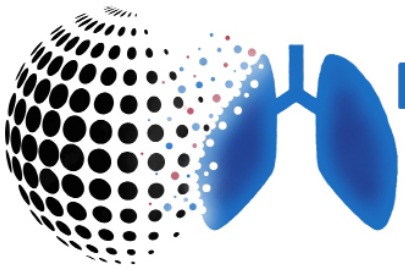

REMAP-CAP
Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Domain-Specific Appendix:
ANTIVIRAL DOMAIN

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

Antiviral Domain-Specific Appendix Version 1.0 dated 10 July 2019

Summary

In this domain of the REMAP-CAP trial, participants with community-acquired pneumonia admitted to participating intensive care units with suspected or microbiological testing-confirmed influenza infection will be randomized to receive one of up to 3 interventions depending on availability and acceptability:

- No antiviral agents (no placebo)
- 5 days of oseltamivir
- 10 days of oseltamivir

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

REMAP-CAP: Antiviral Domain Summary	
Interventions	• No antiviral agents (no placebo) • 5 days of oseltamivir • 10 days of oseltamivir
Unit of Analysis and Strata	The unit-of-analysis for this domain is the influenza present stratum. Analysis and Response Adaptive Randomization are applied by influenza strata. Some patients will be randomized who are in the influenza absent stratum and will be analysed separately, but borrowing will be permitted. The shock strata does not contribute to the unit-of-analysis for this domain.
Evaluable treatment-by-treatment Interactions	Treatment-treatment interactions will be evaluated between interventions in this domain and interventions in the Corticosteroid Domain. No other interactions will be evaluated with any other domain.
Nesting	There is one nest, comprising the 5- and 10-day duration of oseltamivir.
Timing of Reveal	Randomization with Immediate Reveal and Initiation.
Inclusions	Inclusion criteria are the same as the REMAP see Core Protocol Section 7.4.1, and • Influenza infection is suspected by the treating clinician or has been confirmed by microbiological testing
Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following: • More than 24 hours has elapsed since Intensive Care Unit (ICU) admission • Known hypersensitivity to oseltamivir • Patient has already received two or more doses of oseltamivir or other neuraminidase inhibitors • Intention to commence or continue, if already commenced, an antiviral active against influenza other than oseltamivir • The treating clinician believes that participation in the domain would not be in the best interests of the patient
Intervention-Specific Exclusions	Nil, not applicable.
Outcome measures	Primary REMAP endpoint: all-cause mortality at 90 days. Secondary REMAP endpoints refer to Core Protocol Section 7.6.2 Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrolment): • Virologic endpoints (at selected sites): o Change from baseline in influenza virus levels measured at D3 and D7 or ICU discharge in upper and lower respiratory tract specimens. o Incidence of emergence of amino acid changes associated with reduced susceptibility to oseltamivir at D3 and D7 or ICU discharge. • Serious adverse event (SAE) as defined in 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, Section 1.2 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. 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 Antiviral Domain-Specific Working Group (DSWG) on 10 July 2019.

4. ANTIVIRAL DOMAIN GOVERNANCE

4.1. *Domain members*

Chair: Dr. Srinivas Murthy

Members: Professor Derek Angus
Dr. Scott Berry
Professor Marc Bonten
Professor Allen Cheng
Dr. Lennie Derde
Professor Herman Goossens
Dr. Sebastiaan Hullegie
Professor Menno de Jong
Professor John Marshall
Dr. Colin McArthur
Dr. Tim Uyeki

Professor Steve Webb

4.2. *Contact Details*

Chair:

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5. ANTIVIRAL DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

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

Chair _____ Date 10 July 2019

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 suspected or microbiological testing-confirmed influenza virus infection in patients with concomitant severe community-acquired pneumonia (CAP) who are admitted to an Intensive Care Unit (ICU).

6.2. *Domain-specific background*

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 in 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 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 pandemic, the objective of this domain is to determine the effectiveness of different antiviral strategies in severely ill patients with pneumonia and confirmed influenza virus infection.

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. 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)

Detection of antiviral efficacy is through both clinical and biologic endpoints. 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.

There is a possible interaction between the efficacy of antivirals and immunomodulation with corticosteroids 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.

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 severely 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 with severe CAP who have suspected or microbiological testing-confirmed influenza virus infection.

We hypothesize that the probability of all-cause mortality at 90 days after enrollment will differ based on the allocated antiviral strategy. The following interventions will be available:

- No antiviral agent (no placebo)
- Oseltamivir (enterally) twice daily for 5 days or until hospital discharge (whichever occurs first)
- Oseltamivir (enterally) twice daily for 10 days or until hospital discharge (whichever occurs first)

We hypothesize that the treatment effect of different antiviral strategies is different depending on allocation status in the Corticosteroid Domain. This is a treatment-by-treatment interaction between the interventions in the Antiviral Domain and the Corticosteroid Domain.

Each participating site has the option to opt-in to two or three 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 oseltamivir routinely as part of their current treatment approach are not encouraged to participate in the option that includes the no-oseltamivir intervention. Sites that do not utilize oseltamivir routinely are encouraged to participate in the no oseltamivir and oseltamivir for 5 days interventions. Sites that do not perform routine testing for influenza in patients with severe CAP should not participate in this domain.

8. TRIAL DESIGN

This domain will be conducted as part of the REMAP-CAP trial (see Core Protocol Section 7). Treatment allocation will be adaptive, as described in the Core Protocol Section 7.5.2.

8.1. *Population*

The REMAP enrolls patients with severe CAP admitted to ICU (see Core Protocol Section 7.3).

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 (see Core Protocol Section 7.4). Patients eligible for the REMAP may have conditions that exclude them from the Antiviral Domain.

8.2.1. Domain inclusion criteria

Influenza infection is suspected by the treating clinician or 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:

- More than 24 hours has elapsed since ICU admission
- Known hypersensitivity to oseltamivir
- Patient has already received two or more doses of oseltamivir or other neuraminidase inhibitors
- Intention to prescribe an antiviral active against influenza other than oseltamivir
- 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

Nil.

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 (enterally) twice daily for 5 days or until hospital discharge (whichever occurs first)
- Oseltamivir (enterally) twice daily for 10 days or until hospital discharge (whichever occurs first)

It is required that all sites will participate in the 5-day intervention, and each site has the option to opt-in to one or both 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

8.3.3. Antiviral administration in patients negative for influenza

In patients with suspected influenza who receive an allocation status to receive oseltamivir but who subsequently test negative for influenza after allocation should have treatment with oseltamivir ceased unless the treating clinician believes that doing so is not clinically appropriate.

8.4. *Concomitant care*

Additional antiviral agents active against influenza should not be administered. In patients who have received an allocation status in the Antibiotic Domain, and have microbiological testing confirmed influenza continuation of empiric anti-bacterial agents will be as per the Antibiotic Domain-Specific Appendix (Section 8.3).

8.5. *Endpoints*

8.5.1 Primary endpoint

The primary endpoint for this domain is the REMAP primary outcome (all-cause mortality at 90 days) as specified in Core Protocol Section 7.6.1.

8.5.2 Secondary endpoints

All secondary endpoints as specified in the Core Protocol Section 7.6.2.

The domain-specific secondary outcome measures (occurring during the index hospitalization, censored 90 days after enrollment) will be:

- Virologic endpoints, at selected sites:
    - Change from baseline in influenza virus levels, measured at D3 and at D7 or ICU discharge (whichever occurs first) in upper and lower respiratory tract specimens.

- Incidence of emergence of amino acid changes in influenza viruses associated with reduced susceptibility to oseltamivir at D3 and D7 or ICU discharge, whichever occurs first, in upper and lower respiratory tract specimens all patients.

- Serious adverse event (SAE) as defined in 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, 3, and D7 or ICU discharge, whichever occurs first, for participating patients in selected sites, from paired sampling of nasopharyngeal swabs of all patients and tracheal aspirates from patients who are intubated.

Samples will be stored locally and batch shipped for central analysis at national or regional reference labs for quantitative influenza virus titers and resistance testing, as described above in secondary endpoints. 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 in Core Protocol Section 8.9, will be collected for this domain.

9.3. *Criteria for discontinuation*

Refer to Core Protocol Section 8.7 for criteria for discontinuation of participation in the REMAP-CAP trial.

9.4. *Blinding*

9.4.1. Blinding

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

9.4.2. Unblinding

Not relevant.

10. STATISTICAL CONSIDERATIONS

10.1. *Domain-specific stopping rules*

If a Platform conclusion of equivalence in the primary endpoint is demonstrated 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 Sections 7.8.6 to 7.8.9.

10.2. *Unit-of-analysis and strata*

The unit-of-analysis, for both analysis of treatment effect and the Response Adaptive Randomization (RAR), will be the influenza present stratum, as specified in the Core Protocol. The population that will be used to determine a Statistical Trigger and Platform Conclusion are patients in the influenza present stratum as defined in Core Protocol, i.e. microbiological testing-confirmed influenza or patients enrolled in the domain who do not have influenza testing performed. Some patients will be randomized who are in the influenza absent stratum and will be analyzed separately. The statistical model will permit borrowing as specified in Core Protocol Section 7.8.3.3.

Safety analyses will be conducted at each adaptive analysis for patients randomized in this domain who are in the influenza absent stratum, as defined in Core Protocol (i.e. patients who are tested and are negative for influenza). At the time of a Platform Conclusion, results will be reported for all randomized patients, patients in the influenza present stratum, and patients in the influenza negative stratum.

The shock 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 and Initiation (see section 7.8.3.6 in Core Protocol)

10.4. *Interactions with interventions in other domains*

An *a priori* interaction with the Antibiotic Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Macrolide Duration Domain is not considered possible and will not be incorporated into the statistical models used to analyze this domain.

An *a priori* interaction with the Corticosteroid Domain is considered possible and will be incorporated into the statistical models used to analyze this domain.

No interaction is evaluable between the Ventilation Domain and this domain.

10.5. *Nesting of interventions*

There is one nest within this domain, comprising the 5- and 10-day duration of oseltamivir (see Section 7.8.3.8 in Core Protocol). The rationale for this is that the treatment effect of both oseltamivir interventions is more likely to be similar than no oseltamivir.

10.6. *Threshold odds ratio delta for equivalence*

The threshold odds ratio delta for equivalence in this domain is that specified in the Core Protocol (Section 7.8.8).

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.
- 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

11.ETHICAL CONSIDERATIONS

11.1. *Data Safety and Monitoring Board*

The DSMB should be aware that the superiority, inferiority, or equivalence of different interventions with respect to the primary endpoint is possible, and if equivalence is demonstrated, determination of the optimal intervention may be based on secondary endpoints, such as hospital length-of-stay or virus shedding.

There will be patients enrolled into this domain who will be subsequently determined to be influenza-negative. These patients will likely have been exposed to a small number of oseltamivir doses before test results become available. The DSMB will receive and evaluate outcomes in these patients to determine safety events relevant to antiviral administration, in addition to the patients that are influenza-positive, and report to the chair of the ITSC where relevant.

11.2. *Potential domain-specific adverse events*

The antiviral agent used in this domain has a known low toxicity profile. Nausea 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 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 Core Protocol Section 8.13).

11.3. *Domain-specific consent issues*

The antiviral to be tested in this domain is 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).

Investigators will be able to choose to not include the no-oseltamivir (no placebo) intervention at their site. The recommendation of the trial is that sites should only participate in the no-oseltamivir intervention if that sites current policy is to not administer oseltamivir or if the site has concerns about the balance between safety and benefit of oseltamivir. Sites that routinely use oseltamivir can participate in this domain by restricting the allocation options at their site to the two interventions that result in administration of oseltamivir. 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. Enrolment criteria are used to exclude patients from individual interventions for appropriate clinical reasons (e.g. hypersensitivity to study drug). To ensure adequate recruitment into all three arms proposed, sites that participate in the 'no antiviral agent' intervention are encouraged to restrict the interventions to the no antiviral agent and the 5-day oseltamivir arm.

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.

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.

If the predominant circulating influenza virus strains, either regionally or globally, have been identified by public health authorities to be resistant to oseltamivir then 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 Core Protocol Section 2.5. This domain has not received any additional domain-specific funding.

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. 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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