Next Generation Health Technology Assessment

Project Title: Next Generation Health Technology Assessment to support patient-centred, societally oriented, real-time decision-making on access and reimbursement for health technologies throughout Europe

Grant Agreement Number: 825162

Date: 4 October 2021	Lead Beneficiary: NICE
Nature: Report	Diss Level: Public

Best-practice guidance for the health technology assessment of diagnostics and treatments for COVID-19

Authors

Jamie Elvidge[1], Ashley Summerfield[2], Saskia Knies[3], Bertalan Németh[4], Zoltán Kaló[4], Wim Goettsch[3,5], Dalia Dawoud[1]

On behalf of the COVID-19 HTA best-practice guidance development group*

October 2021

1. Science Policy and Research Programme, National Institute for Health and Care Excellence (NICE), UK
2. Medicines Analysis, NHS England and NHS Improvement, UK
3. National Health Care Institute (Zorginstituut Nederland), Netherlands
4. Syreon Institute, Hungary
5. Utrecht Centre for Pharmaceutical Policy, Utrecht University, Netherlands

Citation:
Elvidge J, Summerfield A, Knies S, Németh B, Kaló Z, Goettsch W, Dawoud D, On behalf of the COVID-19 HTA best-practice guidance development group. "Best-practice guidance for the health technology assessment of diagnostics and treatments for COVID-19". October 2021. DoI: 10.5281/zenodo.5530468

*COVID-19 HTA best-practice guidance development group members

Neil Bertelsen, Past Chair of HTAi Patient and Citizen Involvement Interest Group, UK
Ailsa Brown, NHS Healthcare Improvement Scotland, UK
Jon D Campbell, Institute for Clinical and Effectiveness Research (ICER), USA
Arturo Cabra, International Society for Pharmacoeconomics and Outcomes Research (ISPOR), USA
Jaime Caro, McGill University, Canada
Stijntje Dijk, Erasmus University, Netherlands
Trudy Foster, NHS Forth Valley, UK
Peter Graham, Gilead Sciences, UK
Eline Krijkamp, Erasmus University, Netherlands
James Larcombe, NHS County Durham, UK
Anne Lee, NHS Healthcare Improvement Scotland, UK
Ben Messer, British Thoracic Society, UK
Mark Miller, BioMereux, France
Dionysios Ntais, MSD, UK
Brian O'Rourke, Chair of the ISPOR Health Technology Assessment Council, Canada
Oresta Piniazkho, Ministry of Healthcare, Ukraine
Nina Pinwill, NHS England and NHS Improvement, UK
Juan Carlos Rejón Parrilla, Andalusian Health Technology Assessment Unit (AETSA), Spain
Kawaldip Sehmi, International Alliance of Patients' Organizations, UK
Matthew D Stevenson, University of Sheffield, UK
Sheela Upadhyaya, National Institute for Health and Care Excellence (NICE), UK
Thomas Walker, National Institute for Health and Care Excellence (NICE), UK

Acknowledgements

The authors would like to thank the following individuals for their input into or support for the development of this guidance:

Roisín Adams, Tarry Ahuja, Lucy Beggs, Jacoline Bouvy, Adam Brooke, Jagpreet Chhatwal, Y-Ling Chi, Carla Deakin, Diana Delnoij, Jane Eddleston, Julian Elliott, Anna Melissa Guerrero, Alex Haines, Kevin Harris, Jasdeep Hayre, Daniel Horner, Li Jiu, Páll Jónsson, Justine Karpusheff, Jeanette Keusel, Karen Lee, Francois Maignen, Kamila Malinowska, Gergő Merész, Andrew Mitchell, Diane Playford, Johan Ponten, Maarten Postma, Rachid Rafia, Mihai Rotaru, Murali Shyamsundar, John Spoors, Tina Taube, Isabelle Tongio, Michael Toolan, Tari Turner, Goedele van Haasteren, Albert Vollaard, Junfeng Wang, Alan Wailoo, Melanie Whittington, Darshan Zala.

Glossary of abbreviations

ARDS	Acute respiratory distress syndrome
BMI	Body mass index
CADTH	Canadian Agency for Drugs and Technologies
CCA	Cost-consequence analysis
CEA	Cost-effectiveness analysis
CUA	Cost—utility analysis
ECMO	Extracorporeal membrane oxygenation
FDA	US Food and Drug Administration
HTA	Health technology assessment
ICER	Institute for Clinical and Economic Review
IHTAM	Innovation of Health Technology Assessment Methods Framework
NICE	National Institute for health and Care Excellence
OBA	Outcomes-based (commercial) agreement
RCT	Randomised controlled trial
RWE	Real-world evidence
SARS	Severe acute respiratory syndrome
SEIR	Epidemiological “susceptible, exposed, infected, recovered” model
ZIN	Zorginstituut Nederland

Next Generation Health Technology Assessment

TABLE OF CONTENTS

Executive summary

Since 2020, the novel SARS-CoV-2 virus and its associated disease (COVID-19) pandemic has placed healthcare systems and wider economies in an unprecedented crisis. To date, health technology assessment (HTA) agencies have not been at the forefront of decision making about the use of vaccines, diagnostic tests, treatments and public health interventions for COVID-19. Instead, policymakers have prioritised rapid action in response to the pandemic emergency. While reimbursement decisions have often been informed by the scientific community (including epidemiologists, virologists, and modellers), they included little or no consideration of value for money nor cost-effectiveness.

As vaccination programmes take effect, healthcare systems are starting to move away from the emergency approaches taken in the early pandemic. With a less urgent need to act, and pressure on healthcare budgets, healthcare systems with established HTA agencies should be evaluating technologies for COVID-19.

However, these assessments are likely to pose more challenges than those posed by any other technologies that HTA agencies have dealt with. These include the limited and uncertain clinical evidence base, a very rapidly evolving scientific understanding of the disease pathway and its clinical management, the operational challenges and the need for frequently updating guidance due to the extremely fast paced publication of new “evidence”. Many of these challenges are expected to remain for some time, and different HTA agencies may approach them in different ways.

To support HTA agencies with consistent and pragmatic approaches, we have developed this best-practice guidance for the assessment of technologies for COVID-19. We focused on diagnostic and therapeutic technologies, as the most commonly assessed by HTA agencies. For therapeutics, we focused on treatments rather than post-exposure prophylaxis, however, the recommended approach is unlikely to be much different for prophylactic options.

The recommendations herein are based on findings from a survey and workshop of HTA agencies, a workshop with health economic modellers, and reviews of COVID-19 methods guidance, clinical guidelines, and economic evaluations. They have also been discussed with, and refined with input from, a multistakeholder group at a policy sandbox event. The recommendations span several themes relevant to HTA, and some of the key proposals are summarised below. Foremost among them is the recommendation that the pandemic is used as an opportunity to implement a responsive, “living” approach to HTA.

Assessing clinical effectiveness

Randomised controlled trials (RCTs) should remain the gold standard for clinical evidence for technologies for COVID-19. However, during a pandemic, the best evidence available to HTA

agencies may be less robust than RCTs, such as uncontrolled real-world evidence (RWE), studies published as pre-prints, or evidence that is not perfectly generalisable to the local setting. HTA agencies should be prepared to assess technologies for COVID-19 using these sources of evidence, if they are the best available at the time of the assessment. Agencies should also consider accepting existing "living" systematic reviews to inform their clinical effectiveness assessments, to save time and resources and avoid duplication of efforts. Similarly, published core outcome sets for COVID-19 could be used to identify the most appropriate clinical outcomes.

For all recommendations about clinical effectiveness, see section 2.

Assessing value for money

HTA agencies that use cost–utility analysis should continue to do so when assessing technologies for COVID-19. Other types of economic evaluation, such as cost–consequences analysis, can also be considered where they are likely to be useful. Both the healthcare (payer) perspective and the societal perspective should be considered relevant to decision making about COVID-19 technologies. A societal perspective is likely to be more important when the pandemic situation is urgent and when funding is provided from a central government, rather than a specific healthcare payer budget. HTA agencies should continue to use their standard cost-effectiveness thresholds and modifiers in COVID-19 assessments for now, but should engage in research to identify whether there are different societal preferences during and following a pandemic.

For all recommendations about cost effectiveness, see section 3.

Economic modelling

To inform assessments of cost effectiveness across a wide range of COVID-19 technologies, or sequences of technologies, the use of a whole-disease pathway model including both diagnosis and treatment is recommended. The model should ideally be an individual-level simulation to capture the heterogeneous patient population, the complex pathway, and the potential impact of some technologies on transmission or system capacity.

The model should accommodate a wide range of options, including allowing it to run an individual-level or cohort-level model, capture disease transmission (e.g., by linking to an epidemiological or infectious disease model), and incorporate system capacity effects. Capacity effects will be more important to consider during surges of infection that lead to increased pressure on healthcare resources beyond their capacity constraints. The model should also include the flexibility to disable any of these options, to facilitate a less complex modelling approach where appropriate. For example, a simple cohort-level model may be acceptable when assessing a straightforward, narrowly defined decision problem, or multiple

technologies at the same position in the treatment pathway. Any economic model should capture the long-term COVID-19 outcomes and treatment effects.

The model should be frequently updated to reflect the most up-to-date understanding of the disease and changes in the standard of care. A "living", adaptable whole-disease pathway model could be collaboratively developed by HTA agencies, with input from multiple stakeholders, and made freely available for use and adaptation to support a globally responsive HTA approach to COVID-19 technologies.

For all recommendations about modelling, see section 4.

Considering uncertainty

Most COVID-19 assessments will have a high level of uncertainty. Agencies should be transparent about the data gaps and assumptions made and should consider the results of extensive sensitivity and threshold analyses. Probabilistic results should still be used and could be accompanied by value of information analysis to inform future research needs. A transparent, pragmatic, "living" HTA approach should be implemented, with a commitment to responsively review decisions as new and better evidence emerges, including potentially reversing previous decisions by reinvesting or disinvesting in technologies.

For all recommendations about characterising and mitigating for uncertainty, see section 5.

Affordability and procurement

HTA agencies should routinely consider the expected budget impact of COVID-19 technologies, including any required service redesign and system burden, to identify technologies that would be difficult for the healthcare system to implement. This could trigger commercial discussions between the technology developer and healthcare payer. Alternatively, it could trigger the HTA agency to explore subgroup analyses, to identify groups for whom a technology is most cost effective and inform the prioritisation of its use. Commissioners and payers may explore novel payment models for COVID-19 technologies. Managed access agreements, including a period of data collection to resolve key uncertainties, may be particularly well suited to a living HTA approach.

For all recommendations relating to procurement, see section 6.

Considering other elements of value

When assessing COVID-19 technologies, HTA agencies should consider whether there are relevant benefits that are not adequately captured in the clinical and cost effectiveness assessment, such as reduced inequity, reduced fear of infection, and scientific innovation. If it is not possible to include these effects quantitatively (for example, by capturing them in utility values), then they should be considered using a qualitative, deliberative approach.

For all recommendations about other elements of value, see section 7

Stakeholder engagement

The far-reaching effects of the pandemic mean HTA agencies should ensure a broad range of stakeholders can contribute to the assessment of COVID-19 technologies. Input from clinical and patient experts may be particularly informative where that are evidence gaps and uncertainties. A “tiered” approach to patient and public engagement is recommended, including circumstances to approach citizens’ groups and organisations that represent high-risk groups. HTA agencies could consider using innovative methods to facilitate broad engagement, such as digital and online communication tools.

For all recommendations about engaging with HTA stakeholders, see section 8.

Next Generation Health Technology Assessment

Visual summary of key recommendations

Assessing clinical effectiveness

- Adaptive RCTs preferred for efficacy
- Promote high-quality RWE to fill evidence gaps
- Use "living" evidence reviews
- Carefully consider generalisability to the relevant setting
- Prespecify subgroup analyses
- Refer to the list suggested core outcomes and core outcomes sets

Assessing value for money

- Use cost—utility analysis, if usually preferred, with supportive cost-effectiveness and cost-consequence analyses where useful
- Consider both a healthcare and a broad societal perspective
- Use robust data from related conditions where necessary
- Use usual threshold values, but engage in research about preferences during a pandemic

Economic modelling

- Ideally, use simulation models to account for patient heterogeneity
- Include long-term outcomes, disease transmission and system capacity
- Calibrate uncertain inputs to ensure plausible outputs, e.g. using RWE
- Develop a whole-disease model for COVID-19, as an epidemiological (SEIR) with nested diagnosis and treatment components
- Allow simpler analyses where they may be acceptable for decision-making
- Regularly update the model to support "living" HTA

Handling uncertainty

- Transparently report evidence gaps, assumptions made and the pandemic context
- Extensive subgroup, extreme value and threshold analyses
- Use probabilistic analysis
- Consider using value of information analysis to inform research priorities
- Mitigate uncertainty by implementing a "living" HTA approach
- Responsively update decisions (including reinvestment and disinvestment) based on new information

Stakeholder engagement

- Ensure a broad range of stakeholders can contribute to HTA process
- Including citizens, patients, carers and proxies, and organisations that represent specific groups who are at higher risk or underrepresented
- Prioritise based on a tiered approach
- Consider novel approaches to engagement, such as digital and online tools

Other important factors

- Affordability should be assessed using budget impact analysis
- Affordability concerns should trigger commercial discussions
- A "living" HTA approach would facilitate managed access agreements
- Consider other potentially relevant elements of value, including equity, reduced fear of contagion, and scientific advancement
- Try to capture them quantitatively (e.g. in utility values), otherwise narratively

1. Introduction

HTA agencies have continued to function during the unprecedented challenges presented by the novel SARS-CoV-2 virus and its associated disease (COVID-19) pandemic. Faced by an escalating emergency, policymakers have largely made decisions about public health interventions, vaccination programmes, testing strategies, and treatments for COVID-19 without full HTA (1,2). As a result, various diagnostic tests and treatments have entered clinical practice based on preliminary results or effectiveness data from observational studies alone, with some later shown to lack efficacy in large well-conducted clinical trials, such as hydroxychloroquine (3).

This approach may be justifiable in a health crisis of such magnitude, where the "rule of rescue" prevails (4) as standard HTA requires both evidence and time, both lacking in the early part of a pandemic. Further, with high-income countries' governments appearing to sign 'blank cheques' in their efforts to tackle the emergency, the need for standard HTA – identifying the most efficient allocation of scarce healthcare resources – becomes less important.

As vaccination programmes continue to take effect, the urgent threat to healthcare systems should begin to come under control, but economies are likely to enter period of prolonged austerity. Healthcare systems will start to consider the best way of dealing with the unintended consequences of the mitigation measures used, such as the impact of lockdown on mental health, disruption to other services, and the long waiting lists for elective surgeries. All this means policymakers will have to be more selective about the technologies they reimburse to diagnose or treat COVID-19, favouring options that offer the biggest health benefits relative to their cost. In countries where HTA agencies have been established, they are best placed to inform these decisions. Some have already been asked to assess technologies for COVID-19, and many more novel and repurposed products are in the pipeline.

Therefore, as part of the HTx (Next Generation Health Technology Assessment) project, we have developed this interim guidance to provide a set of consistent, pragmatic ways for HTA agencies to approach some of the key challenges they are likely to face when assessing COVID-19 technologies.

HTx is a Horizon 2020-funded project supported by the European Union lasting for 5 years from January 2019. Its main aim is to create a framework for the next generation

of HTA to support patient-centred, societally oriented, real-time decision-making on access to and reimbursement for health technologies throughout Europe.

The HTx project: where does this work fit?

This work was undertaken as part of a dual pilot of methods that are either developed by or to be used within the HTx project. Firstly, HTx has delivered a novel framework to support innovation in HTA methods: '**Guidance for the Innovation of Health Technology Assessment Methods – the IHTAM framework**' (5). The IHTAM framework provides a systematic way for HTA stakeholders to innovate methods, by following 3 phases:

1. Identification: Learn from past experiences and existing methods, imagine a better approach, and identify the needs of stakeholders to reach it.

2. Development: Dedicate resources to designing new methods or processes to address the identified needs, and subject them to pilot testing.

3. Implementation: Establish a plan to implement the novel methods, apply them to real-world practice, evaluate their performance and transfer to other settings.

To date, IHTAM has not been tested in the context of a real-world case study.

The COVID-19 pandemic started midway through the HTx project and continues to pose unprecedented challenges for healthcare systems and HTA agencies. We hypothesised that it may expose areas where existing HTA methods could be improved, either in general or to enhance the discipline's preparedness for a future pandemic. This presented a timely opportunity to pilot the IHTAM framework. To identify whether there is need for a change in the standard approach used by HTA agencies (the "identification" phase of IHTAM), we performed the following tasks:

- Reviewed existing methodological guidance from HTA and regulatory agencies relating to the assessment of COVID-19 technologies.

- Conducted a survey and workshop of HTA agencies to identify their perceived barriers to assessing COVID-19 technologies.

- Convened a workshop of health economists to identify their perceived barriers to developing decision models for assessing the cost effectiveness of COVID-19 technologies.

- Conducted a systematic literature review of economic evaluations of COVID-19 technologies.

- Reviewed clinical guidelines and liaised with clinical experts to gain a clear understanding of the current COVID-19 disease and clinical pathways and develop a conceptual model of the disease pathway.

The key challenges identified from this work are detailed in section 0 of this report.

After establishing a case for developing HTA methods guidance for assessing COVID-19 related technologies, we proceeded to develop it with input from relevant stakeholders (the "development" phase of IHTAM). This included:

- Drafting proposed good-practice guidance to address the key challenges identified when assessing COVID-19 technologies.
- Develop a conceptual basis for a COVID-19 disease model for the assessment of COVID-19 technologies.
- Convened a **policy sandbox** event to test the proposed guidance and co-develop final guidance with a multidisciplinary panel of HTA stakeholders, comprising 21 representatives of clinical experts, health economists, HTA agencies, a payer, patient advocates, a health economics and outcomes research professional body, and technology manufacturers.

The resulting good-practice recommendations for assessing COVID-19 technologies are detailed in sections 2 to 8 of this report.

Using a policy sandbox in the development phase was an opportunity to pilot the use of this approach in developing HTA methods and processes. A policy (or regulatory) sandbox provides a 'safe' environment to test novel methods or processes, isolated from live processes to avoid any potentially negative external consequences. This approach has not yet been used in HTA (6). It will be used to test the acceptability of HTx outputs relating to shared decision making and payment models in preparation for their implementation in practice. Using a policy sandbox to develop HTA methods guidance for COVID-19 has provided valuable experience of applying the approach in HTA, which will inform and benefit the later policy sandboxes to be conducted in HTx Work Package 4.

Moving into the final phase of IHTAM ("implementation"), next steps include wide dissemination of the guidance to support its uptake among HTA agencies, and engaging with agencies that wish to use it for their assessments of COVID-19 technologies. Further research may include using the guidance to inform the development of a COVID-19 disease model.

1.1. The need for this guidance

1.1.1. Challenges for HTA

It has been acknowledged that assessing therapeutic and diagnostic technologies for COVID-19 is unlikely to be straightforward (7,8). However, a review of the methods guidance available from regulatory and HTA agencies has revealed that there is limited guidance available to inform stakeholders about how these agencies intend to approach assessing COVID-19 related technologies. Of the guidance identified, the National Institute for Health and Care Excellence (NICE) and the US Food and Drug Administration (FDA) provide the most comprehensive recommendations, largely informing trial design, analysis planning and the use of non-randomised evidence (9,10). However, most recommendations simply reiterate pre-existing best practices and preferred methods, and there is almost no tailored guidance about how to assess the cost effectiveness of COVID-19 technologies.

To confirm the need for tailored guidance, we engaged with representatives of HTA agencies using a mixed methods approach, by conducting a survey followed by a roundtable workshop to identify the difficulties they expect to face in these assessments, or have faced already if they have started to conduct such assessments. We also convened a workshop of health economists to identify the key challenges faced when modelling COVID-19.

The challenges facing HTA agencies, as identified from the survey and workshop, were largely in line with those identified by the ISPOR HTA Council (11). Many are not unique to COVID-19, though. For example, HTA agencies are accustomed to evaluating technologies for rare diseases that may lack high-quality clinical effectiveness evidence and considerable uncertainty. It is also common to be presented with a heterogeneous evidence base and make judgement calls as to how generalisable the data are to the local setting. Difficulties in estimating and assessing cost effectiveness, by relying on uncertain data and assumptions, and making reimbursement decisions under scrutiny from external pressures, are also common challenges faced in other disease areas.

1.1.2. Unique challenges posed by COVID-19

However, in addition to the routine challenges faced by HTA agencies, they will occur in the context of wider pandemic-related instability that will make assessing COVID-19 technologies uniquely difficult.

The priorities of healthcare systems are also likely to vary over time depending on the pandemic context, which has shifted from the highly uncertain, urgent early pandemic situation to a period of variable peaks and troughs in infection rates and the emergence of novel variants. Scientific understanding of COVID-19 continues to evolve; so too, clinical practice. Many technologies for COVID-19 are being developed, including some novel treatments and many that are being repurposed for COVID-19 (less often seen for rare diseases), meaning the clinical pathway is expected to change rapidly. An HTA decision made at the height of infection rates or when there is no effective existing treatment, might not be the optimal decision soon after, when infection rates are lower, a new variant has emerged, or the clinical pathway has changed.

The societal burden of infection waves has been unprecedented, with dramatic and costly mitigation strategies, including business and school closures, furloughed workers, travel restrictions, and reduced social contact. COVID-19 has also had a knock-on impact on other healthcare services, such as routine diagnostic and elective procedures being scaled back (12,13). Despite this, during peak waves of infections, secondary healthcare services were observed to become overwhelmed, with demand for hospital beds and ventilators exceeding supply (14,15). A treatment may be considered more valuable if it reduces the need for, or threat of, severe societal restrictions, and if it reduces demand for hospital services at a time when they are particularly stretched. This is not typically a consideration in 'routine' HTAs for non-infectious diseases.

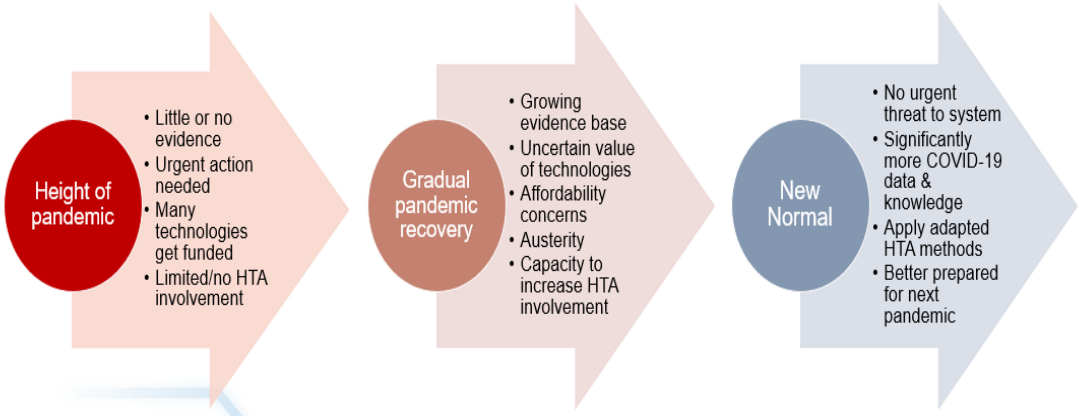
The limited supply of vaccinations has been a key theme during the pandemic (16,17). Some governments acted quickly to ensure they secured vaccines, but similar supply chain issues could exist for effective diagnostic and therapeutic technologies. Waiting for a lengthy HTA process to conclude before procuring a treatment may risk being put at the back of a long queue, behind other systems that snapped up the available supply earlier. HTA agencies may be able to identify subgroups to help prioritise the most efficient use of scarce supply, but such advice may be controversial, involving moral and ethical considerations (18,19). While HTA agencies may be familiar with responding to external pressure from a small number of stakeholders in a specific disease area, the far-reaching societal effects of COVID-19 mean an HTA decision for a COVID-19 technology is likely to be scrutinised more widely and publicly than usual. Additionally, with the large number of investigative trials in progress, HTA agencies will face continued pressure to produce robust guidance about COVID-19 technologies more rapidly than usual. This has been demonstrated in the US, where the Institute for Clinical and Economic Review (ICER) has recently stated its intention to jointly assess five treatments for COVID-19 (20).

1.1.3. The role of this guidance

Many of the challenges identified will remain problematic for some time. HTA has an important role to play to ensure healthcare systems can access cost-effective technologies for COVID-19, but usual processes might not be optimal for this; a more pragmatic and responsive approach may be needed. Accordingly, this guidance intends to provide a stepping stone to gradually increase the rigour of assessments, as securing value for money becomes a more important objective for policymakers. As healthcare systems recover, it is expected that HTA agencies will move on to apply the methods they routinely use in other conditions to technologies for COVID-19.

1.2. How to use this guidance

This guidance is targeted at HTA agencies to support their assessment of therapeutic and diagnostic technologies for COVID-19. It is intended to provide interim guidance to increase the rigour of HTA as the pandemic continues, during which time many of the challenges facing HTA agencies will persist. This guide should be viewed as a step towards the future reinstatement of usual, thorough HTA processes, when healthcare systems have recovered. Recommendations in this guidance that are found to provide effective ways of working may be adopted into the new normality of HTA methods and processes.



When assessing diagnostic or therapeutic technologies for COVID-19:

- HTA agencies should consider using the recommendations contained within to implement a consistent, pragmatic way of assessing COVID-19 technologies.
- Manufacturers of COVID-19 technologies may use this guidance to inform their evidence generation plans and the development of evidence dossiers for submission to HTA agencies.

- Other stakeholder groups, such as clinicians, patients, carers, and payers, may use this guidance to inform their engagement in, and expectations of, HTA processes.

Although this guidance has been developed in the context of the COVID-19 pandemic, the approaches detailed herein should be transferable to future infectious disease pandemics. It is hoped that this will allow HTA to respond quickly if similar situations arise in the future.

2. Assessing clinical effectiveness

2.1. Types of clinical evidence

The clinical effectiveness evidence base for COVID-19 technologies is still immature, with relatively few randomised controlled trials, heterogeneous populations and settings, short study durations, and a high prevalence of evidence that has not undergone full peer review. The evidence base will continue to improve, with over 4,500 planned, recruiting or active trials for COVID-19 technologies registered on https://clinicaltrials.gov/. Important evidence gaps will remain for some time. Furthermore, as the pandemic situation and scientific understanding of COVID-19 evolve, heterogeneity in the evidence is likely to remain present. For example, the increasing presence of antibodies in populations over time means the serology status of trial participants has become an important characteristic that may affect the efficacy of some treatments (21,22). Requiring trials in local populations may be overly restrictive, so HTA agencies in many countries are likely to rely on non-local (international or multinational) studies for decision making. Therefore, during a global pandemic, it is particularly important that evidence is made accessible and transparent (demonstrated by academic journals publishing COVID-19 studies as open-access articles). Non-randomised sources, such as real-world studies, could inform areas of uncertainty quickly and in a locally relevant setting, and in some cases may be the best available evidence to support decision making. Challenges remain regarding how to quality assess and report such evidence.

Several recommendations in this section (2.1) have been adapted from HTAi evidence standards (23) and NICE's support for the developers of technologies for COVID-19 (9) and evidence standards for diagnostic tests (24).

2.1.1. Clinical trials

Recommendations

For therapeutics:

Peer-reviewed, multicentre, randomised and controlled trials remains the gold standard evidence for evaluating the relative effectiveness of different interventions.
HTA agencies should expect and prefer to be presented with evidence from adaptive and pragmatic trials, because new information about the condition is emerging rapidly. This design can also improve trial efficiency.
Adaptive trials should adhere to guidance in the CONSORT extension statement for randomised trials using adaptive designs (25).

For diagnostics:

Clinical effectiveness is typically determined through a peer-reviewed test accuracy study, but alternative designs may be suitable (for example, in low-prevalence populations).

The QUADAS-2 tool (26) can be used to guide study design and support HTA agencies when assessing the suitability of diagnostic studies for decision making.

For all technologies:

HTA agencies should carefully and transparently consider the generalisability of evidence to their local decision problem or setting.

Due to the limited and disparate evidence base for COVID-19 technologies, HTA agencies should be willing to consider evidence that may not be perfectly generalisable to their local decision problem or setting.

Consider extensive sensitivity analysis if there is plausible rationale that the outcomes observed would be different in an agency's local decision problem or setting.

2.1.2. Non-randomised evidence

Recommendations

The use of peer-reviewed, well-designed and conducted non-randomised studies should be acceptable for COVID-19 technologies (and technologies to diagnose or treat a future pandemic), as there are likely to be gaps in the available randomised trial evidence.

Observational and RWE may be particularly suitable for hypothesis generation as well as assessing:

- Relative effectiveness in non-trial settings.
- Relative effectiveness in populations who were not enrolled in the trials.
- Long-term health outcomes, particularly survival and health-related quality of life.
- Emergent longer term safety outcomes.
- The current clinical pathway, including the composition of standard care, and how these change over time.
- Identifying subgroups with different risk profiles, who may be more likely to benefit from new treatments.
- Epidemiological data, such as the disease reproduction (R) rate.

Ideally, RWE should be of high quality and conducted across multiple centres and/or databases, with transparent reporting of study protocols (registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance) and results.

Several checklists and guidance documents have been developed to improve and assess the conduct and quality of non-randomised studies, including recent recommendations (27). Several others have been summarised by the GetReal initiative (28). It is recommended that RWE is collected and reported according to one or more of these guides, to allow HTA agencies to transparently assess its quality.

With an immature and disparate evidence base, HTA agencies should be aware that non-randomised evidence may be the best evidence available for decision making. With the appropriate consideration of its generalisability, robustness and uncertainty, agencies should be prepared to make decisions based on such data sources.

Studies conducted in federated data networks or using trusted research environments might offer higher quality evidence given the larger sample sizes and/or increased precision.

2.1.3. Evidence synthesis

Recommendations

HTA agencies should consider the use of existing "living" clinical evidence reviews and meta-analyses to inform their clinical effectiveness decisions (29–31).

- While many agencies would prefer to conduct their own evidence reviews in normal times, the publicly available and frequently updated living reviews provide a pragmatic way of assessing the clinical effectiveness of treatments for COVID-19. Using these sources will reduce duplication of work and may allow for quicker assessments.

HTA agencies should carefully and transparently consider the generalisability of evidence from an external living review, consistent with the recommendations in section 2.1.1.

Where high quality randomised and non-randomised studies exist, evidence synthesis approaches that combine randomised and non-randomised evidence (32) will be informative. HTA agencies should be willing to consider this type of analysis to ensure all the available relevant evidence is used to inform their decision making.

Be aware that evidence that has not undergone full peer review ("grey literature", such as preprint articles, conference presentations and press releases) is less likely to be robust than peer-reviewed evidence. This may be more acceptable for decision making during more urgent phases of the pandemic. In these circumstances, the guidance to identify such evidence from CADTH may be useful (33).

2.2. Population

Recommendations

For therapeutics:

The target population should be clearly specified in relation to the following characteristics:

- Demographic information (including age, sex, ethnicity, socioeconomic status, smoking status, BMI)
- Vaccination status (unvaccinated, partially vaccinated, fully vaccinated; type of vaccine; time since vaccination)
- Serology status (presence of an antibody response)

- Disease confirmation method (symptoms only, PCR-confirmed, rapid test confirmed)
- Symptom status (asymptomatic, symptomatic)
- Severity (mild, moderate, severe or critical illness)
- Recovery status
- Duration of symptoms (ongoing symptomatic disease, post-COVID-19 syndrome)
- Need for respiratory support by type (low-flow supplemental oxygen, high-flow supplemental oxygen, non-invasive ventilation, mechanical ventilation, extracorporeal membrane oxygenation [ECMO])
- Presence of comorbidities (34).

Trials with participants in multiple COVID-19 severity groups should have subgroup or interaction analyses planned to identify differential treatment effects. Similarly, subgroup analyses should be planned for populations in whom a higher risk of illness from COVID-19 has been demonstrated, such as people with immunosuppression, cancer, and obesity. Ideally, all subgroup analyses should be prespecified.

The exclusion of special populations should be avoided in favour of subgroup analyses. If excluded, this should be clearly justified. Such subgroups may include: children, older people, pregnant women, people with protected characteristics, healthcare workers, people with poor functional status, and people with significant comorbidity.

For diagnostics:

The target population should closely match the intended population to be tested in practice in terms of, for example:

- Demographic information (including age, sex, ethnicity, socioeconomic status, smoking status, BMI)
- Symptom status (asymptomatic, symptomatic)
- Severity (mild, moderate, severe or critical illness)
- Presence of comorbidities (34)
- Relevant previous test results
- Testing method, including the setting and experience of the person delivering the test.

2.3. Comparator

The clinical pathway for COVID-19 is changing rapidly in response to new evidence, improved understanding of the disease, and the introduction of new technologies. With many trials in progress, assessments risk becoming out of date quickly when new technologies enter the decision space. It is likely that this high volume of rapid research would also occur in the event of a similar future infectious disease pandemic.

Recommendations

In principle, the comparator used to assess clinical effectiveness should represent the current locally available treatment standard.
For example, dexamethasone has been established as a routine treatment for treating COVID-19 in the hospital setting and should therefore be reflected, where appropriate, as a comparator for novel technologies in that setting.

To prepare for rapid changes to the clinical pathway and new comparators entering the decision space, assessments should routinely include exploratory analyses for a hypothetical new technology (see section 3.2).

2.4. Core outcomes

HTA agencies advised that clinical studies of technologies for COVID-19 have reported various clinical outcomes, with inconsistency between studies and over time. This will partially be a result of learning from experience and developing a better understanding of the disease, for example through increasing knowledge about the long-term symptoms of COVID-19 (35–37). Now, to allow for consistent assessments and for different technologies to be compared, it is important that studies report relevant outcomes in a consistent way.

Recommendations

For therapeutics:

The following COVID-19 clinical outcomes should routinely be considered in HTA of treatments for mild to moderate illness or in the community:

- Disease transmission, symptoms, admission to secondary care and care setting (including community-based secondary care), serious adverse events, (time to) recovery, health-related quality of life, other measures of wellbeing, mortality.

The following COVID-19 clinical outcomes should routinely be considered in HTA of treatments for severe or critical illness in a secondary care setting:

- Disease transmission, symptoms, length of stay, requirement for respiratory support (by type), requirement for critical care, respiratory failure, organ failure, serious adverse events, (time to) recovery, health-related quality of life, other measures of wellbeing, mortality.
- Time to recovery should not be used as a proxy for length of stay as discharge does not always take place promptly after resolution of symptoms, particularly for the elderly, where arranging transfer of care can result in delayed discharge.

The following COVID-19 clinical outcomes should routinely be considered in HTA of treatments for long-term disease:

- Long-term symptoms (35–37), duration of symptoms, requirement for respiratory support (by type), respiratory failure, organ failure, serious adverse events, other

long-term complications (post-intensive care syndrome, post-tracheostomy complications, mental health conditions), (time to) recovery, health-related quality of life, other measures of wellbeing, mortality.

The following core outcome sets may also be useful sources of additional clinical outcomes of interest:

- COMET core outcomes database (38)
- Cochrane living meta-analysis outcome set (29).

Other outcomes of interest include development of resistance, viral mutations, and the corticosteroid-sparing effect of treatments now dexamethasone has become established as a routine treatment for COVID-19 in the hospital setting.

For therapeutic technologies that are being repurposed for the treatment of COVID-19, it may be pragmatic to generalise long-term safety outcomes from data collected within the indications for which they are currently licensed to their use in COVID-19.

Engage with representatives of COVID-19 patients, which may include recovered patients or proxies, in future development or choice of outcomes (see section 8.2).

For diagnostics:

The following additional outcomes are proposed for test accuracy studies:

- Diagnostic accuracy (sensitivity, specificity)
- True positive, true negative, false positive and false negative test results
- Time from sample to result
- Indeterminate results
- Test failure.

The following additional outcomes should routinely be considered in HTA of diagnostic tests for COVID-19:

- Direct health effects
- Impact on downstream outcomes, such as: care decisions (e.g., time in isolation, treatment given), behavioural changes, clinical outcomes, transmission of COVID-19 in the community, infection rate in the relevant test setting.
- Ease of use.

3. Assessing value for money

3.1. Type of evaluation

Many HTA agencies prefer to use cost—utility analysis (CUA) to estimate and compare the value for money/cost effectiveness of technologies. However, to date, there has been little research into the health-related quality of life of people with acute or long-term COVID-19 symptoms. Therefore, published CUAs have relied on assumptions to inform utility values, or have generalised values from other conditions to COVID-19. Consequently, the resulting qualiy-adjusted life year estimates are uncertain. More robust evidence is being produced for disease-specific outcomes, such as the need for hospitalisation and ventilation, and survival (see section 2.4). These health outcomes could potentially be used in a cost-effectiveness (CEA) or cost—consequences analysis (CCA).

Recommendations

HTA agencies that routinely consider CUA should continue to do so for COVID-19 technologies, while acknowledging the higher level of uncertainty associated with quality-of-life estimates.

Pragmatically, preference-based utility values from related conditions should be sought to inform utilities until COVID-19 data become available, such as:

- Influenza-like symptoms for mild to moderate and ongoing symptomatic disease
- Severe acute respiratory syndrome (SARS) for severe disease
- Acute respiratory distress syndrome (ARDS) for critical disease
- Post-intensive care studies for long-term recovery
- Interstitial lung disease for long-term organ damage.

The same approach can be used to inform resource use and cost data.

It is recommended that model input values are collected, identified, and assessed according to established best practices. Guidance exists for utility values (39) and other types of parameters (40).

For appropriate core COVID-19 outcomes, additional CEA or CCA may be useful for decision making and should be provided where appropriate.

- For example, if a technology given in the hospital setting is effective at reducing the need for mechanical ventilation, this could be captured as cost per ventilation avoided.
- Similarly, a diagnostic technology effective at identifying positive cases could be assessed using cost per infection avoided.

CEA or CCA may be particularly useful to support rational decision making in tightly focused decision problems, where the additional uncertainty introduced by utility values would be unhelpful.

- For example, HTA agencies may be required to retrospectively assess treatments that were procured and introduced into clinical practice during the emergency phase of the pandemic, to inform their efficient implementation going forward.
- From this position, a CCA or CEA may be sufficient to identify the optimal choice between technologies with similar mechanisms of action, target populations and treatment goals.

Equity factors could be included in an economic evaluation using distributional cost-effectiveness analysis methods (41,42), as a scenario analysis or a secondary assessment after estimating cost effectiveness. This may be informative when assessing the value of therapeutics and diagnostics for COVID-19, which has affected some groups within society more severely than others (see section 7).

3.2. Comparator

A particular challenge caused by the pandemic situation is the speed at which clinical practice and scientific understanding of the disease are changing. This poses a challenge for economic evaluation, because the appropriate comparator can quickly become out of date. If the comparator is no longer relevant, then the cost-effectiveness estimates for a technology are not relevant for decision making. This will require a flexible approach to defining the decision problem. Ongoing epidemiological studies that characterise current practice will be valuable to inform the most relevant comparator at the time of conducting an appraisal.

Recommendations

A consistent approach to assessing costs and effectiveness for the comparator in an economic evaluation should be taken.

- For example, if the control arm of an effectiveness study included a treatment that is not used in the HTA agency's country, it is not appropriate to remove only the costs associated with that treatment. An attempt should also be made to extricate the benefits of that treatment. If this is not possible or lacks robustness, then the cost of that treatment should also be included in the assessment.

HTA should routinely include an exploratory two-way sensitivity analysis, introducing a hypothetical new technology at the same point in the clinical pathway and simultaneously varying its relative effectiveness and difference in price between extreme values.

- This would help HTA agencies to prioritise resources when new comparators enter the decision space shortly after an assessment. An agency can quickly gain an understanding of the likely cost effectiveness of the new entrant.
- Agencies could transparently expedite decisions about technologies that are either likely to be highly cost effective or cost ineffective.

- This may also encourage manufacturers to consider the likely cost effectiveness of their technology early in their pricing considerations, leading to quicker assessments.

3.3. Analysis perspective

In many countries, HTA focuses on healthcare outcomes by using a healthcare payer perspective to inform decisions about how to allocate a finite healthcare budget. However, the early societal impact of COVID-19 has been vast, going far beyond healthcare systems in its effect on society. Some governments expanded healthcare budgets in their urgent response to the pandemic, diverting resources from other parts of society. This has led to calls for a societal perspective to be taken when assessing interventions for COVID-19, to fully capture the benefits of an effective test or treatment (43). As countries begin to recover from the pandemic and healthcare systems move to a more stable response phase, the societal consequences of COVID-19 may become less pronounced and therefore less relevant for decision making relating to allocation of healthcare specific budget and resources.

Recommendations

Ideally, economic evaluations for HTA will include both a healthcare payer and societal perspective. The base-case analysis should reflect the HTA agency's usual preferred perspective.

The societal perspective should attempt to capture both societal costs and health outcomes.

- For example, including only the expected costs associated with reduced labour productivity due to COVID-19 is not sufficient. Other costs include, for example, informal and social care costs incurred by older people who survive due to an effective COVID-19 treatment.
- Societal health outcomes may include the effect on family members; reduced fear of the disease, with the knowledge that effective treatments exist; and potential scientific benefits from innovative technologies. These could potentially be captured quantitatively in the utility values used in a CUA.
- The ISPOR Value Flower (44) and EUnetHTA HTA Core Model (45) may be considered to identify potential elements of value to capture in a societal analysis (see section 7).

There is no universally agreed best methodological approach to conducting an analysis from a societal perspective. Sources of guidance for appropriately considering the societal impact include the NICE consultation on value-based technology assessments (46), the ZIN economic evaluation methods guidance (47), and a framework for capturing effects on non-health sectors (48).

The importance of conducting the analysis from a societal perspective depends on the prevailing pandemic situation. At the peak of a pandemic or surge in infections, an effective test or treatment would confer vast societal benefits and would be more likely to be cost effective from a societal perspective. Therefore, an appraisal should explicitly consider the context of the pandemic at that time.

In less urgent times, and when the funding source is the healthcare rather than central government budget, agencies should not be expected to consider societal effects in their assessments if this is not the perspective they normally use in their assessments.

3.4. Long-term outcomes

Most randomised clinical trials report short-term outcomes relevant to the acute phase of disease, and there are limited high-quality data on the long-term effects. However, there is growing evidence and acceptance that COVID-19 has the potential to cause important long-term effects on health-related quality of life and possibly survival. It is now apparent that omitting long-term consequences (e.g., by assuming all people who recover from COVID-19 return to their pre-COVID health status and activities) is an incorrect assumption.

Long-term effects can occur in people who had any level of COVID-19 disease severity (49). However, the most serious negative long-term effects of COVID-19, such as post-COVID syndrome and organ damage, appear to be more likely in people who had more severe illness (50). Therefore, an effective treatment that prevents hospitalisation or intensive care admission, or a diagnostic test that detects infection earlier to reduce further transmission, may reduce the incidence of severe long-term consequences.

Scientific knowledge about the long-term effects ("long COVID") is still growing (36). With the limited evidence base, long-term outcomes are likely to be a major source of uncertainty for HTA decision making.

Recommendations

To accurately understand the value of a technology, long-term outcomes associated with COVID-19 should be considered in HTA. It is not appropriate to assume that all patients recover to their pre-disease state of health or daily activities.

Economic evaluations should take a lifetime horizon to capture all potential differences in outcomes (e.g., survival, long-term quality of life) between interventions, unless this can justifiably be done over a shorter duration.

The best available evidence should be used to inform long-term outcomes, and while data are scarce, these may be from proxy data sources. For example:

- Real-world COVID-19 epidemiological studies and data reported to regulatory agencies, such as the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA) and UK Medicines and Healthcare products Regulation Agency (MHRA), can be used to inform the incidence of negative long-term outcomes.
- For repurposed medicines, it may be reasonable to generalise long-term safety data collected within the indications for which they are currently licensed to their use in COVID-19.
- Epidemiological studies for plausibly similar conditions (e.g., interstitial lung disease) conducted in non-COVID-19 populations may provide suitable long-term survival data.
- Also consider accepting evidence for related conditions to inform resource use and utility values.

Long-term outcomes should be prioritised for extensive sensitivity analysis (see section 5.1). This will allow HTA agencies to retrospectively evaluate decisions once higher-quality evidence about long-term outcomes becomes available.

3.5. Cost-effectiveness threshold

During a pandemic, the appropriate threshold level for cost effectiveness – the benchmark used to decide whether a technology offers value for money or not – is unclear.

On one hand, when the pandemic situation is critical or where there is a lack of effective technologies, policy imperatives to avoid vast societal consequences of the disease mean the threshold is likely to be higher (i.e., less stringent, indicating stronger preference for COVID-19 technologies). Higher thresholds may also encourage manufacturers to research the development or repurposing of technologies for COVID-19 quickly, increasing the speed that effective treatments might become available.

Conversely, when evaluating potentially large-scale interventions with a high level of clinical uncertainty, a lower (stricter) threshold may allow healthcare systems to manage the risk of making the wrong decision and to maintain affordability (51). As the height of the pandemic abates, the societal consequences of COVID-19 become less pronounced and the critical need for novel technologies falls, the threshold may implicitly fall over time.

Recommendations

Encourage, support, or conduct research to identify societal preferences for COVID-19 technologies, including how they vary as the pandemic context changes, to inform whether an HTA agency's cost-effectiveness threshold should be different for the assessment of these technologies during the pandemic period. The findings may also assist HTA agencies to respond rapidly to future infectious disease pandemics.

Until the findings of such research are known, HTA agencies should maintain a consistent approach to assessments by using their usual cost-effectiveness thresholds to determine the value for money of COVID-19 technologies.

4. Modelling approaches

A number of atypical approaches have been proposed to model COVID-19 and capture the full effects of diagnostic and therapeutic technologies. These pose challenges for HTA agencies, which often focus on narrow decision problems that do not require complex approaches. Therefore, agencies must consider how to capture these atypical features in their decision making.

4.1. Simulation models

Models used to conduct economic evaluation in HTA take a variety of forms. Common types are simple probability or decision "trees", more suitable for short-term outcomes and one-off risks; more sophisticated cohort models, often used to model cancer treatments, in which patients move between two or more different health states over time (e.g., according to calculated transition probabilities or by portioning overall survival into different possible states); "hybrid" models, combining tree and cohort components; and the most flexible and complex individual simulation models, which map out the journey of individual patients to track their outcomes. Economic models to assess diagnostic or therapeutic technologies can be 'nested' within a larger epidemiological or "SEIR" (susceptible, exposed, infectious, recovered) model (53).

As identified from a review of the literature, all these model types have been used to estimate the cost effectiveness of diagnostic or therapeutic technologies for COVID-19 (52,54–58). However, as the evidence base and our understanding of the disease have developed, and following a workshop of health economic modellers, it appears that simulation models are likely to be best placed to estimate the potential true value of effective technologies for COVID-19. Simulation models offer more flexibility to handle the heterogeneity in COVID-19 patients, the evolving and complex disease and clinical pathway, the presence of different risks based on a patient's characteristics and history

of disease, the transmission of infection between different people, and effects on system capacity. They would also facilitate the assessment of value for money across a wide array of potential COVID-19 technologies. Downsides to simulation models include taking longer to run, and either needing access to more data or requiring more explicit assumptions. To inform any particular technology's assessment of value for money, a less complex modelling approach (e.g., a cohort-level module within the policy model) may be acceptable. For example, for narrowly defined decision problems, a less complex (e.g., cohort-level) model may provide a suitable indication of cost effectiveness for decision-making.

Recommendations

Ideally, an individual-level simulation model (or a sufficiently well-defined cohort simulation) would be used to estimate the cost effectiveness of the wide array of potential technologies for COVID-19.

Good practices should be followed in the development of simulation models, such as the SIMULATE checklist (59,60) and NICE Decision Support Unit guidance (61).

For straightforward, narrowly defined decision problems, a simpler approach, such as a cohort-level model, may be suitable to inform decision making.

- For example, to determine the best option (or ranking) among 2 or more treatments with the same mechanism of action at the same position in the disease pathway.

HTA agencies should consider developing a generic "living" disease model for the diagnosis and treatment of COVID-19 that can be adapted to different jurisdictions (see section 4.6).

4.2. Disease transmission

As an infectious disease, a person with COVID-19 risks infecting other people. It is possible to model the dynamics of infected people transmitting the disease to uninfected people. Doing so may be necessary to understand the value of a technology that reduces disease transmission. For example, a test that accurately identifies a person with COVID-19 means they can minimise contact with others, reducing the risk of transmitting the infection. A small number of modelling studies have attempted to integrate epidemiological modelling – which can capture disease randmission – with economic modelling, in the context of assessing COVID-19 policies in the UK (53).

Recommendations

For therapeutics:

Transmission dynamics may not be necessary to demonstrate the value of all effective treatments for COVID-19. For example, not all treatments for acute or long-term disease

will reduce infectiousness, which is highest in the early (often asymptomatic) stage of the disease.

In circumstances where it is plausible that a treatment may reduce transmission, such as by reducing virus shedding, then this should be considered in the HTA.

For diagnostics:

To accurately understand the value of a diagnostic technology, transmission dynamics should be considered.

For all technologies:

The most appropriate modelling approach to capture transmission dynamics is likely to be an epidemiological (or SEIR) model. This would be able to capture transmission within the community, and therefore the effect of an accurate diagnostic test on the spread of disease.

The economic model to assess therapeutic technologies should be nested within the SEIR model, to allow a focused HTA of treatments that do not confer an effect on transmission.

It is recommended that SEIR models developed for HTA follow good practice guidance (62). HTA agencies may use this checklist to assess the conduct and appropriateness of such models.

4.3. System dynamics

Early in the pandemic, and during subsequent infection surges, healthcare systems faced pressures on their capacity. If hospitals or critical care services reach full capacity and are unable to care for additional patients, people would potentially go untreated, or capacity would need to be created by rapidly diverting resources from other parts of the healthcare system or wider society (e.g., by delaying elective surgery). An effective COVID-19 treatment that prevents admission or reduces length of stay would have the wider benefit of reducing the strain on system capacity. Therefore, capacity constraints are much more likely to be relevant for decision making at the start of a pandemic or during infection waves.

Modelling approaches have been developed to capture system effects (52,63,64). The primary difficulty when doing so is identifying robust data to inform the analysis. Hospital capacity will fluctuate over time and is subject to many confounding factors, so data obtained from a single centre may not be generalisable to every hospital. Methods have also been developed to quantify the impact of healthcare resources being diverted from other disease areas (65).

Recommendations

The importance of considering the effect of a technology on system dynamics depends on the prevailing pandemic situation.

If capacity is strained, HTA agencies should include capacity effects in their assessments, either quantitatively using system dynamics in a model that takes into account capacity constraints, or qualitatively where data are unavailable to do so.

In less urgent times, when capacity is not overstretched, agencies should not be expected to consider system effects and capacity constraints quantitatively in their assessments. Reductions in healthcare resource use should simply be captured in the cost-effectiveness analysis in these cases.

4.4. Antimicrobial resistance

Several therapeutic technologies in development for treating COVID-19 are antimicrobials. The use of antimicrobials increases the likelihood of developing resistance to these agents. The risk of antimicrobial resistance could potentially be considered in HTA for those treatments. However, capturing antimicrobial resistance in a decision model, and accurately quantifying its effects, will be time consuming and subject to significant uncertainty.

Recommendation

HTA agencies should consider the potential effects of technologies on antimicrobial resistance into their assessments, at least qualitatively.

- For example, if two technologies, are being assessed with similar costs and benefits, but one is an antimicrobial, consider the risk of developing antimicrobial resistance in decision making.

4.5. Model calibration

Where suboptimal or uncertain data have been used to inform an economic evaluation, such as assumptions, proxy data from other conditions, or non-randomised evidence, its results will be uncertain and may lack face validity. It may be preferable to allow uncertain inputs to vary, rather than be strictly evidence based, for the model outputs to be valid. This can be achieved by 'calibrating' intermediate model outputs (e.g., the number of patients admitted to intensive care) to be consistent with observed or clinically plausible values.

Recommendation

Where highly uncertain data have been used to inform an economic evaluation, the model should be calibrated using RWE to ensure its outputs are plausible.

- For example, if an assumption has been made to inform a particular input value, allow that value to vary to ensure a key model output (e.g., number of intensive care admissions) is consistent with what is observed in the most appropriate data (e.g., locally relevant outcomes observed in a real-world study).
- The model may need to be recalibrated when new information becomes available, as part of a responsive, "living" HTA approach (see sections 4.6 and 5.2).

4.6. A "living" disease model

To support taking a rapid, responsive approach to assessments for COVID-19 technologies (see section 5.2), it would be beneficial and ultimately more efficient to have a common, flexible, and up-to-date disease model to assess their value for money/cost effectiveness. Compared with narrowly defined models, a COVID-19 whole-disease model would better characterise the impact of a technology on the pathway of care, linked decision points, and optimal sequences of tests and treatments.

Once such a model is built, assessments would become faster as it could rapidly be updated with new clinical evidence, and would remove the burden from technology manufacturers to build de-novo economic models and generate their own cost-effectiveness evidence. It would also reduce the burden on evidence review groups and HTA assessors of critically appraising several models submitted by different manufacturers, and eliminate the risk of the model being considered not fit for decision-making which results in wasted time and resources.

Recommendations

HTA agencies should consider developing a living whole-disease model for the diagnosis and treatment of COVID-19 (or a future pandemic disease). A generic model that could be adapted for different jurisdictions would reduce duplication and allow for consistent and responsive decision making between agencies over time.

We propose that a living COVID-19 diagnosis and treatment pathway model should follow the good practices recommended in this section, by having the following features:

Take the structure of an individual-level simulation nested within a SEIR model, developed according to recently published good practices (62), allowing:

- Diagnostic and therapeutic technologies to be assessed using the same model.
- Downstream effects and outcomes from the whole clinical pathway to be captured.
- Impact on disease transmission and system dynamics (capacity) to be captured.
- The option to implement a simpler, cohort-level analysis.

- Cost—utility and relevant cost-effectiveness and cost-consequence results to be estimated.

Include the long-term effects of COVID-19.

An example model concept has been developed for assessing COVID-19 technologies, based on clinically validated disease pathway based on current understanding and in consultation with international panel of clinical experts (see Appendix 11.1). The model is provided in Appendix 11.2. HTA agencies may wish to consider this as a framework for developing or commissioning their own models.

Exhibit transparency, by being made available as an open-source model with accessible coding (for example, using clear annotation).

Use a flexible modular format, allowing components such as transmission effects, system dynamics and a societal perspective to be switched on or off as needed. This would allow the complexity of the model to be changed as needed, for example:

- When assessing a straightforward, narrowly defined decision problem (for example, to quickly prioritise or inform procurement decisions when there are 2 or more biologically equivalent novel treatments targeting the same position in the disease pathway), the model could be simplified by switching complex components off (for example, by setting transmission probabilities to 0) or reverting to a cohort-level model.
- When assessing a treatment that does not have an effect on disease transmission, transmission effects could be switched off.
- When an assessment is happening during a large infection wave with hospitals operating at full capacity, system dynamics could be switched on.
- Ideally, the full disease model would then be updated to reflect the decision.

Have periodic or responsive (living) updates to reflect new evidence, changes to the clinical pathway and scientific understanding, allowing:

- Robust, up-to-date input into early procurement negotiations during urgent pandemic contexts, if needed.
- Rapid review of previous decisions.
- Prioritisation of which technologies should be subjected to a full HTA.
- Transparency in updating decisions in response to new information.
- Support the efficient implementation of technologies (for example, to retrospectively assess treatments that entered clinical practice without full HTA).

4.7. Practical considerations

Although there are examples of cross-border collaboration between HTA agencies (BeNeLuxA Initiative, Visegrad Group), jointly developing and maintaining a living disease model would be a novel type of collaboration. This would involve several practical considerations, including, among others, the following:

- **Commissioning and ownership.** Agreement would be required about who develops the model, who owns it, and how to share the financial cost. For example, HTA agencies that jointly fund the model may share ownership, with provision for free access to the model for agencies in low-income settings.
- **Data access and transfer.** Agreements to use data to populate the model, such as clinical trial results, should include the provision that it will be shared between HTA agencies. Even then, national regulations may limit data being transferred across borders. If data cannot be made available to all HTA agencies, then only the skeleton model structure, populated by publicly available and dummy data only, would be made freely available.
- **Management.** Agreement would be required about who should update the living model to include new data and information, how updates are triggered (e.g., periodically, or responsively), and how this ongoing work is funded. Individual HTA agencies may wish to populate the open-source model with local data or care settings.
- **Review.** An agreed process would be required for HTA agencies to review the model to ensure it is fit for purpose in their setting. A review process would also be required for external stakeholders to critique or validate the model, including who has the final say on which suggestions to act upon (the model developer, or the funding HTA agencies).
- **Barriers to use.** Potential barriers that would make the common model less accessible should be minimised. For example, it is likely that the model would require a user guide. Consideration should be given to translating the user guide into multiple languages. Similarly, the software used should be widely accessible, both physically (e.g., low cost) and in terms of the technical skill required to operate it. Upskilling of technical teams might thus be required. legal considerations specific to each jurisdcition might also need to be considered.

5. Uncertainty

5.1. Characterising uncertainty

With an immature, disconnected and incomplete evidence base, decisions about COVID-19 technologies are likely to be made in the context of substantial uncertainty. The presence of uncertainty is common in HTA; for example, agencies are used to assessing technologies based on immature evidence. However, for COVID-19 technologies, the unprecedented pandemic situation has created a wider context of instability and uncertainty (see section 1.1.2) that cannot be resolved in a single decision problem or point in time. This will require pragmatism in HTA decision making. It will also require upskilling committee members to be able to make decisions under much higher level of uncertainty. Still, it remains important to acknowledge evidence gaps, appropriately characterise the uncertainty, and understand its potential impact on the optimal decision.

Recommendations

HTA agencies should be pragmatic about accepting assumptions, proxy data or incomplete information to inform their assessments when a decision is needed in the context of limited evidence during a pandemic. Agencies should be explicit and transparent about the key uncertainties.

Due to the changing pandemic context, even inputs that seem reasonably certain today may quickly become less appropriate. Therefore, parameters should be subjected to extensive sensitivity and scenario analysis.

- It may be difficult to define a plausible range of values to use in scenario analyses. To reflect this uncertainty using a wide range of potentially plausible values should be encouraged.

In particular, HTA agencies should expect uncertainty in long-term outcomes for some time and be prepared to make decision in this context. Long-term assumptions should be given particularly close attention in sensitivity analyses.

- For example, use recent epidemiological data to inform a wide range of potentially plausible scenario analyses for the incidence and duration of long-term COVID-19 symptoms.
- If the cost-effectiveness estimate is sensitive to potentially plausible scenarios for long-term outcomes, HTA agencies may prefer to use a lower cost-effectiveness threshold (see section 3.5) or consider a commercial agreement (see section 6.2) to mitigate the risk.
- HTA agencies should be willing to update decisions in response to new evidence about long-term outcomes (see section 5.2).

Extensive threshold analysis should routinely be presented to demonstrate the value a parameter would need to take to reach a critical level for decision making (e.g., the cost-effectiveness threshold). Appropriate expert advice or literature should be used to understand the plausibility of that value being observed in reality.

In cases where the technology price is not yet known, all parameters (including efficacy) should be varied in two-way sensitivity analysis with the price, across a wide range of potentially plausible prices.

Ideally, assessments should use probabilistic results as the basis for decision making. This should characterise the parameter uncertainty of all inputs using the best available evidence.

However, simulations and whole-disease models may have long computation times to run probabilistic analysis. Therefore, in some circumstances, determinstic analyses may be accptable for decision making. For example:

- Uncertainty in model inputs is shown to have an approximately linear effect on the results.
- The pandemic context requires an urgent preliminary decision, so deterministic results can provide an indicative cost-effectiveness estimate, to be subsequently checked against a probabilistic analysis.

Consider calculating the expected value of perfect information, as an extension to probabilistic cost-effectiveness analysis, to indicate which parameters are most likely to benefit from further research. This will promote more impactful research, manage the "infodemic" that has accompanied the pandemic (66), and inform the living approach to the Assessment (see 5.2).

5.2. A responsive, "living" approach to HTA

HTA agencies could mitigate against the high uncertainty by taking a pragmatic "life cycle" approach to assessing COVID-19 technologies, transparently accepting different types of evidence and reporting where assumptions have been made, alongside a commitment to responsively reviewing decisions in light of changes to the evidence base, clinical practice or scientific understanding (67). To implement a lifecycle or "living" approach to HTA, the following considerations should be made:

Recommendations

Accept and advise that clinical assessments may be uncertain and cost-effectiveness analyses will necessarily be more exploratory in nature, indicating likely value for money rather than a definitive estimate.

Clearly communicate the context of the pandemic situation at the time of the assessment, including that the evidence used was the best available and may be superseded by new

information, and explain the ramifications of a change in decisión in response to new evidence to the public.
Transparently exhibit a willingness to reviewing decisions in response to new information, possibly at short notice, in a “health technology management” approach (8). Make clear that HTA documents are subject to change if there is a clear rationale to do so, for example in response to changes in the evidence base or scientific understanding. This is particularly important to be communicated with the public.
A living HTA approach may help to facilitate the use of novel procurement models with data collection (see section 6.2), by allowing agreements to be reviewed in a responsive way once the required evidence becomes available.
HTA agencies should be prepared to reverse previous decisionsabout using a technology, and be clear on this being an option, in response to new evidence; for example, by recommending that the healthcare system disinvests in a technology that it previously considered to be cost effective, which now appears to be cost ineffective.
Actively engage in horizon scanning activities and closer working with other organisations, such as healthcare regulators and companies, to better understand and prepare for the technologies that are likely to require HTA decision making.

6. Affordability and procurement

6.1. Considering affordability

Effective tests and treatments for COVID-19 have the potential to be large-scale interventions, increasing the risk of a divergence where technologies found to be cost effective are not affordable for healthcare systems to provide (68). This occurs when the price of a technology, the cost of redesigning services to provide it, or the intended patient population is simply too high (even though the health benefits on offer represent cost-effectiveness), or if funds have already been committed to other services and cannot be displaced. This may be particularly acute for treatments targeting severe COVID-19, where treatment costs are more likely to be incurred up front, or diagnostics tests, which may require significant service redesign. HTA is a much less effective resource allocation tool if it leads to decisions that healthcare systems cannot afford to act upon.

To consider affordability concerns in decision making, HTA agencies could support commercial discussions between payers and the developers of cost-effective technologies to ensure the total budget impact is acceptable to the healthcare system. Examples include identifying the level of simple discount required to bring the budget impact within some affordability limit, working within a cap on the total spend defined by the payer. To inform whether commercial discussions are needed, cost-effectiveness analyses may be accompanied by budget impact assessments, using outputs from the cost-effectiveness model to estimate total healthcare costs in the years following reimbursement. This may be particularly useful in lower-income settings (69). Using a lower (stricter) cost-effectiveness threshold when assessing technologies that are likely to be widely used may also be a prudent approach to addressing affordability concerns (see section 3.5).

Affordability may be less of an issue during early, emergency pandemic situations, or during new waves of infections, as the large societal burden, capacity issues, reduction in other healthcare services, and availability of wider government funding easily offset the impact on the healthcare budget. However, in less-urgent times, affordability, in support of the payer, should be an important consideration in HTA decisions about access to COVID-19 technologies.

Recommendations

HTA should routinely include a budget impact analysis, to identify technologies that would be unaffordable for the healthcare system to provide (either due to its price or the cost of necessary service redesign).

Good practices should be followed in the development of budget impact analyses models (70). In particular, it is important that extensive sensitivity analysis is performed, given the uncertain future COVID-19 clinical pathway and long-term outcomes.

When a potentially cost-effective technology is considered likely to have an unaffordable budget impact, support the payer to engage with the manufacturer to explore commercial arrangements that will improve affordability.

6.2. Managed access agreements

Healthcare commissioners and payers may wish to explore innovative payment models for COVID-19 technologies, to reduce affordability concerns and reduce the risk associated with uncertain decision making. A novel approach to procurement has already been taken by some governments in the case of vaccines, where advance purchasing was used to secure the required quantities of vaccine very early in their development. For diagnostics and therapeutics, advance purchasing would mean systems risk reimbursing ineffective or cost-ineffective technologies. For example, purchasing hydroxychloroquine, colchicine or lopinavir-ritonavir in advance of the RECOVERY study conclusions about those technologies would have been a poor decision (3,21).

For COVID-19 treatments, outcomes-based agreements (OBAs) may be considered as part of a managed access approach as systems begin to recover from the worst of the pandemic. For example, an outcomes-based managed access agreement could include reimbursement alongside a period of data collection, with the collected data used to resolve important areas of uncertainty and review the reimbursement decision. Key uncertainties identified by the HTA process can inform commissioners and payers about the value of data collection. These arrangements would be particularly suited to a living HTA approach (see sections 4.6 and 5.2), as the data collected could be used to update or validate the appraisal (67).

Recommendations

HTA agencies should focus on identifying the key uncertainties around the value of the technology, including those that may be resolvable with further data collection, and engage with commissioners and payers who wish to use this information to consider implementing outcomes-based approaches.

When reviewing data collected as part of a managed access agreement, HTA agencies should consider whether there is evidence of waning effectiveness against new variants of COVID-19.

For novel antimicrobials in development which are associated with the risk of increasing antimicrobial resistance, HTA agencies could support commissioners and payers in adopting a subscription-based model (71) to avoid the potential overuse and misuse of these agents.

6.3. Supporting implementation when supply is limited

Global demand for effective technologies for COVID-19 may exceed availability, due to limited manufacturing capacity or problems with supply chains. Lengthy decision-making processes may compromise a healthcare system's ability to access a technology, even if it is found to be clinically and cost effective. Pragmatic and expedited decision making – for example, by using living systematic reviews, a living COVID-19 disease pathway model and considering other elements of value qualitatively – may reduce the time to decision-making. Additionally, if necessary, HTA could support the prioritisation of patient subgroups for cost-effective technologies that are subject to limited supply (though this would involve important moral and ethical considerations (18,19)).

Recommendations

HTA should routinely include extensive subgroup analysis, using the best evidence available (which may include clinical expert opinion or RWE, e.g., to calibrate model outputs based on clinical trial data to observed outcomes in a subpopulation of interest).

Where possible, to support procurement when supply is limited, HTA agencies should provide policymakers a ranking of technologies and sequences of treatments in order of their net benefit.

- This can quickly inform the appropriate alternative options for procurement if a technology is subject to supply problems, by transparently showing the treatment or sequence the provides the next-highest level of net benefit.

7. Considering other elements of value

There are various other elements beyond clinical and cost effectiveness that an HTA agency could consider to determine the value of a technology. These may be particularly relevant when taking a societal analysis perspective. However, data may be lacking to do this in a quantitative way. The ISPOR Value Flower (44) and EUnetHTA HTA Core Model (45) describe examples of elements that may not be captured in a typical assessment of clinical and cost effectiveness. Some elements from the ISPOR Value Flower that may be pertinent to COVID-19 include:

- Equity. Where there is evidence that a pandemic disease has affected some groups within society more severely than others, decision makers may favour reimbursing treatments that reduce health inequality by targeting more disadvantaged subgroups. For example, COVID-19 has been shown to affect people differently based on their demographic and socioeconomic status (72–75). Methods exist to incorporate distributional aspects into economic evaluation (see section 3.1). These may allow HTA agencies to quantitatively capture equity in their assessments, but as a minimum, agencies should include a qualitative view on whether a technology is likely to reduce health inequality in their assessments.
- Reduced fear of contagion and disease. Effective tests may reduce people's fear of contracting an infectious disease like COVID-19, by increasing confidence that cases will be identified and appropriately isolated. Effective treatments may reduce people's fear of the disease itself, by increasing the range of therapeutic options available.
- Scientific advancement. Decision makers may place more value on innovation in the context of a pandemic. Encouraging research would increase the likelihood of effective new technologies entering the market quickly and the pool of scientific knowledge (and therefore reduce the uncertainty) about COVID-19.

Recommendations

HTA must always consider whether there are other elements of value conferred by a technology that have not been adequately captured in the assessment of clinical and cost effectiveness.

The ISPOR Value Flower (44) and HTA Core Model (45) may be considered as sources of potential other elements of value of technologies for COVID-19, such as the effect on equity, fear of contagion and disease, and scientific advancement.

In principle, other elements of value should be captured quantitatively within the evaluation. For example, utility values could be used to reflect the wider benefits of an effective technology.

If it is not possible to capture other elements of value robustly or meaningfully in a quantitative way, HTA agencies should factor them into their assessments qualitatively.

- For example, if a technology is borderline cost effective compared with current practice, it might still be recommended if it is likely to confer benefits in other elements of value that have not be quantitatively captured in the analysis.

Encourage, support, or conduct research to identify societal preferences for other elements of value that COVID-19 technologies may provide, to inform how important those elements are for consideration in HTA decision making.

8. Stakeholder engagement

8.1. General approach to engagement

A broad range of stakeholders should be engaged in the HTA process for COVID-19 technologies, such as clinical guideline developers, payers, technology developers, patients and carers, clinicians, and the public (citizens). Their expert perspectives may help to define the scope of the assessment, directly inform the assessment, and respond to the preliminary reimbursement decision. Due to the likely presence of substantial uncertainty in the COVID-19 evidence base, input from stakeholder groups may be an important source of information, such as providing local clinical expert opinion or identifying real-world datasets. Understanding different stakeholder perspectives may inform whether assumptions made are appropriate (e.g., the use of proxy utility values from other conditions) or identify uncaptured elements of value that are important for decision making.

In any assessment, there is an unavoidable trade-off between the extensiveness of stakeholder engagement and time required to reach a reimbursement decision. For COVID-19, many technologies are expected to enter the decision space in quick succession and external pressure to provide rapid HTA guidance is likely to remain. Therefore, agencies should use their recent experience of remote working to explore innovative technological ways to engage with stakeholders, ensuring wide participation in a short amount of time. Some HTA agencies have already developed novel approaches, such as CADTH's dedicated COVID-19 evidence portal (76). Simple visualisation tools to communicate trade-offs and decisions can help to present information in an accessible format and facilitate engagement. For example, UK decision-makers used simplified graphics to demonstrate the potential benefits and risk of COVID-19 vaccination (77).

Recommendations

HTA agencies should ensure a broad range of stakeholders are able to contribute to the decision-making process, for example by providing evidence during the assessment or responding to draft reimbursement decisions.

Consider innovative stakeholder engagement approaches to balance broad engagement with the need for timely decision-making.

- For example, HTA agencies could consider using simple visualisation approaches, online polling or survey tools, and virtual stakeholder engagement workshops, to ensure broad, rapid and accessible stakeholder engagement.

8.2. Patient and public involvement

As an infectious disease, it is difficult to define a specific patient group to engage with during the HTA of COVID-19 assessments. Usual approaches of identifying patients, such as approaching patient organisations or the care setting which a test or treatment is delivered, may not be suitable. COVID-19 patient organisations are unlikely to be well established for some time. More widely, all citizens are theoretically at risk from COVID-19 illness and are certainly at risk from the negative social, economic, physical, and psychological consequences of public health measures (e.g., societal lockdowns), which are more likely to be implemented without effective tests and treatments. Citizen groups could be a useful resource for this engagement, and some HTA agencies have experience of successfully reaching them (78–80).

Some groups are at an increased risk of the most serious illness from COVID-19. These include people with pre-existing health conditions, people who are immunocompromised, older adults, racial and ethnic minority groups, and people with disabilities (81). People with more serious illness from COVID-19 also have a higher risk of experiencing long-lasting negative effects (50). By extension, those groups are at a higher risk of long-term health effects. Citizens' rights groups, and established organisations that advocate for specific at-risk populations, could be identified to ensure the perspectives of marginalised and at-risk groups are heard.

Even well-defined COVID-19 patient groups may be problematic to involve in the HTA process. For example, patients receiving mechanical ventilation are a critically ill population who may be unconscious or have difficulty remembering their experience. Here, carers, family members and healthcare professionals may be suitable proxies for patient engagement.

As described above, there will be a trade-off between extensive stakeholder engagement and the ability to produce rapid decisions. Therefore, a tiered approach to patient and public involvement may provide a pragmatic way to focus HTA engagement efforts. Longer term, an international registry of COVID-19 patient and public experiences would provide a common resource for this engagement and minimise the duplication of effort from HTA agencies.

Recommendations

The following tiered approach is proposed to guide patient and public involvement in assessments of technologies for COVID-19:

- For technologies that do not target a specific COVID-19 patient group, such as diagnostic tests, citizens' rights groups, citizens, and organisations that represent specific at-risk populations should be targeted for engagement.
- For technologies that target mild, moderate or long-term COVID-19, people who have experienced the disease are likely to be able to provide insights on their experience of the disease, treatment, and unmet needs. Therefore, individual patients should be targeted for engagement, including people in specific at-risk groups.
- For technologies that target severe or critical COVID-19, people who have experienced the disease may provide insights on their experience, but proxies such as families, carers and healthcare professionals should also be targeted to describe the disease and treatment experience. Organisations that represent specific at-risk populations may provide insight on differences in the experience for those groups.

Encourage, support, or instigate efforts to establish an international patient and public experience registry for COVID-19, as a common resource to catalogue the experience of the disease and care among the public, patients with mild, moderate, severe and critical illness (or their proxies), long-term patients, and carers.

9. Conclusion

The recommendations proposed in this document have been co-developed with a range of stakeholders to address challenges facing HTA agencies when assessing diagnostic and therapeutic technologies for COVID-19.

The guidance recognises the need for pragmatic decision making given the variable pandemic context, with rapidly changing disease characteristics, evidence, clinical practice, and pressures on healthcare systems and decision makers. It also encourages HTA agencies to be more accepting of different types of evidence to inform their assessments and be willing to make decisions based on the best-available evidence when they are needed. This should be done within the context of using a responsive, "living" approach, where there is transparency about the evidence gaps and pandemic context at the time of this decision, and agreement that assessments will be rapidly revisited as new or better evidence becomes available. A common, jointly developed disease model for COVID-19 would support this approach, and while HTA agencies do not typically collaborate closely on modelling efforts, doing so would avoid duplication of work and subsequently provide efficiency gains to the decision-making process. Implementing these recommendations would, thus, facilitate moving from a health technology assessment to a health technology management process.

In most instances, the guidance is not prescriptive about the precise approaches that should be applied, moreover it signposts HTA agencies to resources and methods that may be suitable and should be considered. In all cases, HTA agencies are at liberty to choose what approaches are most suitable for their decision problem, though it is hoped that the broad range of relevant themes addressed here – from assessing clinical effectiveness to improving stakeholder engagement – will provide a helpful range of good practices for agencies to consider implementing.

By adopting some or all of the proposed recommendations, it is hoped that HTA agencies can provide more timely, robust, evidence-based decisions about the value of COVID-19 technologies as healthcare systems move away from the initial pandemic crisis and seek to ensure efficient, affordable care for COVID-19 going forward. Further, these learnings should improve pandemic preparedness, providing a blueprint for HTA to rapidly support decision making in response to a future infectious disease pandemic.

10. References

1. Donaldson C, Mitton C. Health economics and emergence from COVID-19 lockdown: the great big marginal analysis. HEPL. 2020 Aug 6;1–5.

2. Walsh F. How breakthrough coronavirus drug dexamethasone was found [Internet]. BBC; 2020 [cited 2021 Jul 11]. Available from: https://www.bbc.co.uk/news/health-53096736

3. The RECOVERY Collaborative Group. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020 Nov 19;383(21):2030–40.

4. Jonsen AR. 3. Bentham in a Box: Technology Assessment and Health Care Allocation. Law Med Health Care. 1986 Sep;14(3–4):172–4.

5. Jiu L, Vreman R, Mantel-Teeuwisse AK, Goettsch W. PNS6 Developing a Conceptual Framework to Guide the Innovation of Methods for Health Technology Assessment. Value in Health. 2020 Dec;23:S644.

6. Leckenby E, Dawoud D, Bouvy J, Jónsson P. The Sandbox Approach and its Potential for Use in Health Technology Assessment: A Literature Review. Appl Health Econ Health Policy [Internet]. 2021 Jul 13 [cited 2021 Aug 27]; Available from: https://link.springer.com/10.1007/s40258-021-00665-1

7. Leahy J, Hickey C, McConnell D, Cassidy O, Trela-Larsen L, Barry M, et al. Coronavirus Disease 2019: Considerations for Health Technology Assessment From the National Centre for Pharmacoeconomics Review Group. Value in Health. 2020 Nov;23(11):1423–6.

8. Lorgelly PK, Adler A. Impact of a Global Pandemic on Health Technology Assessment. Appl Health Econ Health Policy. 2020 Jun;18(3):339–43.

9. NICE. Evidence collection guide for medicinal products to prevent or treat COVID-19 [Internet]. 2020 [cited 2021 Mar 15]. Available from: https://www.nice.org.uk/covid-19/support-for-developers-of-medicinal-products-for-covid-19

10. US Food and Drug Administration (FDA). COVID-19: Developing drugs and biological products for treatment of prevention. Guidance for industry [Internet]. 2020 May [cited 2021 Jul 22]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention

11. O'Rourke B, Cabra A, Orsini LS, Guerino J. COVID-19: challenges and opportunities for the global health technology assessment community. Value & Outcomes Spotlight. 2021 May;7(3):12–4.

12. Carr A, Smith JA, Camaradou J, Prieto-Alhambra D. Growing backlog of planned surgery due to covid-19. BMJ. 2021 Feb 9;n339.

13. Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. The Lancet Oncology. 2020 Aug;21(8):1023–34.

14. Liddell K, Skopek JM, Palmer S, Martin S, Anderson J, Sagar A. Who gets the ventilator? Important legal rights in a pandemic. J Med Ethics. 2020 Jul;46(7):421–6.

15. White DB, Lo B. A Framework for Rationing Ventilators and Critical Care Beds During the COVID-19 Pandemic. JAMA. 2020 May 12;323(18):1773.

16. Callaway E. The unequal scramble for coronavirus vaccines — by the numbers. Nature. 2020 Aug 27;584(7822):506–7.

17. Torjesen I. Covid-19 vaccine shortages: what is the cause and what are the implications? BMJ. 2021 Mar 19;n781.

18. Moosa MR, Luyckx VA. The realities of rationing in health care. Nat Rev Nephrol. 2021 Jul;17(7):435–6.

19. Rockwood K. Rationing care in COVID-19: if we must do it, can we do better? Age and Ageing. 2021 Jan 8;50(1):3–6.

20. Institute for Clinical and Economic Review (ICER). ICER to assess treatments for COVID-19 [Internet]. 2021 Aug [cited 2021 Sep 2]. Available from: https://icer.org/news-insights/press-releases/icer-to-assess-treatments-for-covid-19/

21. The RECOVERY Collaborative Group. RECOVERY trial finds Regeneron's monoclonal antibody combination reduces deaths for hospitalised COVID-19 patients who have not mounted their own immune response. Press release [Internet]. 2021 Jun [cited 2021 Aug 13]. Available from: https://www.recoverytrial.net/news

22. Taylor PC, Adams AC, Hufford MM, de la Torre I, Winthrop K, Gottlieb RL. Neutralizing monoclonal antibodies for treatment of COVID-19. Nat Rev Immunol. 2021 Jun;21(6):382–93.

23. Health Technology Assessment International (HTAi). Evidence standards and quality assessment for COVID-19 therapeutic interventions. Position statement [Internet]. 2020 [cited 2021 Aug 16]. Available from: https://htai.org/hta-support-for-covid-19/position-statements-and-hta-reads/

24. NICE. Evidence standards framework for SARS-CoV-2 and anti-SARS-CoV-2 antibody diagnostic tests [Internet]. 2020 [cited 2021 Jul 22]. Available from: https://www.nice.org.uk/Media/Default/About/what-we-do/covid-19/Diagnostic-tests-for-COVID-19-evidence-standards-framework.pdf

25. Dimairo M, Pallmann P, Wason J, Todd S, Jaki T, Julious SA, et al. The Adaptive designs CONSORT Extension (ACE) statement: a checklist with explanation and elaboration guideline for reporting randomised trials that use an adaptive design. BMJ. 2020 Jun 17;m115.

26. Whiting PF. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Ann Intern Med. 2011 Oct 18;155(8):529.

27. Kent S, Salcher-Konrad M, Boccia S, Bouvy JC, Waure C de, Espin J, et al. The use of nonrandomized evidence to estimate treatment effects in health technology assessment. Journal of Comparative Effectiveness Research. 2021 Jul 19;cer-2021-0108.

28. GetReal Initiative. RWE Navigator: assuring quality and credibility of RWE [Internet]. [cited 2021 Jul 19]. Available from: https://rwe-navigator.eu/use-real-world-evidence/assure-quality-and-credibility-of-rwd/

29. Boutron I, Chaimani A, Meerpohl JJ, Hróbjartsson A, Devane D, Rada G, et al. The COVID-NMA Project: Building an Evidence Ecosystem for the COVID-19 Pandemic. Ann Intern Med. 2020 Dec 15;173(12):1015–7.

30. European Network for Health Technology Assessment (EUnetHTA). COVID-19 treatments: rolling collaborative reviews. [Internet]. 2021 [cited 2021 Jul 27]. Available from: https://www.eunethta.eu/covid-19-treatment/

31. Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Kum E, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ. 2020 Jul 30;m2980.

32. Sarri G, Patorno E, Yuan H, Guo J (Jeff), Bennett D, Wen X, et al. Framework for the synthesis of non-randomised studies and randomised controlled trials: a guidance on conducting a systematic review and meta-analysis for healthcare decision making. BMJ EBM. 2020 Dec 9;bmjebm-2020-111493.

33. Canadian Agency for Drugs and Technologies (CADTH). Grey Matters: a practical tool for searching health-related grey literature [Internet]. 2019 [cited 2021 Aug 12]. Available from: https://www.cadth.ca/resources/finding-evidence/grey-matters

34. Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. Journal of Clinical Epidemiology. 2008 Dec;61(12):1234–40.

35. Centers for Disease Control and Prevention. Post-COVID conditions [Internet]. 2021 [cited 2021 Aug 31]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html

36. National Health Service (NHS). Long-term effects of coronavirus (long COVID) [Internet]. 2021 [cited 2021 Aug 31]. Available from: https://www.nhs.uk/conditions/coronavirus-covid-19/long-term-effects-of-coronavirus-long-covid/

37. World Heath Organization (WHO). Update 54 - Clinical long-term effects of COVID-19 [Internet]. 2021 [cited 2021 Aug 31]. Available from: https://www.who.int/publications/m/item/update-54-clinical-long-term-effects-of-covid-19

38. The COMET Initiative. Core outcome set developers' response to COVID-19 [Internet]. 2021 [cited 2021 Jul 6]. Available from: https://www.comet-initiative.org/Studies/Details/1538

39. Brazier J, Ara R, Azzabi I, Busschbach J, Chevrou-Séverac H, Crawford B, et al. Identification, Review, and Use of Health State Utilities in Cost-Effectiveness Models: An ISPOR Good Practices for Outcomes Research Task Force Report. Value in Health. 2019 Mar;22(3):267–75.

40. Kaltenthaler E, Tappenden P, Paisley S, Squires H. NICE DSU Technical Support Document 13: Identifying and Reviewing Evidence to Inform the Conceptualisation and Population of Cost-Effectiveness Models [Internet]. London: National Institute for Health and Care Excellence (NICE); 2011 [cited 2021 Aug 19]. (NICE Decision Support Unit Technical Support Documents). Available from: http://www.ncbi.nlm.nih.gov/books/NBK425832/

41. Asaria M, Griffin S, Cookson R, Whyte S, Tappenden P. Distributional Cost-Effectiveness Analysis of Health Care Programmes - A Methodological Case Study of the UK Bowel Cancer Screening Programme: DISTRIBUTIONAL COST-EFFECTIVENESS ANALYSIS. Health Econ. 2015 Jun;24(6):742–54.

42. Cookson R, Mirelman AJ, Griffin S, Asaria M, Dawkins B, Norheim OF, et al. Using Cost-Effectiveness Analysis to Address Health Equity Concerns. Value in Health. 2017 Feb;20(2):206–12.

43. Schnitzler L, Janssen LMM, Evers SMAA, Jackson LJ, Paulus ATG, Roberts TE, et al. The broader societal impacts of COVID-19 and the growing importance of capturing these in health economic analyses. Int J Technol Assess Health Care. 2021;37(1):e43.

44. Lakdawalla DN, Doshi JA, Garrison LP, Phelps CE, Basu A, Danzon PM. Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report [3]. Value in Health. 2018 Feb;21(2):131–9.

45. Kristensen FB, Lampe K, Wild C, Cerbo M, Goettsch W, Becla L. The HTA Core Model ® —10 Years of Developing an International Framework to Share Multidimensional Value Assessment. Value in Health. 2017 Feb;20(2):244–50.

46. NICE. Value based assessment of health technologies—consultation paper [Internet]. 2014 [cited 2021 Jul 29]. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/methods-of-technology-appraisal-consultation

47. Zorginstituut Nederland. Guideline for economic evaluation in healthcare [Internet]. 2016 [cited 2021 Jul 29]. Available from: https://english.zorginstituutnederland.nl/publications/reports/2016/06/16/guideline-for-economic-evaluations-in-healthcare

48. Walker S, Griffin S, Asaria M, Tsuchiya A, Sculpher M. Striving for a Societal Perspective: A Framework for Economic Evaluations When Costs and Effects Fall on Multiple Sectors and Decision Makers. Appl Health Econ Health Policy. 2019 Oct;17(5):577–90.

49. del Rio C, Collins LF, Malani P. Long-term Health Consequences of COVID-19. JAMA. 2020 Nov 3;324(17):1723.

50. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature. 2021 Jun 10;594(7862):259–64.

51. Institute for Clinical and Economic Review (ICER). ICER presents alternative pricing models for remdesivir as a treatment for COVID-19. Press release [Internet]. 2021 Jan [cited 2021 Aug 13]. Available from: https://icer.org/news-insights/press-releases/

52. Stevenson M, Metry A, Messenger M. Modelling of hypothetical SARS-CoV-2 point-of-care tests on admission to hospital from A&E: rapid cost-effectiveness analysis. Health Technol Assess. 2021 Mar;25(21):1–68.

53. Duarte A, Walker S, Metry A, Wong R, Panovska-Griffiths J, Sculpher M. Jointly Modelling Economics and Epidemiology to Support Public Policy Decisions for the COVID-19 Response: A Review of UK Studies. PharmacoEconomics. 2021 Aug;39(8):879–87.

54. Águas R, Mahdi A, Shretta R, Horby P, Landray M, White L, et al. Potential health and economic impacts of dexamethasone treatment for patients with COVID-19. Nat Commun. 2021 Dec;12(1):915.

55. Campbell J, Whittington M, Rind D, Pearson S. Alternative pricing models for remdesivir and other potential treatments for COVID-19; updated report. [Internet]. Institute for Clinical and Economic Review; 2020 [cited 2021 Jun 3]. Available from: https://icerreview.org/topic/covid-19/

56. Jo Y, Jamieson L, Edoka I, Long L, Silal S, Pulliam JRC, et al. Cost-effectiveness of remdesivir and dexamethasone for COVID-19 treatment in South Africa [Internet]. Health Economics; 2020 Sep [cited 2021 Aug 19]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.09.24.20200196

57. Padula W, Malayaya S, Reid N, Tierce J, Alexander G. Economic value of treatment and vaccine to address the COVID-19 pandemic: a US cost-effectiveness and budget impact analysis. The Lancet Preprints [Internet]. 2020 [cited 2021 Jul 1]; Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3586694

58. Sheinson D, Dang J, Shah A, Meng Y, Elsea D, Kowal S. A Cost-Effectiveness Framework for COVID-19 Treatments for Hospitalized Patients in the United States. Adv Ther. 2021 Apr;38(4):1811–31.

59. Marshall DA, Burgos-Liz L, IJzerman MJ, Osgood ND, Padula WV, Higashi MK, et al. Applying Dynamic Simulation Modeling Methods in Health Care Delivery Research—The SIMULATE Checklist: Report of the ISPOR Simulation Modeling Emerging Good Practices Task Force. Value in Health. 2015 Jan;18(1):5–16.

60. Marshall DA, Burgos-Liz L, IJzerman MJ, Crown W, Padula WV, Wong PK, et al. Selecting a Dynamic Simulation Modeling Method for Health Care Delivery Research—Part 2: Report of the ISPOR Dynamic Simulation Modeling Emerging Good Practices Task Force. Value in Health. 2015 Mar;18(2):147–60.

61. Davis S, Stevenson M, Tappenden P, Wailoo A. NICE DSU Technical Support Document 15: Cost-Effectiveness Modelling Using Patient-Level Simulation [Internet]. London: National Institute for Health and Care Excellence (NICE); 2014

[cited 2021 Aug 19]. (NICE Decision Support Unit Technical Support Documents). Available from: http://www.ncbi.nlm.nih.gov/books/NBK310370/

62. Zawadzki RS, Gong CL, Cho SK, Schnitzer JE, Zawadzki NK, Hay JW, et al. Where Do We Go From Here? A Framework for Using Susceptible-Infectious-Recovered Models for Policy Making in Emerging Infectious Diseases. Value in Health. 2021 Jul;24(7):917–24.

63. Caro JJ, Möller J, Santhirapala V, Gill H, Johnston J, El-Boghdadly K, et al. Predicting Hospital Resource Use During COVID-19 Surges: A Simple but Flexible Discretely Integrated Condition Event Simulation of Individual Patient-Hospital Trajectories. Value in Health. 2021 Aug;S1098301521016090.

64. NICE. Emergency and acute medical care in over 16s: service delivery and organisation—chapter 41 cost-effectiveness analyses. NICE guideline 94 [Internet]. 2018 [cited 2021 Aug 19]. Available from: https://www.nice.org.uk/guidance/ng94/evidence

65. Gravesteijn B, Krijkamp E, Busschbach J, Geleijnse G, Helmrich IR, Bruinsma S, et al. Minimizing Population Health Loss in Times of Scarce Surgical Capacity During the Coronavirus Disease 2019 Crisis and Beyond: A Modeling Study. Value in Health. 2021 May;24(5):648–57.

66. The Lancet Infectious Diseases. The COVID-19 infodemic. The Lancet Infectious Diseases. 2020 Aug;20(8):875.

67. Trowman R, Powers A, Ollendorf DA. Considering and communicating uncertainty in health technology assessment. Int J Technol Assess Health Care. 2021;37(1):e74.

68. Lomas JRS. Incorporating Affordability Concerns Within Cost-Effectiveness Analysis for Health Technology Assessment. Value in Health. 2019 Aug;22(8):898–905.

69. Carvalho N, Jit M, Cox S, Yoong J, Hutubessy RCW. Capturing Budget Impact Considerations Within Economic Evaluations: A Systematic Review of Economic Evaluations of Rotavirus Vaccine in Low- and Middle-Income Countries and a Proposed Assessment Framework. PharmacoEconomics. 2018 Jan;36(1):79–90.

70. Sullivan SD, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, et al. Budget Impact Analysis—Principles of Good Practice: Report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value in Health. 2014 Jan;17(1):5–14.

71. NICE. Antimicrobial resistance: developing and testing innovative models for the evaluation and purchase of antimicrobials [Internet]. 2021 [cited 2021 Jul 15]. Available from: https://www.nice.org.uk/about/what-we-do/life-

sciences/scientific-advice/models-for-the-evaluation-and-purchase-of-antimicrobials

72. Office for National Statistics. Why have black and south Asian people been hit hardest by COVID-19? [Internet]. 2020 [cited 2021 Jul 19]. Available from: https://www.ons.gov.uk/

73. Public Health England. Disparities in the risk and outcomes of COVID-19 [Internet]. 2020 [cited 2021 Jul 15]. Available from: https://www.gov.uk/government/publications/covid-19-review-of-disparities-in-risks-and-outcomes

74. Rentsch CT, Kidwai-Khan F, Tate JP, Park LS, King JT, Skanderson M, et al. Patterns of COVID-19 testing and mortality by race and ethnicity among United States veterans: A nationwide cohort study. Zelner J, editor. PLoS Med. 2020 Sep 22;17(9):e1003379.

75. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020 Aug 20;584(7821):430–6.

76. Canadian Agency for Drugs and Technologies (CADTH). What does the evidence say? CADTH COVID-19 evidence portal. [Internet]. 2020 [cited 2021 Aug 17]. Available from: https://covid.cadth.ca/

77. Winton Centre for Risk and Evidence Communication. Communicating the potential benefits and harms of the Astra-Zeneca COVID-19 vaccine [Internet]. University of Cambridge; 2021 Apr [cited 2021 Sep 14]. Available from: https://wintoncentre.maths.cam.ac.uk/news/communicating-potential-benefits-and-harms-astra-zeneca-covid-19-vaccine/

78. Cleemput I, Devriese S, Kohn L, Devos C, van Til J, Groothuis-Oudshoorn CGM, et al. What Does the Public Want? Structural Consideration of Citizen Preferences in Health Care Coverage Decisions. MDM Policy & Practice. 2018 Jul;3(2):238146831879962.

79. Health Technology Assessment International (HTAi). Interest groups—patient and citizen involvement [Internet]. 2021 [cited 2021 Aug 17]. Available from: https://htai.org/interest-groups/pcig/

80. NICE. Public involvement at NICE—annual report 2019/20 [Internet]. 2020 [cited 2021 Aug 17]. Available from: https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement/public-involvement-programme

81. Centers for Disease Control and Prevention. COVID-19: people at increased risk [Internet]. 2021 [cited 2021 Jul 19]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html

11. Appendices

11.1. Validated general overview of the COVID-19 disease and clinical pathway

We reviewed relevant clinical guidance and engaged directly with a range of clinical experts to establish a validated overview of the COVID-19 disease pathway. This was used as a basis for developing an example conceptual model for COVID-19, that HTA agencies may wish to use as starting point for assessing diagnostics and therapeutics in their own settings. The pathway was most recently updated on September 3rd, 2021.

Figure 1 shows a potential clinical course of COVID-19, including symptoms (blue), care settings (red), respiratory support (green), potentially available treatments (yellow), and health effects (orange) that may occur at different stages of the disease. This was developed based on review of the clinical guidelines and evidence listed at the end of this document, and in conjunction with 8 clinical experts from the UK, Netherlands, and Australia, covering the following specialties: emergency and critical care, general practice, infectious disease, intensive care, and rehabilitation. Darker items indicate more intensive disease or care, for example a higher symptom burden or escalation of respiratory support measures.

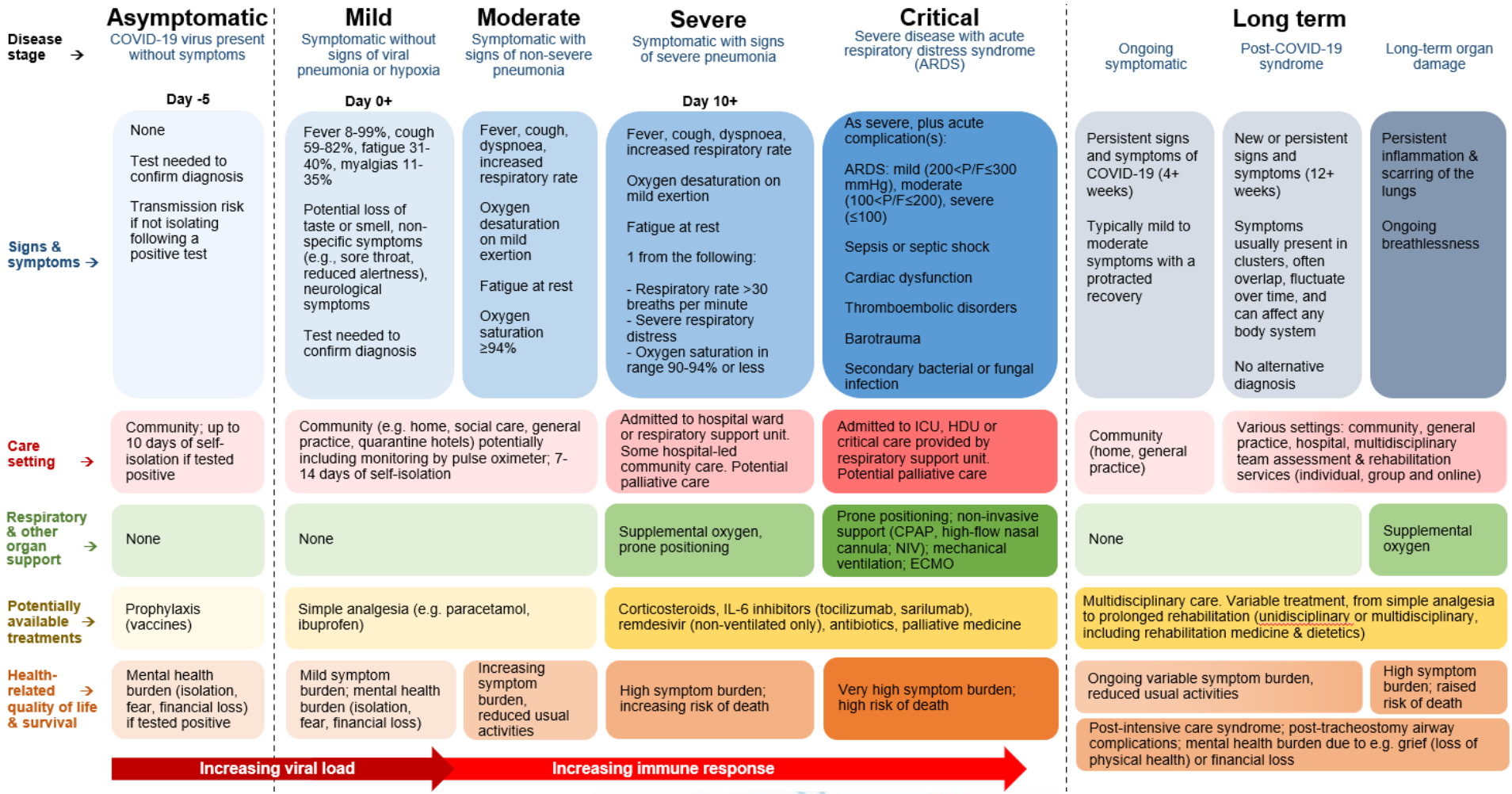


Figure 1. Validated overview of the COVID-19 disease and clinical pathway

11.2. Conceptual model for assessing the cost effectiveness of technologies for COVID-19

The example model structure in Figure 2 indicates key events or states of health that should be captured when modelling technologies for COVID-19. Specific resource use and health effects for each stage can be derived from the clinical and disease pathway (Figure 1).

It is proposed that this model would be nested within a wider SEIR model capturing disease transmission, indicated by healthy people in the community being described as “at risk of being infected” and people with undetected COVID-19 in the community as “risk of transmission to others”.

The arrows depict potential events a person could experience; for example, a person would need to have COVID-19 before it is possible for them to be defined as “recovered”, or to go on to experience long-term effects. Note that for simplicity, arrows to the “Death” health state are not shown, but people would be subject to varying risks of death from every other state of health.

Note that the aqua test result labels show the health state a person would enter after having a test. People could still be in those states of health if they do not have a test at all. For example, not everybody with mild or moderate disease in the community, not self-isolating, will have had a false negative test result. Some people may have minimal symptoms and therefore never get tested but would still enter that health state.

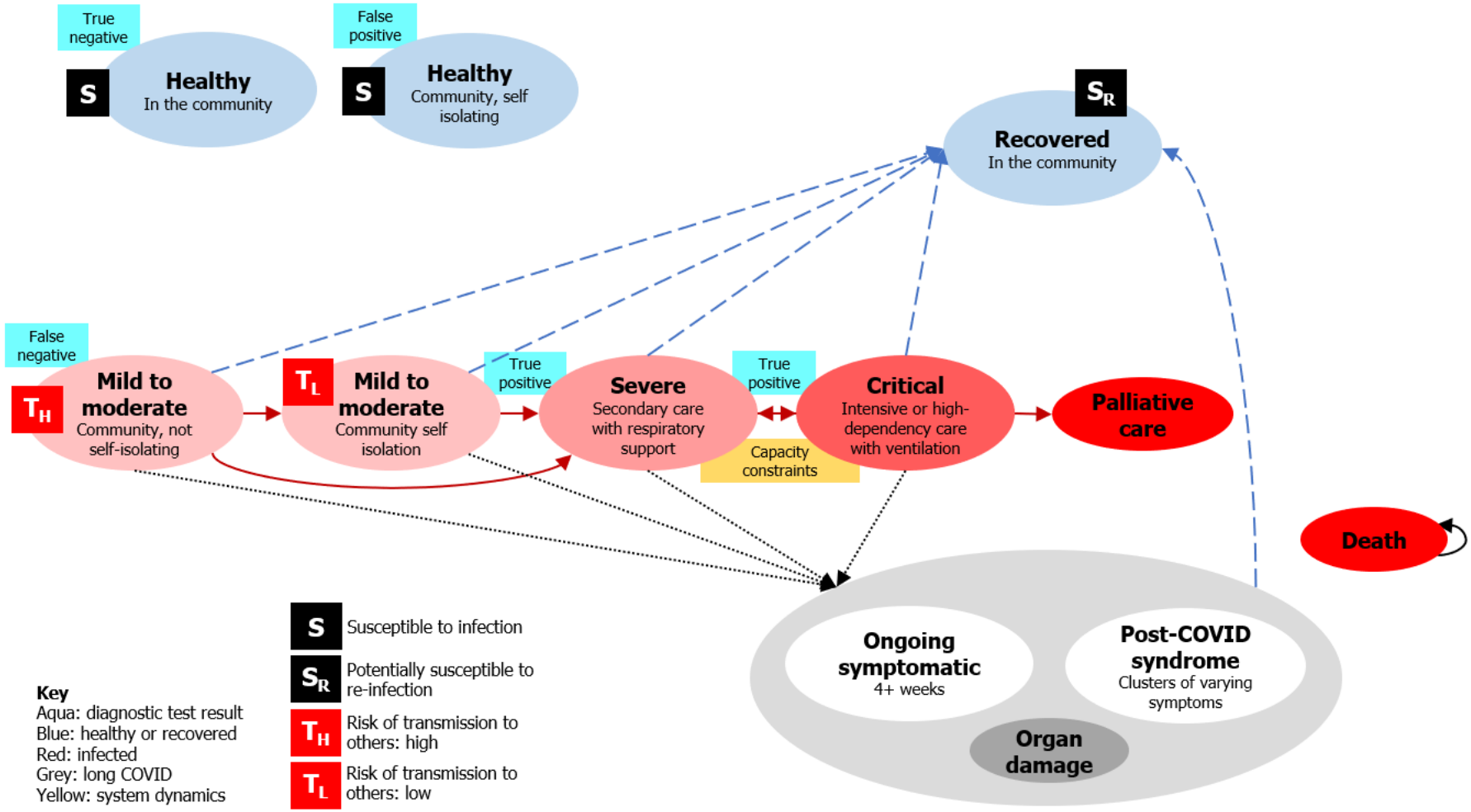


Figure 2. Example of a conceptual model for assessing the cost effectiveness of diagnostics and treatments for COVID-19