アダプティブ・プラットフォーム試験の設計：REMAP-CAP を例に

Design choices of adaptive platform trials: REMAP-CAP as an example

December 2, 2022

生物統計情報学シンポジウム

「プラットフォーム臨床試験の統計学的課題と今後の展望

～国内外における取り組みと事例に基づく議論～」

場所：東京大学大学院 情報学環・福武ホールおよびオンライン

東京大学 一原直昭

Nao Ichihara , The University of Tokyo

The presenter

- Involved in
  - Design, statistics, and management of clinical registries and observational studies
  - Regional and global management of REMAP-CAP
  - Design and planning of other APTs in/outside Japan
- Has no conflict of interest

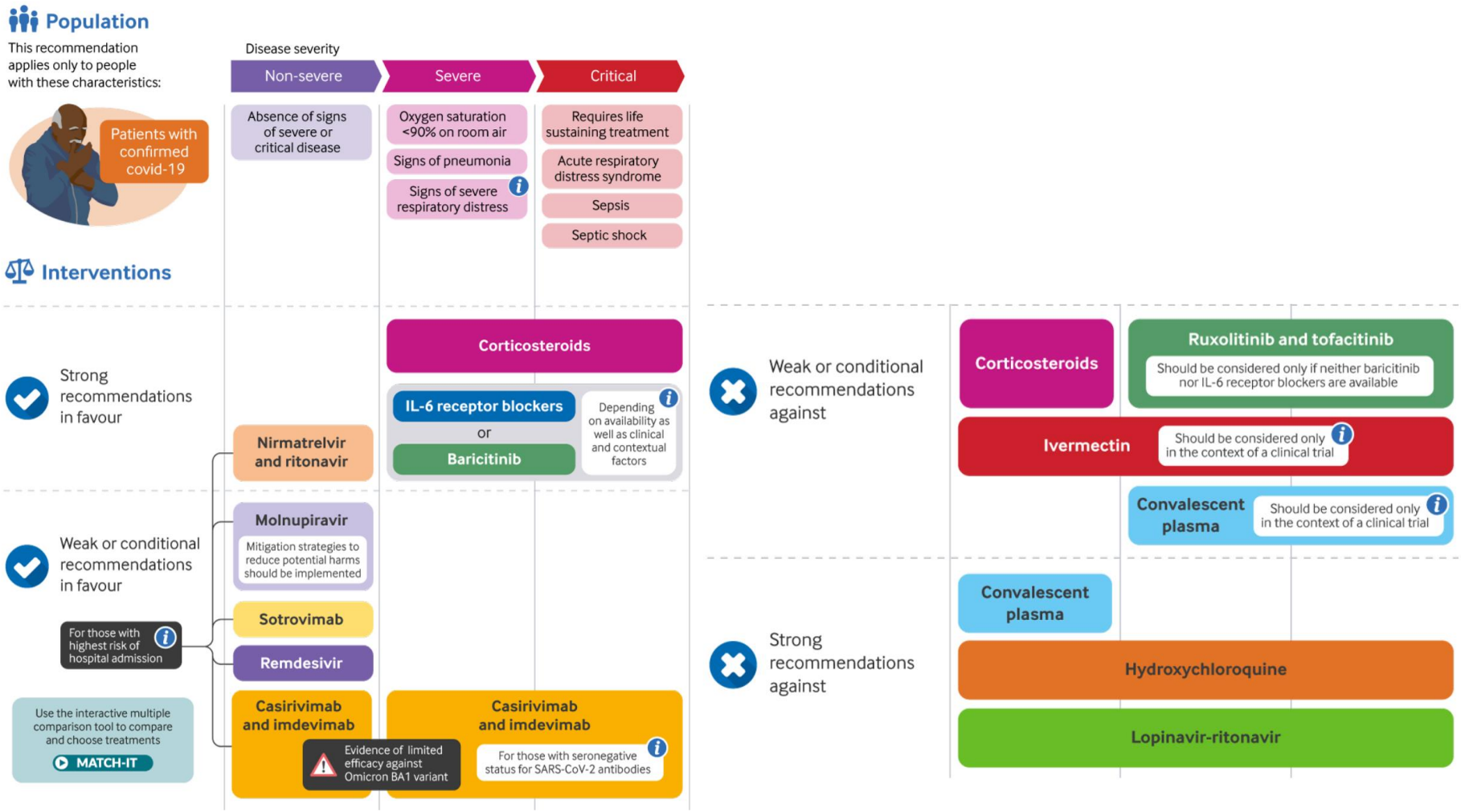
This presentation

- The background, purpose, design features, and history of REMAP-CAP as an example of an adaptive platform trial (APT)
- Emphasis will be put on importance of design choices that reflect the purpose of the clinical trial
- Some other non-statistical issues
- Specific example for a generic conclusion

Establishing effective treatment during the COVID-19 pandemic

Successes and failures

Success: effective treatment was rapidly established against COVID-19



World Health Organization. Therapeutics and COVID-19 Living Guideline. 22 April 2022.

Failure: lack of consorted effort in clinical study and limited number of large trials

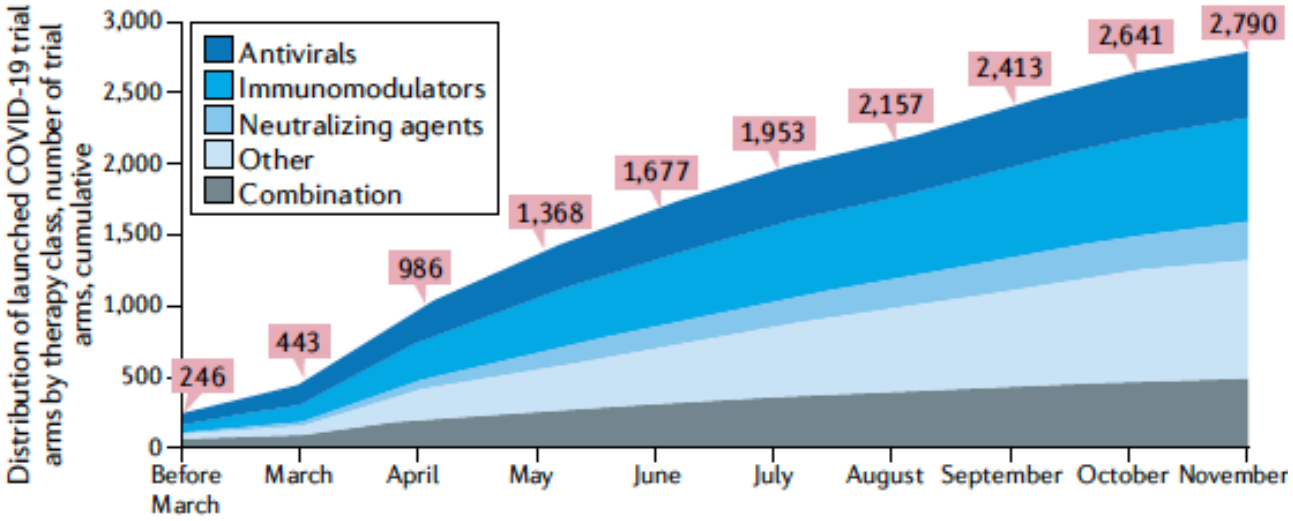
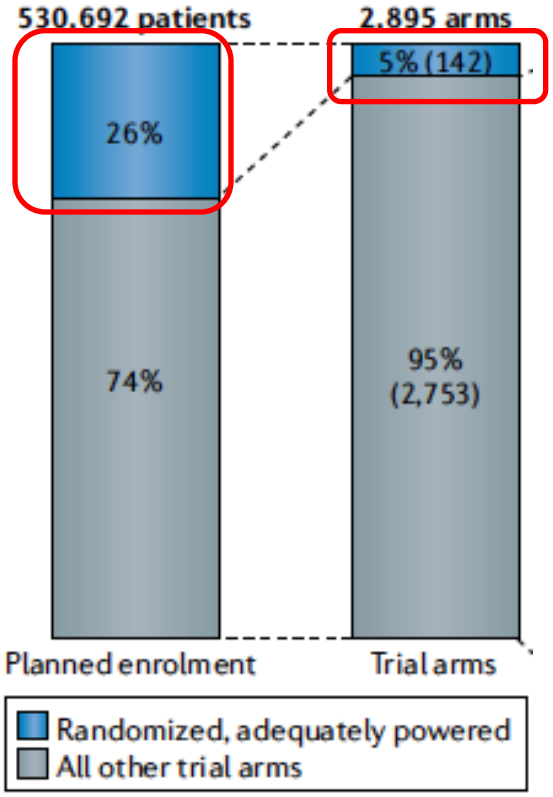
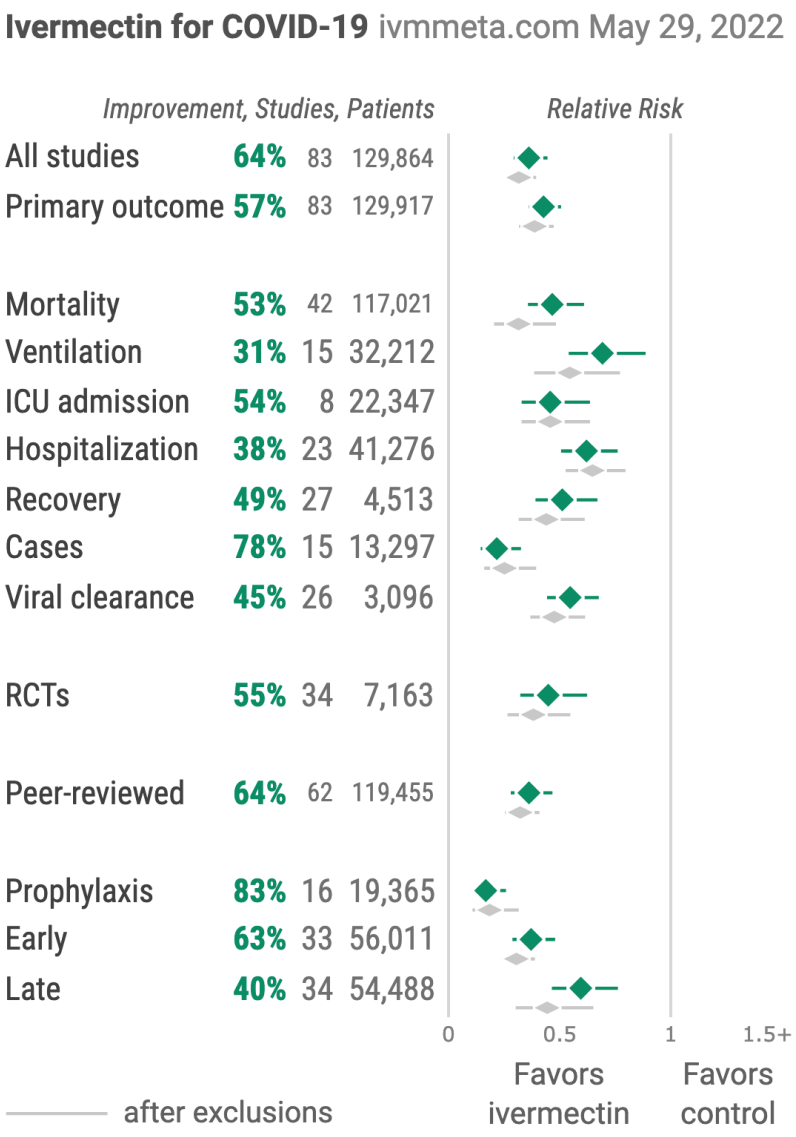


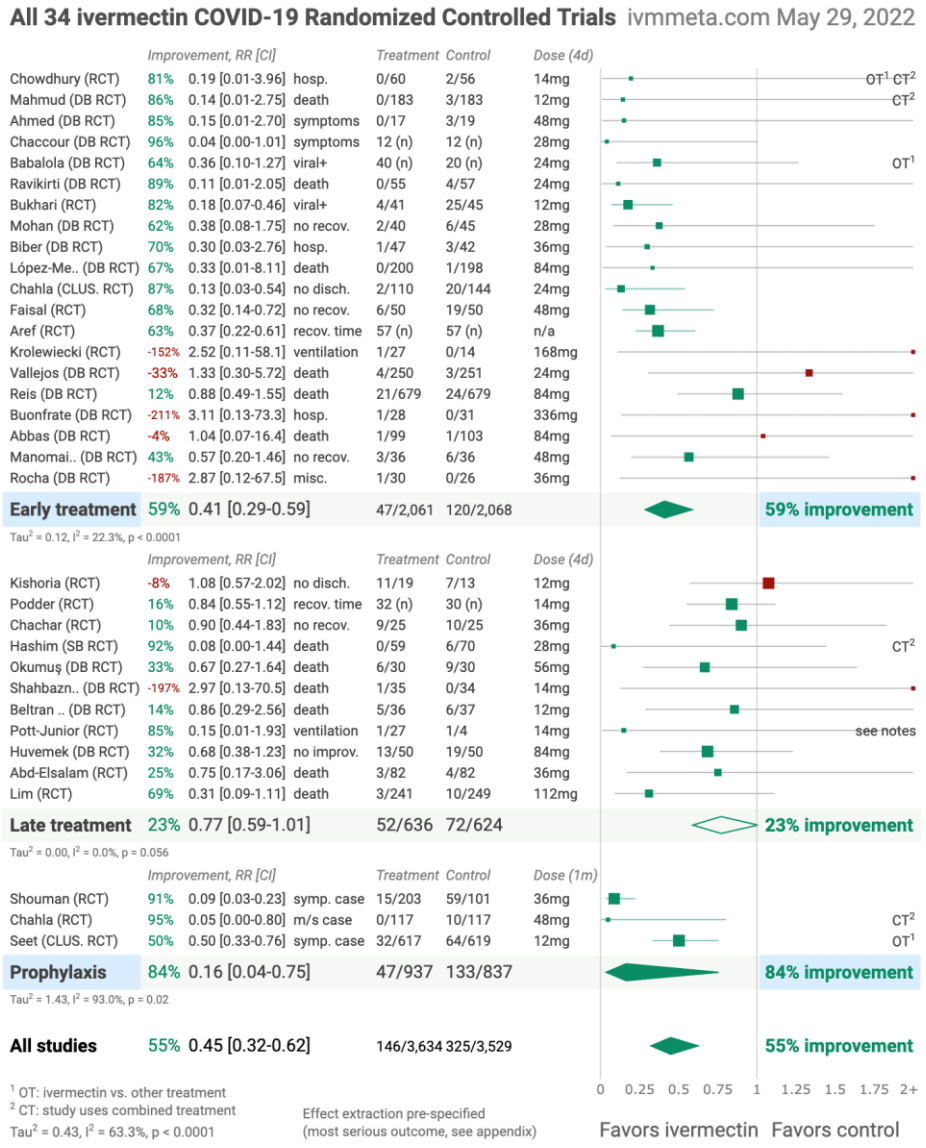
Fig. 1 | **Expansion of the clinical trial landscape for COVID-19 therapeutics in 2020.** Source: ClinicalTrials.gov and WHO clinical trial registry. *As of 20 Nov 2020. See Supplementary information for details.



Nat Rev Drug Discov. 2021;20(4):254-255.

Are small clinical trials meaningful because they contribute through meta-analysis?

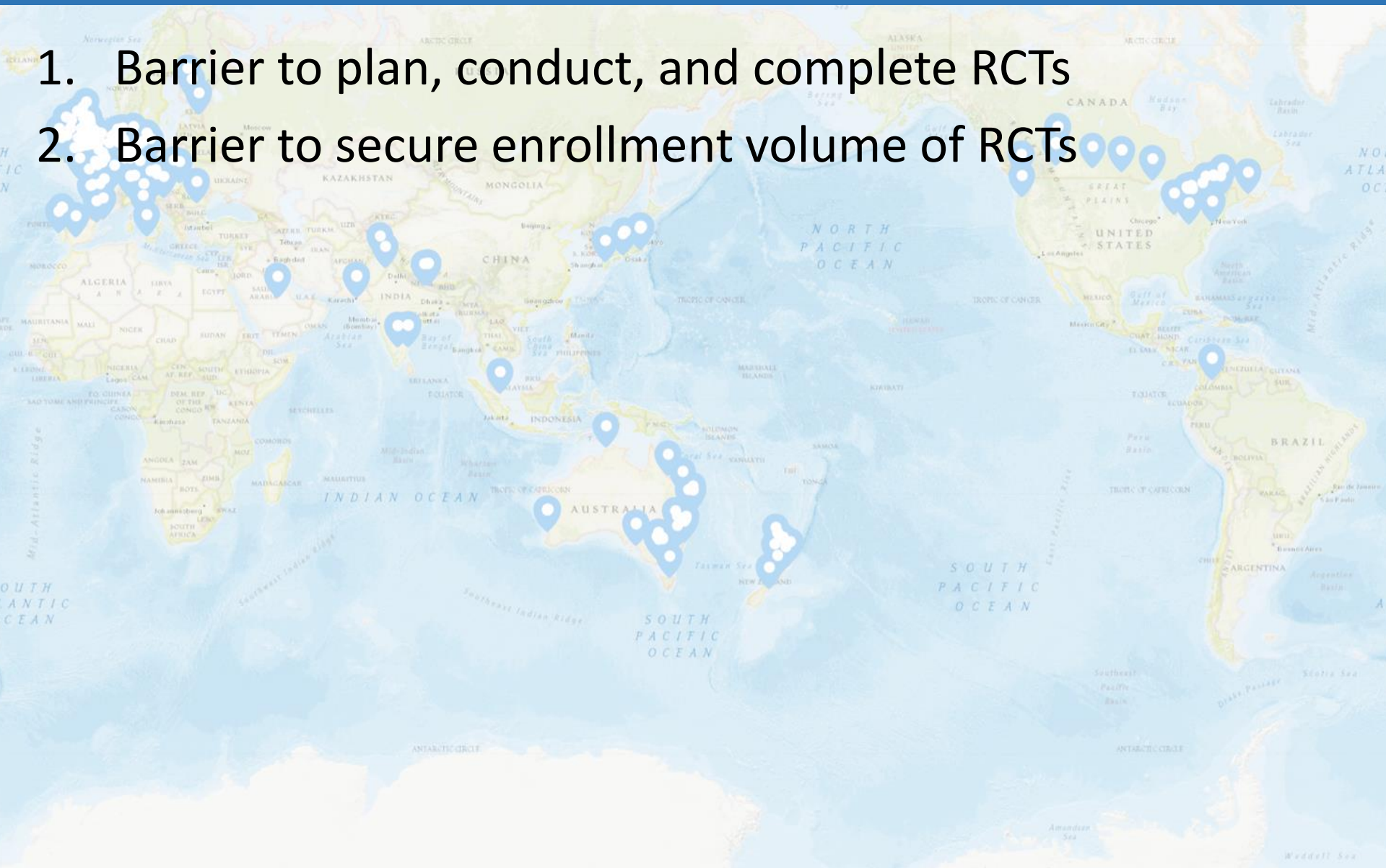


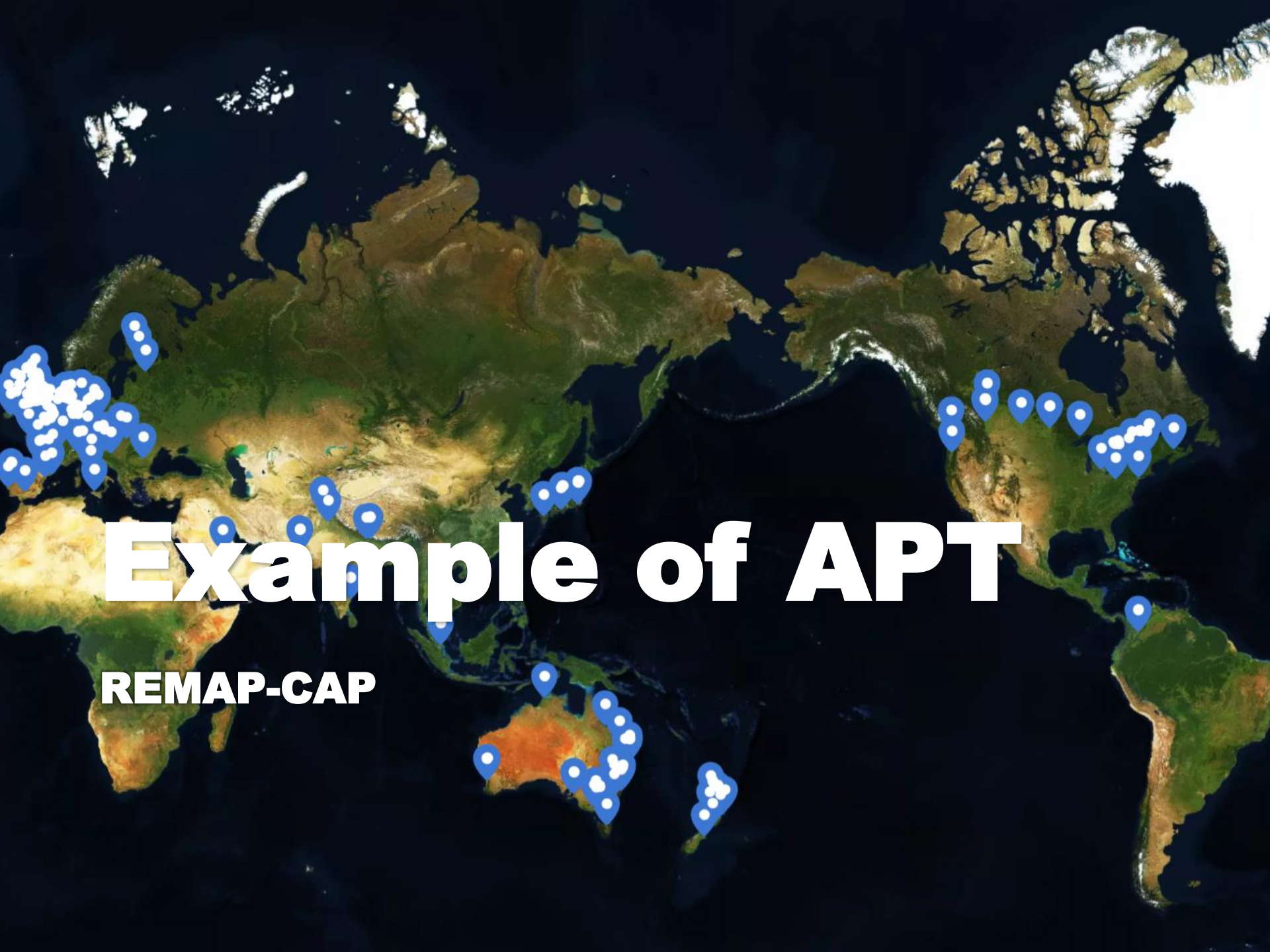


https://ivmmeta.com/

Two major barriers in clinical trials (Pandemic and non-pandemic times)

1. Barrier to plan, conduct, and complete RCTs
2. Barrier to secure enrollment volume of RCTs



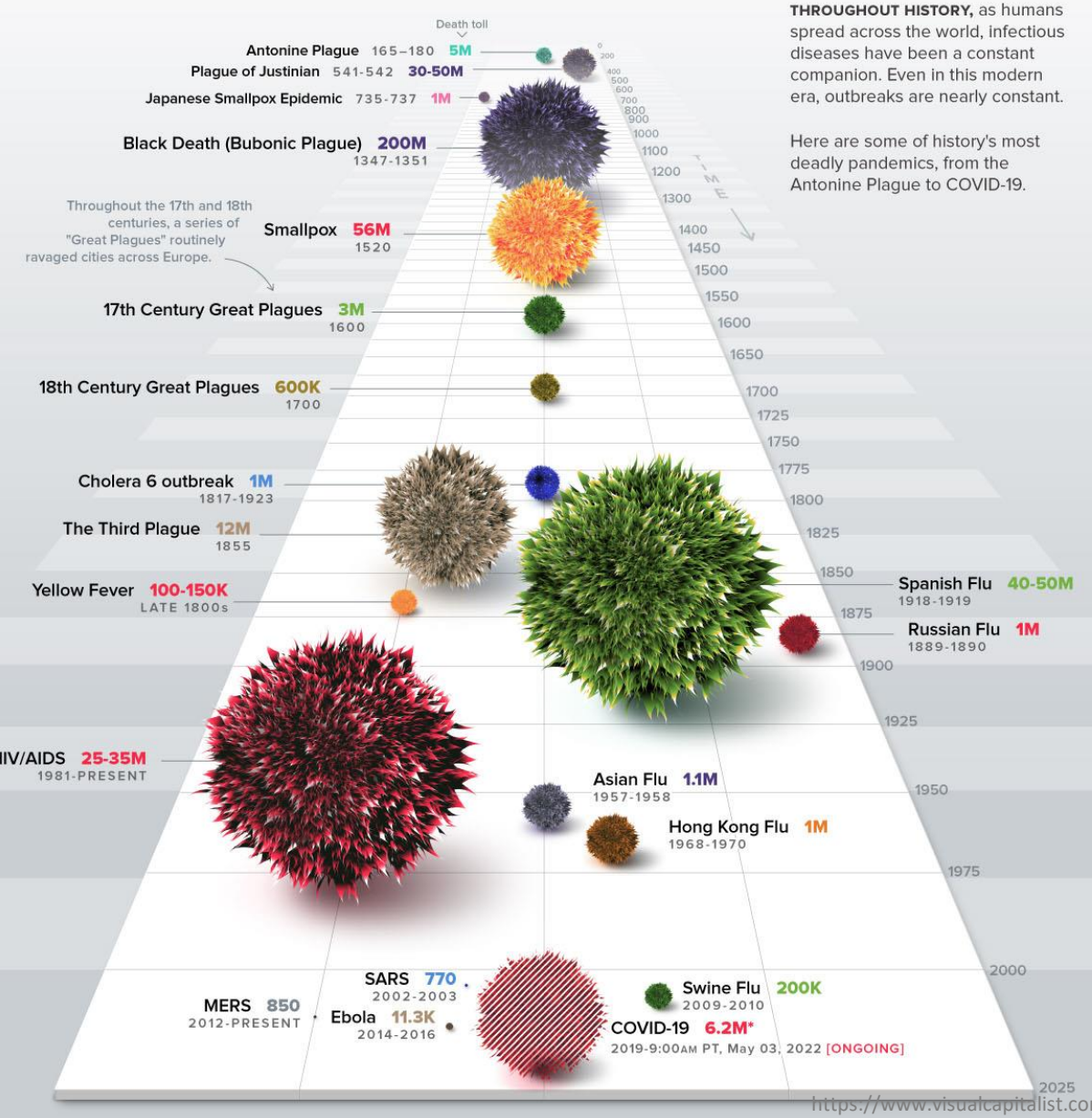

Example of APT
REMAP-CAP

HISTORY OF **PANDEMICS**

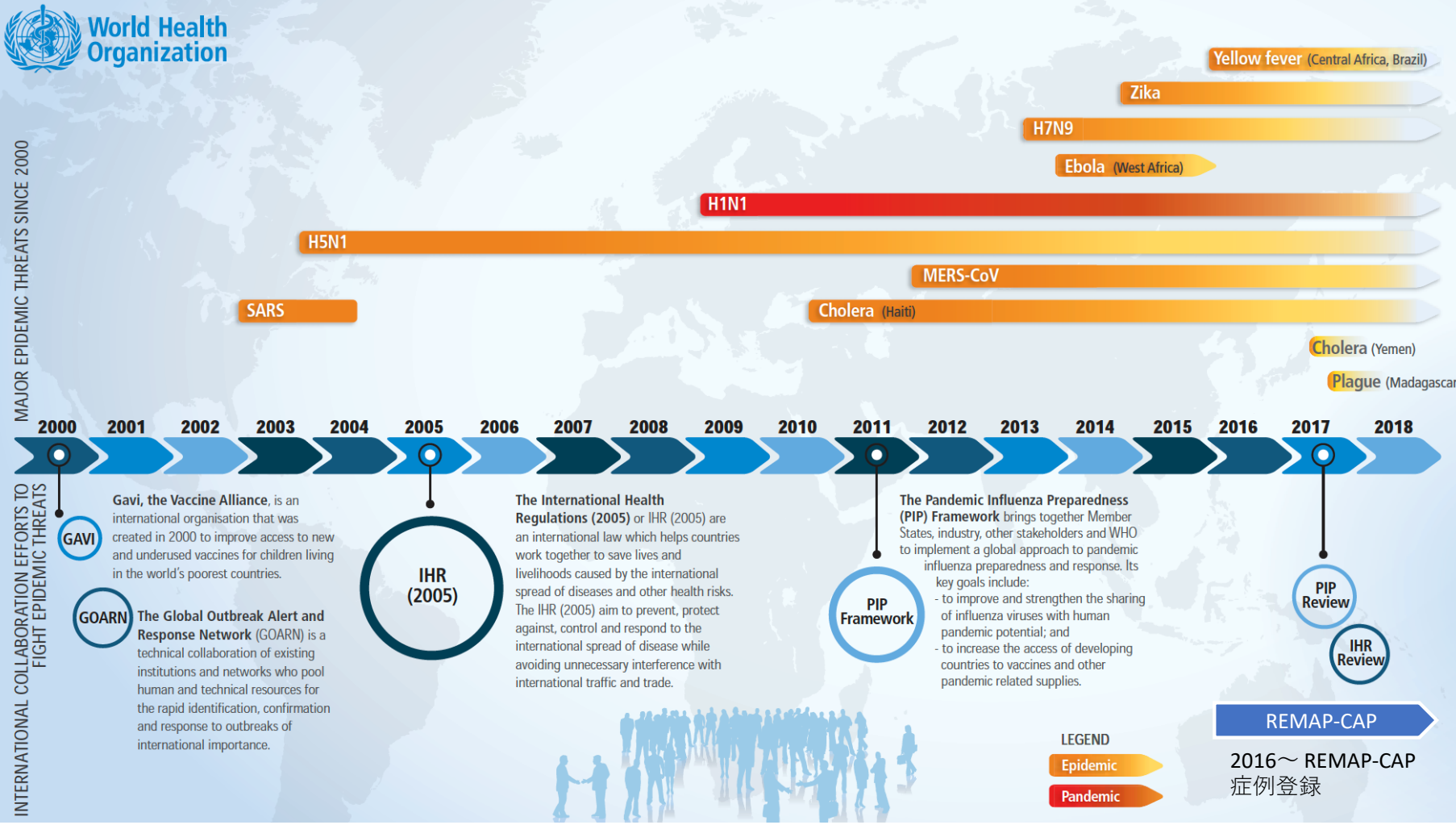
PAN·DEM·IC (of a disease) prevalent over a whole country or the world.

THROUGHOUT HISTORY, as humans spread across the world, infectious diseases have been a constant companion. Even in this modern era, outbreaks are nearly constant.

Here are some of history's most deadly pandemics, from the Antonine Plague to COVID-19.



Infection epidemics since 2000

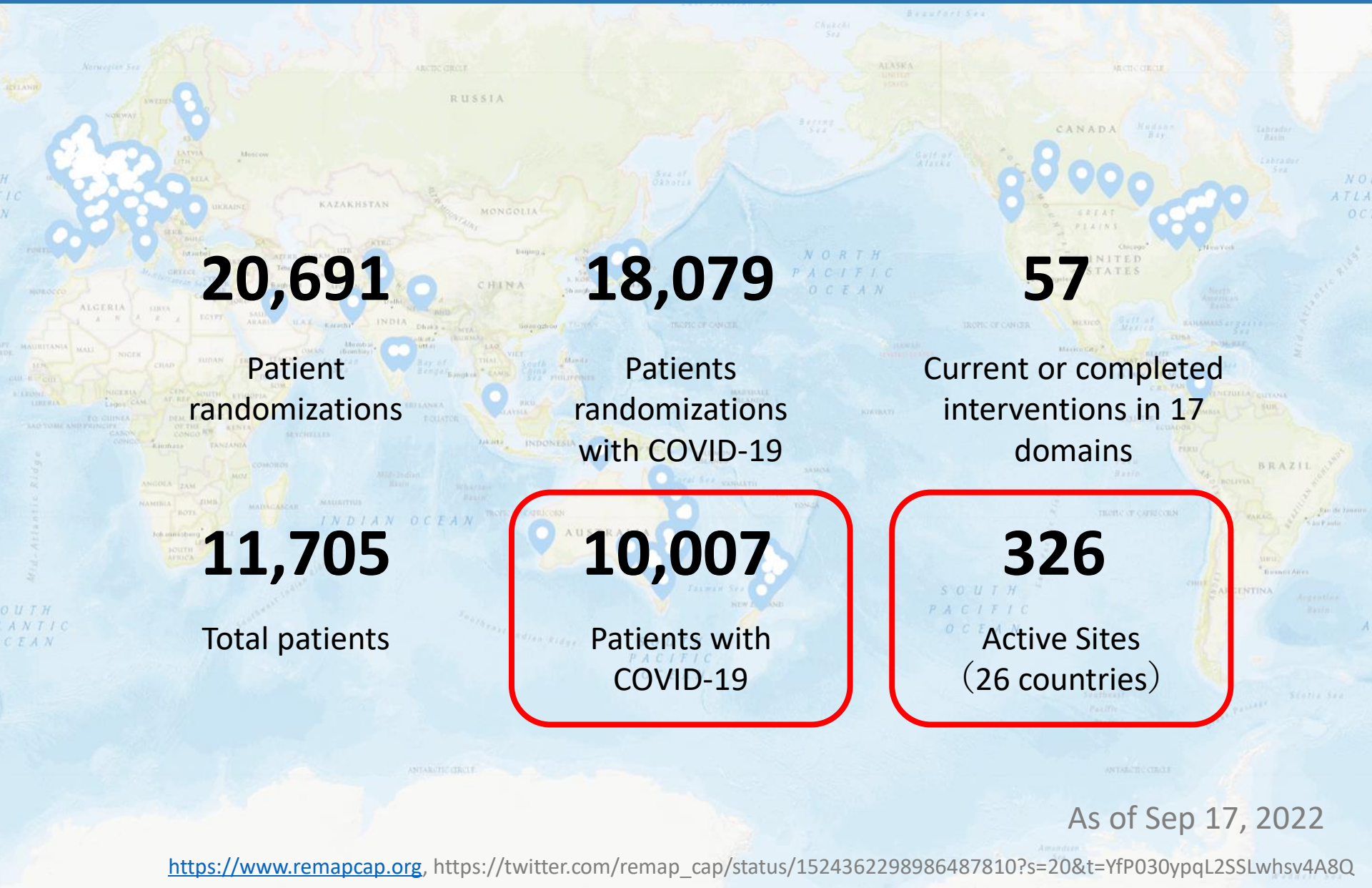


http://apps.who.int/iris/bitstream/handle/10665/272442/9789241565530-eng.pdf?ua=1

REMAP-CAP

- An APT
- Population: adult patients with CAP or “pandemic disease” (currently COVID-19)
- Tests multiple treatments in multiple domains
- Primary endpoints:
  - 90-day mortality in CAP patients
  - OSFD, censored on Day 21, in pandemic disease (COVID-19) patients

REMAP-CAP



20,691
Patient randomizations

18,079
Patients randomizations with COVID-19

57
Current or completed interventions in 17 domains

11,705
Total patients

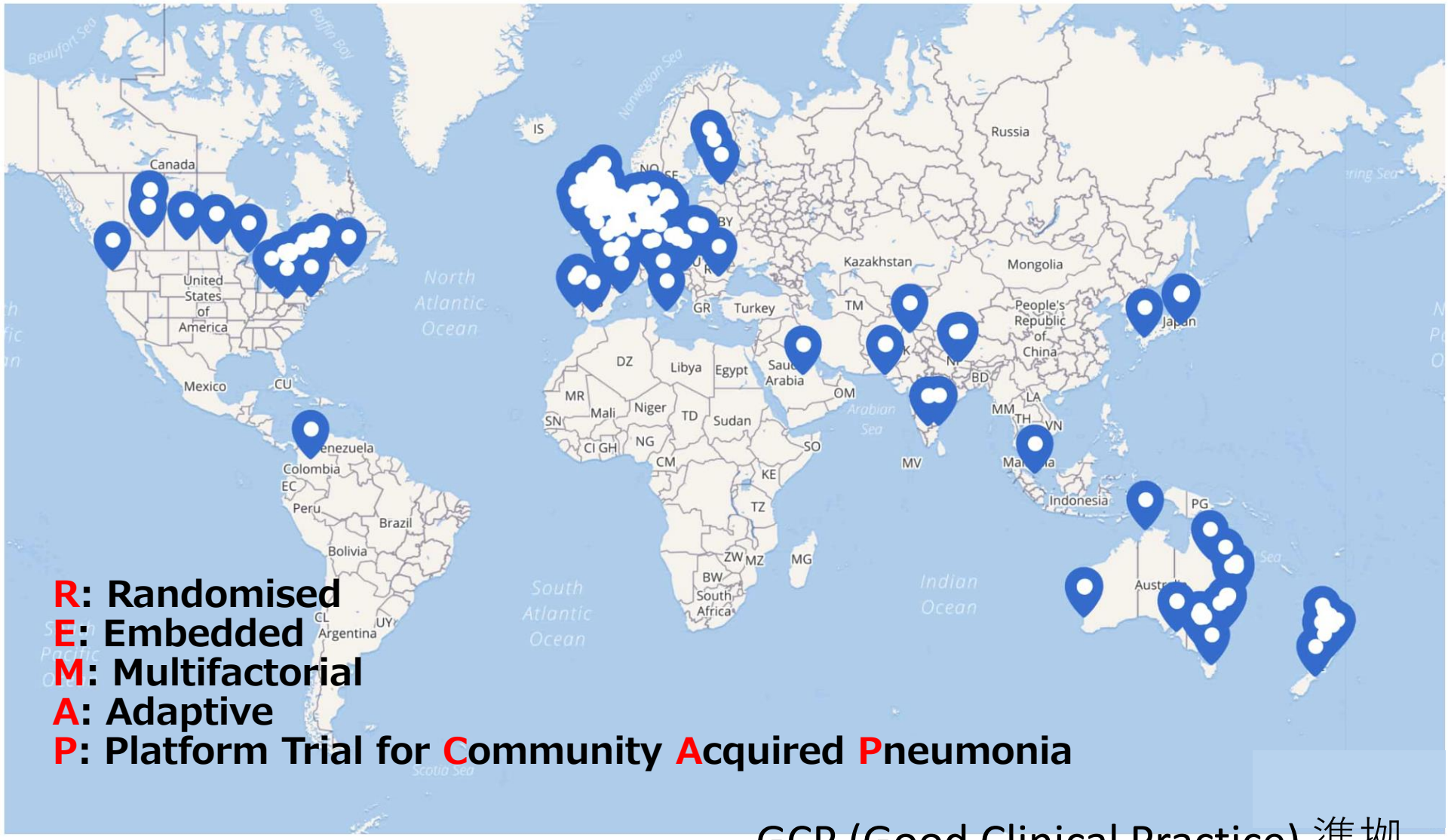
10,007
Patients with COVID-19

326
Active Sites
（26 countries）

As of Sep 17, 2022

https://www.remapcap.org, https://twitter.com/remap_cap/status/1524362298986487810?s=20&t=YfP030ypqL2SSLwhsv4A8Q

REMAP-CAP



R: Randomised
E: Embedded
M: Multifactorial
A: Adaptive
P: Platform Trial for Community Acquired Pneumonia

GCP (Good Clinical Practice) 準拠

Endorsed by WHO

REMAP-CAP

UMC Utrecht · anzic · CCCTG Canadian Critical Care Trials Group

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

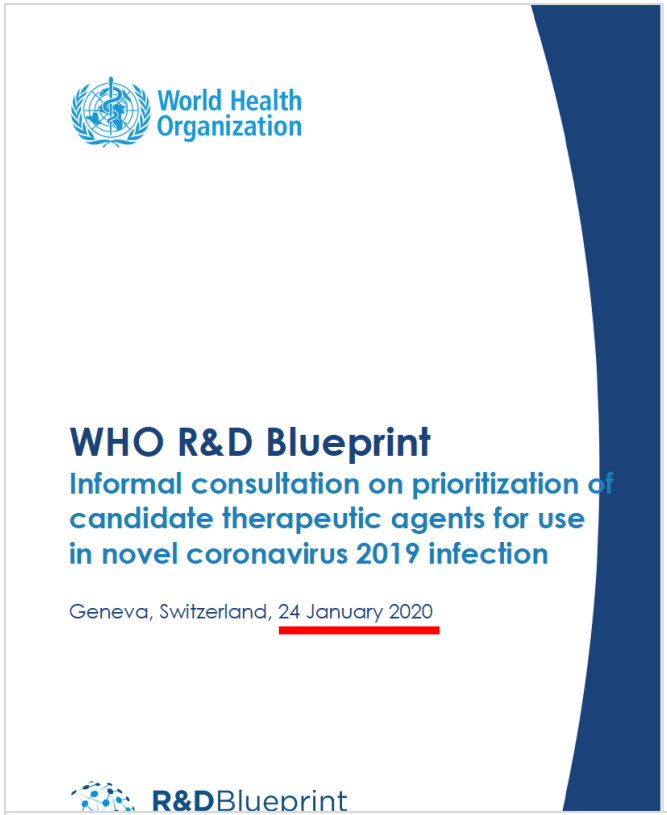
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP):

PANDEMIC APPENDIX TO THE CORE PROTOCOL (REMAP-COVID)

REMAP-CAP Pandemic Appendix to the Core Protocol Version 2.0 dated 18 May 2020

6.3. WHO endorsement

REMAP-CAP has been designated by the WHO as a Pandemic Special Study. Under this designation, it has been tasked with helping answer crucial questions during a declared pandemic, as listed above. This designation ensures that knowledge translation of clinical trial results can occur directly



World Health Organization

WHO R&D Blueprint

Informal consultation on prioritization of candidate therapeutic agents for use in novel coronavirus 2019 infection

Geneva, Switzerland, 24 January 2020

R&DBlueprint

Coronavirus- Outline of designs for experimental vaccines and therapeutics
Draft version Jan 27, 2020

R&DBlueprint
Powering research to prevent epidemics

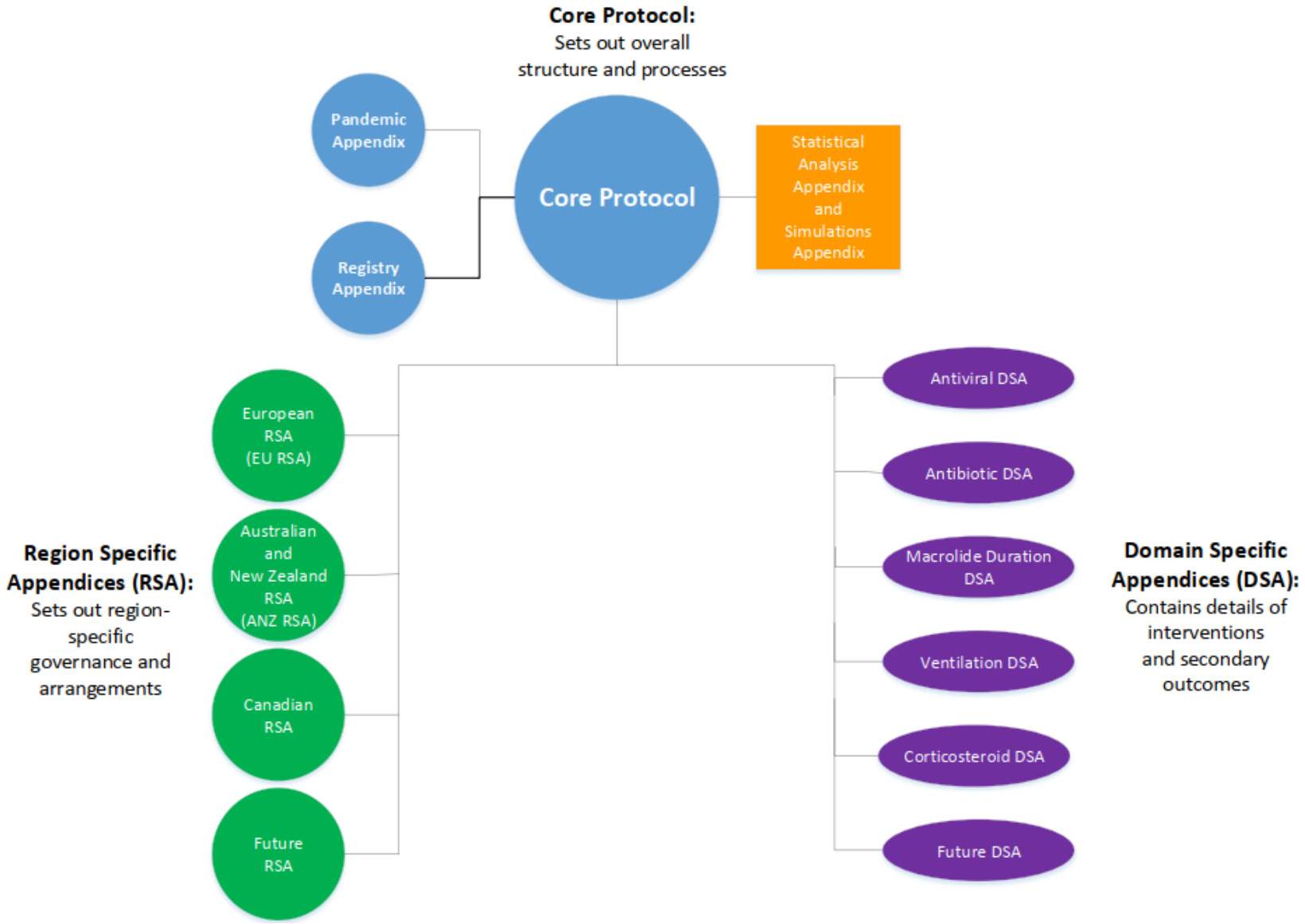
- As WHO deliberates on the ideal clinical trial platform; a platform trial model that enables the evaluation of multiple/different interventions simultaneously and sequentially and is well-suited to the challenge at hand such as the REMAP-CAP trial - a platform trial in severe community-acquired pneumonia is up and running in Australia, New Zealand, Canada, the UK, and a dozen EU countries, and designed to be rapidly adapted to the needs of a pandemic should be examined. REMAP-CAP trial is, however, not currently recruiting in China, but the platform, or at least the model, is well worth exploring as a mechanism to launch studies quickly.

REMAP-CAP

- Purpose: fast provision of evidence for responding to a global epidemic of respiratory infection (=pandemic)
- Principles
  - Ensure scale through pragmatism
  - International “collaboration” with literally multilateral relationship among researchers. Emphasis on inclusion of LMICs and countries with limited resources, e.g., Japan, with or without financial capability to contribute to the platform
- Design/operational features (reflecting the specific purpose)
  - Running APT through non-pandemic periods
  - Adapting the protocol in response to a pandemic
  - Open label (with exceptions) + “hard endpoints”
- Given effective trade-off between speed through scale and implementation of some bias-minimizing design features, REMAP-CAP is designed to hit a balance optimized for a pandemic

Components of the protocol

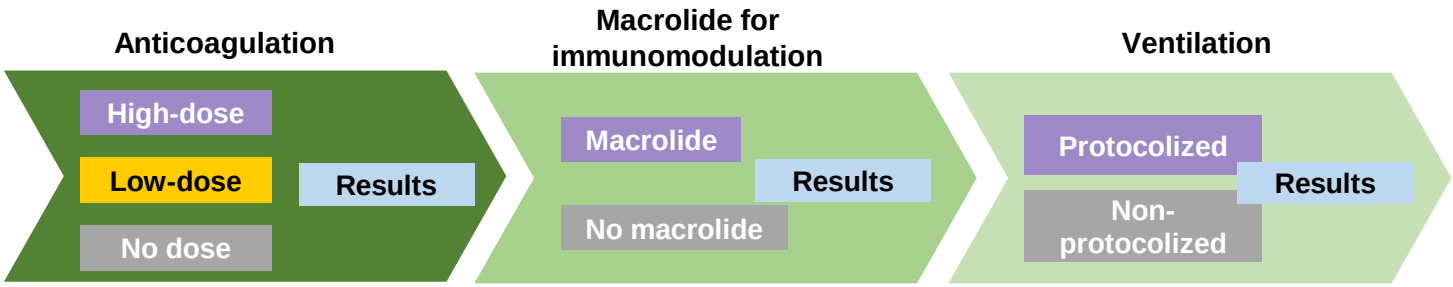
REMAP-CAP



Adaptive Platform Trial (APT)

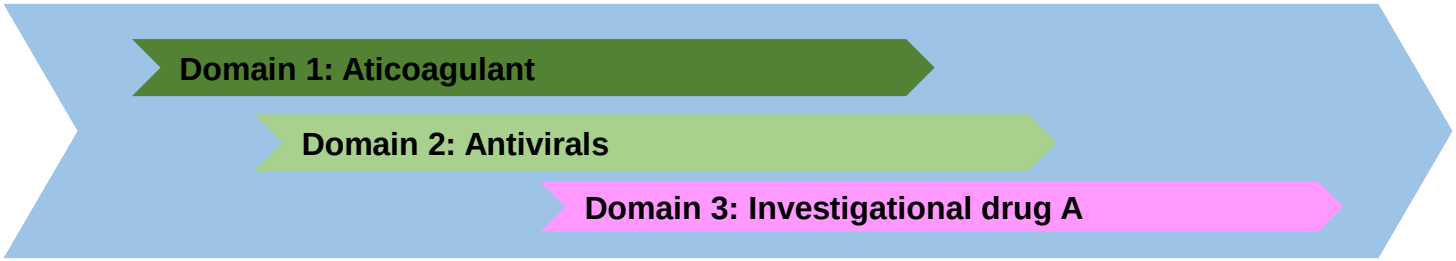
REMAP-CAP

Conventional design: Separate resources for each clinical question



RCTs are executed for each treatment domain. No routine co-enrollment.
Costly, time-consuming, and causes burden on sites.

APT: Shared resources + question-specific "domains"



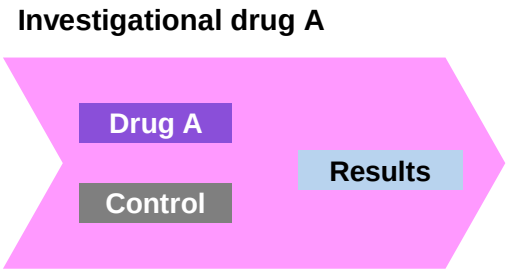
Cost-effective, fast, and less risky

Angus DC. **Fusing Randomized Trials With Big Data: The Key to Self-learning Health Care Systems?** *JAMA.* 2015;314(8):767–768.

Permanent adaptive platform trial for rapid response to a pandemic

REMAP-CAP

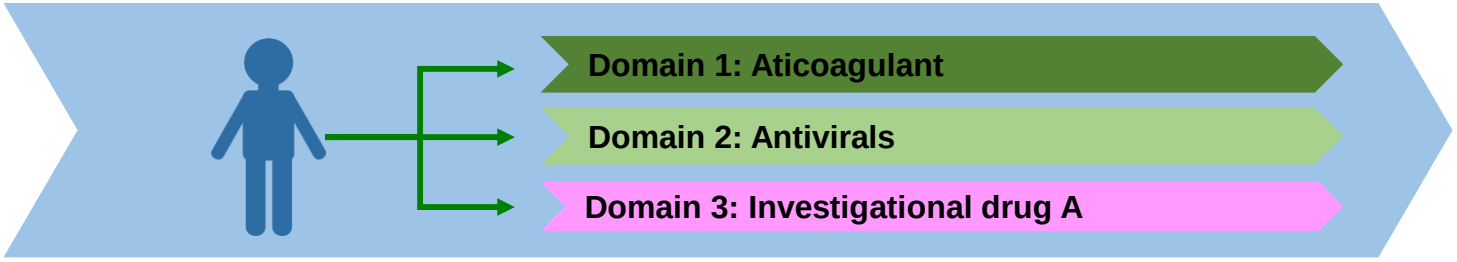
Conventional design| Start a new RCT



Design/protocol writing, ethics review, organizing study group, engaging participating sites…

Costly, time-consuming, and risky

REMAP-CAP| Add a “domain” to an existing platform



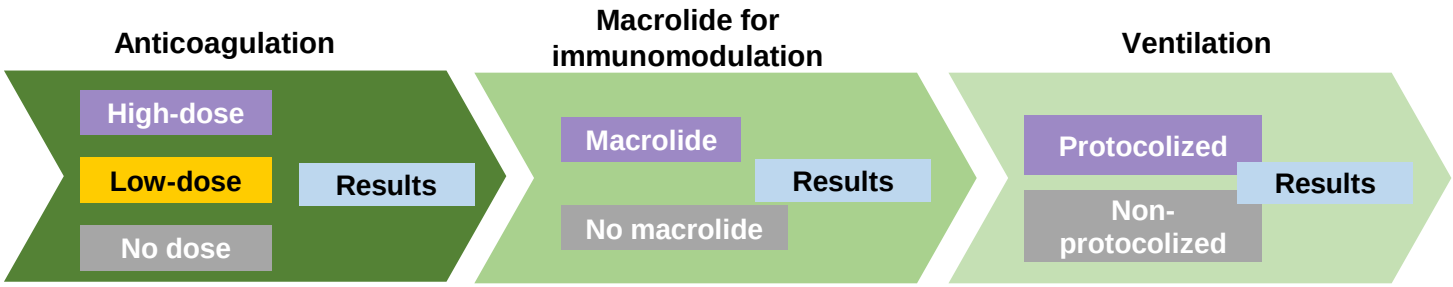
Cost-effective, fast, and less risky

Angus DC. **Fusing Randomized Trials With Big Data: The Key to Self-learning Health Care Systems?** *JAMA.* 2015;314(8):767–768.

Multifactorial design

REMAP-CAP

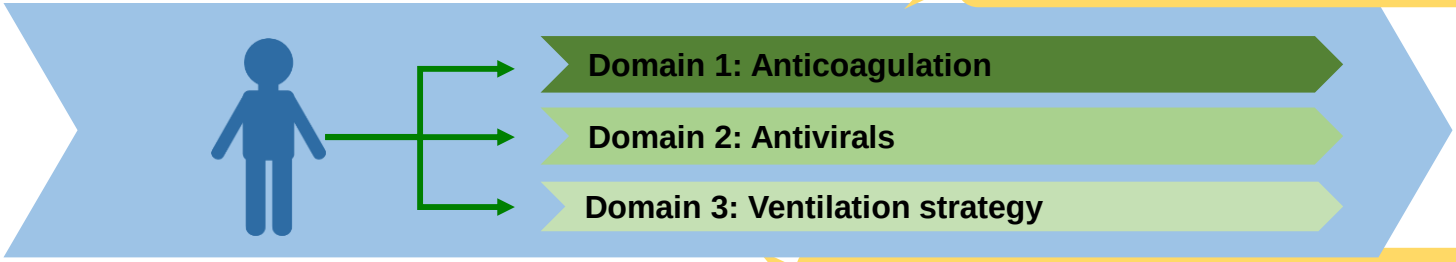
Conventional design| Multiple RCTs



RCTs are executed for each treatment domain. Costly, time-consuming, and causes burden on sites.

REMAP-CAP| Multifactorial design

Platform is operated indefinitely with domains replaced



A single patient can participate in multiple domains, each of which corresponding to an RCT

Effectively run multiple RCTs; efficient

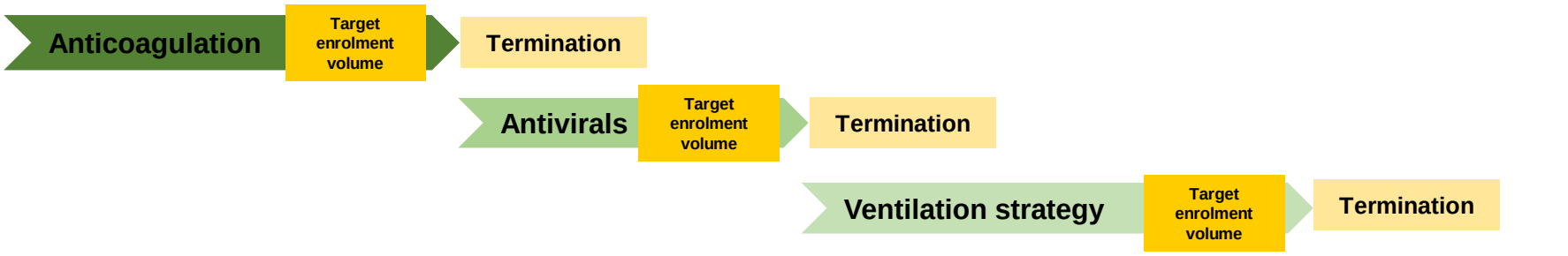
Streamlining site participation; efficient, less burden on sites

Angus DC. **Fusing Randomize** 67–768.

Repeated interim analysis
Based on Bayesian statistics

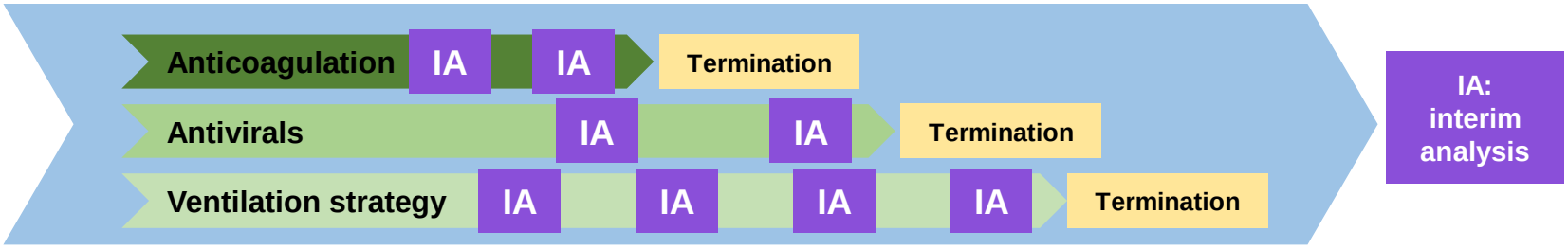
REMAP-CAP

Conventional design | Pre-determined enrolment volume



Enrolment is continued until pre-determined target volume is reached;
(1) Potentially wasteful enrolment
(2) Risk of failure to deliver conclusive results even with planned enrolment volume

REMAP-CAP | Repeated analysis based on Bayesian statistics



Interim analysis is conducted at a pre-specified interval, and enrolment is terminated with statistical conclusion;
(1) No wasteful enrolment
(2) No risk associated with pre-determined enrolment volume

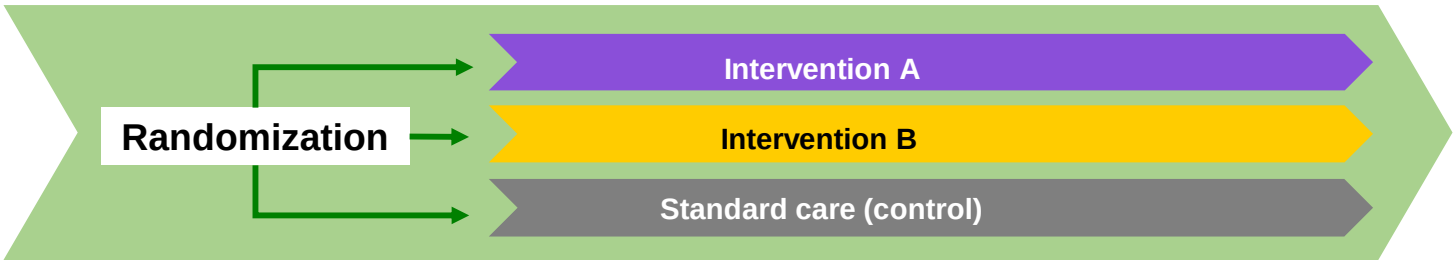
Especially effective with limited preexisting knowledge, e.g., in a pandemic

Angus DC. **Fusing Randomized Trials With Big Data: The Key to Self-learning Health Care Systems?** *JAMA.* 2015;314(8):767–768.

Response adaptive randomization (RAR)

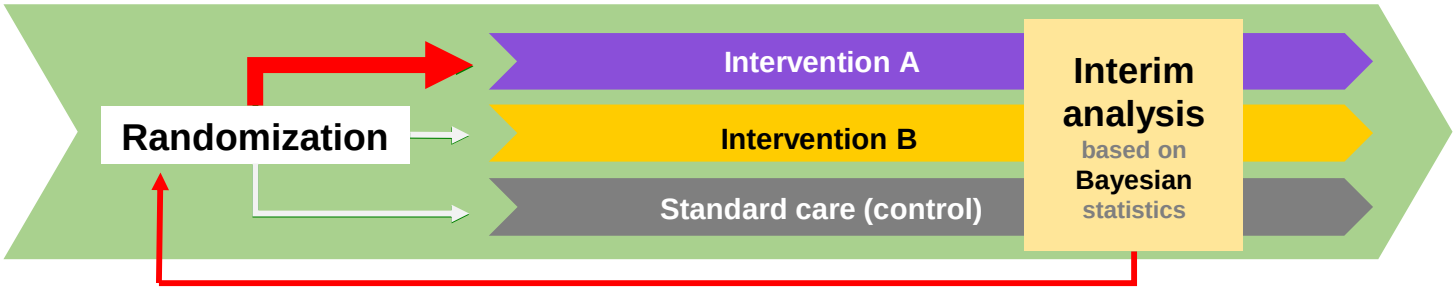
REMAP-CAP

Conventional design | Fixed-ratio randomization



Randomization ratio is fixed; (1) psychological barrier for participation, (2) potential ethical concern, (3) challenging to compare many treatments

REMAP-CAP | Response-adaptive randomization

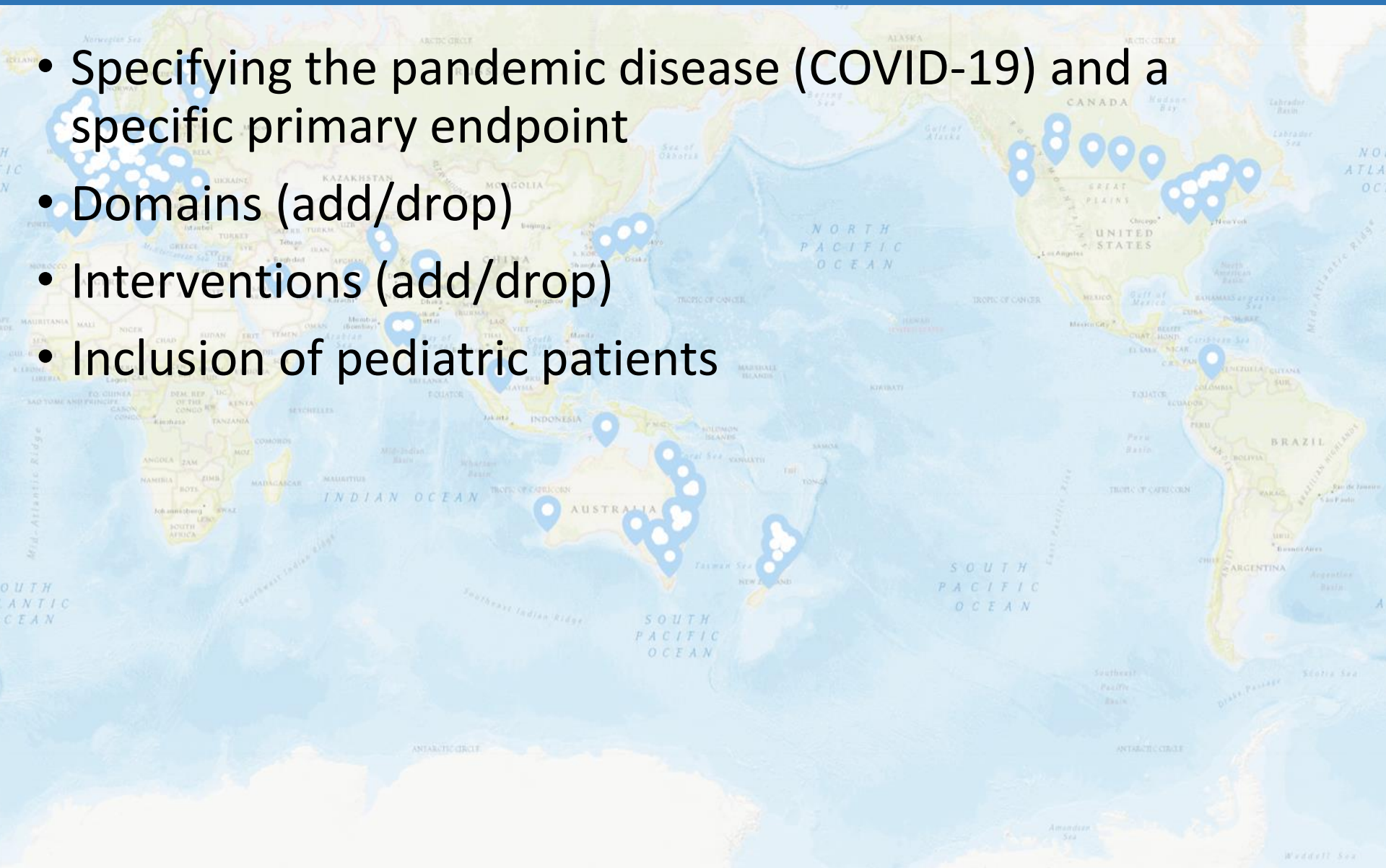


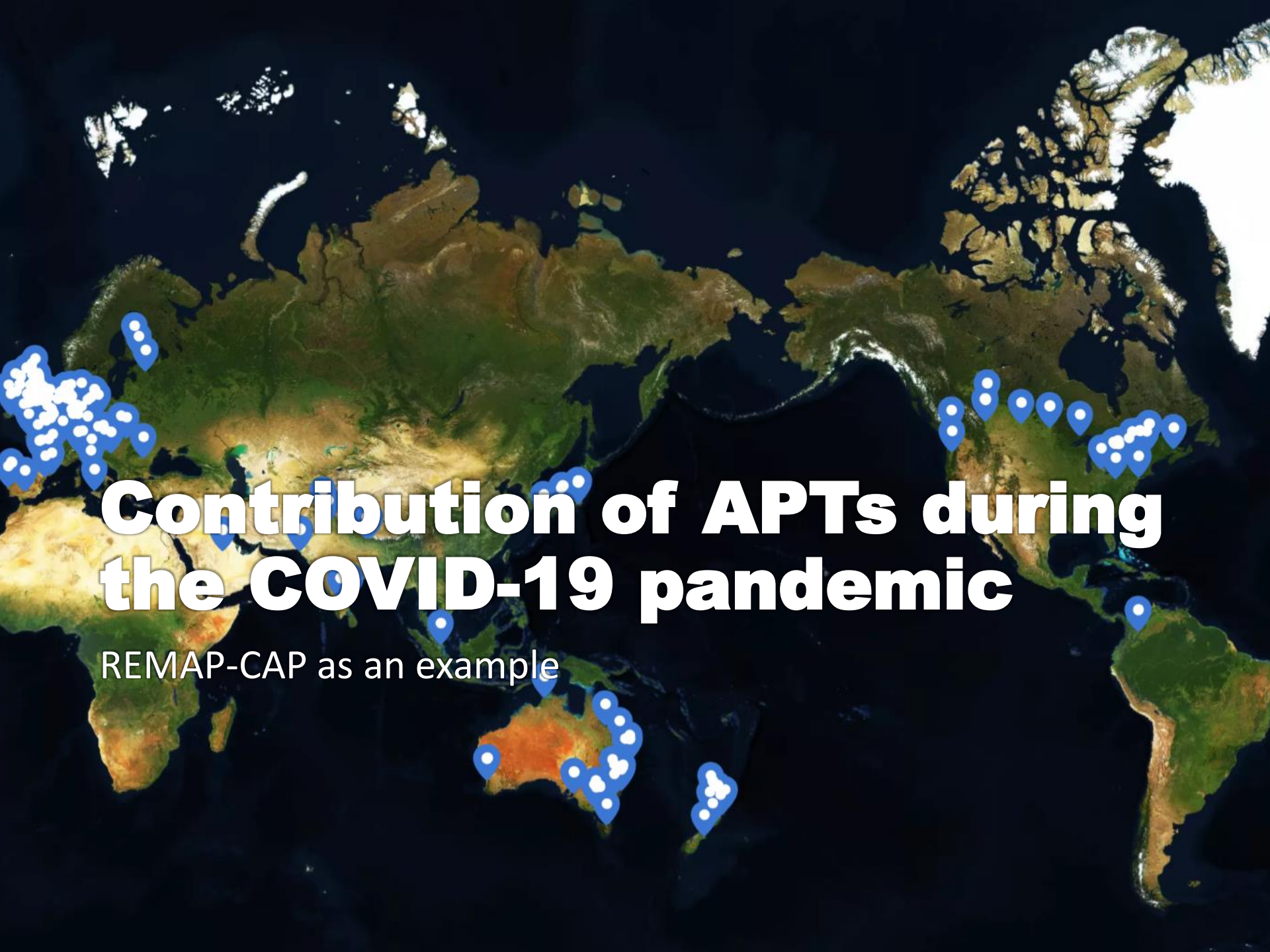
Reflecting results of interim analyses, randomization ratio is adjusted to “favor” the more promising treatments, and patients will likely receive the best treatment.
(1) Reduces psychological barrier, (2) mitigates ethical concern,
(3) Identify the best treatment when there are multiple candidate treatments

Protocol adaptation in REMAP-CAP

REMAP-CAP

- Specifying the pandemic disease (COVID-19) and a specific primary endpoint
- Domains (add/drop)
- Interventions (add/drop)
- Inclusion of pediatric patients





Contribution of APTs during the COVID-19 pandemic

REMAP-CAP as an example

WHO Living Guideline

Therapeutics and COVID-19

LIVING GUIDELINE

22 APRIL 2022

World Health Organization

WHO Living Guideline

3. Introduction

Info Box

As of 15 April 2022, there have been over 502 million confirmed cases of COVID-19 *(10)*. The pandemic has thus far claimed approximately 6.2 million lives *(10)*. Vaccination is having a substantial impact on hospitalizations and death in a number of high-income countries, but limitations in global access to vaccines mean that many populations remain vulnerable *(10)(11)*. Even in vaccinated individuals, uncertainties remain about the duration of protection and efficacy of current vaccines – and the efficacy of existing treatments for COVID-19 – against emerging SARS-CoV-2 variants.

Taken together, there remains a need for more effective treatments for COVID-19. The COVID-19 pandemic – and the explosion of both research and misinformation – has highlighted the need for trustworthy, accessible, and regularly updated living guidance to place emerging findings into context and provide clear recommendations for clinical practice *(12)*.

This living guideline responds to emerging evidence from RCTs on existing and new drug treatments for COVID-19. More than 5000 trials investigating interventions for COVID-19 have been registered and are ongoing or completed (see Section 9 for emerging evidence and linked appendix) *(13)*. Among these are large national and international platform trials (such as RECOVERY, WHO SOLIDARITY, REMAP-CAP, and ACTIV), which recruit large numbers of patients in many countries, with a pragmatic and adaptive design *(14)(15)(16)(17)*. An overview of ongoing trials is available from the Infectious Diseases Data Observatory, through their living systematic review of COVID-19 clinical trial registrations *(13)* and the WHO website.

Several living network meta-analyses associated with this guideline incorporate emerging trial data and allow for analysis of comparative effectiveness of multiple COVID-19 treatments. To inform the living guidance, we also use additional relevant evidence on safety, prognosis, and patient values and preferences related to COVID-19 treatments. A recently updated living systematic review of 232 risk prediction models in hospitalized patients with with COVID-19 did not identify credible and applicable risk prediction tools that could inform recommendations in this ninth version of the guideline *(18)*.

Best evidence demonstrates remaining uncertainties concerning treatment effects for all outcomes of importance to patients. There is also a need for better evidence on prognosis and values and preferences of patients with COVID-19.

World Health Organization. Therapeutics and COVID-19 Living Guideline. 22 April 2022.

WHO Living Guideline

8. Uncertainties, emerging evidence and future research

The guideline recommendations for COVID-19 therapeutics demonstrate remaining uncertainties concerning treatment effects for all outcomes of importance to patients. There is also a need for better evidence on prognosis and values and preferences of patients with COVID-19 infection. Here we outline key uncertainties for IL-6 receptor blockers identified by the GDG, adding to those for ivermectin, corticosteroids, remdesivir and hydroxychloroquine and lopinavir/ritonavir in previous versions of the living guideline. These uncertainties may inform future research, i.e. the production of more relevant and reliable evidence to inform policy and practice. We also outline emerging evidence in the rapidly changing landscape of trials for COVID-19.

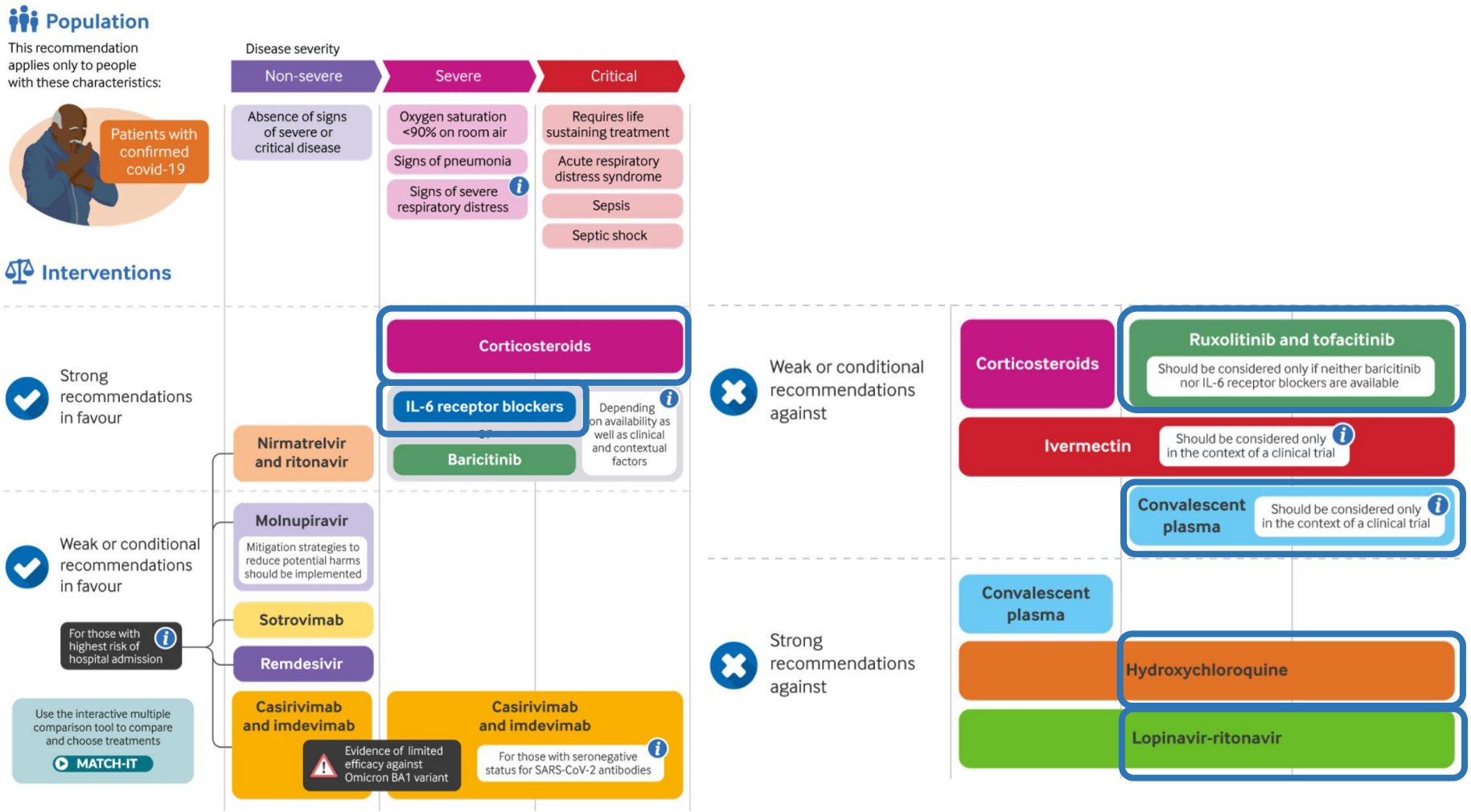
Emerging evidence

The unprecedented volume of planned and ongoing studies for COVID-19 interventions – over 3300 RCTs as of 1 July 2021 – implies that more reliable and relevant evidence will emerge to inform policy and practice *(14)*. An overview of registered and ongoing trials for COVID-19 therapeutics and prophylaxis is available from the Infectious Diseases Data Observatory, through their living systematic review of COVID-19 clinical trial registrations *(14)*, the WHO website and other repositories, such as the COVID-NMA initiative.

Whereas most of these studies are small and of variable methodological quality, a number of large, international platform trials (e.g. RECOVERY, SOLIDARITY and DISCOVERY) are better equipped to provide robust evidence for a number of potential treatment options *(15)(16)(17)(18)*. Such trials can also adapt their design, recruitment strategies and selection of interventions based on new insights, exemplified by the uncertainties outlined above.

World Health Organization. Therapeutics and COVID-19 Living Guideline. 22 April 2022.

Contribution of REMAP-CAP
To establishing COVID-19 treatment



World Health Organization. Therapeutics and COVID-19 Living Guideline. 22 April 2022.

COVID-19治療確立に REMAP-CAPが果たした役割

REMAP-CAP

Corticosteroid

JAMA Network

QUESTION Does intravenous hydrocortisone, administered either as a 7-day fixed-dose course or restricted to when shock is clinically evident, improve 21-day organ support-free days in patients with severe coronavirus disease 2019 (COVID-19)?

CONCLUSION This randomized clinical trial was stopped early and no treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions.

POPULATION

273 Men
111 Women

Adults with suspected or confirmed COVID-19

Mean age: 60 years

LOCATIONS

121 Sites in 8 countries

INTERVENTION

384 Patients randomized
379 Patients analyzed

143
Fixed-dose hydrocortisone
Intravenous hydrocortisone, 50 mg or 100 mg, every 6 hours

152
Shock-dependent hydrocortisone
Intravenous hydrocortisone, 50 mg, every 6 hours

108
No hydrocortisone
Standard of care with no hydrocortisone (or other corticosteroid) use

PRIMARY OUTCOME

Organ support-free days (days alive and free of intensive care unit-based respiratory or cardiovascular support) within 21 days with death counted as -1 day

FINDINGS

Median organ support-free days

Fixed-dose hydrocortisone
0 days (interquartile range, -1 to 15)

Shock-dependent hydrocortisone
0 days (interquartile range, -1 to 13)

No hydrocortisone
0 days (interquartile range, -1 to 11)

Median adjusted odds ratio for improvement vs no hydrocortisone (95% credible interval), and probability of superiority:

1.43 (0.91 to 2.27), **93%** in the fixed-dose group

1.22 (0.76 to 1.94), **80%** in the shock-dependent group

The Writing Committee for the REMAP-CAP Investigators. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. Published September 2, 2020. doi:1001/jama.2020.17022

Results from REMAP-CAP

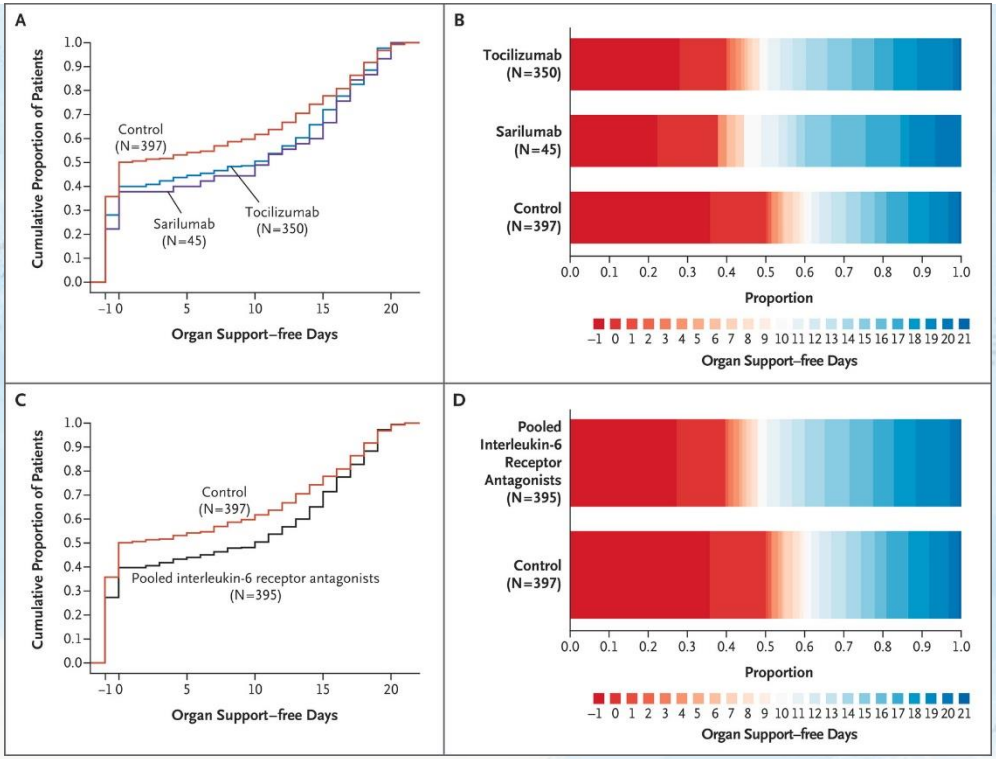
Immune modulators

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

The REMAP-CAP Investigators*

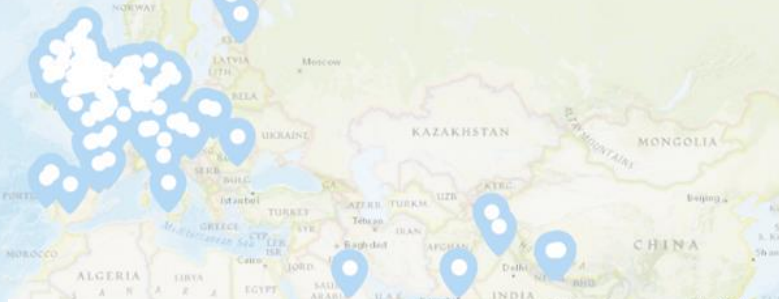


N Engl J Med. 2021 Feb 25

Results from REMAP-CAP

REMAP-CAP

Antivirals and hydrooxychloroquine



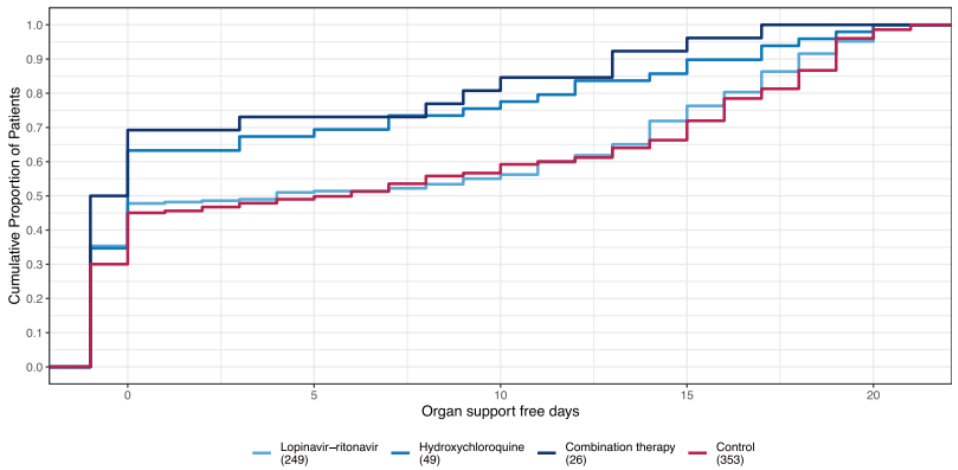
Intensive Care Med
https://doi.org/10.1007/s00134-021-06448-5

ORIGINAL

Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial

Yaseen M. Arabi[1,2,3*], Anthony C. Gordon[4,5], Lennie P. G. Derde[6,7], Alistair D. Nichol[8,9,10], Srinivas Murthy, Farah Al Beidh[4], Djillali Annane[12,13,14], Lolowa Al Swaidan[2,3,15], Abi Beane[16], Richard Beasley[17], Lindsay R. Zahra Bhimani[19], Marc J. M. Bonten[7,20], Charlotte A. Bradbury[21,22], Frank M. Brunkhorst[23], Meredith Buxt, Adrian Buzgau[25], Allen Cheng[25,26], Menno De Jong[27], Michelle A. Detry[18], Eamon J. Duffy[28], Lise J. Estcc, Mark Fitzgerald[18], Rob Fowler[31,32,33], Timothy D. Girard[34,35], Ewan C. Goligher[36], Herman Goossens[37], Rashan Haniffa[38,39,40], Alisa M. Higgins[9], Thomas E. Hills[17,41], Christopher M. Horvat[34,35,42], David T. Huan, Andrew J. King[35], Francois Lamontagne[43,44], Patrick R. Lawler[31,36,45], Roger Lewis[18,46], Kelsey Linstrum[34,3, Edward Litton[47,48,49], Elizabeth Lorenzi[18], Salim Malakouti[50], Daniel F. McAuley[51,52], Anna McGlothlin[18], Shay Mcguinness[17,25,53], Bryan J. McVerry[34,35], Stephanie K. Montgomery[34,35], Susan C. Morpeth[54], Paul R. Mouncey[55], Katrina Orr[56], Rachael Parke[17,53,57], Jane C. Parker[9], Asad E. Patanwala[58,59], Kathryn M. Rowan[60], Marlene S. Santos[19], Christina T. Saunders[18], Christopher W. Seymour[34,35], Manu Shankar-Hari[61,62], Steven Y. C. Tong[63,64], Alexis F. Turgeon[65,66], Anne M. Turner[17], Frank Leo Van de Veerdonk[67], Ryan Zarychanski[68], Cameron Green[9], Scott Berry[18], John C. Marshall[19,69], Colin McArthur[70], Derek C. Angus[34,35] and Steven A. Webb[9,48] on behalf of the REMAP-CAP Investigator

A



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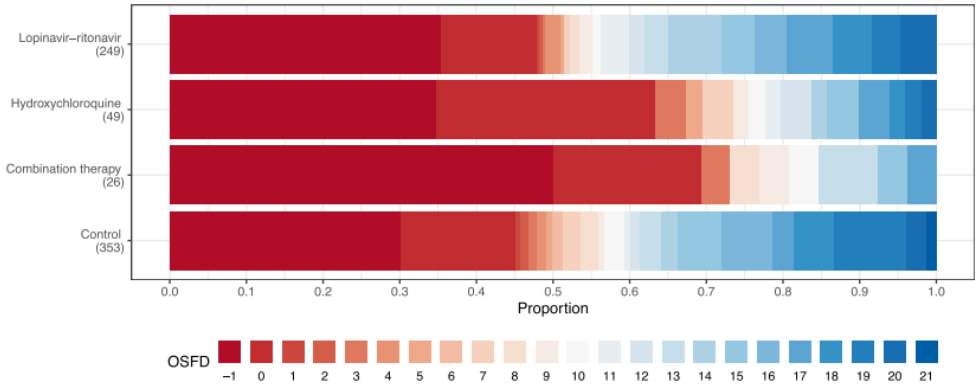


J Crit Care. Published 12 July 2021.

Results from REMAP-CAP

REMAP-CAP

Anticoagulation

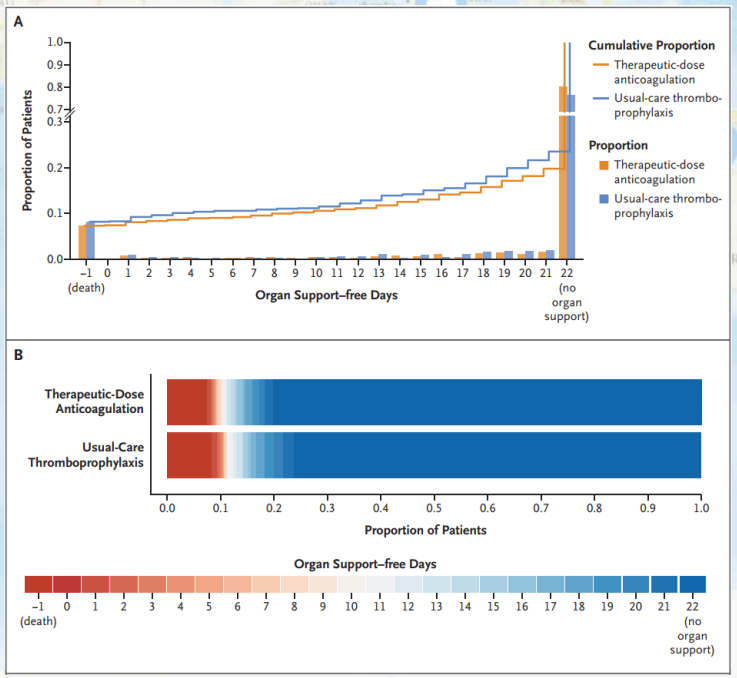
Through collaboration with other large scale trials

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*



N Engl J Med. Published Aug 4, 2021.

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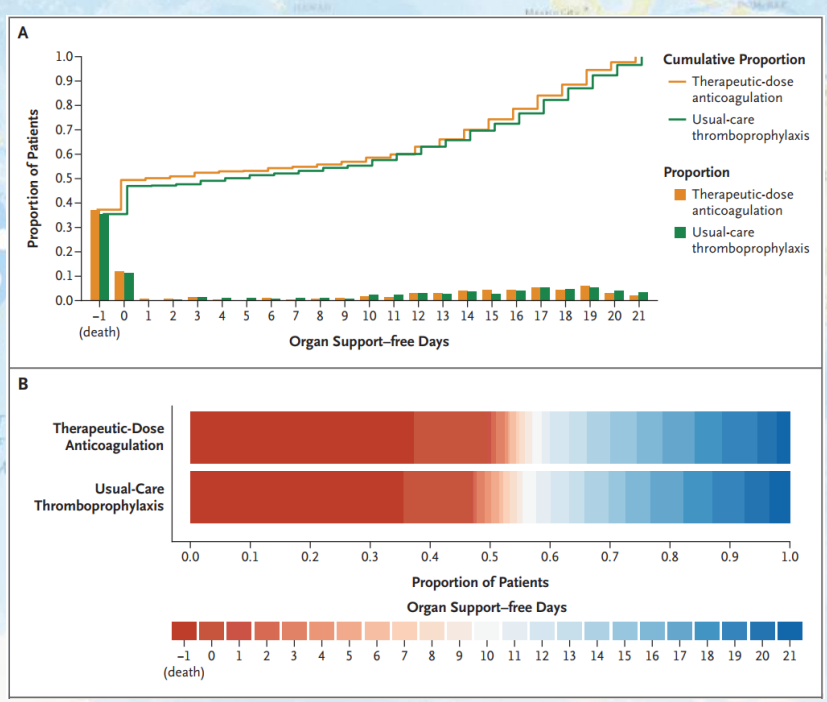


N Engl J Med. Published Aug 4, 2021.

Results from REMAP-CAP

REMAP-CAP

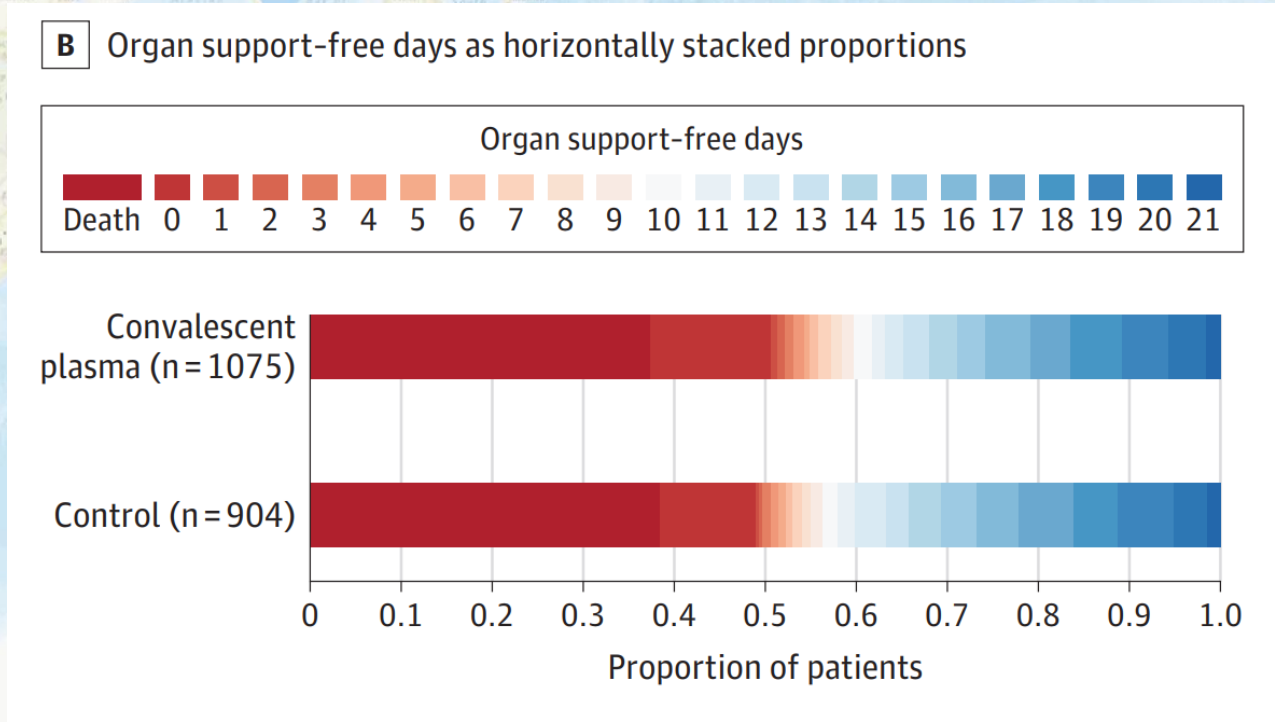
Convalescent plasma

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



Publications from REMAP-CAP

REMAP-CAP

Corticosteroids

Original Investigation | Caring for the Critically Ill Patient FREE

September 2, 2020

Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

The Writing Committee for the REMAP-CAP Investigators

Anticoagulation

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

Immunomodulators

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

The REMAP-CAP Investigators*

Convalescent Plasma

Original Investigation | Caring for the Critically Ill Patient ONLINE FIRST FREE

October 4, 2021

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

Article Information

JAMA. Published online October 4, 2021. doi:10.1001/jama.2021.18178

Antivirals

ORIGINAL

Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial

Check for updates

Antiplatelets

and more to come…

COVID-19治療法確立に貢献：パンデミック初期におけるスピード感

REMAP-CAP

Corticosteroid

Original Investigation | Caring for the Critically Ill Patient FREE

September 2, 2020

Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

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The Writing Committee for the REMAP-CAP Investigators

January 31, 2020

WHO declared PHEIC

*Public Heal Emergency of International Concern
国際的に懸念される公衆衛生上の緊急事態

January 31, 2020

Revised protocol was published **

**Pandemic Appendix only revised

March 9, 2020

The first patient was enrolled in the Corticosteroid domain of REMAP-CAP

June 16, 2020

Press release on effectiveness of corticosteroid from the RECOVERY Trial

June 17, 2020

Patient enrollment for REMAP-CAP Corticosteroid domain was terminated

August 12, 2020

Patient follow-up of the REMAP-CAP Corticosteroid domain was completed

September 2, 2020

Results of the REMAP-CAP Corticosteroid domain was published on JAMA

Meta-analysis: pathway for establishing treatment

REMAP-CAP

Corticosteroid

Original Investigation | Caring for the Critically Ill Patient FREE

September 2, 2020

Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

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JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Immune modulators

The NEW ENGLAND JOURNAL of MEDICINE

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NIH COVID-19 Treatment Guidelines

About the Guidelines | Overview | Management | Therapies

Home / Therapies / Immunomodulators / Interleukin-6 Inhibitors

Therapies

Interleukin-6 Inhibitors

Anticoagulation

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NIH COVID-19 Treatment Guidelines

Search

About the Guidelines | Overview | Management | Therapies | Special Populations

Home / Therapies / Statement on Anticoagulation in Hospitalized Patients

Therapies

Statement on Evusheld for PrEP

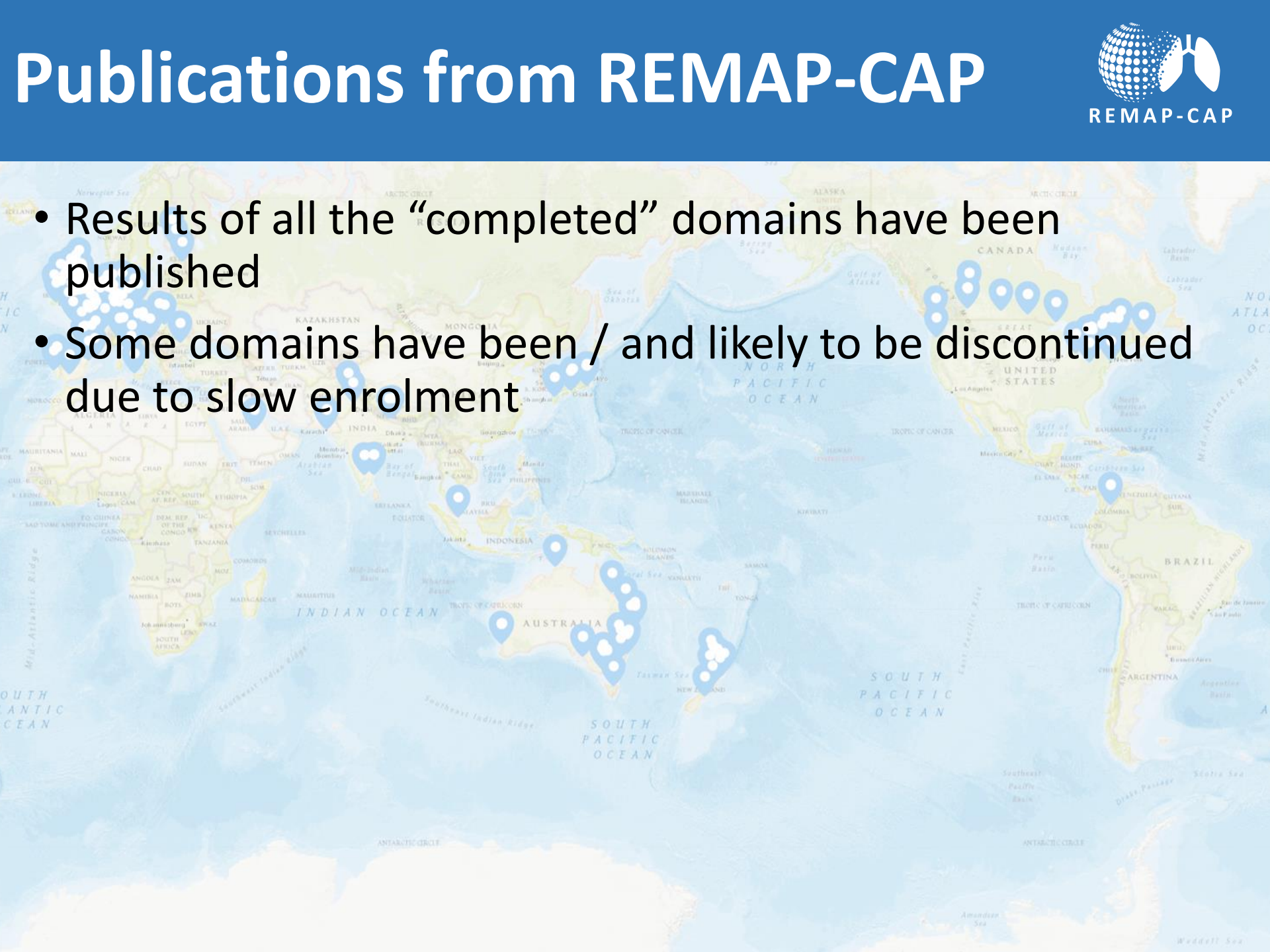
Statement on Anticoagulation in Hospitalized Patients

The COVID-19 Treatment Guidelines Panel's Statement on Anticoagulation in Hospitalized Patients With COVID-19

Last Updated: January 5, 2022

Publications from REMAP-CAP

- Results of all the “completed” domains have been published
- Some domains have been / and likely to be discontinued due to slow enrolment




Definition of an APT

Adaptive Platform Trials (APTs)

"the broad goal of finding the best treatment for a disease by simultaneously investigating multiple treatments"

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.

Growing interests in APTs because of

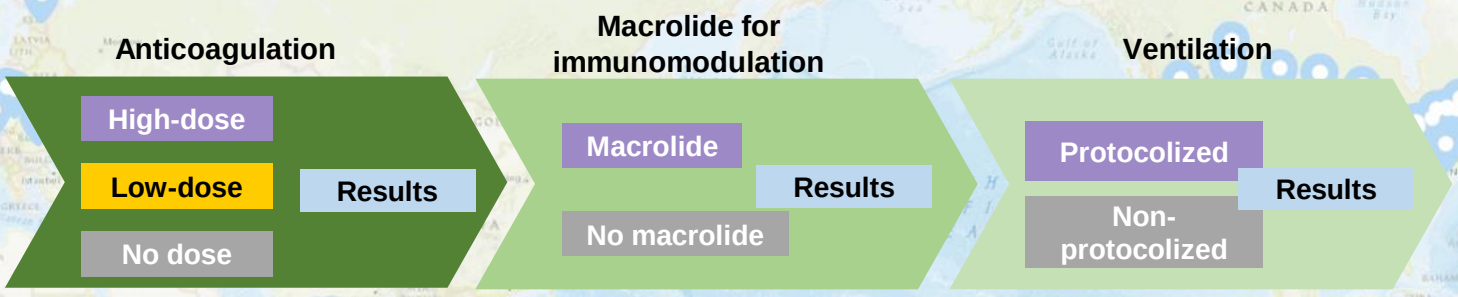
"the need to rapidly evaluate multiple potential treatments"

"the ethical imperative to achieve the best possible outcomes in trial participants"

JAMA. 2015;313(16):1619.

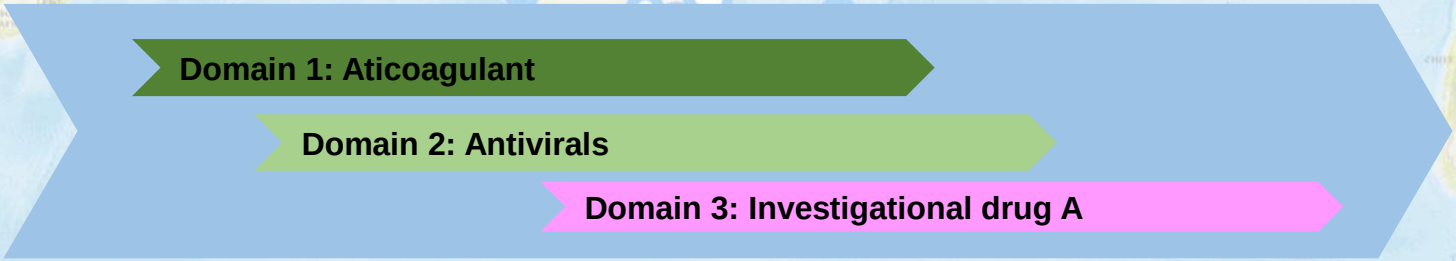
Adaptive Platform Trials (APTs)

Conventional design: Separate resources for each clinical question



RCTs are executed for each treatment domain. No routine co-enrollment.
Costly, time-consuming, and causes burden on sites.

APT: Shared resources + question-specific "domains"



Cost-effective, fast, and less risky

Angus DC. **Fusing Randomized Trials With Big Data: The Key to Self-learning Health Care Systems?** *JAMA.* 2015;314(8):767–768.

Design features associated with APTs

- Multifactorial design
  - Maximum value per patient
  - Challenge with co-enrollment across multiple traditional studies
- Use of non-concurrent control
- Repeated analysis based on Bayesian statistics
- Response-adaptive randomization
- Protocol adaptation beyond addition/deletion of interventions/domains, e.g.,
  - Addition of new populations and strata

Advantages of APTs

- Cost-effectiveness through resource sharing
  - Management of the protocol
  - Management of study database (EDC)
  - Management of data, e.g., monitoring
  - Management/support of sites
  - Statistics
- Scalability
  - Enables a complex organization, e.g., international collaboration
- Resource building and continuous improvement through long-term operation
  - Patient and family engagement

Strategies associated with APTs

Large simple trial (LST) and international collaboration,
Permanent multi-study clinical research network,
Contributorship-based academic assessment

Large Simple Trials (LSTs)

"pragmatically designed studies that enroll a large number of participants according to a relatively straightforward protocol"

Typical features

- Multicenter, multinational
- Large enrolment volume
  - Sensitive
- External validity
- Cost-effective

- Simple protocol
  - Limited number of inclusion and exclusion criteria
    - Heterogeneous population
    - Close to the real-world
  - Allows embedding the trial into routine clinical practice
    - Avoid administrative burden
  - Randomization
  - Typically, open-label
  - Endpoints – not "surrogate endpoints"
    - "Hard" and objectively measurable
    - Directly relevant

Saesen R, Huys I. COVID-19 clinical trials: see it big and keep it simple. *BMJ Evidence-Based Medicine.* 2021;***26***:147–148.

Relatively simple data collection in REMAP-CAP

REMAP-CAP

- Screening
- Baseline
- Day X
- No mandatory lab tests or any other non-routine measurements
- Discharge outcome
- Day 90 outcome
- (Optional Day 180 outcome)
- Serious adverse events
- Protocol deviation

(Extreme example) Simple data collection in WHO SOLIDARITY

- Open-label RCT
- 100+ countries
- Data are collected only at the times of:
  - randomization (baseline)
  - discharge or death (discharge outcome)

Is REMAP-CAP an exploratory trial, or a confirmatory trial?

REMAP-CAP

- Pragmatic trial specializing in response to a pandemic which defies the “exploratory vs. confirmatory trials” framework
- However, in existing “exploratory vs. confirmatory trials” framework, most of its domains do not fulfill requirements as a confirmatory trial, e.g., collection of detailed safety data, and is considered exploratory
- This more reflects the pragmatism of REMAP-CAP as a strategy for expand its scale, rather than its fundamental design. REMAP-CAP can be used as a platform for confirmatory trials, with examples of:
  - Immune Modulation 2 Domain
  - ACE2-RAS Domain

International collaboration

- Ubiquitously discussed, infrequently achieved
- Multilateralism vs. single strong leadership
- REMAP-CAP is based on multilateral collaboration
  - Designed and launched by researchers in: UK, EU, Canada, AUS/NZ, and US
  - Other regions have joined since (now 30+ countries)
- Key functions are distributed across regions
  - Chairperson of the steering committee changes every year (previous ITSC chair served for 2+ years as an exception)
  - Global Project Manager is based in Australia. Manages protocol documents, EDC, Website, etc.
  - UK ICNARC serves as the DCC (Data Coordinating Center). Previously, Monash.
  - Many specific committees
    - Design team
    - Pharma Liaison
    - PPI
- Financing
  - Regional sponsors are responsible for funding operational cost in each region
  - Central costs are distributed across regions through negotiation, with a principle to incorporate (1) recruitment volume, and (2) financial capacity

A Permanent Multi-study Clinical Research Network

- Some of APTs' advantages can be achieved through a *platform of trials*, or integration of multiple trials at the organizational level, not necessarily a *platform trial*, or integration of multiple trials at the protocol level
  - *Platform of trials* ≒ permanent multi-study clinical research network

A Permanent Multi-study Clinical Research Network

A traditional CRN

- Developed based on existing networks of researchers ("… Study Group")
- Representatives of the sites are listed as "authors" of the manuscript
  - Questionable practice
- Difficult to engage sites beyond existing networks
- Often without any financial compensation

A permanent multi-study CRN

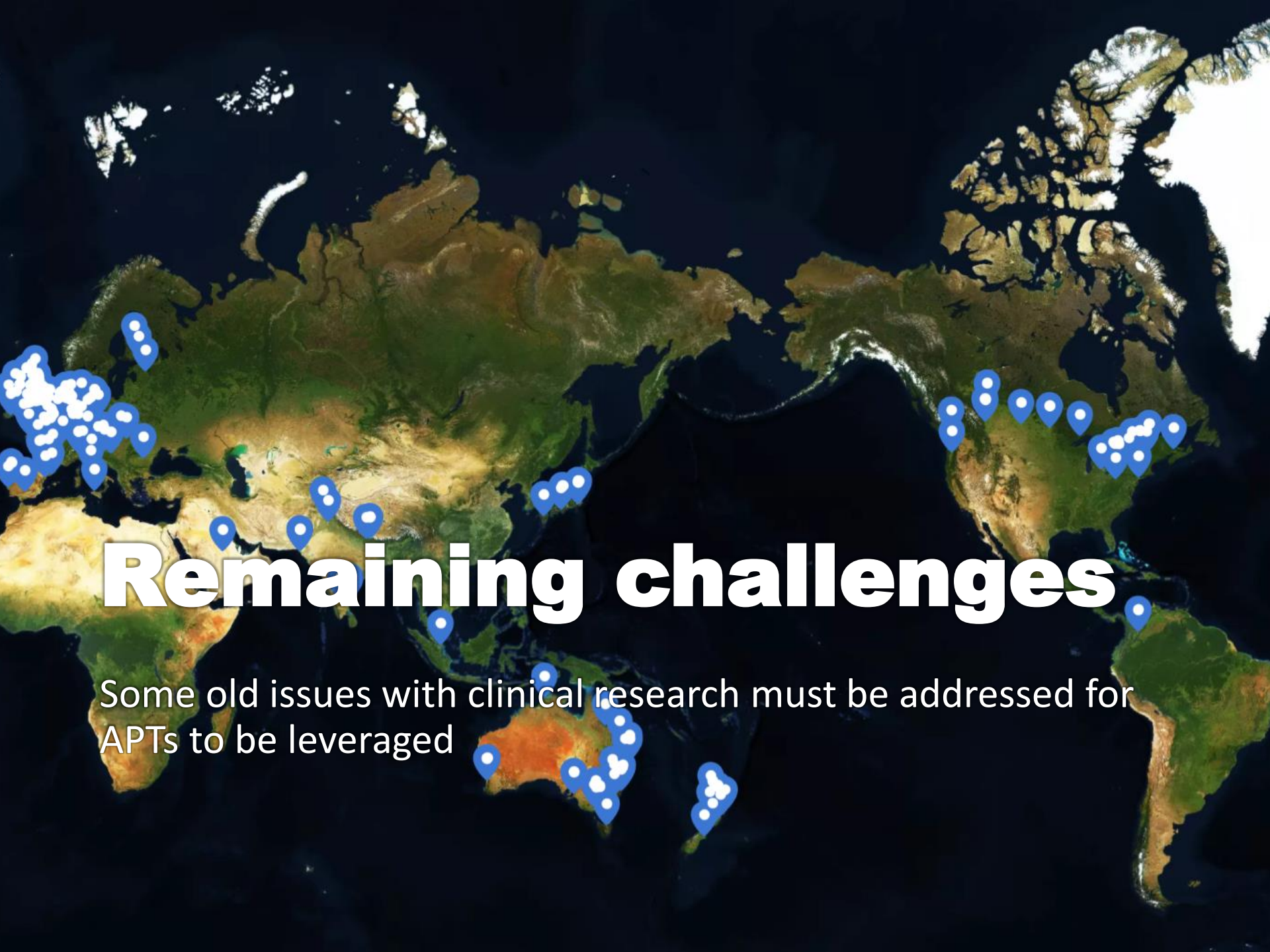
- Participation of sites with limited resources for clinical trials
- Site participation
  - does not lead to "authorship"
  - serves as an opportunity for developing skills in clinical trials
- Expansion beyond networks of researchers
- Resource sharing across studies and disciplines
  - Economic efficiency
- Financial compensation
- Resource building/problem solving beyond specific studies

A Permanent Clinical Research Network: Functions

- Support for sites
  - Securing trained CRCs/CRAs (clinical research coordinators/associates)
  - Training/education of clinical staff
- Minimize administrative burden
  - Standardized admin process, e.g., contract, data collection including EDC, monitoring, and payment
- Remote access to source data, i.e., EHR
- “Regulatory science”

Evaluating contribution to complex/large-scale clinical research

- Complex protocols, e.g., APTs, and complex research organizations, e.g., pmCRNs, require contribution of experts to the "central" resources
- Poorly aligned with the current environment of the academia that encourages a larger number of publications per person
- Authorship cannot be the sole indicator
  - From "publish to perish" to contributorship-based academic assessment



Remaining challenges

Some old issues with clinical research must be addressed for APTs to be leveraged

Remaining challenges: Team/organization building

- Operational complexity
  - "(re-)building an airplane while flying it"
  - Governance/leadership
- Think protocols. Think beyond protocols (organizations).
- Involvement of junior investigators and allied health professionals
  - From authorship to "contributorship"

Remaining challenges: mitigating publication bias and promoting large-scale collaboration

- Publication bias
  - Published study results are still biased even with study registration. How can we ensure completion and publication of “negative” studies?
- Limited large-scale collaboration
  - Clinical research resources are excessively dispersed: especially patients and trained personnel
  - “Publish or perish” culture encourages small studies - need to redesign academic incentives

Remaining challenges: Leveraging design features with trade-offs and improving predictability of regulator decisions

- Design choices with trade-offs: when?
  - Use of non-concurrent control: Feasibility/efficiency/cost/scale vs. bias avoidance
  - Response-adaptive randomization: perceived ethical benefit and potential increase in patient recruitment vs. bias avoidance and efficiency (required enrollment volume)
- Researcher-regulator exchange
  - Effectively leveraging APTs' design choices that involve trade-offs necessitates predictability of regulators' responses to study results
  - Regulatory agencies must provide more effective prospective consultation

Remaining challenges: Reporting results of APTs

- Increased complexity of trials needs to be addressed by corresponding transparency measures: additional items specifically for APTs
  - Clinical trials (trial registries)
  - Clinical trial results (manuscripts)
    - Non-concurrent control, e.g., enrollment volume in each month
    - Co-enrollment with other trials/domains
- Existing guideline:
  - The Adaptive designs CONSORT Extension (ACE) statement: a checklist with explanation and elaboration guideline for reporting randomised trials that use an adaptive design