Evidence Assessment and Analysis Report commissioned by the NIHR Evidence Synthesis Programme on behalf of the National Institute for Health and Care Excellence Diagnostics Assessment Programme – Protocol

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Title of the project

Exploratory economic modelling of SARS-CoV-2 viral detection point of care tests and serology tests

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Plain English Summary

Testing to see whether people have COVID-19 is beneficial. People who have COVID-19 can self-isolate and limit the spread of the virus, whilst those that don't do not need to self-isolate. Testing to see whether people have already had COVID-19 may also be beneficial as they may have protection against the virus (although the level and duration of this are currently uncertain) and do not need to socially distance as strictly, or need to self-isolate if they have been in contact with a person with COVID-19. Using tests that can be used outside of a laboratory and can give a result quicker than current laboratory-based testing has the advantage that the decision to isolate or not can be taken earlier. Such tests are called 'point of care tests'.

There are many uncertainties including the diagnostic accuracy of any tests (that is, how many people with COVID-19 that are correctly identified and how many without COVID-19 that are correctly identified), the number of people that someone with COVID-19 will be close enough to infect and the risk of infection.

There are a number of settings where point of care tests could help if they are accurate enough. These include hospitals, care homes, prisons, dentists and schools. There are many different strategies that can be used with point of care testing ranging from testing all people (including staff) to testing people believed to be at high risk and to testing no-one.

The work is to estimate how much health is gained by COVID-19 related testing. This can be measures as the number of COVID-19 cases avoided, the number of unnecessary self-isolations, the number of deaths avoided, and combined into the increase in quality-adjusted life years (QALYs). Any extra costs of point of care testing will be estimated and the cost per QALY gained will be presented which represents a measure of cost-effectiveness.

The cost-effectiveness will vary between setting and the strategy employed. As results are needed quickly some settings and strategies for testing will be prioritised. These decisions will be made by NICE and may change through the project. This protocol is thus subject to change as new evidence and priorities emerge.

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 of hypothetical (i) point of care tests (POCT) to help detect SARS-CoV-2 and (ii) serology tests. The anticipated quicker turnaround time associated with POCTs can lead to more efficient resource use as patients can be triaged based on estimated COVID-19 status and could allow at-risk contacts to be traced more quickly.

The objective of the work will be to ascertain which parameters are most influential on the results (including morbidity, mortality, number of COVID-19 transmissions) and on cost-effective measures (in terms of cost per quality-adjusted life years gained and in terms of modelled outputs such as cost per mortality avoided).

The tests evaluated are hypothetical using target product profiles (TPP) defined by the medicines and healthcare products regulatory agency. (MHRA[2]). Due to the large number of potential settings within the NICE final scope (hospitals, care homes, dentistry, doctors, prisons, schools and colleges, entry and exit points to the country, workplaces and within the community) and the potential for different positioning of tests within each setting, the EAG will discuss with NICE the prioritisation order of the work undertaken. Settings and use cases within each setting are provided in the NICE scope.[1]

It is expected that the work is segmented so that results for higher-priority settings will be available before those of lower-priority settings. Initial discussions with NICE indicate that currently viral detection tests are a higher priority than serology tests and that hospitals, followed by care homes and other residential settings are the highest priority settings. It is possible that these views may change within the course of the project and NICE and the EAG acknowledge the need for flexibility within the project and for regular discussions between the two groups.

The EAG's work will be informed by the settings and use cases described in the NICE scope. The order that this work is done in will be decided in ongoing discussion with NICE and will be informed by current need for testing and the EAG's resources. It is anticipated that the EAG and NICE will have frequent communication about the work

1.2 Place of the hypothetical POCTs in the treatment pathway

During the project the EAG will be working closely with NICE and other bodies, for example MedTech In Vitro Diagnostics Cooperatives, to (i) understand the care pathway in each setting analysed and (ii) to ascertain where appears to be potentially optimal positioning of POCTs. Due to the requirements for results to be generated in a timely manner, not all settings and possible positioning of the POCTs will be evaluated in the first (or later) set of results.

1.3 Clear definition of the tests

Only hypothetical TPPs will be evaluated. TPPs defined by the MHRA are contained in the NICE scope[1] although these may be updated in the course of the project.

1.3.1 Viral detection tests

Viral detection POCTs can be used alone or in conjunction with confirmatory laboratory-based testing. The ability of tests to detect SARS-CoV-2 will vary over the course of an infection, with infectiousness currently estimated to be at its highest the day before symptom onset.[3] Viral detection POCTs can be used as a triaging tool, although if the diagnostic accuracy was high enough these potentially could be used for diagnostic purposes.

POCTs that can provide an alternative diagnosis, such as influenza and other coronaviruses, alongside testing for SARS-CoV-2 are being developed. These may provide clinicians reassurance that negative results for SARS-CoV-2 are not false.

1.3.2 Serology tests

Serology tests can be used as POCTs, self-tests or as a laboratory-based tests. Serology tests are intended to detect the presence of antibodies (IgG, or a combination of IgG, IgA and IgM) with tests currently performed in a laboratory. The MHRA has published TPPs for POCTs[4], self-tests and for laboratory tests.[5]

1.4 Populations and relevant subgroups

As all people may be infected with SARS-CoV-2, including asymptomatically, or have had SARS-CoV-2, also including asymptomatically, there is no clearly defined patient group amongst those attending a particular setting. However, some people may be at higher risk of worse outcomes following infection with the SARS-CoV-2 virus. These include older people, those with underlying health conditions, those with compromised immunity and people from black and south Asian family origin. People with COVID-19 symptoms may also represent a relevant subgroup for testing with viral detection POCTs. People who have recovered from confirmed SARS-CoV-2 or who have been vaccinated against SARS-CoV-2 may represent relevant subgroups for serology POCTs.

1.5 Relevant comparators

POCTs for SARS-CoV-2 have laboratory-based testing or no testing as comparators. If it is identified that laboratory testing is not a perfect reference standard, which could be due to multiple reasons including poorly-acquired genetic matter and problems in transportation, then exploratory analysis adjusting for the imperfect reference standard may be undertaken. Comparators for serology testing will be no testing for laboratory-based tests, or no testing or laboratory testing for POCTs or self-tests.

1.6 Outcomes

The NICE scope[1] lists a large number of outcomes for both viral detection POCTs and serology tests. The full list is not replicated here although selected outcomes (mortality, morbidity, length of stay in hospital, length of time self-isolating, the number of people self-isolating, the number of people infected with COVID-19, and the costs of testing) have been highlighted. The EAG notes that there is some circularity between items listed as outcomes in the scope and model inputs. For example, '*test failure rate*' is listed as an outcome, yet this will be determined by a model input relating to the proportion of tests that return unusable results. It is anticipated that not all model outcomes will be reported in the final reports. Discussions with NICE will determine those that are considered the highest priority

The cost-effectiveness of viral detection POCTs versus usual practice will be expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained. A patient lifetime horizon will be used to take differential mortality between strategies into account. Other measures of cost-effectiveness, such as cost per unnecessary self-isolation will be estimated. A similar set of analyses are envisaged for serology tests, noting that the placement of

serology POCT tests in the patient pathway will differ to the anticipated use of viral detection POCTs.

Further details of the proposed health economic analysis are presented in Section 3.

1.7 Other considerations

It is acknowledged that this research is not aligned with typical diagnostic assessments for NICE and that there is a need for the prioritisation of settings, and in evaluating positional strategies for POCTs. It is anticipated that there will be much more interaction between NICE and the EAG to ensure that the results produced within the limited timescales are as useful to the NICE Diagnostic Advisory Committee as possible. Re-running of models may be required as new evidence emerges.

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

As the POCTs being assessed are hypothetical there will be no systematic review to inform the performance (for example, diagnostic accuracy, or time requirements) of the tests.

It is believed that the majority of relevant evidence relating to SARS-CoV-2 will not be published in peer-reviewed journals although may be published in pre-publication databases such as MedRxiv.[6] As such, it is anticipated that the EAG will not undertake systematic literature reviews for model parameters but will instead use publicly available data from bodies such as Public Health England (PHE), request confidential data from bodies such as PHE or rely on expert advice to populate the model. The EAG will try to keep abreast of newly published evidence relating to SARS-CoV-2 / COVID-19 and anticipates that where NICE or the specialist committee members recruited to the Diagnostic Advisory Committee become aware of potentially relevant research that this would be signalled to the EAG.

If a parameter within the modelling is believed to be clearly improved by a review of the literature then targeted reviews would be undertaken.

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 testing 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, NICE, specialist committee members or external bodies that the EAG and NICE will be in contact with, 2) not be published in a peer-review journal, or 3) not generalisable to the decision problem in England.

The EAG will try to keep abreast of newly published evidence relating to models of the use of SARS-CoV-2 viral detection point of care tests and serology tests and anticipates that where NICE or the specialist committee members recruited to the Diagnostic Advisory Committee become aware of potentially relevant research that this would be signalled to the EAG.

3.2 Evaluation of costs, quality of life and cost effectiveness

A series of health economic models will be developed in Simul8 to assess the cost-effectiveness of COVID-19 related tests. The economic analysis will adopt the perspective of the NHS and PSS although wider societal perspectives may be included in sensitivity analyses such as the impact on productivity can be explored. Health outcomes and costs will be evaluated over a lifetime horizon. Cost-effectiveness will be expressed in terms of the incremental cost per QALY gained. Costs will be valued at current prices. In line with the NICE Reference Case, health outcomes and costs will be discounted at a rate of 3.5% per year. A series of models is anticipated as different settings may require different structural assumptions, as may the use of viral detection POCTs compared to serology tests. Whilst the EAG would strive to use the same foundation model for all evaluations, for some evaluations it is expected that it would be cleaner to have a separate model.

3.2.1 Model structure

It is anticipated that the structure of the model developed for this assessment will be an individual patient model developed in Simul8. The advantages of an individual patient model approach are multiple and include: 1) each patient being assigned characteristics, such as age and COVID-19 status, which can be dynamically adjusted as the time in the model progresses, 2) that potential cross-infection in settings can be explicitly modelled using individual patients and their characteristics, 3) that capacity constraints can be explicitly modelled and 4) that the possibility for members of staff within a setting to infect users can be explicitly modelled. Simul8 is an established, validated, package that runs quickly and facilitates the modelling needed. Whilst Simul8 is not a standard package used in assessments for NICE the use of it within the exploratory modelling has been sanctioned by NICE to expedite the generation of results. The EAG has considerable experience in using Simul8, including in complex problems.[7]

3.2.2 Diagnostic pathways modelled

Patient care pathways will be identified via consultation with experts as described in Section 1.2. Prioritisation of exploratory positioning of tests and settings will be undertaken in conjunction with NICE considering the time available.

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[8], the Personal Social Services Research Unit[9], the British National Formulary[10]), through personal communication with relevant bodies and clinical experts, as required and if applicable through published and unpublished literature. It is anticipated that NICE or clinical experts will provide plausible ranges of prices for the hypothetical tests

Health-related quality of life values, based on literature or other sources, will be dependent on the health status of the individual patient. For example, it is expected that the utility of patients in an intensive care unit would be lower than those discharged from hospital. Equally, patients with chronic comorbidities associated with SARS-CoV-2 would have a lower average utility than patients who had not sustained these comorbidities. It is likely that SARS-CoV-2-specific utilities will not be found. The EAG will look for utility values that may be generalisable to the decision problem if needed. Utility values will be age-adjusted using ratios reported in Ara and Brazier.[11]

3.2.4 Model Analyses

Incremental cost-effectiveness ratios (ICERs) will be estimated based on the costs and QALYs associated with each testing strategy and setting combination evaluated. The cost per selected outcome measures (listed in Section 1.6) avoided will also be considered.

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 test strategies 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.[12]

Analyses of strategies that differentiate testing between specific patient subgroups (for

example, all vs symptomatic) or between testing only patients, only staff, or both groups may be undertaken. Such strategies will be discussed with NICE as the project progresses and as the prioritisation order is updated.

4. Handling information from the companies

It is not anticipated that much information will come from test developers as the tests being evaluated are hypothetical with diagnostic accuracy being taken from TPPs published by the MRHA. However, there remains the possibility that evidence related to the decision problem is submitted.

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

There are no conflicts of interest within this project team.

6. Timetable/milestones

It is likely that the work will be segmented in order that the settings, positioning of tests and type of test (viral detection or serology) deemed most important are evaluated first. Table 1 details the timelines for the initial work, which currently would encompass testing strategies in hospitals, care homes and other residential facilities, although the exact priorities within these settings have currently not been agreed.

Table 1: Time milestones

Milestone	Date to be completed
Final date for Manufacturer/sponsor data submissions	Not Appropriate

Progress Report	21st September 2020
Draft Assessment Report	14th October 2020
Final Report to NICE	11th November 2020

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

Details of the EAG

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REFERENCES

1. National Institute for Health and Care Excellence. Exploratory economic modelling of SARS-CoV-2 viral detection point of care tests and serology tests. Final scope. 2020. https://www.nice.org.uk/guidance/gid-dg10038/documents/final-scope (Accessed 16 July 2020).
2. Medicines & Healthcare Products Regulatory Agency (MHRA). TARGET PRODUCT PROFILE. Point of Care SARS-CoV-2 Detection Tests. 2020. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/895745/TPP_Point_of_Care_SARS-CoV-2_Detection_Tests.pdf (Accessed 16 July 2020).
3. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X*, et al.* Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nature Medicine* 2020;26:672-5.
4. Medicines & Healthcare Products Regulatary Agency (MHRA). Target Product Profile: antibody tests to help determine if people have recent infection to SARS-CoV-2: Version 2. 2020.
5. Medicines & Healthcare Products Regulatary Agency (MHRA). Target Product Profile: enzyme Immunoassay (EIA) Antibody tests to help determine if people have antibodies to SARS-CoV-2. 2020.
6. Cold Spring Harbor Laboratory. B, Yale.,. MEDRXIV - the reprint server for Health Sciences. 2020. https://www.medrxiv.org/ (Accessed
7. Stevenson M, Uttley L, Oakley J, Carroll C, Chick SE, Wong R. Systematic review of Creutzfeldt-Jakob disease (CJD) risk via surgical interventional procedures and economic evaluation of management policies to reduce this risk. *Health Technol Assess* 2020;24:1-182.
8. NHS Improvement. National Cost Collection for the NHS. 2020. https://improvement.nhs.uk/resources/national-cost-collection/ (Accessed 16 July 2020).
9. Personal Social Services Research U. Unit Costs of Health and Social Care 2015. 2015. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2018/ (Accessed 09 May 2019).
10. British National Formulary. MedicinesComplete. London: Pharmaceutical Press.; 2020. https://about.medicinescomplete.com/publication/british-national-formulary/ (Accessed 16 July 2020).
11. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;13:509-18.
12. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D*, et al.* Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Value Health* 2013;16:e1-5.