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Title: Platform Trials to Assess Therapeutics in Patients Hospitalized with Influenza

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Abstract:

Evidence-based, effective treatments for hospitalized patients with influenza have yet to be identified. Traditional randomized controlled trials have struggled to provide definitive guidance due in part to small sample sizes and logistical challenges. Adaptive platform trials, such as REMAP-CAP and RECOVERY, offer a transformative approach to evaluating influenza therapeutics. REMAP-CAP and RECOVERY utilize flexible, efficient designs that enable the simultaneous assessment of multiple interventions, adaptation to emerging data, and large-scale recruitment. Both platforms are currently evaluating antiviral and immunomodulatory therapies for severe influenza, building on their success in identifying effective treatments for COVID-19. Establishing global platform trials for influenza will facilitate the generation of high-quality evidence to guide seasonal influenza treatment and also enhance pandemic preparedness. A coordinated international effort to sustain platform trials beyond pandemic periods is essential for improving clinical outcomes, optimizing resource utilization, and ensuring readiness for future pandemics.

Lack of Influenza Treatments Approved for Hospitalized Patients

Despite the significant burden of influenza, there is a notable lack of rigorous evidence from randomized clinical trials to support the treatment of patients hospitalized with moderate to severe disease. Although supportive observational data exist, particularly from the A(H1N1)pdm09 pandemic experience (1), no therapeutics have been proven to improve clinical outcomes in hospitalized patients with influenza. The evidence supporting treatment with antivirals, such as oseltamivir and baloxavir, is primarily from outpatient settings and in patients with symptom onset within 48 hours. Randomized controlled trials (RCTs) of neuraminidase inhibitors and baloxavir in inpatients have been modest in size, typically with just a few hundred patients recruited (2). A recent meta-analysis found that oseltamivir and peramivir might reduce duration of hospitalization in patients with severe seasonal influenza but concluded that "the effects of all antivirals on mortality and other important patient outcomes are very uncertain due to scarce data from randomised controlled trials" (3). The Post-pandemic Review of anti-Influenza Drug Effectiveness (PRIDE) research consortium, pooled data from 18,309 patients who survived to hospital discharge after 2009 influenza A(H1N1) virus infection.(4) They found that early initiation of neuraminidase inhibitor treatment was associated with a shorter length of stay in hospital in adults, children and pregnant patients. However, using retrospective non-randomized observational data and excluding non-survivors are limitations. There have been small, inconclusive trials of antibody therapies, one trial of a host-directed small molecule antiviral DAS181(5), and no successful trials of host immunomodulatory therapies (6).

This absence of robust, evidence-based treatments for hospitalized patients has meant that guidelines for treating severe influenza vary around the world. For instance, the European Centre for Disease prevention and Control (ECDC) expert opinion document states,

'Treatment during seasonal influenza epidemics should be recommended on an individual basis'(7). Furthermore, the duration of therapy is additionally unclear with a C-III recommendation (weak recommendation based on low quality evidence) from the Infectious Diseases Society of America for longer durations (beyond 5 days) of antiviral treatment for patients with severe disease (8). These low certainty, weak recommendations for a major cause of mortality and morbidity around the world underscore the need for targeted research in this area.

The A(H1N1)pdm09 pandemic highlighted the challenges in conducting successful RCTs during an influenza outbreak. A review of clinical research during that time found that the response was wholly inadequate (9). Despite the global impact of the A(H1N1)pdm09 pandemic, few RCTs were completed, and those that were often faced issues such as insufficient sample sizes and logistical difficulties. As a consequence, we still have limited understanding of effective treatments, both antivirals and immunomodulators, for moderate to severe influenza.

Need for Large Randomized Controlled Trials (RCTs)

To make progress in the treatment of severe influenza, there is a need for ambitious, large-scale trials. The sample size of published RCTs of treatments for patients hospitalized with influenza is generally less than 500, and often less than 200 (10-13). These trial have used a variety of different outcome including vital signs(12), ordinal clinical scales(11), time to hospital discharge (13) and mortality(13). Such trials are underpowered to detect modest but potentially important clinical effects. For example, the average duration of hospitalization with influenza in the UK is 9 days (14). Detecting a two-day improvement in time to hospital discharge would require at least 1300 patients to be randomized. In a hospitalized population where 12.5% of patients die or require ventilatory support (2), then more than 8000 patients would need to be

randomized to reliably detect a 20% reduction in this outcome (90% power with 2-tailed significance of 0.01). In summary, clinical trials of influenza treatments need to be far more ambitious.

There are, however, numerous challenges to conducting such trials. There is no consensus on the most important clinical endpoints for influenza clinical trials. Mortality rates are clearly important, but reliably demonstrating a mortality improvement in patients hospitalized with seasonal influenza would need a very large sample size (e.g. 15,000 patients if mortality were 6%). Reducing time spent in hospital and intensive care units is an important outcome to both patients and healthcare systems, especially when faced with winter pressures, that could be identified in a smaller trial with only a few thousand patients. Surrogate outcomes based on improvements in symptoms or clinical observations may allow detection of treatment effects with yet smaller trials, and are suitable for early phase studies, but the importance of improvements in these outcomes is often uncertain, making them less likely to inform practice. Another limitation of both surrogate outcomes and duration of hospitalization is that treatments directly affecting the inflammatory response may lead to improvements that do not necessarily correlate with improved major clinical outcomes (for example, the direct antipyretic effect of dexamethasone has been suggested as the reason it reduces length of hospital stay in community-acquired pneumonia (15)).

The fact that influenza is seasonal in temperate climates means that recruitment is limited to a short period at the most challenging time of the year, when clinical teams are under the most pressure. In addition, the exact timing, scale and severity of seasonal epidemics is not predictable, so trials need to plan for multiple seasons and/or geographic diversity of sites. Despite the lack of evidence to support the use of existing antiviral drugs in this population, many guidelines suggest these treatments be considered or strongly recommend that they be

utilized (16, 17), which challenges many clinicians' personal equipoise to consider randomization to generate the high-quality evidence that is still needed.

Success of Platform RCTs for Patients with COVID-19

Platform RCTs have demonstrated significant success during the COVID-19 pandemic. Despite the many thousands of trials registered to evaluate treatments for COVID-19, the most impactful evidence to inform treatment decisions in hospitalized patients came from a limited number of large trials, many of which were platform trials. The success was seen in both acute care platforms as well as from platforms evaluating longer term complications (18). These trials are designed to be adaptive, allowing for the simultaneous testing of multiple treatments and the ability to modify protocols based on interim results, so that new interventions can be added as other ones reach conclusions without requiring whole new trials to be set-up. This flexibility enabled rapid identification of effective treatments, such as dexamethasone and tocilizumab, alongside concomitant assessment by regulatory agencies and guideline groups, that allowed them to become standard care for severe COVID-19. Particular features of these trials include a factorial or ‘domain’ design, allowing the simultaneous evaluation of different therapeutic interventions and a study of interaction between different treatments. This design is particularly efficient. These trials are also designed to be streamlined “point-of-care” trials, delivered by frontline health workers with the minimum of extra effort. This facilitates large scale recruitment despite the often immense pressures on health care systems during outbreaks. REMAP-CAP and RECOVERY are adaptive platform trials whose successes during the COVID-19 pandemic hold lessons for future trials of influenza. As discussed below, both of these platforms are actively evaluating influenza therapies.

REMAP-CAP

The Randomized Embedded Multifactorial Adaptive Platform for Community Acquired Pneumonia (REMAP-CAP) trial was designed in view of the difficulties of conducting research in the 2009 H1N1 pandemic (19). It was designed, in collaboration with patients, specifically to be running internationally prior to a pandemic and then adapt when a pandemic arose. It has a modular design, with a domain structure where treatments with similar mechanisms of action are compared. The design also allows that not all sites globally need to take part in every domain and new interventions and domains can be added or removed as the trial adapts over time. The Bayesian design provides an alternative approach compared with the frequentist design used in more traditional trials. In REMAP-CAP and other Bayesian trials, rather than needing to reach fixed sample sizes based on expected event rates and effect sizes, conclusions are made once pre-defined triggers are met for efficacy and futility compared to control groups, or superiority and equivalence to other treatments. Regular reviews of accumulating data allow conclusions to be declared as soon as these predefined triggers are met, rather than waiting for fixed sample sizes to reached based on pre-trial assumptions that are fixed at the time of design. As in all trials larger effects sizes are easier to detect and therefore this approach allows early identification of the most effective treatments. In total, more than 10,000 patients with severe COVID-19 were recruited and with the multi-factorial design there were 18,500 randomizations, leading to published results for 14 different treatments, including long-term follow-up (20).

The Bayesian design in REMAP-CAP also incorporates response-adaptive randomization, enabling efficient evaluation of better performing therapies in multi-arm comparisons. This approach adjusts the randomization ratios of participants to interventions demonstrating better performance at regular intervals as the trial progresses, rather than maintaining fixed

proportions across all available treatments for the duration of the trial. This design feature facilitated the prompt identification of tocilizumab as a highly effective treatment for patients with severe COVID-19, despite relatively small numbers of patients, allowing more patients access to this effective treatment early and still allowing further evaluation of other immune modulating therapies in the same domain (21).

Dynamic borrowing is an additional feature of the REMAP-CAP Bayesian model, where data from related subgroups informs the analysis of a treatment effect (22). This can be particularly useful when combining adult and pediatric populations. In the case of influenza, there are likely to be fewer children seriously ill in hospital, and even fewer would be expected to die. Therefore, any separate analysis in children or even a traditional subgroup analysis in children is likely to be underpowered. Using dynamic borrowing, if the treatment effect of an intervention is similar in adults and children then the estimate of treatment effect in children 'borrows' information from the adult population, generating evidence more rapidly. If the treatment effects are divergent then less borrowing occurs. During the pandemic, the comparison between participant sub-groups combined with the application of dynamic borrowing revealed that tocilizumab and sarilumab were equivalent, (21, 23) but divergent treatment effects of therapeutic heparin in patients were found with different severities of COVID-19 illness (24, 25).

RECOVERY

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial was set up in March 2020 as the first COVID-19 wave began in the UK. An overriding consideration was the need to include large numbers of hospitalized patients to quickly and reliably identify, or rule-out,

a moderate impact of treatments on mortality (e.g. a reduction of 10-20%). Without compromising patient safety or essential data quality, the trial procedures were streamlined to minimize burden on busy clinical and research staff, enabling recruitment even as hospitals were under severe pressure, and at sites not usually involved in clinical trials (26, 27). Randomization and follow-up forms were brief and focused on essential data collection (see appendix). Eligibility criteria were simple with few exclusions, and apart from the receipt of trial treatments, clinical management was left to the patient's medical team. This allowed recruitment of a wide range of patients and meant results were widely applicable.

To allow the evaluation of the many COVID-19 therapies that had been, or would be, proposed, an adaptive platform design was chosen. This has had two major benefits; i) as treatments change, front line staff remain familiar with the trial and its procedures, and the trial collaboration, infrastructure, and regulatory approvals do not need to be recreated from scratch, and ii) participants can enter more than one treatment comparison simultaneously, making recruitment efficient.

RECOVERY quickly became the fastest recruiting COVID-19 treatment trial worldwide, in its first two years enrolling 47,000 participants and testing 15 treatments. Because each participant took part in an average of two treatment comparisons, this equated to 90,000 patients in single-comparison trials. By producing unambiguous results on important clinical outcomes (death, ventilation and duration of hospitalization), many RECOVERY results have had an immediate impact on the global management of COVID-19, in particular its early identification of the benefit of corticosteroids in patients with hypoxia (28). Because most neutral results from RECOVERY were powered to exclude a meaningful benefit of treatment, these also led to rapid changes in practice and allowed therapeutic research to

move forwards to other areas (e.g. abandonment of convalescent plasma therapy which had been widely used on the basis of supportive observational data) (29). A conventional (frequentist) statistical approach has aided the transparency and impact of trial results.

Application of RECOVERY and REMAP-CAP Trials to Influenza

The rationale for the RECOVERY and REMAP-CAP trial designs, and the methodologies used during the COVID-19 pandemic can be applied to influenza research, even if recruitment at the same speed and scale is not possible. These trials' adaptive designs and ability to test multiple interventions simultaneously make them well-suited for influenza outbreaks. For instance, at the time of writing both trials are evaluating the antiviral agents oseltamivir and baloxavir, as well as the combination of both therapies, alongside dexamethasone. In addition, REMAP-CAP is evaluating the immunomodulating drugs tocilizumab and baricitinib, shown to be effective in COVID-19, in critically ill patients with influenza (see Figures 1 and 2). Inclusion and exclusion criteria are outlined in Table 1. Both trials include virological sampling in a subset of patients to determine viral genotype and emergent antiviral resistance during treatment. However, neither trial includes intensive virological sampling (in REMAP-CAP swabs are taken on inclusion, day 3 and day 7, and in RECOVERY a single swab is taken at inlcusion and day 5), and the focus is on major clinical endpoints. Smaller clinical trials and observational studies with more detailed and virological characterization, including sampling at later timepoints, can complement these large clinical endpoint trials.

REMAP-CAP started enrolling patients with suspected influenza in November 2019, and in December 2022 modified this to confirmed influenza. As of February 2025, the influenza domains are open in 128 sites in 18 countries and there are 725 patients with confirmed influenza included. RECOVERY started influenza recruitment in March 2023 and is open at

86 sites in 9 countries. Recruitment is 720 to the baloxavir comparison, 200 to the oseltamivir comparison, and 260 to the dexamethasone comparison.

Strengths of platform trials

1. **Multifactorial Adaptive Design**: Allows for the testing of multiple treatments simultaneously and the ability to adapt based on interim results, adding new treatments rapidly over time without setting up new infrastructure and only modifying existing regulatory approvals and site training materials.
2. **Streamlined point-of-care**: Focus is on recruiting large numbers of patients to increase statistical power, generalizability and reliability of the findings.
3. **Global Collaboration**: Involving multiple international sites, enhancing the generalizability of the findings.
4. **Adaption in case of pandemic:** In interpandemic periods platforms can evaluate treatments for other important diseases and then rapidly adapt if and when a pandemic arises.

Weaknesses of platform trials

1. **Open-Label Design**: Potential for bias as both participants and researchers are aware of the treatment allocations, however, outcomes such as mortality are unbiased. Open-label designs are typically used to avoid issues of multiple different placebos in a multifactorial platform. Blinded interventions can potentially be incorporated in suitable platform designs but add an extra level of complexity that may not be warranted, especially in a pandemic.
2. **Pragmatic design & minimal data collection**: Risks the possibility that heterogeneity of treatment effects may be missed in certain subgroups of patients. See

Table 2 for key outcomes collected within REMAP-CAP and RECOVERY, including secondary outcomes that are only collected within patient subgroups.

3. **Complex Design**: The adaptive nature of platforms can complicate the interpretation of results for those unfamiliar with such analyses. Innovative designs and novel statistical methods (such as the Bayesian adaptive methods) require careful pre-trial simulations, modification of the trial design, and re-simulation in an iterative manner by experienced teams.
4. **Dependency on Infrastructure**: More complex designs rely on well-established clinical and research infrastructure, which may not be available in all settings.
5. **Global Collaboration**: The benefits of global collaboration are clear, but such large international efforts bring substantial logistical challenges. How do you sustain international funding, manage governance, data protection and data ownership across multiple regions with varying regulation and laws?

What is needed for success

In all areas of medicine, robust evidence to guide clinical practice is best provided by large randomized controlled trials that evaluate the effect of treatments on patient-centered outcomes. Influenza is no different. As detailed above, there are some unique challenges to influenza research, in that it is largely a seasonal illness, with varying strains that lead to different severity of disease. There is the constant threat of a new pandemic infection, but its timing cannot be predicted. As infectious diseases cross national borders, there must be international solutions (30). This could be in the form of a large global platform or coordinated/federated national platforms that agree to work in a collaborative way, sharing common definitions and endpoints to facilitate data sharing and analysis. These platforms would enable the evaluation of both existing drugs and newly developed therapies. In

interpandemic periods these platforms would generate timely evidence for effective treatments for seasonal influenza. Establishing such infrastructure now would ensure readiness to adapt to future pandemics and facilitate collaborative international working and the efficient sharing of data in a timely manner in future pandemics. International long-term funding, which may include coordination of national funders to support international collaboration, is crucial to sustain such platforms. In this way, we can advance the care of patients with moderate to severe seasonal influenza and sporadic zoonotic influenza, and be better prepared for the inevitable influenza pandemic.

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Figure 1: Overview of REMAP-CAP platform design and treatments investigated within the influenza stratum (early 2025).

Figure 2: Overview of RECOVERY influenza comparisons (early 2025).

Table 1: Main inclusion and exclusion criteria and summary intervention details for REMAP-CAP and RECOVERY

Inclusion criteria	Exclusion criteria
REMAP-CAP platform*	
• Adults and children admitted to hospital acutely unwell due to a lower respiratory tract infection • Confirmed influenza infection (for the influenza stratum)	• Expected to be discharged from hospital today or tomorrow. • Death is deemed to be imminent and inevitable during the next 24 hours and the patient, or treating clinician are not committed to full active treatment. • More than 14 days from hospital admission • Previous participation in this trial within the last 90 days.
REMAP-CAP Anti-viral domain	
Control – no influenza antivirals Oseltamivir dosed as per local guidelines, or 75mg 12 hourly (adjusted for renal dysfunction) for 5 days or 10 days (randomized) Baloxavir dosed by weight (<40 kg 2mg/kg, 4-80Kg 40mg, >80Kg 80mg) on days 1 & 4 Combination of oseltamivir and baloxavir (doses and duration as above)	
	• Already received ≥2 doses of doses of oseltamivir or ≥1 dose of baloxavir for this illness. • More than 96 hours since hospital admission • More than 48 hours since ICU admission • Pregnancy (baloxavir exclusion)
REMAP-CAP Corticosteroid domain	
Control – no corticosteroid Dexamethasone 6mg daily for 10 days or until discharge (whichever is sooner) Shock-only hydrocortisone 50mg 6 hourly while remains in septic shock (ICU patients only)	
• Receiving supplemental oxygen	• Receiving or planned to receive corticosteroids for alternate indication • More than 24 hours since ICU admission
REMAP-CAP Immune modulation domain	
Control – no immune modulation therapy Tocilizumab – 8mg/kg (max 800mg). Children <30kg, 12mg/kg) Baricitinib – 4mg daily for 10 days or until discharge (whichever is sooner) (age and renal functon adjusted)	
• Receiving respiratory support more than simple supplemental oxygen (i.e. high-flow nasal cannula therapy, non-invasive ventilation including continuous positive airway pressure, or invasive mechanical ventilation) • Age ≥2 years of age	• More than 48 hours of respiratory support in intensive care unit • Known immunosuppression • Already received any IL-6 or IL-1 receptor antagonists or JAK inhibitor • Confirmed mycobacterial, or fungal infections • Liver enzymes (ALT/AST) more than five times the upper limit of normal (tocilizumab exclusion) • Baseline platelet count < 50 x 10^9/L (tocilizumab exclusion)

	• A baseline eGFR/CrCl <15 mL/min and/or receipt of renal replacement therapy (baricitinib exclusion)
All RECOVERY influenza comparisons	
• Hospitalized with intended overnight admission • Confirmed influenza A or B • Pneumonia syndrome (typical symptoms of acute respiratory infection plus objective evidence of acute lung disease) • No restrictions based on time since symptom onset or duration of hospitalisation (but prespecified analyses will evaluate treatment effects by time since symptom onset)	• Patient's responsible clinician considers trial treatment to be definitely indicated or contraindicated for any reason**
RECOVERY baloxavir marboxil comparison	
Dose 40mg (or 80mg if weight >=80kg) on day 1 and day 4	
• Pregnant and breastfeeding women are eligible*** • Children aged >= 12 weighing >=40kg are eligible*** • Immunocompromised patients eligible	• Receipt of the baloxavir marboxil during the current illness
RECOVERY oseltamivir comparison	
Dose 75mg bd for 5 days (10 if immunosuppressed in the opinion of the managing doctor, dose adjusted in renal impairment)	
• Pregnant and breastfeeding women are eligible*** • Children of any age are eligible*** • Immunocompromised patients eligible	• Receipt of a neuraminidase inhibitor during the current illness
RECOVERY corticosteroid comparison	
Dexamethasone 6mg od for 10 days or until discharge (whichever is sooner)	
• Hypoxia (oxygen requirement or oxygen saturations <92% on air) • Pregnant and breastfeeding women are eligible (but should receive prednisolone or hydrocortisone instead of dexamethasone) *** • Children of any age are eligible*** • Immunocompromised patients eligible	• Receipt of systemic corticosteroids during the current illness (if >24h treatment with a glucocorticoid equivalent dose of >10mg prednisolone/day) • SARS-CoV-2 co-infection
Within REMAP-CAP, patients are first assessed for eligibility to the platform, before specific inclusion and exclusion criteria are applied for each domain.* * This applies to eligibility for the specific treatment comparison only (i.e. if oseltamivir had been received or was considered definitely indicated the patient may still be eligible for the baloxavir and corticosteroid comparison. The decision to give oseltamivir or not should be made before randomizing)* **** In certain countries children and/or pregnant and breastfeeding women are excluded*	

1

Table 2:

Data collected for all patients	Data collected for patient subgroups only
REMAP-CAP	
Mortality at 90 days (primary), as well as at 28 days and 6 months Incidence and duration of respiratory and cardiovascular organ support (measured as organ support free days) Symptom severity Incidence of ICU admission (& readmission) Duration of ICU and hospital stay Longer-term follow-up including health-related quality of life and disability Serious adverse events	Influenza resistance monitoring Secondary infections (bacteremia and pulmonary aspergillus) in the immune modulation domain
RECOVERY	
Mortality (co-primary) Duration of hospitalization (co-primary) Receipt of invasive/non-invasive ventilation Renal replacement Non-influenza infections Acute kidney & liver injury Thrombosis Bleeding Arrrhythmia Hypo-/hyper-glycaemia Seizure Adverse events (only Serious Adverse Reactions require reporting) Outcomes are based on information from routine care, with no mandated trial tests. In the UK long-term outcomes are ascertained by linkage to healthcare registry data.	Influenza RNA levels & resistance markers (UK sites only)
ICU: intensive care unit	

Figure1

Click here to access/download;Figure;REMAP_CAP Platform.pptx

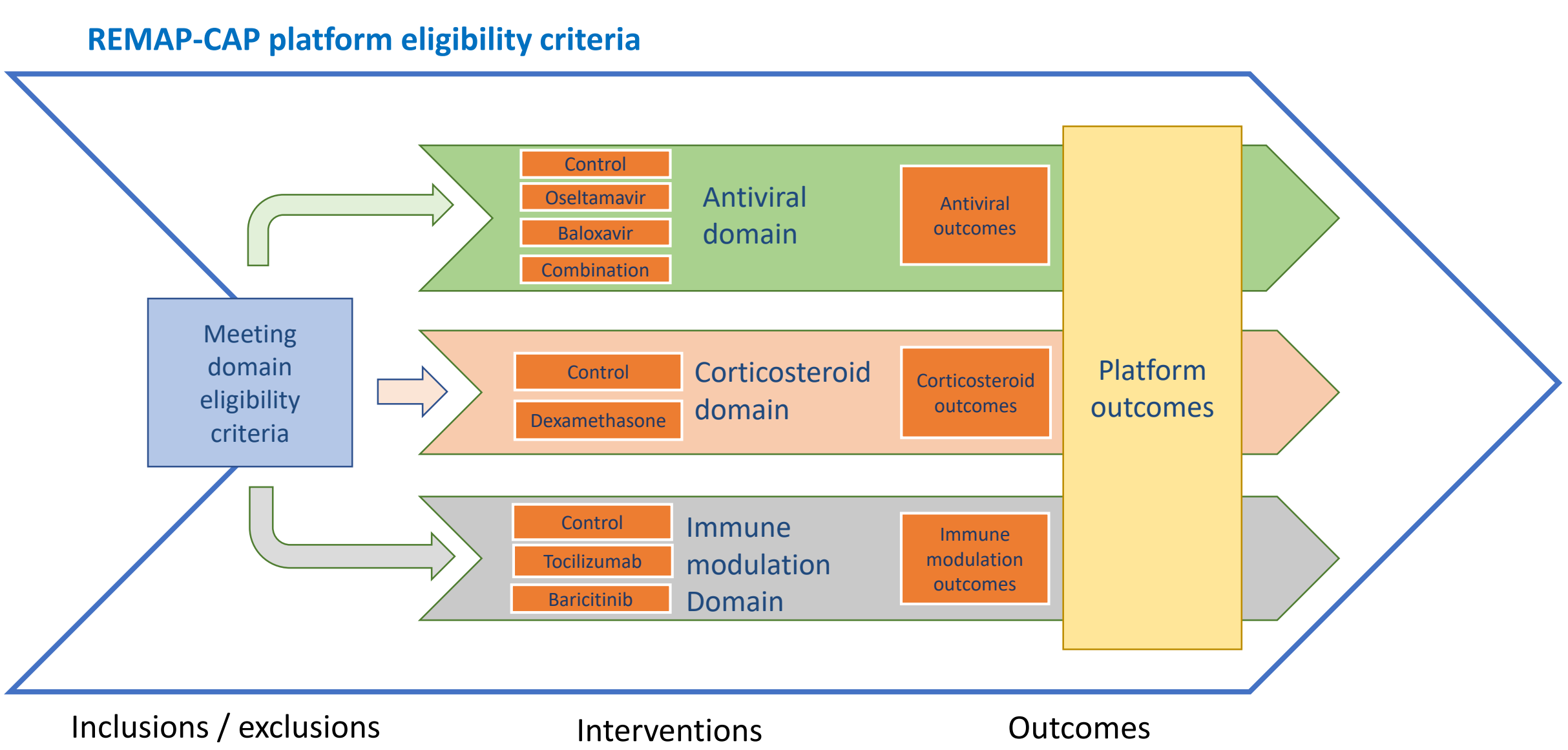

Figure2

Click here to access/download;Figure;RECOVERY influenza comparison figure.pdf