The Platform Trial:

Lessons from COVID-19

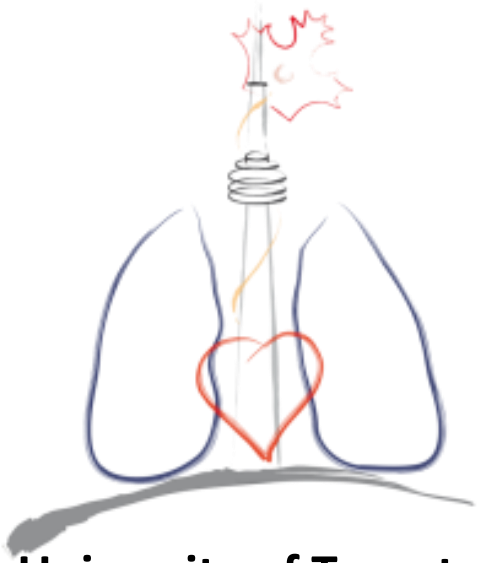
CONGRÈS INTERNATIONAL DE SOINS PALLIATIFS MCGILL

MCGILL INTERNATIONAL PALLIATIVE CARE CONGRESS

John C. Marshall MD FRCSC

Montréal
October 20, 2022

ST. MICHAEL'S
UNITY HEALTH TORONTO



University of Toronto

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Disclosures

- **Advisory Board – Adrenomed**
- **DSMB Chair – AM Pharma**
- **Grant Support – CIHR**
- **Canadian PI – REMAP-CAP**

Learning Objectives

At the conclusion of this presentation, participants will be able to:

- **Describe the differences between a platform trial and a conventional RCT**
- **Discuss the advantages of the platform trial model for comparative effectiveness research**
- **Identify the opportunities and challenges of the model**

CanMEDS Competencies

- Scholar
- Health advocate
- Collaborator
- Leader

The NEW ENGLAND JOURNAL of MEDICINE

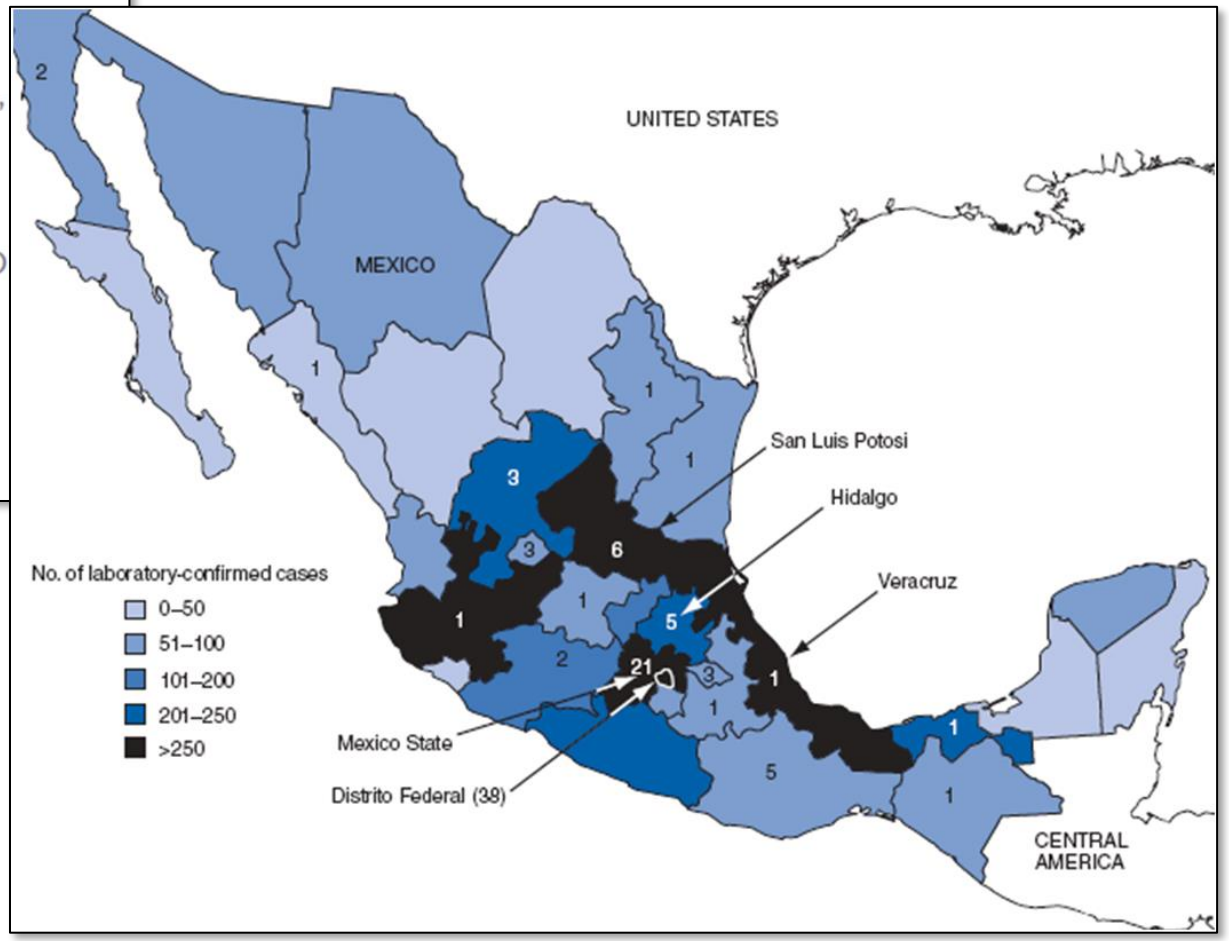
ORIGINAL ARTICLE

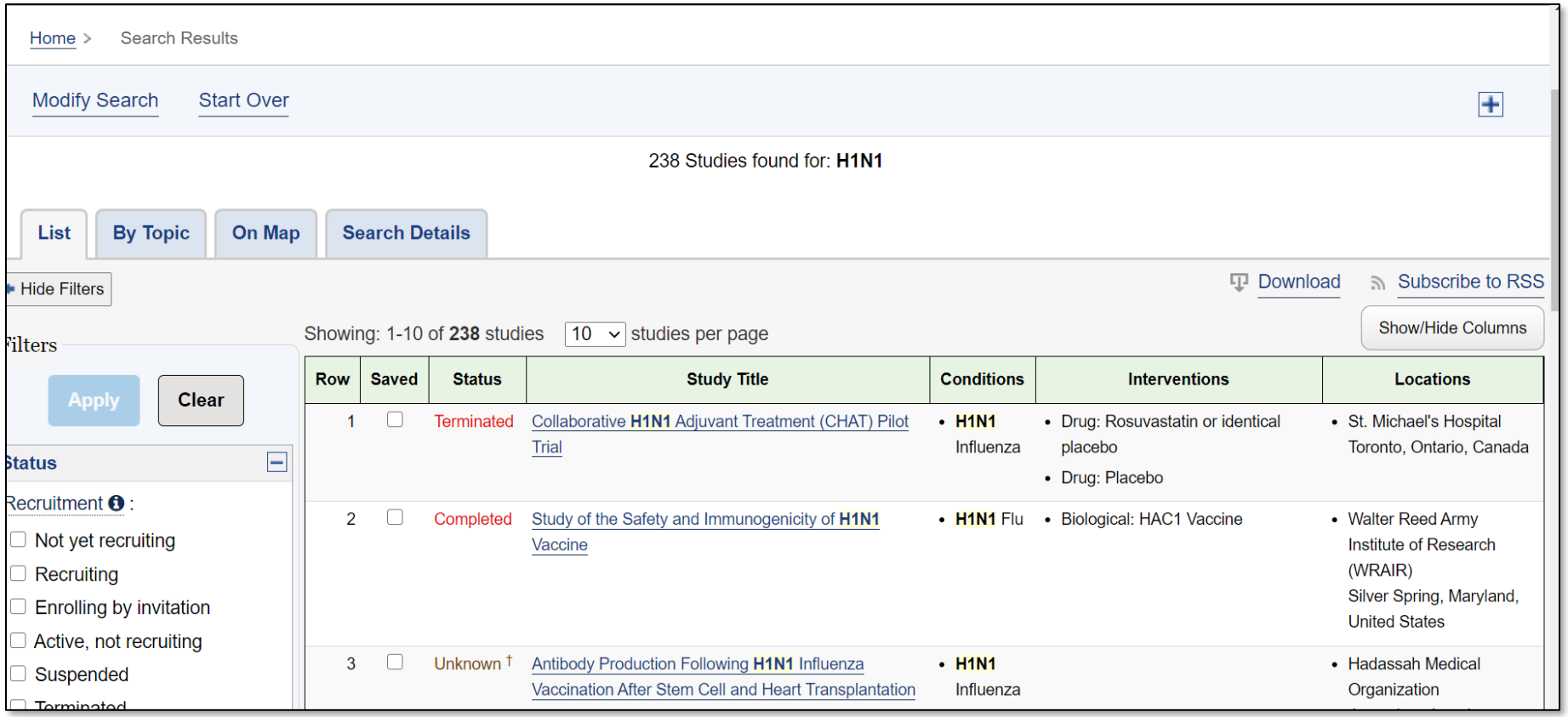
Identification of Severe Acute Respiratory Syndrome in Canada

Susan M. Poutanen, M.D., M.P.H., Donald E. Low, M.D., Bonnie Henry, M.D., Sandy Finkelstein, M.D., David Rose, M.D., Karen Green, R.N., Raymond Tellier, M.D., Ryan Draker, B.Sc., Dena Adachi, M.Sc., Melissa Ayers, B.Sc., Adrienne K. Chan, M.D., Danuta M. Skowronski, M.D., M.H.Sc., Irving Salit, M.D., Andrew E. Simor, M.D Arthur S. Slutsky, M.D., Patrick W. Doyle, M.D., M.H.Sc., Mel Krajden, M.D., Martin Petric, Ph.D., Robert C. Brunham, M.D., and Allison J. McGeer, M.D., for the National Microbiology Laboratory, Canada, and the Canadian Severe Acute Respiratory Syndrome Study Team*

Severe Acute Respiratory Syndrome (SARS)

H1N1 Influenza





H1N1 Influenza 238 studies

InFACT

The International Forum for Acute Care Trialists

The International Forum for Acute Care Trialists (InFACT) seeks to improve the care of acutely ill patients around the world through the promotion of high quality clinical research into the causes, prevention, and optimal management of acute, life-threatening illness.

ISARIC

International Severe Acute Respiratory Infections Consortium

Jeremy Farrar

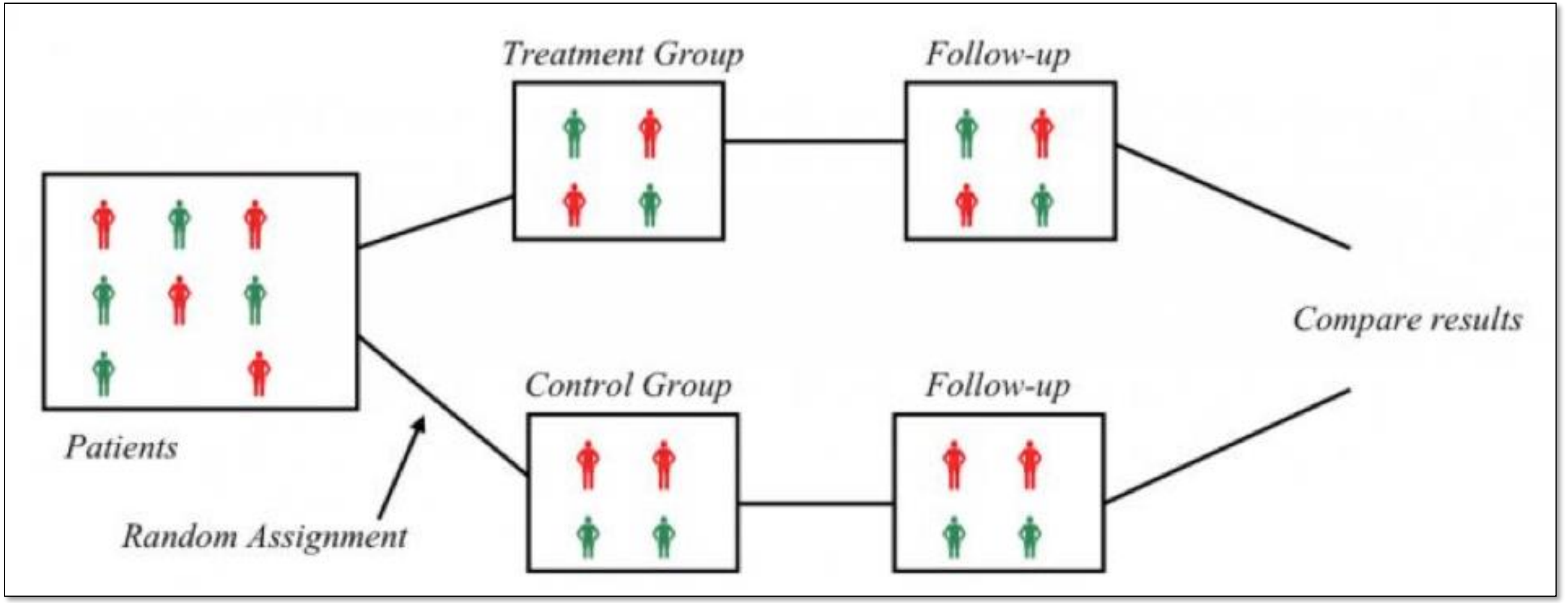
- 50+ research groups
- Links to WHO and funders
- Promoting global collaboration through focus on pandemic preparedness

InFACT/ISARIC/LKSKI Colloquium on Pandemic Research Preparedness

June 2011

To successfully conduct research during a pandemic, the necessary infrastructure needs to be in place, and the trial ready to recruit in advance of the pandemic.

Conventional RCTs Study an Intervention



VIEWPOINT

The Platform Trial
An Efficient Strategy for Evaluating Multiple Treatments

Scott M. Berry, PhD
Berry Consultants LLC, Austin, Texas; and Department of Biostatistics, University of Kansas Medical Center, Kansas City.

Jason T. Connor, PhD
Berry Consultants LLC, Austin, Texas; and University of Central Florida College of

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 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.

Table. General Characteristics of Traditional and Platform Trials[a]

Characteristic	Traditional Trial	Platform Trial
Scope	Efficacy of a single agent in a homogeneous population	Evaluating efficacy of multiple agents in a heterogeneous population; explicitly assumes treatment effects may be heterogeneous
Duration	Finite, based on time required to answer the single primary question	Potentially long-term, as long as there are suitable treatments requiring evaluation
No. of treatment groups	Prespecified and generally limited	Multiple treatment groups; the number of treatment groups and the specific treatments may change over time
Stopping rules	The entire trial may be stopped early for success or futility or harm, based on the apparent efficacy of the single experimental treatment	Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s)
Allocation strategy	Fixed randomization	Response-adaptive randomization
Sponsor support	Supported by a single federal or industrial sponsor	The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination

[a] Platform trials and similar trials may also be called basket, bucket, umbrella, or standing trials.

- *JAMA* 313:1619, 2015

A platform trial studies a disease or a population

Intubated patients at risk for VAP

Intervention E
Reduced sedation

Intervention D
Topical Abx

Intervention C
Probiotics

Intervention

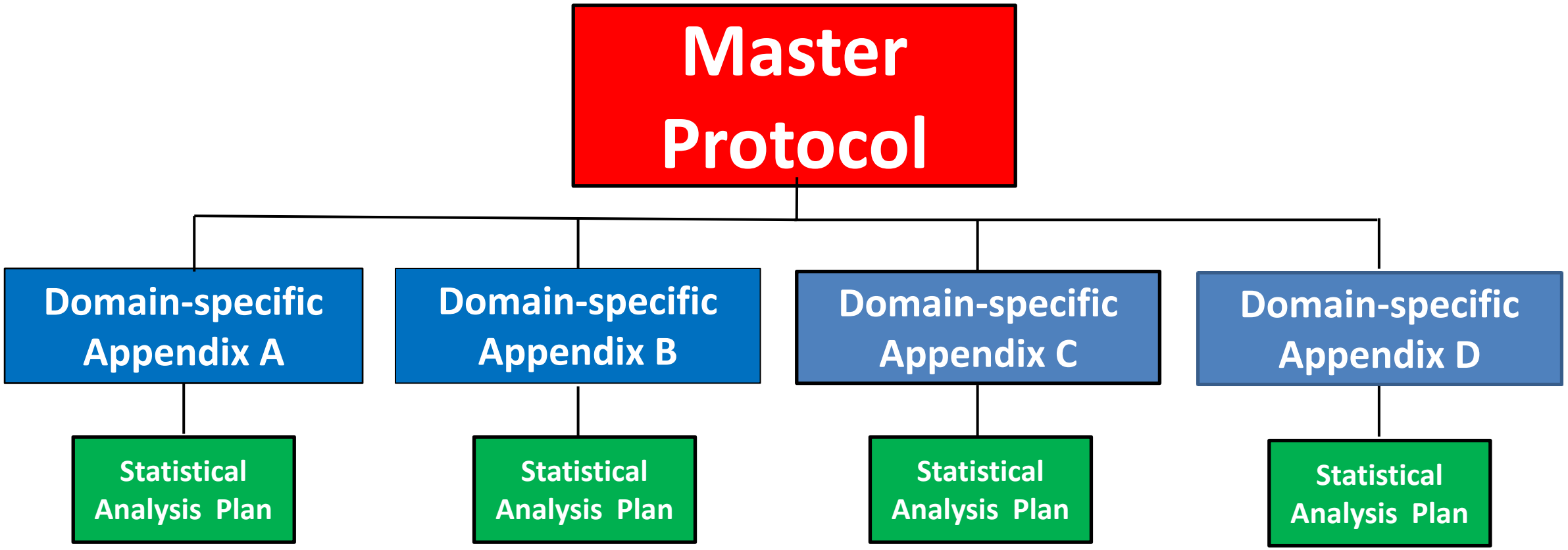
Intervention B
Oral hygiene

Intervention A
Positioning

Domain

Time

Platform Trial Structure



- **Multinational**
- **Multiple data providers**
- **Multiple funders**

REMAP-CAP

Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Domain-Specific Appendix:

CORTICOSTEROID DOMAIN

REMAP-CAP

Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Region-Specific Appendix:

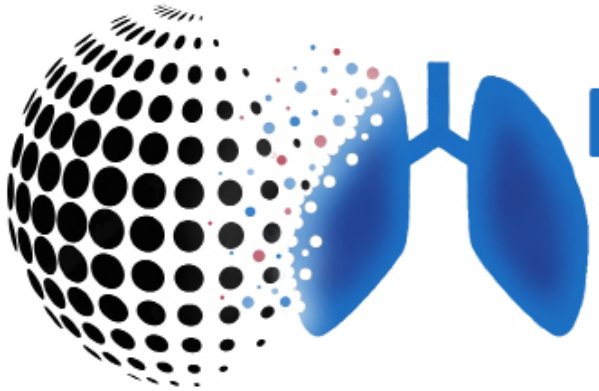
Canada

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Platform for European Preparedness
Against (Re-)emerging Epidemics

Herman Goossens

- **€24 M funding**
- **Adaptive trial led by ESICM Trials Group**
- **Adaptive modeling – Berry Consultants**
- **PREPARE Australia – ANZICS CTG**



REMAP-CAP

Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

NCT02735707

Randomized Embedded Multifactorial Adaptive Platform Trial

1. Adult patient admitted to an ICU for severe CAP within 48 hours of hospital admission with
    a. symptoms or signs or both that are consistent with lower respiratory tract infection (for example, acute onset of dyspnea, cough, pleuritic chest pain) AND
    b. Radiological evidence of new onset consolidation (in patients with pre-existing radiological changes, evidence of new infiltrate)
2. Requiring organ support with one or more of:
    a. Non-invasive or invasive ventilatory support;
    b. Receiving infusion of vasopressor or inotropes or both

Primary Outcome: All-cause mortality at 90 days

R Randomized

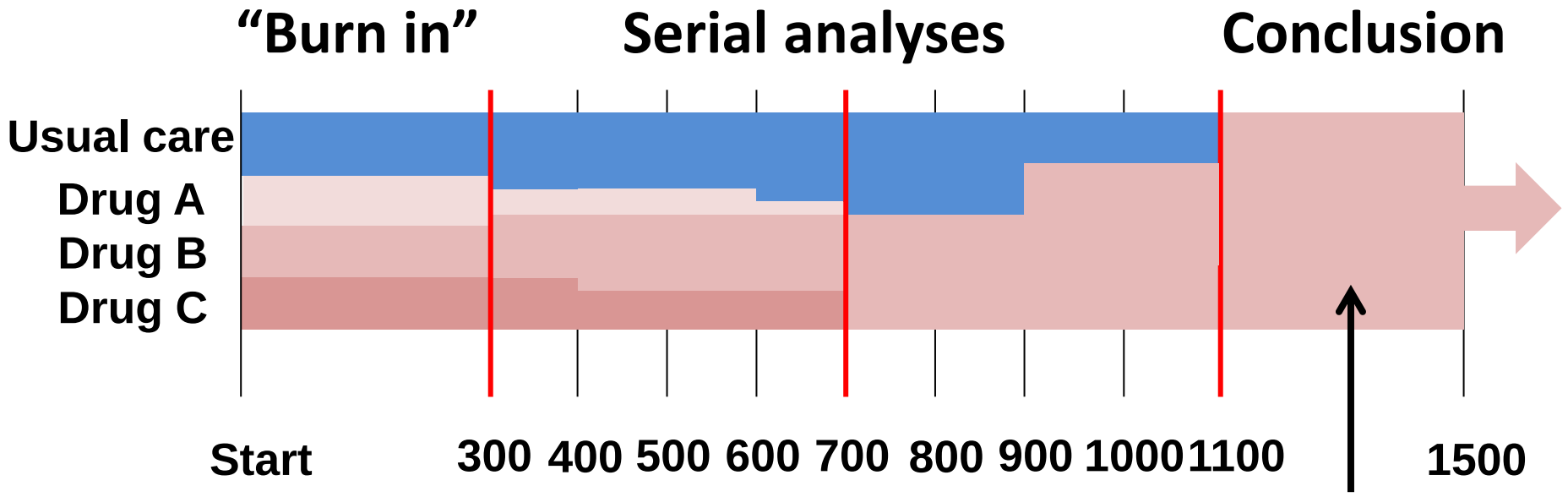
E Embedded in the electronic health record

M Multifactorial - Multiple domains

A Adaptive

P Platform - Perpetual

Response Adaptive Randomization



Adaptive trials review accruing data. Patients are preferentially randomized to the arm(s) that are showing better results.

Domain Conclusions

Superiority: Posterior probability of 99% that OR > 1.2

Equivalence: >0.9 probability that OR between 0.8 and 1.2

Inferiority: Posterior probability of 99% that OR <1

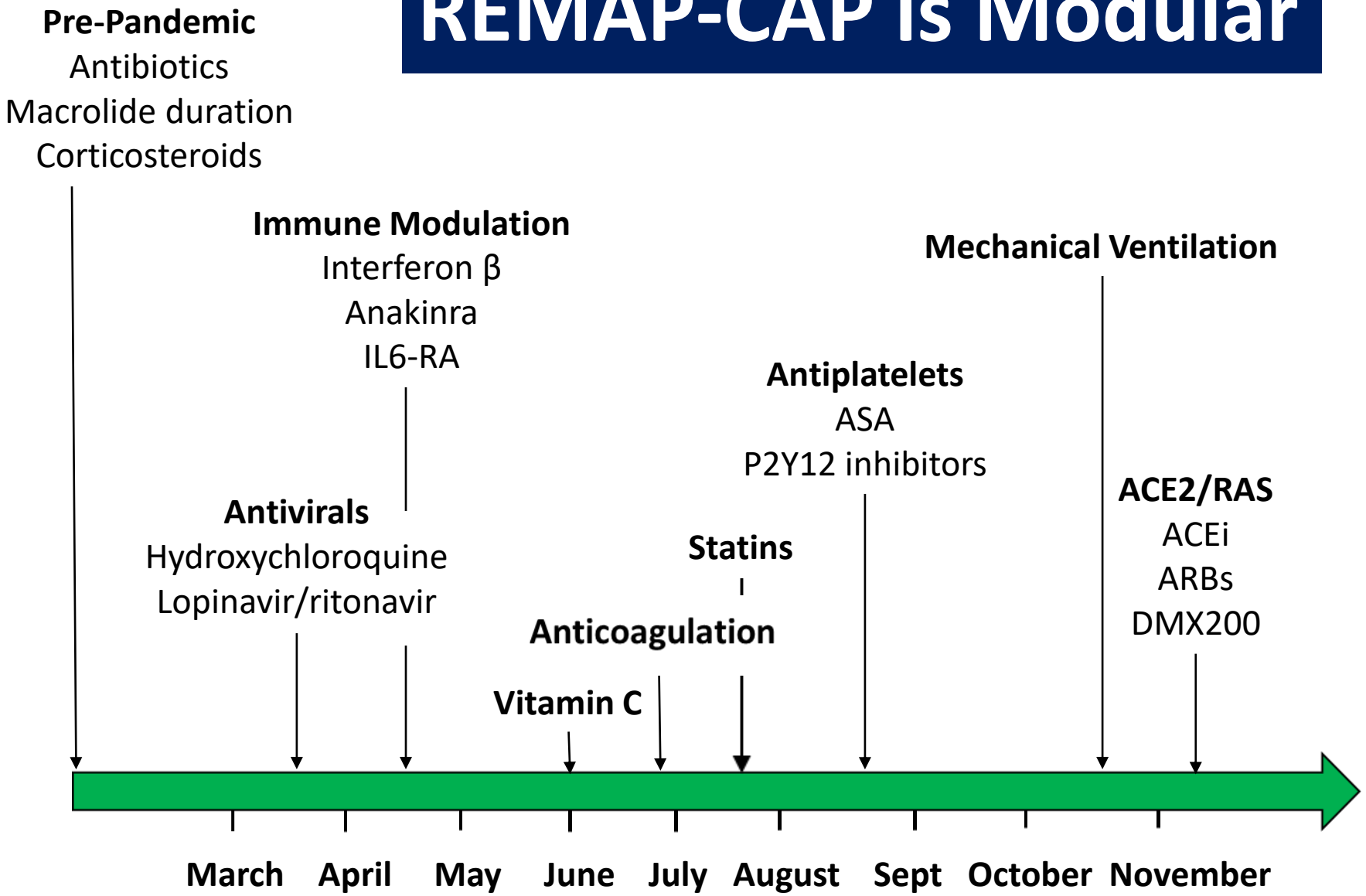
January, 2020

Two States

Severe: Receiving positive pressure respiratory support or vasoactive agents

Moderate: Hospitalized without organ support

REMAP-CAP is Modular



Non-pandemic	Pandemic
Antibiotics Macrolide duration Corticosteroids Influenza Antivirals Mechanical Ventilation	Corticosteroids COVID-19 Antivirals Immune Modulation I Immune Modulation II Immunoglobulin Anticoagulation Vitamin C Simvastatin Antiplatelet agents ACE2/RAS therapies Endothelial protection

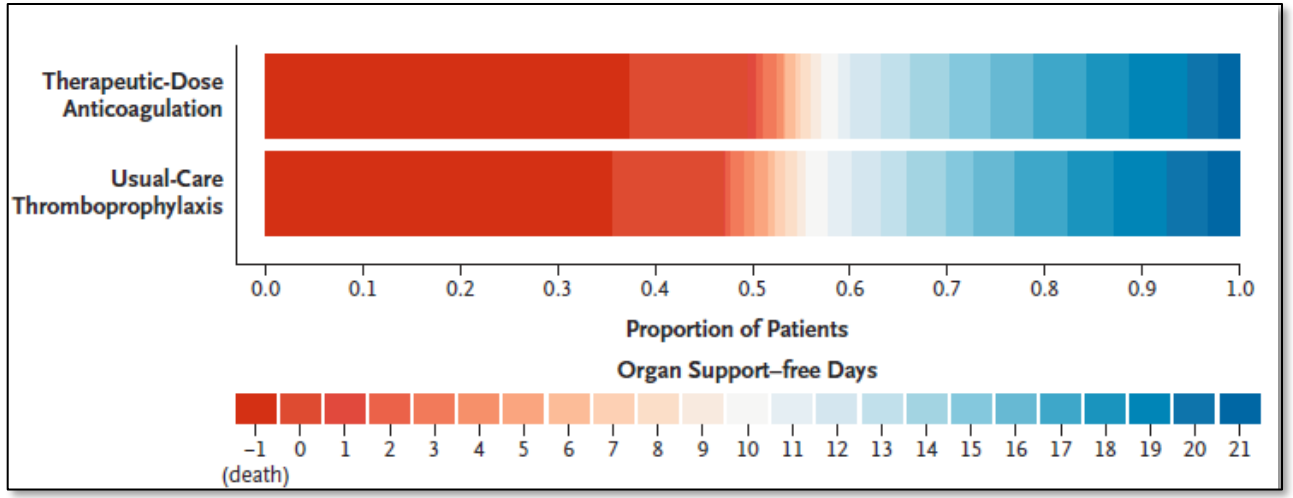
REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP):

PANDEMIC APPENDIX TO THE CORE PROTOCOL

Primary Outcome

Organ support-free days over 21 days, with mortality = -1



REMAP-CAP

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

20,740

Patient randomisations

18,094

Patient randomisations with suspected or proven COVID-19

57

Current or completed interventions in 17 Domains

11,737

Total patients

10,017

Patients with suspected or proven

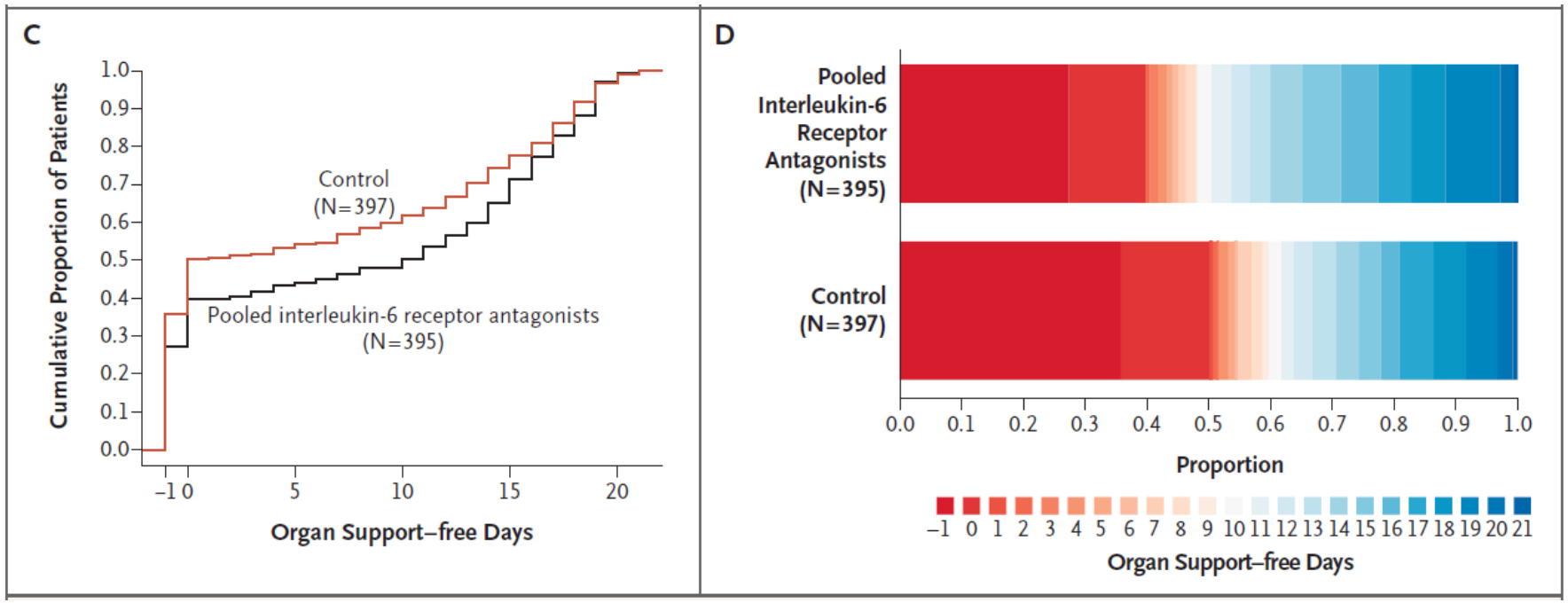
326

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

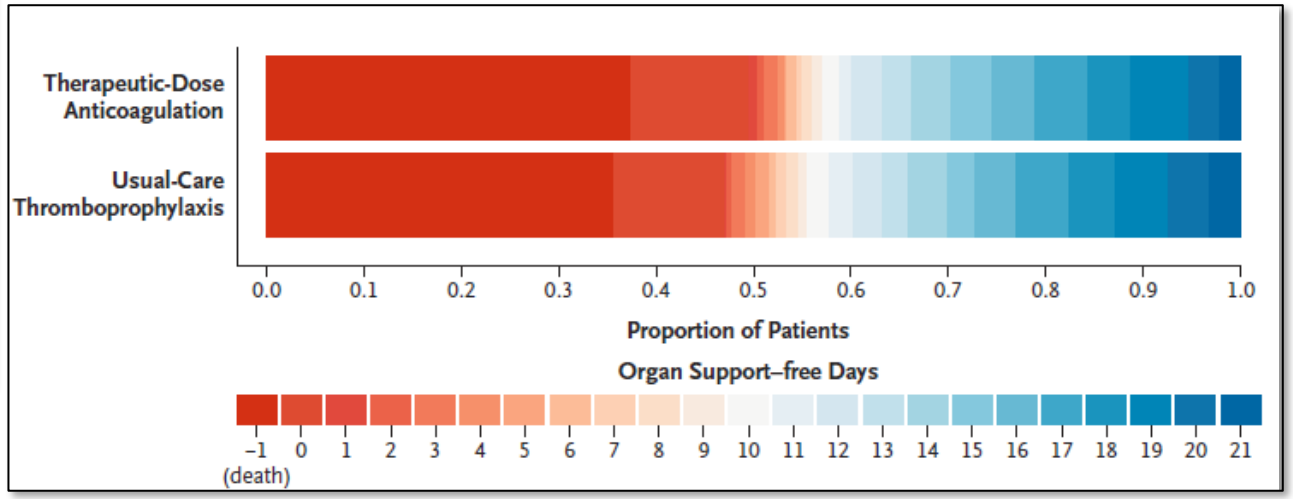


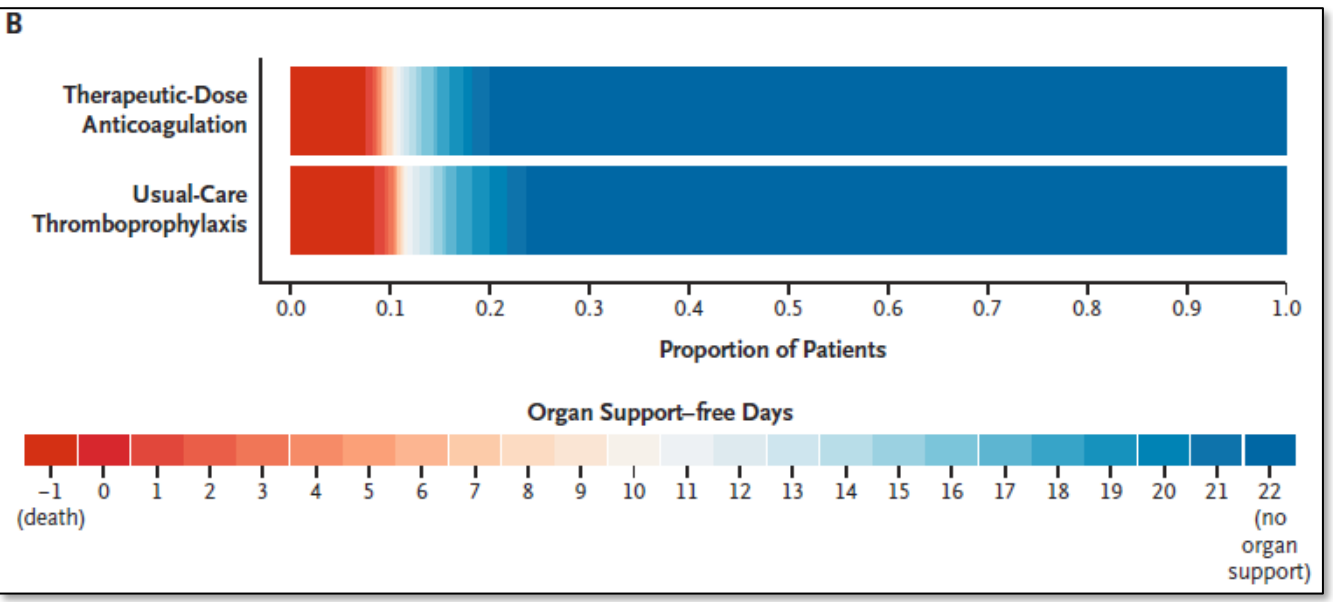
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 26, 2021 VOL. 385 NO. 9

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

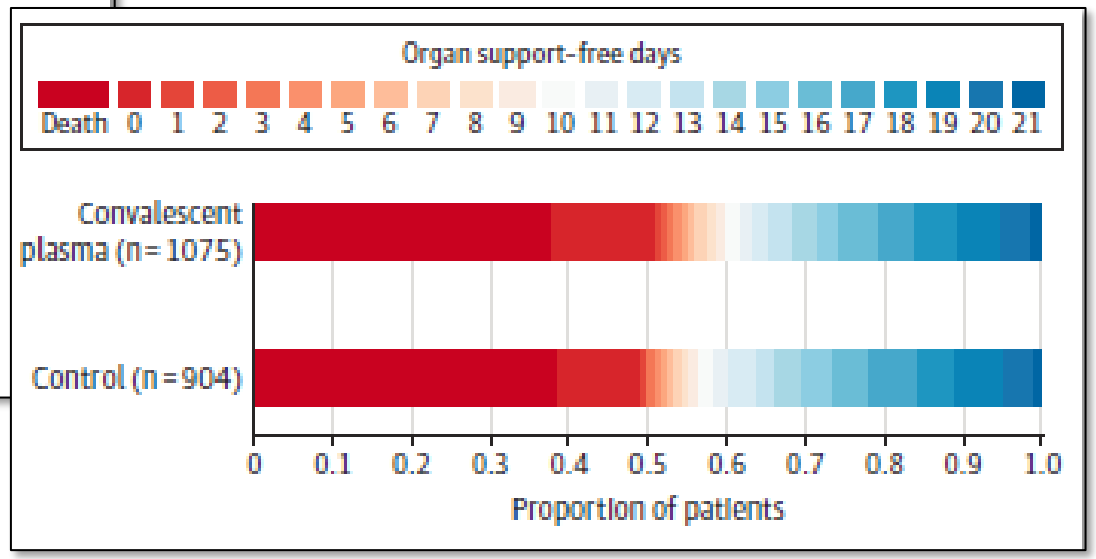
The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Convalescent Plasma on Organ Support–Free Days in Critically Ill Patients With COVID-19
A Randomized Clinical Trial

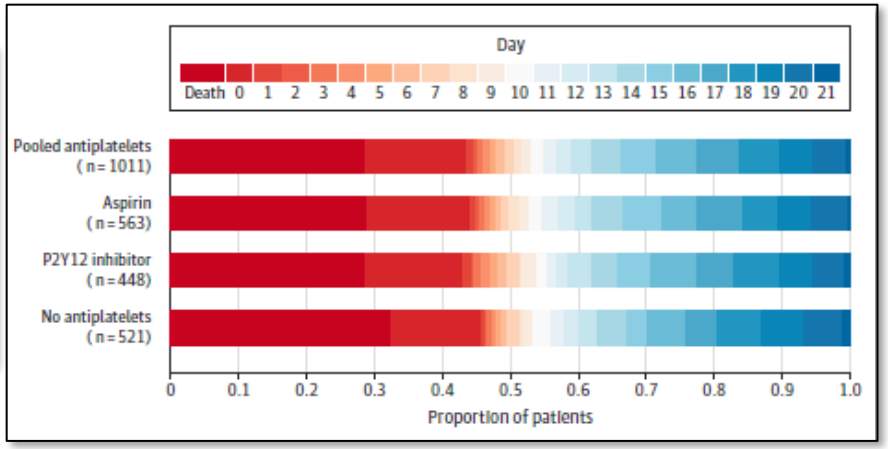
Writing Committee for the REMAP-CAP Investigators



JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Antiplatelet Therapy on Survival and Organ Support–Free Days in Critically Ill Patients With COVID-19
A Randomized Clinical Trial

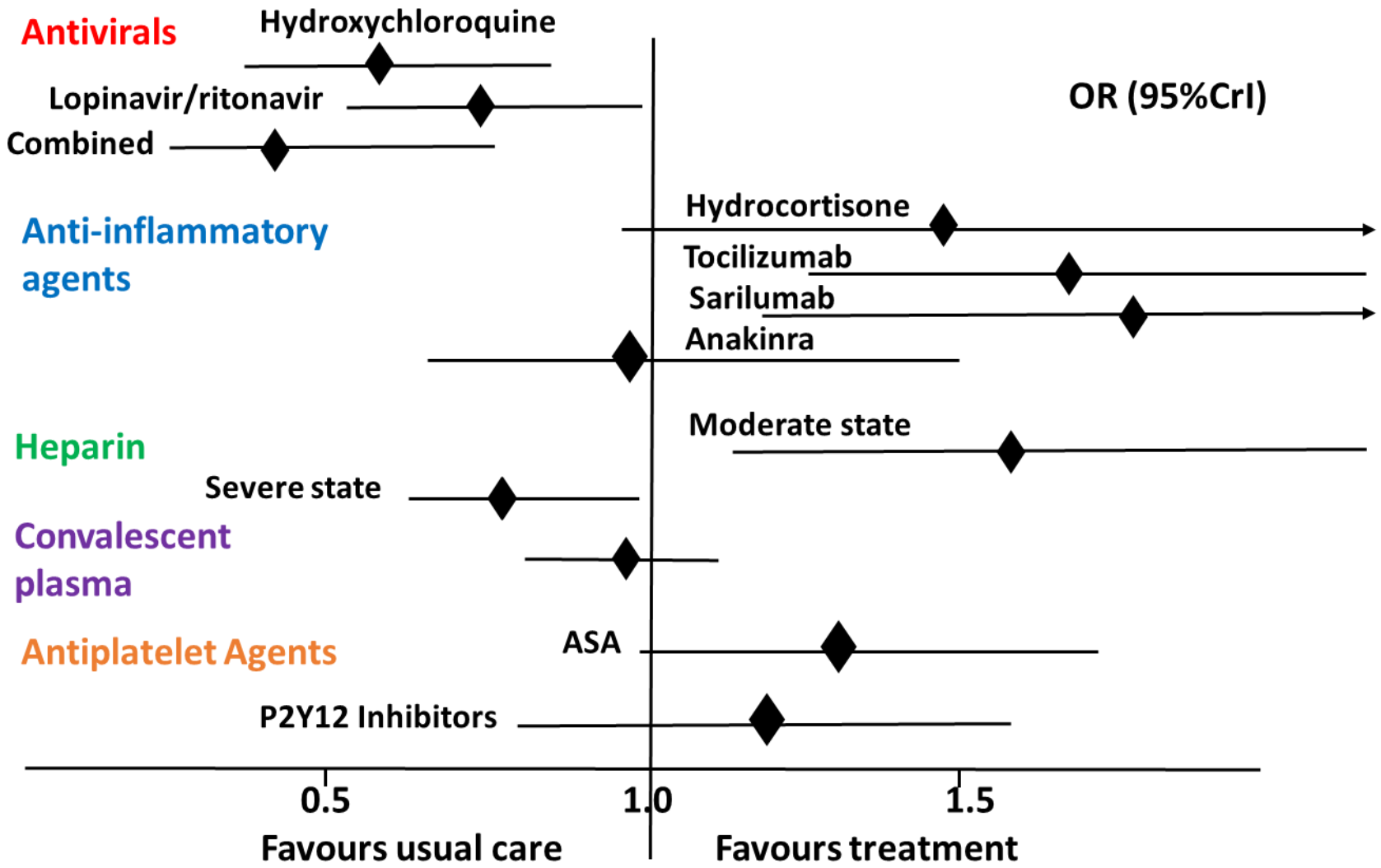
REMAP-CAP Writing Committee for the REMAP-CAP Investigators



Survival to hospital discharge				
No./total (%)	723/1011 (71.5)	402/563 (71.4)	321/448 (71.7)	354/521 (67.9)
Adjusted odds ratio (95% CrI)	1.27 (0.99-1.62)	1.30 (0.97-1.72)	1.18 (0.86-1.62)	1 [Reference]
Adjusted absolute risk difference, % (95% CrI)	5.0 (-0.2 to 9.5)	5.4 (-0.7 to 10.5)	3.5 (-3.4 to 9.5)	
Probability of efficacy, %	97.0	96.0	85.8	

REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

REMAP-CAP So Far …



Pre-publication interim data, not from a locked database and not peer reviewed

ATTACC, REMAP-CAP, and ACTIV IV-4a mpRCT

Primary outcome

State & D-dimer Strata	Proportional Odds Ratio Median (95% CrI)	Trial Statistical Conclusion
Moderate state, low D-dimer	1.57 (1.14 - 2.19)	**Superiority** [Probability of OR>1 = 0.997]
Moderate state, high D-dimer	1.53 (1.09 - 2.17)	**Superiority** [Probability of OR>1 = 0.991]
Moderate state, missing D-dimer	1.51 (1.06 – 2.15)	n/a⏃
Severe state	0.76 (0.60 – 0.97)	**Futility*** [Probability of OR>1.2 < 0.001]

* Posterior probability of **inferiority** [Probability of OR<1 = 0.985]

⏃ Not evaluated for stopping at interim

OR >1 represents benefit. A higher OR occurs when either mortality is improved and/or if those who survive have reduced requirement for organ support

Release date: January 28, 202

NIHR | National Institute for Health Research

- **Hospitals funded to do research**
- **Central coordination reduces duplication**
- **Targets established for recruitment to trials**

UK Publicly Funded Trials

PHASE I & IIa
Safety in healthy individuals

AGILE
Hospital/ Community

Currently trialling:
EIDD-2801
VIR-7831 and VIR-7832
Niclosamide

PHASE IIb
Efficacy and safety in COVID-19 patients

RECOVERY+
Hospital

Currently trialling:
Dimethyl Fumarate

PHASE III
Efficacy in large numbers (1000s) of target patients

PRINCIPLE
Community

Currently trialling:
Inhaled Budesonide
Colchicine

Scheduled to trial:
Favipiravir
Adalimumab

RECOVERY
Hospital

Currently trialling:
Neutralising antibodies (REGN10933 + REGN10987)
Aspirin
Colchicine
Baricitinib
Methylprednisolone*
Immunoglobin*
Hydrocortisone*
Anakinra*

* Paediatric use only

Scheduled to trial:
Namilumab
Infliximab

REMAP-CAP
ICU

Currently trialling:
Lopinavir/ritonavir
Interferon-beta
Anakinra
Simvastatin
Anti-platelet arm (aspirin, clopidogrel, prasugrel and ticagrelor)

Scheduled to trial:
Namilumab
Infliximab

LONG COVID

HEAL
Community

Patients post-discharge for COVID-19

Scheduled to trial:
Atorvastatin
Apixiban

PROPHYLAXIS

PROTECT V
Community

Pre-exposure prophylaxis in vulnerable immuno-compromised patients.

PROTECT CH
Community

Post-exposure prophylaxis in care homes

Scheduled to trial:
Ciclesonide
Intranasal heparin

UK Research and Innovation

Increasing recruitment into covid-19 trials

An urgent priority for the NHS

Ara Darzi, [1] Andrew Goddard, [2] Katherine Henderson, [3] Ravi Mahajan, [4] Clare Marx, [5] Neil Mortensen, [6] Alison Pittard[7]

Since March 2020, UK researchers have established over 70 urgent public health studies to investigate potential treatments, vaccines, and diagnostic tests for covid-19. NHS hospitals have had a vital role in delivering these studies at pace and scale, despite working under extreme pressure. The results are now informing practice worldwide.

In June 2020, the Recovery trial found that dexamethasone, a widely available corticosteroid, improved survival among covid-19 patients on ventilation by 36% (28 day mortality rate ratio 0.64; variation among hospitals and therefore scope for further improvement.

The largest community based covid-19 trial in the UK, Principle,[5 6] evaluates treatments to prevent hospital admission or transmission, including doxycycline and inhaled budesonide. Recruitment has been slow because of the disruption of primary care during the first wave, reaching 2000 participants in December. To aid recruitment Principle now allows patients to participate remotely regardless of the location of their registered general practitioner.

- **7-10% of admissions for COVID-19**
- **20% of all ICU admissions**

Trials save lives. They cannot do so, however, without the participants on which they depend. Recruitment of patients with covid-19 to UK clinical trials must now be prioritised. Although vaccines against

A platform trial studies a disease or a population

Intubated patients at risk for VAP

Intervention E
Reduced sedation

Intervention D
Topical Abx

Intervention C
Probiotics

Intervention

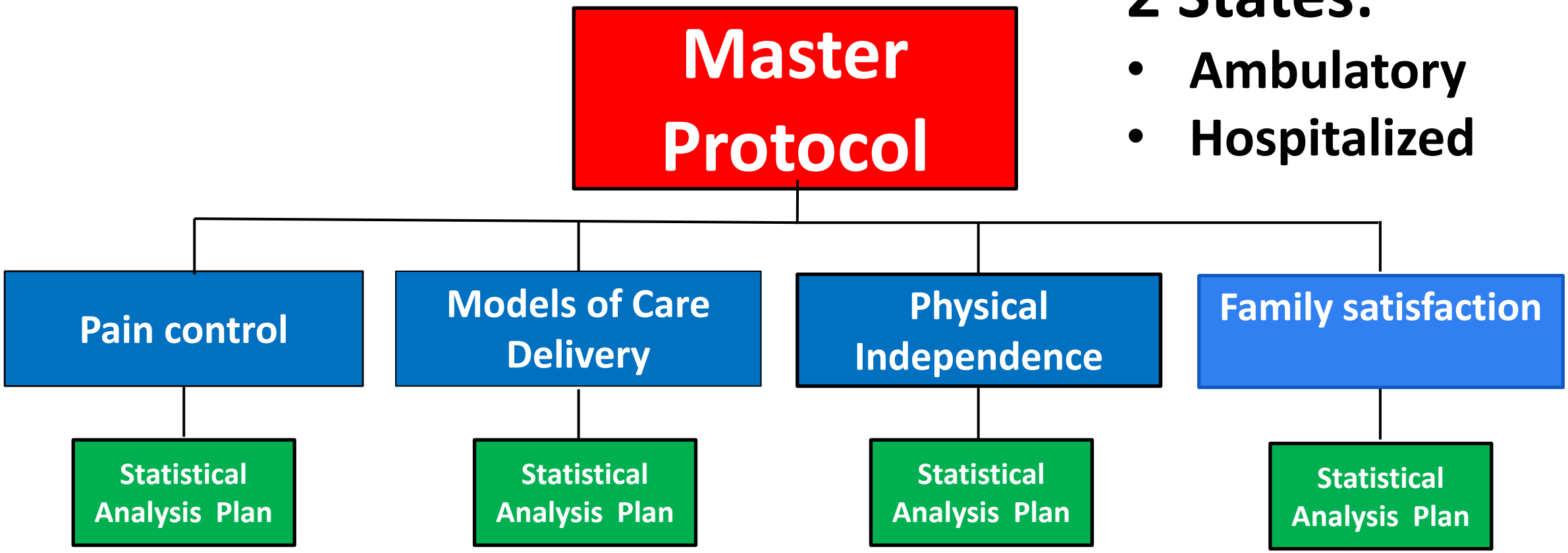
Intervention B
Oral hygiene

Intervention A
Positioning

Domain

Time

A Platform Trial in Palliative Care

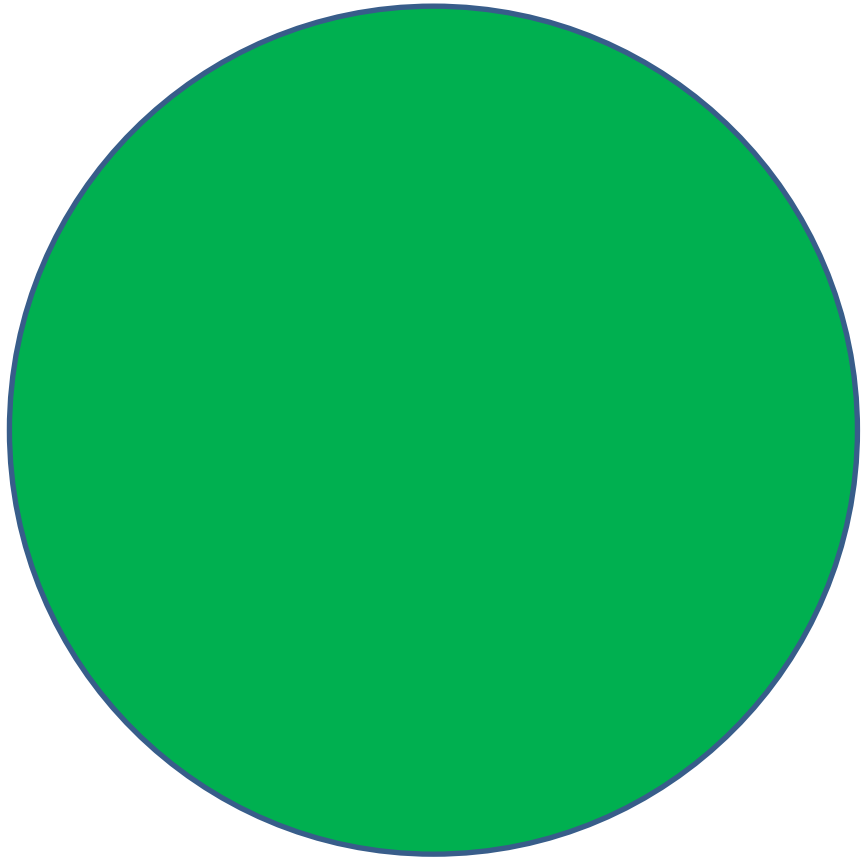


2 States:

- **Ambulatory**
- **Hospitalized**

Research vs. Quality Improvement

	Research	Quality Improvement
Question	Answer unknown	Answer known
Participants	Eligible patients	All patients
Allocation	Random	All
Endpoint	Patient benefit	Process change
Knowledge uptake	Separate KT	Inherent
Consent	Required	None



Can we integrate research and quality improvement to create a learning health care system?

Conclusions

Platform trials provide:

- **The capacity to address multiple questions simultaneously**
- **An efficient tool for collaborative research**
- **A mechanism to integrate research and patient care**


Merci! Thank you!