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 4422

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 was approved and enrolling patients in 52 ICUs in 13 countries in 3 continents. In February, it transitioned into pandemic mode with several design adaptations for COVID-19 disease. 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, -, has launched in 3 continents, was learning best treatment options across 240 separate treatment regimens, and has rapidly adapted to incorporate additional regimens during the COVID-19 pandemic.

Keywords randomized clinical trial; Bayesian adaptive trial; adaptive platform trial; master protocol; community-acquired pneumonia; intensive care; pandemic; COVID-19

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 concerns regarding best treatment options under conditions of uncertainty. These problems are particularly acute in pandemics.{ref]

Until recently, there was no easy resolution to this tension. However, the 21st century ushered in a digital revolution that is transforming our ability to understand biology, capture clinical data, and execute RCTs capable of nuanced estimates of treatment effects and rapid adaptation to pandemics. This paper describes one such effort using a novel design known as a randomized embedded multifactorial adaptive platform (REMAP)[2] to test multiple therapies in patients admitted to the intensive care unit (ICU) with severe community-acquired pneumonia (CAP). We review the study's rationale, design and implementation.

The decision to study severe community-acquired pneumonia

We chose severe CAP because it is extremely common, case-fatality is high, the strength of evidence guiding treatments 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 in rich and poor countries alike.[3-5] Severe CAP, the subset at risk for acute hypoxemic respiratory failure and shock, is also the most common cause of sepsis, a frequent reason for ICU admission, with a mortality rate of 20-50%.[6-8] Finally, viral pneumonia, especially influenza, is the most deadly recurring pandemic infection.[3]

The treatment of severe CAP involves multiple therapies, including anti-microbial regimes, host immunomodulation, organ support, and interventions to prevent complications. Several guidelines address severe CAP treatment but the specific recommendations frequently lack strong evidence. For example, high quality evidence from RCTs supports only 4 of 44 recommendations in current European guidelines[9-11], 11 of 43 in US guidelines[12], and 7 of 93 Surviving Sepsis Campaign Guidelines.[13] Furthermore, several statements are contradictory across guidelines. Not surprisingly, guideline compliance is poor and care is variable[14-17] with potentially adverse consequences.[17,18]

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

Two issues hinder generation of high-quality evidence for care of patients with severe CAP. First, for endemic CAP, the effectiveness of interventions may vary by subgroups or use of concomitant treatments. For example, hydrocortisone effectiveness may vary by etiology of CAP (viral or bacterial), presence of shock, and anti-microbial. Traditional RCT designs are not well suited for assessing complex treatment-treatment and treatment-subgroup interactions. Second, RCTs launched in pandemics, such as the 2009 H1N1 influenza or 2019 COVID-19 pneumonia outbreaks, even when using 'just-in-time' procedures, are often implemented too slowly to generate useful knowledge.[19,20]

A new approach

Our solution for better evidence generation in severe CAP, the REMAP, combines two designs: a point-of-care RCT and an adaptive platform trial.[2,21,22] Point-of-care RCTs boost capture of eligible patients via a clinical moment, or 'point-of-care,' that triggers the trial apparatus,[23,24] ideally in the electronic health record.[21] This approach is used for pragmatic comparative effectiveness studies.[25,26] 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 and test multiple therapies simultaneously and sequentially.[22,27,28] They are thus an experimental platform, rather than a series of experiments. They are adaptive in that they incorporate rules for changes in entry criteria, study arms, and the proportion randomized to each arm over time. There are several adaptive platform trials outside critical care.[29,30]

Description of the REMAP design

REMAP combines a point-of-care RCT and an adaptive platform trial to create a design that, like a former, embeds the trigger for patient recruitment in routine clinical care but, like the latter, then enrolls these patients into a 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[31], and efficient. Embedding also facilitates low operational complexity at the bedside, even though the internal clinical trial machinery may be complex. Thus, with REMAP-CAP, the any patient admitted to the ICU with acute respiratory insufficiency due to suspected pneumonia is flagged for enrollment and randomization. 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 monitoring and data collection will also be embedded where possible in routine care. The trial design also coordinates with national ICU registries to permit comparison with unenrolled patients and avoid data collection redundancy (Appendix).

The trial is 'multifactorial' in that it tests multiple interventions within multiple therapeutic domains and 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. Pandemic COVID-19-specific domains are also now launched, as described below. Each 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 is hypothesized. REMAP-CAP commenced with two strata: presence or absence of shock and presence or absence of suspected (or proven) influenza infection.

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 interventions within other domains or by strata. Which interactions are evaluated are pre-specified. The trial uses response-adaptive randomization (RAR),[32] with the probability of randomization to any particular regimen adjusted over time to favor better performing interventions, 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. For example, if one hydrocortisone dosing strategy appears beneficial for patients with shock, but neutral in patients without shock, then the RAR rule increasingly weights the odds for shock patients to receive that strategy but maintains equal allocation for non-shocked patients.

Importantly, interventions may not be appropriate 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. An example of the second 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. 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 temporarily lacks availability of an intervention. In all these instances, the statistical inference model tracks and accommodates for these varying levels of participation.

Other adaptive trial features include the capacity to introduce new strata, domains, and interventions over time. The 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 (Appendix; www.remapcap.org). 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 in Europe under 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 fund 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 500 patients were enrolled as of March 2020. 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,[33] 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 participation in REMAP-CAP in the prior 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 90-day mortality. 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.[9-11,34] Patients will therefore be randomized (depending on availability and local equipoise) to one of three beta-lactams (ceftriaxone, piperacillin-tazobactam, or amoxycillin-clavulanate) with a macrolide (azithromycin, clarithromycin or roxithromycin), or to a respiratory quinolone (moxifloxacin or levofloxacin). Patients with known allergies are ineligible to receive an agent to which they are allergic but will be allocated among remaining options.

Host immunomodulation with extended macrolide domain

Although macrolides are recommended for 3-5 days for CAP,[12] an extended course may also be beneficial in part because of macrolide anti-inflammatory properties.[35,36] Therefore, patients randomized to any antibiotic arms containing a macrolide can also be randomized to a standard (3-5 days) or experimental 14-day course.

Host immunomodulation with corticosteroid domain

Although severe CAP is associated with a potentially detrimental host immune response, successful immune modulation remains elusive. Benefit with corticosteroids was reported in vasopressor-dependent septic shock, severe Pneumocystis pneumonia, and late acute respiratory distress syndrome[37-41], but the evidence is inconclusive.[42-49] Notably, 2 recent large RCTs reported conflicting results, though both suggested faster resolution of hemodynamic instability.[50,51] 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 while in shock. Sites can choose any two (or all) of these options, depending on equipoise. The effect of corticosteroids will be evaluated separately in patients with or without baseline shock and with or without influenza infection.

Anti-viral domain

The effectiveness of oseltamivir, and other new anti-influenza agents, is not established in the critically ill. The modest impact of oseltamivir in uncomplicated seasonal influenza further raises uncertainty about its value in serious infection.[52-54] There is also no consensus regarding duration of oseltamivir therapy.[55] 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 standard care will participate in the no oseltamivir intervention. We will add baloxavir, alone and in combination with oseltamivir, when more available.[56]

Respiratory support domains

International guidelines support lung protection strategies that minimize excessive volume or pressure.[13,57,58] The guidelines are based on patients with ARDS, but whether this approach is optimal for patients with CAP without ARDS is unknown. Moreover, observational studies demonstrate poor uptake of guideline-recommended ventilatory strategy with many clinicians personalizing ventilatory settings on a patient-by-patient basis.[59] Optimal ventilatory strategy is also complex, involving tidal volume, mode (limiting breaths by pressure or volume), PEEP, and use of spontaneous ventilation.

To start determining optimal ventilatory strategy for patients with CAP, the ventilation domain will randomize patients to 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. This phase has three goals. First, to determine whether adherence to guideline-recommended care can be achieved in trial patients. Second, to identify testable strategies within the spectrum of observed care patterns in the clinician-preferred intervention arm. Third, to identify stratification variables such as presence of ARDS, unilateral versus bilateral involvement, PEEP:FIO_2 ratio, and lung compliance.

Oxygenation support is almost universal for patients with CAP. However, neither the optimal inspired concentration nor optimal haemoglobin saturation target 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 use of a conservative oxygen strategy may be safe and beneficial in pneumonia.[60-62] Some evidence points to improved outcomes with reduced oxygen exposure in several diseases, but recent RCTs results are conflicting.[63-67] An oxygenation strategy domain, harmonized with a large-scale trial in general ICU patients, will compare conservative to liberal oxygenation support.

Adaptation during a pandemic

REMAP-CAP adapts to answer time-critical questions relevant to optimal care of patients with pneumonia due to a pandemic infection in several ways. The platform has a 'sleeping' stratum for patients with proven or suspected pandemic infection that is triggered at each site. A pandemic-specific model tests the effect of different agents and regimens in the pandemic stratum. This model can use an alternative endpoint and be updated more frequently. The pandemic-specific model can incorporate data from non-pandemic patients with regard to all domains that are relevant in both pandemic and interpandemic periods, with consideration of potential interactions. In addition, additional domains, such as novel anti-viral therapies, immunoglobulins or convalescent sera, or other immunomodulation approaches, can be deployed.

In February 2020, REMAP-CAP entered pandemic mode in response to the COVID-19 pandemic with several adaptations, essentially as a sub-platform, REMAP-COVID. These include a COVID-19 inference model for all confirmed and suspected cases that uses 21-day ICU-free days (where death is assigned zero days) as the primary outcome with RAR as frequently as weekly. A specific REMAP-COVID core protocol was written to streamline on-boarding of new sites that only enrol COVID-19 patients. Domains were implemented for COVID-19 antiviral therapy (including hydroxychloroquine and lopinavir-ritonavir) and immune modulation (including interferon-beta, IL1ra, and IL6ra agents), the corticosteroid domain was modified to include a higher dose, and other domains are under construction. The enrolment criteria were modified to allow entry at some sites of hospitalized patients who do not require ICU care for cardiovascular or respiratory support (defined as 'moderate' COVID-19 disease state). The model tracks whether patients are moderate or severe at enrolment, includes interactions between domains (e.g., interferon beta and corticosteroids), and allows for nested analyses (e.g., comparing any anti-viral therapy versus none).

Statistical considerations

Most RCTs are analyzed using frequentist statistics, which calculate the probability of observing patterns 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 assumptions are for a specific trial of a specific size), which in turn require pre-experiment assumptions regarding plausible effect sizes and outcome rates.[68] Although many clinicians are comfortable with this approach, the pre-trial assumptions are frequently incorrect, and the design lacks flexibility to address the complex questions more reflective of clinical practice or to make mid-trial corrections when pre-trial assumptions are wrong.

To allow flexibility yet still generate robust statistical inferences, REMAP-CAP relies on a Bayesian, rather than frequentist, framework.[69] A Bayesian approach calculates the probability a hypothesis is true, given observed data and prior information and beliefs. An advantage is that, as data accrue, the probability that a treatment is best can be updated (the updated probability is called the posterior probability). REMAP-CAP launches with no prior assumptions regarding which interventions are superior, akin to a typical RCT design. However, at regular intervals, newly accrued data is analyzed using a pre-specified inference model to generate updated 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 model estimates the probability of superiority for each 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, region and site, severity of illness, and 13-week time blocks (to adjust for drift). The model includes terms for the common effect of each intervention and selected interactions for all 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 (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 potentially affect mortality such that they can be quickly overwhelmed by the data.

REMAP-CAP begins with randomization balanced across interventions. Thereafter, the Bayesian inference model is re-estimated at regular intervals with updated trial data. The updated posterior probabilities determine new randomization probabilities and can trigger a trial conclusion regarding an intervention's effect. We set superiority as ≥0.99 posterior probability that an intervention lowers mortality, equivalence as ≥0.90 posterior probability that the odds ratio for mortality lies between 0.8 and 1.2, and inferiority as <0.01 posterior probability that the intervention is superior. These thresholds were selected before launch using 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 data, improved participant safety, reduced down-time between trials, and enhanced knowledge translation (Table 2 and Figure 3). Four features improve 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 inferior arms, increasing power to differentiate between the remaining arms. Third, an overarching multifactorial model that drives RAR and stopping rules integrates information on treatment effects from all patient strata. Fourth, because randomization continues until 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 promote greater allocation to better performing interventions and, by corollary, less exposure to poorly performing interventions, over time. As the trial learns, the benefits of reduced uncertainty are translated rapidly into improved odds of exposure to the optimal strategy for participants. Thus, although individuals may still be assigned to interventions that perform poorly, 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 pandemics.[20] 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. When fully embedded in an entire healthcare system, REMAP becomes a platform for continuous quality improvement (and instant knowledge translation), 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 RCT. Local regulations govern consent requirements, with consideration that several comparisons are of alternative standard care options and most are deployed emergently. The current protocol, with the current suite of domains and interventions, is approved in 13 countries, all with deferred consent for domains which test only options within standard care. The rules for changing the odds of randomization and stopping portions of the trial are pre-determined and executed automatically. However, they are overseen by a Data Safety Monitoring Board (DSMB), which has the capacity to override algorithm decisions if the proposed rule is deemed no longer acceptable. When a threshold is passed and conclusions are drawn, that portion of the trial is reported via publication and usual routes of dissemination. New interventions and domains are introduced via protocol modifications, with approval of relevant ethics boards. Of note, REMAP-CAP operates under the International Conference on Harmonisation Good Clinical Practice guidelines and has approval for the study of investigative medicinal compounds. It is therefore possible to evaluate experimental therapies with appropriate caveats regarding specific data that may be required for regulatory approval.

Logistical considerations

Although the trial machinery is very complex, 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 consenting procedures, and the ability of the coordinating center to quickly provide the randomly assigned regimen. Key to this success includes web-based software designed tailored to interface with local clinical and research-related processes. For example, the software is easily accessed by any clinician and, through efficient prompting of a short list of clinical questions, automatically determines eligibility for the platform, domains, and individual interventions.

Discussion

Although we outlined numerous potential advantages of the REMAP trial design, there are considerable barriers. First, the ability to embed the trial requires a new paradigm for engagement between clinicians and researchers in many ICU settings. Such close partnership exists in other fields, such as within oncology trial networks. Similarly, the large acute myocardial infarction trials in the 1980s and 1990s relied on extremely high capture rates. In critical care, the fluid resuscitation trials by the ANZICS CTG also achieved extremely high capture rates,[70,71] in part by generating a culture that any patient requiring resuscitation prompted the clinical team to enroll the patient. These efforts share a common commitment to education, engagement and attention to practical details at participating sites.

One concern will be the use of Bayesian inference and flexible sample sizes. For example, Bassler et al argued that early stopping over-inflates estimation of treatment effects.[72] However, trials that stop early for superiority are trials that, on average, would overestimate treatment effect even if they run to term (just as trials that do not trigger early stopping underestimate the true effect).[73] Assuming appropriate rules are in place, early stopping does not, in and of itself, significantly overestimate treatment effect (or inflate the chance of type one error). The best estimate of treatment effect is the summary of all trial results. If REMAP-CAP generates an early large superiority signal for an intervention, and no other trial data exist, it would be appropriate to consider the true effect size as somewhat smaller.[74]

As with all Bayesian adaptive designs, traditional estimation methods for type 1 and type 2 error are not possible. Rather, these error rates are explored through simulation of trial operating characteristics under different scenarios and assumptions. The U.S. Federal Drug Administration and others provide guidance but there is little question that considerable expertise is required.[75,76] This expertise is currently limited, and concentrated particularly within a few companies. To broaden expertise, all the government grants for REMAP-CAP stipulate efforts to expand competency among local academic trials groups. As such, REMAP-CAP has several regional initiatives and runs an international statistics and reporting interest group (>40 statisticians and trialists from 16 universities; Figure 2). The statistical group for REMAP-CAP provides the design and simulation software for free to academic groups, and serves as a free NIH-supported consultation service for prospective researchers.

There will be issues regarding the reporting of REMAP trials, and all adaptive platform trials.[22] For example, REMAP conclusions are generated from a model that incorporates all the data from the entire trial. It is unclear whether the report should 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. Because most RCTs are frequentist, trial reports that use Bayesian statistics will be unfamiliar to many readers, impeding understanding and dissemination. However, Bayesian trials and analyses are becoming considerably more common, which should reduce this problem.[30,77-79]

In summary, we present a novel class of study design with an example tailored specifically to determine optimal therapies for severe interpandemic and pandemic pneumonia. The design generates information that is broad (reflecting real-world practice) and narrow (generating precision estimates for patients with particular clinical features). The platform can incorporate new study arms, making it ideal for pandemic situations. The design nonetheless will face challenges. However, with funding to launch REMAP-CAP on three continents, we expect many lessons will be learned, aiding broader, more efficient use of REMAPs in critical care and elsewhere.

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, 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.

10. 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.

11. 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.

12. 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.

13. 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.

14. 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.

15. 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.

16. 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.

17. 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.

18. 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.

19. 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.

20. Angus DC. Optimizing the Trade-off Between Learning and Doing in a Pandemic. *JAMA.* 2020.

21. 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.

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

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

24. 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.

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

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

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

28. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *The New Engl J Med.* 2017;377(1):62-70.

29. 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.

30. Park JW, Liu MC, Yee D, et al. Adaptive randomization of neratinib in early breast cancer. *N Engl J Med.* 2016;375(1):11-22.

31. Webb SA, Pettila V, Seppelt I, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *New Engl J Med.* 2009;361(20):1925-1934.

32. 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.

33. 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.

34. 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.

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

36. Rubin BK, Druce H, Ramirez OE, Palmer R. Effect of clarithromycin on nasal mucus properties in healthy subjects and in patients with purulent rhinitis. *Am J Respir Crit Care Med.* 1997;155(6):2018-2023.

37. 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.

38. 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.

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

40. 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.

41. 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.

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

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

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

45. 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.

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

47. 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.

48. 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.

49. 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.

50. 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.

51. 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.

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

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

54. 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.

55. 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.

56. 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.

57. 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.

58. 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.

59. 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.

60. 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.

61. 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.

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

63. 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.

64. 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.

65. Investigators I-R, the A, New Zealand Intensive Care Society Clinical Trials G, et al. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. *N Engl J Med.* 2019:10.1056/NEJMoa1903297.

66. Barrot L, Asfar P, Mauny F, et al. Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome. *N Engl J Med.* 2020;382(11):999-1008.

67. Angus DC. Oxygen Therapy for the Critically Ill. *N Engl J Med.* 2020;382(11):1054-1056.

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

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

70. 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.

71. 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.

72. 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.

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

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

75. LaVange LM SR. Statistical considerations in designing master protocols. Innovations in Breast Cancer Drug Development — Next Generation Oncology Trials Web site. http://wayback.archive-it.org/7993/20161023010547/http://www.fda.gov/downloads/Drugs/NewsEvents/UCM423368.pdf. Accessed April 2, 2020.

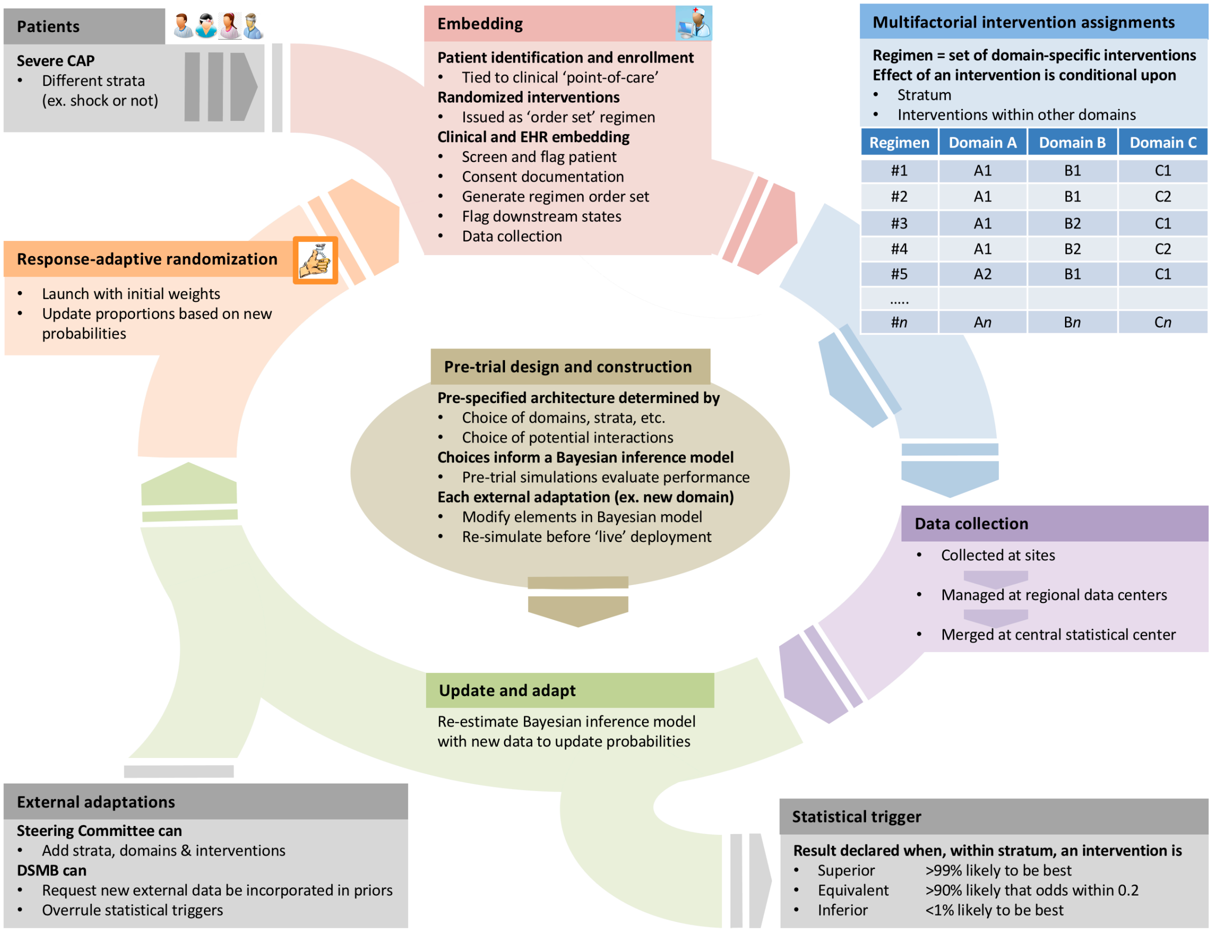
76. U. S. Department of Health and Human Services FaDA. Adaptive Designs for Medical Device Clinical Studies. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm446729.pdf. Accessed April 2, 2020.

77. Rugo HS, Olopade OI, DeMichele A, et al. Adaptive Randomization of Veliparib-Carboplatin Treatment in Breast Cancer. *N Engl J Med.* 2016;375(1):23-34.

78. Goligher EC, Tomlinson G, Hajage D, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome and Posterior Probability of Mortality Benefit in a Post Hoc Bayesian Analysis of a Randomized Clinical Trial. *JAMA.* 2018;320(21):2251-2259.

79. Kapur J, Elm J, Chamberlain JM, et al. Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. *N Engl J Med.* 2019;381(22):2103-2113.

Figure 1. Schematic of the REMAP-CAP design



Patients

Severe CAP
- Different strata (ex. shock or not)

Embedding

Patient identification and enrollment
- Tied to clinical 'point-of-care'

Randomized interventions
- Issued as 'order set' regimen

Clinical and EHR embedding
- Screen and flag patient
- Consent documentation
- Generate regimen order set
- Flag downstream states
- Data collection

Multifactorial intervention assignments

Regimen = set of domain-specific interventions
Effect of an intervention is conditional upon
- Stratum
- Interventions within other domains

Regimen	Domain A	Domain B	Domain C
#1	A1	B1	C1
#2	A1	B1	C2
#3	A1	B2	C1
#4	A1	B2	C2
#5	A2	B1	C1
.....			
#*n*	A*n*	B*n*	C*n*

Response-adaptive randomization
- Launch with initial weights
- Update proportions based on new probabilities

Pre-trial design and construction

Pre-specified architecture determined by
- Choice of domains, strata, etc.
- Choice of potential interactions

Choices inform a Bayesian inference model
- Pre-trial simulations evaluate performance

Each external adaptation (ex. new domain)
- Modify elements in Bayesian model
- Re-simulate before 'live' deployment

Data collection
- Collected at sites
- Managed at regional data centers
- Merged at central statistical center

Update and adapt

Re-estimate Bayesian inference model with new data to update probabilities

External adaptations

Steering Committee can
- Add strata, domains & interventions

DSMB can
- Request new external data be incorporated in priors
- Overrule statistical triggers

Statistical trigger

Result declared when, within stratum, an intervention is

• Superior	>99% likely to be best
• Equivalent	>90% likely that odds within 0.2
• Inferior	<1% likely to be best

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

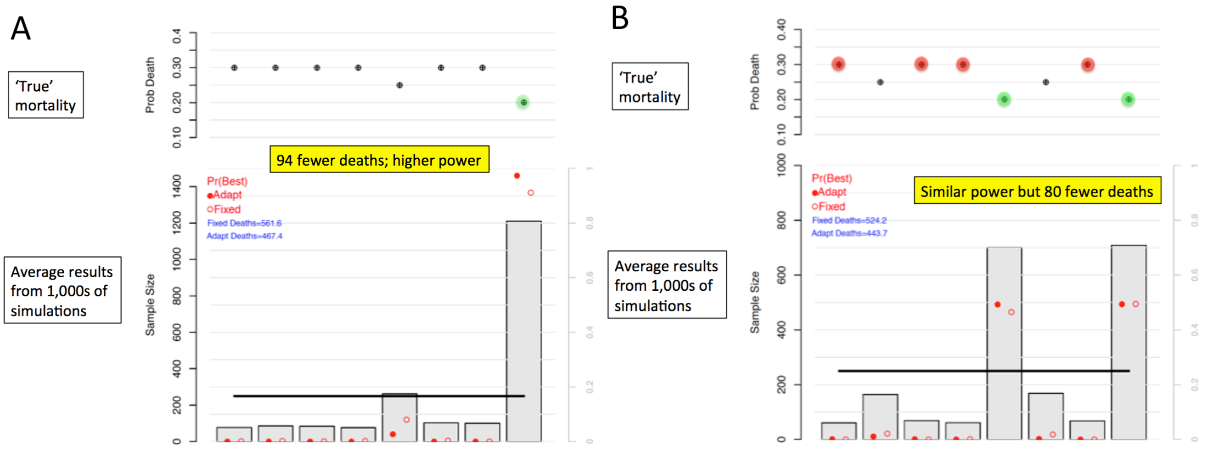
Platform. The entire trial is envisioned, like all adaptive platform trials, as a learning engine that can test multiple interventions both in parallel and sequentially. Thus, the focus is on the condition, CAP, itself, and not on any particular intervention. This approach allows a standard approach 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

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).

This table describes REMAP-CAP in inter-pandemic mode, and excludes the COVID-19 adaptations (described in the Pandemic section of the text).

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	✓		✓		✓	