Informed consent during pandemics: Experimental medicine, experienced consent

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No known cure exists for COVID-19, and medical practitioners are exhausted and at their wits' end trying to find treatments that prevent patients from ending up in hospital or intensive care, or even dying. A variety of treatments tried by medical practitioners include standard registered medicine, investigational or so-called experimental, unapproved or preapproved medicines, emergency or compassionate-use authorised medicine and pre-market approved medicine. However, the medicines that can be accessed via each of these categories are at different stages of efficacy testing and knowledge about adverse effects, dosages and risks. To obtain ethical and legal informed consent, medical practitioners must deal with a lot of medical uncertainty, and care must be taken to ensure that the patient understands the difference in risks they may be willing to take depending on the medicine's stage of development. Often additional information is required to obtain ethical consent as opposed to legal consent. A purely legal approach to informed consent, especially when dealing with the medical uncertainties of health emergencies and pandemics, may lead to patients' consent lacking in enough substance to be truly considered legal and ethical. Informed consent as respect for autonomy in this sense requires more than the patient's explicit agreement or compliance with a certain treatment proposal. This article explains the difference in consent content attached to each different stage of a medicine's development, especially considering the additional difficulties posed by obtaining truly informed consent during a pandemic with uncertain characteristics, treatment and solutions.

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People often fail to recall major portions of the purpose, content and implications in respect of the informed consent they have given for medical treatment or research. A study by Cassileth *et al*.[1] found that only 60% of oncology patients understood the purpose and nature of their treatment, and that 55% could recall at least one major risk factor or possible complication. Patients' medical status was among the three factors that influenced their recall of the consent they gave. Similarly, Sanchini *et al*.[2] found that 62% of research participants understood the purpose and nature of the clinical trial, and that 40% could list at least one possible major risk or complication that may result from their participation in the trial. In addition to medical status and education, they also found that age played an important factor in the comprehension and recall of informed consent.

No known cures exist for COVID-19, and medical practitioners are exhausted and at their wits' end trying to find treatments that prevent patients from ending up in hospital or intensive care, or even dying. Some treatments tried by medical practitioners included the antiviral remdesivir, the only COVID-19 treatment that has been formally approved by the Food and Drug Administration, but which failed to prove any improvement in recovery time or mortality, the corticosteroid dexamethasone, which had dramatic results reported, tocilizumab, which lowered mortality rates, and an expensive anti-inflammatory drug that was initially approved to treat rheumatoid arthritis.[3] However, despite initial positive results, there seem to be insufficient data to recommend either for or against the use of any of these treatments specifically for COVID-19. Many of these treatments, including ivermectin and an increasing variety of vaccines, are being made available to patients in various stages of development and/or approval. Some are still subject to clinical trials, while others are being prescribed in terms of compassionate-use programmes or at preapproval marketing stage. At the time of submission of this article, four vaccines had been approved in Canada,[4] and the South African Health Products Regulatory Authority (SAHPRA) had only just approved the Johnson & Johnson vaccine. Since then, many more vaccines have been approved.

The administering of medicines and vaccines in circumstances in which patients are gravely ill, or of advanced age (which is one of the comorbidity factors of COVID-19), or in the context of clinical trials, compassionate-use programmes or preapproval stage often entails the explanation of uncertain medical information and consequences to patients in precarious medical and emotional conditions that may only serve to confuse them further and lead to poorly informed choices or a complete lack of ethical or legal informed consent.[5]

Objective

The inherent risk and foreseeable effects of any medicine administered to a patient depend largely on the data collected in respect of that medicine's safety, efficacy and dosage as determined during the different phases of its clinical trials. This information is further scrutinised by SAHPRA before it formally approves and registers medicine for marketing purposes.[6] In these circumstances, medical practitioners can provide a patient with definitive and known risks

and consequences in respect of the status of the medicine or vaccine being administered, to enable legal and ethical informed consent. The medicine's status will subsequently determine the content of the informed consent, and this article will discuss the differences in informed consent applicable to the specific medical regimen under which the medicine or vaccine is administered, especially taking the medical condition and knowledge about the medicine into account.

Standard access to medicine

Access to medicine in South Africa (SA) is regulated by the Medicines and Substances Act No. 101 of 1965 (Medicines Act),[6] and administrated by SAHPRA according to a strictly regulated process in which the medicine producer must apply for approval and registration of its medicine before it is entitled to legally sell and market the medicine. SAHPRA will only approve a medicine for registration once it has familiarised itself with the particulars of the relevant sample medicine, and after satisfying itself that the medicine is safe, efficient and suitable for the purpose for which it is intended to be used.[7] The aim of this process is to ensure the safety of patients when medical practitioners prescribe this medicine in accordance with the conditions and purposes of the medicine's registration. This makes the process of obtaining informed consent easier to the extent that medical practitioners, considering the registered particulars of the medicine, should be able to predict the effects, including possible adverse effects, and other consequences of taking this medicine, and be able to inform the patient accordingly. The patient should have adequate information to enable him or her to provide clear and certain informed consent.

However, patients may wish to access medicines earlier via other routes, such as investigational use, clinical trials, emergency or compassionate-use programmes or preapproval access.

Investigational medicines and clinical trials

Investigational medicines, also called experimental, unapproved or preapproved medicines, are medicines that are still in development or under investigation and have not been approved by any regulatory authority.

All medicine usually undergoes rigorous, extensive and incremental testing, starting with laboratory, cell and animal studies to establish a new treatment, after which its safety for human use will be tested in a phase I clinical trial, its effectiveness in phase II and the dosage in phase III. These studies are critical for companies to establish whether their medicines are suitable for regulatory and marketing approval.

Although the National Health Act (NHA) does allow health services for experimental purposes,[8] this access still strictly falls within a clinical trial regulatory framework. Section 11(1) of the NHA stipulates that the health establishment must inform the patient that the health service (s)he is going to receive 'is for experimental or research purposes or part of an experimental or research project', and such services may only commence with the written authorisation of all parties involved, i.e. the patient, the medical practitioner, the head of the health establishment and the relevant health research ethics committee. Section 71 only allows the use of experimental medicine with the written consent of the patient after (s)he has been informed of 'the objects of the research or experimentation and any possible positive or negative consequences on his or her health'.[9] The fact that an independent authority, such as the ethics committee and the head of the health establishment, also need to approve and authorise the use of medicine for 'experimental' purposes eases the burden for the medical practitioner, who must obtain informed consent from the patient. However, as opposed to the standard access route, the patient must be made aware of the experimental nature of the medicine, which necessitates the provision of additional information regarding possible unanticipated risks due to uncertainties that still exist, hence the need for further experimentation. Section 12 confirms the obligation on health establishments to disseminate information that is appropriate, adequate and comprehensive.[10]

Because no pharmaceutical treatment has shown any efficacy for the treatment of COVID-19, several unregistered medicines have been suggested as potential investigational therapies, while several registered medicines have also been prescribed 'off-label' as treatment for COVID-19 for indications that have not been approved by any regulatory authority. Such 'off-label' prescriptions are still considered to be investigational in nature, and subject to the above national laws and regulations.

In SA, medical practitioners sought legal access to ivermectin, an anti-parasitic drug used in animals, for the experimental treatment of COVID-19 patients suffering from serious symptoms, after SAHPRA insisted that ivermectin was 'unproven in the management of COVID-19 infections', and did not exclude the possibility of harmful effects or death.[11] Many medical practitioners argued to the contrary, and explained that ivermectin has shown promise in previous trials and, in the absence of any cures or better treatment options for COVID-19 symptoms, that they should be allowed to use ivermectin during this pandemic.[12]

The information required by the patient to consent to ivermectin legally and ethically, in circumstances where the health regulatory authority, medical practitioners and available clinical trial results contradict one another and are non-conclusive, is extensive considering the uncertainties and professional differences. Patients need to be informed of all conceivable consequences of taking this medicine, while these consequences may be completely unknown to medical practitioners when being used for COVID-19, as a disease for which ivermectin has not been previously tested. Patients can at best be presented with the same uncertainty that medical practitioners experience in the context of any off-label use for the treatment of a novel infection such as COVID-19, which places a heavy burden of risk on the patient to accept numerous uncertainties as part of his or her informed consent. This leaves a patient between a rock and a hard place, which begs the question whether the consent provided by the patient in these circumstances constitutes legal and ethical informed consent at all.

Emergency or compassionate-use authorisation

In the context of emergency or compassionate use of an unregistered medicine, consent based on uncertain and constantly changing information may constitute legal and ethical consent in times of health emergencies or disasters. Section 21 of the Medicines Act specifically provides for the selling of any unregistered medicine during a specified period and for a specific purpose, such as a pandemic. On this basis and in the midst of ongoing professional disputes and pending court cases regarding ivermectin,[13] SAHPRA

issued the Ivermectin Controlled Compassionate Use Programme Guideline on 28 January 2021.[14] This programme is premised on section 21 and regulation 29 of the general regulations made in terms of the Medicines Act, and allows medical practitioners to apply to SAHPRA for the authorisation and sale of ivermectin for the specific purpose of treating individually named patients for COVID-19 – while ivermectin remains unregistered for human use. To manage the quality and safety of ivermectin, SAHPRA indicated that this compassionate access programme will follow a tiered access approach, and SAHPRA will continue to monitor any adverse events via stringent reporting measures. Medical practitioners who manage to gain access to ivermectin via this route are therefore obliged to report on any patient outcomes on SAHPRA's COVI-Vig programme.

In comparison, it is interesting to note that access to unregistered medicine for purposes of compassionate use in the USA is only allowed when a public health emergency has been declared, there is no adequate, approved and available alternative treatment for the relevant disease, such as COVID-19, there are findings that it is reasonable to believe that the unregistered medicine 'may be effective' and the known and potential benefits outweigh the known and potential risks. In SA, the government chose to manage the COVID-19 pandemic in terms of the Disaster Management Act No. 57 of 2002 (DMA),[15] instead of the State of Emergency Act No. 64 of 1997 or the NHA. The DMA defines a disaster as a 'natural or human-caused occurrence which (a) causes or threatens to cause – (*i*) death, injury or disease; (*ii*) damage to property, infrastructure or the environment, (*iii*) disruption of the life of a community; (b) is of a magnitude that exceeds the ability of those affected by the disaster to cope with its effects using only their own resources'.[15] Although there seems to be consensus on the government's choice of pandemic management regulatory model, the disputes between medical practitioners and SAHPRA regarding the status, effectiveness and safety of ivermectin beg the question whether the compassionate-use programme is justifiable or provides sufficient guidance. This programme is, for example, silent on any additional information that must be provided to the patient to ensure that the patient is adequately informed, willing and able to give ethical and legal informed consent, considering the uncertainties.

From a consent perspective, this programme creates far more questions than answers. Not only are the effect, safety and possible adverse effects of the use of ivermectin in humans uncertain, but medical professionals differ on critical aspects of this medicine and whether it should be used, albeit for compassionate reasons, during a global health emergency that is managed as a disaster in SA. In these circumstances, complete transparency with patients is non-negotiable. Patients must be informed and kept updated with regard to the status of ivermectin, the latest safety tests and any reported adverse effects. A further complexity is the medical status of the patient at the time of consent. When compassionate-use access of an unregistered medicine is sought, the patient is often gravely ill and desperate, and may not be physically or mentally able to provide legal or ethical informed consent, especially considering the medical disputes between professionals and the uncertainty regarding dosage, efficacy, safety and risks involved with an unregistered medicine such as ivermectin.

Pre-market approval

Sometimes when the safety and efficacy of a medicine have been proven, a regulatory authority grants pre-market approval for the medicine to be rolled out prior to the registration process being completed. The safety and efficacy of the Johnson & Johnson vaccine were tested in the international ENSEMBLE study, which was conducted across Latin America, the USA and SA with more than 43 000 participants.[16] In this study, the vaccine proved to be 57% efficacious in SA and 85% effective overall in preventing severe infection, and included participants exposed to the 501.V2 variant, suffering from comorbidities such as diabetes and HIV/AIDS and participants >60 years old.

To make this vaccine available to frontline healthcare workers in SA, while still attending to the formalities of registering this medicine with SAHPRA, Johnson & Johnson could proceed with a so-called 'rolling' application with SAHPRA. A rolling application means that Johnson & Johnson could proceed with determining the long-term effects of its vaccine, while the Sisonke open-label programme allowed the SA government to make this vaccine immediately available to healthcare workers. Because the safety and efficacy of the vaccine had already been clinically proven, SAHPRA could in the meantime continue to process the approval and registration of the vaccine. It is important to note that the Sisonke programme was indeed a clinical trial, described as an 'open label, single-arm phase 3b vaccine implementation study of the investigational single-dose Janssen COVID-19 vaccine candidate [which] aims to monitor the effectiveness of the investigational single-dose Janssen (Johnson & Johnson) vaccine candidate at preventing severe COVID-19, hospitalisations and deaths among healthcare workers as compared to the general unvaccinated population in SA'.[17] What looks like and is known as pre-market approval access is still presented and regulated as an investigational medicine and part of a clinical trial in SA.

The consent requirements for access to medicine subject to a rolling or pre-market approval registration application rest between those of a registered medicine and a clinical trial. This Johnson & Johnson vaccine has already passed safety, efficacy and dosage testing in phases I to III of the clinical trial process. The only outstanding requirement was to obtain formal approval and registration from the relevant regulatory authority. Medical practitioners could advise patients regarding the safety and efficacy of the vaccine, but had to inform patients that the long-term effects of the vaccine had not been tested yet, and that the vaccine was still subject to regulatory approval. Long-term effects and adverse events may still occur, even after safety and efficacy have been positively tested. The AstraZeneca vaccine, for example, has passed safety and efficacy testing, but has been suspended and investigated after cases of blood clots and thromboembolic events were reported by patients after receiving the vaccination.[18]

Functional informed consent

It is important to differentiate between institutional or the legal form of informed consent, also known as effective consent, and informed consent as a symptom of respecting the autonomy of the patient. According to Beauchamp and Childress,[19] effective consent defines the 'social rules of consent that must obtain legally valid consent from patients and subjects before proceeding with therapeutic procedures or research.' Seen in this light, the SA social rules of informed consent,

as provided for in the above discussed laws and regulations, do not necessarily amount to an act of autonomy, as they require the components of competence and disclosure, which constitute a much narrower focus than the philosophical model of consent that includes understanding and being properly informed in addition to competence and disclosure.

Even the World Health Organization advised that it can be 'ethically appropriate to offer individual patients experimental medicine interventions on an emergency basis outside clinical trials, provided that no proven effective treatment exists; it is not possible to initiate clinical studies immediately; the patient or his or her legal representative has given informed consent; and 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'.[20] Access to unproven, experimental treatments is ethically allowed in the presence of the listed circumstances and subject to compliance with national laws. To obtain such ethical informed consent, care must be taken to ensure that the patient understands these listed circumstances, and this additional informational requirement is indicative of the broader focus of ethical consent as opposed to legal consent.

A purely legal approach to informed consent, especially when dealing with the medical uncertainties of health emergencies and pandemics, may lead to patients' consent lacking in enough substance to be truly considered legal and ethical. Informed consent as respect for autonomy in this sense requires more than the patient's explicit agreement or compliance with a certain treatment proposal.

Conclusion

Obtaining adequately informed consent for access to off-label, experimental or pre-market approved medicine in a desperate attempt to save lives and livelihoods during a health pandemic, which consent withstands legal and ethical scrutiny, is no easy task. Not only does the content of the consenting process change with the fluid information available on vaccines in development and the emergence of new virus variants, but the medical deterioration of the patient and people's natural failure to recall important information such as risks and complications constantly change the information that is required to be disseminated to enable a patient to exercise ethical and legal informed consent. An exhaustive list of information points will therefore serve no purpose, as this will also need to change constantly. The following topical issues, in addition to standard information for purposes of obtaining informed consent, must be explained, and can serve as a practical guideline for use specifically during a pandemic:

- the registration status of the medicine and/or stage of clinical testing or development
- the known characteristics of the medicine and what should be known about the medicine under normal circumstances, but is still subject to clinical testing
- the availability, or not, of alternative treatments that are proven to be effective and safe
- the stage at which the patient is receiving the medicine, and what is known about the effects of medicine and what must still be established
- the known and predictable outcomes of taking the medicine, and an explanation of the uncertainties surrounding the effects of the medicine when administered for the pandemic-causing disease
- the fact that emergency use of the intervention is monitored on a continuing basis, with results documented and shared in a timely manner with the wider medical and scientific community
- the involvement of bioethicists in the consent process to ensure proper information dissemination and facilitate the communication process with patients, when medical practitioners are usually inundated by the influx of newly infected patients.

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