National Institute for Health and Care Excellence

and

National Institute for Health Research

Evidence collection guide for medicinal products to prevent or treat COVID-19

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Working in collaboration, NICE and NIHR have produced advice on clinical evidence generation for developers of medicinal products to prevent or treat COVID-19.

This guide should be read in conjunction with relevant regulatory guidance documents and the NICE guide to the methods of technology appraisals 2013. Clinical studies do not have to conform to this advice in order to be evaluated by NICE.

Confirmatory trials

Clinical trials must be authorised by relevant regulatory authorities in accordance with the legal requirements. Each trial, and any subsequent protocol amendments, must be prospectively registered in the clinical trials database of the authorising regulatory authority and in a registry that appears in the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP).

Design

- Interventional, comparative, randomised, multicentre clinical trials are preferred.
- Ideally, participants and investigators should not be aware of the treatment allocation and outcome assessment should also be blinded, although it is recognised that such blinding may be difficult to implement for institutional trials or investigator sponsored studies. If a blinding procedure cannot be implemented, preference should be given to clinical outcomes that can be assessed with as little subjectivity as possible and the adjudication of the endpoints should ideally be performed independently. The implementation of a blinding procedure should not significantly delay the start of the trial.
- Stratified randomisation, to take account of factors that could be predictors of outcome, should be considered. The research centre is one such factor that should be included because standard of care could vary significantly between sites and countries.
- The design of the trial should ideally be based on internationally agreed recommendations and guidelines (for example, on the WHO R&D Blueprint COVID-19 therapeutic trial synopsis), and should have clear and well-defined objectives (for example, the evaluation of the efficacy or effectiveness and the safety of a new intervention with curative intent, pre-exposure prophylaxis or post-exposure prophylaxis).
- The efficiency of trials could be improved by using adaptative designs (for example, adaptive randomisation, pick-a-winner/drop the loser designs, conduct of interim analyses). Platform protocol designs could be used if multiple interventions are or could be under investigation.

- The primary hypothesis should be a superiority hypothesis. The number of hypotheses tested in the study (primary and secondary) should be minimised. The trial should focus on clinically relevant hypotheses, endpoints and effect sizes.
- The sample size of the trial needs to be justified, with reference to the type I error, power of the test, expected effect size, and lower efficacy bound that it is desired to rule out.
- In order to minimise the conduct of unnecessary clinical trials and provide patients with an effective therapy as early as possible, the conduct of interim analyses for futility or early efficacy can be considered. Any interim analyses for trial adaptions and early tests of the primary null hypothesis should be preplanned, fully described in the protocol, and include appropriate control of the type I error. An independent data monitoring committee should ideally be employed for these analyses, even in open-label trials.
- If a clinical trial is stopped because of positive efficacy results at an interim analysis, follow-up of the participants already enrolled in the trial should continue. Consideration should be given to the justification for having participants continue in the comparator arm in order to obtain longer-term randomised data.
- The information collected in the studies could be based on the templates provided by the WHO (see the Global COVID-19 clinical platform case record form and case record form: pregnancy module).

Population

- The intended indication (prevention, supportive or curative intent), the population (severity of disease, comborbidities) and the setting (primary care, hospital, intensive care unit, care home) should be clearly defined. The COVID-19 case definitions and diagnostic criteria should be provided, with preference given to the current WHO case definitions in its interim guidance on global surveillance for COVID-19. Whenever possible, the UK case definitions for possible COVID-19 should be documented. Similarly, Public Health England's criteria for inpatient definition should be used or documented in the trial.
- The sampling method and type of test used to confirm COVID-19 (for example, RT-PCR or serological test type) should be described. Only validated testing

methods should be used and the diagnostic performance characteristics of the test(s) used should be recorded when possible.

- A full range of baseline participant characteristics (demographics and baseline disease characteristics) should be collected so that the relevance of the trial population to the NHS patient population can be evaluated. This includes sex, age, ethnicity and comorbidities as a minimum. Smoking status, residence in care home, and functional and confinement status should also be collected. It is also important to record whether social distancing, self-isolation and confinement measures are in place during the study.
- Ideally, clinical studies should enroll a population representative of the full range of patients who have COVID-19 treated in the NHS, including those at risk of developing severe or fatal COVID-19. In particular, the inclusion and exclusion of populations at risk should be described and justified (for example: children or older people with age range specified; older people in care homes; pregnant women; those with protected characteristics, such as those from ethnic minority groups; healthcare workers; people with poor functional status; people with other significant comorbidities, such as lung conditions, diabetes, cardiac and renal insufficiency, underlying immune suppression or obesity).
- The analysis of important subgroups, such as those identified above or defined by the NHS as high-risk patients, should be prespecified, as should potential coefficients in any adjusted analysis of treatment effect.

Intervention

- The nature of the intervention (for example, antiviral or product used to treat COVID-19 cytokine release syndrome), the rationale for use and the investigated dose should be described and justified.
- The contra-indications, special precautions for use, special monitoring requirements and drug-drug interactions should be described in the protocol.

Comparator

- Clinical studies should include a comparator arm reflecting best supportive care in the absence of a specific therapy, reflecting the WHO coronavirus disease (COVID-19) technical guidance: patient management, the NICE COVID-19 rapid guideline: critical care in adults (NG159) and the Public Health England and

Department of Health and Social Care COVID-19: guidance for health professionals whenever possible and applicable.

- The comparator(s) should be clearly defined and described. If a clinician's choice comparator arm is used, the clinician's choice for a particular participant should be made and recorded before randomisation, regardless of the group to which the participant is randomised.

Background therapy

- The disease management (for example, decision to hospitalise the participants, decision to ventilate, supportive care and background treatments) should reflect NHS practice as closely as possible. In open-label trials, it must be ensured that the condition is managed in the same way across all arms of the trial.
- Special attention should be given to the social care offered to the trial participants and the care setting should at least reflect the level of care offered in the UK.
- Treatments permitted in the trial should be outlined in the study protocol (if possible) and all treatments that participants have had during the trial must be recorded.
- Any rescue medications allowed in the study, including investigational products or products authorised in other indications and used off-label, should be described in the protocol and their use during the trial recorded.

Outcomes

- For the primary endpoint of studies aimed at COVID-19 treatment, preference should be given to clinical outcomes focusing on the recovery or survival, or both, of the participants. Recovery can be defined by time to reaching certain states on the WHO ordinal scale for clinical improvement. The use of the COMET COVID-19 core set of outcomes is strongly recommended and the outcomes included within the Cochrane living meta-analysis should be taken into consideration. The choice of endpoint should be guided by the disease severity and population investigated in the trial. For endpoints for prevention studies, please see the section on special considerations for prevention studies.
- In all cases, and particularly if a composite primary endpoint including both recovery and all-cause mortality is used, the follow-up of the participants should

allow recording of the full clinical recovery or death of each participant. Each outcome within a composite endpoint should also be collected individually and presented separately when the trial is reported.

- Secondary endpoints should try to capture the progression of the disease (for example, COVID-19 clinical symptoms and severity on the WHO ordinal scale, ventilatory support and intubation, multiorgan failure, need for and duration of hospitalisation, need for and duration of intensive care).
- Adverse effects, particularly serious adverse effects, should be recorded and reported in accordance with the sponsor's legal obligations, with a focus on serious, severe, fatal or life-threatening adverse effects.
- If not used as the primary endpoint, the trial must capture all-cause mortality.
- Patient-reported outcomes, including health-related quality of life (HRQL), should ideally be captured whenever clinically appropriate and feasible. The collection of HRQL may not be appropriate during hospitalisation in an intensive care unit, and should ideally be collected within the study immediately before and after the episode. The EQ-5D instrument is the preferred measure of HRQL for NICE. The EQ-5D-5L version can be included within the trial and the results mapped to the EQ-5D-3L for use within an economic evaluation, as recommended in the NICE position statement on the use of the EQ-5D-5L value set.
- Virological outcomes can be evaluated as secondary endpoints in any trial investigating a direct acting antiviral agent. It is important that the method of sampling and the diagnostic test used are the same across all sites. Surrogate outcomes, such as change in viral load from baseline, can therefore be collected in the trial, but the primary hypothesis of the study and any interim analysis should be based on final clinical outcomes.
- COVID-19 studies should be designed to capture outcomes that may be specific to certain populations (for example, Kawasaki-like hyperinflammatory shock in children). The longer-term outcomes of the disease after recovery should also be investigated (for example, the neurological, renal, cardiovascular and mental health complications of COVID-19 and long-term complications of acute respiratory distress syndrome; see supplementary data collection).

Duration

- The duration of the clinical trial will depend on the nature of the intervention (for example, preventative, supportive or curative intent) and the primary hypothesis. For therapeutic studies, the primary endpoint may be measured within a few weeks (for example, 28 days). Considering the usual short duration of the acute phase of COVID-19, the duration of the trial and the follow-up of the participants should allow the observation of the final clinical outcome (for example, recovery or death) in all the participants enrolled in the study. The number lost to follow-up would be expected to be low. The investigators should endeavour to follow all the participants enrolled in the trial, including those who withdrew from it.

Special considerations for prevention studies

- Pre-exposure prophylaxis (PrEP) is the use of a medication for primary prevention of COVID-19 in uninfected persons.
- Post-exposure prophylaxis (PEP), or secondary prevention, is short-term treatment to reduce the likelihood of COVID-19 after potential exposure (to a person, or a group of persons, possibly or probably infected by SARS-CoV-2), for example, occupationally. PEP studies should also be designed to demonstrate the extent to which PEP therapy can prevent disease progression and decrease hospitalisations in persons with confirmed symptomatic COVID-19 disease.
- In the case of PrEP studies, cluster randomised clinical trials (for example, using hospital medical units or care homes as units of allocation) could be considered. The Cochrane handbook on cluster randomised clinical trials can be referred to for advice on the design (including the assessment of bias), conduct and analysis of such trials.
- The target populations and intended use should be clearly defined (for example, healthcare professionals exposed to patients with COVID-19 or those in high-risk scenarios, such as close contact at work). The SARS-CoV-2 status of the persons enrolled in the studies should be established and documented before and during the trial by RT-PCR, using a predefined procedure.
- PrEP and PEP studies should be conducted in settings that include the use of personal protective equipment, social distancing, self-isolation and confinement measures that are in place to minimise the spread of infection.

- Contact-tracing mobile applications could be investigated to help design and conduct PEP studies.
- Outcomes specific to PrEP and PEP studies should be used in addition to the outcomes previously described, including:
  - The incidence of acquired microbiologically confirmed SARS-CoV-2 infections. Viral RNA in respiratory specimens should be detected by RT-PCR before and after exposure, and after possible infection. This should include testing of infected but asymptomatic participants.
  - The incidence of COVID-19 symptomatic disease, including severe and fatal cases.
  - Time to hospitalisation.
  - For PEP studies, the incidence of SARS-Cov-2 infections in other people 14 days after the contact with the 'index' (that is, the confirmed) case.
  - For cost-effectiveness evaluation purposes, it will be important to accurately capture the endpoints that will allow for appropriate modelling of the pandemic in the UK (for example, to obtain an accurate estimate of the basic reproductive ratio, R_0). Key epidemiological determinants of the magnitude and timescale of the epidemic include the interval between infection and onset of symptoms and between onset and hospital admission, the degree and duration of the infectiousness of the agent, and the extent of contact and mixing between infectious and susceptible people enabling transmission of the virus. Other important information includes time from hospital admission to death, and time from hospital admission to discharge. Considering that public health interventions can affect many of these factors, it is important to accurately record what interventions were in place at the time of the study and to collect this information in a setting from which the findings can be extrapolated to the NHS.

Reporting

- All studies (completed or not, successful or not) should be promptly reported in the clinical trials regulatory databases and published in peer-reviewed literature, preferably in open-access journals.
- The studies published in the literature should conform to the CONSORT guidance.

- All trials should include some form of statement on the data sharing arrangements. The availability of individual or aggregate patient data in the public domain should be noted and data protection laws must be strictly adhered to.

Supplementary data collection

Observational or real-world data collection should not replace the conduct of well-designed clinical trials. Such data are considered complementary to evidence collected through comparative clinical trials to address uncertainty or evidence gaps identified during clinical development. Data collection should be considered when a medicine becomes available in the NHS outside of clinical trials (for example, through early access approaches).

The key considerations for observational data collection in COVID-19 are:

- The purpose of data collection should be to address evidence gaps and areas of uncertainty. For example, this could be to better characterise the clinical effectiveness of the technology when used in the NHS, to obtain evidence on NHS clinical practice, to collect clinical-effectiveness data on populations of patients not enrolled in the clinical studies or to monitor medium to long-term safety.
- The research question should be prespecified and a protocol for the conduct of the observational study, including a statistical analysis plan, should be developed. The data collected in the study should be quality assured when possible and any deviations from the protocol should be reported and justified.
- The regulatory framework for collecting observational data, for example, the requirement or not for a clinical trial application, should be considered.
- The burden on the healthcare system should be minimised and therefore consideration should be given to using existing databases. In the UK, these could include the Clinical Practice Research Datalink (CPRD) (for primary care outcomes), Hospital Episode Statistics (for secondary care outcomes) or the ISARIC 4C data platform (for COVID-19 specific outcomes collection in secondary care). Mortality data could be collected from the Office for National Statistics if NHS number, date of birth and postcode are also collected. Patient-led platforms, where patients enter their own outcomes, could be considered if they capture

medication use and can adequately capture symptoms at the severe end of the disease spectrum.

- If new registries are being considered, their quality should be assessed using the REQueST tool.
- Participant characteristics should be collected so that the generalisability of the findings from clinical trials to routine clinical practice can be evaluated.
- It is important to record the mortality that can reasonably be attributed to COVID-19 in real-world practice. The follow-up of participants should try to capture the time to full recovery, all-cause mortality, and deaths directly or indirectly related to COVID-19 even in the absence of formal confirmation of the diagnosis. Different scenario analyses can be presented (for example, mortality in confirmed COVID-19 cases, mortality in probable or possible COVID-19 cases).
- For therapeutic interventions, the SARS-CoV-2 status of all participants having the medicine in clinical practice should be established when possible (possible cases, probable cases, confirmed cases) and the testing method recorded. For preventative interventions, all participants showing symptoms of COVID-19 should be tested for SARS-CoV-2 and the testing method recorded.
- Any resistance to the intervention (primary or secondary) or SARS-CoV-2 mutation should be monitored.

Updates to the guide

The guide will be reviewed during the COVID-19 pandemic and, if needed, updated in response to changes in COVID-19 treatment or prevention.

Engagement with NICE

These recommendations are designed to provide general advice on the design and conduct of clinical data collection in the treatment and prevention of COVID-19, in the context of a rapidly evolving field. Therefore, sponsors of clinical trials are encouraged to engage as early as possible with NICE to obtain fast track scientific advice on the design of their specific studies. Requests for scientific advice on COVID-19 studies will be prioritised. Joint regulatory and HTA scientific advice with NICE and the Medicines and Healthcare products Regulatory Agency (MHRA) should be considered.

Get in touch for information about free fast track advice through the NICE scientific advice webpage.

Engagement with the NIHR

If studies are to be conducted in the UK, sponsors of clinical trials are encouraged to get in touch with the NIHR Study Support Service.

Disclaimer

The advice contained within this guide is based on the scientific and methodological knowledge publicly available at the time of writing and cannot account for future changes and developments in scientific knowledge, regulatory requirements or any referenced material from external sources.

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