

The cost-effectiveness of in-patient care for COVID-19: implications for health technology assessment in South Africa

Authors

Susan Clearyⁱ
Tommy Wilkinsonⁱ
Cynthia Tamandjou Tchuemⁱ
Sumaiyah Docratⁱ
Geetesh Solankiⁱⁱⁱ

Institutionalising health technology assessment, including strengthening capacity and funding of analyses, will assist decision-making and sustainability in the National Health Insurance environment.

Health technology assessment aims to enable the prioritisation of efficient and equitable services and enhance responsiveness to population preferences. Resting on foundations of distributive and procedural justice, it is a fundamental component of a universal health coverage system. The required decision-making for the COVID-19 response stimulated the demand for evidence-informed processes and provides an opportunity to demonstrate how health technology assessment can be conducted in the South African environment. This chapter contributes to strengthening health technology assessment by reflecting on insights gained from research on the cost-effectiveness of in-patient care for COVID-19.

Rapid economic evaluations of in-patient interventions for COVID-19, including intensive care, dexamethasone and remdesivir were conducted. These evaluations aimed to inform urgent health policy decisions related to the COVID-19 response and to demonstrate the use and feasibility of a pragmatic approach to health technology assessment. Costs from the health systems perspective, deaths, and disability-adjusted life years (DALYs) averted were estimated. Incremental cost-effectiveness ratios were

compared to the estimated marginal productivity of the public health system to gauge cost-effectiveness. Open access models were published to encourage transparency and policy translation.

Results indicated that purchasing private sector intensive care was unlikely to be cost-effective, dexamethasone was cost-effective, and remdesivir was cost-saving. Corresponding national policy included a signed service-level agreement to purchase private ICU beds for public patients, and recommendations in favour of dexamethasone and against remdesivir. Policy decisions did not align with findings of two of the three economic evaluations.

These analyses and associated policy dissemination demonstrate that health technology assessment need not wait for the perfect system. Rigorous, transparent and rapid economic evaluation to support such assessment for urgent, priority policy decisions can be conducted in the South African context. Institutionalising health technology assessment, including strengthening capacity and funding of analyses, will assist decision-making and sustainability in the National Health Insurance environment.

i Health Economics Unit, University of Cape Town

ii Health Systems Research Unit, South African Medical Research Council



Introduction

The COVID-19 pandemic has placed unprecedented pressure on health systems around the world. The challenge to developing an efficient, fair and effective COVID-19 response entails the distribution of limited healthcare funding across the range of potential treatment strategies, prevention measures and public health initiatives to best manage the COVID-19 pandemic overall. The challenge becomes more acute given that the response must incorporate how to improve health for the whole population – there is limited merit in prioritising resources to stem the impact of COVID-19 if this means greater loss of life due to de-prioritisation of other causes.

To meet this challenge, many countries have adopted health technology assessment (HTA) processes to guide resource allocation for health care. HTA aims to enable the prioritisation of efficient and equitable services and to enhance responsiveness to population preferences. It is a fundamental component of a universal health coverage (UHC) system and rests on foundations of distributive and procedural justice – with the former requiring consideration of evidence on health outcomes and opportunity cost of investment decisions, and the latter requiring transparent deliberation in decision-making. HTA goes beyond an analytical exercise. It is a multidisciplinary process that uses explicit methods and procedures to determine the value of a health technology^a at different points in its lifecycle.¹ It aids in assessing the likely health benefits that can be expected from a new intervention, as well as the expected net costs of the option and compares these to the health outcomes that might be gained if limited resources were spent in other ways.

This chapter describes the efforts made by a group of researchers to respond to this prioritisation challenge through generating evidence on the cost-effectiveness of alternative in-patient interventions for severe and critical COVID-19 patients. At the time of initiating these analyses, the COVID-19 epidemic had overwhelmed available acute and Intensive Care Unit (ICU) capacity in a number of countries, and early epidemic forecasting models predicted that South Africa's ICU beds would be exhausted by July 2020.² This prompted efforts to explore ways to address the expected shortfall, including through sourcing ICU space from the private sector.

In addition to the focus on intensive care, international clinical trials indicated that two medications – dexamethasone and remdesivir – had the potential to save lives and enhance recovery. Dexamethasone, a corticosteroid that has been used in routine clinical practice for decades, was shown to be effective in the management of COVID-19 as part of an integrated strategy.³ Similarly, remdesivir was identified as a promising therapeutic for

COVID-19⁴ and was made available in South Africa under Section 21 of the Medicines and Related Substances Act.⁵ Unlike dexamethasone, remdesivir was not an established medicine for the treatment of other conditions and had a relatively high price.

The purpose of this chapter is to contribute to the strengthening of HTA for the South African health system by reflecting on the insights gained from analyses of the cost-effectiveness of these three interventions for COVID-19. Results are presented in their historical context, using the data that were available at the time of model finalisation during 2020. In the discussion, reflection is provided regarding how evidence has changed, how the original results compare to the current policy decisions (as of mid-July 2021), and how this experience might be relevant to the future implementation of health technology assessment in South Africa.

Approach

In April 2020, a grouping of researchers came together under the banner of MOSAIC (Modelling COVID-19 Strategies in South Africa Collective) with the aim of providing rapid HTA-related policy guidance and public engagement for the South African COVID-19 healthcare response. While MOSAIC members ultimately engaged in a number of policy spaces, this chapter focuses on analyses of the cost-effectiveness of three in-patient interventions for COVID-19. These interventions included one model of care (intensive care versus general ward care in critical patients) and two medication options (dexamethasone versus status quo and remdesivir versus status quo in admitted patients).

From the outset, MOSAIC's analytical approach centred on four key considerations: uncertainty, rapidity, rigour, and transparency. In May 2020, uncertainty was a key consideration, particularly given that South Africa had limited experience with COVID-19. There was nevertheless a need to make rapid investment decisions around in-patient care, among others, and the importance of making the right healthcare investments was perceived to be extremely high, pointing to the need for rigorous modelling. Given the preceding arguments, transparency was also considered to be crucial; indeed, transparency is one of the key criteria for achieving procedural justice within HTA.⁶

Methodology

While the details of MOSAIC's economic evaluation methodology are available in published sources,^{7,8} a brief summary of key aspects of the approach adopted is provided to illustrate how these four considerations were applied in practice. Three economic evaluation models were developed to assess the value for money of the following interventions:

- Intensive care versus general ward care for critical COVID-19 in-patients across public and private hospitals

a The term 'health technology' refers to a variety of interventions designed to improve health, such as medicines, vaccinations, diagnostics and screening programmes.

- Treatment with dexamethasone versus treatment as usual (i.e. without dexamethasone) for COVID-19 in-patients within public and private hospitals
- Remdesivir and remdesivir plus dexamethasone versus treatment as usual for COVID-19 in-patients in public hospitals.

In terms of the overall analytical approach, the International Decision Support Initiative (iDSI) reference case⁹ for the conduct of economic evaluation was followed to contribute towards the ethos of rigour and transparency. All analyses took a health systems perspective; the scope of costs included the full costs of in-patient care from admission to discharge or death in 2020 South African Rand; health outcomes were assessed as disability-adjusted life years (DALYs) averted and deaths averted; incremental cost-effectiveness ratios (ICERs) – expressing the difference in costs and health outcomes between alternative strategies – were compared to the marginal productivity of the South African public health system, and estimated at

ZAR 38 465 per DALY averted.¹⁰ If ICERs are lower than the estimated marginal productivity, the intervention in question is potentially cost-effective.

While economic evaluations of in-patient care do not always require sophisticated mathematical models, considerations of uncertainty and transparency necessitated the development of fully tailorable Markov models in our analysis. The models were initially developed in TreeAge Pro Healthcare 2020 (which enables extensive checking of modelling process validity) before being exported and redesigned in a user-friendly format in Microsoft Excel.¹¹⁻¹³ These models and an accompanying user guide⁸ were uploaded to an open access platform. This served as a mechanism for providing full transparency on sources of data and calculation approaches while also enabling the user to explore uncertainty through modifying any parameter in the model. Figure 1 provides a summary of the structure of the models, as well as a summary of the types of data needed to populate the models.

Figure 1a: Structure of Markov model for each comparator

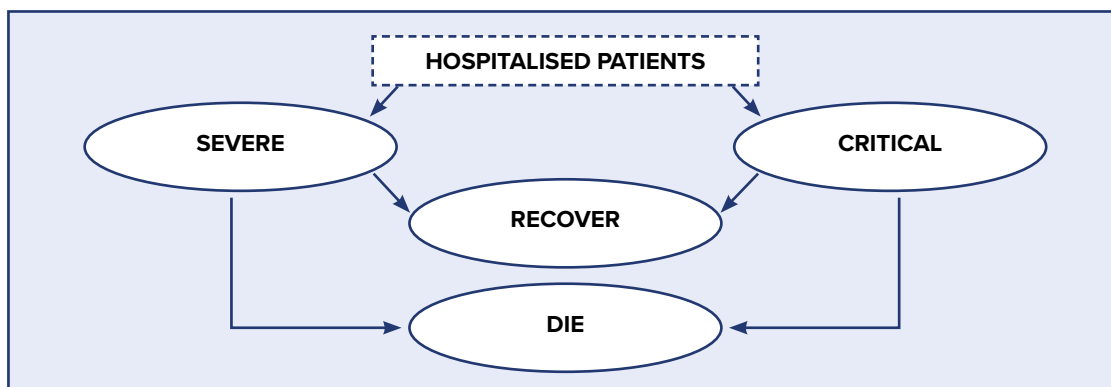
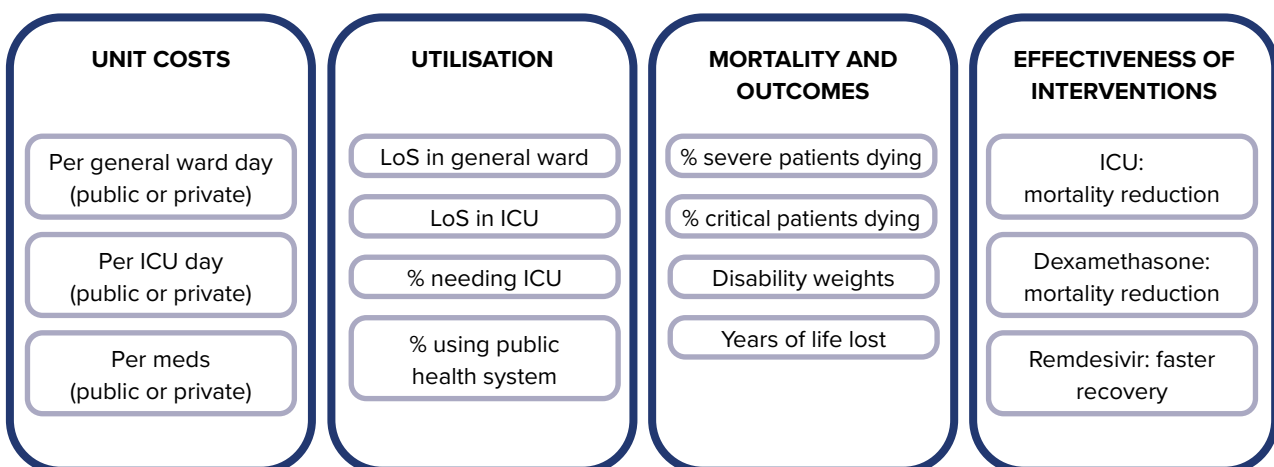


Figure 1b: Summary of types of data required for each comparator or cost-effectiveness question



Given the lack of South African COVID-19 experience in May 2020 and limitations on primary data collection, utilisation (e.g. proportion of admitted patients needing ICU; length of stay) and death rates were initially taken from meta-analyses of available studies (largely from China and Europe).⁷ In contrast, the remdesivir analysis was based on local data^{14,15} that became available after the first wave of COVID-19. In all models, estimates of utilisation were linked to South African unit costs that were based on tariffs (for private hospital costs), the *District Health Barometer 2016/17* datafile¹⁶ (public hospital costs), the NDoH Master Procurement List (dexamethasone price) and media reports (remdesivir price).¹⁷ Disability weights were taken from similar respiratory conditions in the 2017 Global Burden of Disease study¹⁸ while years of life lost (YLL) were taken from a local actuarial analysis using New York city age-at-death data,¹⁹ which was recalculated by MOSAIC when local age-at-death data became available. The effectiveness of interventions was assessed as follows:

- ICU: the upper confidence interval on death rates in critical patients managed in ICU from MOSAIC's meta-analysis⁷ was applied to those managed in general wards (0.88) in contrast to 0.54 (95% CI: 0.24-0.88) in those managed in ICU.
- Dexamethasone: a rate ratio reduction in deaths of 0.65 (95% CI: 0.48–0.88) and 0.80 (95% CI: 0.67–0.96) was applied in ventilated ICU patients and non-ventilated patients with oxygen, respectively.³ These parameters are multiplied against status quo death rates to estimate reduced death rates for those managed with dexamethasone.
- Remdesivir: an adjusted rate ratio for time to recovery of 1.31 (95% CI: 1.12-1.54) was used.⁴ Length-of-stay parameters were divided by this rate ratio to estimate reductions in time in hospital for those managed with remdesivir.

These models built on each other, enabling rapid assessment of modelling process validity¹⁵ and the generation of results. While the evidence base on the effectiveness of treatments has continued to evolve, we report on the results that were obtained in the models during 2020 in order to provide an overview of results within their historical context. However, in the discussion, we provide updates regarding how the evidence base has changed (as of July 2021) and what this means for cost-effectiveness findings.

Results

Analytical results

Tables 1a–1c provide details of the cost-effectiveness/utility results across the three economic evaluations. As mentioned, the ICU and dexamethasone models

considered investment decisions for both public and private hospitals and were based on a meta-analysis of available international studies for proportion of cases needing ICU, length of stay and survival rates, and New York City data on years of life lost (linked to age at death). The remdesivir model considered public sector hospitals only and was based on South African data for utilisation, survival and years-of-life-lost parameters which became available following the first wave of COVID-19. Interested readers are referred to the open access models^b for a full overview of key parameter changes, but a quick comparison between Table 1a or 1b versus 1c provides insight into the high levels of uncertainty on these parameters. In brief, in comparison to international studies included in the meta-analysis, South African hospitals during the first wave of COVID-19:

- triaged a lower percentage of admitted patients to ICU;
- per admitted patient, had a lower length of stay in general wards and higher length of stay in ICU;
- had lower survival among severe patients treated in general wards and higher survival among critical patients treated in ICU patients; and
- had a lower average age at death, leading to higher years of life lost.

While these differences tended to balance each other out if applied to the original ICU and dexamethasone models, they underscore the importance of fully acknowledging uncertainty and allowing for rapid updating of analyses of novel infections and related health system responses.

Tables 1a–1c also illustrate the mean cost per admission, counts of general ward and ICU days, deaths and DALYs for each intervention. Within the tables, strategies are ordered from lowest to highest cost in order to compute incremental cost-effectiveness ratios (ICERs) which summarise the additional cost per death or DALY averted by comparing cost differences and health outcome differences between one strategy and the previous listed strategy.

As shown in Table 1a, ICU care is unlikely to be cost-effective. ICERs exceed ZAR 70 000 per DALY averted, which is higher than the estimated marginal productivity of the South African health system (ZAR 38 465 per DALY averted). As shown in published sensitivity analyses⁷, a key driver of cost-effectiveness in this model was death rates in those admitted to ICU as well as years of life lost. In general, ICU becomes cost-effective if survival improves to approximately 80% and if death is averted in younger patients (generating higher averted YLL).

Dexamethasone, either on its own or in combination with remdesivir, is highly cost-effective, with ICERs lower than ZAR 600 per DALY averted.

In the case of the remdesivir model, any interventions that exclude remdesivir are 'absolutely dominated', meaning

b https://zivahub.uct.ac.za/projects/MOdeling_COVID-19_Strategies_In_South_AfriCa_MOSAIC_Collective/80900

that the strategies that include remdesivir are cost-saving (and hence by definition cost-effective). This is because remdesivir shortens time to recovery and discharge, which averts considerable in-patient costs to the extent that this outweighs the added cost of the medication. At the time of analysis, the published adjusted rate ratio for recovery for those managed with remdesivir was 1.31 (95% CI 1.12–1.55)⁴

which was subsequently revised to 1.29 (95% CI 1.12–1.49) within the final trial publication.²¹ However, evidence from other trials did not fully support the finding of faster time to recovery, generating considerable uncertainty about the cost-effectiveness of remdesivir, as outlined further in the discussion.

Table 1a: Cost-effectiveness/utility results for intensive care management of COVID-19 in public and private hospitals (ZAR 2020)

Strategy	Cost	DALYs	Deaths	ICU days	General Ward days	Incr. cost per DALY averted	Incr. cost per death averted
No ICU (critical patients managed in general wards)	75 127.25	1.48	0.27	-	18.85		
ICU (critical patients managed in ICU)	103 030.20	1.10	0.20	1.85	17.00	73 091.37	390 797.60

Table 1b: Cost-effectiveness/utility results for dexamethasone management of COVID-19 in public and private hospitals (ZAR 2020)

Strategy	Cost	DALYs	Deaths	ICU days	General Ward days	Incr. cost per DALY averted	Incr. cost per death averted
Status quo	103 030.20	1.103	0.200	1.85	17.00		
Dexamethasone	103 191.05	0.797	0.143	1.85	17.00	525.90	2 818.47

Table 1c: Cost-effectiveness/utility results for dexamethasone and remdesivir management of COVID-19 in public hospitals (ZAR 2020)

Strategy	Cost	DALYs	Deaths	ICU days	General Ward days	Incr. cost per DALY averted	Incr. cost per death averted
Remdesivir	37 641.69	2.153	0.156	0.73	5.80		
Remdesivir plus dexamethasone	37 723.80	1.687	0.122	0.73	5.80	176.36	2 411.36
Status quo	45 280.49	2.153	0.156	0.95	7.60	Absolutely dominated	Absolutely dominated
Dexamethasone	45 388.05	1.687	0.122	0.95	7.60	Absolutely dominated	Absolutely dominated

DALYs = disability adjusted life years; ICU = intensive care unit; Incr. = incremental

Dissemination and links to policy

The analytical outputs of an economic evaluation are an essential but partial input to a wider HTA process. As South Africa's institutional co-ordination of HTA processes is in development, targeted dissemination and policy engagement activities were conducted for the analyses. Fully executable models were made available in the

public domain¹¹⁻¹³, lay-language op-eds were published^{22,23}, and local media and stakeholder engagement activities were held – and in the case of the remdesivir analysis, results were presented to the COVID-19 Rapid Review Sub-committee of the National Emergency Medicine List Committee (NEMLC). The associated policy decisions are detailed in Table 2.

Table 2: Summary of economic evaluation results and policy decisions

	ICU care	Dexamethasone	Remdesivir
Policy decision under consideration	Purchase ICU beds from private sector to meet expected public sector shortfalls	Recommend dexamethasone for COVID-19 in-patients	Recommend remdesivir for COVID-19 in-patients
Economic evaluation result	Not cost-effective	Cost-effective	Cost-saving
Decision-maker	NDoH, Provincial DoH	National Essential Medicines List Committee	National Essential Medicines List Committee
Policy decision made	Recommendation to purchase from private sector if needed	Strong recommendation in favour of dexamethasone ²⁴	Conditional recommendation against remdesivir ²⁵

In what follows, we discuss each decision in more detail. Firstly, on ICU, the policy decision at the time was to sign a service-level agreement that would enable provincial governments to purchase ICU beds from private hospitals at an agreed tariff rate and structure. The initial intention of our economic evaluation was to assist in obtaining agreement on the reimbursement for services rendered. However, it is also useful to compare the results of the economic evaluation to critical care triage guidelines in South Africa. In effect, these guidelines facilitate transparent prioritisation of patients to ICU based on utilitarian principles, i.e. prioritising patients who have the best chance of survival with acceptable quality and where the most life years are to be gained.²⁶ Triage decisions such as these could make private-sector purchased ICU care a cost-effective intervention in the South African setting.⁷ Given that they both rest on utilitarian principles, economic evaluation and critical care triage guidelines are highly complementary approaches.

Secondly, in the case of dexamethasone, MOSAIC's analysis suggests that the addition of this medication in severe or critical patients hospitalised with COVID-19 would be highly cost-effective. This finding is driven by the low price of dexamethasone (and other steroids such as prednisone) as well as the relatively large impact on mortality. To date, the NEMLC Therapeutics Guidelines Sub-Committee for COVID-19 has conducted two reviews of dexamethasone, most recently in October 2020. The committee has given a strong recommendation in favour of dexamethasone for hospitalised patients receiving respiratory support.²⁴ Similarly, in the 31 March 2021 version of the World Health Organization's

'Living Guideline', systemic corticosteroids (such as dexamethasone) are recommended in both severe and critical hospitalised patients.²⁷

Thirdly, in the case of remdesivir, the analysis shows that cost savings are driven by the adjusted rate ratio for time to recovery as provided by the original clinical trial.^{4,21} A threshold analysis shows that a 17% reduction in this parameter would render remdesivir cost-ineffective. Similarly, a recent South African economic evaluation showed that remdesivir would be cost-saving provided that it averts at least one ICU day.²⁸ The NEMLC Therapeutics Guidelines Sub-Committee for COVID-19 has conducted five reviews of remdesivir with the most recent conducted in December 2020.²⁵ As indicated in these reviews, the evidence for remdesivir from more recent clinical trials has been mixed with lack of evidence for mortality benefit and other clinically meaningful outcomes. This finding is echoed by the 31 March 2021 version of the World Health Organization's 'Living Guideline'.²⁷ In contrast, as of 1 July 2021, remdesivir continues to be recommended for use in hospitalised patients requiring supplemental oxygen by the United States National Institute of Health²⁹ and in those needing low-flow supplemental oxygen by the United Kingdom National Health Service.³⁰

The misalignment of the cost-effectiveness analysis with the resultant policy decisions for ICU care and remdesivir does not indicate that the policy decisions were wrong or that the economic analysis was incorrect; even within a fully-fledged HTA process, economic evaluation evidence

would be only one among many considerations informing a policy decision. The resultant policy decisions do indicate, however, that the existing criteria for both inclusion of relevant evidence into the decision process and for making actual policy decisions do not sufficiently address the role of value for money with implications for fair allocation of resources within a UHC framework. Particularly in a time of a health emergency, it is understandable for decision-makers to adopt a 'rule of rescue' approach where the broader considerations of allocative efficiency of health spending may become less important. Similarly, where conditions are particularly fluid and the evidence base relating to costs, effects, utilisation and prices are shifting by the day, any type of economic evaluation will be subject to considerable uncertainty, and decision-makers may quite reasonably determine that a 'best guess' by accountable experts, using whatever evidence and prior knowledge is available, may be the most appropriate way to make investment decisions. While the conditions for relying on rule of rescue and 'expert judgement' may have been present in the early stages of the COVID-19 pandemic, the evolving evidence base and considerations for the wider health of the South African population demand that a more inclusive and comprehensive approach to health investment be taken.

The timeliness of analysis to support HTA is often cited as a limiting factor for meaningful policy implementation.³¹ In the case of COVID-19, rapid reviews of evidence should be updated regularly, and the same updates would be required for economic evaluation models. For this reason, MOSAIC prioritised the development of open access, simplified models. One of the benefits of these models is that it is possible for analysts to identify the key parameters that drive the results and that should be updated as the evidence base evolves. This facilitates a pragmatic methodological approach that maintains core analytical principles while prioritising the evidence needed for decision-making.

A previous assessment of the state of health technology assessment in South Africa, published in the 2017 *South African Health Review*, noted that further development of HTA policy and legislative frameworks was needed to establish a comprehensive national HTA programme.³² Recent consultation on new HTA methods for the NEMLC process is a positive development that builds on the growing experience and willingness to incorporate explicit HTA methods in decision-making. Urgent and non-urgent health policy decisions will be made with or without HTA, and even countries with highly developed HTA processes such as Thailand, Canada and England do not apply HTA to all health policy decisions. The consideration is not whether South Africa should have a HTA system, but the extent to which we can develop and produce evidence on cost-effectiveness, equity, access, and other ethical considerations to inform policy-making.

Conclusions

The COVID-19 pandemic is expected to further widen the healthcare demand–supply gap and amplify the need to develop HTA capacity to guide resource allocation for health care. Institutionalising HTA, including strengthening capacity and funding for evidence generation, will assist decision-making and the sustainability of our health system.

The analysis and associated policy dissemination presented in this chapter demonstrate that HTA in South Africa need not wait for the perfect system, and that rigorous, transparent and rapid economic evaluation to support HTA for urgent, priority policy decisions can be conducted in the South African context using available data. While decision-making related to the COVID-19 response was particularly urgent and uncertain, these experiences have shown what is possible and clarify the case for improvement.

Recommendations

The pandemic has illustrated the high level of technical capacity and commitment of South African researchers towards improving health and health care. It has been heartening to witness the notable contributions (largely pro bono) made from a variety of disciplines. This chapter provides reflections from one group of researchers seeking to contribute towards pandemic decision-making through an HTA lens. From this perspective, the following recommendations are made:

- Through building on 'reference case' approaches, it is possible to rapidly develop rigorous economic evaluation models for priority decisions. It is recommended that South Africa adopt an economic evaluation reference case that is published and implemented in future investment analyses.
- Transparency is a fundamental aspect of procedural justice in HTA. It is recommended that the analytical models used in decision-making are published through open access platforms in order to facilitate learning, revision and appeals processes.
- A database of key unit costs should be developed and used across analyses. In addition to facilitating rapidity, this approach will enhance the comparability of economic evaluation models and the generalisability of findings.
- Local researchers and those with HTA capacities require a paradigm shift towards social responsibility and technical support for decision-making, even if this does not lead to highly citable publications.
- While many countries have initiated HTA through an initial focus on medicines, a key cost-driver in the South African context is human resources and the configuration of the health system platform. It is recommended that researchers continue to broaden

their focus towards the economic evaluation of models of care (e.g. ICU) and health systems strengthening.

- While much can be achieved through pro bono work in times of crises, developing HTA capacity and ensuring rapid turnaround on analyses requires that funding and remuneration for these analyses becomes increasingly predictable.

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