Trial Design for Pandemics

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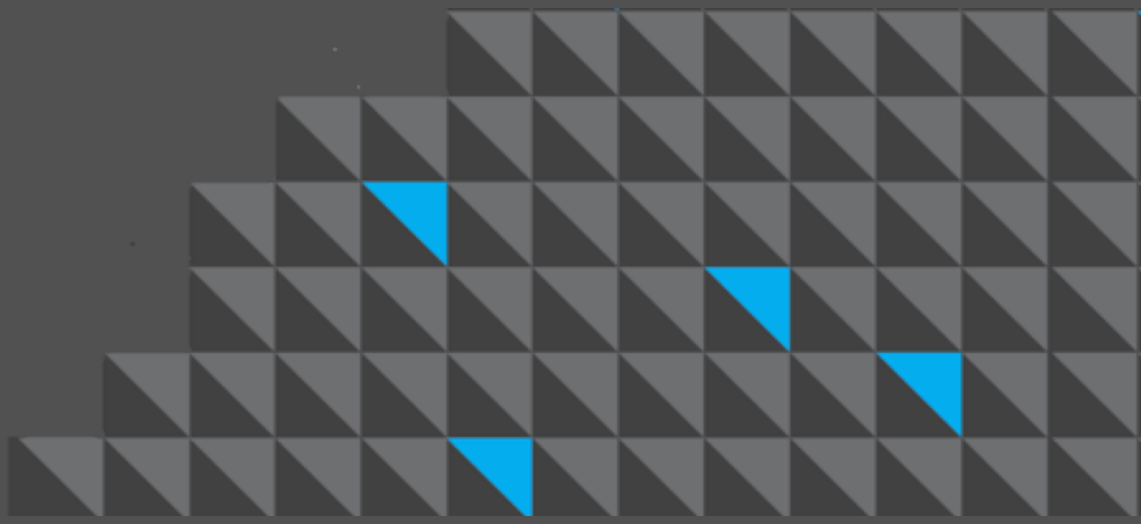
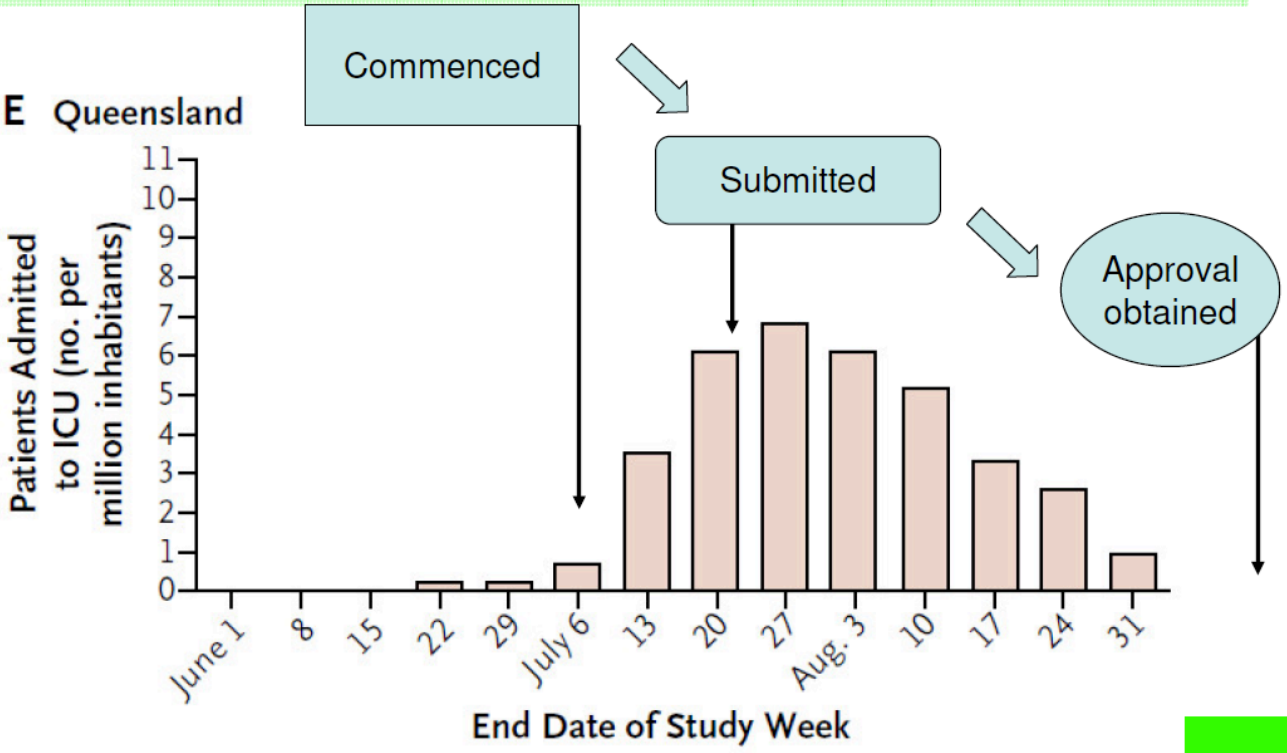



KEEP
CALM
IT'S NOT
BUSINESS AS
USUAL

Ethics Application



NEJM 2009: 361

We need global preparedness for the next pandemic

Pre-planned

Pre-approved

Practiced

The purpose of clinical trials is to generate **EVIDENCE** to inform change in clinical practice.

Some priors

1. Randomisation is necessary for valid causal inference

2. Both generation and implementation of evidence are time-critical

3. Trials should be agnostic to intervention, don't care how we improve outcomes, interested only in improving outcomes
   - Universe of candidate interventions likely to be large
   - Includes current interventions of uncertain benefit
   - Includes novel interventions

4. Any intervention can be effective, ineffective, or harmful

5. Effect of interventions can be contingent on other factors such as concomitant therapies or patient characteristics

More priors

6. Wholly pragmatic, want to know what works as quickly as possible

7. Need to define what “improve outcome” means, might be different during a pandemic

8. Infrastructure is critical- sample size necessary for statistical confidence in proportion to effect size (may be large) / data must be accurate (which means limiting amount of data) / data must be entered quickly
   - Screen
   - Recruit
   - Deliver intervention
   - Know delivery has occurred
   - Record outcome
   - Analyse, implement, disseminate in real-time

Can something be designed that is fit-for-purpose?

Platform Trials

VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

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The drug development enterprise is struggling. The development of new therapies is limited by high costs, slow progress, and a high failure rate, even in the late stages of development. Clinical trials are most commonly based on a "one population, one drug, one disease" strategy, in which the clinical trial infrastructure is created to test a single treatment in a homogeneous population.

This approach has been largely unsuccessful for multiple diseases, including sepsis, dementia, and stroke. Despite promising preclinical and early human trials, there have been numerous negative phase 3 trials of treatments for Alzheimer disease[1] and more than 40 negative phase 3 trials of neuroprotectants for stroke.[2] Effective treatments for such diseases will likely require combining treatments to affect multiple targets in complex cellular pathways and, perhaps, tailoring treatments to subgroups defined by genetic, proteomic, benefits when evaluating potentially synergistic combination treatments (eg, treatment A, treatment B, treatment C, and all combinations) if the starting point is the testing of each treatment in isolation.

What Is a Platform Trial?

A platform trial is defined by the broad goal of finding the best treatment for a disease by simultaneously investigating multiple treatments, using specialized statistical tools for allocating patients and analyzing results. The focus is on the disease rather than any particular experimental therapy. A platform trial is often intended to continue beyond the evaluation of the initial treatments and to investigate treatment combinations, to quantify differences in treatment effects in subgroups, and to treat patients as effectively as possible within the trial. Although some of the statistical tools used in platform trials are frequently used in other set-

REMAP Variant of Platform Trials

Opinion

VIEWPOINT

Fusing Randomized Trials With Big Data
The Key to Self-learning Health Care Systems?

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Randomized clinical trials (RCTs) have revolutionized medicine by providing evidence on the efficacy and safety of drugs, devices, and procedures. Today, more than 40 000 RCTs are reported annually, their quality continues to increase, and oversight mechanisms ensure adequate protection of participants. However, RCTs have at least 4 related problems: (1) they are too expensive and difficult; (2) their findings are too broad (average treatment effect not representative of benefit for any given individual) and too narrow (trial population and setting not representative of general practice); (3) randomizing patients can make patients and physicians uncomfortable, especially when comparing different types of access to massive amounts of data, the Achilles' heel is lack of causal inference. No matter how detailed the measurement and how sophisticated the adjustment for all known variables, big data cannot eliminate unmeasured factors coincident with a particular treatment assignment that could explain an apparent change in outcome.[2]

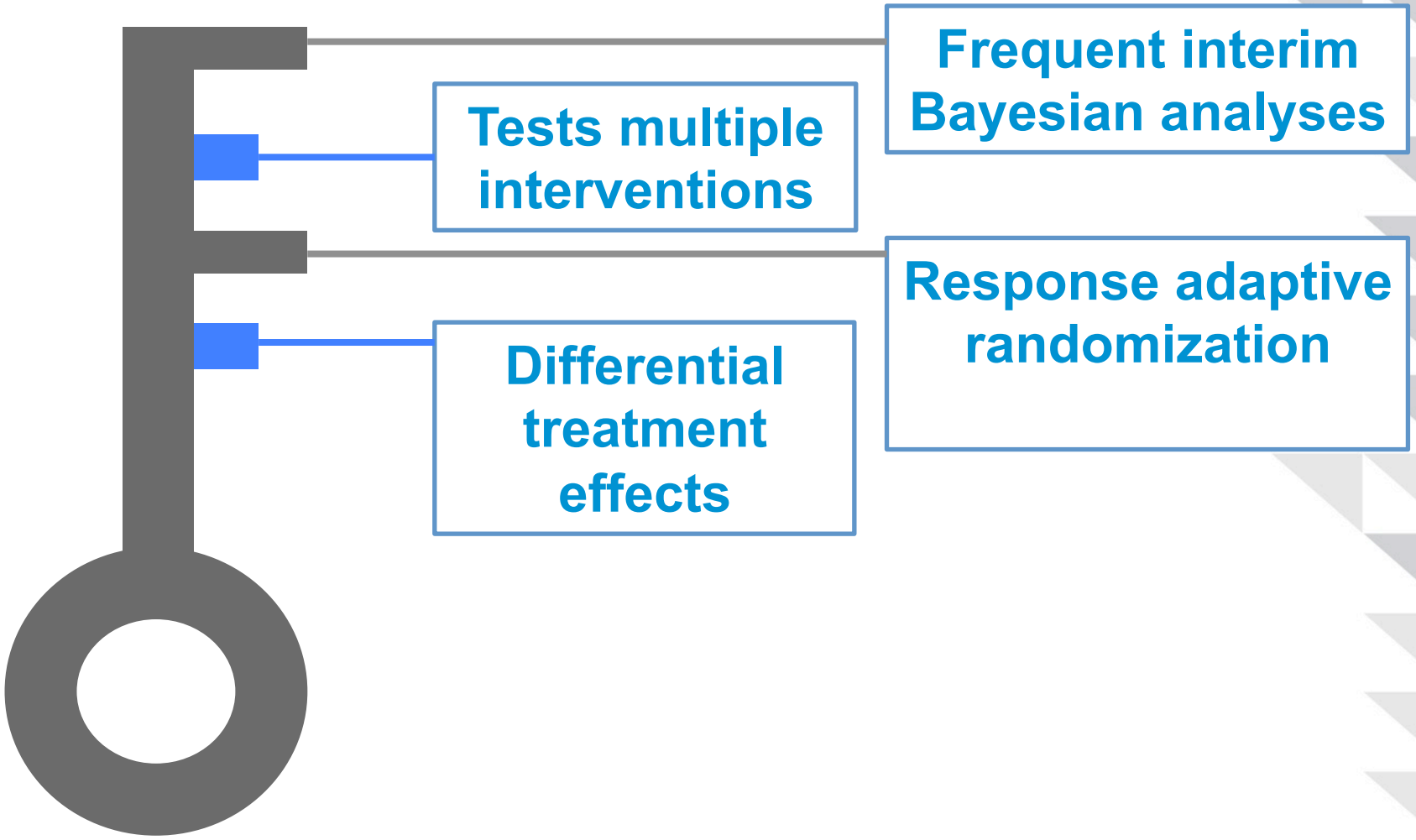
Thus, each approach has complementary strengths: RCTs offer causal inference, and big data offers the potential for low-cost, high-volume, nuanced answers with immediate feedback. Rather than debate which is better, the greatest promise may come from fusing them.

REMAP-CAP

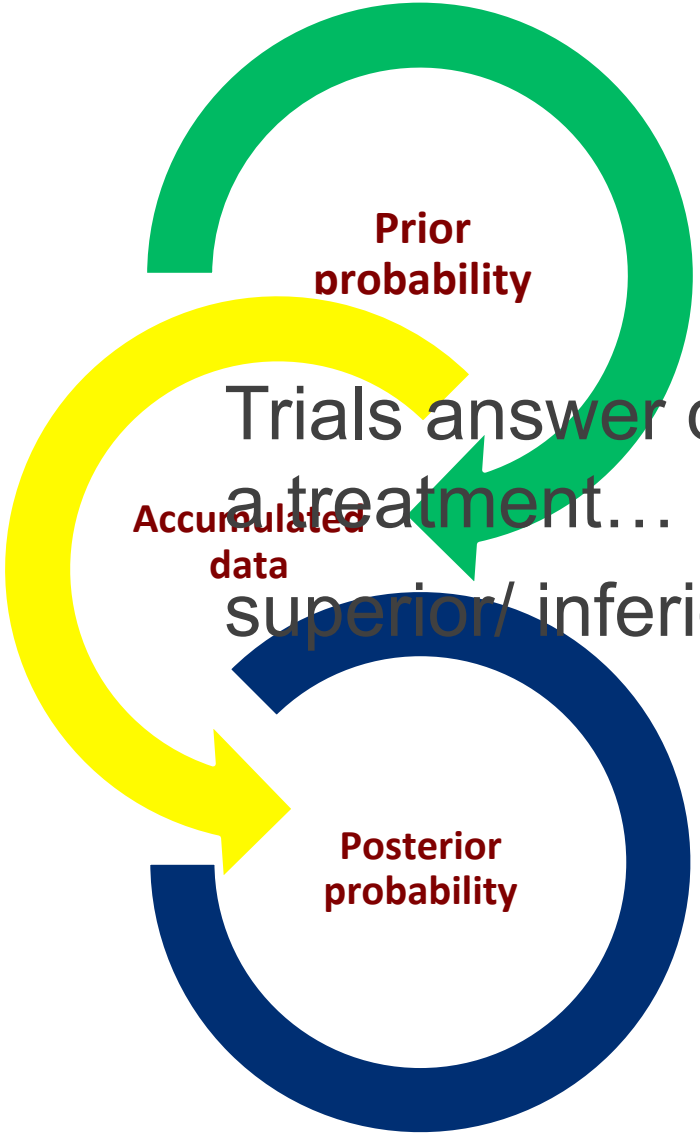
- Funded by EU FP7, NHMRC, NZ HRC, CIHR to recruit in interpandemic period (and want to expand further)
- 7000 patients
- Simultaneous evaluate optimal antibiotic, steroids, duration of macrolide, adding ventilation strategy, oxygen saturation target, and antiviral strategy on 90-day mortality
- Pre-approved to adapt in event of pandemic to evaluate all existing interventions (as a prior), plus new pandemic-specific interventions on…… length of ICU stay contingent on survival to ICU discharge

Adaptive Trials

Key Design Features of REMAP-CAP



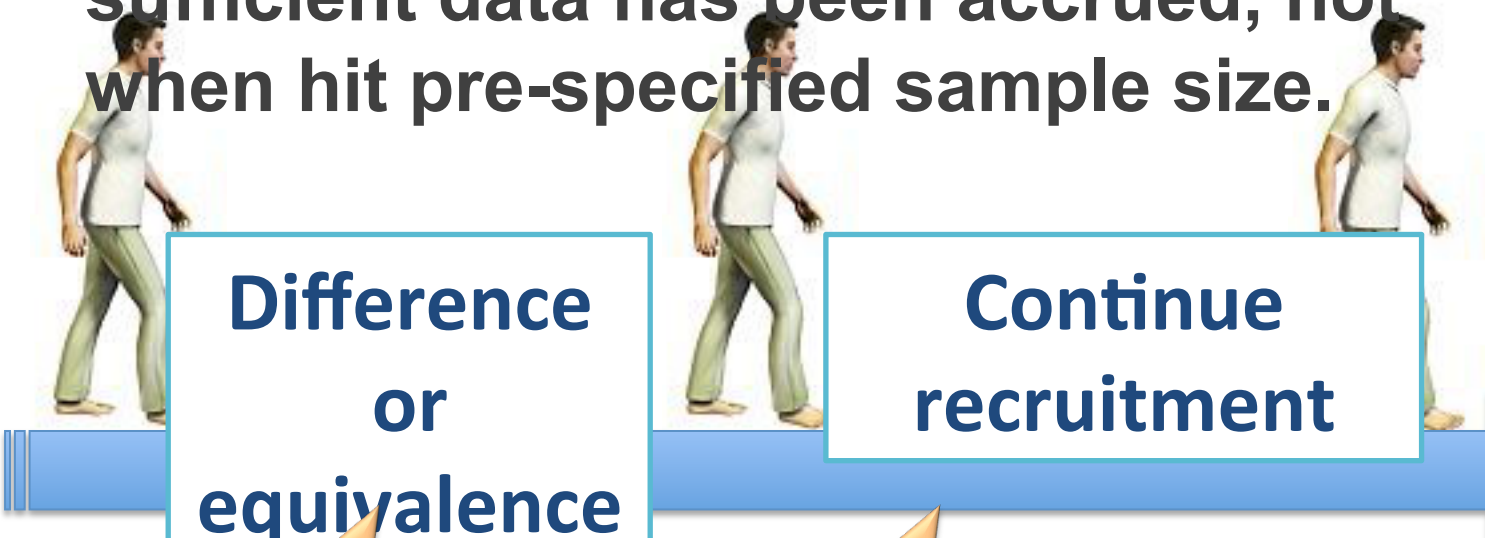
Frequent Interim Analysis



Trials answer questions about a treatment… is it superior/ inferior/equivalent?

Frequent Adaptive Analysis

Frequent adaptive analysis means questions are answered when sufficient data has been accrued, not when hit pre-specified sample size.



Difference or equivalence

Continue recruitment

Randomise and Analyse!!!

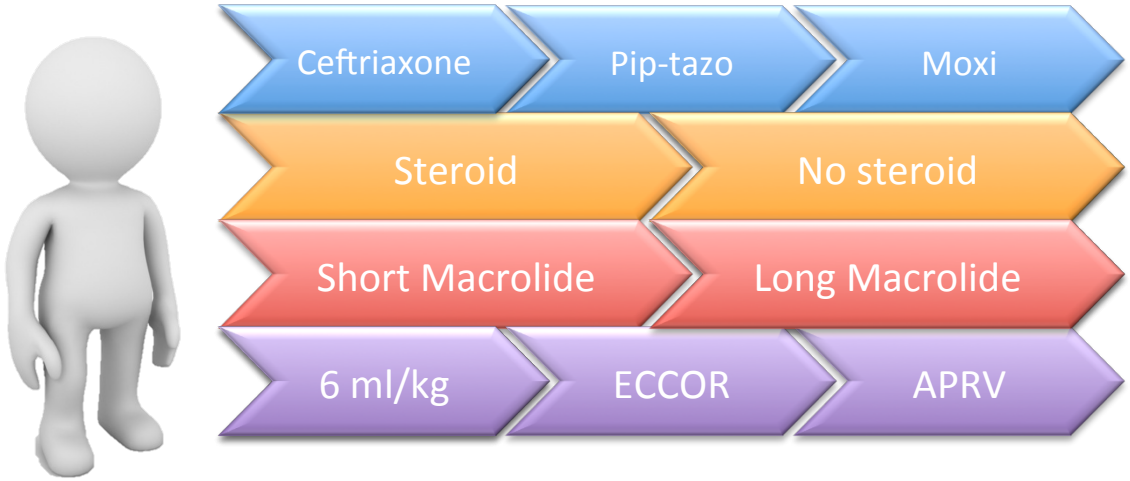
Randomise and Analyse!!!

Randomise and Analyse!!!

Avoids indeterminate results

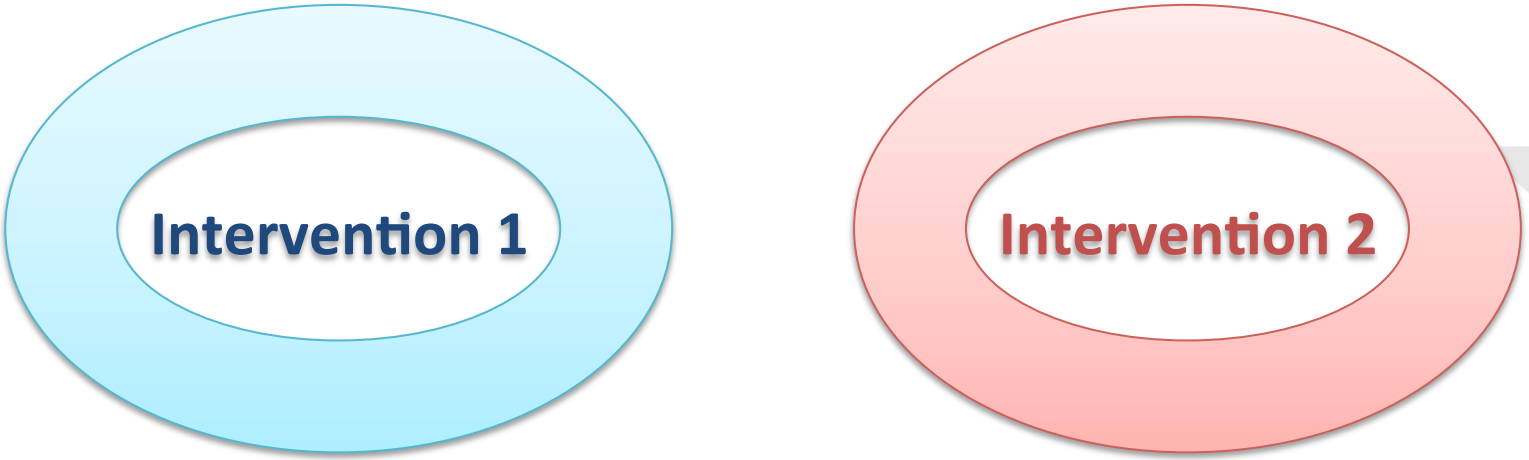
Multifactorial:

Randomisation to multiple components of treatment, simultaneously



Traditional Randomisation

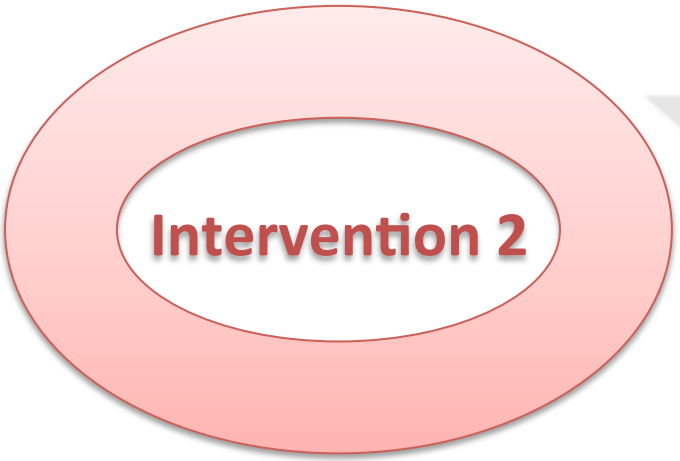
Traditional RCTs have a fixed 1:1 ratio for randomisation proportion….



Response Adaptive Randomisation

Response adaptive randomisation varies proportion depending on trial results

If a group starts doing better with one treatment, more patients are randomized to that treatment



Embedding

Process where clinical staff and clinical information systems play primary role in trial-related processes through integration of the trial into routine work practices

Conclusions

Business as usual will not work in a pandemic

REMAP-CAP practiced during interpandemic period

Being developed so that it is pre-planned and pre-approved for adaptation during a pandemic

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