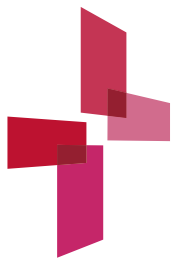


What Questions are Suitable for an Adaptive Platform Trial

Steve Webb, Monash University and St John of God Healthcare

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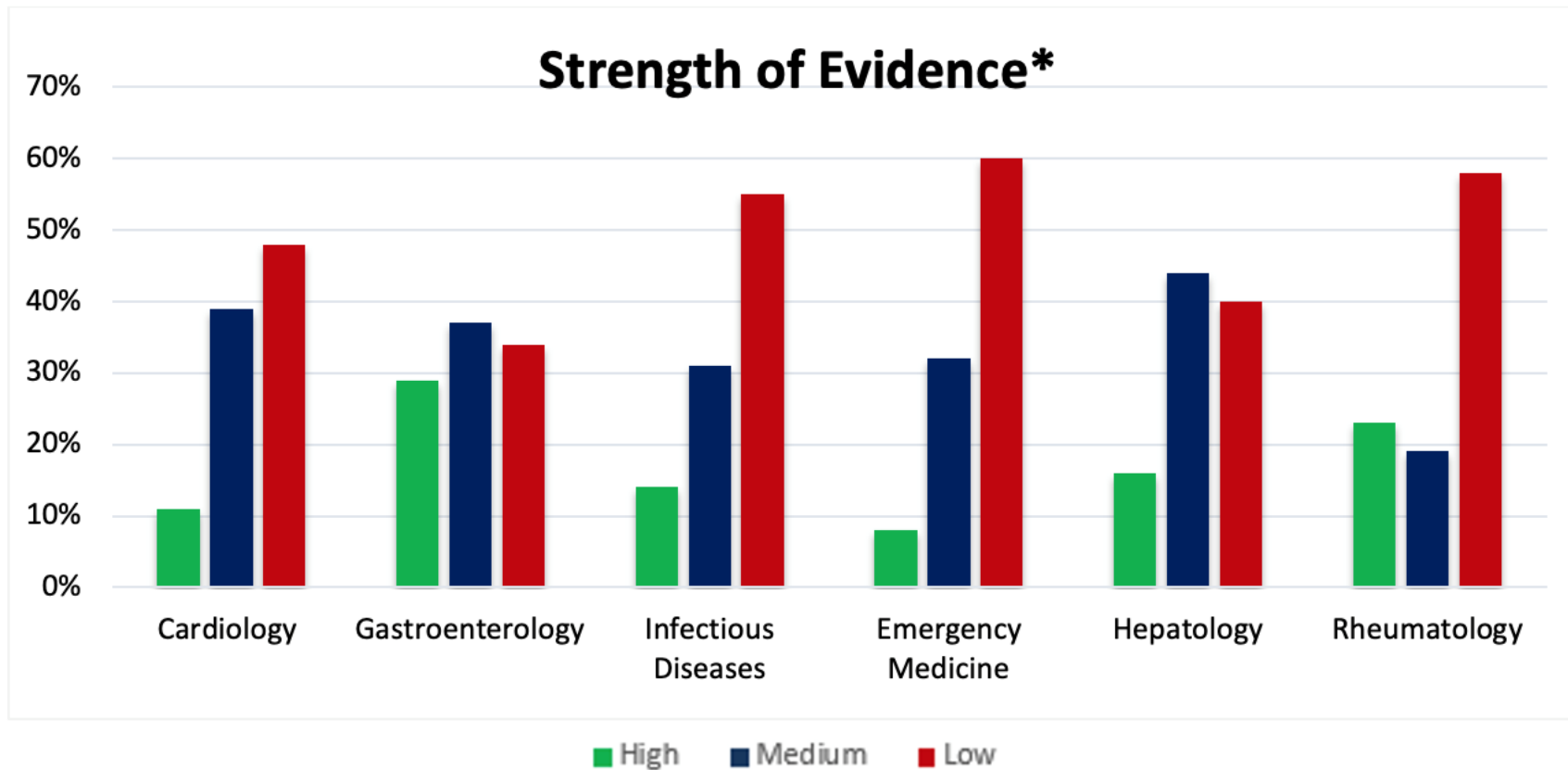


Australian
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www.clinicaltrialsalliance.org.au

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Figure 1: The Frailty of Evidence in Clinical Practice Guidelines



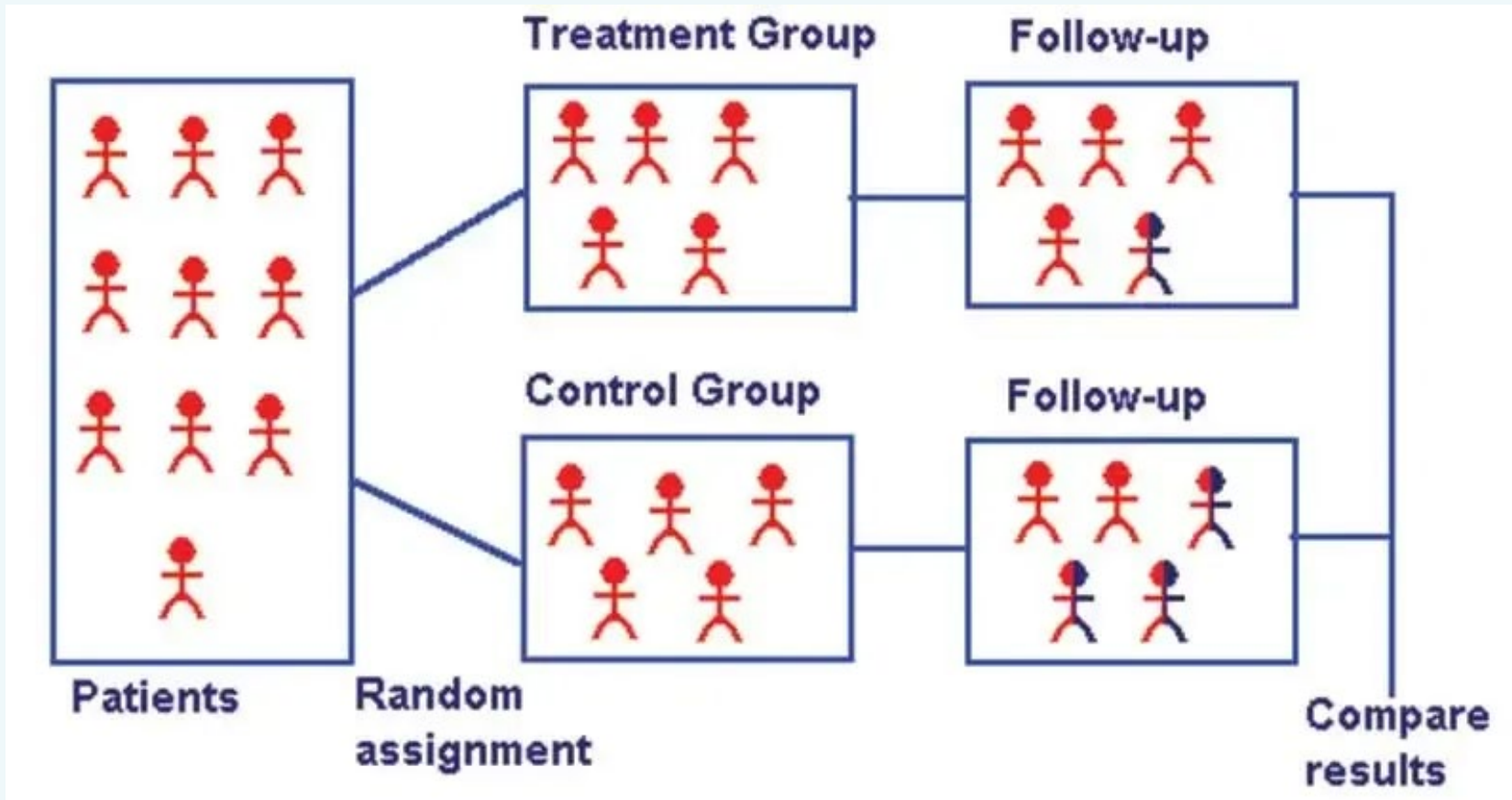
*All papers use similar, but not identical grading systems (Box 1) thus preventing direct comparison

Because trials are expensive, slow, difficult...

More questions than trials can answer...



Conventional, parallel design RCT



Design must be tailored to question

Major Advantage = efficiency,
both operational and statistical

- Answer multiple questions
- Faster
- Cheaper (per question)
- Can evaluate:
 - heterogeneity of treatment effect
 - Treatment-by-treatment interactions

Major Disadvantage = complexity

- Major operational challenges
- Limited availability of statistical expertise
- Higher 'up-front' central costs
- Easier to fail

Key difference between conventional design and an APT

Conventional clinical trial has a treatment as its focus

- Aim is to determine treatment effect of an intervention (typically compared to control)

Adaptive platform trial has a disease as its focus

- Aim is to determine optimal treatment of a disease. Which treatments, in what combination and sequence, at what dose and duration, in which sub-groups

What diseases or conditions should have a platform?

Diseases with high public health impact

Diseases with multiple treatments administered in parallel or in series

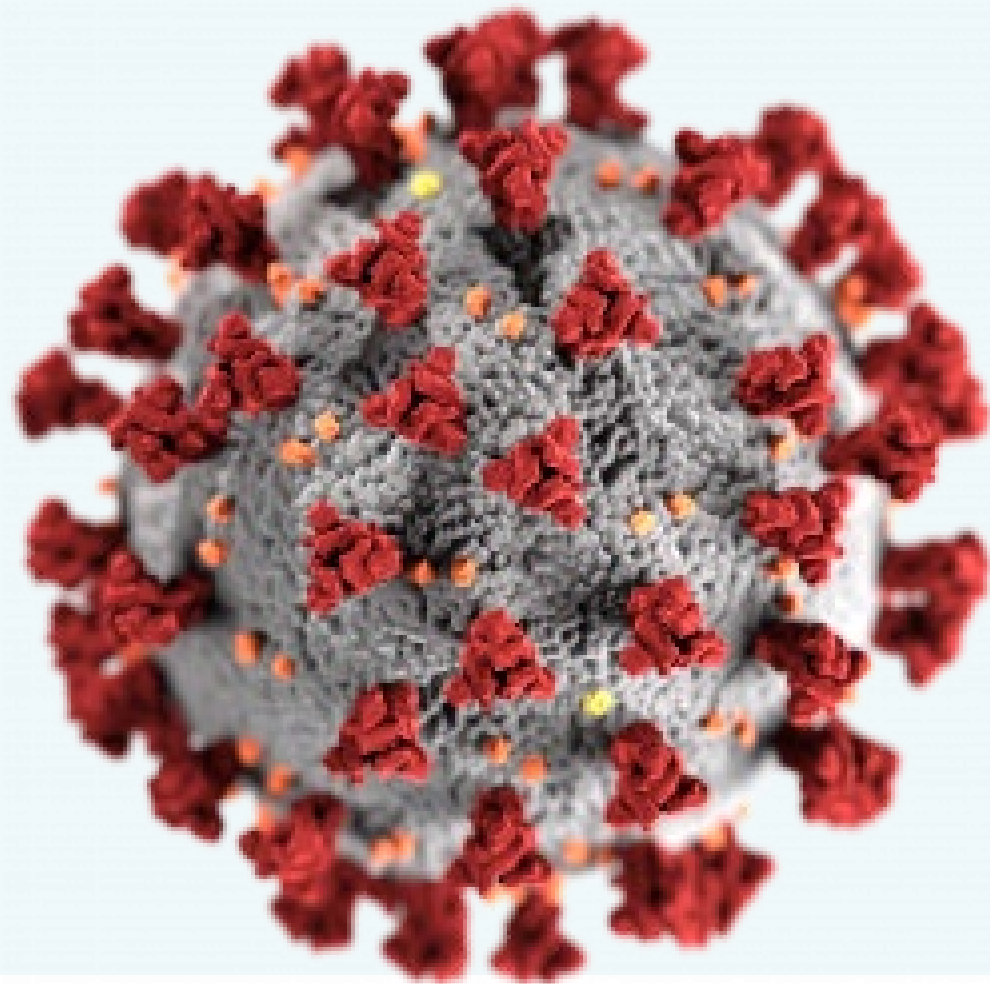
'Substantial uncertainty about optimal treatment, particularly with variation in practice (replace random care with randomised care) and / or lots of new treatments to evaluate

Clinically important outcomes are known relatively quickly after randomisation

Diseases with reasonable *a priori* likelihood of heterogeneity of treatment effect or treatment-by-treatment interactions

Important to public health to generate evidence quickly

Diseases that have available clinical trial infrastructure and access to adaptive trial expertise



Public health impact

Age group (years)	Rank				
	1st	2nd	3rd	4th	5th
Under 1	Perinatal and congenital conditions	Other ill-defined causes	Sudden infant death syndrome	Accidental threats to breathing	Selected metabolic disorders
1-14	Land transport accidents	Perinatal and congenital conditions	Brain cancer	Other ill-defined causes	Suicide
15-24	Suicide	Land transport accidents	Accidental poisoning	Other ill-defined causes	Assault
25-44	Suicide	Accidental poisoning	Land transport accidents	Coronary heart disease	Other ill-defined causes
45-64	Coronary heart disease	Lung cancer	Suicide	Colorectal cancer	Breast cancer
65-74	Lung cancer	Coronary heart disease	Chronic obstructive pulmonary disease	Colorectal cancer	Cerebrovascular disease
75-84	Coronary heart disease	Dementia incl. Alzheimer's disease	Lung cancer	Cerebrovascular disease	Chronic obstructive pulmonary disease
85 and over	Dementia incl. Alzheimer's disease	Coronary heart disease	Cerebrovascular disease	Chronic obstructive pulmonary disease	Heart failure

Although APTs can answer more questions per dollar of trial investment, they're total expense is much higher than a conventional trial

Public health impact

Public health impact = DALYs lost x incidence x cost

- High mortality and / or disability at young age
- Common diseases
- Expensive, either treatment costs and/or societal impact
- Such diseases have additional advantage of large available sample size



Make the platform as broad as feasible

Common or central infrastructure for a platform is expensive

- Operational aspects
- Data management and dynamic data flow
- Statistical analysis

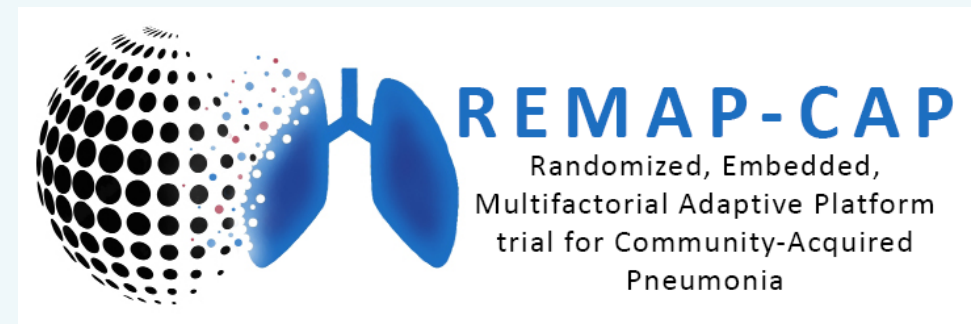
All are expensive and logistically complex, but scalable

Spread high central costs over as many questions as possible

Doesn't necessarily mean a single platform

Can be multiple 'federated' platforms utilising common:

- Data management and coordination
- Single statistical model



Characteristics of treatments for the disease

Multiple treatment domains with multiple treatment options within domains

Low quality evidence regarding current treatment options:

- Effectiveness, comparative effectiveness, and cost-effectiveness within each domain of care
- Optimal combination and / or sequence of treatments; dose and duration

Pipeline of new treatment candidate treatment options

Variation in cost of treatments within domains

Reasonable prior likelihood of differences in outcome and cost

Intensive care



Surviving Sepsis Campaign Guidelines

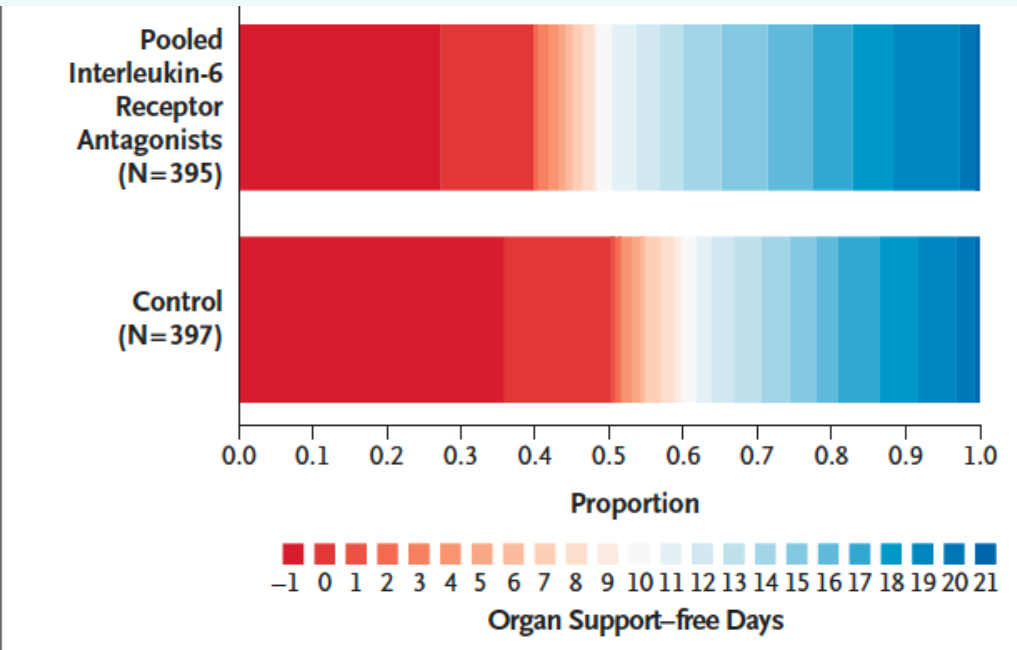
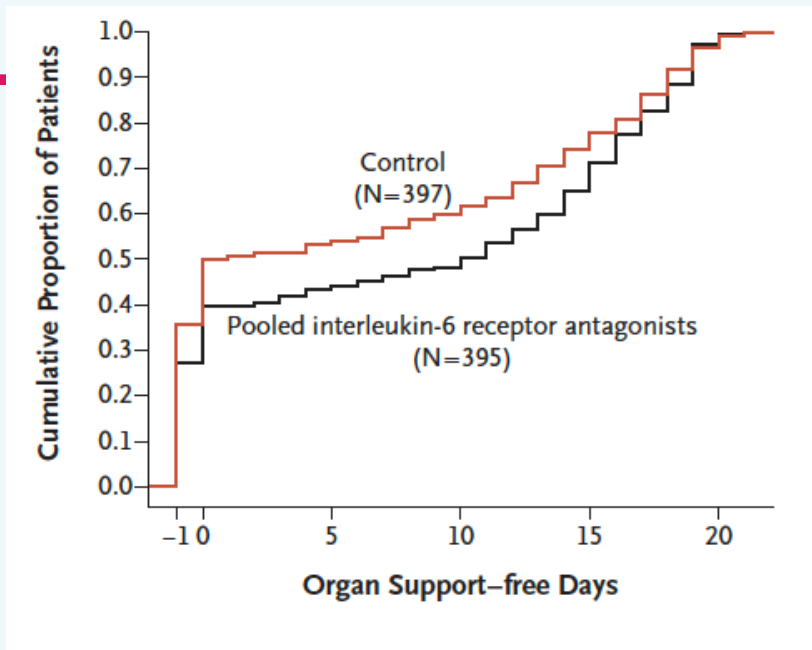
- 13/113 recommendations supported by high quality evidence (mainly things not to do)

Very large number of potentially interacting treatments

1 in 10 patients die before hospital discharge

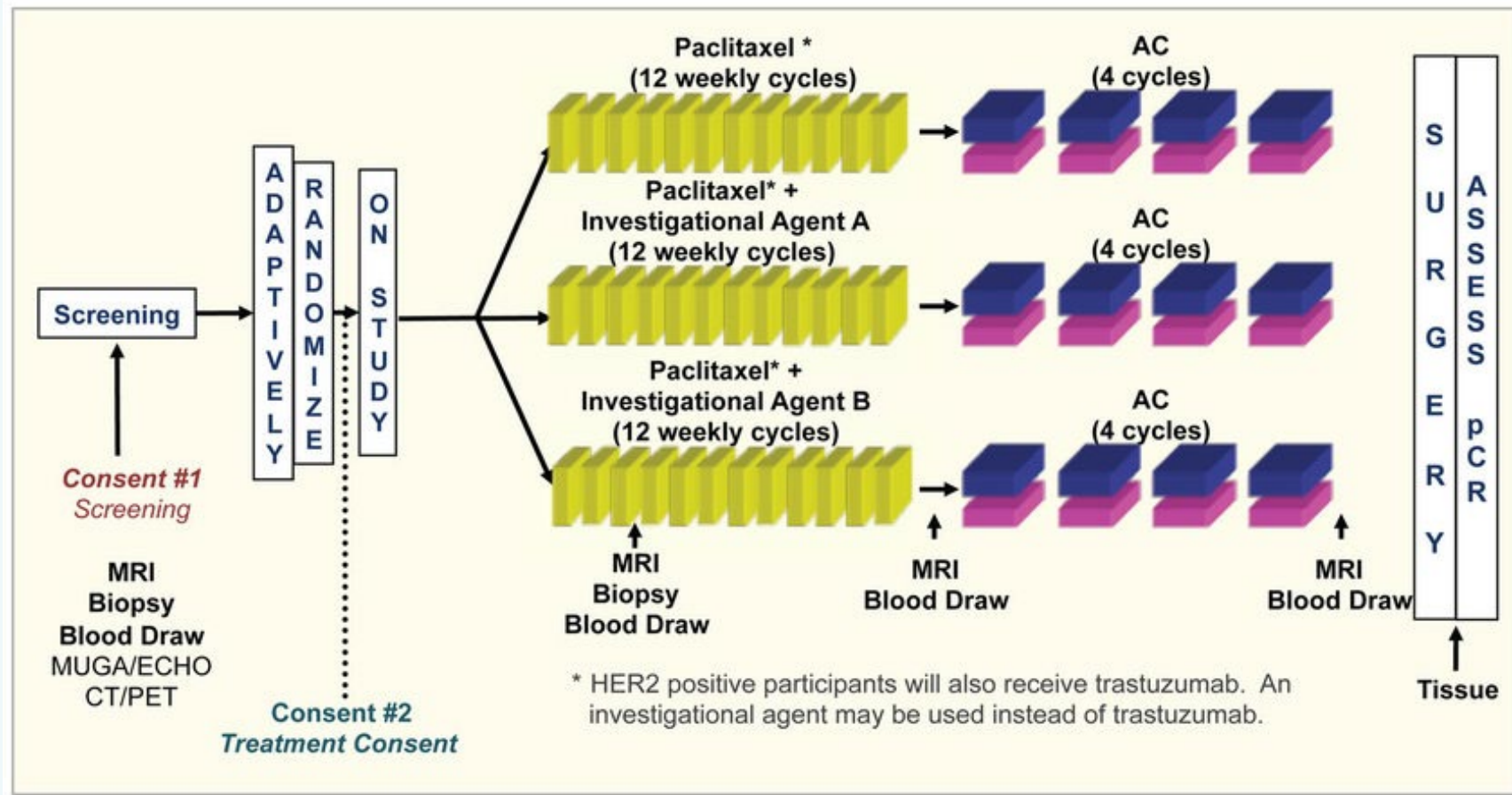
1% of GDP in United States (less in Australia)



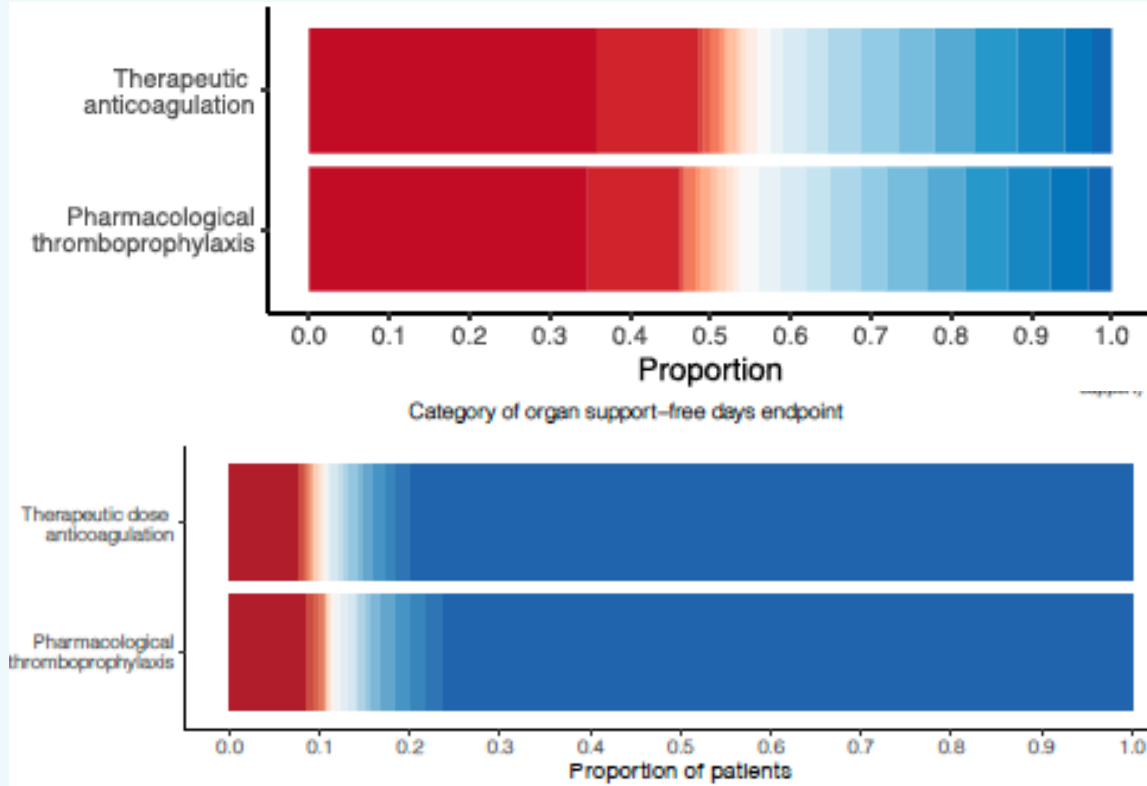


REMAP-CAP adapts on its primary end-point, composite of in-hospital mortality and duration of organ failure support censored at D21 post randomisation

Or a valid surrogate that can be used to predict primary outcome



Diseases with heterogeneity of treatment effect and treatment-by-treatment interactions

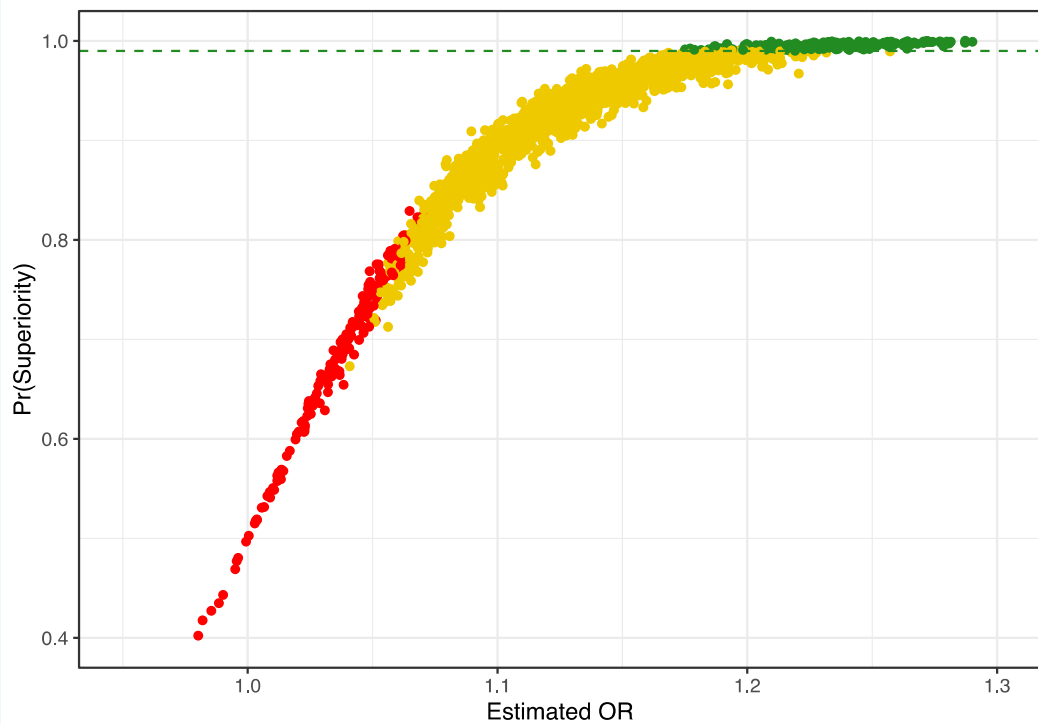


Critically ill patients

Same treatment,
divergent treatment
effect depending on
progression of illness

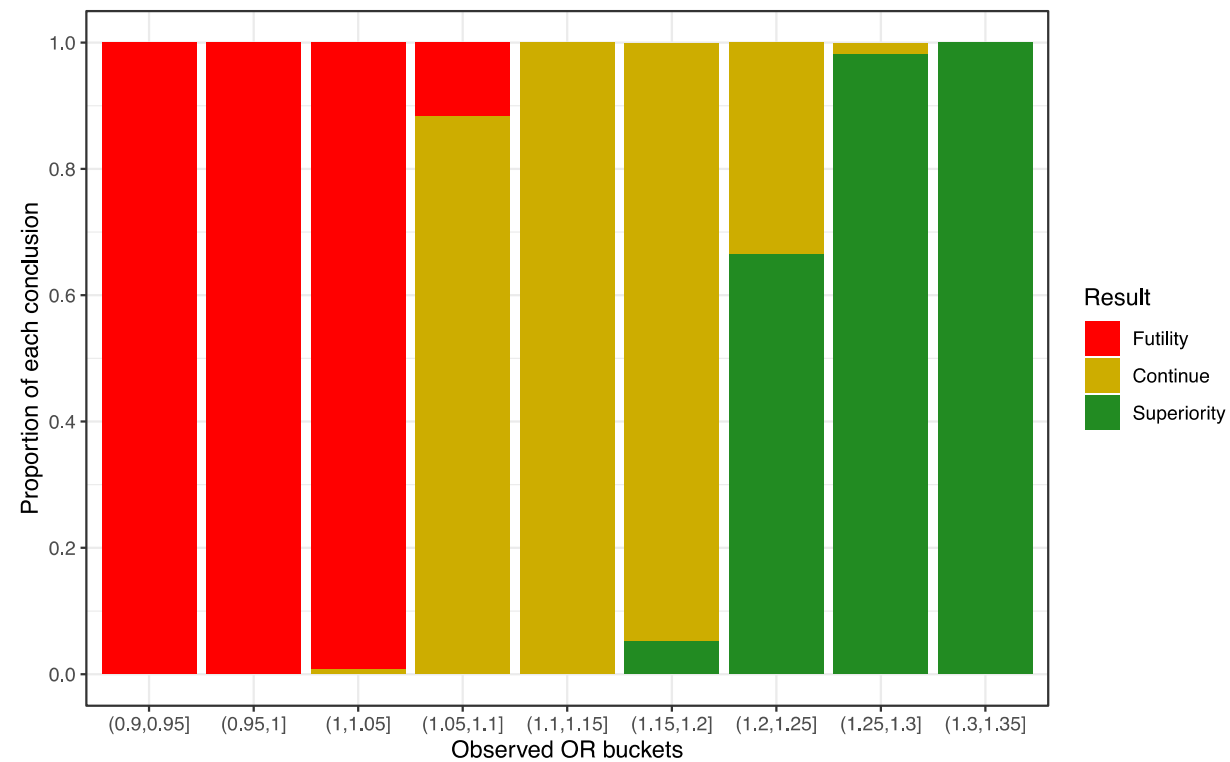
Non-critically ill patients

Statistical expertise



Result

- Futility
- Continue
- Superiority



Operational infrastructure

REMAP-CAP

A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia

20,877

Patient randomisations

18,142

Patient randomisations with
suspected or proven COVID-19

57

Current or completed interventions
in 17 Domains

11,817

Total patients

10,043

Patients with suspected or proven
COVID-19

326

Active Sites

Platform 1 (10 of 165) Preview Inspect Share 100% [Icons] axure

Patients Resources Manage Monitoring Reports Deep Space 9 [Star]

REMAP-CAP 4.0

- REMAP CAP Haere mai
- Domain Criteria
- Landing page-SiteUser
- Landing page-RSC
- Landing page-SAReviewer
- Select Eligibility Checklist
- Landing page-Outcome Asses
- Eligibility
 - Demographics
 - Demographics with checks
 - Platform 1
 - Platform 2 - Time window
 - Platform 3 - Organ failure
 - Domain incl/excl
 - Contraindications
 - Consent-Delayed OK
 - Consent - Prospective requ
 - Patient interest
 - Result
 - Result Pandemic
 - Result Pandemic - Re rando
 - Ineligibility - re randomised
 - Ineligibility - single randomi
 - Re-assessment

Use [Left Arrow] and [Right Arrow] keys to move between pages

Eligibility

- Demographics
- Platform incl/excl 1
- Platform incl/excl 2
- Platform incl/excl 3
- Domain incl/excl
- Contraindications
- Consent
- Patient interest
- Result

Platform inclusion/exclusion 1

1 Is the patient a resident of a nursing home or long-term care facility
Informational text Yes No

2 Prior to this illness was the patient known to be an inpatient in any healthcare facility within the last 30 days
Informational text Yes No

3 Does the patient have signs and/or symptoms that are consistent with lower respiratory tract infection
Informational text Yes No

4 Does the patient have radiological evidence of new onset infiltrate of infective origin
Informational text Yes No

7 **Is community acquired pneumonia-respiratory tract infection (including pneumonia due to COVID) the primary reason for this ICU admission**
The treating clinician believes that community-acquired respiratory tract infection, or complications of respiratory tract infection (e.g. septic shock, respiratory failure, acute kidney injury, multi-organ failure) is the primary reason for the patient's ICU admission Yes No *Existing question wording change.*

8 **Is community acquired respiratory tract infection (including due to COVID) the primary reason for this hospital admission**
The treating clinician believes that community-acquired respiratory tract infection, or complications of respiratory tract infection (e.g. septic shock, respiratory failure, acute kidney injury, multi-organ failure) is the primary reason for the patient's hospital admission Yes No *New question. Should patient location ward or non ICU location*

5 What was the primary reason
Select the most appropriate primary reason

Site feedback

For sites, participation in REMAP-CAP is like any other trial (with exception of frequency of amendments to SSA and CTA)

Get an assignment, give the treatment, enter data into an eCRF

But, have to have clinicians who are willing for their patients' to be randomised

Complexity has to be managed centrally and that requires resources and experience

Conclusions

A new platform requires expensive infrastructure, best for diseases with high public health impact

Best for diseases with complex treatment options, high likelihood of differential treatment effect, and treatment-by-treatment interactions

Need a 'critical mass' of interventions to evaluate with reasonable likelihood of different treatment effects

- uncertainty about current treatments
- novel legitimate candidate interventions

Clinically important outcomes need to be known relatively quickly after randomisation

Diseases that have available clinical trial infrastructure and access to adaptive trial expertise