MEDICINE AND THE LAW

Research on COVID-19 in South Africa: Guiding principles for informed consent

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Research is imperative in addressing the COVID-19 epidemic, both in the short and long term. Informed consent is a key pillar of research and should be central to the conduct of COVID-19 research. Yet a range of factors, including physical distancing requirements, risk of exposure and infection to research staff, and multiple pressures on the healthcare environment, have added layers of challenges to the consent process in COVID-19 patients. Internationally, the recognition that consent for COVID-19 research may be imperfect has led to a range of suggestions to ensure that research remains ethical. Drawing on these guidelines, we propose a consent process for COVID-19 research in the South African context that combines individual consent with delayed and proxy consent for individuals who may be temporarily incapacitated, combined with key principles that should be considered in the design of a consent process for COVID-19 research.

S Afr Med J. Published online 5 June 2020. https://doi.org/10.7196/SAMJ.2020.v110i7.14863

During public health emergencies and disease outbreaks such as the COVID-19 pandemic, there is a moral and ethical obligation to conduct research. Research may help in better understanding the mechanisms and epidemiology of disease, population dynamics, optimal therapeutic approaches, protection for those who are most vulnerable, and prevention of future outbreaks.[1] A key pillar of research is informed consent, which should be paramount in the conduct of COVID-19 research. Yet seeking informed consent may be difficult, particularly if the outbreak reaches that phase of the pandemic at which demand exceeds available resources (including personal protective equipment, medication, intensive care beds, ventilators and specialised equipment, and healthcare workers to use and operate them). Researchers' ability to seek informed consent may also be compromised by pandemic-mitigating measures such as lockdown and physical distancing policies, and by the nature of the patient's illness. Taken together, there may be circumstances in which the consent that is sought is imperfect.

Valid informed consent is consent that is informed, given voluntarily by a competent person.[2] To achieve this type of consent, one would normally expect the consent process to be conducted without time pressure, in a calm and confidential environment, where a prospective participant is able to ask questions and is given time to consider the request for participation. During the COVID-19 pandemic, several or all of these conditions may be compromised. For instance, if hospitals are overwhelmed by COVID-19 patients, it may not be possible to conduct informed consent processes in a calm and confidential environment. Similarly, physical distancing requirements may mean that consent processes are performed telephonically or electronically.

Internationally, the recognition that consent for COVID-19 research may be imperfect has led to a range of suggestions for ensuring that research remains ethical. For instance, some regulators have allowed certain kinds of research – such as research involving patient data – to be conducted without consent.[3] In other cases, there have been adaptations in the way in which informed consent is obtained. In this article, we describe international guidance and suggest a local approach to informed consent that continues to respect the autonomy of vulnerable participants while also enabling research that has social value.

International guidance for informed consent during epidemics

Following the 2002 - 2004 severe acute respiratory syndrome (SARS) and 2014 - 2016 Ebola outbreaks, several international initiatives focused on developing ethics guidance for research conducted during public health emergencies.[1,4,5] There is also additional guidance for research conducted on participants with COVID-19.[6-8] Together, these documents endorse, as a first principle, that informed consent is required for research participation in epidemics in all but exceptional circumstances. The way in which informed consent is collected during outbreaks must be aligned with how informed consent is collected in normal (non-emergency) times. The argument is predicated on the view that urgency of the moment does not justify eroding standards of ethical research conduct. However, as a second principle, these documents recognise that practical and ethical considerations relating to the particular circumstances may mean that the consent process requires 'adaptation'.[9]

Adapting the consent process: Proxy, delayed and waived consent

Deliberations on informed consent adaptations during COVID-19 must include consideration from *whom* consent is sought, *when* consent is obtained, *whether* it is obtained at all, and *how* it is obtained.

Regarding *when* consent is obtained, researchers should explore with research ethics committees (RECs) the use of delayed (or deferred) consent, commonly used where research involves participants who may be temporarily incapacitated but are likely to recover, and where obtaining research samples and data is time-sensitive.[10,11] This may be the case in persons with severe COVID-19 who are likely to recover. Where a delayed consent model is used, arrangements need to be made for individuals to be contacted at a later stage to secure their retrospective approval for ongoing research participation and/or sample and data storage for future use.[4]

Considering *who* consent is obtained from, in cases where capacity to give informed consent is compromised, researchers should consider proxy consent. Proxy consent is consent from a person's next of kin before the start of research procedures, and is often used where research involves people with reduced capacity to consent where their inclusion is ethically justifiable and there is either a favourable risk-to-benefit ratio or a favourable risk-to-generalisable knowledge ratio, where benefits or generalisable knowledge outweigh potential harms.[12,13] Where no statutory proxy is available, the National Health Act No. 61 of 2003[14] specifies the sequence of legally appropriate treatment proxies as the spouse or partner, parent, grandparent, adult child, brother or sister. Always, the 'best interest' principle should be upheld – research should only be conducted where participation is not contrary to the individual's best interest. Once capacity is regained, the participant should provide delayed consent for ongoing research participation and/or the storage and future use of samples and data.

With regard to *whether* consent is obtained at all, there may be certain instances in which RECs may be approached for a waiver of informed consent.[15] RECs may approve such a request, for instance where research involves retrospective record review, or the proposed use of anonymised data or samples stored in a repository created for non-research purposes. RECs may approve a waiver of consent for secondary use of data or samples if the research involves no more than minimal risk of harm, if the waiver would not adversely affect participants' rights and welfare, and if the research could not practically be carried out without the waiver.[9] Where a waiver of informed consent is sought from an REC, the justification provided needs to be aligned with normal considerations during non-emergency times, including whether the risk is considered acceptable, that the research has social value for the community involved, and an explanation that the research cannot be done in any other way, or with other participants.

In terms of *how* consent is obtained, suggested adaptations include consideration of the kinds of information that are provided, how or when the proposed study is explained to participants, and how and when consent is recorded. COVID-19-specific recommendations include increased use of electronic and telephonic means to explain studies and/or capture consent, often in the presence of an impartial witness.[6,7]

Proposed consent decision flowchart

Drawing on available guidance and considering the South African (SA) research environment, we propose a blended approach to informed consent for COVID-19 research that combines the range of consent models described above (Fig. 1). We propose that researchers always seek individual informed consent from patients who have the capacity to consent and where this is practically possible (considering research staff availability and risk of contamination). Where the patient lacks capacity to consent, researchers should seek remote telephonic or electronic proxy consent from the patient's next of kin, combined with delayed consent from patients who recover. If the patient dies, we propose that unless permission to remove samples and data was included in a person's will, researchers should first seek proxy consent from 'the spouse, partner, major child, parent, guardian, major brother or major sister of that person in the specific order mentioned' (section 62(2) of the National Health Act).[14] Where no proxy consent can be obtained, RECs may be approached to consider a waiver of informed consent for obtaining samples from a deceased patient, on a case-by-case basis.[16]

Practical considerations for seeking informed consent

Distinction between COVID-19 severe disease and competence to consent

COVID-19 affects more than patients' physical functioning: it may also affect their emotional, social and occupational functioning, as well as their competence to give informed consent. Objective clinical indicators are not enough to assess the overall effect of disease on competence. The conceptual boundaries between symptoms, disease severity, and health-related quality of life and competence are frequently blurred in practice. In all cases, an evaluation of an individual's cognitive abilities and understanding needs to be undertaken, regardless of the severity of illness. In other words, severely ill patients may still be able to give informed consent, and research staff should assess whether patients presenting with COVID-19 are able to understand the information provided and have the capacity to consent, as well as the ability to communicate their decision.

People seeking informed consent

During times of lockdown or in situations where individuals are encouraged to practise physical distancing, it may not be possible or desirable for research staff to be present at the research site. At the same time, it would be undesirable to rely on healthcare workers to conduct consent processes, particularly when the pandemic reaches 'crisis' proportions. Where it is not possible for research staff to personally seek informed consent, it may be possible to rely on healthcare workers to take on this task *if there is spare capacity* in the facility where the research is conducted. At no time may seeking informed consent undermine or endanger the quality of healthcare provided to the patients. Therefore, in situations where (*i*) it is not legal or safe for research staff to collect informed consent in person, and (*ii*) there are no spare healthcare staff available to seek informed consent, we suggest that researchers, where possible, seek telephonic or electronic consent from the patient, but that these be accompanied by more vigorous assessment of capacity to provide consent – in both written and alternative formats.

Recording informed consent

A challenge during the COVID-19 crisis is that the virus is highly contagious, so that there is not only a risk to the persons seeking consent, but also that the materials on which consent is recorded could be contaminated. This may apply not only to paper documents used to capture signatures, but also to any audio or video equipment used to record consent, such as mobile phones or voice recorders. These materials must be considered a biohazard, and measures should be put in place to safeguard the wellbeing of research staff and those who process and store samples. A range of alternatives have been proposed to deal with this challenge. For instance, the Food and Drug Administration in the USA has formally endorsed telephonic and electronic consent as an alternative to paper-based consent, provided that it is accompanied by efforts to seek delayed consent post-emergency.[7] The European Commission has adopted witnessed verbal consent, duly recorded, as an acceptable alternative.[17] Among these suggestions, what stands out is the importance of ensuring

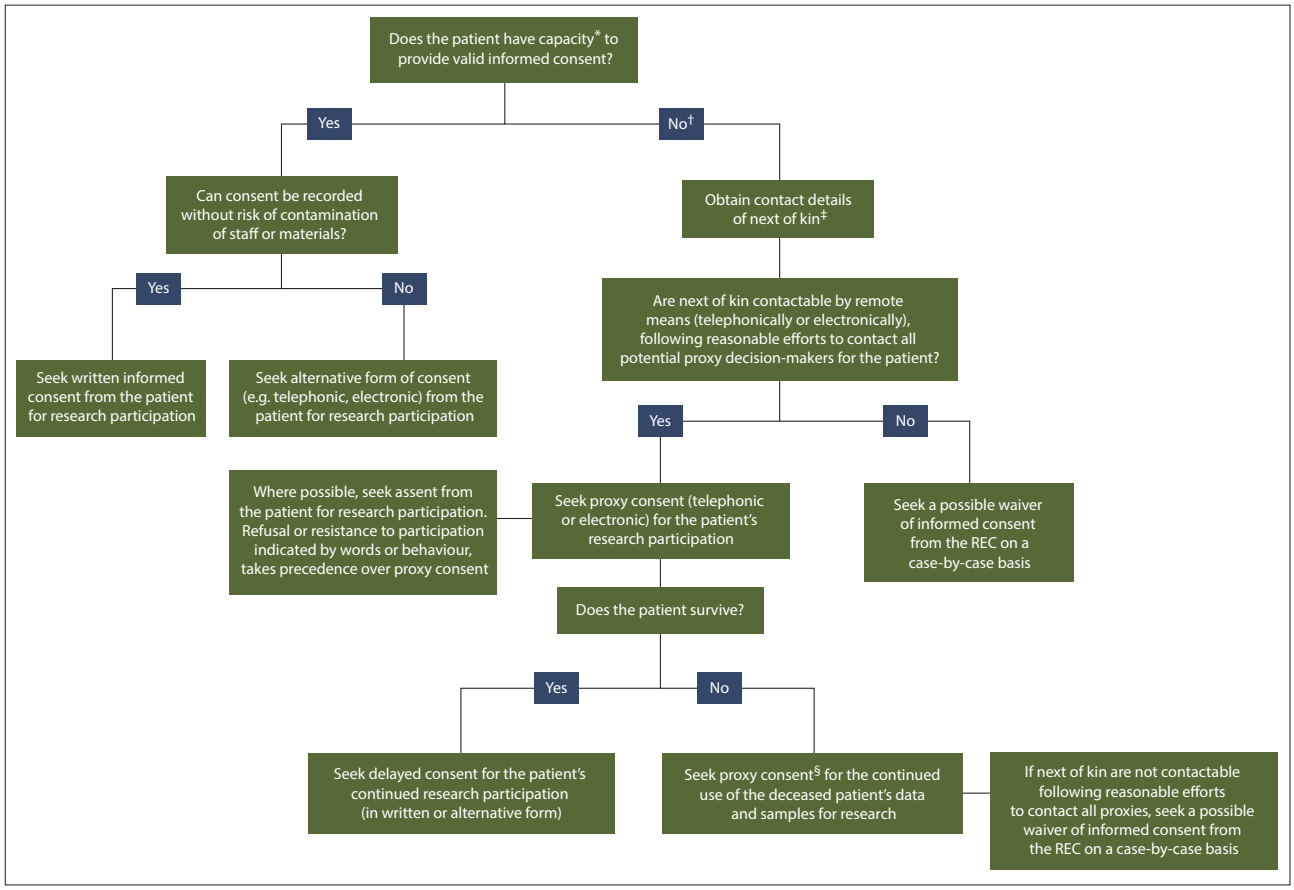

*Fig. 1. Example of a flowchart for consent process for COVID-19 research. (REC = research ethics committee. *It is important to determine whether the patient has both the capacity to decide whether to participate and the ability to communicate that decision.[9] For example, unconscious or severely ill patients would probably not have capacity to provide informed consent. Patients who are on ventilators may have capacity to give informed consent, but may not be able to communicate their decision. COVID-19 patients who are not in the intensive care unit would probably be able to provide informed consent. †Adults who are incapacitated should only take part in research when their participation is indispensable to the research, and a strong ethical justification must be provided for their proposed inclusion.[9] ‡Where no statutory proxy is available, but the ratio of risk of harm to benefit or generalisable knowledge justifies research participation, proxy consent may be ethically permissible. The National Health Act No. 61 of 2003[14] (section 7) specifies the sequence of legally appropriate treatment proxies as spouse or partner; parent; grandparent; adult child; brother or sister. §If no provision for research was made in the patient's will, proxy consent for the use of data and samples from a deceased individual should be obtained from 'the spouse, partner, major child, parent, guardian, major brother or major sister of that person in the specific order mentioned' (section 62(2) of the National Health Act).[14] Note that the order of decision-makers in the Act is slightly different when the patient is alive compared with when the patient is deceased.*

transparency and accountability, for detailing the various decisions made and for indicating how consent was obtained.

The 'ethics ecosystem' of research during emergencies

When designing a consent process for COVID-19 research, it is imperative to consider that informed consent is not the only way to ensure that people are treated as moral equals.[5] Where the consent process is imperfect, other elements of the ethics ecosystem of research need to be strengthened to ensure that the individual's moral agency is respected. Generally, three components of this ecosystem are identified, namely research ethics review, community engagement, and arrangements for the future use of samples and data.

Research ethics review

Robust scientific and REC review, albeit rapid, of proposed research studies is arguably even more important during times of crisis, particularly in situations where informed consent may be imperfect. As emphasised previously, the urgency of generating knowledge that could help address the pandemic is no justification for conducting research that is unethical, and RECs need to be extra vigilant to ensure that processes and procedures are acceptable and fair. This may involve ensuring that only research that has 'social value'[18] is acceptable. RECs need to be vigilant to ensure that, in cases where consent processes are less than ideal, researchers have strengthened other elements of research protection, including provisions for community engagement and comprehensive descriptions of whether samples and data will be retained for future use, how they will be shared, and whether there are any restrictions on future use.

Community and public engagement

A second key component of research that needs to be strengthened if consent may be imperfect is community and public engagement, which enable transparency, preventing an 'avoidance of information disclosure requirements' codified in the consent process.[19] Examples include presenting information on social media and conventional media such as local radio stations, newspapers and television broadcasts, especially in cases where in-person contact is not permissible. Where permissible, researchers should draw on existing engagement activities, seeking feedback on: (*i*) study rationale and

recruitment procedures; (*ii*) the proposed consent process, including proposals to deviate from gold standards or seek waivers for consent; and (*iii*) any other ethical considerations pertinent to the proposed research. Post-research, it is imperative that researchers communicate their study findings.

Future use of samples and data

Finally, where researchers intend to retain samples and data for future use and where the consent process was imperfect, RECs need to decide on the kinds of research these resources could be used for. In cases where adaptations to the consent process were justified by the urgency of the pandemic, it may be inappropriate to use resources for research that is unrelated to the pandemic. For instance, it would be unethical to use samples collected during the COVID-19 pandemic for broad population genomic studies or to interrogate questions completely unrelated to this condition. In line with current practice, researchers should outline plans and justifications for storage, sharing and future use in their application to the REC, and these need to be proportionate and justifiable, considering limitations of the consent process.

Conclusions

In SA, the right to give informed consent before participation in research is entrenched in the Constitution, and remains central to the conduct of research on COVID-19. In this article, we outline key principles for consideration in the design of consent processes for such research (Table 1). As far as possible, duly recorded individual informed consent will need to be collected before participants are enrolled in COVID-19 research, particularly when the research enrols healthy persons or where the pressures on the healthcare system are still manageable. If necessary, the consent process may need to be adapted for practical or safety concerns. This could mean turning to telephonic or electronic means to collect informed consent. Only in extraordinary circumstances – for instance, when patients' competence is compromised – may researchers consider proxy consent from next of kin for the collection of samples, with delayed consent being obtained from participants who survive. Seeking a waiver of informed consent is a last resort and needs to be fully justified to the research ethics committee. Where the consent process is compromised, other elements of the ethics ecosystem for research need to be strengthened. This includes strengthening rapid ethics review, ensuring broad communication about the study, and describing the limits on the future use of samples and data.

Table 1. Guiding principles for designing consent for COVID-19 research in South Africa

- It is imperative that research is properly designed, scientifically valid, and ethically conducted.
- For COVID-19 research, stringent but rapid ethics review is paramount. No research may be conducted without prior approval from a South African human research ethics committee registered with the National Health Research Ethics Council.
- Transparency and communication about research procedures (and the reason for them) is paramount, through the consent process and engagement activities.
- As a matter of course, researchers need to seek informed consent in line with conventional standards.
- Where necessary, the informed consent process may need to be adjusted taking practical issues into consideration. Where this is done, it needs to be properly justified to the research ethics committee when seeking approval. Adjustments to the consent process would only be allowed for research with social value that may potentially help to address the COVID-19 pandemic now and in the future,
- In exceptional circumstances, with full justification, researchers can seek a waiver of informed consent from the research ethics committee,
- Community and public engagement are paramount. Community and public engagement need to be robust, genuine (not tokenistic), long term and include a plan for post-pandemic communication about the research results and plans for long-term sample and data storage.
- A robust governance framework needs to be in place, which includes clear descriptions on whether samples and data will be stored and shared, who they will be shared with (with or without restrictions), and what they will be used for in future. 'COVID-19 research only' may be most appropriate in cases where consent was less than perfect,

Declaration. None.

Acknowledgements. JdV is supported by the National Human Genome Research Institute of the National Institutes of Health under Award No. U54HG009790. TB is supported by a scholarship from the Advancing Research Ethics Training in Southern Africa (ARESA): Leadership Program NIH Fogarty D43 award. NABN is supported by the National Research Foundation, the South African Medical Research Council and the Lily and Ernst Hausmann Trust.

Author contributions. All authors jointly conceived the ideas presented in this article and contributed equally to the writing process.

Funding. This article is not funded.

Conflicts of interest. None.

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Accepted 26 May 2020.