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TwiCs

Trials within Cohorts

(& other groups/ data structures)

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Outline

- 2003…..The surprises
- Trials within Cohorts (TwiCs) approach
- Parallel evolution
- Methodological & delivery challenges

Everyday…

- Patients and clinicians ‘try’ txs
- Reduce uncertainty, improve outcomes

- Use RCTs to remove selection bias, and minimise the impact of known and unknown confounders

The surprises – the system

- Uncertainty in the evidence base
- Cost
- Publication
- Lack of interest

The surprises - RCTs

- 50% fail to recruit
- Unrepresentative populations
- ‘Fully’ Informed consent
- Randomisation rarely understood

How can randomised trials become part of routine care and best use current clinical care pathways?"

…..normalise trials as part of clinical care and enhance communication?

Prioritising Recruitment in Randomised Trials study (PRioRiTy) 2018

Trials within cohorts

(cohort multiple RCT design)

- New framework for inexpensive pragmatic trials

- Fuses - Observational studies + Pragmatic RCT design + ‘Normal’ conversations’

Relton, Nicholl et al, BMJ, 2010

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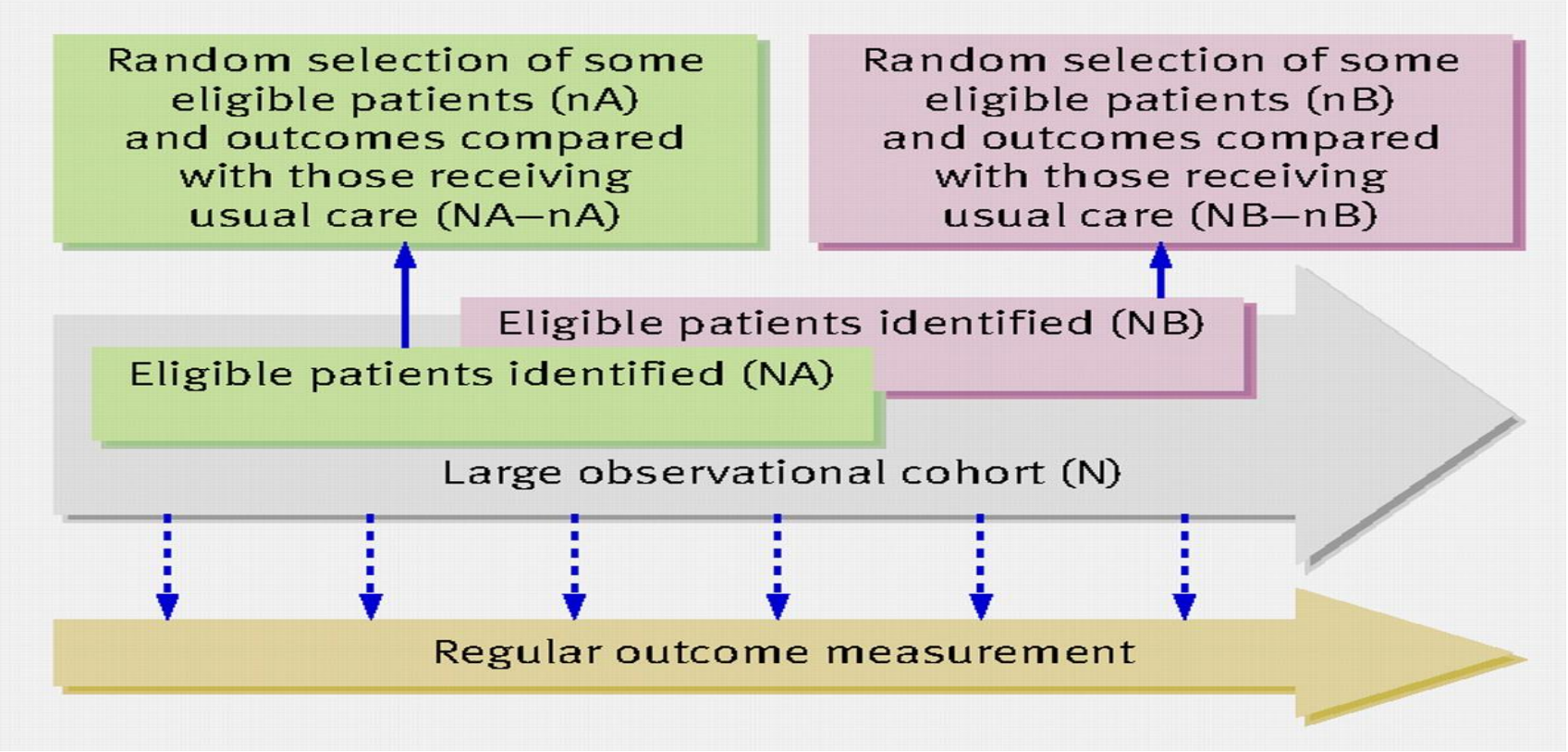
Trials within Cohorts

(cohort multiple RCT design)



Relton, Nicholl et al, BMJ, 2010

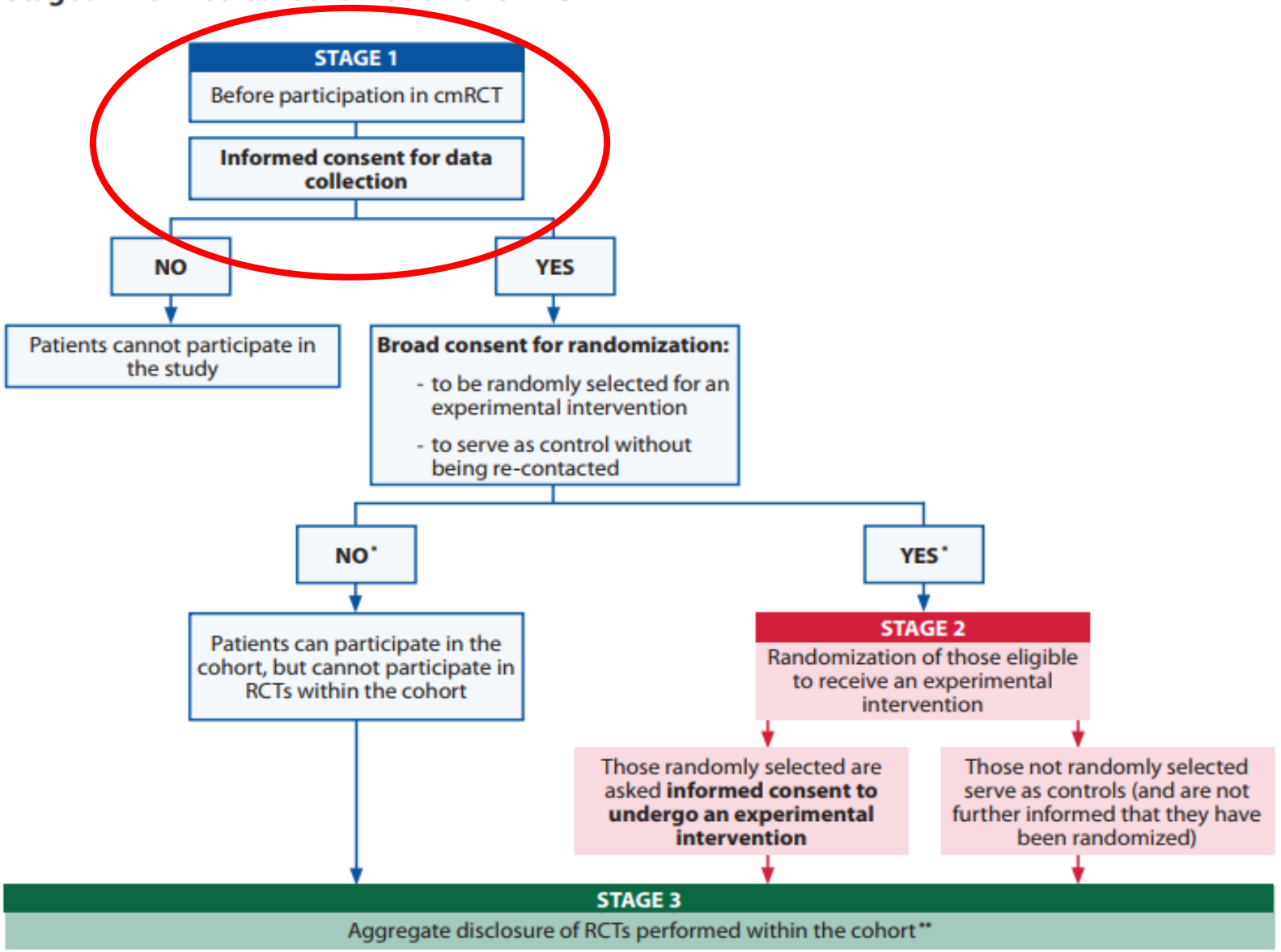
TwiCs design

- Researcher generated **cohort** (observational study) which facilitates
- **Multiple trials** (all with usual care comparators)

TwiCs Informed Consent

- **Informed consent** procedures replicate routine healthcare as far as possible
  - ~~Fully informed consent~~
  - Relevant, adequate consent

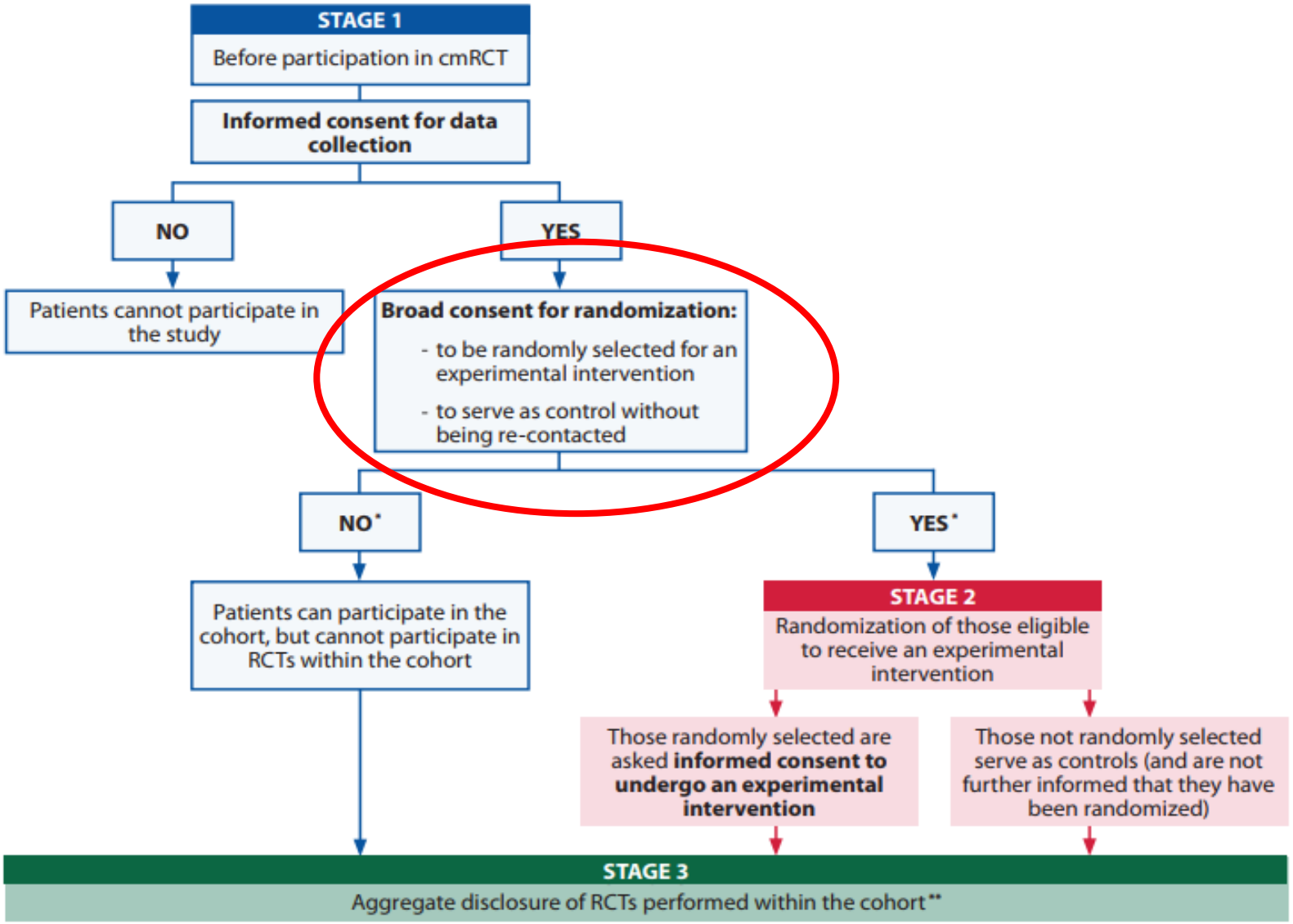
Staged-informed consent model for cmRCT



*Dynamic informed consent model which enables participants to change their previous "yes or no" preference at any moment in time

**Provided after each completed RCT, but only to those who opted-in for aggregate disclosure (asked in stage 1).

Staged-informed consent model for cmRCT



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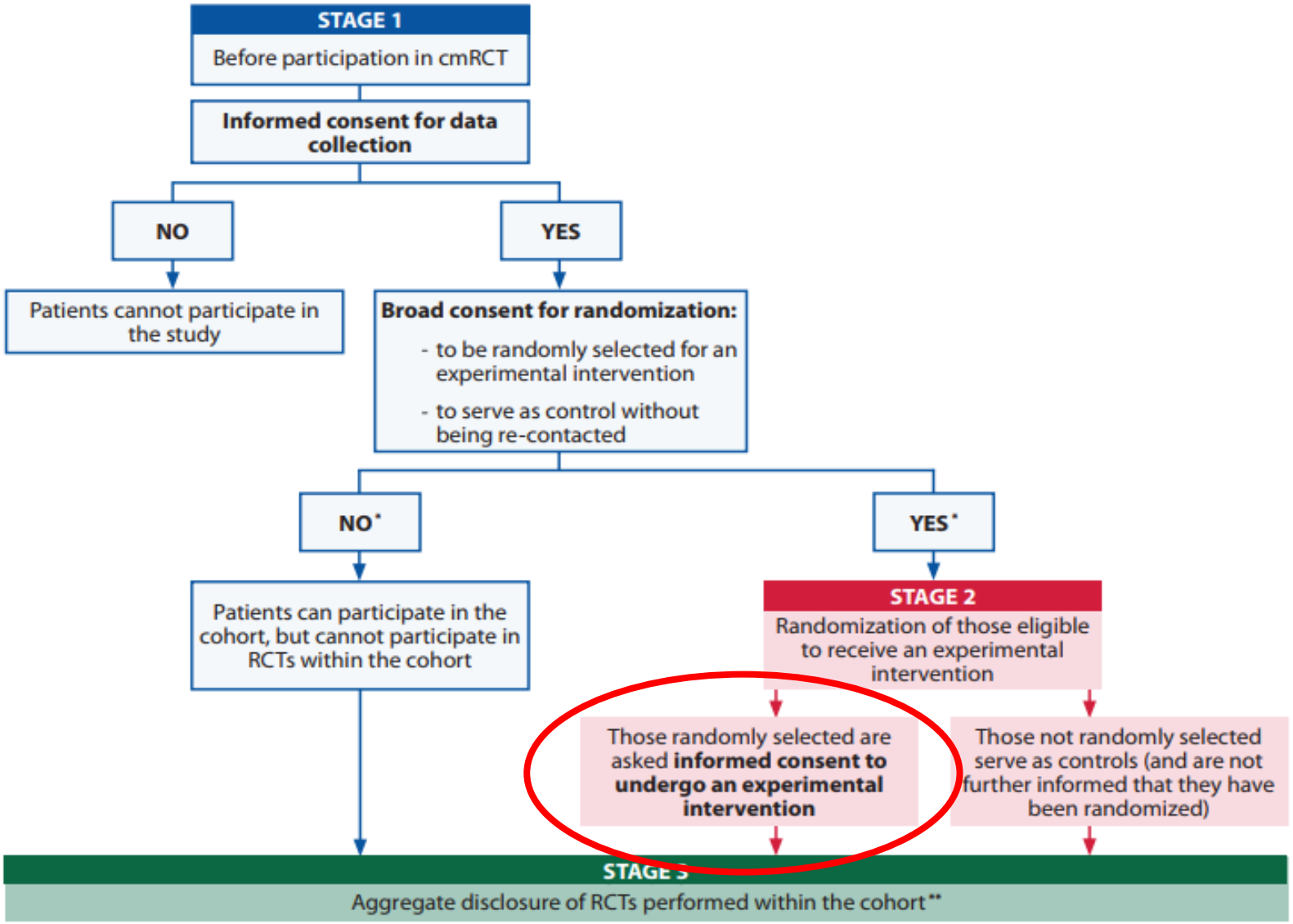

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- Px not told about txs they can't have

"avoid the harm of being allocated to a 'control' group after having an intervention fully explained"

R.Uher (FORBOW cohort, SWELL RCT)

TwiCs 2010-2018

- Funded (NIHR, CIHR….)
- REC approval (Ethics symposium)
- CTIMP & MHRA
- Converting existing cohorts
- CONSORT Guidelines

Use of the TwiCs

- Populations (population, hospital, primary care, national, adapting existing cohorts, rare diseases, cancer, mental health….)
- Interventions (lifestyle, surgical, web based, CTIMPs)
- Comparators (usual care, head-to-head, placebo)
- Recruit to non randomised studies

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Parallel evolution

- Groups – routine or researcher led
- Use existing data collection systems to improve recruitment, efficiencies of scale, and generalisability

  - *Randomised Registry Trials*
  - *Platform trials*
  - *Multi-Arm, Multi Stage*
  - *Hospital administrative*
  - *Electronic Health Record*

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CONSORT Extension

Trials Conducted in Existing Data Structures (including Researcher-generated Cohorts, Registries, Electronic Health Records)

(CIHR funded - Brett Thombs, Ole Frobert, Ed Juszczak, Linda Kwakkenbos, Isabelle Boutron, Clare Relton)

Methodological and delivery challenges

- Ethics
- Economic
- Stats
- System level

Ethics

– Not widely applied
– REC approval
– TwiCs Ethics Symposium 2016

Stats

- Difference in information given to groups
- Acceptability
- Non-acceptance of treatment
  - Crossover
  - Dilute any treatment effect
  - CACE analysis, Instrumental Variable

- Cohort size
- Trial sample size
- Same patient in more than one trial

Economic

- Funding the cohort (new or adapt existing)

- Economies of scale
  - Faster regulatory approvals
  - Research ready cohort
  - Fast & efficient recruitment
  - Degrees of integration

System level

- Acceptability
  - More public/patient willingness to take part in TwiCs?
  - Healthcare systems willingness to use TwiCs (micro & macro level)
- Efficiency
  - Optimal arenas for Trials within Cohorts/ Groups/ Existing Data Structures?

Put research at the heart of the NHS"

(Sally Davies CMO)

Acknowledgements

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For more information

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Introduction to TwiCs

One day course at QMUL

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