# Commentary: Ethical considerations for COVID-19 research

Under normal circumstances, it is accepted that we need strong scientific evidence to provide the best clinical care for patients. This is equally true in pandemic situations.

The World Health Organization (WHO) states, 'during an infectious disease outbreak there is a moral obligation to learn as much as possible, as quickly as possible, in order to inform the public health response and to allow for proper scientific evaluation of new interventions being tested'.[1] Furthermore, it has been stated that 'failure to improve outcomes through rigorous efficient investigations during the pandemic is as ethically irresponsible as failing to provide care itself'.[2]

As for non-outbreak situations, for research to be ethical, it must fulfil the following criteria:

1. scientific rigour
2. clear social value
3. favourable risk:benefit profile (to participants, the public, research and clinical staff)
4. fair selection of participants
5. respect for participants' autonomy, with voluntary participation and, except under exceptional circumstances, following an informed consent process
6. respect for the rights and wellbeing of participants (e.g. confidentiality/privacy issues)
7. independent review by an ethical oversight body.[3,4]

With respect to COVID-19, there is surveillance evidence from other countries, but very little yet from South Africa (SA) – as we know, there are considerable differences in countries' population profiles, burdens of disease, access to healthcare and other socioeconomic and environmental factors that could impact disease expression. The disease may look different here. As the local infection rate of the novel coronavirus is currently exponential, it is important to start collecting data as a matter of urgency across the country to inform public health policy, as well as start producing generalisable data. This ensures that the SA COVID-19 response is appropriate to and reflective of local context and need.[1] In addition to clinical trials of diagnostics and therapeutic interventions, surveillance and epidemiological research become invaluable in the immediate situation, particularly if emergency triage and rationing become necessary.[2,5] In the paediatric context of COVID-19, identifying predictors of early respiratory deterioration and progression of disease can help inform rational use of limited paediatric intensive care unit (ICU) resources.[2] Research on ways to decrease nosocomial transmission to other patients and healthcare workers should also be prioritised.[2]

From an ethical perspective, some confusion arises owing to the clear overlap between some public health and research activities. The only difference, in many cases, is the *purpose* of the data collection – research aims to produce generalisable data and generate or contribute to generalisable knowledge, while public health surveillance aims to benefit the population immediately, through controlling disease spread, and informing and improving health systems and processes.[6] The two approaches should, however, inform each other and wherever possible, be mutually beneficial. Certainly, research cannot be allowed to compromise the public health response. Therefore, it is imperative that duplication be minimised, and co-ordinated research undertaken.[1] In addition to the potential overlap between public health and research data collection, there is the risk of therapeutic misconception in pandemic research, where the participant may conflate research interventions (aimed at generalising knowledge and benefiting future patients) with treatment aimed at individual clinical benefit.[1] This is difficult to avoid in some situations, particularly where only unproven, experimental therapies are available, and may not always be a reason not to enrol the person. However, the researcher should acknowledge and mitigate this risk wherever possible.

Human research ethics committee oversight is essential to ensure that the rights, safety and wellbeing of vulnerable participants are protected. This is perhaps particularly important during the COVID-19 pandemic outbreak, where most infected patients (even those relatively mildly affected) can be considered to be vulnerable, owing to the associated high levels of psychological distress and even stigma associated with the infection.[7] ICU admission, critical illness and other factors (such as age, comorbid factors and socioeconomic circumstances) add to this complex vulnerability, with reduced levels of patient autonomy, along with challenges in obtaining proxy consent in a situation where the next of kin may not be permitted to be with their loved one in the ICU. Careful thought is needed in such cases to ensure optimal protection of participants' rights to autonomy in the context of time-sensitive critical care research.

Respect for persons and their autonomy is arguably one of the most important ethical principles, and is largely upheld through the requirement for informed consent prior to enrolment in research. Although *a priori*/prospective informed consent is the ideal for all prospective clinical studies, whether interventional in nature or not, there are acceptable circumstances where this model can be waived. However, waiving the need for prospective informed consent does *not* mean that *no* consent is ever needed. Investigators should try to obtain prospective consent from the participant or appropriate proxy wherever possible. This may be done directly, telephonically or verbally, depending on the situation, and hybrid approaches may also be considered, with multiple consent models within a single study.[2] Models of deferred consent may be appropriate for research in critically ill patients who may not have sufficient capacity to provide consent at the time of enrolment, and where proxies are not available or able to consent. Under these circumstances it may be appropriate to enrol the participant, collect the data, and when the participant/proxy/guardian regains capacity, obtain deferred consent to continue in the study and/or use the data already collected. We have argued previously that if a participant dies before deferred consent can be obtained, in some contexts these data could be used without consent, given that there is no further harm that can befall the participant, and there may be a feasibility issue in obtaining consent from next of kin, which predisposes to systematic bias affecting scientific validity.[8]

There is a proposal that completely different, communitarian, consent models may be considered in some cases of low-risk, observational emergency/disaster research. Ethics committee-approved COVID-19-related minimal-risk studies may allow participants to be enrolled without *a priori* written informed consent where there has been community engagement and agreement. In some communities, sufficient (saturated) public notification, by community consultation, print, audiovisual, or web media, for example, could publicise enrolment in observational studies as the default, with opportunities available to

opt out.[2] This approach may be worth considering in consultation with research ethics committees.

The balance between individual risk and public benefit in disaster research has to be carefully considered. The WHO supports the statement made by Sumathipala[9] that, although disaster research may help future patients and inform management, 'urgency should never excuse exploitation'. Ethical review aims to balance the ethical principle of autonomy and the individual right to information and privacy against issues of social justice and population ethics.[2]

Pandemic research is, by its nature, time-sensitive, both in terms of the protocol development process and dual ethical and scientific review, as well as needing to recruit participants in a narrow time window. SA research ethics committees have come together at this time, and are committed to conducting accelerated reviews for all study protocols relevant to the pandemic.[2] This does not mean that clinical trial protocols are being expedited, but rather subjected to full ethical review with very tight deadlines. Ensuring due ethical process, even in the face of emergency research is essential, as is clear from the changing face of chloroquine and hydroxychloroquine for the treatment of COVID-19. Chloroquine and hydroxychloroquine initially seemed to be very promising in reducing the severity of COVID-19; however, equipoise may now have been lost. An article published in *The Lancet* reporting results of a multinational registry analysis of almost 100 000 patients showed harm (significantly increased mortality and ventricular arrythmia) and no clear benefit associated with this drug, particularly when combined with a macrolide.[10] In this issue of the *SAJCC,* Zarrouki *et al.*[11] present a letter to the editor highlighting the potential dangers of using unproven drugs in critically ill patients. There is a clear need for high-quality evidence of therapeutic and safety equipoise, along with mitigation strategies to minimise the risk of harm of experimental products used in clinical research. Mehra *et al.*[10] also highlight the importance of developing multisite national and multinational registry collaborations to enable rapid accumulation of 'big data' to inform both clinical research and practice.

In summary, critical care research during the COVID-19 pandemic is in itself an ethical imperative, but the ethical conduct of these studies must be held to the highest standards. This is achievable through collaboration, co-ordination and continued engagement with ethics oversight bodies.

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