APPENDIX II INTERVENTION SPECIFIC APPENDICES (UK-SPECIFIC)

A: USUAL CARE

1. INTRODUCTION, RATIONALE AND PROTOCOL STRUCTURE

ECRAID-Prime's master protocol describes the overall structure and processes of the study, while this Intervention Specific Appendix (ISA) outlines details specific to the study arm. This Usual Care arm will follow current standard care in the specific country and provides a control against which the effect of new interventions that are added to usual care can be assessed. Usual Care in the trial will not be specified or mandated, and it may vary over time according to emerging evidence, evolving national recommendations, and can be tailored by responsible healthcare practitioners according to patient characteristics, the respiratory infection, clinical picture, and individual needs. In addition, individual patients are able use over-the-counter remedies. Usual Care can therefore involve prescribed and/or over-the-counter medication and/or advice on self-care. Use of key treatments will be captured in CRFs and may be considered in analyses.

2. OBJECTIVES

As per ECRAID-Prime's UK-specific master protocol.

3. STUDY DESIGN

3.1 Study Design

Participants randomised to the Usual Care arm will receive usual clinical care according to standard care in the UK, at the discretion of responsible treating clinicians and according to participant's own decisions about self-care for their respiratory tract infection.

3.2 Study Description

All study procedures for the Usual Care arm will be the same as described in the Intervention Specific Appendice (ISA) of an Investigational Product (IP) that needs Usual Care as a control.

3.3 Schematic diagram of study design

As per ECRAID-Prime's UK-specific ISA of the IP that needs Usual Care as a control.

3.4 Duration of the study per participant

As per ECRAID-Prime's UK-specific ISA of the IP that needs Usual Care as a control.

4. STUDY POPULATION

Participants will be only eligible for the Usual Care arm if they meet the in- and exclusion criteria for eligibility to at least one other IP intervention.

ECRAID-Prime started with the following three arms: Usual Care alone (A), Usual Care + Nitric Oxide Nasal Spray (NONS) (B) + Usual Care + Saline Nasal Spray (C), where Usual Care (A) is the control for Saline Nasal Spray (C) and Saline Nasal Spray (C) is the comparator of NONS (B).

Eligibility criteria are specified in ECRAID-Prime's UK-specific master protocol. Any additional inclusion and exclusion criteria will be speficied in ISAs. For the NONS and Saline Nasal Spray evaluations, these are specified in the UK-specific ISA B and ISA C.

4.1 Sample size calculation

For the NONS and Saline Nasal Spray evaluations (UK-specific ISA B and ISA C), the maximum sample size of 333 per arm has a one-sided error rate less than 2.5% and power around 90% for median time to recovery ranging from 12 to 6 days in the control group and a hazard ratio of 1.33. This assumes analysis using a Bayesian piecewise exponential model with weakly informative priors and interim analyses with early stopping rules for futility and superiority when 150 and 225 patients have been recruited to the control group and have been followed for 28 days. Early stopping rules for both superiority and futility are based on thresholds of the posterior distribution that have been justified using simulation (see M-SAP). Success is declared at maximum sample size if the posterior probability of superiority is greater than a final superiority threshold, which again is specified in the M-SAP.

5. STUDY TREATMENTS

This Usual Care arm will follow current standard care in the UK at the discretion of responsible treating clinicians and according to participant's own decisions about self-care and provides a control against which the effect of new interventions that are added to usual care can be assessed.

6. OTHER TREATMENTS AND RESTRICTIONS

Not applicable.

7 TRACEABILITY, STORAGE, ACCOUNTABILITY AND COMPLIANCE

Not applicable.

8 METHODS

8.1 Study parameters/ endpoints

As per ECRAID-Prime's UK-specific master protocol. Any (comparator) IP-specific study endpoints will be specified in the (comparator) IP-specific ISA.

8.2 Randomisation, blinding and treatment allocation

As per ECRAID-Prime's UK-specific master protocol, participants will be randomised using a rapid, secure, web-based randomisation system using non-deterministic minimisation, with a random element. The minimisation factors for the usual care arm will be the same as for the IP this arm will be compared to (as specified in the (comparator) IP-specific ISA).

8.3 Study procedures

As per ECRAID-Prime's UK-specific master protocol.

Any additions and changes to ECRAID-Prime's UK-specific master protocol for the usual care arm will be the same as for the IP this arm will be compared to (as specified in the (comparator) IP-specific ISA).

8.4 Withdrawal of individual participant

As per ECRAID-Prime's UK-specific master protocol.

8.5 Replacement of individual participants after withdrawal
As per ECRAID-Prime's UK-specific master protocol.

8.6 Discontinuation of treatment of individual participants
As per ECRAID-Prime's UK-specific master protocol.

8.7 Premature termination of the study or arm
As per ECRAID-Prime's UK-specific master protocol.

9 SAFETY REPORTING
9.1 Adverse events (AEs)
As per ECRAID-Prime's UK-specific master protocol.

9.2 Serious adverse events (SAEs)
As per ECRAID-Prime's UK-specific master protocol.

9.3 Pregnancy notification
If a participant (women of child-bearing potential) has become pregnant during trial participation, no follow-up of the pregnancy will take place.

10 STATISTICAL ANALYSIS
As per ECRAID-Prime's UK-specific master protocol.

11 ETHICAL CONSIDERATIONS
As per ECRAID-Prime's UK-specific master protocol.

12 ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION
As per ECRAID-Prime's UK-specific master protocol.

13 STRUCTURED RISK ANALYSIS
Not applicable.