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Molnupiravir for treating COVID-19 (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Molnupiravir for treating COVID-19

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of molnupiravir in people with confirmed SARS-CoV-2 infection and mild-to-moderate symptoms, with or without risk factors for severe disease.

BACKGROUND

Description of the condition

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Chu 2020). As of 27 May 2022, the World Health Organization (WHO) had recorded 525,467,084 confirmed cases and 6,285,171 deaths from COVID-19 (WHO 2022a).

The estimated median time from infection to emergence of symptoms is five to six days, and 97.5% of symptomatic cases develop symptoms within 11.5 days of exposure (Lauer 2020).

Available evidence suggests that one-third of SARS-CoV-2 virus infections remain asymptomatic (Oran 2021), but there is still uncertainty around this estimate. Risk factors for severe disease include older age (over 60 years) and the presence of comorbidities, including cardiovascular disease, hypertension, diabetes mellitus, obesity, cancers, kidney disease, liver disease, and respiratory diseases (Chen 2020; Deng 2020; Huang 2020; Williamson 2020).

Vaccination can prevent severe illness and death from COVID-19. According to the WHO, 11,811,627,599 vaccine doses had been administered globally as of 23 May 2022 (WHO 2022a). However, emerging variants of concern, diminishing immunity in vaccinated populations, and breakthrough infections continue to make COVID-19 a moving target (Gopinath 2022; Hacisuleyman 2021).

Description of the intervention

Molnupiravir is an oral drug for treatment of mild-to-moderate COVID-19 in adults who are at high risk of progression to severe disease, hospitalization, or death, and who do not have access to alternative approved treatments (Lee 2021; Painter 2021; Singh AK 2022). Molnupiravir was approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA) on 4 November 2021, and by the US Food and Drug Administration (FDA) on 23 December 2021, for the treatment of mild-to-moderate COVID-19 (Tian 2022). In March 2022, it became the first oral antiviral drug to be included in the WHO treatment guideline for people with non-severe COVID-19 with the highest risk of hospitalization (WHO 2022b; WHO 2022c). In particular, it may be beneficial to individuals who have tested positive for COVID-19 within the previous seven days and who present mild-to-moderate symptoms. Molnupiravir is currently not authorized for use in people aged under 18 years, due to concerns regarding effects on bone and cartilage growth; or for use in pregnant women with severe COVID-19, due to a paucity of data on risk of foetal harm. It is only authorized for use as a five-day course, and is not authorized for pre- or postexposure prophylaxis (Singh AK 2021; Singh AK 2022).

There are limited clinical data on adverse events linked to molnupiravir. Available data suggest that it may cause adverse effects such as nausea, dizziness, and diarrhoea (Singh AK 2021; Singh AK 2022; Tian 2022).

The other currently available antiviral options are nirmatrelvir/ritonavir, remdesivir, and monoclonal antibodies (Ansems 2021; Kreuzberger 2021; Reis 2022; Singh AK 2022). Treatments targeting the immune response form the mainstay of therapy in advanced disease; they include steroids, interleukin (IL)-6 inhibitors, and baricitinib (Kim 2020; Prescott 2020; Singh AK 2022; Tian 2022). Other treatments with limited, inconclusive, or no proven efficacy for the treatment of COVID-19 include ivermectin (Popp 2021a), chloroquine (Singh B 2021), and antibiotics such as azithromycin (Popp 2021b).

How the intervention might work

Molnupiravir was originally developed at Emory University in the USA to treat equine encephalitis, an infectious viral disease posing a threat to human and animal public health (Agostini 2019; Singh AK 2021). The drug (also known as EIDD-2801 or MK-4482) inhibits SARS-CoV-2 virus replication in animal models and human airway epithelial cell cultures (Imran 2021; Toots 2020). It acts as a mutagenizing agent that prevents viral replication in a process called 'error catastrophe' (Malone 2021). By increasing the error catastrophe rate beyond a tolerable biological threshold, it impairs viral reproduction, which leads to viral extinction (Agostini 2019; Painter 2021). Molnupiravir is a prodrug of the antiviral ribonucleoside analogue β-D-N4-hydroxycytidine (NHC; EIDD-2801), which is metabolized in the cell and activated to molnupiravir triphosphate (MTP; EIDD-1931) (Kabinger 2021; Painter 2021). NHC has demonstrated broad-spectrum antiviral activity against multiple ribonucleic acid (RNA) viruses such as the influenza virus, respiratory syncytial virus (RSV), equine encephalitis virus, Marburg virus, chikungunya virus, bovine diarrhoea virus, Ebola virus, and hepatitis C virus (Tian 2022). Research suggests that molnupiravir will be effective against Omicron and other COVID-19 variants of concern (Li 2022; Singh AK 2022; Tian 2022). One study showed that the drug was effective in vitro against the Alpha, Beta, Gamma, Delta and Omicron variants (Vangeel 2022), although these findings need further validation through clinical studies.

Why it is important to do this review

Given the surges of infection and resultant uncertainty surrounding the COVID-19 pandemic across many countries, there is high demand for effective prevention and treatment interventions (Kim 2020). Despite the worldwide vaccination rollout, limitations in access, vaccine hesitancy, breakthrough infections, and multiple COVID-19 variants have influenced the effectiveness of vaccines (Hacisuleyman 2021; Li 2021; Norhayati 2022).

Drugs approved for the treatment of COVID-19 include nirmatrelvir/ritonavir, remdesivir, and monoclonal antibodies (Ansems 2021; Kreuzberger 2021; Reis 2022; Singh AK 2022). Remdesivir is an intravenous formulation that has demonstrated an 87% lower risk of hospitalization or death when given early in non-hospitalized people at higher risk of progression to severe disease (Gottlieb 2022). This drug has not reduced deaths or improved clinical status in hospitalized people with moderate, severe, or critical illness (Ansems 2021). In addition, its intravenous mode of delivery limits its access (Ansems 2021; Tian 2022). Monoclonal antibodies are recommended for treatment of mild-to-moderate COVID-19 in adults and children aged 12 years and over weighing at least 40 kg. However, this drug also has an intravenous mode of delivery, and is less efficacious against COVID-19 variants of concern (Cao 2022; Planas 2021; Singh AK 2022). The combination of nirmatrelvir and ritonavir aims to prevent severe COVID-19 in people with mild or no symptoms, and thus reduce hospitalization and death (Reis 2022). The phase 2/3 EPIC-HR (Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients) trial demonstrated an 89% reduction in COVID-19-related hospitalizations and deaths in

symptomatic, unvaccinated, non-hospitalized adults at high risk for progression to severe COVID-19 (Hammond 2022).

Molnupiravir has high bioavailability, broad-spectrum antiviral activity, and a high threshold to antiviral resistance (higher than that of monoclonal antibodies; Singh AK 2022; Tian 2022). Its oral form makes it convenient for use and administration by patients and healthcare systems (Singh AK 2022; Tian 2022). These traits position it as potentially effective and accessible antiviral drug. Singh and colleagues conducted and updated a systematic literature review to assess the efficacy and safety of molnupiravir (Singh AK 2021; Singh AK 2022). The review identified four completed and published trials – two phase 1 trials, one phase 2 trial, and one phase 3 trial – and several ongoing trials, then provided a narrative summary of the results. There are some gaps in the review's methodology, as the authors did not conduct a comprehensive search of electronic databases (only PubMed, MedRxiv and Google Scholar); assess risk of bias; conduct a GRADE assessment; or pool the data in a meta-analysis (Singh AK 2021; Singh AK 2022).

There is need for clear understanding of current and systematically collated evidence regarding the use of molnupiravir for the treatment of COVID-19. Our review will assess the effectiveness, safety, and tolerability of molnupiravir in people with confirmed COVID-19. The results will provide reliable and up-to-date evidence for policymakers, clinicians and the general public, to enable decision-making for the management of people with COVID-19.

OBJECTIVES

To assess the effects of molnupiravir in people with confirmed SARS-CoV-2 infection and mild-to-moderate symptoms, with or without risk factors for severe disease.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) only. Non-standard RCT designs, such as cross-over trials, are not eligible for the review owing to the nature of COVID-19, which evolves over time with new variants of the SARS-CoV-2 virus (Higgins 2022a). Our review will include data from RCTs in full text publications, preprints, abstracts, trial registries, and reports of ongoing trials.

Types of participants

We will include people with confirmed SARS-CoV-2 infection as defined by study authors (e.g. by reverse transcription polymerase chain reaction (RT-PCR) or antigen test), with or without risk factors for severe disease. We will not limit inclusion by previous SARS-CoV-2 infection, serology status, care received, vaccination status, geographical settings, or demographic factors.

Types of interventions

Intervention

Molnupiravir (any mode of delivery, formulation, dose, and schedule).

Control

No treatment, placebo, or standard of care as defined by study authors (e.g. supportive care with glucocorticoids). We will exclude studies comparing molnupiravir to treatment strategies that include molnupiravir.

Types of outcome measures

The main time point of interest will be 28 to 30 days after randomization. We will also consider other time points such as day 60, or up to the longest follow-up. If there are sufficient data available from other time points, we plan to meta-analyse data in weekly increments, for example week 1 (0 to 7 days), week 2 (8 to 14 days), week 3 (15 to 21 days). We will summarize all reported outcomes at all reported time points for all included studies in the characteristics of included studies table. Where few studies (or only one study) provide data for reported outcomes, we will summarize the results narratively. Eligible studies that do not report the following outcomes of interest will be included in the narrative synthesis but excluded from the meta-analyses.

Primary outcomes

Outpatients

- All-cause hospitalization
- All-cause mortality

Inpatients

- All-cause mortality up to day 28 to 30, up to day 60, or at the longest follow-up

Secondary outcomes

Outpatients

- Change in clinical status*
  - Worsening of clinical status as defined by need for respiratory support (WHO clinical progression scale; Marshall 2020; see Figure 1)
    - Development of moderate-to-severe COVID-19 symptoms (WHO scale greater than 5 to 6)
  - Improvement of clinical status
    - Time to symptom resolution
- Adverse events (any grade, at least one event) up to day 28 to 30, and at longest follow-up
- Viral clearance
- Quality of life

Figure 1. WHO clinical progression scale (Marshall 2020)

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Mechanical ventilation $pO_2/FIO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

Figure: **WHO clinical progression scale**
ECMO=extracorporeal membrane oxygenation. FiO_2=fraction of inspired oxygen. NIV=non-invasive ventilation. pO_2=partial pressure of oxygen. SpO_2=oxygen saturation. *If hospitalised for isolation only, record status as for ambulatory patient.

*For studies that do not use a standardized scale to assess participants, we will categorize clinical status using the information provided.

Inpatients

- Change in clinical status
  - Worsening of clinical status as defined by need for respiratory support (WHO clinical progression scale; Marshall 2020; see Figure 1) up to day 28 to 30
    - Need for oxygen supplementation by mask or nasal prongs (WHO scale greater than 5)
    - Need for non-invasive mechanical ventilation (WHO scale 5 to 6)
    - Need for invasive mechanical ventilation (WHO scale 7 to 9)
  - Improvement of clinical status
    - Weaning from ventilation (oxygen supplementation, non-invasive ventilation or invasive ventilation)
    - Duration of liberation from ventilation or oxygen support
    - Discharge without respiratory deterioration up to day 28 to 30, and at longest follow-up.
    - Time to discharge from hospital
- Adverse events (any grade), defined as number of participants with any event within the study period (including serious adverse events)

- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline and up to 3, 7, and 15 days
- Quality of life, including fatigue and neurological status, assessed with standardized scales (e.g. WHOQOL-100) up to 7 days, 30 days, and at longest follow-up

We will use the 11-point WHO clinical progression scale to determine the clinical status of participants (Marshall 2020). The scale defines clinical status as follows:

- 0: uninfected;
- 1 to 3: ambulatory mild disease;
- 4 to 5: hospitalized moderate disease;
- 6 to 9: hospitalized severe disease; and
- 10: dead.

See Figure 1 for further details.

Search methods for identification of studies

We aim to identify all relevant RCTs irrespective of publication status or language.

Electronic searches

We will search the following databases.

- Cochrane COVID-19 Study Register (CCSR; covid-19.cochrane.org), comprising: Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; Embase; ClinicalTrials.gov (clinicaltrials.gov); WHO International Clinical Trials Registry Platform (ICTRP; who.int/trialsearch); medRxiv (medrxiv.org).
- Web of Science Clarivate: Science Citation Index Expanded; WHO COVID-19 Global literature on coronavirus disease (search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/).
- COVID Network Meta-Analysis (covid-nma.com)

The Information Specialist has developed the following search strategy for the Cochrane COVID-19 study register.

- Search string: Molnupiravir OR EIDD-1931 OR EIDD-2801 OR MK-4482 OR Lagevrio.
- Study characteristics: 1) "Intervention assignment": "Randomised".

We will adapt this search string for other databases.

Searching other resources

We will search the reference lists of included studies and relevant systematic reviews to identify additional studies, and we will contact authors of included studies for more information if needed.

Data collection and analysis

We will use the online systematic review software Covidence to screen the titles, abstracts and full texts; to select studies; and to extract data.

Selection of studies

Teams of two review authors (from EAO, EO, BN, TF) will independently screen all titles and abstracts, and all potentially eligible full texts, against the eligibility criteria. We will resolve any disagreements through discussion, or by consulting another review author or experienced clinician. We will summarize the selection process graphically in a PRISMA flow diagram. In addition, we will detail the reasons for full-text exclusion in the flow diagram and characteristics of excluded studies table.

Data extraction and management

We will develop the data extraction form using Covidence and pilot it on at least two studies. Teams of two review authors (from EAO, EO, BN, TF) will independently extract all data of interest. We will resolve any disagreements through discussion, or by consulting other senior review authors.

We will extract the following information.

- General study information:
  - first author;
  - publication date;
  - title; and
  - source.
- Study characteristics:
  - study setting or country;
  - study design;
  - dates of recruitment;
  - eligibility criteria;
  - length of follow-up;
  - loss to follow-up; and
  - adherence to assigned treatment.
- Participant characteristics:
  - number of participants (recruited, allocated, and evaluated);
  - source of participants;
  - age;
  - sex;
  - disease severity;
  - vaccination status;
  - concurrent treatments; and
  - comorbidities (e.g. obesity, hypertension, heart disease, diabetes, respiratory disease, immunosuppression).
- Interventions:
  - type;
  - route of administration;
  - dosage;
  - timing;
  - frequency;
  - duration of treatment; and
  - duration of follow-up.
- Control:
  - type (placebo/active treatment);
  - route of administration;
  - dosage;
  - timing;
  - frequency;
  - duration of treatment; and
  - duration of follow-up.

- Outcomes: we will extract data on the prespecified outcomes in both the intervention and control arms as follows:
  - for dichotomous outcomes, number of events and participants;
  - for continuous outcomes, mean, standard deviation (SD), and total number of participants; and
  - for time-to-event outcomes, hazard ratios (HRs).

We will also note the number of missing data in each study arm.

Assessment of risk of bias in included studies

Two review authors (EO and TF) will use the Cochrane risk of bias tool (RoB 2; Sterne 2019) to independently assess the risk of bias in each included study, resolving any disagreements through discussion or by consulting other review authors (TK, MM, KC, PR). RoB 2 assesses the following five risk of bias domains:

- bias arising from the randomization process;
- bias due to deviations from the intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

For each domain and overall risk of bias judgement, we will summarize the risk of bias levels as 'low risk of bias', 'some concerns', or 'high risk of bias'. We will provide detailed descriptions of all judgements in risk of bias tables, and present a graphical summary in a figure.

Measures of treatment effect

We will calculate either the risk ratio (RR) or risk difference (RD) for dichotomous outcomes, the mean difference (MD) for continuous outcomes, and the HR for time-to-event outcomes; along with their 95% confidence intervals (CIs). For continuous outcomes measured with different scales, we will synthesize the data using the standardized mean difference (SMD).

Unit of analysis issues

The unit of analysis is the individually randomized participant. We will use the generic inverse variance method for meta-analysis, as it allows for meta-analysis of both individually and cluster-randomized studies. Should we identify a multi-arm study, we will include only the relevant arms, and combine data from the relevant multiple arms in the meta-analysis (Higgins 2022b; Sambunjak 2017). Guided by the *Cochrane Handbook for Systematic Reviews of Interventions*, for including variants of RCT we will combine all relevant intervention groups of the study into a single group, and combine all relevant comparator or control groups into a single comparator group (Higgins 2022b). We will list all treatment arms in the characteristics of included studies table, even if they are not used in the review.

We will include studies that randomize clusters (cluster-randomized trials) but analyse individual participants. For studies that adjust for the effect of clustering, we will extract the cluster-adjusted RR and standard error (SE), and enter the natural log of these into Review Manager (RevMan) Web (RevMan Web 2022) using the generic inverse variance method. For studies that do not adjust their results for the effect of clustering, we will first contact study authors to obtain intraclass correlation coefficient (ICC) values and make appropriate adjustments, or, if these data are not available, we will assume ICCs based on the relevant literature or similar studies. Otherwise, we will extract the simple summary data for all relevant outcomes and calculate the crude RR and 95% CI using RevMan Web (RevMan Web 2022); then adjust for the effects of clustering by inflating the SE of the RR with an estimate of the design effect; and finally, enter the natural logs of the adjusted RR and associated SEs into RevMan Web (RevMan Web 2022), using the generic inverse variance method (Higgins 2022a; Sambunjak 2017). If the studies report no design effect, we will use a common ICC of 0.01, or whichever value is most frequently reported in similar studies (Higgins 2022b).

Dealing with missing data

Parallel-group studies may have continuous outcomes, with means and numbers of participants in each group but not SDs. We will calculate missing statistics such as the SD from reported figures (e.g. SE of the mean in each study arm, or CI of the MD between arms or the mean from each study arm), using the RevMan Web calculator (RevMan Web 2022). If we cannot calculate the SD, we will impute the data needed by borrowing an SD from another study (Higgins 2022a). For studies that do not report separate data for intervention and control groups but do report the overall effect estimates (MD or mean), we will include the reported effect estimate in the meta-analysis if there is also a measure of variance such as the SE or CI. Otherwise, we will contact the corresponding authors for missing study results (for both continuous and dichotomous outcomes). We will assess risk of bias due to missing outcome data using RoB 2 (Sterne 2019).

Assessment of heterogeneity

We will assess heterogeneity among included studies by visually inspecting the forest plots for overlapping CIs; by applying the Chi^2 test for statistical heterogeneity with a 10% level of statistical significance; and by calculating the I^2 statistic, which checks the magnitude of variability in effect estimates due to heterogeneity rather than sampling error. Because inconsistencies and variability depend on a number of factors, we will not use absolute cut-offs to interpret I^2 values. Instead, we will use the following scale as guidance (Higgins 2022a).

- 0% to 40%: might not be important.
- 40% to 60%: might represent moderate statistical heterogeneity.
- 50% to 90%: might represent substantial statistical heterogeneity.
- 75% to 100%: considerable statistical heterogeneity.

Assessment of reporting biases

To minimize publication bias, we will conduct an extensive literature search to identify completed studies or ongoing studies with preliminary results. If we include more than 10 studies, we will investigate publication bias by generating a funnel plot and using Egger's test to assess funnel plot asymmetry (Higgins 2022a).

Data synthesis

If we identify two or more eligible studies with reasonably similar clinical and methodological characteristics, we will conduct a meta-analysis using RevMan Web (RevMan Web 2022). Where possible, we will conduct meta-analyses with intention-to-treat (ITT) data. We will analyse all outcomes at individual or participant level using the inverse variance method, where the weight given to

each study is the inverse of the variance of the effect estimate. This method is suitable when studies report an overall effect estimate without providing data for individual events in separate intervention groups. It allows for meta-analysis of continuous and dichotomous data, and for meta-analyses of individually and cluster-randomized studies.

We will apply the random-effects model, which assumes that the included studies report related but different intervention effects. We will present the results of the random-effects meta-analyses as the average treatment effect with 95% CIs, along with the estimates for the I^2 and Tau^2 statistics. When four or more studies are included in a meta-analysis, we will also present the 95% prediction interval (PI), which is a summary of the spread of underlying effects in the included studies. The PI is useful for showing the extent of between-study variation, and for predicting the possible underlying effect in a future study, though it is imprecise when based on fewer than four studies. We will synthesize continuous data summarized as means and standard deviations using the inverse variance method, to derive the MD with 95% CIs. For continuous data from cluster-RCTs, and for HRs, we will use the generic inverse variance method. We will synthesize dichotomous data summarized by RRs or RDs using the Mantel-Hanzel method (Higgins 2022a; Sambunjak 2017).

Subgroup analysis and investigation of heterogeneity

Where data are sufficient (with two or more studies for each subgroup), and where we detect moderate statistical heterogeneity, we will perform subgroup analyses, stratifying results by:

- severity of illness at study entry (e.g. mild versus moderate disease);
- presence of comorbidities (any comorbidity versus no comorbidity);
- duration of illness (e.g. more than 7 days versus 7 or fewer days from onset);
- COVID-19 vaccination status (e.g. vaccinated versus unvaccinated, and fully vaccinated (2 or more doses) versus partially vaccinated (1 dose));
- age of population (e.g. 18 to 64 years versus 65 years and older);
- country (e.g. low- and middle-income countries versus high-income countries (World Bank 2022)); and
- dominant COVID-19 variants circulating at the recruitment period of study (e.g. Alpha versus Beta versus Gamma versus Delta versus Omicron).

Sensitivity analysis

Where data are sufficient, we will conduct a sensitivity analysis to assess the effect of high risk of bias and the effect of results from preprint reports on the outcomes by excluding these studies from the overall meta-analyses. If there are sufficient cluster-randomized studies, we will conduct a sensitivity analysis to assess the robustness of the results (Higgins 2022b), for example by imputing three different ICC values of 0.01, 0.05, and 0.1.

Summary of findings and assessment of the certainty of the evidence

We will use the GRADE approach to assess the certainty of evidence and summarize the review findings in a summary of findings table (Guyatt 2013). The prioritized outcomes reported in the summary of findings table will include:

- for outpatients:
  - all-cause hospitalization;
  - all-cause mortality;
  - worsening of clinical status;
  - improvement of clinical status; and
  - adverse events.
- for inpatients:
  - all-cause death;
  - worsening of clinical status;
  - improvement of clinical status; and
  - adverse events.

We will present separate summary of findings tables for inpatients and outpatients. The assessment of the overall certainty of evidence will cover:

- risk of bias;
- inconsistency;
- indirectness;
- imprecision; and
- other considerations, such as publication bias.

We will also present estimates of the relative and absolute effects for the selected outcomes. We will use the GRADEpro GDT online software to create the GRADE summary tables (GRADEpro GDT 2022).

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article.

- Contact Editor: Dr Paul Hine, Cochrane Infectious Diseases Group (CIDG)
- Sign-off Editor (final editorial decision): Professor Paul Garner, CIDG Co-ordinating Editor
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Dr Deirdre Walshe, CIDG Managing Editor
- Copy Editor (copy-editing and production): Julia Turner (protocol)
- Peer-reviewers (provided comments and recommended an editorial decision): Dr Rebecca Kuehn, Liverpool School of Tropical Medicine (LSTM), UK (clinical/content review), Dr Susan Gould, LSTM, UK (clinical/content review), Dr Marty Chaplin, LSTM, UK (stats/methods review).

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- Revisions of draft protocol: EAO, EO, BN, TF, MM, TK, KC, PR
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DECLARATIONS OF INTEREST

EAO: is a CIDG Editor, but was not involved in the editorial process of this protocol, and has no known conflicts of interest.
EO: none known.
BN: none known.
TF: none known.
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