The Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP CAP) study: rationale and design

Derek C. Angus[1], Scott Berry[2], Roger J. Lewis[2-4], Farah Al-Beidh[5], Yaseen Arabi[6], Wilma van Bentum-Puijk[7], Zahra Bhimani[8], Marc Bonten[7,9], Kristine Broglio[2], Frank Brunkhorst[10], Allen C Cheng[11,12], Jean-Daniel Chiche[13], Menno De Jong[14], Michelle Detry[2], Herman Goossens[15], Anthony Gordon[5], Cameron Green[12], Alisa M. Higgins[12], Sebastian J. Hullegie[7], Peter Kruger[16], Francois Lamontagne[17], Edward Litton[18], John Marshall[8,19], Anna McGlothin[2], Shay McGuinness[12,20,21], Paul Mouncey[22], Srinivas Murthy[23], Alistair Nichol[12,24,25], Genevieve K O'Neill[12], Rachael Parke[20,21,26], Jane Parker[12], Gernot Rohde[27,28], Kathryn Rowan[22], Anne Turner[21], Paul Young[21,29], Lennie Derde[7,30], Colin McArthur[21,31], Steven A. Webb.[12,18,32]

1. The Clinical Research Investigation and Systems Modeling of Acute Illness (CRISMA) Center, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.
2. Berry Consultants, LLC, Austin, Texas, USA.
3. Department of Emergency Medicine, Harbor-UCLA Medical Center, Torrance, California, USA.
4. Department of Emergency Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California, USA.
5. Division of Anaesthetics, Pain Medicine and Intensive Care Medicine, Department of Surgery and Cancer, Imperial College London and Imperial College Healthcare NHS Trust, London, UK.
6. Intensive Care Department, College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, King Abdulaziz Medical City, Riyadh, Saudi Arabia.
7. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands.
8. Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada.
9. Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, the Netherlands.
10. Center for Clinical Studies and Center for Sepsis Control and Care (CSCC), Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany.
11. Infection Prevention and Healthcare Epidemiology Unit, Alfred Health, Melbourne, Victoria, Australia.
12. Australian and New Zealand Intensive Care Research Centre, School of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia.
13. Medical Intensive Care Unit, Hôpital Cochin, Paris Descartes University, Paris, France
14. Department of Medical Microbiology, Amsterdam UMC, University of Amsterdam, the Netherlands.
15. Department of Microbiology, Antwerp University Hospital, Antwerp, Belgium
16. Intensive Care Unit, Princess Alexandra Hospital, Brisbane, Queensland, Australia
17. Université de Sherbrooke, Sherbrooke, Quebec, Canada.
18. School of Medicine and Pharmacology, University of Western Australia, Crawley, Western Australia, Australia.
19. Interdepartmental Division of Critical Care, University of Toronto, Toronto, Ontario, Canada
20. Cardiothoracic and Vascular Intensive Care Unit, Auckland City Hospital, Auckland, New Zealand.
21. Medical Research Institute of New Zealand, Wellington, New Zealand.
22. Clinical Trials Unit, Intensive Care National Audit & Research Centre (ICNARC), London, UK.
23. University of British Columbia School of Medicine, Vancouver, Canada.
24. Department of Anesthesia and Intensive Care, St Vincent's University Hospital, Dublin, Ireland.
25. School of Medicine and Medical Sciences, University College Dublin, Dublin, Ireland.
26. School of Nursing, University of Auckland, Auckland, New Zealand.
27. Department of Respiratory Medicine, University Hospital Frankfurt, Frankfurt, Germany.
28. CAPNETZ Foundation, Hannover, Germany.
29. Intensive Care Unit, Wellington Hospital, Wellington, New Zealand.
30. Intensive Care Center, University Medical Center Utrecht, Utrecht, the Netherlands.
31. Department of Critical Care Medicine, Auckland City Hospital, Auckland, New Zealand.
32. St. John of God Hospital, Subiaco, Western Australia, Australia.

Funding
The Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE) consortium by the European Union, FP7-HEALTH-2013-INNOVATION-1 (#602525), the Australian National Health and Medical Research Council (#APP1101719), the New Zealand Health Research Council (#16/631), and the Canadian Institute of Health Research Strategy for Patient-Oriented Research Innovative Clinical Trials Program Grant (#158584). Original design supported by a development grant from the British Embassy.

Running head REMAP CAP

Word count 4943

Corresponding author
Derek C Angus, MD, MPH
Department of Critical Care Medicine
University of Pittsburgh
3550 Terrace Street, 614 Scaife Hall
Pittsburgh, PA 15261, USA

Email: angusdc@upmc.edu
Tel: +1 412 647 6965
Fax: +1 412 647 5258

Conflict of interest
See submitted ICMJE forms for declared potential conflict of interests.

Abstract

There is broad interest in improved methods to generate robust evidence regarding best practice, especially in settings where patient conditions are heterogenous and require multiple concomitant therapies. Here, we present the rationale and design of a large, international trial that combines features of adaptive platform trials with pragmatic point-of-care trials to determine best treatment strategies for patients admitted to an intensive care unit with severe community-acquired pneumonia (CAP). The trial uses a novel design entitled a randomized embedded multifactorial adaptive platform (REMAP). The design has 5 key features: i.) randomization, allowing robust causal inference; ii.) embedding of study procedures into routine care processes, facilitating enrollment, trial efficiency, and generalizability; iii.) a multifactorial statistical model comparing multiple interventions across multiple patient subgroups; iv.) response-adaptive randomization with preferential assignment to those interventions that appear most favorable, and v.) a platform structured to permit continuous, potentially perpetual enrollment beyond the evaluation of the initial treatments. The trial randomizes patients to multiple interventions within 4 treatment domains: antibiotics, antiviral therapy for influenza, host immunomodulation with extended macrolide therapy, and alternative corticosteroid regimens, representing 240 treatment regimens. The trial generates estimates of superiority, inferiority and equivalence between regimens on the primary outcome of 90-day mortality, stratified by presence or absence of concomitant shock and proven or suspected influenza infection. The trial will also compare ventilatory and oxygenation strategies and has capacity to address additional questions rapidly during pandemic respiratory infections. As of January 2020, REMAP-CAP is approved and enrolling patients in 52 ICUs in 13 countries in 3 continents. Lessons learned from the design and conduct of this trial should aid in dissemination of similar platform initiatives in other disease areas. (NCT02735707)

Take Home Message

Classic trial designs can fail to provide adequately flexible and rapid answers regarding best treatments for complex diseases. The novel REMAP design combines features of Bayesian statistical inference, master protocols, and point-of-care trials to bridge randomized trials with continuous quality improvement, enabling a learning health system. The first example, REMAP CAP, has launched in 3 continents and is learning best treatment options across 240 separate treatment regimens, with the capacity to incorporate additional regimens during pandemics.

Keywords randomized clinical trial; Bayesian adaptive trial; adaptive platform trial; master protocol; community-acquired pneumonia; intensive care

For centuries, how physicians made treatment decisions was largely unmeasured. In the latter half of the 20th century, with greater audit of healthcare delivery, it became apparent that clinical decisions were often made inconsistently and without strong scientific rationale.[1] This observation led to the rise of evidence-based medicine, which rests on the randomized clinical trial (RCT) to generate reliable evidence of treatment effectiveness and the incorporation of that evidence into treatment guidelines. Today, policymakers use compliance with such guidelines as a measure of healthcare quality. However, experts criticize treatment guidelines both because they frequently lack evidentiary support from RCTs and because evidence based on RCTs can often be too simplistic, failing to capture the nuance of individual patient circumstances.[2] In other words, a physician may not follow a guideline because of legitimate concerns regarding best treatment options under conditions of uncertainty and imperfect information. These problems are particularly acute for the management of epidemics, such as outbreaks of novel influenza strains or corona viruses, where there are significant challenges both to the generation and dissemination of high-quality RCT evidence on best practice.

Until recently, there was no easy resolution to this tension. However, the 21st century has ushered in a digital information revolution that is transforming our ability to understand biology and health, to capture rich clinical information, and to design and execute sophisticated RCTs capable both of far more nuanced estimates of treatment effects and of rapid adaptation to epidemic settings. This paper provides a description of one such effort: a large-scale, international RCT using a novel design known as a randomized embedded multifactorial adaptive platform (REMAP)[2] to simultaneously test multiple therapies in patients admitted to the intensive care unit (ICU) with severe community-acquired pneumonia (CAP). We review the study's rationale and design and the potential challenges associated with its implementation.

The decision to study severe community-acquired pneumonia

We focus on severe CAP (of any microbiological aetiology) because it is extremely common, case-fatality is high, the strength of current evidence guiding treatment selection is limited, and there is substantial variation in care. Worldwide, CAP remains one of the largest contributors to death and disability-adjusted life-years lost, ranking high in rich and poor countries alike.[3-5] Severe CAP, the subset at risk for acute hypoxemic respiratory failure, shock, and organ dysfunction, is also the most common cause of sepsis, a frequent reason for ICU admission, and associated with a mortality rate of 20-50%.[6-8] In addition, influenza, a common cause of CAP during seasonal outbreaks, is the most deadly global recurring pandemic infection.[3]

The treatment of patients with severe CAP involves the initiation of multiple therapies, including empiric and specific anti-microbial regimes, host immunomodulation, vital organ support, and numerous

interventions to prevent and minimize complications of critical illness. Several guidelines address the treatment of severe CAP treatment[9] but the specific recommendations frequently lack strong evidence. For example, high quality evidence from RCTs supports only 4 of 44 treatment recommendations in current European guidelines[10-12], 11 of 43 in US guidelines[13], and 7 of 93 Surviving Sepsis Campaign Guidelines.[14] Furthermore, several statements are contradictory across guidelines. Not surprisingly, guideline compliance is poor and care is highly variable[15-18] with potentially adverse consequences.[19-21]

Challenges to the generation of robust and useful evidence for severe CAP

Two particular issues hinder the generation of high-quality clinical evidence for optimal care of patients with severe CAP. First, for endemic CAP, there may be important differences in the effectiveness of specific interventions, or classes of interventions in different subgroups of patients or depending on what other treatments are prescribed. For example, the effect of hydrocortisone may vary depending on whether the aetiology of CAP is viral or bacterial and on whether the patient is in shock. Traditional RCT designs are not well suited for assessing treatment benefits in the setting of complex interactions between treatments and between treatments and patient characteristics. Second, RCTs launched in response to a pandemic form of severe CAP, such as the 2009 H1N1 influenza or 2019 novel corona virus pneumonia outbreaks, even when using 'just-in-time' procedures, are often implemented too slowly to capture an adequate patient sample and generate useful knowledge.[22]

Seeking a new approach to RCT design

Our solution for better evidence generation in severe CAP, the REMAP, combines two study designs: a point-of-care clinical trial (POC-CT) and an adaptive platform trial.[2,23,24] POC-CTs boost greater capture of eligible patients via a clinical moment, or 'point-of-care,' that triggers the clinical trial apparatus.[25,26] A more recent advance in POC-CTs has been to generate a point-of-care alert within the electronic health record.[23] POC-CTs have currently been designed to compare existing approved therapies using large simple, or pragmatic, designs.[27,28]

Rather than testing individual interventions in a single homogeneous disease state and terminating when that task is complete, adaptive platform trials focus on a broader set of disease states, or set of related diseases, and test multiple therapies simultaneously and sequentially. Further, a platform trial is intended to run perpetually, beyond the initial set of treatments, to evaluate an evolving set of treatment strategies over time.[24,29,30] They might therefore be seen more as an experimental platform, rather than a series of experiments. They are adaptive in that they incorporate pre-specified rules to allow for changes in entry criteria, number of study arms, and the proportion randomized to each arm over time. There are multiple

adaptive platform trials that are either enrolling patients or in the implantation stage in many non-critical care disease areas.[31,32]

Description of the REMAP design

REMAP combines a POC-CT and a platform trial to create a design that, like a POC-CT, embeds the trigger for patient recruitment in routine clinical care but then enrolls these patients into an adaptive platform capable of addressing complex study questions regarding multiple therapies in multiple subsets of patients (Figure 1).[2] Embedding the trial promotes capture of the greatest number of patients, which is key to generalizability, arguably essential for response to a pandemics that 'wave' rapidly through different regions[33], and efficient. Embedding also facilitates low operational complexity at the bedside, even though the internal clinical trial machinery may be highly complex. Thus, with REMAP CAP, the intent is to align enrolment and randomization with the ICU admission such that any patient being admitted to the ICU with acute respiratory insufficiency of suspected pulmonary infectious origin will be flagged. Ideally, all eligible patients will be enrolled, generating an automatic custom order sheet relating to all the intervention assignments. Other aspects of the trial, such as ongoing patient monitoring and data collection will also be embedded where possible in routine care. The trial design also coordinates with existing national ICU registries to avoid redundancy in data collection (Appendix).

The trial is 'multifactorial' in that it tests multiple interventions nested within multiple therapeutic domains and within multiple patient strata (Table 1). In REMAP CAP, the initial interventions are grouped under four domains (an antimicrobial domain consisting of 4 alternative antibiotic strategies and two host immunomodulation domains, one testing alternative hydrocortisone dosing regimens, one testing use of extended macrolide therapy, and one evaluating antiviral therapy). Domains relating to oxygen therapy and respiratory support strategies will be added in the future and the intent is also to have domains prepared for specific activation during epidemics. Each qualifying patient is randomly assigned a specific intervention within each domain; the set of assigned interventions defines the treatment regimen. The strata are patient characteristics identifiable at enrolment for which a differential effect on outcome by intervention has been hypothesised. REMAP CAP has commenced with two pre-defined strata: presence or absence of shock and presence or absence of suspected (or proven) influenza infection.

Within each domain, patients are randomly assigned to different interventions. The trial estimates the effectiveness of one intervention over others within a domain, with the capacity to specify whether effects are affected by the choice of other interventions within other domains or by strata. Which treatment-by-treatment interactions and which treatment-by-strata interactions are evaluated are pre-specified. The trial uses response-adaptive randomization (RAR),[34] with the probability of being randomized to any

particular regimen adjusting over time to increasingly favour interventions that are performing better, eventually triggering a stop when a pre-determined threshold is attained (see Figure 1). Colloquially, RAR allows the trial not to 'play-the-winner,' but to 'probably-play-what-is-probably-the-winner.' The RAR rules define separate randomization proportions for each stratum. Thus, for example, if one of the hydrocortisone dosing strategies appears to be beneficial for patients with shock, but of neutral effect for patients without shock, then the RAR rule will increasingly weight the odds towards shock patients receiving that strategy but will maintain equal allocation for non-shocked patients.

Importantly, some interventions may not be relevant or allowable for a patient, either because the patient is eligible for a domain but has a contraindication for a particular intervention within that domain or because the patient is not in a clinical state that requires treatment within that domain. In the first situation, as long as at least two interventions remain available within the domain, the patient will be randomized and the trial tracks which interventions were excluded. An example of the latter situation would be a respiratory support domain restricted to patients requiring mechanical ventilation. If a patient is enrolled in the trial but not intubated, she will be randomized but the assignment will not be revealed until she enters the state (requiring mechanical ventilation) that triggers deployment of the intervention. Similarly, if an enrolled patient had an allergy to penicillins but could still receive cephalosporins, she could be randomized to the remaining arms in the antibiotic domain. In addition to 'patient-level' exclusions, not all domains and interventions may be available at all sites either because a participating site lacks equipoise or for reasons of temporary lack of availability of an intervention. However, the statistical model used for inference is designed to accommodate varying levels of participation.

Other adaptive trial features include the capacity to introduce new strata, domains, and interventions over time. The general rules and operating characteristics of the platform are detailed in the REMAP CAP core protocol and statistical analysis appendix with separate domain-specific and region-specific appendices to describe interventions and regional participating groups. The use of separate appendices permits an efficient, modular structure where any update to the design requires only that the relevant appendix or appendices be added or modified (Figure 2a).

Study sites, patients, and endpoints

Table 1 summarizes key trial features. REMAP CAP is a global program intended to enrol critically ill patients with CAP worldwide (Clinical trials registration #NCT02735707; Universal Trial Number U1111-1189-1653). The trial was launched first in Europe under Work Package #5 of the Platform for European Preparedness Against (Re-)emerging Epidemics (PREPARE) consortium (https://www.prepare-europe.eu/About-us/Workpackages/Workpackage-5) with funding from the European Union. REMAP CAP

has also launched in Australia and New Zealand supported by the ANZICS Clinical Trials Group and in Canada supported by the Canadian Critical Care Clinical Trials Group, with funding from the respective national governments. Together, these programs provide funding for the first 4,000 patients and are anticipated to recruit in 50 sites in Europe, 35 sites in Australia and New Zealand, and 15 sites in Canada. Other regions of the world will join as funding becomes available. Over 300 patients have been randomised into the platform as of December 2019. The trial is overseen by an international trial steering committee. An overview of trial structure is provided in Figure 2b.

To be included, participants must be admitted to the ICU within 48h of hospital admission, be aged $\geq$ 18 years, have CAP by clinical and radiologic criteria,[35] and require respiratory or cardiovascular organ support. Exclusion criteria include healthcare-associated pneumonia, presumption that death is imminent with lack of commitment to full support, and prior participation in REMAP CAP in the last 90 days. There are also domain-specific exclusion criteria described in the Appendices. The primary objective is to determine the effectiveness of different interventions, alone and in combination, for adult patients with severe CAP in decreasing mortality, where the primary endpoint is defined as mortality during the 90 days post-randomization. Secondary objectives are to determine the effects on hospital and ICU length of stay, ventilator and organ failure free days through 28 days, and functional outcomes at day 180.

Initial domains and interventions

Antibiotic domain

Empiric use of a beta-lactam and a macrolide, or a respiratory quinolone alone are both recommended for severe CAP in treatment guidelines.[10,11,36,37] Patients will therefore be randomized (depending on availability and local equipoise) to one of up to three beta-lactam agents (ceftriaxone, piperacillin-tazobactam, and amoxycillin-clavulanate) with a macrolide (azithromycin, clarithromycin or roxithromycin), or to a respiratory quinolone (moxifloxacin or levofloxacin). Patients with known allergies will not be eligible to receive an agent to which they are allergic but will be allocated among all remaining options.

Host immunomodulation with extended macrolide domain

Although macrolide antibiotics are currently recommended for 3-5 days for treatment of CAP,[13] there is some rationale to believe an extended course may be beneficial, in particular because the host response to CAP can be associated with potentially injurious inflammation which, in turn, may be modified through the anti-inflammatory properties of macrolides.[38,39] Therefore, those patients who are randomized

to any of the antibiotic arms that contain a macrolide may simultaneously be randomized to either a traditional standard course (3 to 5 days) of the macrolide or an experimental 14-day course.

Host immunomodulation with corticosteroid domain

Although severe CAP is associated with a profound and potentially detrimental host immune response, successful immune modulation remains elusive. Some benefit with corticosteroids has been reported in vasopressor-dependent septic shock, severe Pneumocystis pneumonia, and late acute respiratory distress syndrome[40-44], but the evidence for the effectiveness of this approach is not conclusive.[45-52] Notably, 2 recent large RCTs reported conflicting results on mortality, though both suggested faster resolution of hemodynamic instability.[53,54] Patients will therefore be randomized to no steroid, hydrocortisone 50 mg IV q6h for 7d (the same strategy tested previously), or to hydrocortisone at the same dose but prescribed only if shock is present and discontinued once shock has resolved. Sites can choose to include any two or all three of these options for patients enrolled at their site, depending on local equipoise. The effect of allocation within the corticosteroid domain will be evaluated separately in patients with or without vasopressor administration at baseline and with or without confirmed influenza infection.

Anti-viral domain

The effectiveness of oseltamivir, as well as other new antiviral agents active against influenza, has not been established in patients who are critically ill. The relatively modest impact of oseltamivir in patients with uncomplicated seasonal influenza further raises uncertainty about the value of this agent in serious infection.[55-57] There is also no consensus regarding appropriate duration of therapy for oseltamivir.[58] Patients will be randomised to no oseltamivir, oseltamivir 75mg q12h for 5 days, or oseltamivir 75mg q12h for 10 days. Only sites that do not use oseltamivir as part of standard care will be encouraged to participate in the no oseltamivir intervention. We intend to add baloxavir, alone and in combination with oseltamivir, if this new antiviral agent becomes more widely available.[59]

Respiratory support domains

Extensive research and international guidelines support the use of lung protection strategies that minimize excessive volume or pressure.[14,60,61] The guidelines are based largely on patients with ARDS and apply to patients with CAP who have ARDS, but whether this approach to ventilation is optimal for patients with CAP who do not have ARDS is unknown. Moreover, observational studies demonstrate poor uptake of guideline-recommended ventilatory strategy with many clinicians opting to personalize ventilatory settings on a patient-by-patient basis.[62] Optimal ventilatory strategy is also complex, involving combinations of tidal

volume, mode (limiting breaths by pressure or volume), PEEP, and the degree and manner by which spontaneous ventilation is permitted.

To commence the process of determining optimal ventilatory strategy for patients with CAP, the ventilation domain will randomize patients to either guideline-recommended care (set tidal volume of 6 ml/kg of ideal body weight and use of a PEEP:FIO_2 table) or clinician-preferred ventilation. The initial phase of the ventilation domain has three goals. First, to determine whether adherence to guideline-recommended care can be achieved in trial patients. Second, to identify testable ventilatory strategies within the spectrum of observed care patterns in the clinician-preferred intervention arm. Third, to identify potential stratification variables such as presence of ARDS, unilateral versus bilateral involvement, PEEP:FIO_2 ratio, and lung compliance.

Oxygenation support is almost universally provided to patients with CAP. However, neither the optimal inspired concentration nor the preferred target for haemoglobin saturation is known, and the infected lung may be particularly sensitive to injury by reactive oxygen species. Observational studies and a small single center RCT suggest that use of a conservative oxygen strategy may be safe and potentially beneficial in pneumonia.[63-65] Some evidence points to improved outcomes with reduced exposure to oxygen in several disease groups, but recent RCTs reported conflicting results.[66-70] An oxygenation strategy domain, harmonized with a planned large-scale trial of general ICU patients, will compare a conservative to liberal approach to oxygenation support.

Adaptation during a pandemic

REMAP-CAP is designed so that, in the event of a pandemic, the platform can adapt to answer time-critical questions regarding optimal treatment for patients who are critically ill due to pneumonia caused by a pandemic organism. This is achieved in several ways. The platform has a 'sleeping' stratum for patients with proven or suspected pandemic infection that will be triggered, on a site-by-site basis, depending on local pandemic infection activity. A pandemic-specific model will be used to test for the effect of different agents and regimens in the pandemic stratum. This pandemic-specific model can use an alternative endpoint, such as a composite of short-term mortality and days alive and out of ICU, and can be updated more frequently to generate and act upon information more rapidly. The pandemic-specific model can incorporate prior data from non-pandemic patients enrolled in the platform prior to the pandemic with regard to all domains that are relevant in both pandemic and interpandemic periods, with consideration of potential interactions specific to the pandemic. In addition, additional domains, such as novel anti-viral therapies, use of immunoglobulin or convalescent sera, or additional host immunomodulation approaches, can be deployed.

Statistical considerations

Most traditional RCTs are analyzed using frequentist statistics, which calculate the probability of seeing patterns in the data from a trial if a hypothesis is true (including patterns not observed). This approach relies on assumptions about frequency distributions of trial results that would arise if the same trial were repeated ad infinitum (hence the term 'frequentist'). Thus, it requires specific sample sizes (the frequency distribution assumptions are for a specific trial of a specific size), which in turn require pre-experiment assumptions regarding plausible effect sizes and outcome rates.[71] Although many clinicians are comfortable with this approach, the pre-trial assumptions are frequently incorrect, and the design lacks the flexibility either to easily address the complex questions more reflective of clinical practice or to make mid-trial corrections when the pre-trial assumptions are wrong without concern that the integrity of the final analysis is violated.

To allow flexibility and yet still generate robust statistical inferences, REMAP CAP relies on an overarching Bayesian, rather than frequentist, framework for statistical inference.[72] A Bayesian approach calculates the probability a hypothesis is true, given the observed data and prior information and beliefs. The advantage of this approach is that, as more data accrue, the probability that a particular treatment is the best can be continually updated (the updated probability is called the posterior probability). REMAP CAP will launch with no prior assumptions regarding which interventions are superior, akin to a typical RCT design. However, at regular intervals, newly accrued data will be analyzed using a pre-specified Bayesian inference model to generate updated Bayesian posterior probability distributions.

Although sample sizes are flexible, the trial nonetheless has rigorous pre-specified elements that frame the design (Figure 1 and Table 1). The initial set of interventions within domains generates 240 regimens. The trial starts with a 2 x 2 structure based on two strata: presence or absence of shock (defined as receiving an infusion of vasoactive medication) and presence or absence of influenza infection, as assessed at the time of enrolment. The goal is to generate, for each domain, estimates of the difference in effect of any one intervention over another. Depending on the domain, this estimate may be conditional on stratum and intervention assignment within the other domains. The Bayesian inference model estimates the probability of superiority for each randomly-assigned treatment regimen for patients in one or more strata (which strata are applied in each domain varies but is pre-specified), conditional on allocation status in other domains (the domains for which intervention-by-intervention interaction is evaluated is pre-specified), after adjustment for age group, (18-40, 41-65, 66-75, and >76y), country (site, nested in country), severity of illness, and time period (in 13 week blocks to control for potential temporal drift). The model includes terms for the common effect of each intervention and selected intervention-by-intervention and intervention-by-stratum interactions for all 4 starting domains.

The model also accounts for patients who are ineligible for one or more interventions within a domain or for an entire domain. The starting conditions (prior assumptions set before data are accrued) for all terms in the model are specified in the Statistical Appendix. Non-informative prior probabilities are assigned to any direct intervention effects. Other terms (age, region, and interactions, etc.) are weakly assumed to have the potential to affect mortality but are set such that the priors can be quickly overwhelmed by the data.

We begin with a run-in period during which randomization is balanced across interventions. Thereafter, following regular intervals, the Bayesian inference model is re-estimated with updated trial data. The updated posterior probabilities determine the RAR probabilities and can trigger a trial conclusion regarding the effect of an intervention within one or more strata. We set the superiority threshold as $\geq$0.99 posterior probability that an intervention lowers mortality, the equivalence threshold as $\geq$0.90 posterior probability that the odds ratio for mortality lies between 0.8 and 1.2, and the inferiority threshold as <0.01 posterior probability that the intervention is superior. All these design thresholds were selected before the trial commenced based on extensive Monte Carlo simulations to explore the trial's operating characteristics (Appendix).

Advantages of the REMAP design

The REMAP design offers four broad advantages: efficient use of the available data, improved safety for participants, reduced down-time between trials, and enhanced knowledge translation (Table 2 and Figure 3). Three aspects help with efficiency. First, testing multiple interventions simultaneously allows more questions to be evaluated and avoids requiring a separate control group for every two-way comparison. Second, RAR and predetermined thresholds reduce or cease allocation of subjects to arms that are inferior or otherwise no longer of interest, increasing power to differentiate between the remaining arms. Third, under the multifactorial design, an overarching model to drive RAR and stopping rules can integrate information on treatment effects from all patient strata. In addition, because randomization continues until pre-determined superiority, equivalence or inferiority thresholds are met, the platform avoids terminating a domain with indeterminate results.

The REMAP design enhances safety because the adaptive rules not only promote greater allocation to better performing interventions but, by corollary, limit exposure to the harm associated with poorly performing interventions and regimens. Although individuals may still be assigned to interventions that perform poorly, their odds of being exposed to such a factor are reduced and their odds of receiving the better factor are improved over time. Thus, if the trial is testing therapies that affect outcome but for which

the conventional wisdom is equipoise, and exposure outside the trial is balanced, then the patient is, on average, safer in the trial than out of it.

There is considerable downtime between traditional one-at-a-time trials, which is costly and burdensome for clinical trial units and contributes to delay in the acquisition of medical knowledge, or even failure to accrue knowledge in situations like epidemics. Because REMAP is a single perpetual platform trial, this downtime is largely eliminated. Instead, new interventions or domains of interest are simply added to the on-going platform through protocol appendix amendments. Finally, when fully embedded in an entire healthcare system, REMAP becomes a platform for continuous quality improvement, where all patients are flagged at admission, and assigned therapies proportional to the level of certainty that these therapies are optimal.

Ethical approval and trial oversight

Human subjects protection in REMAP CAP falls under the same review process as any other RCT. Local regulations govern requirements for consent, with particular consideration that several comparisons are of alternative standard care options and most are deployed emergently, when the patient may be unable to give consent. The current protocol, with the current suite of domains and interventions, is approved in Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, United Kingdom, all with deferred consent models for domains which test only existing options within standard care. The rules for changing the odds of randomization and for stopping portions of the trial are pre-determined and executed automatically. However, they are overseen by an independent Data Safety Monitoring Board (DSMB), which has the capacity to override algorithm decisions in the event that the proposed rule is deemed no longer acceptable from an ethical, safety, or scientific point of view. When a threshold is passed and conclusions within the trial are drawn, that portion of the trial will be reported via publication and usual routes of dissemination. New interventions and domains are introduced to the platform via protocol modifications, with approval of relevant ethics boards and involvement of the DSMB.

Logistical considerations

Although the trial machinery is very complex in comparison to a typical parallel group RCT, that complexity is made as invisible as possible to the clinical sites. The largest logistical challenges relate to embedding the trial into routine care, which requires identification of the clinical 'point-of-care,' mechanisms for notification to the central coordinating center in as automated a fashion as possible, execution of relevant consenting procedures, and the ability of the coordinating center to feedback the

order set reflective of the randomly assigned regimen in a timely fashion. Key to this success includes the use of web-based software designed and tailored to interface with local clinical and research-related processes. For example, the software is easily accessed by any treating clinician and, through efficient prompting of a short list of clinical questions, automatically determines eligibility for the platform, domains, and individual interventions, and in turn generates the patient's treatment regimen.

Discussion

Although we outlined numerous potential advantages of the REMAP trial design, we recognize there are considerable barriers. First, the ability to effectively embed the trial will require a new paradigm for engagement between clinicians and researchers in many ICU settings. Such close partnership has existed in other fields. For example, there are many oncology trial networks that seek to enroll all eligible patients in an RCT. Similarly, the large acute myocardial infarction trials that began in the 1980s and 1990s relied on extremely high capture rates. In critical care, the recent large fluid resuscitation trials by the ANZICS CTG also achieved extremely high capture rates,[73,74] in part by generating a culture that any patient requiring resuscitation prompted consideration by the clinical team to enroll the patient in the trial. All these efforts shared a common commitment to ensuring adequate education, engagement and attention to practical and logistic details at participating sites.

One potential concern with the design will be the use of Bayesian inference and flexible sample sizes. For example, Bassler et al articulated a view that early stopping leads to over-inflation of treatment effects.[75] However, trials that stop early for superiority are trials that, on average, generate overestimates of treatment effect, even if they run to term (just as trials that do not trigger early stopping, on average, underestimate the true effect).[76] Assuming appropriate rules are in place, early stopping does not, in and of itself, lead to significant overestimation of treatment effect, nor does it inflate the chance of type one error. Thus, the best estimate of treatment effect is the summary of all trial results. If, however, REMAP generates an early large superiority signal for a particular intervention, and there are no other trials testing the same question, then it would be appropriate to consider the true effect size as likely somewhat smaller.[77]

Finally, there will be legitimate issues regarding the reporting of REMAP trials, and indeed for all platform trials. For example, REMAP conclusions are triggered when a posterior probability exceeds a stopping threshold for a portion of the trial. However, that probability is generated from a model that incorporates all the data from the entire trial. It is unclear whether the report should thus include information on all patients enrolled thus far, including those whose data are still contributing to ongoing questions, or to some portion of the patients most directly relevant to the portion of the trial that has stopped.

In summary, we presented what we believe to be a novel class of study design with an example tailored specifically to generate high-quality evidence on the effectiveness of optimal therapies for severe CAP. The design allows generation of information that is both broad, in that it reflects practice in the 'real-world' and narrow, in that it generates precision estimates for patients with particular clinical features. The platform is also capable of incorporating new study arms, making it ideal for the generation of treatment effectiveness in epidemic situations. The design nonetheless will face considerable challenges. However, with funding to launch REMAP CAP on three continents, we expect many lessons will be learned, which will hopefully drive broader and more efficient use of the REMAP approach across other clinical domains.

References

1. Cochrane AL. *Effectiveness and efficiency: random reflections on health services.* Vol 900574178: Nuffield Provincial Hospitals Trust London; 1972.

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

3. Musher DM, Thorner AR. Community-acquired pneumonia. *N Engl J Med.* 2014;371(17):1619-1628.

4. Bjerre LM, Verheij TJ, Kochen MM. Antibiotics for community acquired pneumonia in adult outpatients. *Cochrane Database Syst Rev.* 2009(4):CD002109.

5. Singanayagam A, Chalmers JD, Hill AT. Severity assessment in community-acquired pneumonia: a review. *QJM.* 2009;102(6):379-388.

6. Alvarez-Lerma F, Torres A. Severe community-acquired pneumonia. *Curr Opin Crit Care.* 2004;10(5):369-374.

7. Leroy O, Santre C, Beuscart C, et al. A five-year study of severe community-acquired pneumonia with emphasis on prognosis in patients admitted to an intensive care unit. *Intensive Care Med.* 1995;21(1):24-31.

8. Sligl WI, Marrie TJ. Severe community-acquired pneumonia. *Crit Care Clin.* 2013;29(3):563-601.

9. Woodhead M BF, Ewig S, Garau J, Huchon G, Leven M, et al. . Guidelines for the management of adult lower respiratory tract infections-full version. *Clin Microbiol Infect.* 2011;17(Suppl 6):E1-59.

10. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections--full version. *Clin Microbiol Infect.* 2011;17 Suppl 6:E1-59.

11. Lim WS, Baudouin SV, George RC, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax.* 2009;64 Suppl 3:iii1-55.

12. Eccles S PC, Higgins B, Woodhead M. . Diagnosis and management of community and hospital aqcquied pneumonia in adults: summary of NICE guidance. *BMJ.* 2004;349:g6722.

13. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis.* 2007;44 Suppl 2:S27-72.

14. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Medicine.* 2017;43(3):304-377.

15. Bodi M, Rodriguez A, Sole-Violan J, et al. Antibiotic prescription for community-acquired pneumonia in the intensive care unit: impact of adherence to Infectious Diseases Society of America guidelines on survival. *Clin Infect Dis.* 2005;41(12):1709-1716.

16. Frei CR, Attridge RT, Mortensen EM, et al. Guideline-concordant antibiotic use and survival among patients with community-acquired pneumonia admitted to the intensive care unit. *Clin Ther.* 2010;32(2):293-299.

17. Shorr AF, Bodi M, Rodriguez A, Sole-Violan J, Garnacho-Montero J, Rello J. Impact of antibiotic guideline compliance on duration of mechanical ventilation in critically ill patients with community-acquired pneumonia. *Chest.* 2006;130(1):93-100.

18. McCabe C, Kirchner C, Zhang H, Daley J, Fisman DN. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. *Arch Intern Med.* 2009;169(16):1525-1531.

19. McCabe C KC, Zhang H, Daley J, Fishmand DN. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. *Arch Intern Med.* 2009;169(16):1525-1531.

20. Mortensen EM, Restrepo M, Anzueto A, Pugh J. Effects of guideline-concordant antimicrobial therapy on mortality among patients with community-acquired pneumonia. *Am J Med.* 2004;117(10):726-731.

21. Mortensen EM, Restrepo MI, Anzueto A, Pugh J. The impact of empiric antimicrobial therapy with a beta-lactam and fluoroquinolone on mortality for patients hospitalized with severe pneumonia. *Crit Care.* 2006;10(1):R8.

22. Dodd LE, Proschan MA, Neuhaus J, et al. Design of a randomized controlled trial for Ebola virus disease medical countermeasures: PREVAIL II, the Ebola MCM study. *Journal of Infectious Diseases.* 2016;213(12):1906-1913.

23. Fiore LD, Brophy M, Ferguson RE, et al. A point-of-care clinical trial comparing insulin administered using a sliding scale versus a weight-based regimen. *Clinical trials.* 2011;8(2):183-195.

24. Adaptive Platform Trials Coalition. Adaptive platform trials: definition, design, conduct and reporting considerations. *Nature Reviews Drug Discovery.* 2019;18(10):797-807.

25. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med.* 1993;1993(329):673-682.

26. Wilcox R, Olsson C, Skene A, et al. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction: Anglo-Scandinavian Study of Early Thrombolysis (ASSET). *The Lancet.* 1988;332(8610):525-530.

27. Diuretic Comparison Project (DCP). https://clinicaltrials.gov/ct2/show/NCT02185417. Accessed January, 2020.

28. The ADAPTABLE trial. https://clinicaltrials.gov/ct2/show/NCT02697916. Accessed January, 2020.

29. Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. *JAMA.* 2015;313(16):1619-1620.

30. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *The New England Journal of Medicine.* 2017;377(1):62-70.

31. Barker A, Sigman C, Kelloff G, Hylton N, Berry D, Esserman L. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. *Clinical Pharmacology & Therapeutics.* 2009;86(1):97-100.

32. Park JW, Liu MC, Yee D, et al. Adaptive randomization of neratinib in early breast cancer. *New England Journal of Medicine.* 2016;375(1):11-22.

33. Webb SA, Pettila V, Seppelt I, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *The New England Journal of Medicine.* 2009;361(20):1925-1934.

34. Viele K, Broglio K, McGlothlin A, Saville BR. Comparison of methods for control allocation in multiple arm studies using response adaptive randomization. *Clinical Trials.* 2020;17(1):52-60.

35. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community acquired pneumonia. *N Engl J Med.* 1997;336:243-250.

36. Wiersinga WJ, Bonten MJ, Boersma WG, et al. SWAB/NVALT (Dutch Working Party on Antibiotic Policy and Dutch Association of Chest Physicians) guidelines on the management of community-acquired pneumonia in adults. *Neth J Med.* 2012;70(2):90-101.

37. Eccles S, Pincus C, Higgins B, Woodhead M. Diagnosis and management of community and hospital acquired pneumonia in adults: summary of NICE guidance. *BMJ.* 2014;349:g6722.

38. Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. *Clinical microbiology reviews.* 2010;23(3):590-615.

39. Rubin BK, Druce H, Ramirez OE, Palmer R. Effect of clarithromycin on nasal mucus properties in healthy subjects and in patients with purulent rhinitis. *American journal of respiratory and critical care medicine.* 1997;155(6):2018-2023.

40. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *BMJ.* 2004;329(7464):480.

41. Briegel J, Jochum M, Gippner-Steppert C, Thiel M. Immunomodulation in septic shock: hydrocortisone differentially regulates cytokine responses. *J Am Soc Nephrol.* 2001;12 Suppl 17:S70-74.

42. Jantz MA, Sahn SA. Corticosteroids in acute respiratory failure. *Am J Respir Crit Care Med.* 1999;160(4):1079-1100.

43. Keh D, Boehnke T, Weber-Cartens S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med.* 2003;167(4):512-520.

44. Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest.* 2007;131(4):954-963.

45. Chen Y, Li K, Pu H, Wu T. Corticosteroids for pneumonia. *Cochrane Database Syst Rev.* 2011(3):CD007720.

46. De Pascale G, Bello G, Antonelli M. Steroids in severe pneumonia: a literature review. *Minerva Anestesiol.* 2011;77(9):902-910.

47. Gorman SK, Slavik RS, Marin J. Corticosteroid treatment of severe community-acquired pneumonia. *Ann Pharmacother.* 2007;41(7):1233-1237.

48. Lamontagne F, Briel M, Guyatt GH, Cook DJ, Bhatnagar N, Meade M. Corticosteroid therapy for acute lung injury, acute respiratory distress syndrome, and severe pneumonia: a meta-analysis of randomized controlled trials. *J Crit Care.* 2010;25(3):420-435.

49. Povoa P, Salluh JI. What is the role of steroids in pneumonia therapy? *Curr Opin Infect Dis.* 2012;25(2):199-204.

50. Salluh JI, Soares M, Coelho LM, et al. Impact of systemic corticosteroids on the clinical course and outcomes of patients with severe community-acquired pneumonia: a cohort study. *J Crit Care.* 2011;26(2):193-200.

51. Blum CA, Nigro N, Winzeler B, et al. Corticosteroid treatment for community-acquired pneumonia--the STEP trial: study protocol for a randomized controlled trial. *Trials.* 2014;15:257.

52. Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA.* 2015;313(7):677-686.

53. Venkatesh B, Finfer S, Cohen J, et al. Adjunctive Glucocorticoid Therapy in Patients with Septic Shock. *N Engl J Med.* 2018;378(9):797-808.

54. Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. *N Engl J Med.* 2018;378(9):809-818.

55. Dobson J, Whitley R, Pocock S, Monto A. Oseltamivir treatment for influenza in adults: A meta-analysis of randomised controlled trials. *Lancet.* 2015;385.

56. Ebell MH. WHO downgrades status of oseltamivir. *BMJ.* 2017;358:j3266.

57. Butler CC, Van Der Velden AW, Bongard E, et al. Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial. *The Lancet.* 2020;395(10217):42-52.

58. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2019;68(6):e1-e47.

59. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. *N Engl J Med.* 2018;379(10):913-923.

60. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. . *N Engl J Med.* 2000;342(18):1301-1308.

61. Fan E, Del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med.* 2017;195(9):1253-1263.

62. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA.* 2016;315(8):788-800.

63. Kilgannon JH, Jones AE, Shapiro NI, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA.* 2010;303(21):2165-2171.

64. Girardis M, Busani S. Oxygen Supplementation Among Patients in the Intensive Care Unit. *JAMA.* 2017;317(6):647-648.

65. Girardis M, Busani S, Damiani E, et al. Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit: The Oxygen-ICU Randomized Clinical Trial. *JAMA.* 2016;316(15):1583-1589.

66. Chu DK, Kim LHY, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet.* 2018;391(10131):1693-1705.

67. The ICU-Rox Investigators, the Australia, New Zealand Intensive Care Society Clinical Trials Group, et al. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. *The New England Journal of Medicine.* 2019:10.1056/NEJMoa1903297.

68. The LOCO2 Investigators. Liberal or conservative oyxgenation in acute respiratory distress syndrome. *N Engl J Med.* 2020.

69. Angus DC. Oxygen Therapy in the Critically Ill. *N Engl J Med.* 2020.

70. Young P, Mackle D, Bellomo R, et al. Conservative oxygen therapy for mechanically ventilated adults with sepsis: a post hoc analysis of data from the intensive care unit randomized trial comparing two approaches to oxygen therapy (ICU-ROX). *Intensive Care Med.* 2020;46(1):17-26.

71. Altman DG. Statistics and ethics in medical research: III How large a sample? *British medical journal.* 1980;281(6251):1336.

72. Berry DA. Bayesian clinical trials. *Nature Reviews Drug Discovery.* 2006;5(1):27-36.

73. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med.* 2004;350(22):2247-2256.

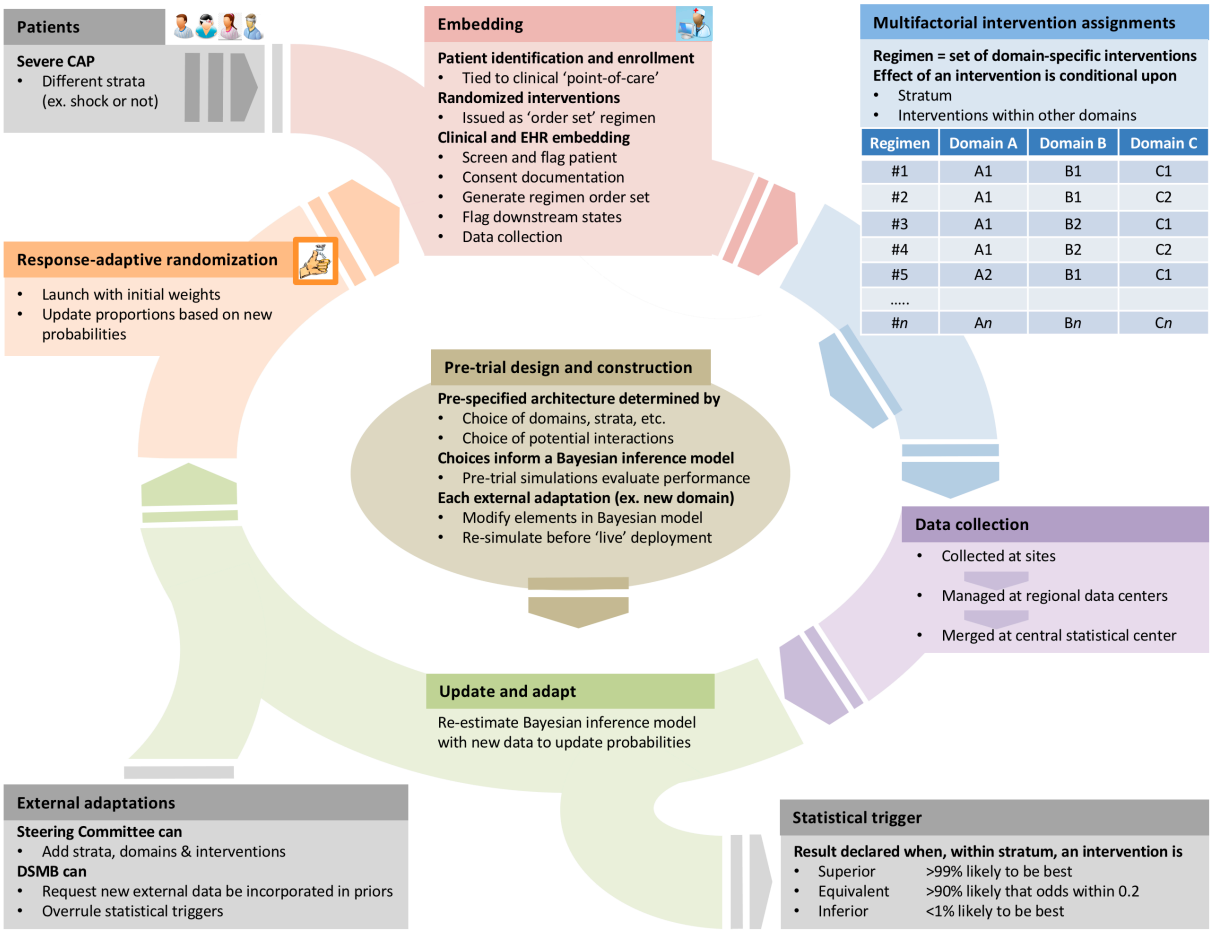
74. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med.* 2012;367(20):1901-1911.

75. Bassler D, Briel M, Montori VM, et al. Stopping Randomized Trials Early for Benefit and Estimation of Treatment Effects: Systematic Review and Meta-regression Analysis. *JAMA.* 2010;303(12):1180-1187.

76. Goodman S, Berry D, Wittes J. Bias and trials stopped early for benefit. *JAMA.* 2010;304(2):156-159.

77. Ellenberg SS, DeMets DL, Fleming TR. Bias and trials stopped early for benefit. *JAMA.* 2010;304(2):156-159.

Figure 1. Schematic of the REMAP CAP design



Pre-trial design and construction. The trial is designed by first specifying broad questions regarding the target population, potentially important subgroups, and the nature and type of interventions to be tested. Using an initial set of interventions, ordered within domains, and combined into regimens, an overarching Bayesian inference model is constructed, and Monte Carlo simulations of how the trial might unfold under alternative 'truths' regarding treatment effects, including heterogeneity of treatment effect across subgroups and treatment-by-treatment interactions.

R

Randomization. Once the design is specified, sites are recruited and trained, appropriate oversight and approval is obtained, and all study execution procedures are deployed, the study launches. The trial begins by randomizing patients with fixed allocations to each treatment arm, proportional to the number of arms. Later, randomization weights are adjusted based on updated probabilities from the Bayesian inference model.

E

Embedding. A key element of the design is tight integration with clinical operations, including using a clinical 'moment', or 'point-of-care' to flag and enroll patients and to deliver the treatment regimen as an 'order set'. Ideally, embedding will take advantage of electronic health record data, not only to help flag and enroll patients, but to deliver patient order sets and to facilitate on-going monitoring and data collection.

M

Multifactorial intervention assignments. The treatment regimens themselves are assigned as a regimen, containing each randomized intervention within each domain. In settings with standard ICU order sets, the regimen would ideally be generated automatically, with inclusion of standard non-randomized ICU care elements as well as those randomized items that are part of REMAP CAP.

A

Adaptation. The heart of the trial is the monthly update of the Bayesian inference model. Each month, the CSC runs a MCMC program using the updated trial data to generate an updated posterior probability for all trial outcomes. If the model generates a probability that has crossed a predetermined threshold, it triggers a platform conclusion. Otherwise, the probabilities are used to update the randomization weights.

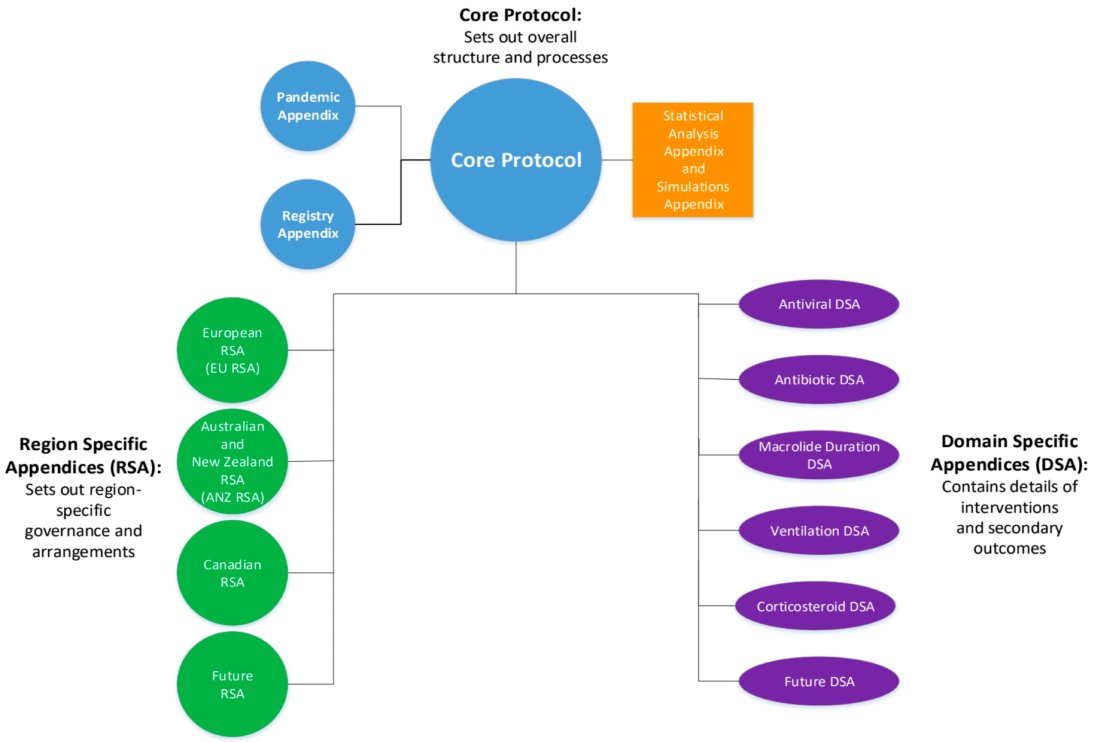
P

Platform. The entire trial is envisioned, like all adaptive platform trials, as a learning engine that can test multiple interventions both in parallel and sequentially. Thus, the focus is on the condition, CAP, itself, and not on any particular intervention. This approach allows a standard approach for enrollment and data collection to be built once and then run perpetually, providing numerous efficiencies.

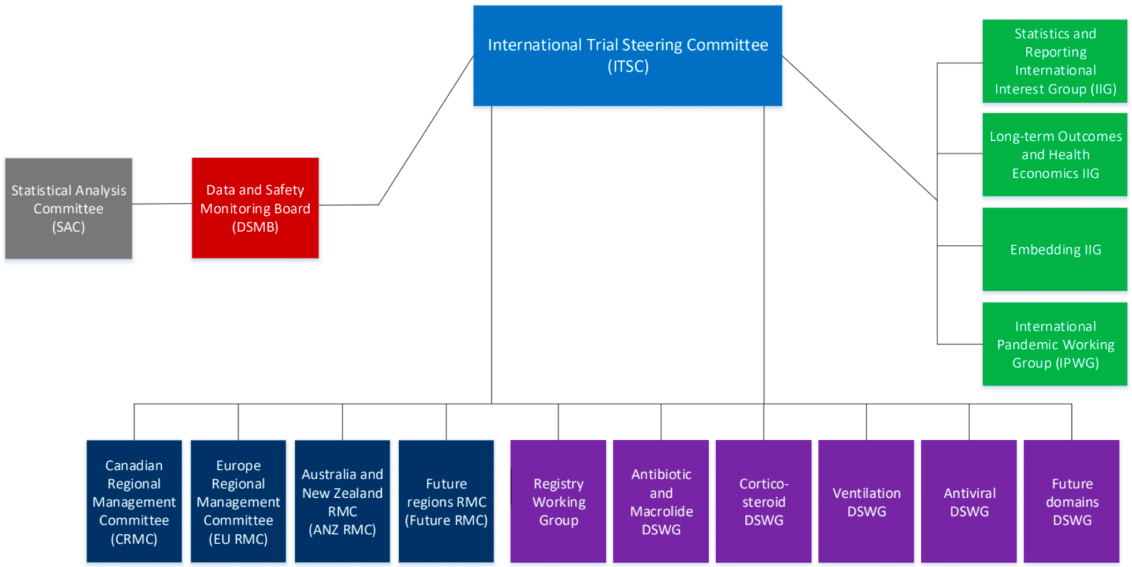
Data collection. Data, ideally via the EHR, is uploaded to regional coordinating centers (RCCs), responsible for local data management and audit and feedback of sites. The RCCs forward data to the central statistical center (CSC).

Figure 2. Overview of the REMAP CAP documentation and oversight

A

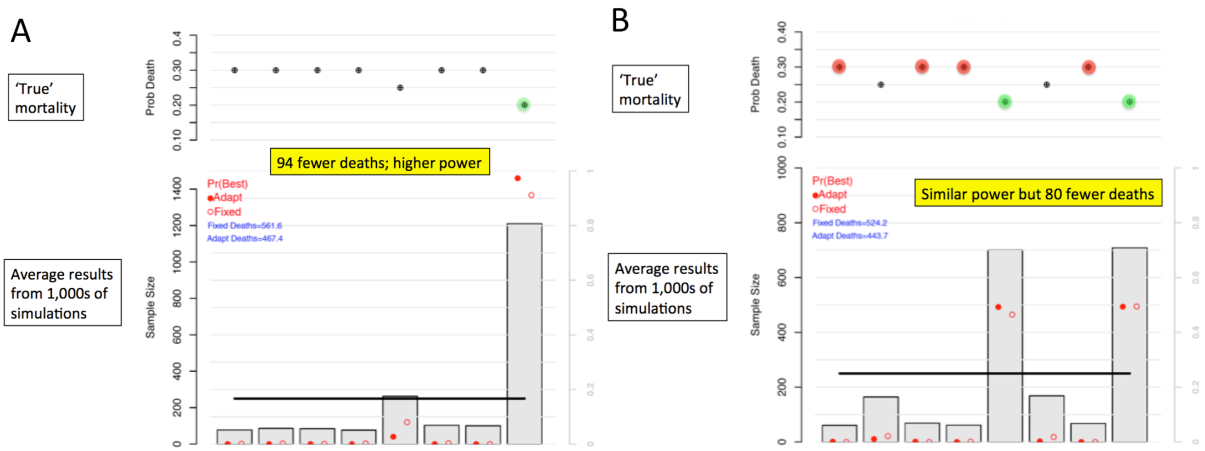


B



Panel A – Structure of the REMAP CAP protocol and appendix documents. Panel B – Organogram of the REMAP CAP oversight.

Figure 3. Trial simulations comparing REMAP to traditional RCT designs



The operating characteristics of alternative study designs are evaluated by running a Monte Carlo program, which randomly draws trial samples from simulated populations with predetermined characteristics (alternative 'truths' about the true yet unknown effect of an intervention or regimen in a population). Each simulated trial accrues patients one at a time until a sample size of 2,000. The simulated trials are repeated 10,000-fold and the summary of all trials under each simulated scenario provides estimates of average trial performance. In all instances, the simulations are of trials testing 8 regimens, consisting of 3 domains with 2 interventions in each domain ($2^3 = 8$ regimens). Results are presented for a comparison of a standard trial design, with equal allocation to each arm, versus a REMAP design, using response-adaptive randomization (RAR) to preferentially assign patients over time to better performing arms. Sample size (primary y-axis) is 250 per arm for the standard design (represented by a black horizontal line) and gray bars for the REMAP design. Probability of superiority (a proxy for power, secondary y-axis) is represented as an open red circle for the standard design and a solid red circle for the REMAP design. The predetermined characteristics of the underlying simulated population are represented in the upper portion of each panel. Panel A summarizes results under a simulated truth where regimen #8 is superior, regimen #5 is second best, and all others are inferior but equivalent. Panel B summarizes results where regimens #5 and #8 are equally good but regimens #1, #3, #4, and #7 are harmful with respect to regimens #2 and #6. In both scenarios, power is similar or superior with the REMAP design yet, because RAR minimizes exposure to arms performing less well, results are generated with fewer deaths.

Table 1. Summary of REMAP CAP features

Feature		
Patients		
Entry criteria	Inclusion criteria	• Admitted to ICU within 48h of hospital admission • Age ≥18y • CAP by clinical and radiologic criteria • Requiring respiratory (non-invasive or invasive ventilation) or cardiovascular (inotropes/vasopressors) support
	Exclusion criteria	• Healthcare-associated pneumonia • Imminent death and no commitment to full active treatment • Prior enrollment in REMAP CAP in the last 90 days
Stratum	Definition	A patient characteristic defined at enrollment used for the generation of specific treatment estimates
	Starting strata	• Presence of shock or not (defined as hypotension or vasopressor requirement after volume resuscitation) • Presence of suspected or proven influenza infection or not
State	Definition	A clinical state that triggers a specific domain
	Example	Mechanical ventilation
	Operationalization	If a domain is only active for patients who enter a state (either at enrollment or later), the patient is randomized to an intervention within that domain but the intervention is only revealed when the patient enters the state. Estimates of intervention effects within a state-specific domain are only generated for those who enter the state.
Sites and regions		
Starting conditions		The study launches at 50 hospitals in Europe, 35 sites in Australia and New Zealand, and 12 sites in Canada
Future additions		Expansion in United States, Brazil, and Saudi Arabia is under discussion. Long-term planning includes other regions.
Interventions		
Nomenclature	Intervention	A treatment being tested in REMAP CAP
	Domain	A specific set of competing alternative interventions within a common clinical mode, which, for the purposes of the platform, are mutually exclusive and exhaustive.
	Regimen	The combination of assigned interventions across domains
Starting conditions		The trial launches with 4 domains. **Antibiotics** • Ceftriaxone plus macrolide • Piperacillin-tazocin plus macrolide • Amoxycillin-clavulanate plus macrolide • Respiratory quinolone **Immunomodulation with an extended macrolide** • Standard course (3-5 days) • Extended macrolide (14 days) **Immunomodulation with hydrocortisone** • No corticosteroid • Shock-dependent hydrocortisone • Hydrocortisone (7-day course) **Antiviral agents active against influenza** • No antiviral agent • Oseltamavir (5 days) • Oseltamavir (10-day course) Patients can be ineligible for randomization within a domain (e.g., the antiviral domain is only active for those within the influenza stratum). Thus, the trial launches with 240 potential regimens (adding 'not eligible' as an option in each domain, # regimens = 5 antibiotic x 3 extended macrolide x 4 steroid x 4 anti-viral = 240).
Future additions		2 additional domains (ventilator support and oxygen management) will be added shortly. The **ventilator support** domain will be restricted to the **state** of mechanical ventilation. Interventions to be tested within this state-specific domain will be guideline-recommended ventilation and clinician-preferred ventilation. The **oxygen management** will compare 2 interventions (usual oxygen titration versus conservative oxygen titration). This domain will be eligible to all patients. Once these domains launch, each with 2 options plus 'not eligible', the number of regimens becomes 240 x 3 x 3 = 2160 regimens.

Table 1 [continued]. Summary of REMAP CAP features	
Embedding	
Description	To ensure capture of all possible patients, streamline integration with clinical care, and reduce study costs, the study has several features that embed it in clinical practice. Ideally, these embedded strategies are built through integration between REMAP CAP trial machinery and usual clinical processes. Strategies include: • Triggering of patient identification and enrollment from a clinical 'point-of-care'. • Verification of eligibility, documentation of consent, and enrollment activation via software interface. • Generation of stratum-specific randomly-assigned REMAP CAP regimen as 'order set'. • Intent to embed, where appropriate, within the electronic health record
Endpoints	
Primary endpoint	• All-cause mortality at 90 days.
Secondary endpoints	• ICU mortality • ICU length of stay • Ventilator-free days* • Organ failure free days* • Proportion of intubated patients receiving tracheostomy • Domain-specific end-points
Statistical methods	
Overview	The trial is built on a Bayesian inference framework. After an initial run-in period, a pre-specified Bayesian inference model is updated each month using the latest trial data to generate updated posterior probabilities of death for each patient regimen-by-stratum group, and hence the probability that any one intervention (or regimen) differs from any other. The model output is used both to update the randomization weights for on-going random assignments and to trigger thresholds for superiority, equivalence, and inferiority.
Multifactorial Bayesian inference model	The model predicts the primary endpoint rate for each patient regimen-by-stratum group, conditional upon patient age; trial site and region; and time era. Terms are included for intervention-by-intervention and intervention-by-stratum interactions and for patients who are ineligible for either an intervention or a domain. The model is also configured in advance for the incorporation of state-specific domains (e.g., ventilator support).
Response-adaptive randomization	The posterior probabilities from the Bayesian inference model are incorporated into an algorithm that provides updated randomization proportions to each regimen by stratum. This algorithm adjusts for sample size to avoid large, potentially spurious changes. Consequently, interventions that are faring well will be randomly assigned more commonly and those faring less well will be assigned less commonly.
REMAP CAP statistical conclusions	When an updated probability triggers a threshold, results are communicated to the DSMB and TSC for public release and decisions regarding on-going treatment assignment.
Superiority	>99% probability that an intervention is superior to alternatives in a domain within one or more strata
Equivalence	>90% probability that odds of death for 2 interventions differ by <0.2
Inferiority	<1% probability that an intervention is superior in a domain
Operating characteristics	All trial parameters were tested through extensive Monte Carlo simulations of anticipated trial performance under different scenarios (Appendix).

Table 2. REMAP design advantages

	Efficient use of information	Safety of trial participants	Avoiding trial down-time	Fusing research with care	Determining optimal disease management	Learning healthcare system
Multifactorial	✓		✓	✓	✓	
Response Adaptive Randomization	✓	✓		✓		✓
Embedding				✓		✓
Frequent adaptive analyses	✓	✓			✓	✓
Analysis by stratum/subgroup	✓	✓			✓	
Evaluation of interaction		✓			✓	
Substitution of new interventions	✓		✓		✓	