MTA of Therapeutics for people with COVID-19 – Protocol

HTA Reference No. ID4038

Title of the project

Therapeutics for people with COVID-19

Name of External Assessment Group (EAG) and project lead

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Plain English Summary

Treatment for patients with COVID-19 is beneficial. Results from studies have shown that treatment can prevent hospitalisations, admission to intensive care units and death. However, treating many people, some of whom may have been well without treatment can be expensive. Unlike expensive new treatments in other disease areas, the National Institute for Health and Care Excellence (NICE) has not investigated the cost-effectiveness of many treatments for COVID-19. This work will assess the cost per quality-adjusted life year gained of selected treatments for COVID-19, allowing NICE to decide if they represent value for money and if one treatment is preferred if many treatments are cost-effective compared with no treatment.

The work will focus on two groups. The first group is those who have needed hospitalisation because of COVID-19, and the second group are those who have not (yet) needed hospitalisation because of COVID-19 but who are believed to be at high-risk of being hospitalised. The cost-effectiveness of treatments will likely depend on the treatment itself, and the setting in which it is being used.

1. Decision problem

1.1 Purpose of the decision to be made

This protocol should be read in conjunction with the NICE scope.[1] The objective of the assessment is to determine the clinical and cost-effectiveness chosen antiviral medications, neutralising monoclonal antibodies (mAbs), and immunomodulatory mAbs for the treatment of people with COVID-19 in an endemic situation. Table 1 summarises characteristics of the treatments included in the NICE scope in terms of class, mode of administration and recommended dose, marketing license status, and indication or population studied in the key studies.

It is anticipated that treatment could increase the health of patients, measured in quality-adjusted life years (QALYs), by reducing the number of deaths, hospitalisations and the requirement for respiratory support. Whilst there is likely to be a savings in the costs associated with hospitalisations and respiratory support, the acquisition costs of the interventions could result in an overall net cost associated with treatment. The primary objective of the work will be to explore the cost effectiveness of the treatments in terms of cost per QALY gained; secondary model outcomes, such as hospital days avoided will also be generated.

Table 1: Treatments covered by the technology assessment (adapted from the published NICE scope)

Generic treatment name (branded name and company)	**Class**	**Mode of administration, (recommended dose)**	**Marketing authorisation status**	**Indication / population in key studies if no marketing authorisation or conditional marketing authorisation exists**
Remdesivir (Veklury, Gilead)	Viral RNA polymerase inhibitor	IV (200 mg loading dose on day 1 for all patients, then dependent on patient characteristics. • For adults and adolescents with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment): 100 mg daily IV for five to ten days) • For Adult patients who do not require supplemental oxygen and are at increased risk of progressing to severe COVID-19: IV (100 mg daily IV for three days)	Conditional marketing authorisation in the UK	Treatment of COVID-19 in adults and adolescents* with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment) Treatment of COVID-19 in adults with pneumonia not requiring supplemental oxygen
Tocilizumab (RoActemra, Roche)	Immunomodulator	SC/IV (8 mg/kg administered once IV with 0.9% sodium chloride over one hour) One additional infusion of tocilizumab 8	Marketing authorisation in the UK	Treatment of COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical

		mg/kg may be administered. The interval between the two infusions should be at least 8 hours		ventilation
Casirivimab and **imdevimab** (Ronapreve, Regeneron and Roche)	Antiviral	IV/SC (600mg of both drugs administered together as one infusion. An SC injection is permitted if an IV approach would lead to a delay)	Marketing authorisation in the UK	Treatment of acute COVID-19 infection.
Baricitinib (Olumiant, Eli Lilly)	Immunomodulator	Oral (4mg daily, the optimal duration is currently unclear)	No marketing authorisation in the UK for COVID-19 to date	Studied in clinical trials, as a monotherapy, in people with COVID-19. Studied in clinical trials in combination with remdesivir in people aged 18 years and older, hospitalised with COVID-19
Sotrovimab (Xevudy, GlaxoSmithKline and Vir Biotechnology)	mAb	IV (500mg over 30 minutes)	Conditional marketing authorisation in the UK	Treatment of symptomatic adults and adolescents* with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID infection
Molnupiravir (Lagevrio, Ridgeback	Antiviral	Oral (800mg twice daily for 5 days)	Marketing authorisation in the UK	Treatment of mild to moderate COVID-19 in adults with a positive SARS-COV-2

Biotherapeutics and Merck Sharp & Dohme)				diagnostic test and who have at least one risk factor for developing severe illness
Anakinra (Kineret, Swedish Orphan Biovitrum)	Immunomodulator	SC (100mg daily for 10 days)	No marketing authorisation in the UK for COVID-19 to date	Studied in clinical trials in combination with standard of care, in people hospitalised with COVID-19
Lenzilumab (unknown brand name, Humanigen)	Immunomodulator	IV (three 600mg doses delivered 8 hours apart)	No marketing authorisation in the UK / expediated consideration by the MHRA	Studied in a clinical trial as a monotherapy in people aged 18 years and older, hospitalised with COVID-19
Nirmatrelvir and ritonavir (Paxlovid, Pfizer)	Antiviral	Oral (300mg (nirmatrelvir) and 100mg (ritonavir) twice daily for 5 days)	Conditional marketing authorisation in the UK	Treatment of COVID-19 in adults who do not require supplemental oxygen and who are increased risk for progression to severe COVID-19

IV - intravenous, mAb - monoclonal antibody, SC – subcutaneous * aged 12 years and older with body weight at least 40 kg

1.4 Populations and relevant subgroups

All patient groups with acute SARS-CoV-2 infections whose symptoms range from mild to severe regardless of the hospitalisation status are included. Currently, the external assessment group (EAG) is uncertain whether the time constraints and the available evidence would allow for subgroup analysis by age, immune system competence/comorbidities, seroprevalence, or SARS-CoV-2 variant.

The EAG intends to divide the population into two main groups, those who have been hospitalised due to COVID-19 and those who have COVID-19 but where it has not yet caused hospitalisation, although the patients are deemed to be at high-risk of being admitted to hospital. It is acknowledged that a patient may have been hospitalised due to another reason and incidentally had COVID-19 or contracted COVID-19 whilst in hospital and would be in a similar position to those who had not been hospitalised due to COVID-19. For brevity, all patients not hospitalised due to COVID-19 will be termed 'non-hospitalised patients' noting the aforementioned caveat. Following discussions with NICE, in the EAG's base case, the criteria for a patient being at high-risk will be taken from the Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community (PANORAMIC) clinical study[2] with the exclusion of being 50 years of age or over as a risk factor. Sensitivity analyses will be run as deemed appropriate.

The formation of the two groups of hospitalised and non-hospitalised patients has been made due to different aims of treatment between the groups. For non-hospitalised patients, the aim of treatment is to prevent viral replication and damp inflammation, thus reduce the probability of the development of severe symptoms that could lead to hospitalisation and death. For hospitalised patients with severe to critical COVID-19, the aim of treatment is to reduce the immunoinflammatory response of the body and prevent clinical deterioration.

1.5 Relevant interventions and comparators

The relevant interventions for this research are listed within Table 1. Multiple interventions are indicated for the prevention of severe COVID-19. Severe disease in adults is defined as having clinical signs of pneumonia plus at least one of the following: respiratory rate >30 breaths/minute, severe respiratory distress, or saturation of peripheral oxygen <90% on room air and would require hospitalisation.[3]

Comparators for these interventions are: (i) other interventions when used in the same position, and (ii) standard of care (SoC) excluding the interventions, which would be dependent on the severity of the patient. SoC is defined as any treatment widely accepted by the NHS as standard of care, which is routinely funded by the NHS with no strong rationale to appraise it, for example supplemental oxygen and dexamethasone. The EAG are aware that the SoC has been an evolving area, and that SoC for earlier clinical trials differs from recent ones. In this regard, the EAG is limited by the available evidence of relative treatment effect as discussed in Section 2, and acknowledge that not adjusting for the variation in the SoC across trials is not ideal. However, the EAG believes the results from the MTA could still be informative particularly for comparisons among treatments whose clinical trials were conducted recently. Sensitivity analyses related to SoC will be performed if feasible within the timescales of the project.

1.6 Outcomes

The NICE scope[1] lists nine possible outcomes to explore: mortality; requirement for respiratory support; time to recovery; hospitalisation (requirement and duration); time to return to normal activities; virological outcomes (viral shedding and viral load); symptoms of post-COVID-19 symptoms; adverse effects of treatments; and health-related quality of life. It is anticipated that not all model outcomes, such as virological outcomes will be included in the final report due to the agreed timelines. If needed, discussions will be undertaken with NICE to determine those that are considered the highest priority.

The cost-effectiveness of the nine treatments will be expressed in terms of incremental cost-effectiveness ratios (ICERs) which will be reported in terms of cost per QALY gained. A patient lifetime horizon will be used to take differential mortality between treatments into account. Further details of the proposed health economic analysis are presented in Section 3.

1.7 Other considerations

This research is not aligned with a typical NICE multiple technology appraisal (MTA) primarily due to the shortened timescales which will require the EAG to pragmatically assess where time savings can be made without impacting on the main conclusions. NICE will be kept informed of such decisions. It is anticipated that re-running of models may be required as new evidence emerges, for example if studies reporting new data on the efficacy of interventions, potentially to new variants of SARS-CoV-2, are published, however, this will be dependent on when the MTA is taken to a NICE Appraisal Committee.

2. Report methods for assessing the outcomes arising from the use of the interventions

COVID-19 clinical research has accelerated dramatically worldwide, with over 5000 registered trials investigating therapeutic interventions for COVID-19.[4] The need for rapid information on COVID-19 has resulted in a paradigm shift, especially in the communication of scientific results. Traditional systematic reviews can date quickly but 'living' systematic reviews search for evidence much more regularly than standard reviews and incorporate relevant new evidence as it becomes available.

The COVID-NMA initiative,[5] supported by the World Health Organization (WHO) and Cochrane, is a living systematic review of registered randomised trials, in which all available evidence related to COVID-19 is continuously collected, critically appraised, and synthesised using pairwise comparisons. Several living network meta-analyses that incorporate emerging trial data and allow for analysis of comparative effectiveness of multiple COVID-19 treatments, have also been developed and published. The living WHO guideline[4] accommodates dynamically updated evidence from all registered randomised trials of existing and new pharmacological COVID-19 treatments. The metaEvidence initiative,[6] supported by the University Hospital of Lyon and the University of Lyon, is also a living meta-analysis and evidence synthesis of therapies for COVID-19 and is an emerging online resource that provides direct access to the efficacy and safety results reported in the studies for potential drugs for COVID-19. The risk of bias, synthesised by meta-analysis, is also reported. Due to the limited timelines of the projects, we will undertake a pragmatic review approach in identifying and reviewing relevant evidence from these sources.

3. Report methods for synthesising evidence of cost-effectiveness

3.1 Identifying and systematically reviewing published cost-effectiveness studies

The benefits associated with systematically reviewing the literature relating to published economic models on COVID-19 related to treatments in Table 1 are not believed to be large. It is anticipated that any studies found would fall into one or more of the following groups. 1) be known to the EAG or NICE, 2) not be published in a peer-review journal, or 3) not be generalisable to the decision problem in England. Given the timelines of the project the EAG will not undertake a review of previous cost-effectiveness models.

3.2 Evaluation of costs, quality of life and cost effectiveness

The Decision Support Unit External Assessment Centre at ScHARR developed a health economic model in Excel to assess the cost-effectiveness of neutralising monoclonal antibodies for the treatment of COVID-19 in patients at risk of hospitalisation. The ERG plans to adapt this model to align with the current MTA in terms of population(s) studied, relative treatment effects of comparators, and related costs and outcomes. In line with the NICE Reference Case, health outcomes and costs are evaluated over a lifetime horizon adopting an NHS and personal social services perspective, with health outcomes and costs are discounted at a rate of 3.5% per year.[7] Cost-effectiveness is expressed in terms of the incremental cost per QALY gained.

3.2.1 Model structure

The model starts with a decision tree where patients are divided according to their initial COVID-19 hospitalisation status. For patients in hospital due to COVID-19 there is a series of partitioned survival models used to estimate outcomes in terms of mortality and hospital stay. During the hospital stay patients are classified into five health states based on their hospitalisation/oxygen requirements as per the ordinal scale defined in the ACTT-1 trial.[8] These health states are: not requiring supplemental oxygen and no longer requiring ongoing medical care, not requiring supplemental oxygen but requiring ongoing medical care (related to COVID-19 or to other medical conditions), requiring any supplemental oxygen, requiring noninvasive ventilation or use of high-flow oxygen devices, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). Each of these health states is associated with different cost and utility impacts.

For patients not hospitalised by COVID-19, the model estimates the proportions of patients who require subsequent hospitalisation for those on intervention and those on standard of care. For those requiring hospitalisation, the model described above is used to estimate patient outcomes.

3.2.2 Care pathways modelled

Patient care pathways will be checked in consultation with experts. Prioritisation of exploratory positioning of treatments will be undertaken should timelines allow, and clinical experts believe these analyses are informative.

3.2.3 Costs and health outcomes

Resource costs will be valued using unit costs obtained from routine costing sources (e.g.,

NHS Reference Costs, the Personal Social Services Research Unit, the British National Formulary, and electronic market information tool (eMIT)), through personal communication with relevant bodies and clinical experts, as required and if applicable through published and unpublished literature. Where appropriate, any commercial-in-confidence agreements for treatments will be incorporated in the analyses with results presented in a confidential appendix. All costs will be inflated to the current year.

Health-related quality of life values will be dependent on the health state and populated with the best sources identified. Upon model entry, baseline utility values will be estimated using the equation reported in Ara and Brazier[9] and adjusted for the poorer quality of life associated with COVID-19. During the hospitalisation episode, decrements in utility values are applied with values taken from the published literature.[10] A reduced quality of life is assumed to persist over the long-term post-COVID-19 for a period of time, after which the utility value returns back to the pre-COVID-19 baseline value. The original model assumed that long-term COVID-19 persists for 52 weeks after discharge, however the EAG will aim to identify more recent evidence to populate this duration.

3.2.4 Model Analyses

ICERs will be estimated based on the costs and QALYs associated with interventions and comparators.

Central estimates of cost-effectiveness will be estimated based on the expectation of the mean using probabilistic sensitivity analysis (PSA). Fully incremental analyses of all treatment choices will be considered and presented if deemed useful. Deterministic sensitivity analyses will be performed to identify key drivers of cost-effectiveness. The results of the PSA will be presented using cost-effectiveness planes and cost-effectiveness acceptability curves. Reporting of the economic analysis will follow the CHEERS checklist.[11]

4. Handling information from the companies

Unpublished information might be submitted from sponsoring companies. Any 'commercial in confidence' (CIC) data provided by a manufacturer and specified as such will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g., in brackets). Any 'academic in confidence' data provided by the manufacturer, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness model will also be

highlighted and redacted before release. Incremental analyses that rely on CIC data will be redacted. The EAG will strive to produce results that are as transparent as possible to the general public and may choose not to use CIC, if an alternative source exists, which produces similar results that would not need these results or the model to be redacted.

5. Competing interests of authors

Paul Dark is the National Deputy Medical Director of NIHR CRNCC. His NHS host hospital R&I Department has been contracted and paid to provide advice on the use of Tocilizumab for ROCHE and Sortrovimab for GSK both in COVID-19. He supported the activity as a named NHS expert employed by the Northern Care Alliance NHS Foundation Trust (Salford Care Organisation) but received no personal payments. There are no other conflicts of interest within this project team.

6. Timetable/milestones

Table 2 details the timelines for the initial work.

Table 2: Time milestones

Milestone	Date to be completed
Protocol submission	1st April 2022
Stakeholder meeting to discuss approach and methods	14th April 2022
Draft Assessment Report	To be determined
Final Report to NICE	30th June 2022

Additional information that is needed by NETSCC, HTA and NICE.

Please send this as a WORD document when you submit your protocol to Htatar@soton.ac.uk.

Details of the EAG

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Professor Paul Dark and Ronan McMullan provided clinical advice to the EAG for preparing the MTA protocol and are anticipated to be part of the EAG.

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