Adaptive Platform Trial Scientific Meeting

September 28 – 29 • Toronto, Canada

CanTreatCOVID

Canadian Adaptive Platform Trial of Treatments for COVID in Community Settings

Introduction to Adaptive Platform Trials

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Disclosures (none)

*Learning Objectives

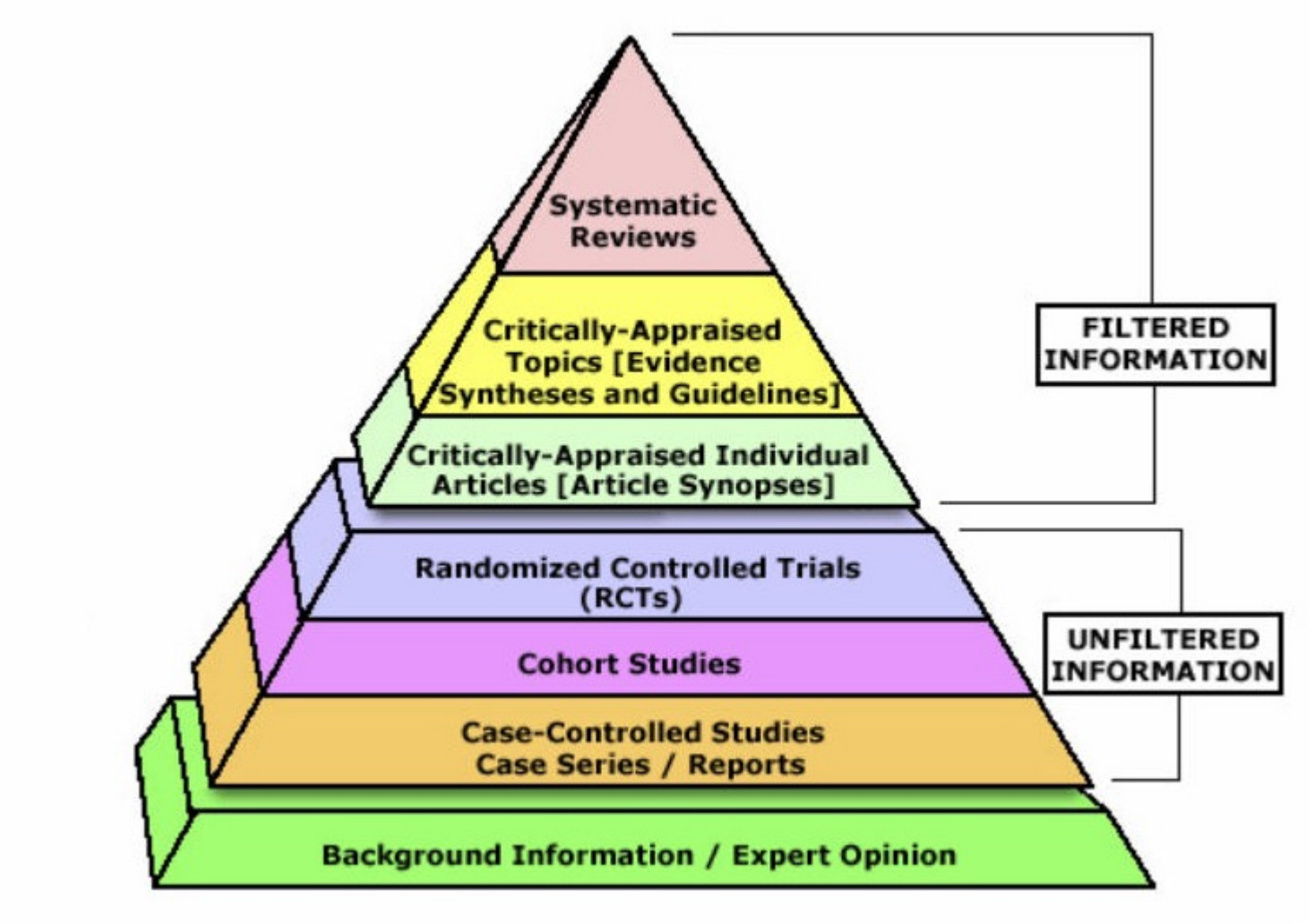
At the end of this session, participants will be able to:

*1) describe what an adaptive platform trial is

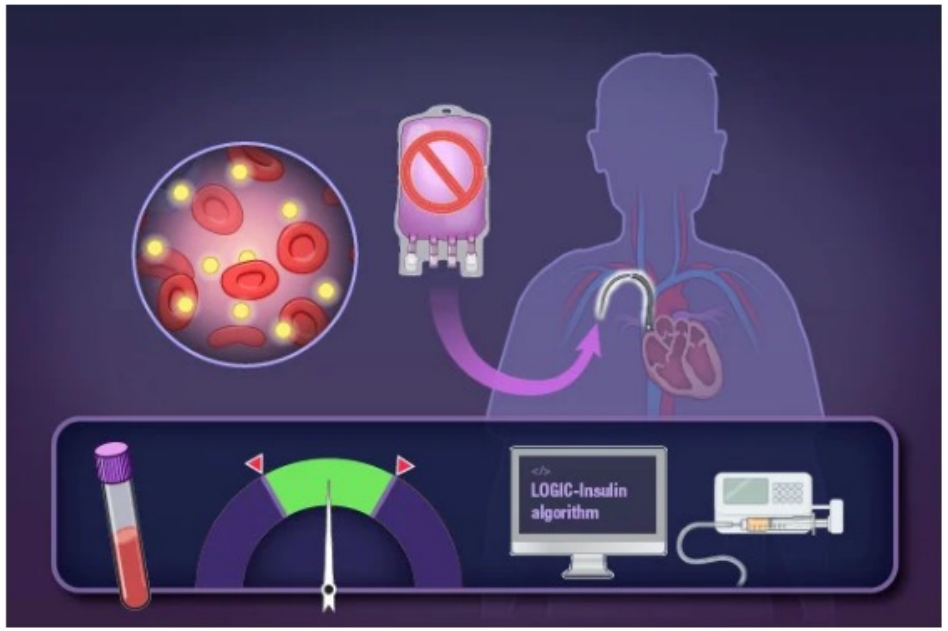
*2) explain the key design elements of an adaptive platform trial

*3) identify the advantages of APTs vs traditional RCTs

Evidence-based Medicine



Randomized Controlled Trial

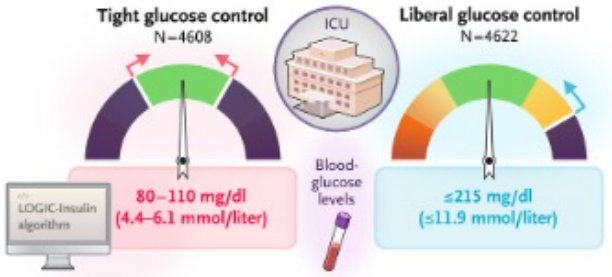


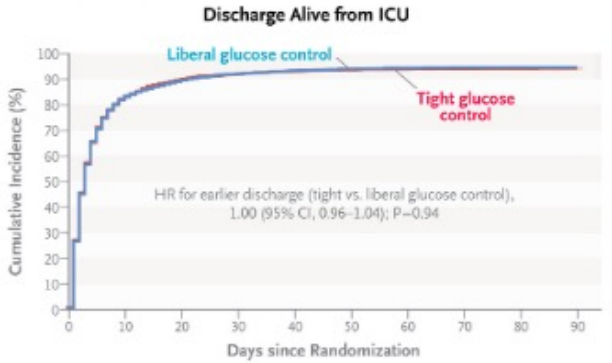
ORIGINAL ARTICLE

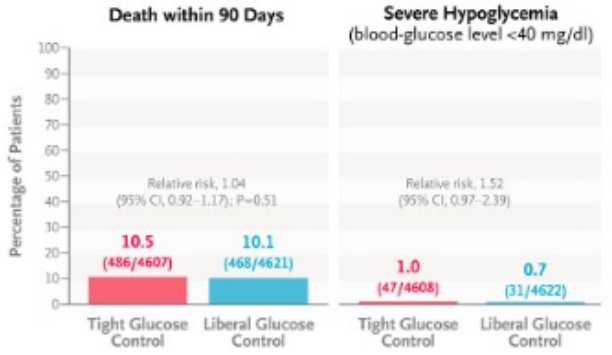
Tight Blood-Glucose Control in Patients in the ICU

J. Gunst and Others

In this randomized, controlled trial involving critically ill patients not receiving early parenteral nutrition, tight glucose control did not affect the length of time that ICU care was needed or mortality.







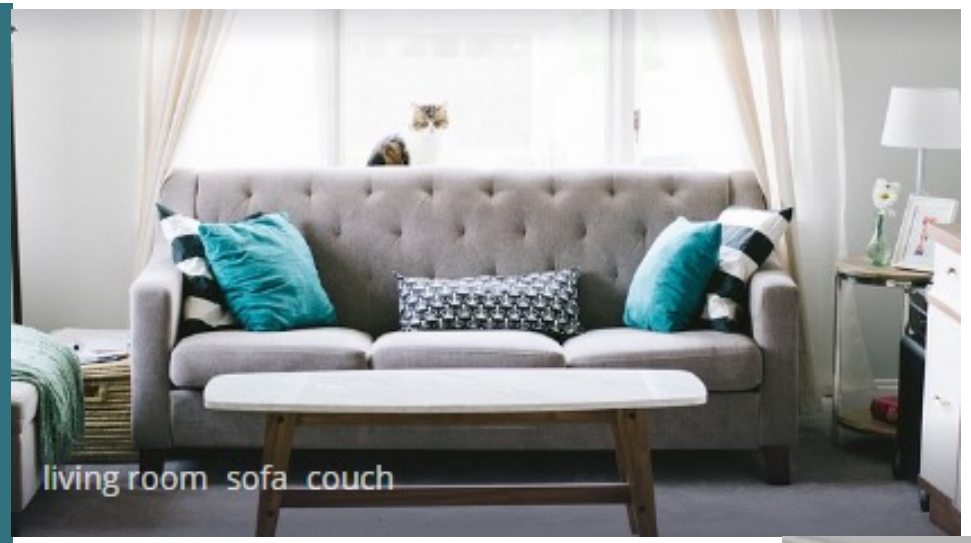
CONCLUSIONS

Among critically ill patients in the ICU who had not received early parenteral nutrition, tight blood-glucose control did not affect either the length of time that ICU care was needed or patient mortality.

Traditional RCT

Versus

Adaptive Platform Trials



Randomized Controlled Trials

- Pilot RCT

- Phase 1 – safety
- Phase 2 – dose finding
- Phase 3 – efficacy
- Phase 4 – post-marketing

- 1) Superiority
- 2) Equivalence
- 3) Non-inferiority

Adaptive Platform Trials

- Pilot RCT

- Phase 1 – safety
- Phase 2 – dose finding
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- 1) Superiority
- 2) Equivalence
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Adaptive Platform Trials

Basic Design

- Focus on a disease / condition
- Master Protocol
- Specific Subprotocols
- Set up decision rules to trigger termination (or addition) of an intervention
- Create a platform that can be used continuously

Basic Design

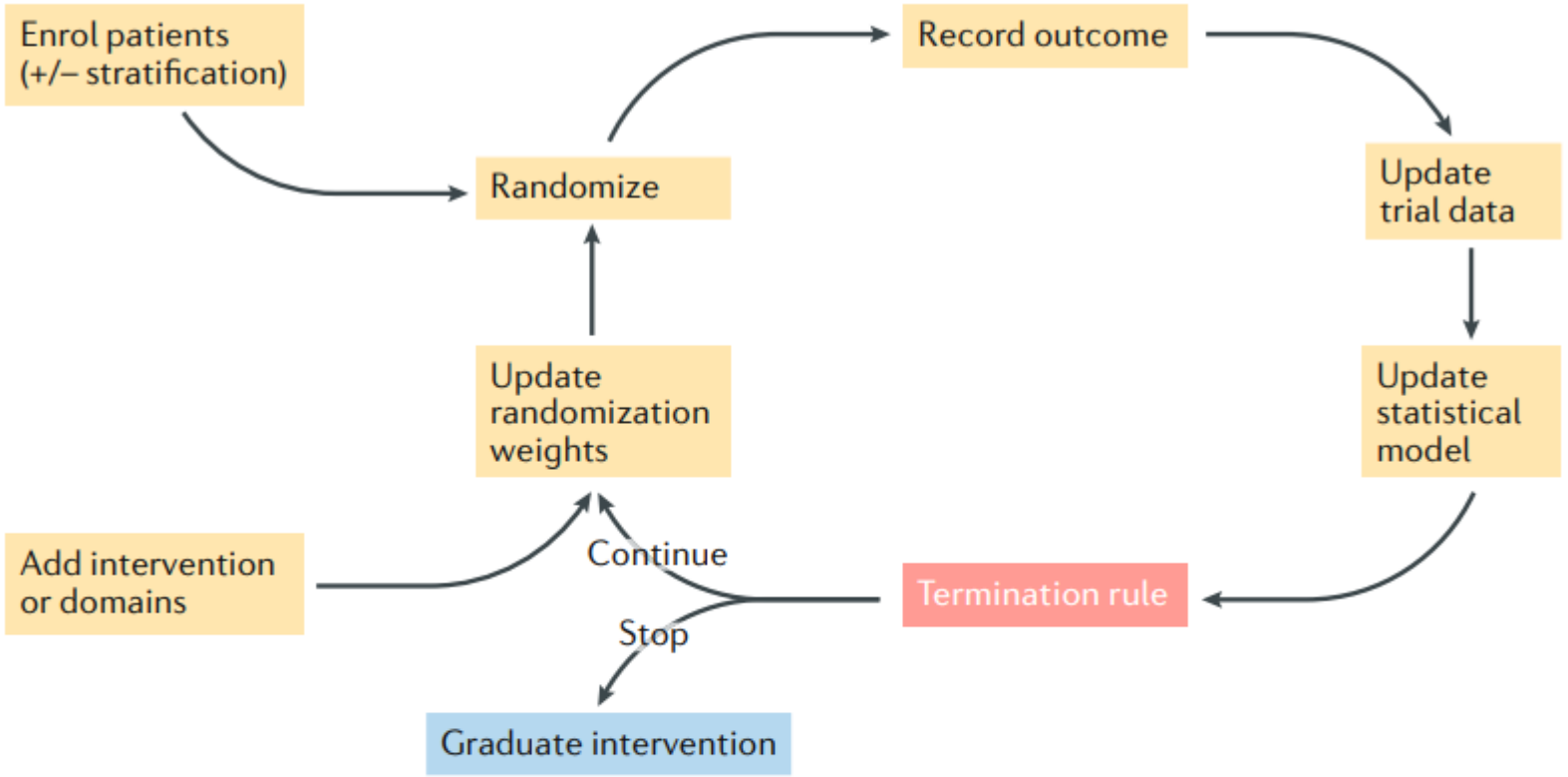


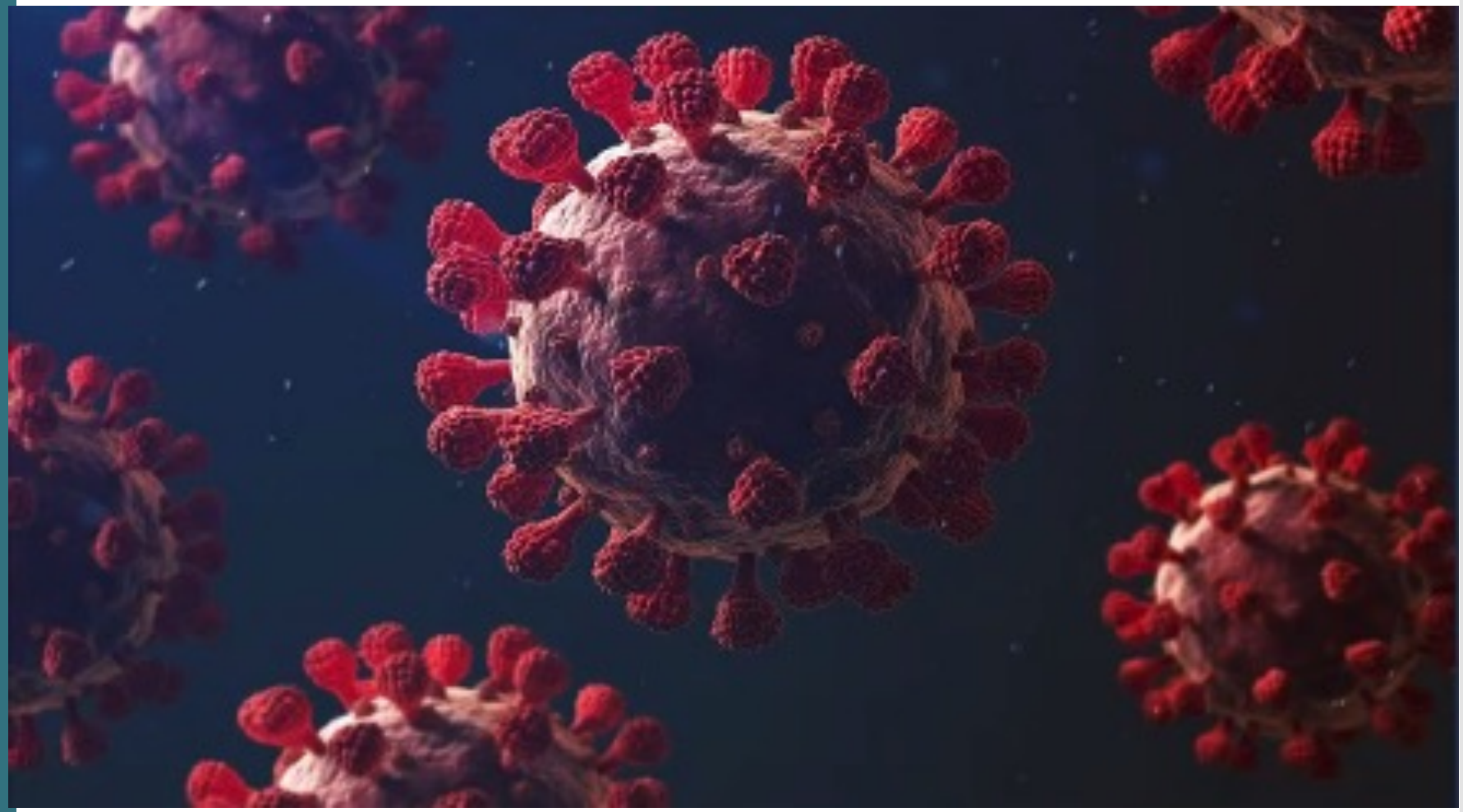
Fig. 1 | **General operational flow of an adaptive platform trial.** Although specifics vary for each identified step and additional features may be added, most adaptive platform trials (APTs) have a common set of activities. Enrolling patients, randomization, recording outcomes and updating trial data are in common with traditional randomized controlled trials. In APTs, however, this information is used in real or near-real time to update a statistical model that is then used to make decisions about termination for graduation (for example, demonstration of superiority) or futility of one part of the trial (for example, a comparison of one particular therapy to control) and for updating consequent randomization probabilities. Not shown: randomization and randomization updates are often specific for different patient subtypes.

Nature Reviews Drug Discovery Aug 2019

Adaptation

- Patient selection and stratification – inclusion/exclusion criteria
- Study interventions
- Randomization
- Outcomes

COVID-19 Pandemic



Adaptive Platform Trials

- ATTACC
- REMAP-CAP
- CANTREATCOVID
- RECLAIM

RECLAIM TRIAL

www.reclaimtrial.ca

REcovering from

COVID-19

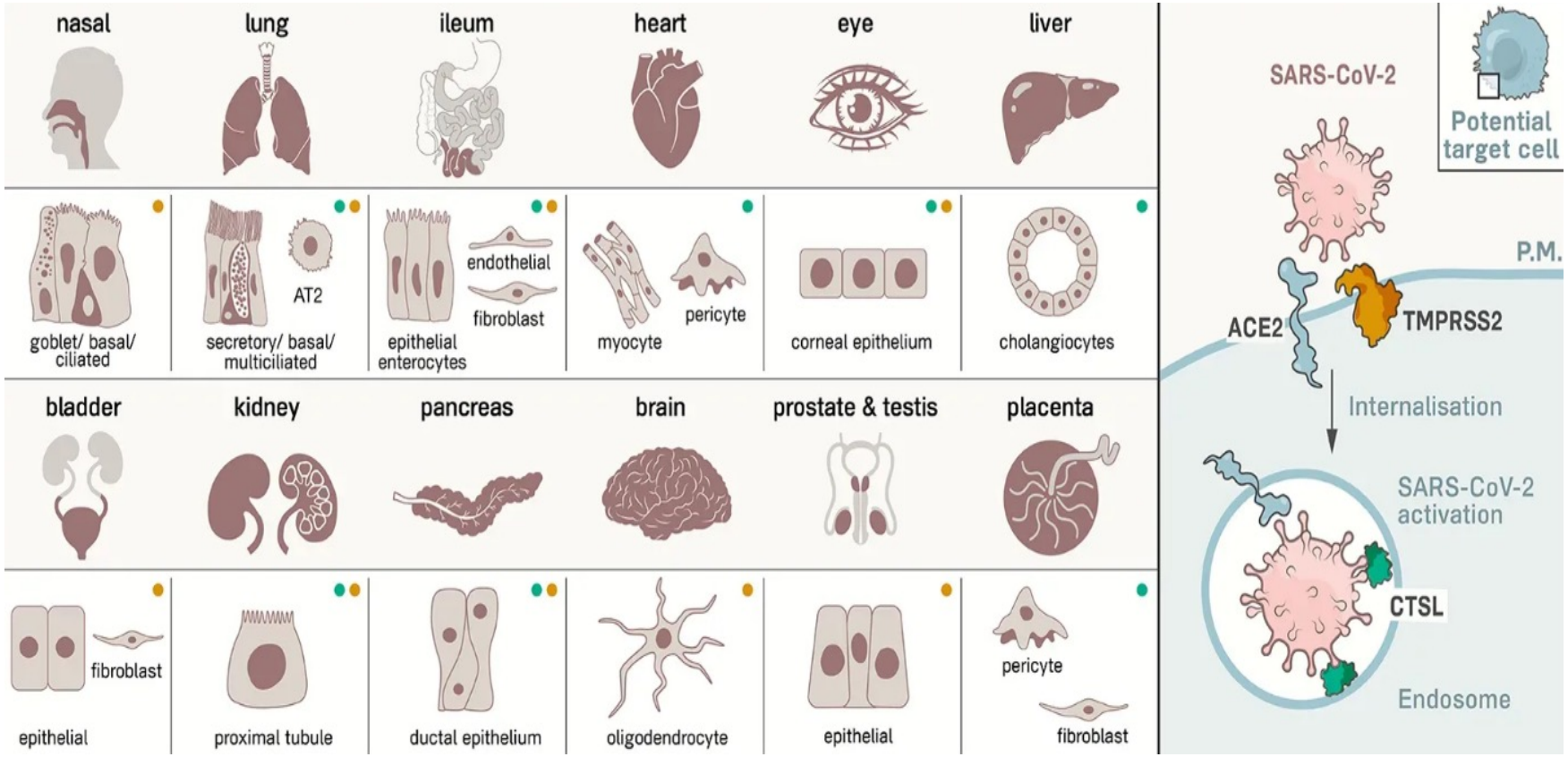
Lingering Symptoms

Adaptive

ntegrative

Medicine

200+ Lingering Symptoms



Long COVID

- Post COVID Condition or Long COVID (WHO definition)
- 1.4M Canadians; nearly 15% of those infected with COVID (Stats Can data)
- Some as long as 3 years [first case Oct 15, 2019; CANCOV data]
- Common symptoms: fatigue, shortness of breath, palpitations, brain fog, dizziness, headaches, insomnia, anxiety

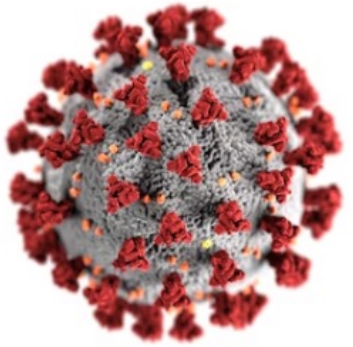
Multisystem disease with episodic disability

Long COVID

Pathogenic Mechanisms

Potential pathogenic mechanisms (based on WHO report*):

1) Immune dysregulation
2) Inflammation
3) Endothelial dysfunction
4) Viral or viral particle persistence
5) Thrombotic microclots
6) Mitochondrial dysfunction
7) Perturbations to microbiome

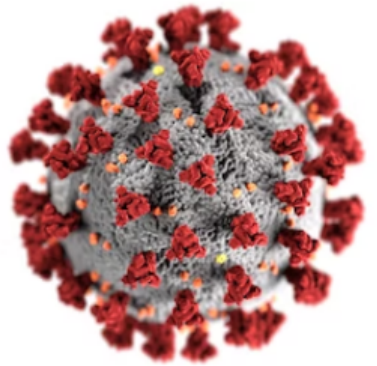


*WHO Report: Expanding our understanding of Post COVID-19 condition. 2021. ISBN 978-92-4-002503-5

What are the Interventions?

Potential pathogenic mechanisms (based on WHO report*) that we are targeting:

1) Immune dysregulation
2) Inflammation
3) Endothelial dysfunction
4) Viral or viral particle persistence
5) Thrombotic microclots
6) Mitochondrial dysfunction
7) Perturbations to microbiome



Investigators, patient partners, outside experts met Sept 10, 2021 and voted on the first round of therapies to be tested

* *WHO Report: Expanding our understanding of Post COVID-19 condition. 2021. ISBN 978-92-4-002503-5*

RECLAIM: Inclusion/ Exclusion Criteria

Inclusion criteria:

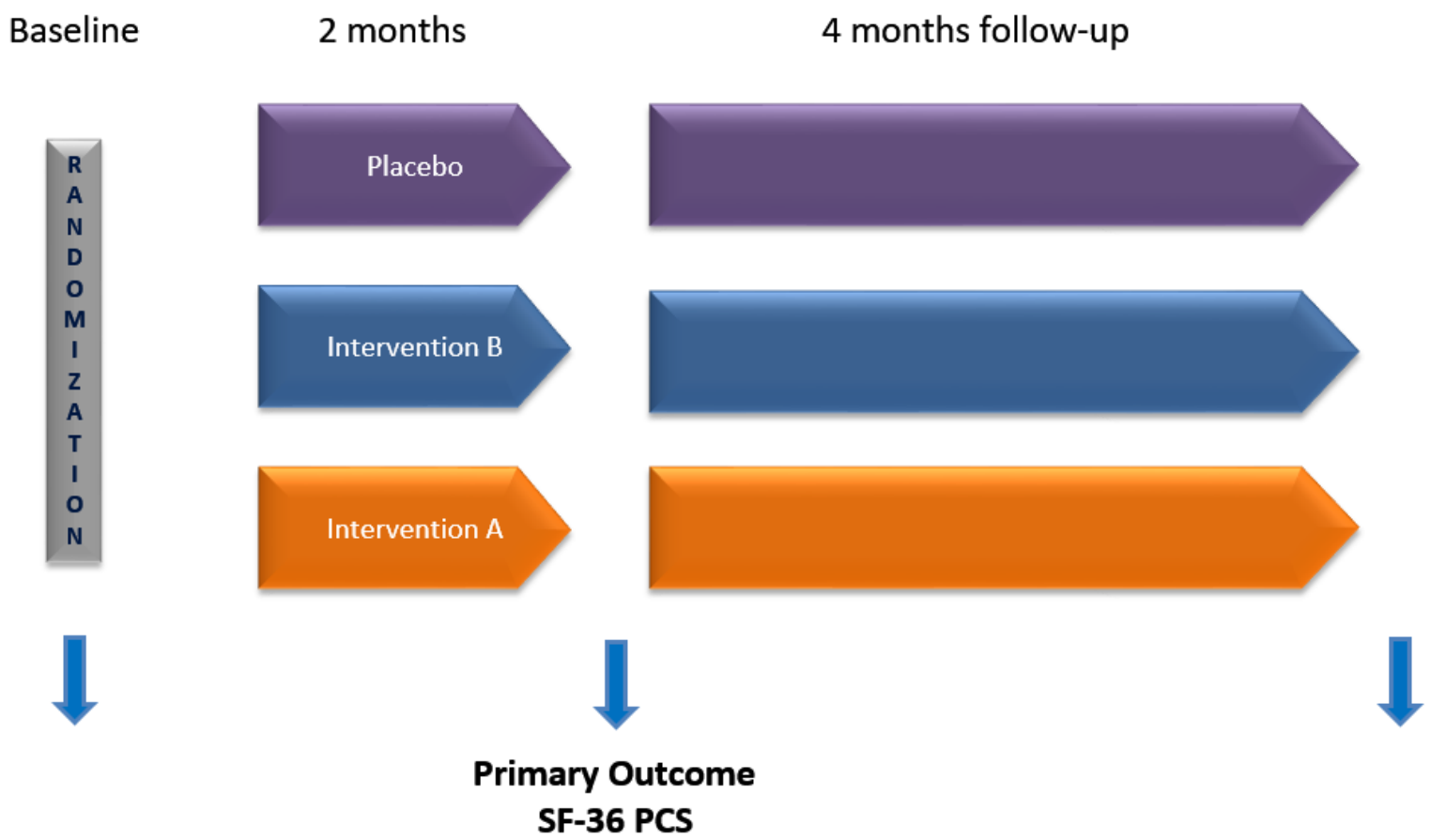
1. Age ≥18 years;
2. Positive COVID-19 test (RT-PCR test, RAT, antibody tests at least 3 months prior to randomization)
   OR
   Presumed COVID-19 assessed by the site investigator (no positive COVID-19 test) with acute illness after October 15, 2019, and at least 3 months prior to randomization.
3. Treated with standard of care therapies for at least 4 weeks prior to entry into trial.
4. Lingering COVID-19 symptoms beyond 3 months from onset of acute COVID and symptoms have lasted at least 2 months. The onset of COVID is considered the earliest of two dates: the date of positive testing or the date of first symptoms.
5. Lingering symptoms from COVID-19 present at the time of randomization.
6. Female patients of childbearing potential (as assessed by the overseeing Investigator) who are sexually active must agree to practice true abstinence or use at least one highly effective method of contraception while on study treatment. Highly effective methods of contraception must be discussed and approved by the overseeing Investigator (refer to Section 5 Contraception).
7. Must be able to provide informed consent and both willing and able to comply with study requirements.

Exclusion criteria:

1. Patients who had mechanical ventilation or extracorporeal membrane oxygen (ECMO) for COVID-19.
2. Current end-organ failure, organ transplantation, or current hospitalization in acute care hospital.
3. Contraindications to all of the study interventions,
4. Co-enrollment in another interventional trial (co-enrolment in an observational study is permitted).
5. Currently pregnant or breastfeeding.

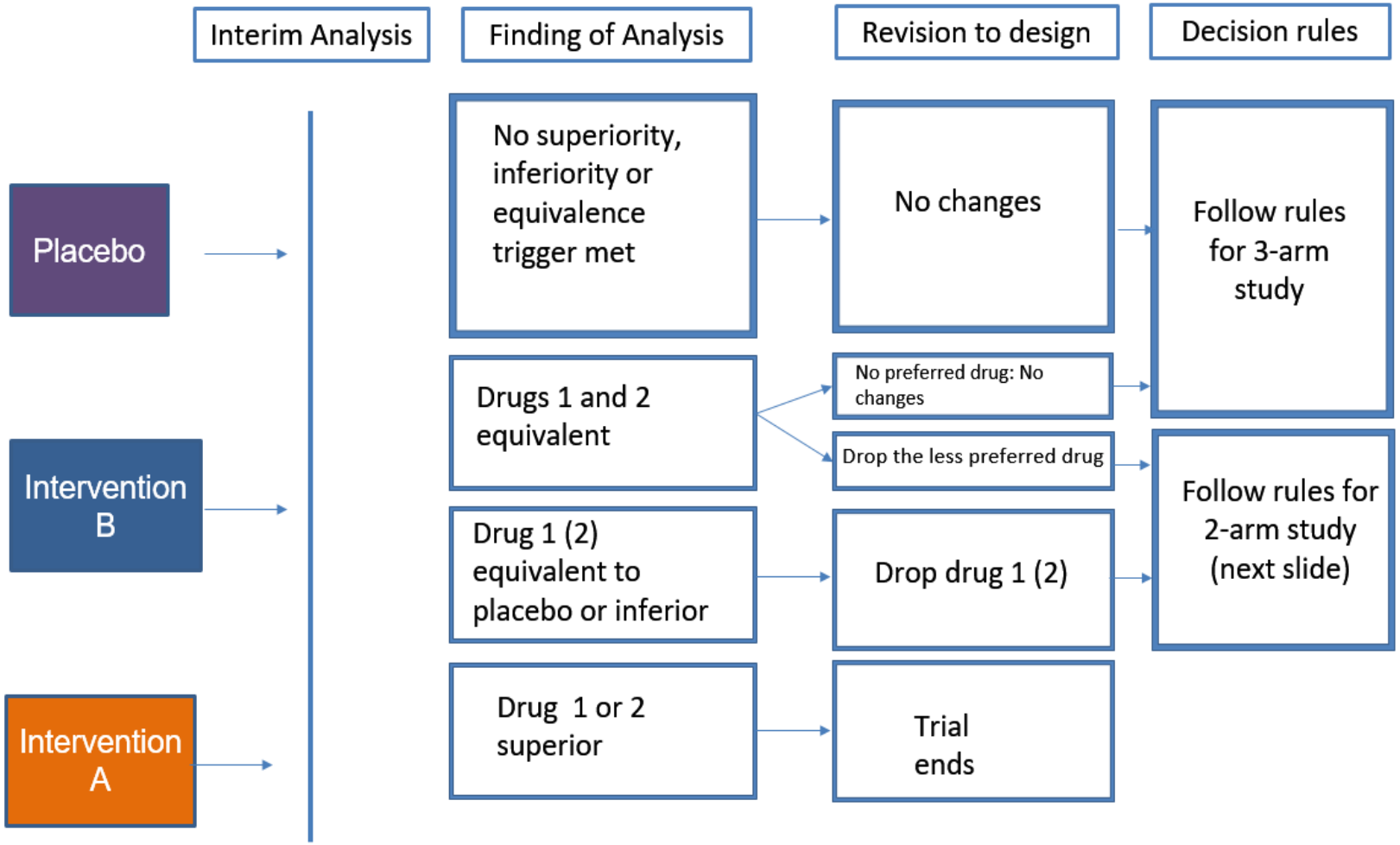
RECLAIM Design

Structure of RECLAIM

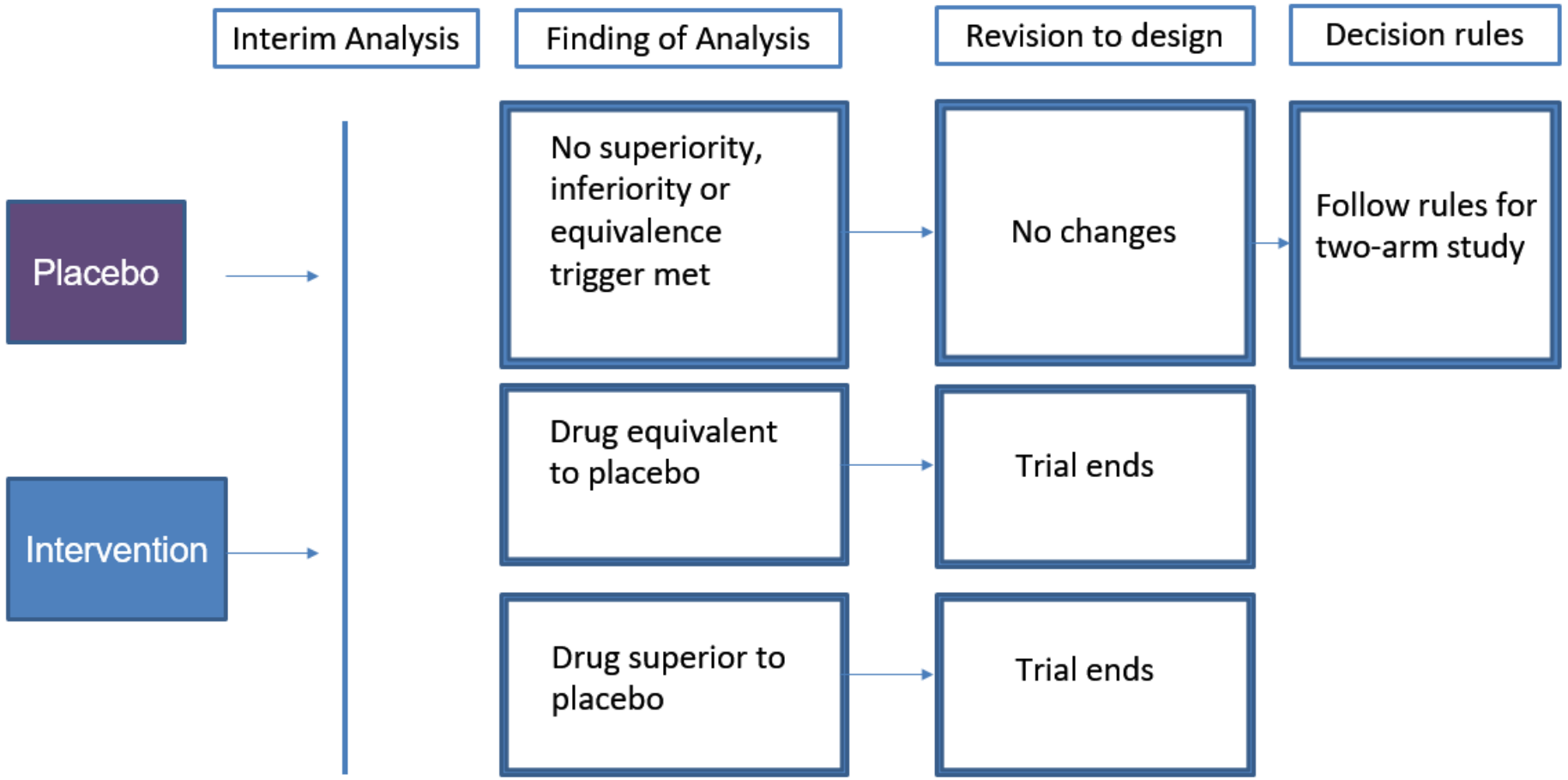


Adaptation Rules

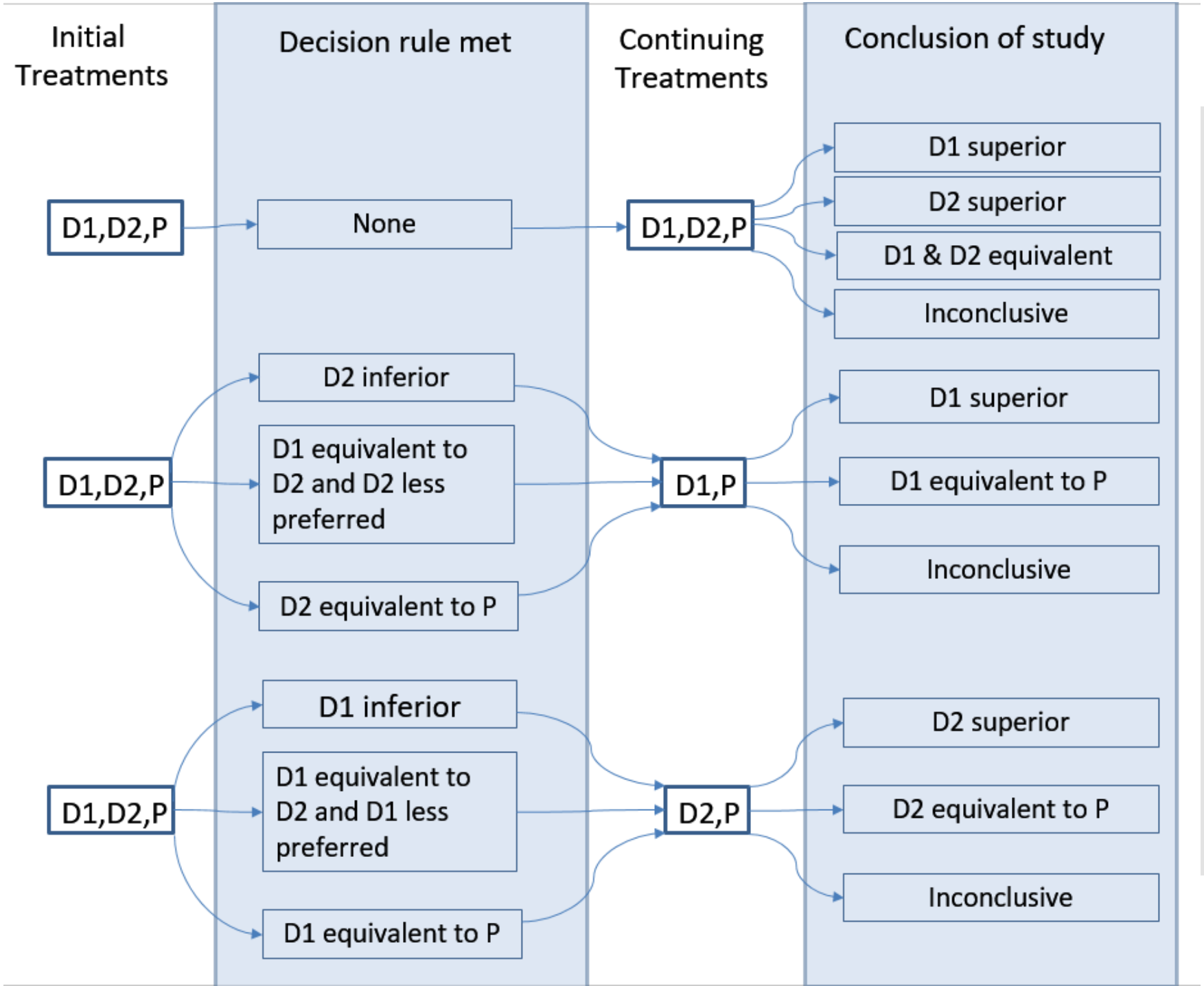
RECLAIM ADAPTATION: Rules for three-arm study



Rules for two-arm study



Adaptation Rules




RECLAIM
Trial
Recovering from COVID-19 Lingering Symptoms
Adaptive Integrative Medicine

Future Adaptations

- Other intervention arms: drugs, TCM
- Hyperbaric Oxygen Therapy (HBOT)
- Hi-OXsr

Advantages of APTs vs Traditional RCTs

Adaptive Platform Trials

- Can test multiple interventions at the same time or in sequence
- Smaller placebo/control group
- Can use Bayesian approach to adapt randomization so that more patients are randomized to more promising therapies (RAR)
- Use the right sample size
- Generate new knowledge more efficiently
- Can embed in clinical practice to create "learning health systems"

Traditional RCTs

- Answer one question
- Time consuming
- Costly

Thank you

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CAN-TAP-TALENT

www.cantaptalent.ca