Domain-Specific Appendix:
INFLUENZA ANTIVIRAL DOMAIN

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

Influenza Antiviral Domain-Specific Appendix Version 2.2 dated 16th October, 2023

In this domain of the REMAP-CAP trial, participants with community-acquired pneumonia admitted to participating sites with microbiological testing-confirmed influenza infection will be randomized to receive one of up to 6 interventions depending on availability and acceptability:

- No antiviral agents (no placebo)
- 5 days of oseltamivir
- 10 days of oseltamivir
- Baloxavir marboxil ("baloxavir" from henceforth) on days 1 and 4
- 5 days of oseltamivir + baloxavir on days 1 and 4
- 10 days of oseltamivir + baloxavir on days 1 and 4

At this participating site the following interventions have been selected within this domain:

☐ No antiviral agents (no placebo)

☒5 days of oseltamivir

☐10 days of oseltamivir

☐ Baloxavir on days 1 and 4

☐ 5 days of oseltamivir + baloxavir on days 1 and 4

☐ 10 days of oseltamivir + baloxavir on days 1 and 4

This domain includes patients aged ≥ 28 days old. In this region, this domain will be offered to eligible participants aged:

☐ ≥ 28 days and < 12 years old

☐ ≥ 12 years and < 18 years old

☐ ≥ 18 years old

This DSA applies to the following states and stratum:

Stratum	Pandemic infection suspected or proven (PISOP)			Pandemic infection neither suspected nor proven (PINSNP)		
Core protocol documents	REMAP-CAP Core Protocol + Pandemic Appendix, or REMAP-COVID Core Protocol			REMAP-CAP Core Protocol		
Illness Severity State	Moderate State		Severe State	Moderate State		Severe State
Interventions offered at this site	Ward	ICU	ICU	Ward	ICU	ICU
	☐ No antiviral ☒5 days oseltamivir ☐10 days oseltamivir ☐ Baloxavir on days 1 and 4 ☐ 5 days oseltamivir + baloxavir on days 1 and 4 ☐ 10 days oseltamivir + baloxavir on days 1 and 4	☐ No antiviral ☒5 days oseltamivir ☐10 days oseltamivir ☐ Baloxavir on days 1 and 4 ☐ 5 days oseltamivir + baloxavir on days 1 and 4 ☐ 10 days oseltamivir + baloxavir on days 1 and 4	☐ No antiviral ☒5 days oseltamivir ☐10 days oseltamivir ☐ Baloxavir on days 1 and 4 ☐ 5 days oseltamivir + baloxavir on days 1 and 4 ☐ 10 days oseltamivir + baloxavir on days 1 and 4	☐ No antiviral ☒5 days oseltamivir ☐10 days oseltamivir ☐ Baloxavir on days 1 and 4 ☐ 5 days oseltamivir + baloxavir on days 1 and 4 ☐ 10 days oseltamivir + baloxavir on days 1 and 4	☐ No antiviral ☒5 days oseltamivir ☐10 days oseltamivir ☐ Baloxavir on days 1 and 4 ☐ 5 days oseltamivir + baloxavir on days 1 and 4 ☐ 10 days oseltamivir + baloxavir on days 1 and 4	☐ No antiviral ☒5 days oseltamivir ☐10 days oseltamivir ☐ Baloxavir on days 1 and 4 ☐ 5 days oseltamivir + baloxavir on days 1 and 4 ☐ 10 days oseltamivir + baloxavir on days 1 and 4

REMAP-CAP: Influenza Antiviral Domain Summary	
Interventions	• No antiviral agents (no placebo) • 5 days of oseltamivir • 10 days of oseltamivir • Baloxavir on days 1 & 4 • 5 days of oseltamivir + baloxavir on days 1 and 4 • 10 days of oseltamivir + baloxavir on days 1 and 4
Unit of Analysis, Strata and State	This domain is analysed in the interpandemic model. The unit-of-analysis for this domain is the influenza present stratum. Within this stratum, the unit-of-analysis is further defined by age strata and by illness severity state at the time of enrollment, defined as either the Moderate State or Severe State. Borrowing is permitted between states and strata. Response-adaptive randomisation will be applied to all patients, using probabilities derived from the influenza present stratum.
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any domain.
Nesting	There is one nest, comprising the 5- and 10-day duration of oseltamivir.
Timing of Reveal	Randomization with Immediate reveal or Delayed Reveal and Initiation.
Inclusions	Inclusion criteria are hospitalized patients within either moderate or severe states and • Influenza infection is confirmed by microbiological testing • Patient is aged ≥ 28 days old
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • If in the Moderate State, more than 96 hours has elapsed since hospital admission • If in the Severe State, more than 48 hours has elapsed since ICU admission, unless the patient has already been assigned a treatment in another domain in the Moderate State, in which case exclusion will occur if more than 48 hours has elapsed since commencement of sustained organ failure support in an ICU • Patient has already received two or more doses of oseltamivir or other neuraminidase inhibitors • Patient has already received one or more doses of baloxavir • Patient is already receiving, or a clinical decision has been made to commence, an antiviral active against influenza other than oseltamivir or baloxavir or both. • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	• Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent • Known or suspected pregnancy will result in exclusion from interventions that include baloxavir
Outcome measures	Primary endpoint: As specified in the REMAP-CAP core protocol Secondary endpoints: refer to REMAP-CAP Core Protocol.

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1. ABBREVIATIONS

BMI	Body Mass Index
CAP	Community Acquired Pneumonia
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
ECDC	European Centre for Disease prevention and Control
eGFR	estimated Glomerular Filtration Rate
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
ISIG	International Statistics Interest Group
ITSC	International Trial Steering Committee
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RAR	Response Adaptive Randomization
RSA	Region-Specific Appendix
SAE	Serious Adverse Event

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see glossary, Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study); a Statistical Analysis Appendix (details of the current statistical analysis plan and models); Simulations Appendix (details of the current simulations of the REMAP); multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain); and multiple Region-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s), within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions within each domain is covered in a DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject to a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analytic model will also change over time in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the International Statistics Interest Group (ISIG) and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase

over time. Information that is specific to each region that conducts the trial is contained within a RSA. This includes information related to local management, governance, and ethical and regulatory aspects. It is planned that, within each region, only that region's RSA, and any subsequent modifications, will be submitted for ethical review in that region.

The current version of the Core Protocol, DSAs, RSAs and the Statistical Analysis Appendix is listed in the Protocol Summary and on the study website (www.remapcap.org).

3. INFLUENZA ANTIVIRAL DOMAIN-SPECIFIC APPENDIX VERSION

The version of the Antiviral Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the Influenza Antiviral Domain-Specific Working Group (DSWG) on 10 July 2019

Version 2: Approved by the Influenza Antiviral Domain-Specific Working Group (DSWG) on 01 November 2022

Version 2.1: Approved by the Influenza Antiviral DSWG on 14 February 2023

Version 2.2: Approved by the Influenza Antiviral DSWG on 16 October 2023

4. INFLUENZA ANTIVIRAL DOMAIN GOVERNANCE

4.1. Domain members

Chair: Dr. Srinivas Murthy

Members: Professor Derek Angus
Professor Wendy Barclay
Dr. Scott Berry
Professor Marc Bonten
Professor Allen Cheng
Professor Graham Cooke
Professor Paul Dark

Dr. Josh Davis

Professor Lennie Derde

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5. INFLUENZA ANTIVIRAL DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The Influenza Antiviral Domain-Specific Working Group (DSWG) have read the appendix and authorize it as the official Influenza Antiviral Domain-Specific Appendix for the study entitled REMAP-CAP. Signed on behalf of the committee,

Chair  Date 16th October, 2023

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain within the REMAP-CAP to test the effectiveness of different antiviral strategies for patients admitted to hospital with microbiological testing-confirmed influenza virus infection.

6.2. Domain-specific background

6.2.1. Influenza

Seasonal influenza is estimated to cause approximately 300,000 to 650,000 respiratory deaths worldwide (Iuliano et al., 2018). Achieving improvements in influenza mortality is a key focus of public health agencies around the world, through improvements in prevention, diagnostics and therapeutics.

Currently, recommended antiviral agents have not been studied in placebo-controlled, randomized comparative studies to demonstrate a benefit on survival of the severely ill hospitalized patient with proven influenza infection (Dobson et al., 2015, Heneghan et al., 2016, Jefferson et al., 2014, Uyeki et al., 2019). A number of systematic reviews and meta-analyses have been performed, with conflicting results depending upon the analytic strategy employed and the datasets used (Dobson et al., 2015, Jefferson et al., 2014, Muthuri et al., 2014). All prior fully-enrolled randomized studies have been performed in otherwise healthy outpatients, with debatable relevance to the severely ill hospitalized population. These mostly reveal a reduction in fever and symptom duration of approximately 1-2 days when oseltamivir is initiated early in the symptom course (Jefferson et al., 2014, Dobson et al., 2015). Meta-analyses of observational studies and individual-patient data meta-analyses of studies performed in hospitalized adults reveal that there is a possible benefit for

reducing mortality in adults, although this result is inconsistent across studies (Doll et al., 2017, Muthuri et al., 2014, Yang et al., 2012, Heneghan et al., 2016, Choi et al., 2017, Wolkewitz and Schumacher, 2016).

Given the importance of ensuring a robust evidence base for a high-burden disease with a possibility for a future influenza pandemic, the objective of this domain is to determine the effectiveness of different antiviral strategies in severely ill hospitalized patients with pneumonia and confirmed influenza virus infection, both in the ward and in the intensive care unit, and across age ranges

6.2.2. Oseltamivir

Oseltamivir is a neuraminidase inhibitor that has been approved for the early treatment of uncomplicated influenza virus infection. Part of the justification for its use, in the absence of a mortality benefit in outpatient studies of early oseltamivir treatment of uncomplicated influenza that were not powered for assessing impact upon survival, is in reducing viral transmission duration (Fry et al., 2015), reducing the frequency of complications (Venkatesan et al., 2017), and decreasing hospital resource requirements (Muthuri et al., 2014). These benefits have mostly accrued to individuals who are treated early in their course, with effect sizes decreasing with delays in initiating therapy.

Given its decades of widespread use, oseltamivir has a fairly well-known safety profile, with rates of nausea and vomiting in approximately 3-4% of patients, with possible increases in neuropsychiatric adverse events in some reports that are difficult to causally attribute (Dobson et al., 2015, Heneghan et al., 2016, Jefferson et al., 2014). In the critically ill, its enteral formulation is generally well tolerated and well-absorbed, although randomized, placebo-controlled data in this population are lacking (Lytras et al., 2019).

Current guidelines vary in their recommendations for the use of oseltamivir in the severely ill patient with influenza, both in adults and in children. The Infectious Diseases Society of America (IDSA) guidelines recommend neuraminidase treatment for any patient hospitalized with influenza, regardless of illness duration prior to hospitalization (A-II) (Uyeki et al., 2019). European Centre for Disease prevention and Control (ECDC) expert opinion documents state ‘Treatment during seasonal influenza epidemics should be recommended on an individual basis’, acknowledging limitations in the available evidence base (2017). Duration of therapy is additionally unclear, with a C-III recommendation from the IDSA for longer durations (beyond 5 days) of antiviral treatment for patients with severe disease (Uyeki et al., 2019).

6.2.3. Baloxavir

Baloxavir is a newer influenza antiviral that has been licensed for use in multiple countries. Baloxavir is a small molecule inhibitor of the influenza virus cap-dependent endonuclease. As such it acts via a different mechanism of action to oseltamivir. *In vitro*, baloxavir has antiviral activity at low nanomolar concentrations against both influenza A and B, including viruses with resistance to neuraminidase inhibitors. Baloxavir can prevent influenza when used for prophylaxis following household influenza exposure (Ikematsu et al., 2020). In clinical trials in mildly ill, non-hospitalized patients, single-dose baloxavir has demonstrated efficacy in the early treatment of uncomplicated influenza in adolescents and adults and in the early treatment of uncomplicated influenza in adolescents and adults at high risk of poor outcomes, when assessed using outcomes focused on time to alleviation of symptoms and virologic endpoints (Hayden et al., 2018; Ison et al., 2020). Whether baloxavir, with or without a neuraminidase inhibitor, is effective in the treatment of patients admitted to hospital because of influenza is unknown. A recently completed randomized trial (NCT03684044) in 363 hospitalized patients showed no benefit in time to clinical improvement (97.5 vs 100.2 hours, median difference -2.7, two-sided 95% CI -53.4 – 25.9) (Kumar et al., 2022), although with a significant reduction in duration of viral shedding with combination antiviral therapy.

Baloxavir is well-tolerated. When used to treat influenza in the community at high risk of poor outcomes, the safety profile of baloxavir was similar to placebo (Ison et al., 2020). Baloxavir was well tolerated in a phase one study, up to the maximum tested dose of 80 mg. Baloxavir is a pro-drug rapidly converted to the active metabolite S- exhibiting linear pharmacokinetics with a half-life of 48.9 to 90.9 hours. When used for the treatment of uncomplicated influenza and influenza in patients at risk of poor outcomes, baloxavir is given as a single dose of 40 mg or 80 mg, depending on patient weight. In the trial assessing baloxavir for hospitalized influenza patients (NCT03684044), doses of 40 mg or 80 mg are given on days 1 and 4 (with the option of an additional dose on day 7 for those who do not improve).

Treatment with baloxavir may result in the emergence of influenza virus variants with reduced susceptibility, identified in up to 9.7% of adolescents and adults with uncomplicated influenza who received baloxavir, and whether this occurs at higher or lower rates in critically ill patients with influenza is unknown.

Combination therapy with neuraminidase inhibitors allows for theoretical synergistic benefit against influenza virus replication. Additionally, use of combination therapy may protect against emergence of drug-resistant strains, an important concern for baloxavir use.

6.2.3.1. *Antivirals in COVID-19*

As we have learned from COVID-19, the use of antivirals for severely ill patients with acute viral infections may be of limited benefit (Pan et al., 2020). At this stage, no antiviral has been demonstrated to be effective when administration is commenced in patients who are critically ill and some antiviral agents may have been harmful (Pan et al, 2020; Arabi et al., 2021). As such, the role of antiviral therapies in severe viral infections is undergoing re-evaluation and any trial must evaluate for heterogenous treatment effect based on severity of illness among the hospitalized population.

6.2.4. Evaluation of effectiveness of antivirals

Detection of antiviral efficacy is through both clinical and biologic endpoints. Evaluation of clinical effectiveness is best achieved by measurement of patient-centered endpoints including clinical deterioration, survival, and speed of recovery. Determining a benefit on viral shedding after treatment is an important public health endpoint, with the hope that this leads to a decrease in transmissibility during outbreaks, both in the community and hospital settings. The impact on individual outcomes of duration of influenza viral shedding during treatment is unknown. (Ison et al., 2010) Ongoing surveillance for emergence of antiviral resistant influenza viruses due to treatment, as well as in circulating influenza viral strains and their impact on antiviral efficacy, (Sugaya et al., 2007) specifically under the framework of a randomized trial, will be valuable to inform long-term efficacy of antiviral strategies.

6.2.5. Potential interaction between antiviral therapy and immune modulation therapy

There is a possible interaction between the action of antivirals and immunomodulation with corticosteroids or other immunomodulators among severely ill patients with influenza, with putative harmful effects with high-dose steroids and beneficial effects to lower-dose corticosteroids (Hui et al., 2018). As with other antiviral studies, these have not been evaluated in prospective, comparative analyses.

6.2.6. Domain rationale

Given the risks of antiviral-resistant influenza viruses (Moscona, 2009), the costs of stockpiling antiviral medications for future pandemics (Lugner and Postma, 2009), and the lack of high-quality randomized studies in hospitalized patients, including the possibility of heterogeneity of treatment effect between critically ill and non-critically ill patients, there is a need for comparative data in this population to document benefit of antivirals in the treatment of influenza.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of different antiviral strategies for patients admitted to hospital who have microbiological testing-confirmed influenza virus infection.

We hypothesize that the probability of improvement in the primary outcome after enrollment will differ based on the allocated antiviral strategy. The following interventions will be available:

- No antiviral agent (no placebo)
- Oseltamivir twice daily for 5 days
- Oseltamivir twice daily for 10 days
- Baloxavir on days 1 and 4
- Oseltamivir twice daily for 5 days + baloxavir on days 1 and 4
- Oseltamivir twice daily for 10 days + baloxavir on days 1 and 4

All interventions are administered until the stated duration of therapy has been reached or until hospital discharge (whichever occurs first). For baloxavir containing interventions, a third dose can be administered on day 7, if, in the opinion of the treating clinician, there has been insufficient clinical improvement.

Each participating site has the option to opt-in to at least two and up to six interventions, to be included in the site randomization schedule depending on local clinical preference, usual practice, acceptable practice, and the availability of the agent at that site. Sites that use an active antiviral routinely as part of their current treatment approach are not encouraged to participate in the no antiviral intervention. However, sites are encouraged to review their current practice in association with paucity of data on effectiveness of influenza antiviral agents in hospitalized patients. Sites that do not perform routine testing for influenza are not able to participate in this domain.

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial. Treatment allocation will be adaptive, as described in Core Protocol documents.

8.1. Population

The domain enrolls patients who are admitted to hospital with microbiologically confirmed influenza.

8.1.1. State

This domain is available for patients who have microbiologically confirmed influenza infection in either the Moderate or Severe State.

8.1.2. Domain-specific strata

Domain-specific strata are not applied to patients at the time of assessment for this domain.

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in the REMAP-CAP Core Protocol (including as modified in this DSA, of either moderate or severe state patients, and children down to 28 days of age, corrected gestational age). Patients eligible for the REMAP may have conditions that exclude them from the Influenza Antiviral Domain.

8.2.1. Domain inclusion criteria

Patients will be eligible for this domain if:

- Influenza infection has been confirmed by microbiological testing.
- Patient is aged ≥ 28 days old

8.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- If in the Moderate State, more than 96 hours has elapsed since hospital admission

- If in the Severe State, more than 48 hours has elapsed since ICU admission, unless the patient has already been assigned a treatment in another domain in the Moderate State, in which case exclusion will occur if more than 48 hours has elapsed since commencement of sustained organ failure support in an ICU
- Patient has already received two or more doses of oseltamivir or other neuraminidase inhibitors
- Patient has already received one or more doses of baloxavir
- Patient is already receiving, or a clinical decision has been made to commence, an antiviral active against influenza other than oseltamivir or baloxavir, or both.
- The treating clinician believes that participation in the domain would not be in the best interests of the patient

8.2.3. Intervention exclusion criteria

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons.

Patients who are eligible for only a single intervention at a site (i.e. all other interventions are contraindicated) are not eligible for this domain.

Criteria that exclude a patient from a one or more interventions are:

- Known hypersensitivity to an agent specified as an intervention in this domain will exclude a patient from receiving that agent
- Known or suspected pregnancy will result in exclusion from interventions that include baloxavir

8.3. Interventions

8.3.1. Antiviral interventions

Patients will be randomly assigned to receive one of the following open-label antiviral strategies. All interventions will be commenced immediately after allocation status is revealed.

☐ No antiviral agent (no placebo)

☒ Oseltamivir twice daily for five days

☐ Oseltamivir twice daily for ten days

☐ Baloxavir on days 1 and 4 after reveal of randomized treatment assignment

☐ Oseltamivir twice daily for 5 days + baloxavir on days 1 and 4 after reveal of randomized treatment assignment

☐ Oseltamivir twice daily for 10 days + baloxavir on days 1 and 4 after reveal of randomized treatment assignment

All interventions are administered until the stated duration of therapy has been reached or until hospital discharge (whichever occurs first).

It is required that all sites will participate in the 5-day oseltamivir intervention. Each site has the option to opt-in to one or more of the remaining interventions based on local practice.

8.3.2. Recommended oseltamivir dosing

Dosing is determined by the treating clinician and the following are provided as a guide. The standard dose for oseltamivir for adult patients is 75 mg enterally twice per day. No dosage adjustment is suggested for Body Mass Index (BMI), pregnancy, or for extracorporeal membrane oxygenation. Dose adjustment for renal dysfunction will be per local guidelines. If no local guideline exists, recommendations based on estimated Glomerular Filtration Rate (eGFR) are as follows:

Agent	**eGFR <30 ml/min**	**Hemo(dia)filtration (1-1.8 L/hr exchange)**	**Hemo(dia)filtration (>1.8 L/hr exchange)**
Oseltamivir	30 mg twice daily	30 mg twice daily	75 mg, twice daily

Dosing for children is as per local guidelines. A standard dose for oseltamivir in children is 6 mg/kg/day, divided into two doses, up to children of 40 kg. Dose adjustment for renal dysfunction in children will be per local guidelines.

8.3.3. Recommended baloxavir dosing

Baloxavir will be administered as follows:

Agent	**Weight < 40 kg**	**Weight 40-80 kg**	**Weight > 80 kg**
Baloxavir	2 mg/kg on days 1 and 4 to max of 40 mg	40 mg on days 1 and 4	80 mg on days 1 and 4

No dose adjustment is necessary for renal impairment, hepatic impairment, or extracorporeal membrane oxygenation. For baloxavir containing interventions, a third dose can be administered on day 7, if, in the opinion of the treating clinician, there has been insufficient clinical improvement.

8.4. Concomitant care

Additional antiviral agents active against influenza, other than those specified in the platform should not be administered. All other treatment that is not specified by assignment within the platform will be determined by the treating clinician.

8.5. Endpoints

8.5.1 Primary endpoint

The primary endpoint for this domain is the REMAP primary outcome as specified in the REMAP-CAP Core Protocol.

8.5.2 Secondary endpoints

All secondary endpoints as specified in the REMAP-CAP Core Protocol.

9. TRIAL CONDUCT

9.1. Microbiology

Microbiological testing will be performed as per local practice, including bacterial and viral testing to guide clinical care. Domain-specific data collection will consist of viral sampling collected at baseline, D3, and D7, for participating patients in selected sites, from sampling of nasopharyngeal swabs of all patients.

Samples will be stored locally and analyzed locally or batch shipped for central analysis at national or regional reference labs (where necessary) for quantitative influenza virus titers and resistance testing in a relevant sample. These results will not be clinically available to treating teams. Samples may be retained dependent on local ethical approval and consent requirements.

9.2. Domain-specific data collection

9.2.1. Clinical data collection

No additional clinical data, in addition to that specified in the Core Protocol will be collected for this domain.

9.3. Criteria for discontinuation

Refer to core protocol documents for criteria for discontinuation of participation in the REMAP-CAP trial.

9.4. Blinding

9.4.1. Blinding

All antiviral medications will be administered on an open-label basis.

9.4.2. Unblinding

Not relevant.

10.STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

The following Platform conclusions are possible in this domain within each state:

- Effectiveness of any active intervention compared with no influenza antiviral
- Superiority within the domain
- Futility for an active antiviral compared with no influenza antiviral
- Equivalence among active antivirals
- Noninferiority among active antiviral strategies
- Inferiority of any active intervention

Prior to a declaration of effectiveness, the statistical trigger of equivalence is available for any pair of active antiviral agents and will result in these interventions being pooled for ongoing analysis, to optimise statistical efficiency. This will occur without a public declaration of equivalence.

One or more active antivirals can be declared to be futile in comparison with the no antiviral intervention. If this occurs there will be a public declaration of futility with the likely adaptation being removal of futile antiviral interventions from the randomization schedule. This will be an operational decision and will not require an amendment to the DSA, noting that if the point estimate of a futile intervention is in the direction of worse outcome than the no antiviral comparator, that removal from the randomization schedule is pre-specified to be mandatory. As specified in the Core

protocol, futility thresholds will always be achieved before harm thresholds in the setting of regular adaptive analyses.

In the event of one or more active antiviral interventions being declared effective, the no antiviral intervention will be removed from the randomization schedule. This is pre-specified, via this version of the DSA, and can occur without further amendment of this DSA. In this situation, the domain will continue to randomise to the active antiviral interventions to determine the comparative effectiveness of active antiviral interventions. The triggers of equivalence or non-inferiority may be applied following removal of the no antiviral intervention and, if this occurs, it will be through an a priori documented operational decision specified in the Current State document, with noninferiority thresholds to be declared in future versions of the Core protocol. This will include specification of the reference control against which non-inferiority is evaluated. Such a decision can only be made at the time a conclusion is reached as the decision is dependent on patterns of clinical practice at that time.

If a Platform conclusion of equivalence is reached among active antivirals, after a declaration of effectiveness, the DSMB and the ITSC may consider continuation of randomization if clinically relevant differences in secondary endpoints have not been demonstrated and it is considered plausible that clinically relevant differences in one or more secondary endpoints may be capable of being demonstrated. In all other respects the stopping rules for this domain are those outlined in the Core Protocol.

10.2. Unit-of-analysis and strata

The primary unit-of-analysis, for both analysis of treatment effect and the Response Adaptive Randomization (RAR), will be the influenza present stratum (i.e. microbiological testing-confirmed influenza), as specified in the core protocol documents. The statistical model will permit borrowing between states as specified in the Core Protocol.

Some patients who were suspected to have influenza, but were not confirmed to have influenza on microbiological testing have been enrolled in earlier versions of this DSA. This category of patient is no longer eligible for enrollment. All patients who have been enrolled in this domain and do not have microbiologically confirmed influenza will be analyzed and reported, noting that because of enhancements in the availability of microbiological testing the clinical relevance of this report will be limited. Borrowing from the influenza-negative stratum will not occur for the influenza-confirmed stratum.

Response Adaptive Randomization may be applied. If RAR is applied, the cap on the maximum or minimum proportion of patients assigned to an intervention that is specified in core protocol documents may be modified by the Statistical Analysis Committee (SAC) if needed to reduce the likelihood of sites being unblinded or to improve power. If required, any such modifications will be an operational decision of the Design Team specified in the Current State document and applied by the SAC.

The age strata will contribute to the unit-of-analysis for this domain. The shock strata will not contribute to unit-of-analysis for this domain. If applied in a future amendment of the Core Protocol, a COVID-19 strata will not contribute to unit-of-analysis for this domain.

10.3. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with immediate reveal, or with Delayed Reveal and Initiation, for situations where randomization occurs before influenza test results are available with Reveal at time of confirmed positive result.

10.4. Interactions with interventions in other domains

An *a priori* interaction with the Corticosteroid Domain or Influenza Immunomodulator domains, while possible, will not be incorporated in the statistical model.

Interactions with all other domains are either not evaluable or not considered possible and will not be incorporated into the statistical model or models in which this domain is evaluated.

If an interaction is specified with a future domain, it is sufficient for the interaction to be specified only in the DSA of such a future domain.

10.5. Nesting of interventions

There is one nest within this domain, comprising the 5- and 10-day duration of oseltamivir (see REMAP-CAP Core Protocol). The rationale for this is that the treatment effect of both oseltamivir interventions is more likely to be similar than interventions that do not contain oseltamivir.

10.6. Statistical triggers

The threshold probability for statistical triggers for superiority, effectiveness, inferiority, equivalence, futility, and non-inferiority are those specified in the relevant core protocol documents. The threshold odds ratio delta for superiority, inferiority, equivalence, futility, and non-inferiority in this domain are specified in the relevant core protocol documents. At the time of launch of this domain the REMAP-CAP Core Protocol does not include triggers for futility and non-inferiority. The threshold probability of statistical triggers for futility and non-inferiority will be those specified in future versions of relevant core protocol documents.

10.7. Post-trial sub-groups

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The *a priori* patient sub-groups of interest are:

- Immunocompromised, defined as receiving immunosuppressive treatment or having immunosuppressive disease.
- Duration of symptoms prior to randomization
- Proven concomitant bacterial co-infection, defined as having isolation or detection of a known pathogen that causes CAP from blood, pleural fluid, or lower respiratory tract specimen.
- Shock strata
- All remaining potentially evaluable treatment-by-treatment interactions with other domains, a priori, the interaction between interventions in the influenza immunomodulation domain and corticosteroid domain are of particular interest.

If there are potentially important results within one or more of these pre-specified post-platform conclusion subgroups, after the occurrence of a pre-specified threshold for the unit-of-analysis described above, this domain may re-start (new stage) without necessarily requiring a subsequent amendment with eligibility restricted to a sub-group with possible beneficial treatment effect. This will be an operational decision of the ITSC, as advised by the DSWG.

Heterogeneity of treatment of effect will also be evaluated by machine learning techniques (such as causal forest).

11.ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB are convened under the guidance provided in the core protocol and the DSMB charter. The statistical triggers relevant to this domain are specified above. If requested by the DSMB, domain-specific safety secondary endpoints will be provided to the DSMB as part of the regular safety reports.

11.2. Potential domain-specific adverse events

The antiviral agents used in this domain have known safety profiles. Nausea, diarrhea, and vomiting are recognized adverse events in ambulatory patients but this is of limited relevance to critically ill patients. Additionally, it is expected that a high proportion of critically ill patients who will be enrolled in this trial will experience mortality or substantial morbidity. There are no domain-specific adverse events requiring specific data collection instruments for oseltamivir or baloxavir administration.

Other SAEs should be reported only where, in the opinion of the site-investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see relevant core protocol documents).

11.3. Domain-specific consent issues

Oseltamivir and baloxavir are approved by the FDA for the treatment of uncomplicated influenza in outpatients whose symptoms have not lasted more than two days (2019). Guidelines in some regions recommend administration of oseltamivir to all hospitalized patients with suspected or microbiological testing-confirmed influenza, regardless of symptom duration (Uyeki et al., 2019). However, this is based on low quality evidence, especially for ICU patients. Some clinicians do not administer oseltamivir to some or all patients with microbiological testing-confirmed influenza because of uncertainty about the effectiveness of oseltamivir in critically ill patients with influenza (see Background Section 6). The role of baloxavir in severely ill influenza patients is unclear. The role of antivirals in acute viral infections in severely ill patients, as demonstrated in COVID-19, is also unclear.

Investigators will be able to choose to not participate in the no antiviral (no placebo) intervention at their site. The recommendation of the trial is that sites should participate in the no antiviral intervention. This recommendation is based on the failure of any antiviral to demonstrate effectiveness in critically ill patients receiving antiviral agents for the treatment of COVID-19 and sparse data on the effectiveness of oseltamivir in this population. Sites that routinely use oseltamivir can participate in this domain by restricting the allocation options at their site to the interventions that result in administration of an active antiviral agent. Additionally, clinicians are directed to not enroll an individual patient if the treating clinician believes that participation in this domain is not in the best interests of the patient. Enrollment criteria are used to exclude patients from individual interventions for appropriate clinical reasons (e.g. hypersensitivity to study drug).

Where all interventions that are available at the participating site are regarded as being part of the acceptable spectrum of standard care and given the time imperative to commence antivirals, entry to the study, for participants who are not competent to consent, is preferred to be via waiver-of-consent or some form of delayed consent. Informed consent can be sought where required.

Additional sampling will only occur at selected participating sites. The only samples obtained will be airway specimens, for the purposes of influenza virus analyses. These samples will be stored regionally for analyses. No genetic information about the individual patient will be obtained.

Pregnant women are susceptible to influenza and are at higher risk of a worse outcome; they are not excluded from this domain but they are excluded from interventions that include baloxavir (due to a lack of safety data in pregnancy).

If the predominant circulating influenza virus strains, either regionally or globally, have been identified by public health authorities to be resistant to oseltamivir and/or baloxavir then this domain, or specific interventions within this domain, may be suspended, either locally or globally. This will be through the decision-making of the ITSC, in conjunction with one or more RMCs if the distribution of oseltamivir resistant isolates is regional.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the REMAP-CAP trial are specified in the REMAP-CAP Core Protocol. This domain has received domain-specific support from Roche Global in the form of drug supply.

12.2. Funding of domain interventions and outcome measures

Oseltamivir will be provided by participating hospitals on the basis that if the patient was not participating in the trial, appropriate antivirals may have been indicated and provided by the treating hospital. Baloxavir will be provided by Roche, or by participating hospitals. For sites participating in the viral sampling component, the costs of additional sampling, shipping, central storage and analysis will be met by the trial.

12.3. Domain-specific declarations of interest

All investigators involved in REMAP-CAP maintain a registry of interests on the REMAP-CAP website. These are updated periodically and publicly accessible on the study website.

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