Domain-Specific Appendix:
INFLUENZA ANTIVIRAL DOMAIN

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

Influenza Antiviral Domain-Specific Appendix Version 3 dated 5th November, 2024

In this domain, participants meeting platform entry criteria 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

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:

Age Stratum	≥ 28 days old and <12 years old		≥ 12 years and < 18 years old		≥ 18 years old	
Illness Severity State	Moderate State	Severe State	Moderate State	Severe State	Moderate State	Severe State
Domain-specific strata	N/A	N/A	N/A	N/A	N/A	N/A
Interventions specified in this DSA	• No antiviral • 5 days oseltamivir • 10 days oseltamivir • Baloxavir on days 1 & 4 • 5 days oseltamivir + baloxavir on days 1 & 4 • 10 days oseltamivir + baloxavir on days 1 & 4	• No antiviral • 5 days oseltamivir • 10 days oseltamivir • Baloxavir on days 1 & 4 • 5 days oseltamivir + baloxavir on days 1 & 4 • 10 days oseltamivir + baloxavir on days 1 & 4	• No antiviral • 5 days oseltamivir • 10 days oseltamivir • Baloxavir on days 1 & 4 • 5 days oseltamivir + baloxavir on days 1 & 4 • 10 days oseltamivir + baloxavir on days 1 & 4	• No antiviral • 5 days oseltamivir • 10 days oseltamivir • Baloxavir on days 1 & 4 • 5 days oseltamivir + baloxavir on days 1 & 4 • 10 days oseltamivir + baloxavir on days 1 & 4	• No antiviral • 5 days oseltamivir • 10 days oseltamivir • Baloxavir on days 1 & 4 • 5 days oseltamivir + baloxavir on days 1 & 4 • 10 days oseltamivir + baloxavir on days 1 & 4	• No antiviral • 5 days oseltamivir • 10 days oseltamivir • Baloxavir on days 1 & 4 • 5 days oseltamivir + baloxavir on days 1 & 4 • 10 days oseltamivir + baloxavir on days 1 & 4
Interventions submitted for approval in this jurisdiction	☐ No antiviral ☒ 5 days oseltamivir ☐ 10 days oseltamivir ☐ Baloxavir on days 1 & 4 ☐ 5 days oseltamivir + baloxavir on days 1 & 4 ☐ 10 days oseltamivir + baloxavir on days 1 & 4	☐ No antiviral ☒ 5 days oseltamivir ☐ 10 days oseltamivir ☐ Baloxavir on days 1 & 4 ☐ 5 days oseltamivir + baloxavir on days 1 & 4 ☐ 10 days oseltamivir + baloxavir on days 1 & 4	☐ No antiviral ☒ 5 days oseltamivir ☐ 10 days oseltamivir ☐ Baloxavir on days 1 & 4 ☐ 5 days oseltamivir + baloxavir on days 1 & 4 ☐ 10 days oseltamivir + baloxavir on days 1 & 4	☐ No antiviral ☒ 5 days oseltamivir ☐ 10 days oseltamivir ☐ Baloxavir on days 1 & 4 ☐ 5 days oseltamivir + baloxavir on days 1 & 4 ☐ 10 days oseltamivir + baloxavir on days 1 & 4	☐ No antiviral ☒ 5 days oseltamivir ☐ 10 days oseltamivir ☐ Baloxavir on days 1 & 4 ☐ 5 days oseltamivir + baloxavir on days 1 & 4 ☐ 10 days oseltamivir + baloxavir on days 1 & 4	☐ No antiviral ☒ 5 days oseltamivir ☐ 10 days oseltamivir ☐ Baloxavir on days 1 & 4 ☐ 5 days oseltamivir + baloxavir on days 1 & 4 ☐ 10 days oseltamivir + baloxavir on days 1 & 4

Influenza Antiviral Domain Summary	
Interventions	The following interventions are specified in this domain: • 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
Timing of Reveal	Randomization with Immediate reveal and initiation, or Delayed Reveal and Initiation.
Population	This domain will be offered to the following patient categories: • Pediatric, Adolescent, and Adult Age Strata • Moderate and Severe Illness Severity States
Domain-Specific Inclusions	Patients will be eligible for this domain if: • Patient is aged ≥ 28 days old • Influenza infection is confirmed by microbiological testing
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 commencement of sustained organ failure support • 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	Criteria that exclude a patient from 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
Outcome measures	Primary endpoint: As specified in Core Protocol documents Secondary endpoints: refer to Core Protocol documents.
Platform Conclusions	The following Platform Conclusions are possible for this domain: • Efficacy of any active intervention compared with 'no antiviral' intervention • Superiority of any active antiviral intervention • Futility of an active antiviral compared with 'no antiviral' intervention • Equivalence among active antiviral interventions • Inferiority of any active antiviral intervention
Unit of Analysis, Strata and State	The unit-of-analysis for this domain corresponds to the patients who receive an allocation within this domain, further subdivided 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 randomization will be applied to all patients, using probabilities derived from Influenza Infection Confirmed Stratum.
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any domain.

Nesting	There is one nest, comprising any intervention containing oseltamivir.

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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
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 (principles of statistical analysis and models); a Patient, Pathogen and Disease Appendix to the Core Protocol (PANDA); 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 the relevant 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 Appendix. 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 Statistical Design Team 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.

3. INFLUENZA ANTIVIRAL DOMAIN-SPECIFIC APPENDIX VERSION

The version of the Influenza 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

Version 2.3: Approved by the Influenza Antiviral DSWG on 10th May, 2024

Version 3: Approved by the Influenza Antiviral DSWG on 5th November, 2024

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

Professor Herman Goossens

Professor Anthony Gordon

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Professor John Marshall

Dr. Colin McArthur

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Professor Graham Taylor

Dr. Steve Tong

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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. Signed on behalf of the committee,

Chair _____ Date 5th November, 2024

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain to test the effectiveness of different antiviral strategies for hospitalized patients 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). World Health Organization guidelines issue a conditional recommendation, based on low-quality evidence, for oseltamivir use. 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. A recently completed randomized trial in 173 children demonstrated that baloxavir was well-tolerated, with a comparable adverse event rate to oseltamivir (Baker et al., 2020).

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 hospitalized patients with 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

8. TRIAL DESIGN

8.1. Population

8.1.1. Age Strata

This domain is available to patients who are in the Pediatric, Adolescent or Adult Age Strata, as defined in Core Protocol Documents. Eligibility within these strata may be further constrained by domain-specific eligibility criteria specified below. Participating sites may choose to offer this domain to patients in one or more (or all) of these Age Stata.

8.1.2. Illness Severity State

This domain is available for patients who are in either the Moderate or Severe State. These States are defined in Core Protocol documents. Participating sites may choose to offer this domain to patients in one or both of these Illness Severity States

8.1.3. 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 relevant Core Protocol documents. Patients eligible for the Platform 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:

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

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 commencement of sustained organ failure support
- 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. In such cases, patients will be randomly allocated a remaining intervention from among those available at that site.

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. Patients in whom all interventions are contraindicated will be treated according to the current standard of care at the clinician's discretion.

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 participating site has the option to opt-in to one or more of the remaining interventions 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.

8.3.2. 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.

8.3.4. Discontinuation of study intervention

The allocated intervention should be discontinued if there is development of a SAE which, in the opinion of the treating clinician, could be related to participation in this domain. The study interventions can be temporarily or permanently discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

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 primary outcome as specified in the Core Protocol.

8.5.2 Secondary endpoints

All secondary endpoints as specified in the 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 while the patient remains in hospital 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

Additional domain-specific data will be collected:

- Administration of antiviral medications active against influenza

9.3. Criteria for discontinuation

Refer to relevant Core Protocol documents for criteria for discontinuation of participation in this trial.

9.4. Blinding

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

10.STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

The following Platform conclusions are possible in this domain:

- Efficacy of any active antiviral intervention compared with 'no antiviral' intervention
- Superiority of any active antiviral intervention within the domain
- Futility of an active antiviral compared with 'no antiviral' intervention
- Equivalence of any pair of active antiviral interventions
- Inferiority of any intervention

Prior to a declaration of efficacy, 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 optimize 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 active 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 randomize to the active antiviral interventions to determine the comparative effectiveness of active antiviral interventions. The trigger of equivalence 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. 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 efficacy, 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), corresponds to patients who have received an allocation within this domain (i.e. Influenza Infection Confirmed Stratum). The unit-of- analysis is further subdivided by Illness Severity State (defined as the Moderate and Severe Illness Severity States) and two Age Strata (defined as Pediatric Age Stratum and a combination of Adolescent and Adult Age Strata, which will be combined for analytic purposes). The statistical model will permit borrowing between Strata and 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 will not be permitted between the Influenza Infection Not Confirmed Stratum and Influenza Infection Confirmed Stratum.

10.3. Application of Response-Adaptive Randomization

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.

10.4. 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 and Initiation, or with Delayed Reveal and Initiation, for situations where randomization occurs before influenza test results are available, with reveal of allocation occurring at time of confirmed positive result.

10.5. 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.

10.6. Nesting of interventions

There is one nest within this domain, comprising the oseltamivir-containing interventions (see Core Protocol documents). 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, regardless of baloxavir administration.

10.7. Threshold probability for superiority, efficacy, and inferiority

The threshold probability for statistical triggers for superiority, efficacy, inferiority, are those specified in the relevant core protocol documents.

10.8. Threshold odds ratio delta for equivalence and futility

If two interventions within this domain, for a unit-of-analysis, have at least a 0.90 probability of being within a pre-specified delta for the primary endpoint then these interventions will be deemed as being equivalent. The size of the pre-specified odds ratio delta is 0.10. The threshold probability of a statistical trigger for futility will be those specified in the Core Protocol.

10.9. Informative priors

This domain will launch with priors that are uninformative for main effects.

10.10. 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:

- Immune Suppressed Strata
- Duration of symptoms prior to randomization
- Bacterial Infection Diagnosed Strata.
- 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 may also be evaluated by multiple methods including 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 severely ill patients. 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 risk assessment

Participating sites will have reviewed the interventions in this domain and their clinical appropriateness for evaluation in this population. Enrollment in this domain will only occur if the treating clinician believes that participation is not contrary to the best interests of the patient. The risks and benefits of participation will be outlined in local consent documentation.

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 severely ill 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). 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. Enrollment criteria are used to exclude patients from individual interventions for appropriate clinical reasons (e.g., hypersensitivity to study drug).

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.

11.4. Domain-specific consent issues

In the absence of evidence of effectiveness of any interventions specified in this DSA or alternative intervention that lies within this domain, the use of a 'no antiviral' control is both appropriate and ethical.

Clinicians may choose not to enroll individual patients if they feel that participation is not in patient's best interests, and safety criteria are used to exclude patients from this domain for appropriate clinical reasons.

For patients who are not competent to consent, and in accordance with local jurisdictional requirements, where permitted entry into this domain is preferred to be via waiver-of-consent or some form of delayed consent. In any jurisdiction in which prospective agreement is necessary, reveal of assignment status will only occur after prospective agreement has been obtained.

During a pandemic, including an influenza pandemic, visiting by relatives of affected patients may not be possible. In such situations, alternative methods for confirming consent including electronic and telephone communication, as permitted by an appropriate ethical review body, may be acceptable methods for confirming agreement to participate in this (and other) domains of the platform.

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.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the Platform are specified in Core Protocol documents. 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 may 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

A registry of interests for all members of the International Trial Steering Committee is maintained on the trial website. These are updated periodically and publicly accessible on the study website.

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14.APPENDIX 1: REGION-SPECIFIC MODIFICATIONS FOR JAPAN

The following modifications to this DSA apply at participating locations in Japan. In all other respects, this domain will be administered as specified elsewhere in this DSA.

14.1. Eligibility Criteria

In Japan, the following exclusion criterion will apply, in addition to those domain-specific eligibility criteria specified in this DSA.

14.1.1. Domain Exclusion Criteria

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

- Severe renal impairment (eGFR ≤ 10 mL/min/1.73m^2) or receiving renal replacement therapy

14.2. Interventions

14.2.1. Oseltamivir dosing

In Japan, oseltamivir will be administered as follows, according to renal function:

Agent	**Receiving renal replacement therapy**	**Renal impairment (Creatinine Clearance ≤ 30 mL/min)**	**Normal renal function (Creatinine Clearance > 30 mL/min)**
Oseltamivir	75mg, once every five days	75mg, once daily	75 mg, twice daily

14.2.2. Baloxavir dosing

In Japan, baloxavir will be administered as follows:

Agent	**Weight < 80 kg**	**Weight ≥ 80 kg**
Baloxavir	40 mg on days 1 and 4	80 mg on days 1 and 4