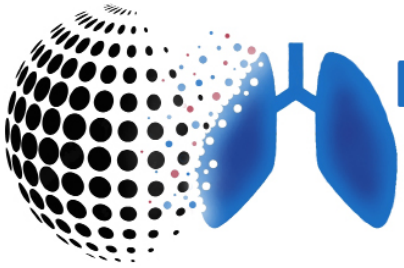


Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP):

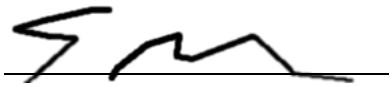
PATIENT, PATHOGEN AND DISEASE APPENDIX (PANDA) TO THE CORE PROTOCOL

Patient, Pathogen and Disease Appendix (PANDA) to the Core Protocol Version 1.0 dated 5th November, 2024

Table of Contents

1. Background 3
2. Patient Characteristics 4
3. Pathogens 4
3.1. Defining pathogen status 5
3.2. Pathogen status for domain eligibility 6
3.3. Pathogen status for analysis strata 6
3.4. Definitions of pathogen analysis strata 6
3.4.1. Approach to novel pandemic pathogens 7
4. Diseases and clinical features 7
4.1. Acquisition of infection 8
4.2. Disease entity 8
4.3. Illness severity 9
4.4. Specific clinical features or syndromes 10
4.5. Diseases and clinical features for eligibility 11
4.6. Disease and clinical feature analysis strata 11
5. Consistent categorization of pathogens, diseases and clinical features 12
6. Continuity with pre-existing domains 12

The ITSC have read the appendix and authorize it as the official PaNDA for the study entitled REMAP-CAP. Signed by the ITSC Chair, on behalf of the ITSC

ITSC Chair  Date 5th November, 2024

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1. BACKGROUND

The Core Protocol specifies Platform-level enrollment criteria for hospitalized patients with respiratory tract infection. This Patient, Pathogen ANd Disease Appendix (PANDA) defines how such patients may be further categorized by pre-infection characteristics, respiratory pathogens, diseases and disease characteristics. Category memberships can be either fixed at Platform enrollment or are dynamic over the course of disease ("State"), including disease progression ("Stage"), and may be applied by Domains as inclusion or exclusion criteria and to define analysis populations ("Strata"). The Platform enrolls patients with varying baseline characteristics, treated in differently resourced health systems, with respiratory tract infections resulting from infection with specific pathogens or combinations of pathogens (e.g., influenza with bacterial co-infection), and manifesting as different diseases (e.g., pneumonia) and progressing through stages of disease severity sometimes with specific additional clinical features (e.g., shock or acute respiratory distress syndrome). Each of these characteristics can be used to determine eligibility for domains, or define categories that may have differential treatment effects.

The PANDA describes how specific patient, pathogen, disease, illness severity and additional clinical features are defined and categorized. Each domain may use these categories to constrain eligibility and to stratify analysis. How these are applied in each domain is specified in the eligibility section and the unit-of-analysis section of the Domain Specific Appendix. If a Domain utilizes delayed reveal of randomized treatment allocation, dynamic categorization required for eligibility must be reassessed at the time of the reveal.

It is anticipated that while Domains will commonly use many of these categories to constrain enrollment to a population of interest, the analysis of each Domain will only involve limited or no further sub-categorization. Such analytic strata will only be applied where there is a high likelihood

of heterogeneity of treatment effects. This appendix therefore provides definitions for category standardization across different domains to be applied as required.

2. PATIENT CHARACTERISTICS

Age: Age is defined in three categories, Adult (aged 18 years or older), Adolescent (aged 12 years or older and less than 18 years), or Pediatric (aged 28 days or older and less than 12 years) at the time of Platform enrollment.

Immune suppression: Patients who have increased susceptibility to infection due to receipt of immunosuppressive treatment or due an immunosuppressive disease at the time of Platform enrollment are categorized as immune suppressed. Qualifying immunosuppressive diseases and treatments are defined in an operational document.

Regional income level: Regional income level categories are defined by World Bank Income Classification (high, upper middle, lower middle, low) of the country of patient enrollment. Domains may pool income level categories, for example, distinguishing two categories: high-income and non-high income (incorporating upper-middle, lower-middle, and low).

3. PATHOGENS

The following pathogen categories are recognized:

- Influenza virus
- SARS-CoV-2
- MERS-CoV
- Respiratory syncytial virus (RSV)
- Any recognized viral respiratory pathogen other than influenza, SARS-CoV-2, MERS-CoV or RSV (grouped together)
- Bacteria known to cause respiratory tract infection
- A novel pandemic respiratory pathogen

It is possible that additional defined pathogens may be included in this appendix over time due to the changing epidemiology of respiratory tract infections or due to a changing focus of the Platform.

As co-infection is a common finding in the respiratory tract, Domains can constrain eligibility and define analysis populations to include or exclude patients with an assigned pathogen status in one or

more of these categories. A patient's pathogen status is defined by the matrix of all relevant pathogen groups.

3.1. Defining pathogen status

Clinical treatment decisions are often made prior to the availability of microbiological test results and may rely on history, examination and supporting investigations such as inflammatory markers and imaging ("clinical assessment") to include or exclude potential infecting pathogen(s) relevant to those decisions. Even after all microbiological and other clinical information is available it may not be possible to identify the pathogen(s) responsible for an episode of infection.

In this Platform, pathogen status may be assigned based on clinical assessment, microbiological testing, or both. Each DSA will specify which pathogens are relevant to the domain. For each pathogen, a hierarchy of infection likelihood exists consisting of 'confirmed', 'suspected but not confirmed' (divisible, for bacterial infection, into two subcategories: 'probable' and 'possible'), 'not suspected', and 'excluded' (i.e. tested and not detected) based on clinical assessment and microbiological test results. For the presence of a pathogen to be 'confirmed' or 'excluded', there must be supportive microbiological testing.

Domains can select the infection likelihood threshold that is required for eligibility. Domains may also constrain eligibility according to additional criteria related to the nature of the sample undergoing microbiological tests, the time-window in which the sample is collected, or microbiological testing types. If not specified by a domain, guidance about qualifying microbiological testing will be provided in operational documents. Each pathogen status used for analysis is defined as a binary variable at Platform level.

It is acknowledged that, for bacterial infection or co-infection, results from commonly used microbiological testing strategies may take a significant time (e.g., culture) and have low sensitivity. Therefore, the population considered to have bacterial infection is defined primarily by clinical assessment plus any microbiological data available at the time of eligibility assessment rather than final microbiological test results. For other pathogens, the clinical features are non-specific and microbiological tests have a high sensitivity and, in this case, microbiological testing may be more important than clinical suspicion. For some pathogens, clinical features may be sufficiently similar that a domain considers them collectively (e.g., 'confirmed viral respiratory tract infection' may be a group defined as the detection of any virus known to cause respiratory tract infection on microbiological testing).

3.2. Pathogen status for domain eligibility

In addition to Platform inclusion and exclusion criteria, a domain can restrict eligibility by specifically including or excluding patients with a specific pathogen status (including co-infection) as domain eligibility criteria. For example, a domain could include participants with influenza virus infection, exclude patients with confirmed SARS-CoV-2 infection and exclude participants who have confirmed bacterial co-infection. For the purposes of eligibility, domains may include patients with differing likelihood thresholds for the same pathogen (e.g., one domain may include patients with suspected or confirmed influenza infection and another may constrain eligibility to confirmed infection only). Confirmation of qualifying pathogen status may occur through a delayed reveal process if commencement of assigned treatment can reasonably be deferred.

3.3. Pathogen status for analysis strata

Pathogen analysis strata allow differential treatment effects to be assessed in participants with specific pathogens (or groups of pathogens) at eligibility assessment and improves covariate balance within pathogen strata.

A single statistical model requires pathogen analysis strata to be defined based on information available at eligibility assessment, no later than time of reveal of treatment allocation. For some participants, additional microbiological test results which are indicative of infection status at baseline may become available after reveal of treatment allocation. These microbiological test results do not influence pathogen strata for the primary analysis but can contribute to the definition of populations for additional safety analyses, secondary analyses or post-platform conclusion subgroups of interest for specific domains.

3.4. Definitions of pathogen analysis strata

This Appendix defines pathogen analysis strata that contribute to the unit-of-analysis for the following pathogens:

Influenza virus infection is stratified as influenza confirmed (influenza virus detected on microbiological testing with a compatible clinical assessment) and influenza not confirmed.

SARS-CoV-2 infection is stratified as SARS-CoV-2 infection confirmed (SARS-CoV-2 detected on microbiological testing with a compatible clinical assessment) and SARS-CoV-2 not confirmed.

MERS-CoV infection is stratified as MERS-CoV infection confirmed (MERS-CoV detected on microbiological testing with a compatible clinical assessment) and MERS-CoV not confirmed.

RSV infection is stratified as RSV infection confirmed (RSV detected on microbiological testing with a compatible clinical assessment) and RSV not confirmed.

Respiratory virus infection (influenza, SARS-CoV-2, MERS-CoV, RSV and any other recognized viral respiratory pathogen grouped together) is stratified as viral infection confirmed (a recognized viral respiratory pathogen is detected on microbiological testing with a clinically compatible illness) and respiratory viral infection not confirmed.

Bacterial infection is stratified as bacterial infection diagnosed (comprising cases where infection with a recognized bacterial respiratory pathogen is confirmed or probable) and bacterial infection not diagnosed (comprising cases where infection with a recognized bacterial respiratory pathogen is neither confirmed nor probable i.e., bacterial infection was assessed as only possible or not suspected).

Pandemic respiratory pathogen infection is stratified as pandemic respiratory pathogen infection confirmed (the pandemic respiratory pathogen is detected on microbiological testing with a clinically compatible illness) and pandemic respiratory pathogen infection not confirmed.

It is acknowledged that patients hospitalized with respiratory tract infection may not have a causative pathogen diagnosed by clinical assessment or confirmed by microbiological testing. Such participants may be considered to be a separate pathogen analysis stratum.

3.4.1. Approach to novel pandemic pathogens

It is acknowledged that a new pandemic pathogen may be completely novel and, in this situation, the default is for a novel pathogen to be considered separate from other pathogens as above. However, if the pandemic pathogen is considered to be sufficiently similar to an existing pathogen (e.g., pandemic influenza virus and seasonal influenza virus) it will be an operational decision as to whether borrowing, pooling, or an independent analysis occurs in the primary statistical model.

4. DISEASES AND CLINICAL FEATURES

The Platform recruits patients with a broad range of respiratory tract infections. In clinical practice these respiratory tract infections are often considered in terms of specific diseases (such as ‘pneumonia’ or ‘upper respiratory tract infection’), illness severity (‘Moderate’, ‘Severe’, or

'Recovering') with possible additional clinical features (such as 'shock' or 'hypoxia'). Categories of diseases, illness severity and clinical features present at randomization (including delayed reveal) may be used by domains to constrain eligibility, or to define membership of analysis strata, or both. Categorization defined by attributes which are dynamic over the course of disease represent "States" which are assigned at the time of enrollment and randomization.

Although there are several dynamic disease and clinical features described in this appendix, the Platform uses progression to a new Illness Severity State to permit assessment to receive additional allocations in other domains. Participants who have been enrolled in one Illness Severity State may therefore only receive allocations in additional domains where their subsequent Illness Severity State represents progression to a new disease stage. For example, enrollment of a patient with moderate illness severity may be followed by subsequent randomization with severe illness or when recovering from their acute infection, but not in any other order. If a domain is available in more than one Illness Severity State, participants may receive an allocation in that domain only once.

4.1. Acquisition of infection

Respiratory tract infection can be acquired in the community or in hospital. This Appendix defines the following categories at the time of randomization:

- **Community-acquired,** defined as acute infection acquired outside of the hospital and manifesting within 48 hours of hospital admission
- **Hospital-acquired**, defined as infection not incubating at the time of hospital admission and manifesting 48 hours or more after hospital admission
- **Ventilator-associated**, a subcategory of hospital-acquired infection, additionally defined as infection in an invasively ventilated patient manifesting 48 hours or more after endotracheal intubation

4.2. Disease entity

Respiratory tract infection can manifest as a range of disease entities. This Appendix defines the following disease entity states at the time of randomization:

- **Respiratory tract infection**, defined in two categories, lower or upper, with lower defined as infection of the airways below the level of the larynx (including tracheitis, bronchitis, bronchiolitis, and pneumonia) and upper defined as infection of the airways at the level of the larynx and above, excluding isolated otitis media or mastoiditis

- **Pneumonia**, defined in two categories, present or absent, with present defined as radiological evidence of new onset infiltrate consistent with infection (in patients with pre-existing radiological changes, evidence of new infiltrate)

4.3. Illness severity

Respiratory illness severity can change over time as a patient's disease progresses and illness severity is an important determinate of both clinical outcome and potential differential treatment effect. Randomization is only permitted once in each defined disease stage and illness severity analytic strata are always applied for domains that randomize patients in more than one stage of illness severity. This Appendix defines stage of illness in the following three categories of illness severity at the time of randomization:

- The **Moderate State**, defined as hospitalized patients who are:
    - not receiving qualifying organ failure support AND
    - not in the Recovering State
- The **Severe State**, defined as hospitalized patients:
    - receiving qualifying organ failure support AND
    - not in the Recovering State
- The **Recovering State**, defined as hospitalized patients who are:
    - clearly recovering from their acute respiratory tract infection AND
    - unlikely to require or receive a significant escalation in level of organ failure support for the remainder of their hospital admission

Qualifying organ failure support is defined as:

- Invasive mechanical ventilation
- Non-invasive ventilation (bilevel positive airway pressure or continuous positive airway pressure by mask or helmet)
- High-flow nasal oxygen with a fractional inspired oxygen concentration of 0.4 or higher and with flow rate of at least 30 liters per minute (or at least 2 liters per minute per kilogram of bodyweight in children less than 15 kilograms)
- Continuous infusion of vasopressors, inotropes or both

Patients are not eligible for randomization in the Moderate State if they have been previously randomized in the Severe State, if they have previously been randomized in the Recovering State, or

if they have received invasive mechanical ventilation at any time during this acute admission. A participant is eligible to be randomized in the Severe Illness Severity State if they have previously been randomized in the Moderate Illness Severity State, but not if they have previously been randomized in the Recovering Illness Severity State. A patient may transition between moderate, severe, and recovering illness severity stages while remaining potentially eligible within the Platform but is assigned to the Illness Severity State that applies at the time of each randomization.

4.4. Specific clinical features or syndromes

Respiratory tract infection can be associated with specific clinical features or syndromes. This Appendix defines the following categories:

- **Acute Hypoxemic Respiratory Failure** is a State defined in two categories, present or absent, with 'present' defined as patients with all of the following:
    - New or worsening respiratory symptoms that developed within 2 weeks prior to the onset of oxygen/respiratory support
    - Currently receiving respiratory support (meeting the Severe Illness Severity State organ failure definition) with $FiO_2 \geq 0.40$
    - The hypoxemia is caused by acute respiratory infection (and not primarily due to other causes such as acute heart failure, fluid overload, or pulmonary embolism)

- **Hypoxemic State**, defined in 3 categories comprising:
    - patients who are not receiving invasive mechanical ventilation
    - patients who are receiving invasive mechanical ventilation and have a ratio of arterial partial pressure of oxygen to fractional inspired concentration of oxygen (P:F ratio) of ≥ 200 mmHg (or saturation to fractional inspired concentration of oxygen ratio of ≥235) or are receiving invasive mechanical ventilation with the Positive End-Expiratory Pressure (PEEP) set to less than 5 cm of water (irrespective of the P:F ratio), and
    - patients who are receiving invasive mechanical ventilation with a PEEP of 5 cm of water or more and have a P:F ratio of <200 mmHg (or a S/F < 235)

- **Acute Respiratory Distress Syndrome** is a State defined in two categories, present or absent, with 'present' defined as patients with <u>all</u> of the following:

- Pulmonary edema precipitated by respiratory tract infection and not exclusively or primarily attributable to cardiac failure or fluid overload with hypoxemia not primarily attributable to atelectasis
- Within one week of the estimated onset of new or worsening respiratory symptoms
- Bilateral opacities on chest imaging not fully explained by effusions, atelectasis, or nodules/masses
- Receiving respiratory support with high-flow nasal oxygen (HFNO) at a flow rate of at least 30 liters per minute (or at least 2 liters per minute per kilogram of bodyweight in children less than 15 kilograms) OR invasive mechanical ventilation (IMV), non-invasive ventilation (NIV) or continuous positive airways pressure (CPAP) with PEEP or CPAP ≥5cm H_2O. (This criterion is not required in resource-limited settings where none of these modalities are available)
- P_aO_2:F_IO_2 ratio ≤300 mmHg or S_pO_2/F_IO_2 ratio ≤315 with S_pO_2 ≤97% (altitude-adjusted if >1000m)

- **Shock State**, defined in two categories, present or absent, with 'present' defined as patients receiving a continuous infusion of intravenous vasopressor or inotrope medications

4.5. Diseases and clinical features for eligibility

A domain can include or exclude a patient with specific infection acquisition, diseases entity, illness severity or accompanying clinical features as domain eligibility criteria. For example, a domain could include only participants with pneumonia, and exclude patients with shock.

4.6. Disease and clinical feature analysis strata

Disease and clinical feature analysis strata allow differential treatment effects to be assessed in participants with defined diseases and clinical features present at the time of reveal of treatment allocation and to improve covariate balance within disease and clinical feature analysis strata. Clinical and radiological findings which become evident after reveal of treatment allocation (e.g., the development of infiltrates on serial chest x-rays or new shock) will not contribute to the definition of analysis strata because they may represent disease progression rather than baseline status.

5. CONSISTENT CATEGORIZATION OF PATHOGENS, DISEASES AND CLINICAL FEATURES

Categorization described in this appendix will be applied as appropriate for all relevant domains to ensure efficient and reliable eligibility assessment processes. Consistent categorization allows the Platform to evaluate treatment effects across multiple interventions in different domains, including treatment-by-treatment interactions. Where a domain would like to evaluate treatment-by-treatment interactions in a specific population not defined in this Appendix, this is only possible if the other domain(s) identifies the same population.

6. CONTINUITY WITH PRE-EXISTING DOMAINS

There are active domains for which the DSAs were approved prior to Version 4 of the Core Protocol and this Appendix. Where Domain-Specific Appendices do not specify pathogen, disease, or clinical features, or where participants were enrolled under previous versions of protocol documents, best-estimate categorization will be determined using available data.