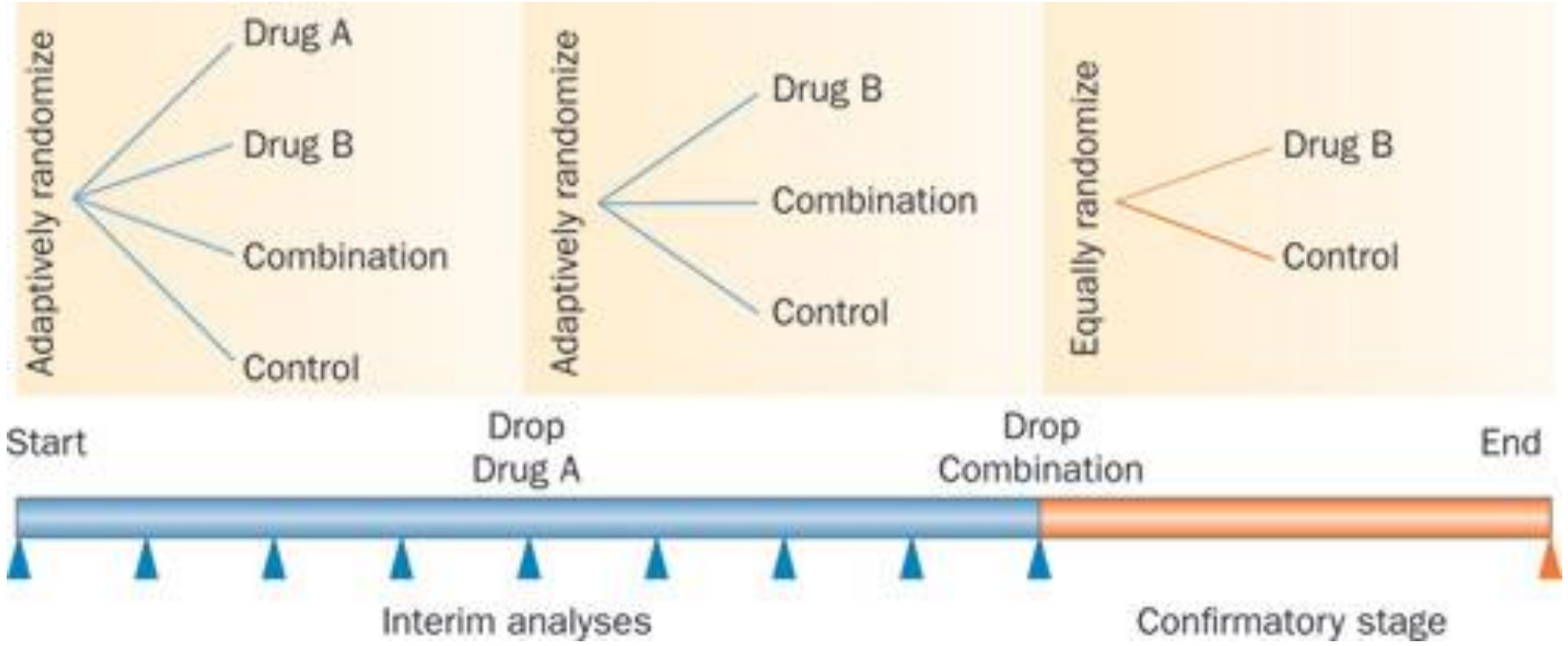
Primary outcome of SSI is available,

by definition,

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

MAMS design

exploits 30d outcome measure



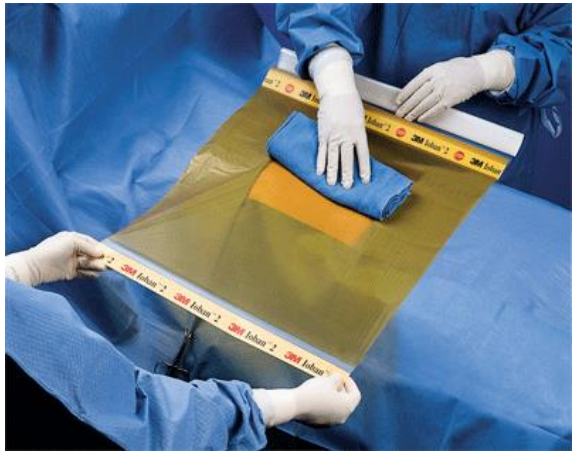
ROSSINI II – Interventions…?

63 shortlisted

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



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

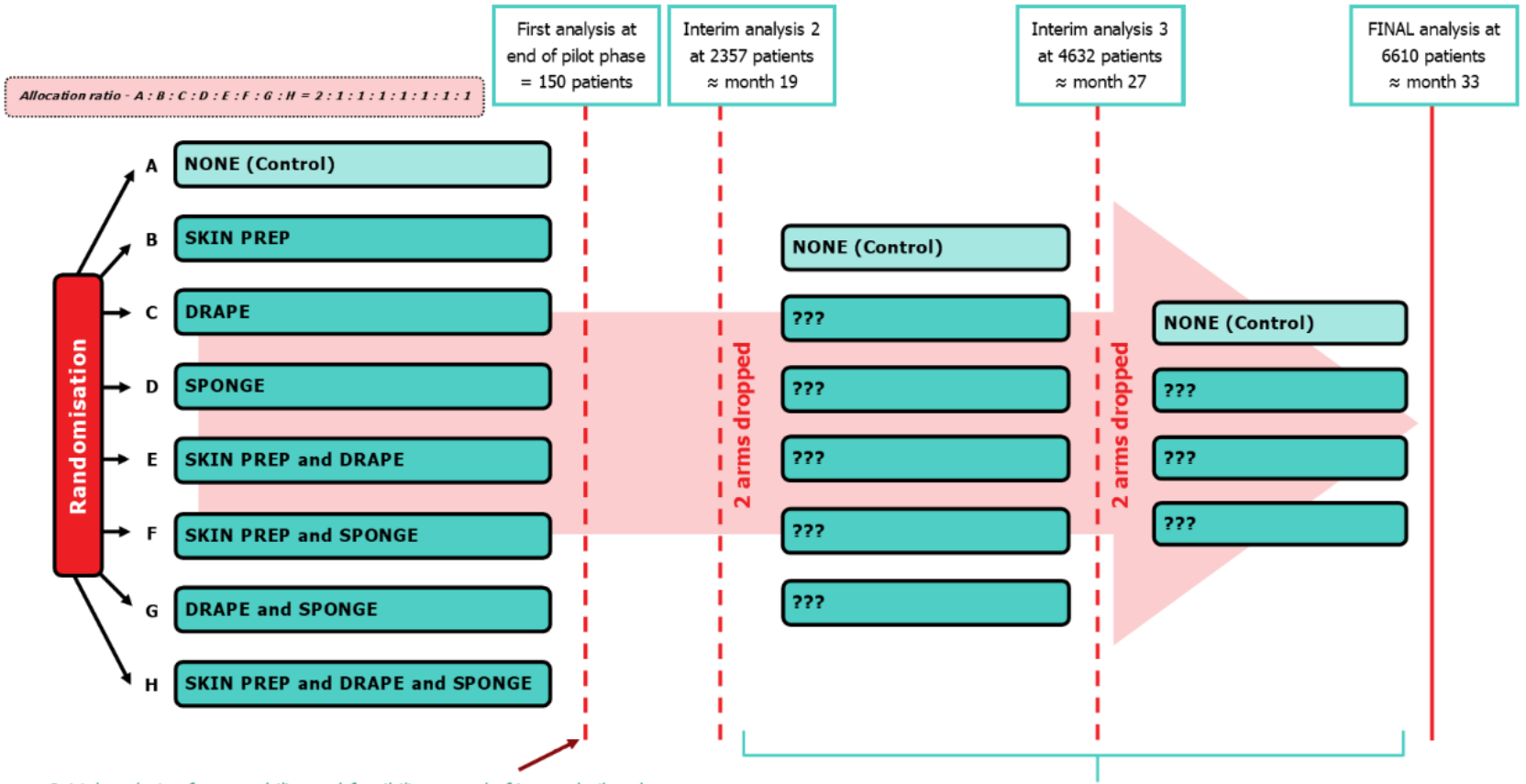
- Inclusions
  - **All abdominal surgery** – any incision; any indication; emergency and elective
  - *Including Laparoscopic-assisted with specimen extraction site >5cm*
- Primary endpoint
  - **SSI within 30 days of operation** assessed by blinded observer (CDC criteria)
- Secondary endpoints
  - Quality of life; health resource usage; patient + operation factors

Trial Schema

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

Intervention 2 - Iodophor-impregnated incise drape [DRAPE]

Intervention 3 - Gentamicin-impregnated collagen implant/ sponge [SPONGE]



Initial analysis of acceptability and feasibility at end of internal pilot phase. Modifications made to arms if necessary. Second internal pilot can be requested by DMEC if concerns over arm adherence/ acceptability or overall recruitment rates.

STOP/ GO decision to drop arms dependant on any combination of:

A. Clinical effectiveness

B. Adherence to arm allocation

C. Clinician Acceptability

Recruitment

Internal Pilot Phase

- 6 Months
- 10 Sites (opening 2 per month)
- 150 Patients (recruiting 4 patients per site, per month)

Month	Sites	No. of Patients
1	2	8
2	4	24
3	6	48
4	8	80
5	10	120
6	10	150

Main Phase

- 33 Months (including 6 from Pilot)
- 62 Sites (opening 4 sites per month)
- 6610 Patients (recruiting 5 patients per site, per month)

Month	Sites	No. of Patients
7	10	210
8	14	280
9	18	370
10	22	480
11	26	610
12	30	760
13	34	930
14	38	1120
15	42	1330
16	46	1560
32	62	6400
33	62	6710

Approximately 6610 patients will be required to detect a 5% absolute risk reduction in the intervention arm(s) (15% to 10%) with 85% power.

Progress

- HTA – funding awarded (£1.89M)
- Companies on-board – *free* interventions
- Pilot phase has starting mid-march 2019
- n = 6610
- 80-100 sites needed
- **WE WANT YOUR SITE!**

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