Funding considerations for the use of experimental therapies for COVID-19 in the South African private sector

The dearth of effective treatment options for COVID-19 has created many challenges for the global health community.[1] These challenges have extended to the preservation of evidence-based medicine (EBM) principles, as the speed of spread and disease severity have necessitated a review of the traditional models of knowledge translation, both from a public health perspective and in terms of direct clinical care.[2] As a result, there has been a tradeoff in our reliance on EBM in guiding treatment decisions, in favour of a pragmatic, practice-based approach in the use of experimental therapies (off-label and unregistered) outside the realms of a clinical trial setting.[3,4]

Aside from the obvious disparities between private and public healthcare in South Africa (SA)'s healthcare system, the consideration of experimental therapies under pandemic conditions has exposed some of the less obvious discrepancies that create unique ethical and medicolegal dilemmas and that require some reflection.

COVID-19 and prescribed minimum benefits

The Council for Medical Schemes (CMS) is the statutory body responsible for the regulatory oversight of the medical schemes industry in SA. The prescribed minimum benefits (PMBs) are a set of defined benefits, enshrined in the Medical Schemes Act No. 131 of 1998,[5] to ensure that all medical scheme members have access to certain minimum health services, regardless of the benefit option they have selected.[6] From time to time, the CMS is required to determine the minimum PMB entitlement of an insured person as it pertains to specific clinical conditions.

The most recent version of the CMS' PMB definition guideline for COVID-19[7] excludes off-label medicines and the unlicensed drug remdesivir from PMB entitlement. This means that while the management of COVID-19 as a whole qualifies for unlimited funding in the SA private sector irrespective of benefit option, the use of these investigational agents is subject to discretionary funding by medical schemes, or is for the patient's own pocket. Out-of-pocket payments in these circumstances have their own ethical considerations. Patients are vulnerable, isolated, often critically ill and do not necessarily have a full grasp of the associated treatment costs. In the context of COVID-19, obtaining true informed consent may be further compromised by pandemic-mitigating measures such as physical distancing policies and in-hospital infection control measures, as well as by the nature and severity of a patient's illness, thus rendering them insufficiently competent to provide consent.[8]

The CMS further notes that the 'NDoH [National Department of Health] acknowledges that investigational medicines should be used in the realm of a clinical trial, but given the nature of the pandemic, a pragmatic approach might be required, and such medicines should be used under the Monitored Emergency Use of Unregistered Interventions (MEURI) framework'.[7]

MEURI framework

The MEURI framework is an ethical protocol introduced by the World Health Organization (WHO) during the 2014 Ebola outbreak in West Africa to guide the use of unproven interventions outside of a research setting under pandemic conditions.[9]

There is an ethical imperative for the global health community to conduct research on potential therapeutic agents in times of a public health crisis, providing that these interventions are tested for safety and efficacy using rigorous methods and simple but appropriately designed clinical trials. Moreover, the WHO considers it ethical to make investigational interventions available outside of clinical trials for 'emergency use', provided that clinical data from their use are systematically collected and shared. The main intention of this provision is to learn as much as possible, as quickly as possible, without compromising patient care, local community values or health-worker safety.[9] The term 'MEURI' was thus coined to differentiate the use of investigational therapies within the context of such public health crises from 'compassionate use', which is understood to be the use of an investigational medicine outside of a clinical trial. It was believed that this latter term may be inaccurate in circumstances in which an untested intervention is used and data on its efficacy are systematically collected from individual use. Therefore the term MEURI is intended to replace 'compassionate use' so as to more clearly define the boundaries between clinical trials and compassionate use of investigational medicines outside of a clinical trial setting.[10]

The MEURI framework requires that:[11,12]

(*i*) no proven effective treatment exists for a specific disease;
(*ii*) it is not possible to initiate clinical studies immediately;
(*iii*) data providing preliminary support of the intervention's efficacy and safety are available, at least from laboratory or animal studies, and use of the intervention outside clinical trials has been suggested by an appropriately qualified scientific advisory committee on the basis of a favourable risk-benefit analysis;
(*iv*) the relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use;
(*v*) adequate resources are available to ensure that risks can be minimised;
(*vi*) the patient's informed consent is obtained; and
(*vii*) the emergency use of the intervention is monitored, and the results are documented and shared in a timely manner with the wider medical and scientific community.

A framework such as this lends itself well to application in the management of COVID-19, given that there is no proven effective treatment for the condition, and immediate clinical studies are not possible, certainly not in the non-academic private sector.

Applicability in South Africa

While the framework may not be legally enforceable in SA, it does provide a basis for ensuring clinical governance standards applicable

to non-trial settings. The requirement for data collection and reporting comparable to clinical trial standards is intended to ensure that the societal benefit of exposing a subset of the population to unproven therapies ethically justifies their use, for the purposes of establishing safety and efficacy. On this basis, the application of an effective MEURI framework in a non-academic private healthcare facility opting to use experimental therapies would require that provision be made for the development of clinical protocols, ethics approval and the requisite skills and resources for data collection, analysis and reporting.

Our observations within the SA context are that the lack of clearly defined authorities to guide the application of the MEURI framework, combined with the relative autonomy with which clinicians practise in the private sector, has contributed to the use of these agents outside of recommended MEURI standards. Furthermore, we note from within the private funding sector that this has ultimately led to a sporadic and unco-ordinated approach, with a considerable number of local patients having been exposed to these agents with very little outcome in terms of societal learning, owing to inadequate data collection and reporting. The missed opportunity of much-needed population insights into the management of COVID-19 thus does raise the question as to whether any form of discretionary funding is in fact an appropriate use of resources in an economically constrained healthcare environment. This may be compounded by a lack of consideration of resource allocation requirements in any ongoing support of patients who may inadvertently experience treatment-related adverse effects.

COVI-Vig

The launch of the SA Health Products Regulatory Authority (SAHPRA)'s COVI-Vig reporting system on 20 August 2020[13] (accessible on the SAHPRA website, www.sahpra.org.za) may be viewed as a valuable monitoring solution for facilities struggling to implement a MEURI framework. While COVI-Vig is not intended to satisfy all the requirements of an effective MEURI framework, it does offer a centralised platform for systematic data collection and review of the benefits and risks encountered by individuals exposed to these various treatment modalities, either for the prevention (pre- or post-exposure prophylaxis) or treatment of COVID-19 infection. Consistent and timely data capture and analysis will be and could have been beneficial in supporting ongoing surveillance of the use of experimental therapies, in view of the high level of local uncertainty regarding subsequent COVID infection waves.

Roles of private sector stakeholders

As our healthcare system collectively overcomes COVID-19, it is important to reflect on the symbiotic relationship that exists between the provision of healthcare and the funding thereof. As healthcare funds are allocated to support members seeking care for the management of COVID-19, there is a heightened requirement for good governance and accountability when dealing with the funding of investigational interventions. This is true not only for the patient involved, but also for the broader insured population whose pooled funds are used to fund such care, and as regards the societal responsibility we have in maximising the knowledge gained from sharing the experiences of patients exposed to these therapies.

The use of investigational therapies for the management of COVID-19 has highlighted opportunities for the private sector to support research to an extent that advances public good, as well as the potential for improved public/private sector collaboration to enhance healthcare delivery in SA. As various stakeholders collaborate with the intention of enabling access to care in these challenging times, we welcome the development and application of both the MEURI framework and the COVI-Vig reporting system, and call on all participants in the healthcare continuum to seek ways of inculcating these important mechanisms in their respective business processes. This will contribute significantly to enhancing accountability in resource allocation, while promoting the greater societal good through the recording and analysing of these clinical experiences and outcomes.

Conflicts of interest. ZA is employed by Medscheme Holdings (Pty) Ltd, a healthcare administrator managing local and international healthcare portfolios. RJW is employed by Liberty Health (Pty) Ltd, a private health insurer operating in SA and across the broader African continent.

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