ASCOT
AustralaSian COVID-19 Trial

REMAP-CAP

COVID-19 Clinical Trials in NZ

Dr Susan Morpeth
Infectious Diseases Physician & Clinical Microbiologist, Middlemore Hospital, CMDHB

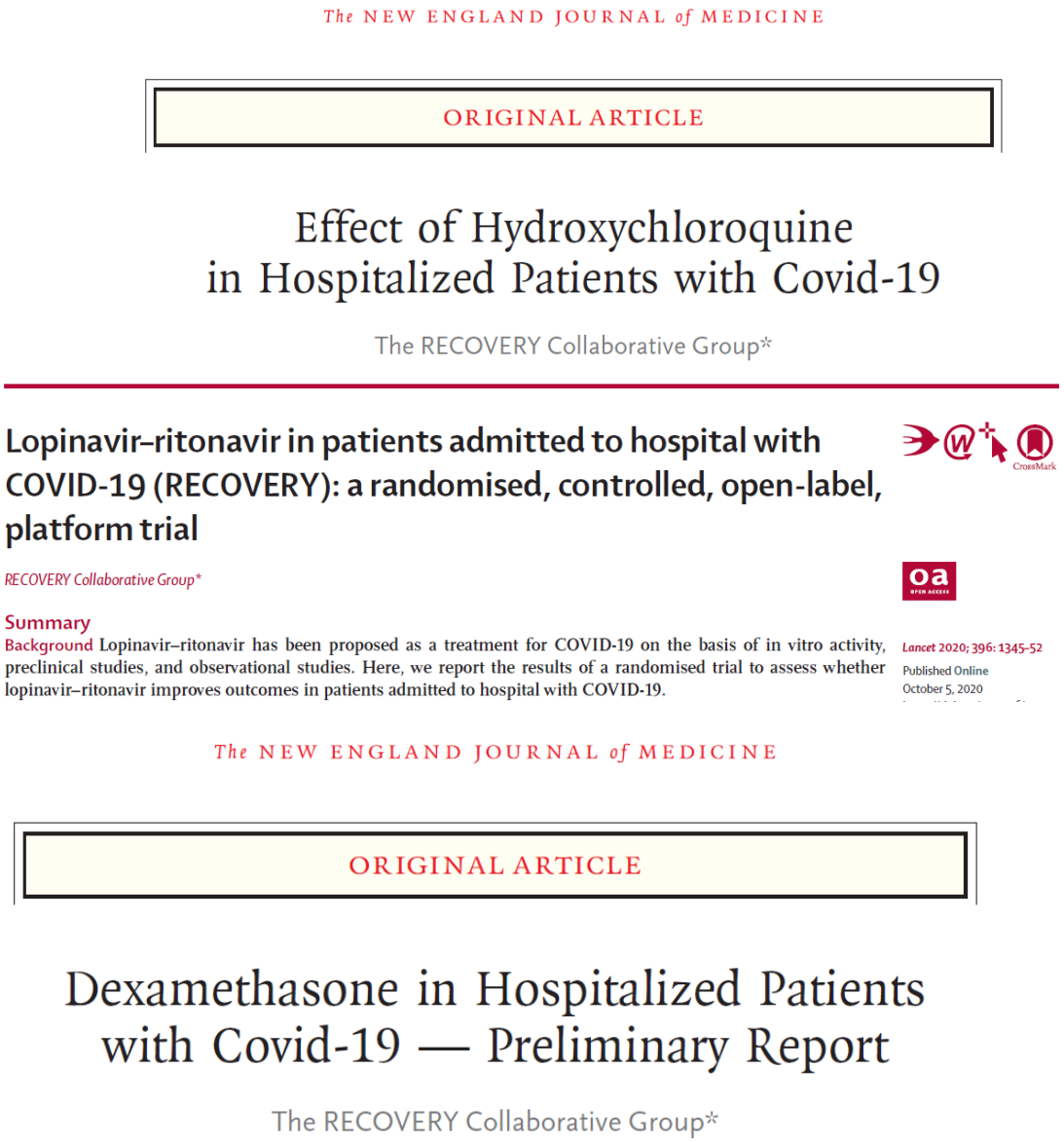
One Health Aotearoa, December 2020

Outline

- Key RCTs in COVID-19 treatment
- Establishing COVID-19 clinical trials in NZ
- ASCOT ADAPT
- REMAP-CAP
- Challenges and future developments

Key RCTs in COVID-19

- **RECOVERY**
  - UK
  - Hydroxychloroquine (no benefit), Lopinavir-ritonavir (no benefit), Dexamethasone (selective mortality benefit)
  - Recently stopped azithromycin
  - Now testing tocilizumab, convalescent plasma, monoclonal antibodies, colchicine, aspirin



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19

The RECOVERY Collaborative Group*

Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

RECOVERY Collaborative Group*

Summary

Background Lopinavir–ritonavir has been proposed as a treatment for COVID-19 on the basis of in vitro activity, preclinical studies, and observational studies. Here, we report the results of a randomised trial to assess whether lopinavir–ritonavir improves outcomes in patients admitted to hospital with COVID-19.

Lancet 2020; 396: 1345-52
Published Online
October 5, 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

Key RCTs in COVID-19

- **Solidarity**
  - WHO
  - Remdesivir, Interferon, Lopinavir-ritonavir, Hydroxychloroquine (all no benefit)
  - What next?
- **ACTT-1**
  - USA/NIH
  - Remdesivir (reduced time to recovery, no mortality benefit)

MedRxiv (October 15) version

Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results

WHO Solidarity trial consortium*

World Health Organization

Health Topics | Countries | Newsroom | Emergencies

Home / Solidarity Therapeutics Trial produces conclusive evidence on the effectiveness of repurposed drugs for COVID-19

Solidarity Therapeutics Trial produces conclusive evidence on the effectiveness of repurposed drugs for COVID-19 in record time

15 October 2020 | News release | Geneva | Reading time:

In just six months, the world's largest randomized control trial on COVID-19 therapeutics has generated conclusive evidence on the effectiveness of repurposed drugs for the treatment of COVID-19.

Interim results from the Solidarity Therapeutics Trial, coordinated by the World Health Organization, indicate that remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon regimens appeared to have little or no effect on 28-day mortality or the in-hospital course of COVID-19 among hospitalized patients.

The NEW ENGLAND JOURNAL

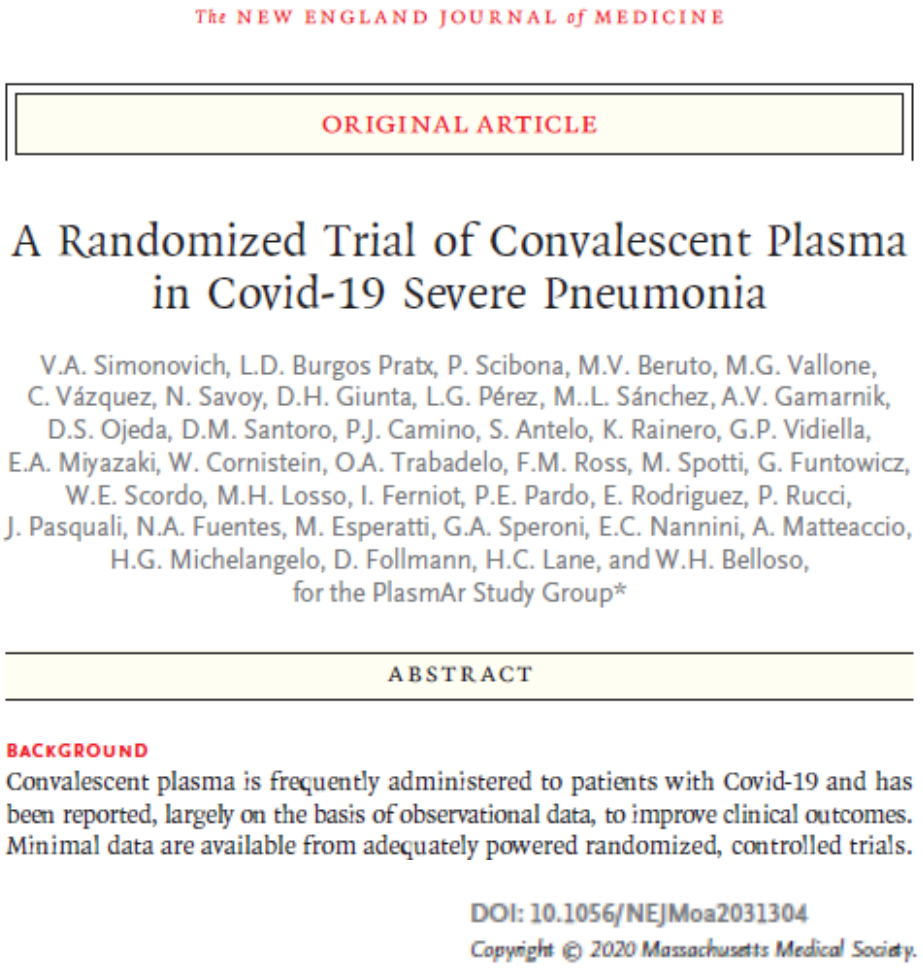
ORIGINAL ARTI

Remdesivir for the Treatn
— Final Rep

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

Key RCTs in COVID-19

- **PlasmAr**
  - Argentina
  - 228 patients got high-titre convalescent plasma; 105 placebo
  - No difference in ordinal scale outcome or mortality
- RECOVERY
  - expected to report soon,
  - >4000 patients



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

V.A. Simonovich, L.D. Burgos Pratx, P. Scibona, M.V. Beruto, M.G. Vallone, C. Vázquez, N. Savoy, D.H. Giunta, L.G. Pérez, M..L. Sánchez, A.V. Gamarnik, D.S. Ojeda, D.M. Santoro, P.J. Camino, S. Antelo, K. Rainero, G.P. Vidiella, E.A. Miyazaki, W. Cornistein, O.A. Trabadelo, F.M. Ross, M. Spotti, G. Funtowicz, W.E. Scordo, M.H. Losso, I. Ferniot, P.E. Pardo, E. Rodriguez, P. Rucci, J. Pasquali, N.A. Fuentes, M. Esperatti, G.A. Speroni, E.C. Nannini, A. Matteaccio, H.G. Michelangelo, D. Follmann, H.C. Lane, and W.H. Belloso, for the PlasmAr Study Group*

ABSTRACT

BACKGROUND

Convalescent plasma is frequently administered to patients with Covid-19 and has been reported, largely on the basis of observational data, to improve clinical outcomes. Minimal data are available from adequately powered randomized, controlled trials.

DOI: 10.1056/NEJMoa2031304

Key RCTs in COVID-19

- **REMAP-CAP**
  - Global platform trial
  - ICU-level patients
  - Pre-dates COVID-19 pandemic
  - Includes NZ
  - Findings:
    - Hydrocortisone effective
    - Lopinavir-ritonavir not effective
    - Tocilizumab effective

MEDIA RELEASE

hrc nz Health Research Council of New Zealand

FRIDAY 20 NOVEMBER 2020

Preliminary findings show arthritis drug to be effective in treating sickest COVID-19 patients

Critically ill patients with COVID-19 who are given a drug that reduces inflammation by modifying the immune system require less time receiving intensive care treatment, an international study has found.

The early findings, which are yet to be published, come from the REMAP-CAP clinical trial. New Zealand's participation in the trial is coordinated by the Medical Research Institute of New Zealand and funded by the Health Research Council and Ministry of Health.

The findings show that treatment with the immune modulator 'tocilizumab' reduced time spent on organ support* in intensive care among critically ill patients with severe COVID-19, compared to patients who did not receive any immune modulation treatment.

Establishing COVID-19 clinical trials in NZ

- HRC call March 2020
  - ASCOT (RCT of hospitalised patients)
  - REMAP-CAP (RCT of ICU level patients)
  - Prevention (RCT in HCW)
  - COHESION (cohort study)
    - aims to determine local relevant predictors of death or ICU admission from COVID-19

REMAP-CAP

ASCOT
AustralaSian COVID-19 Trial

Australasian COVID-19 Trial: ASCOT

- Initial protocol frequentist
- Now adaptive platform: ASCOT ADAPT
- Hospitalised patients, not ICU level care
- Protocol development, HRC grant application, HDEC submission, SCOTT submission, local governance

- Initially hydroxychloroquine (HCQ) & lopinavir-ritonavir (LPV/r)
- Convalescent plasma added, HCQ & LPV/r stopped
- India joined Australia & NZ

ASCOT

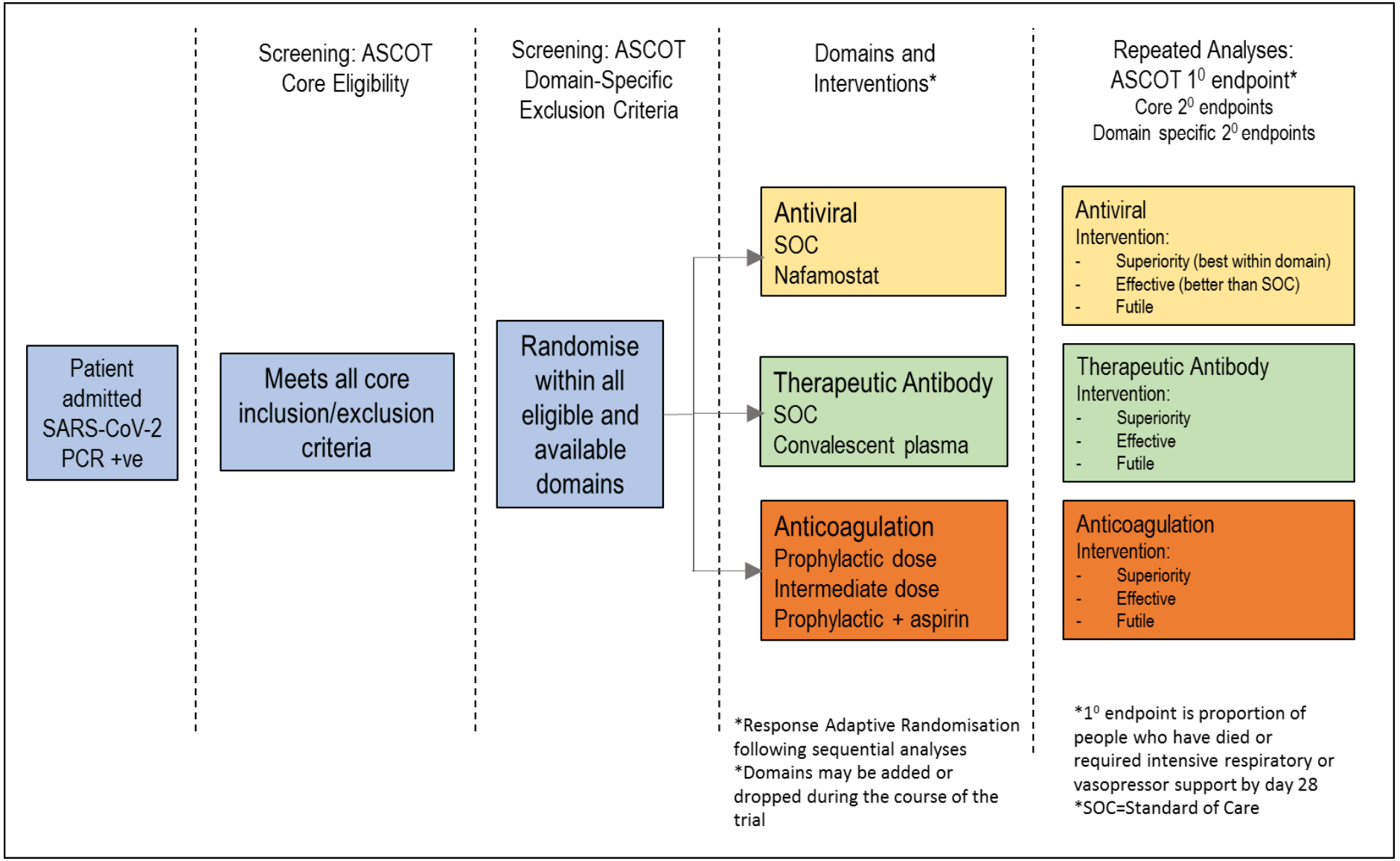
AustralaSian COVID-19 Trial

ASCOT
AustralaSian COVID-19 Trial

ASCOT ADAPT

- Adaptive platform trial, Bayesian analysis, response-adaptive randomisation
- Core protocol
  - Antiviral domain
  - Antibody domain
  - Anticoagulant domain

ASCOT
AustralaSian COVID-19 Trial



Bayesian adaptive designs

"An adaptive design is a clinical study design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial."

Food & Drug Administration and European Medicines Agency have guidelines for conduct of such studies

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

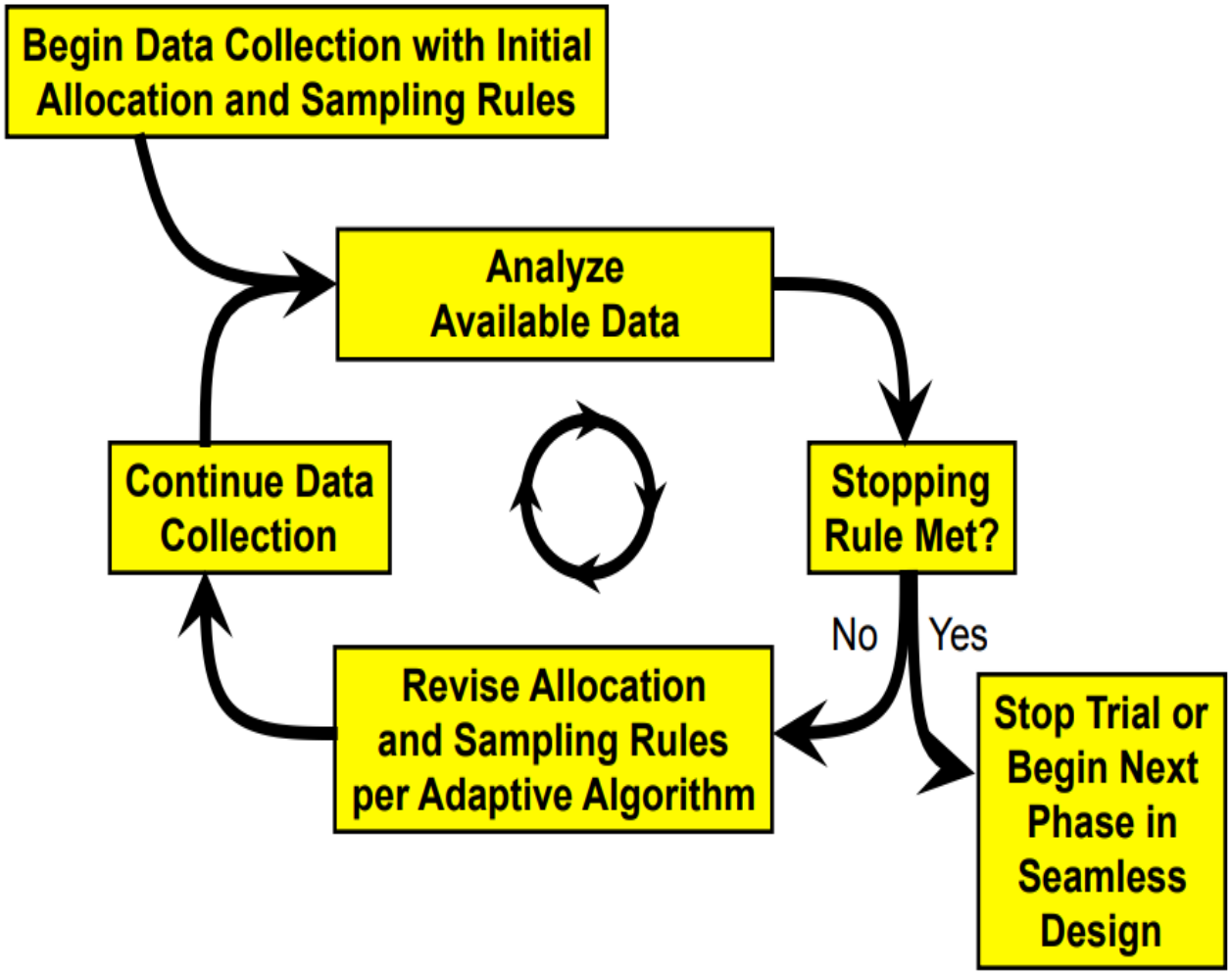
Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

From the Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD. Address reprint requests to Dr. LaVange at the Office of Biostatistics, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Blvd., Silver Spring, MD 20993, or at lisa.lavange@fda.hhs.gov.

HIGH-QUALITY EVIDENCE IS WHAT WE USE TO GUIDE MEDICAL PRACTICE. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered. The conduct of "precision medicine" trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. There is also increasing interest in performing mechanism-based trials in which eligibility is based on criteria other than traditional disease

The Adaptive Process



ASCOT ADAPT: Key clinical questions

- Looking for regimens that are safe and effective in reducing morbidity and mortality among hospitalised patients with COVID-19

- Core primary outcome:
  - Death from any cause, or requirement of new intensive respiratory support (invasive or non-invasive ventilation) or vasopressor/inotropic support in the 28 days after randomisation

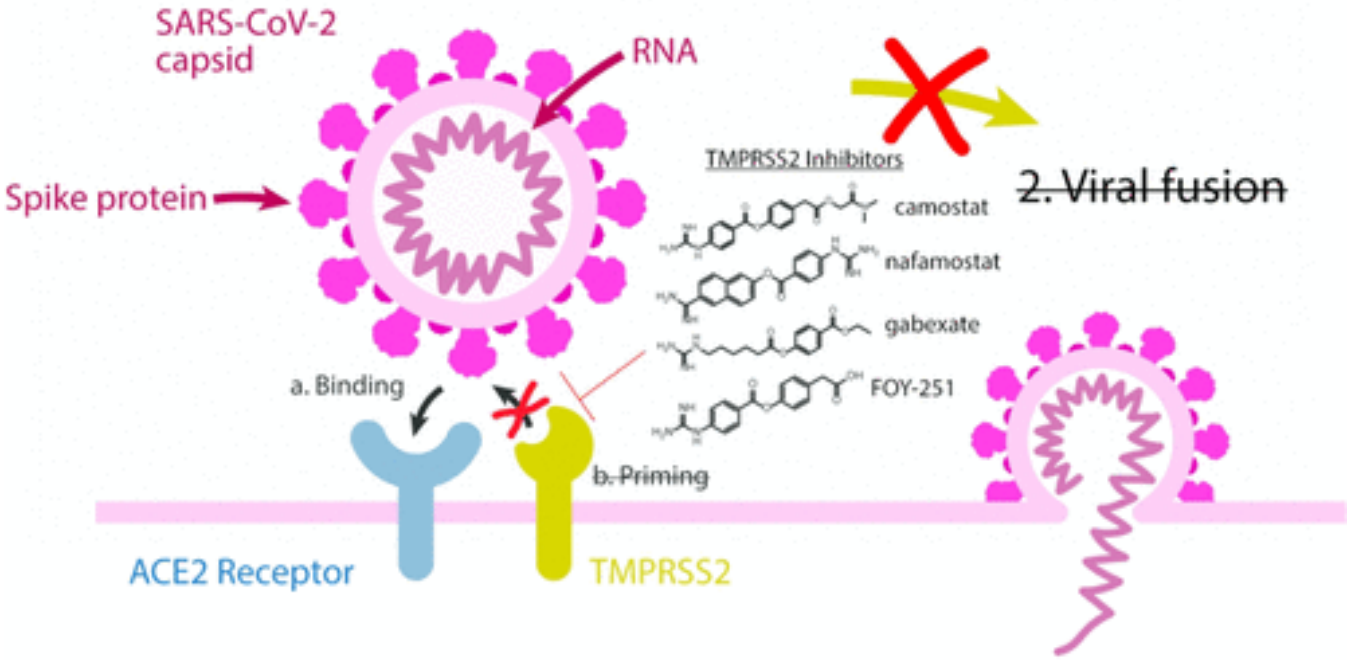
ASCOT
AustralaSian COVID-19 Trial

ASCOT ADAPT Antiviral domain

- Standard supportive care
  - Including steroids where appropriate
- Hydroxychloroquine
- Lopinavir-ritonavir
- Interferon-beta-1a
- Interferon + ribavirin
- Nafamostat

ASCOT
AustralaSian COVID-19 Trial

Nafamostat



- TMPRSS2 has an extracellular protease domain that cleaves the spike protein to initiate membrane fusion.
- Nafamostat is a TMPRSS inhibitor

Shrimp et al, ACS Pharmacol. Transl. Sci. 2020

Potency of Nafamostat

Drug name	IC_{50} in Vero, μM[a]	IC_{50} in Calu-3, μM[b]	Fold change
Nafamostat mesylate	13.88	0.0022	0.00016
Camostat mesylate	>50	0.187	0.00374
Remdesivir	11.41	1.3	0.11

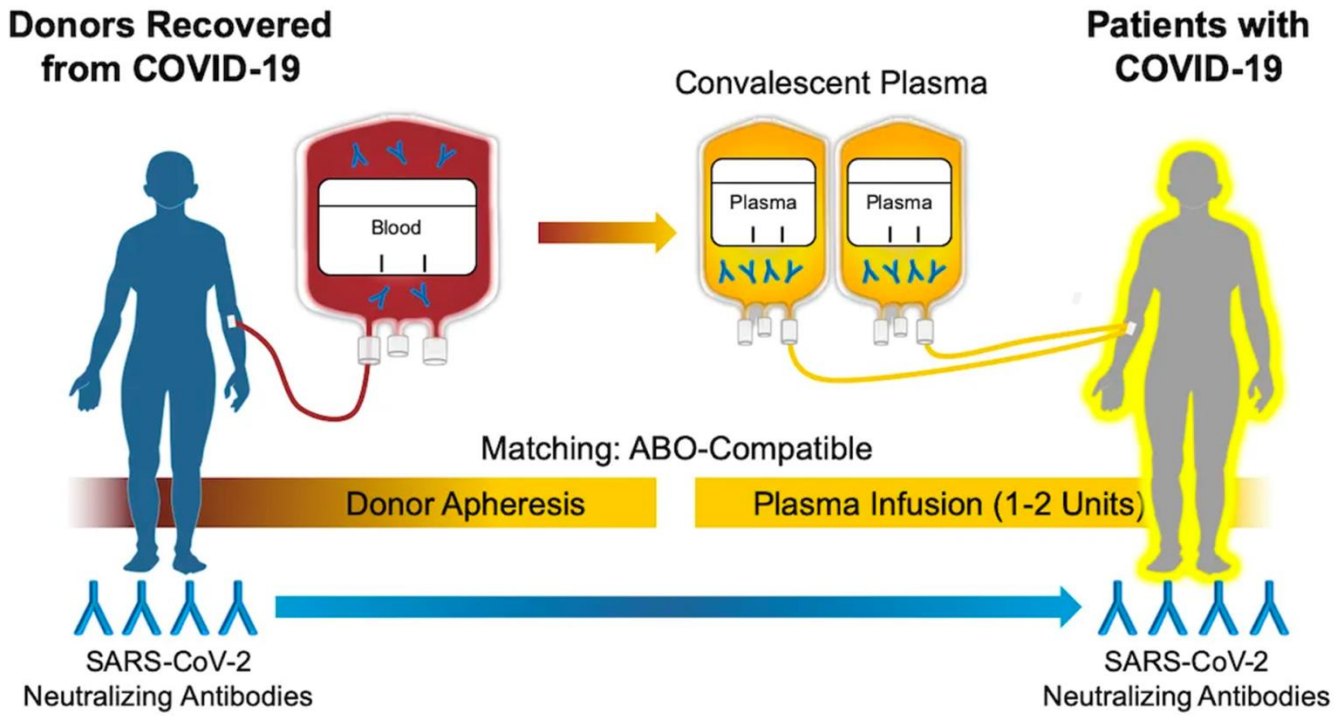
Calu-3 = human lung cell line
Vero = African green monkey kidney cell line

Short $t_{1/2}$ = Constant IV infusion

Ko et al, J Med Virol. 2020

ASCOT ADAPT
Antibody domain

- Convalescent plasma
  - Does neutralising antibody titre matter?



ASCOT ADAPT Anticoagulation domain

- Standard dose thromboprophylaxis
- Intermediate dose thromboprophylaxis
- Standard dose thromboprophylaxis + aspirin

ASCOT
AustralaSian COVID-19 Trial

REMAP-CAP

- Randomised embedded multifactorial adaptive platform study of severe community-acquired pneumonia
- Large international study in NZ, Australia, UK, Europe, Saudi Arabia, US and Canada, led by ANZICS group
- Running for 3 years already prior to SARS-CoV-2 pandemic
- Despite platform already being open, still takes too long to add domains during a pandemic

REMAP-CAP in NZ

- Antiviral domain
  - On hold
- Antibody domain
  - Convalescent plasma vs SOC
- Immune modulation domain
  - Tocilizumab (IL-6 receptor antagonist) vs Anakinra (IL-1 receptor antagonist) vs SOC
- Anticoagulation domain
  - prophylactic vs therapeutic anticoagulation with heparin

Challenging environment

- Pressured environment during pandemic
- Same bureaucratic hurdles to get through
- Politics and social media
- Retracted HCQ article
- Trials reporting by press release, then pre-print of non-peer-reviewed paper, then publication
- Need for a cohesive national approach to COVID research as seen in the UK

Future developments

- Nafamostat/camostat?
- New antiviral agents?
- Monoclonal antibodies?
- Vaccines…

Acknowledgements

- Too many people to fit on a slide!
- The entire ASCOT ADAPT study group, especially Steve Tong, Josh Davis and Justin Denholm
- ASCOT in NZ; Sandy Slow, Tom Hills, Mike Maze, MMCT group
- REMAP-CAP study group, especially Steve Webb, Colin McArthur

The Cure


Monday you can
stay indoors.
Tuesday, Wednesday,
stay indoors.
Thursday stay indoors
instead.
Its Friday, stay indoors.