Efficient Designs: New Concepts in Clinical Trials

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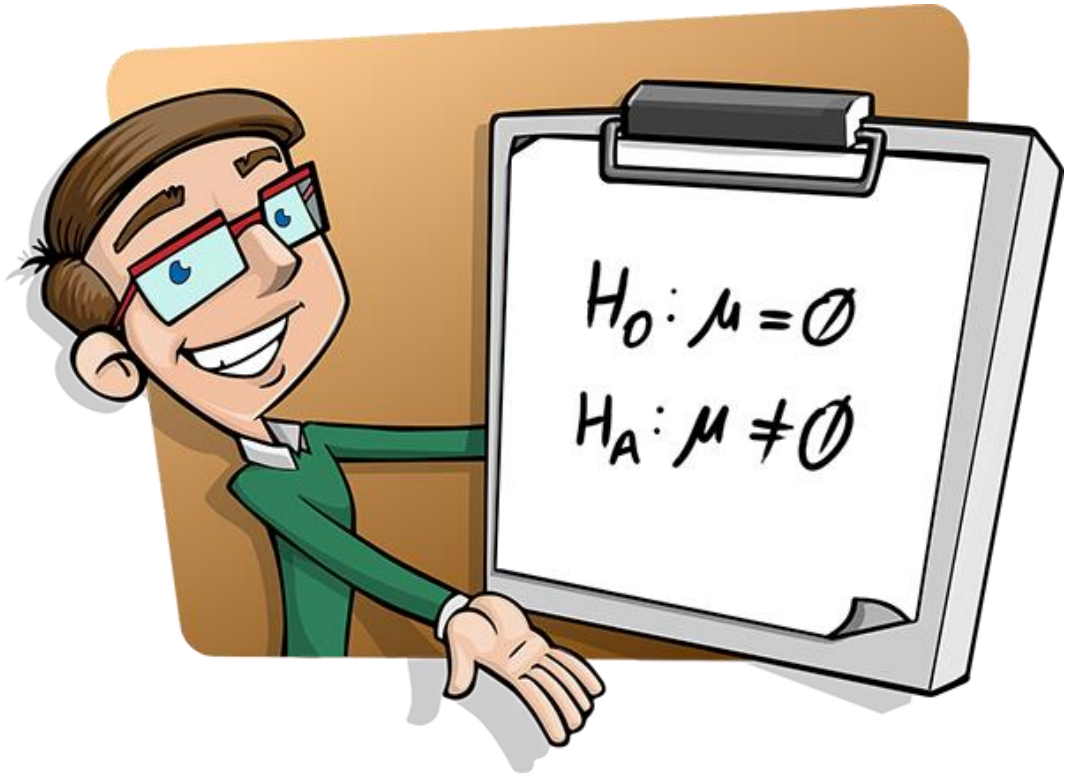
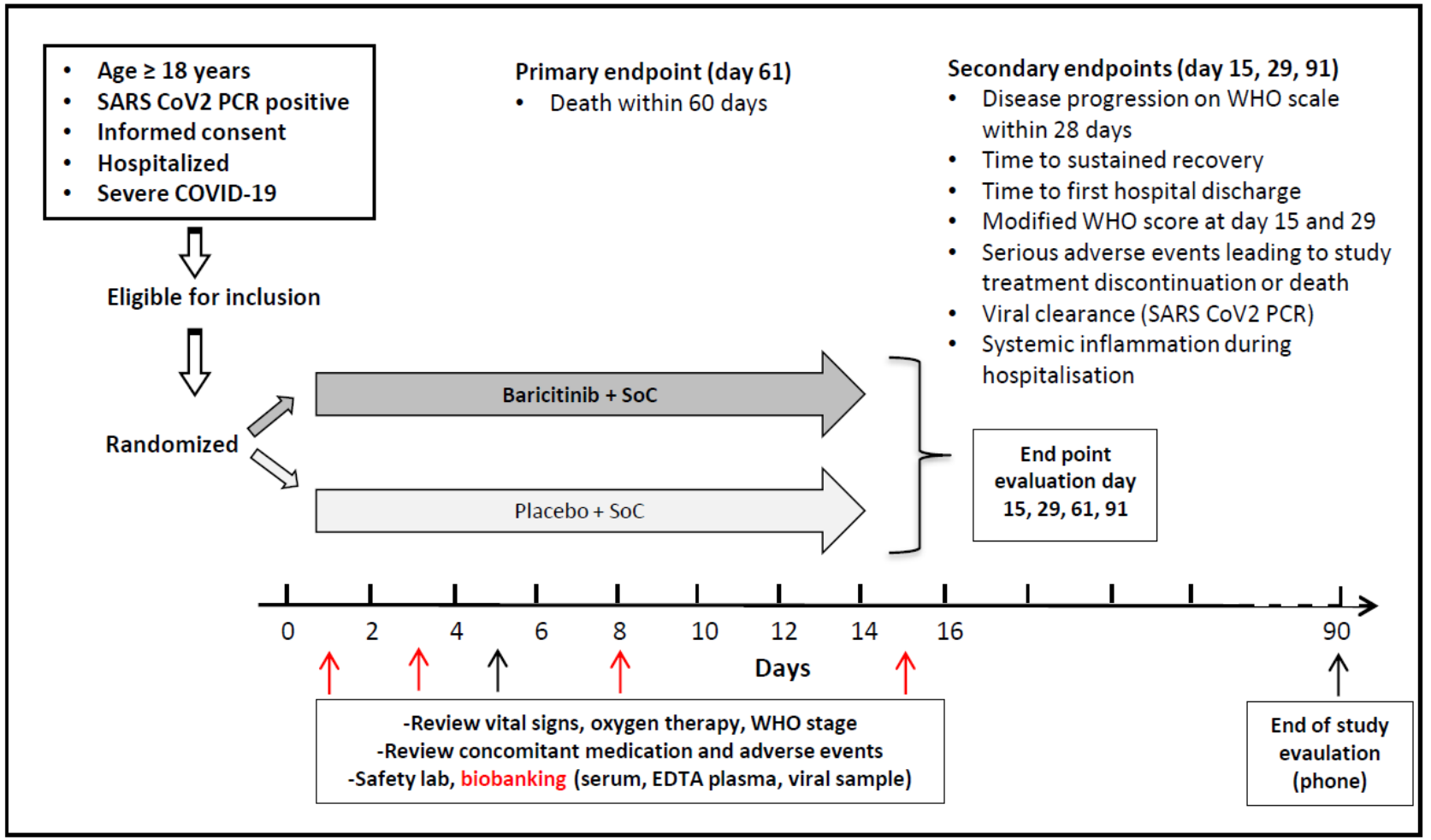


Introduction

- What are efficient trial designs?
  - Comparison?
    - Parallel group design

Parallel group trials



Pros:

- Simple
- Few assumptions
- Easy implementation
- Easily interpreted
- Solid

Cons:

- Inefficient
- Rigid
- Often large
- Only answers one question

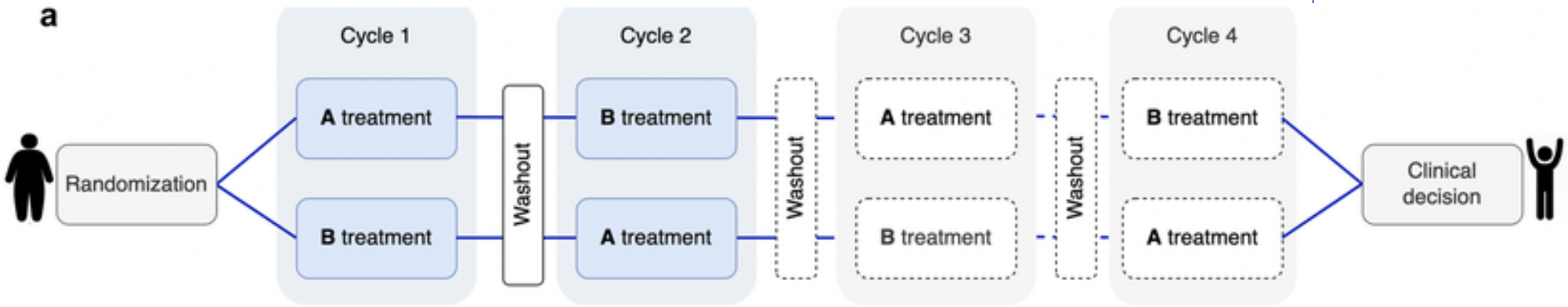
Example:
Bari-SolidAct
Mortality 10% vs 15%
1900 patients

Introduction

- What do we want to gain?
  - Shorter time
  - Fewer participants
  - Answer more clinical/scientific questions
  - Reuse infrastructure/data collection
- What are the drawbacks?
  - More complex
  - Challenging to contain false discovery rate
  - Operationally and clinically demanding

N-of-1 trials

- Carry-over effects
- Back to basic after wash-out
- Chronic, stable conditions
- Pros: efficient
- Cons: Strong assumptions



Grammatikopoulou, M.G., Gkouskou, K.K., Gkiouras, K. *et al.* The Niche of *n*-of-1 Trials in Precision Medicine for Weight Loss and Obesity Treatment: Back to the Future. *Curr Nutr Rep* **11**, 133–145 (2022). https://doi.org/10.1007/s13668-022-00404-5

Example: Burst-trial (N-of-1 trial)
P: Chronic peripheral neuropathic pain
I: Spinal cord stimulation
C: No Spinal cord simulation
O: Pain NRS 0-10 over last 7 days

Six treatment periods (I or C) of 2 weeks
Three cycles of two treatments (I or C)
12 weeks
10 patients

Factorial designs

- Two interventions and control

	Control	Food intervention
Control	Control	Food
Skin Intervention	Skin	Food + Skin

Pros:
- Assess two interventions in one trial
- Possible to assess the interaction
- Possibly efficient if the assumption of no interaction is valid

Cons:
- Difficult to interpret if there is an interaction

Example: PreventADALL
P: New born babies
I: Skin care (oil baths) and peanut, milk, wheat and egg introduction
C: No intervention
O: 1) Atopic dermatitis at 12 months
2) Food allergy at 36 months

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)32983-6/fulltext

Cluster-randomised trials

- Randomise clusters instead of individual patients
- E.g. hospitals, regions or departments

Example: LAPS trial
P: First time pregnant women
I: Follow Zhang's guideline
C: Follow WHO partogram
O: Caesarean sections

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)31991-3/fulltext

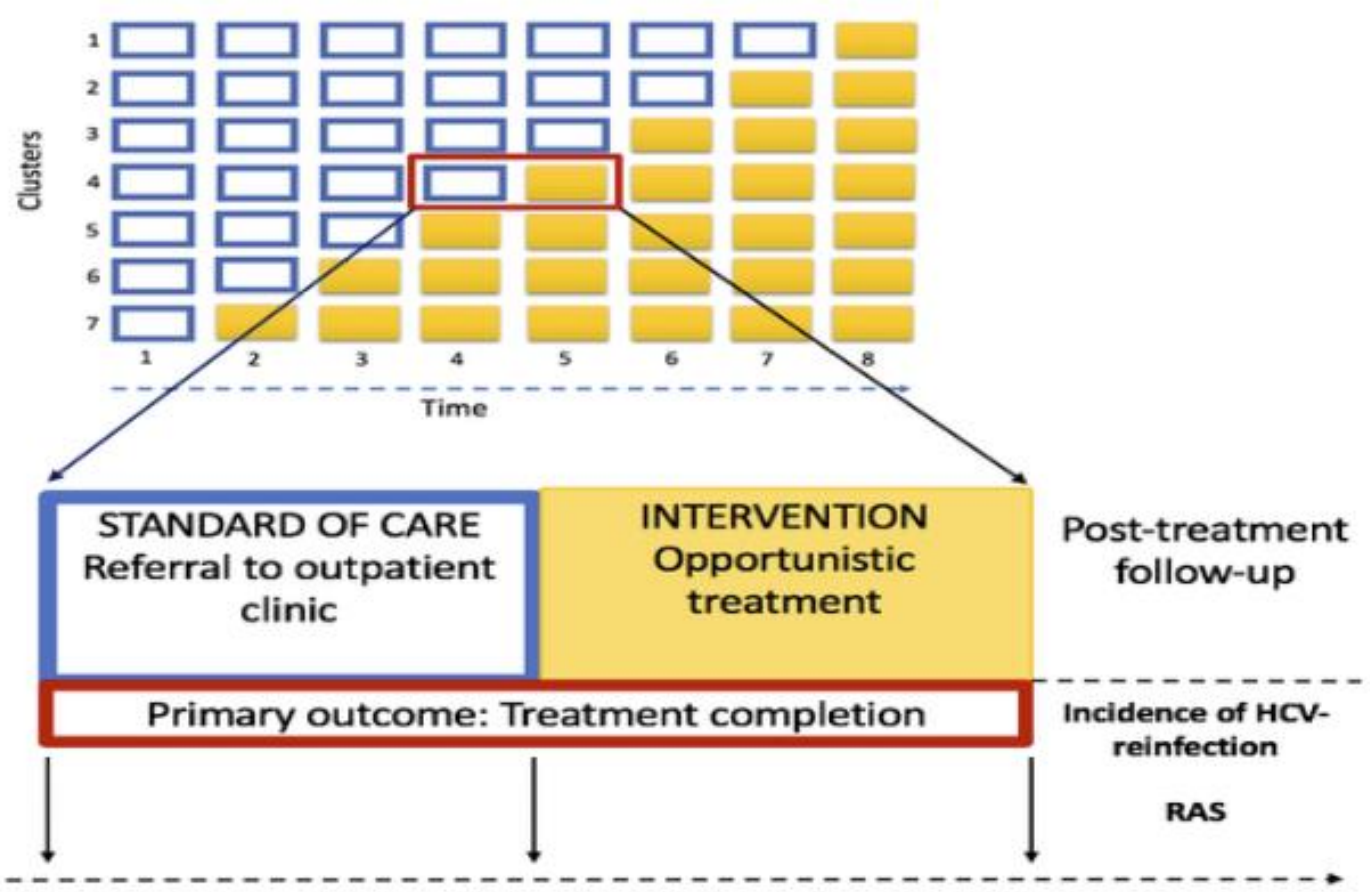
Pros:
- Pragmatic
- Quick enrolement
- Simple

Cons:
- Large sample size
- Many sites
- Generalisability?
- Causal interpretation?
- Best suited for strategies or non-drug interventions

Stepped-wedge cluster-randomised trials

- Randomise the timing of intervention between clusters

Stepped-wedge cluster-randomised trials

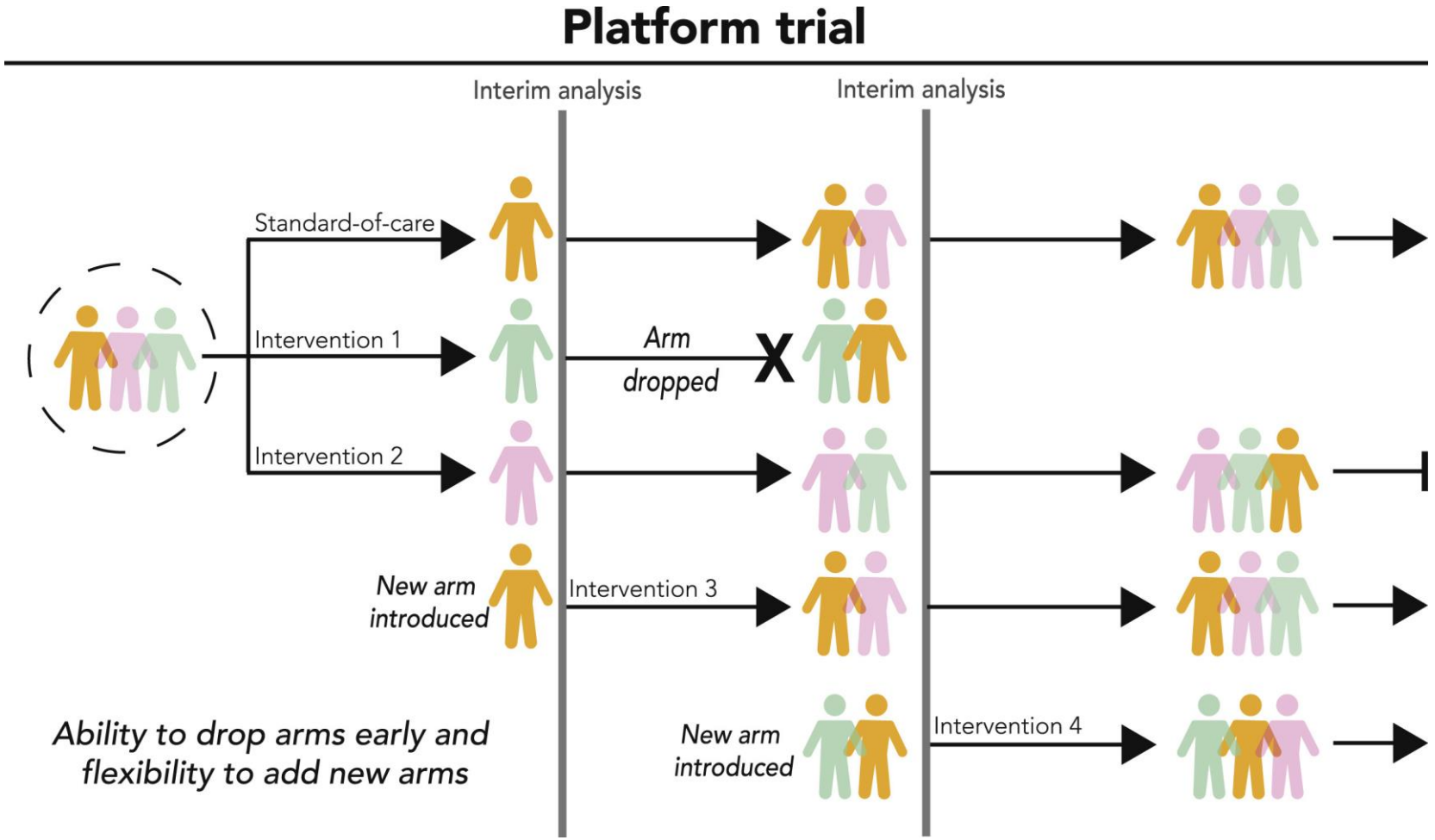


Example: OPPORTUNI-C
P: Adults with Hepatitis C
I: Opportunistic treatment during hospitalisation
C: SoC Referral to outpatient clinic
O: Treatment completion

Platform trials

- A single trial infrastructure assessing multiple treatments for a single disease
- Master protocol
- Additional sub-protocols with new interventions
- Often common controls
- Basket and umbrella trials in cancer typical examples
- IMPRESS-NORWAY, EU-SolidAct, RECOVERY etc

Platform trials

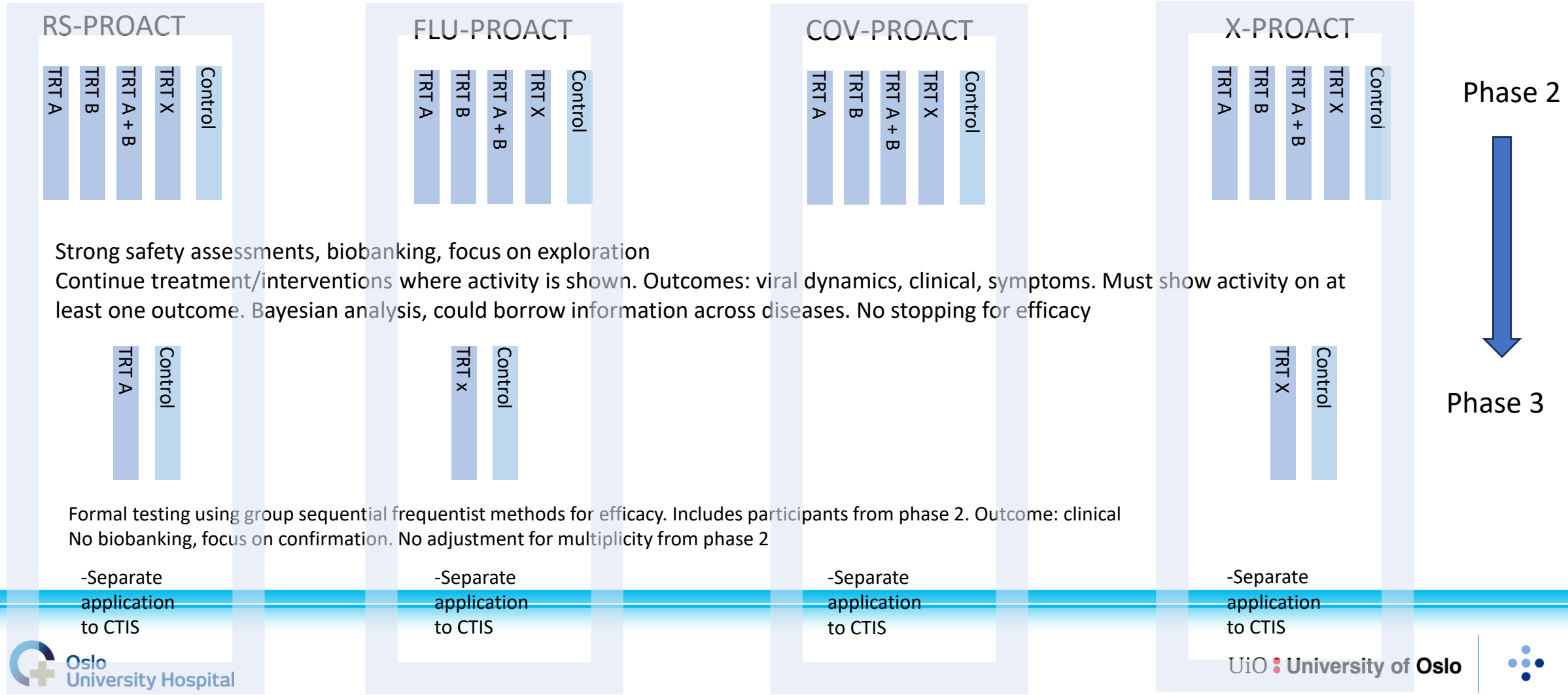


https://www.jclinepi.com/article/S0895-4356(19)30987-4/fulltext

Adaptive platform trials

- Adaptations can include
  - Interim analysis with early stopping (group sequential designs)
  - Adaptive randomisation
  - Take out or include new sub-populations
- Include both phase 2 and 3

EU-PROACT
Master protocol
Population: Hospitalised subjects with Viral Respiratory Tract Infection
- Overall design, used in Clinical trials agreements, used as text repository for the disease specific protocols



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Register-randomised trials

- Use already established registers to capture data
- Challenges in the informed consent and randomisation
- Example: TASTE trial
  - P: patients with ST-segment elevation myocardial infarction
  - I: routine intracoronary thrombus aspiration before primary percutaneous coronary intervention (PCI)
  - C: PCI alone
  - O: Death from any cause
- Very quick inclusion, fast answer

Pragmatic trials

- Lower the bars for achieving clear answers to the research question
- Focus on real world evidence
- Continuum between very unpragmatic to very pragmatic
- May introduce heterogeneity, larger sample sizes
- Cluster-randomised trials and register-randomised trials are examples of pragmatic trials
- Buzz-word to allow more leniency?

Non-randomised trials

- All included patients receive the experimental treatment
- Compare against historic controls
  - Actual data
  - Aggregated data (e.g. 95% mortality)

- Are the historical controls still relevant?
- What do you compare against
  - Mean outcome? Upper 95% confidence interval? Other?
- Remember the causal question!
  - Observational trial, use causal inference methods?