

## MEDICINE AND THE LAW

# Consent for critical care research after death from COVID-19: Arguments for a waiver

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Pandemics challenge clinicians and scientists in many ways, especially when the virus is novel and disease expression becomes variable or unpredictable. Under such circumstances, research becomes critical to inform clinical care and protect future patients. Given that severely ill patients admitted to intensive care units are at high risk of mortality, establishing the cause of death at a histopathological level could prove invaluable in contributing to the understanding of COVID-19. Postmortem examination including autopsies would be optimal. However, in the context of high contagion and limited personal protective equipment, full autopsies are not being conducted in South Africa (SA). A compromise would require tissue biopsies and samples to be taken immediately after death to obtain diagnostic information, which could potentially guide care of future patients, or generate hypotheses for finding needed solutions. In the absence of an advance written directive (including a will or medical record) providing consent for postmortem research, proxy consent is the next best option. However, obtaining consent from distraught family members, under circumstances of legally mandated lockdown when strict infection control measures limit visitors in hospitals, is challenging. Their extreme vulnerability and emotional distress make full understanding of the rationale and consent process difficult either before or upon death of a family member. While it is morally distressing to convey a message of death telephonically, it is inhumane to request consent for urgent research in the same conversation. Careful balancing of the principles of autonomy, non-maleficence and justice becomes an ethical imperative. Under such circumstances, a waiver of consent, preferably followed by deferred proxy consent, granted by a research ethics committee in keeping with national ethics guidance and legislation, would fulfil the basic premise of care and research: first do no harm. This article examines the SA research ethics framework, guidance and legislation to justify support for a waiver of consent followed by deferred proxy consent, when possible, in urgent research after death to inform current and future care to contain the pandemic in the public interest.

*S Afr Med J* 2020;110(7):629-634. <https://doi.org/10.7196/SAMJ.2020.v110i7.14918>

As the COVID-19 pandemic exacts its toll with escalating morbidity and mortality in most major regions of the world,<sup>[1]</sup> the African continent waits in line to receive its share of viral mayhem. Despite prompt state action in which the South African (SA) National Department of Health (NDoH) invoked the Disaster Management Act 57 of 2002,<sup>[2]</sup> allowing several extraordinary containment measures to limit the spread of disease, the country may soon experience the worst public health crisis in its history. Researchers, clinicians, front-line health workers, captains of industry, politicians and civil society have rallied together to seek solutions intended to minimise illness and death.

Ethics deliberations during the early phase of the pandemic have focused on fair allocation of scarce resources – mainly beds in intensive care units (ICUs) with or without invasive ventilation.<sup>[3-7]</sup> While mechanical ventilation forms an integral part of international treatment guidelines<sup>[8]</sup> for the clinical management of COVID-19-related severe acute respiratory infection, it appears that traditional ventilation protocols may not benefit, and indeed may be harmful to, some mechanically ventilated patients.<sup>[9]</sup> Given the unexpected and unusual clinical expression of pulmonary disease in many patients presenting to critical care units, scientific research to guide clinical

decision-making has become imperative.<sup>[10]</sup> Although COVID-19 mortality is high in patients admitted to ICUs, autopsies are not being routinely conducted globally given the high associated risk, especially in contexts with severe shortages of personal protective equipment (PPE) and lack of biosafety-approved mortuary facilities.<sup>[11,12]</sup> It is the exception rather than the rule to see data of full autopsies to establish cause of death during this pandemic.<sup>[10,13-15]</sup> SA is no exception, with no published autopsy pathology data currently available.

A compromise could be collection of samples of lung tissue immediately after death in ICU settings to better understand the underlying pathology.<sup>[16,17]</sup> Scientific data collected in this manner could provide clues to the pathogenesis of mortality and thereby assist in the clinical management of future patients.<sup>[18]</sup> An argument for this type of research being in the public interest can hence be justified.

Pandemics or humanitarian crises challenge clinicians and scientists in many ways, especially when the virus is novel and disease expression becomes variable or unpredictable. Under such circumstances, research becomes critical to inform clinical care.<sup>[19-21]</sup> Despite this compelling research imperative, it is important that medical care and service delivery must always take precedence

over research,<sup>[22]</sup> especially if the crisis worsens. In resource-limited settings, research is often conducted by the same people who provide care and therefore 'rightly takes second place to the provision of life-saving assistance.'<sup>[23]</sup> In contrast, in resource-rich environments, there may be specific personnel assigned exclusively to research, so that critical human resources would not be diverted away from care.<sup>[24]</sup>

Assuming that there is both sufficient staff and time for research and care in SA and that all researchers involved in the project have PPE and training, this type of critical care research would be invaluable to inform the optimal management of the severe respiratory complications resulting from COVID-19. The research team would need to develop a detailed standard operating procedure to ensure efficient conduct of the planned research project, even in a busy ICU setting. The ethical conduct of research under normal circumstances would include obtaining voluntary informed consent unless unique circumstances make this impractical, impossible or even unethical.<sup>[25]</sup>

### ICU research often precludes a regular consent process

Conducting research on critically ill patients in an emergency room or ICU is not unprecedented and is possibly most needed due to inherent high mortality rates in this domain. Several important studies yielding important clinical data that have shaped and guided critical care practice have been conducted globally over many decades.<sup>[26-29]</sup> In anticipation, international research ethics guidance has made provision for such research, albeit usually in a living patient under relatively calmer circumstances.<sup>[30,31]</sup> SA is no exception. The 2015 guidance issued by the NDoH, *Ethics in Health Research: Principles, Processes and Structures*,<sup>[32]</sup> specifies in section 3.4.2 that ICU research may be characterised by communication challenges either due to ventilation or to cognitive impairment as a result of sedation. Under these circumstances, and 'wherever possible', consent for 'planned intensive care research should be obtained from potential participants before admission to that care'. Should this not be possible, in 'particular circumstances, the REC [research ethics committee] may approve delayed consent. Note this does not mean that informed consent is waived.' According to the guideline,<sup>[32]</sup> a delay in obtaining informed consent may be approved if:

- the research is based on valid scientific hypotheses that support a reasonable possibility of more benefit than that offered by standard care
- participation is not contrary to the medical interests of the patient
- the research interventions pose no more risk of harm than that inherent in the patient's condition or alternative methods of treatment
- as soon as reasonably possible, the participant and his/her relatives or legal representatives will be informed of the participant's inclusion in the research, be requested to give delayed consent, and be advised of the right to withdraw from the research without any reduction in quality of care. This clearly applies to a living person.

### Guidance on research during pandemics

Although the national guidance<sup>[32]</sup> does not refer to pandemics directly, they are included in section 3.4.1 as 'major incidents' and include 'any sudden event that occurs where local resources are constrained, so that responding urgently and appropriately is difficult', including in the context of outbreaks of deadly disease. A major incident 'may take the form of an unusual and sudden demand on local resources or other emergency with consequent

ethical implications for patient care'. In such contexts, research would be 'important for advancing emergency health care interventions and treatments, and for refining resource allocation policies'. The potential benefits of major incident research include 'improved triage methods and procedures, effective treatment for life-threatening conditions and improving therapies for survival and quality of life'. Despite the extreme vulnerability of patients in such contexts, the guidance advises that RECs should be 'cautious about being overly restrictive about the type of research that may be conducted'. This is complicated by the fact that proposals for major incident research usually demand expedited processing, which would reduce the time available for thoughtful deliberation by the REC. It is acknowledged that informed consent will have to be obtained quite rapidly and at a time when 'vulnerability of patients and families is likely to be extreme'. Patients may be incapacitated (i.e. unconscious or on a ventilator), which points to the likelihood of difficulties with the usual approach to informed consent. Consequently, RECs may consider 'alternative approaches such as proxy consent or delaying consent in particular circumstances'. Here too the guidance applies to living patients and families, although their extreme vulnerability is acknowledged.

### Surrogate decision-makers or proxy consent for persons who lack capacity

In section 3.2.4.3 of the national research ethics document,<sup>[32]</sup> guidance is provided for the conduct of research in adults incapable of giving adequate informed consent. The guidance highlights the legal position in SA where 'proxy decision makers are not permitted for adult persons who lack capacity unless the proxy is a court-appointed curator'. While the National Health Act 61 of 2003 and the Mental Health Care Act 17 of 2002 make provision for proxy decision-makers for treatment, they do not refer to proxy decision-making for research. However, since the guidance argues that it would be 'unethical to exclude a category of persons from research participation without adequate justification', an ethical argument could be made for using the statutory treatment proxies to provide permission for participation in research that complies with specific stipulations. In unusual circumstances, e.g. major incident research (see section 3.4.1), it may be ethically acceptable to permit proxy consent also in a situation where no statutory proxy is available but the ratio of risk of harm to knowledge justifies it. In particular circumstances, the REC may approve delayed consent. Again, the guidance cautions that this does not mean that informed consent is waived. RECs should ensure that a clear and full justification for the proposed delay accompanies the research proposal. The individual circumstances of the patient must be carefully considered to prevent inadvertent violation of personal or cultural values. The REC may approve a delay in obtaining informed consent for emergency care research if the conditions specified above are met. Again, there is a presumption that the patient is alive.

### Seeking consent after death

The term most commonly used in respect of consent from proxy decision-makers after death is 'next of kin'. This terminology has its origin in Roman law and was used to apportion property between male relatives of a family. It became irrelevant in the UK when the Estates Act of 1925 was used for this purpose.<sup>[33]</sup> However, the term is widely used in the medical setting in SA and elsewhere. Some argue, using the definition of next of kin to include blood relatives only,<sup>[34]</sup> that it may be confusing in traditional extended families and communities where, contrary to conventional practice, the spouse

may not be regarded as 'next of kin'. In SA, information disclosed after the death of a patient may be disclosed with the consent of the next of kin or the executors of the patient's estate. There appears to be general agreement that the law in SA does not specify who next of kin is.<sup>[35]</sup> However, medical practitioners in SA rely on the National Health Act (NHA),<sup>[36]</sup> chapter 2, section 7, which specifies acceptable decision-makers in cases where a patient is unable to consent while alive. The hierarchy of surrogate decision-makers in the NHA is as follows: 'the spouse or partner of the user [patient] or, in the absence of such spouse or partner, a parent, grandparent, an adult child or a brother or sister of the user [patient], in the specific order as listed'. As such, the spouse or partner is often consulted first even after death.

While respect for autonomy is narrowly interpreted in an individualistic society that defines a person as rational, autonomous, individual and separate from others, other notions of personhood exist, especially in some sub-Saharan African contexts including SA. More traditional notions of personhood are relational, communitarian and extended.<sup>[37]</sup> The family and community are regarded as the moral agent because the family is regarded as the most important aspect of identity. Given this cultural diversity in SA and its impact on healthcare and the lack of definition of next of kin in the law, it is important to explore the meaning of next of kin in different cultural contexts. This may have relevance after death too.

### Collection of biological material from deceased persons

SA law recognises the importance of posthumous bodily integrity. In chapter 8 of the NHA,<sup>[36]</sup> section 62(2) specifies proxy consent, but the hierarchy after death differs from that during life. 'Spouse, partner, major child, parent, guardian, major brother or sister', in that order, may donate 'specific tissue' to an institution or person.<sup>[36]</sup> If these family members are not located, the Director-General of Health may authorise the use of the tissue, provided the 'prescribed steps' are taken to locate the person authorised to consent.<sup>[36]</sup> While these steps are not detailed in this section of the Act, other sections relating to donation of tissue for genetic testing, *inter alia*, describe the steps as follows: the Director-General of Health would need to obtain 'the name, address and telephone number of the spouse, partner, major child, parent, guardian, major brother or major sister of the deceased person from: (i) any person working in the relevant hospital, institution or facility where the deceased died; or (ii) any person who visited the deceased before he or she died'.<sup>[36]</sup> Legal expert advice is 'that these steps should also be followed for other donations of human tissue by the Director-General under the National Health Act'.<sup>[38]</sup> Clearly, this can be a lengthy process that will not be practical in a public health crisis.

In chapter 8, section 66, the NHA refers to postmortem examination of bodies. Here, either the patient may have given consent while alive or, in the absence of such consent, spouse, partner, major child, parent, guardian, major brother or sister – in that specific order. In the absence of such surrogates, section 67 refers to removal of tissue at postmortem examination and obtaining of tissue by institutions and persons. Subsection 1(a) indicates that the Minister of Health may authorise such removal of tissue for specific purposes including medical research, or a medical practitioner in charge of clinical services in a hospital (superintendent or chief executive officer, it is presumed) may authorise tissue removal for similar purposes, provided that the removal would not be contrary to 'a direction given by the deceased before his or her death'.<sup>[36]</sup> (NHA).

In terms of the Disaster Management Act,<sup>[2]</sup> COVID-19 has been declared a notifiable condition. Section 14 of the gazetted regula-

tions of chapter 3 of the NHA relating to the surveillance and control of notifiable medical conditions<sup>[39]</sup> specifies the following in regulation 2:

- '(a) A case or carrier of a notifiable medical condition ... or a medical condition deemed to be notifiable by the Minister, must subject himself or herself to further medical examination;
- (b) The medical examination referred to in sub-regulation (a) may include but is not limited to a clinical examination followed by the taking of biological specimens necessary for laboratory confirmation.' This applies to a living person.

In the event of death, section 15 of the regulations indicates that 'the head of a provincial department must apply to a High Court for an order to conduct an autopsy on the body of a patient who has presumably died of a notifiable medical condition, in order to ascertain the exact cause of death, and only where this is in the interest of public health and is on special request by an interested person'.<sup>[39]</sup>

The 2015 NDoH research ethics guideline,<sup>[32]</sup> in respect of the collection of biological material for research after death, allows for proxy consent when a patient or donor is unable to consent (section 3.3.6) or in the absence of a will or written statement of a deceased person. However, proxy consent in an ICU setting with a highly contagious and life-threatening disease has the potential to cause harm.

### Considering potential harm

Due consideration should be given to potential harm that could stem directly from the informed consent process. Two scenarios are envisioned: either patients admitted to the ICU are asked to consent to the use of their biological samples should they die during their ICU stay, or the family are asked to provide proxy consent either prospectively or after the death of the patient. Both scenarios are problematic. In the first instance, the patient may be incapacitated by the underlying medical condition, severe pain or sedation, all of which may preclude obtaining truly informed consent.<sup>[40]</sup> Studies have estimated that only 10% of critically ill patients have sufficient decisional capacity,<sup>[41,42]</sup> while others have argued that it could be increased to roughly 50% if patients are assisted with communication.<sup>[43]</sup> Adequate communication may, however, be challenging in a setting where patients are infected with a highly transmissible pathogen, and staff are wearing PPE. Regardless, appropriate tools and adequate time and training would be needed to assess the decision-making capacity of such patients. This is not practical in the setting of contagion and acute respiratory distress. More importantly, the patient's probable anxiety and fear in the face of possible and even imminent death when admitted with a dread disease may be aggravated by discussion of the post mortem collection of their samples.<sup>[40]</sup> It is also true that only 26 - 61.5% of the patients with COVID-19 admitted to the ICU will die, although it is currently not possible to predict death accurately in the absence of validated prognostic criteria.<sup>[44,45]</sup> The consent discussion will therefore not only be unnecessary, but also not hold out the potential for any benefit, for a large proportion of patients. So, while it is possible that some patients could have the capacity to consent, it can be argued that such a discussion could be harmful to patients in distress, especially in the ICU setting where family and counselling support will not be available.

The second scenario poses problems of obtaining consent from family members who are either distressed by 'the emotional, psychological and logistic impact of the sudden hospitalisation'.<sup>[40]</sup>

or in a state of bereavement after the death of a loved one. The psychological stress of having a family member in an ICU is known to result in anxiety (present in up to three-quarters of family members) and depression (in about a third),<sup>[46,47]</sup> learned helplessness,<sup>[48]</sup> and acute post-traumatic stress disorder.<sup>[49]</sup> Distress and grief can distort cognition and impair family members' capacity to critically evaluate the proposed research.<sup>[50]</sup> Some regulations therefore include the requirement that 'a senior clinician supported by a staff member with appropriate skills in grief and bereavement counselling', with the help of an interpreter when needed, obtain consent.<sup>[51]</sup> This approach has also been supported by researchers, based on the argument that bereaved family members should be formally recognised as a vulnerable group owing to diminished autonomy in the context of profound grief.<sup>[52]</sup> Moreover, concerns have been raised that family members may not be the best proxy decision-makers in such a setting. Studies comparing surrogate and delayed consent have reported discrepancies between the wishes of the surrogate and the patient of 16 - 20.3%, depending on the risk level of the study.<sup>[53,54]</sup>

Finally, the scientific integrity of the study could be harmed. Time constraints and workload pressures in a busy ICU may make obtaining adequately informed consent unfeasible.<sup>[40]</sup> For instance, a prospective observational study of research recruitment practices in 23 adult ICUs across Canada showed that consent was missed in 28.8% of eligibility events and that operational reasons prevented consent in a further 28.5% of cases.<sup>[41]</sup> This non-inclusion of eligible patients could introduce bias in studies or limit the generalisability, and hence the scientific value, of the results, as well as delaying needed study conclusions by delaying recruitment.

### Waiver of consent and deferred proxy consent for obtaining postmortem specimens?

Early publications relating to respiratory distress syndromes emerging from China, where the pandemic started, indicate that written informed consent was waived by the ethics regulatory authority,<sup>[18]</sup> or the authors do not mention whether consent was obtained at all, just that the study was conducted in keeping with the Declaration of Helsinki.<sup>[16]</sup> Article 30 of the Declaration discusses research with participants who are not able to provide informed consent. This includes unconscious patients. While obtaining consent from the legally authorised representative is advised, 'if no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.'<sup>[55]</sup>

Other international regulations and guidelines also allow for a waiver of consent for emergency research under very specific circumstances. For instance, the US Food and Drug Administration<sup>[31]</sup> in regulation 21 CFR 50.24 and the conforming amendments contained in 21 CFR Parts 56, 312, 314, 601, 812, and 814 provides a narrow exception to the requirement of obtaining informed consent from patients or legally authorised representatives prior to enrolment in emergency research. Pertinent conditions that have to be met include that the patient must be in a life-threatening situation, obtaining consent is not feasible, there is a chance of direct benefit for the participant, and the research cannot reasonably be carried out without the waiver.<sup>[56]</sup>

Assuming that the principles of beneficence and non-maleficence were met during life, and that the limited collection and storage of

specimens obtained after death have the potential to directly inform the care of future patients, and where scientific reasons mandate that such collection should not be delayed (such as degradation of histology specimens), the question of a waiver of consent needs to be considered. Naturally, immediate or antemortem consent by a legal proxy would be ideal, unless this causes harm. However, in the context of COVID-19, the majority of clinical situations do not allow relatives to be present at the bedside or in hospitals. The delayed acquiring of consent would be likely to imply one of two situations. First, the collection of specimens should be delayed until proxy consent is obtained. If delays in obtaining consent are lengthy (e.g. more than a few hours), this situation could jeopardise the scientific quality of samples obtained, thereby negating the ethical validity of performing the study at all. Second, the specimens could be obtained at death, and delayed consent obtained at a later point by a proxy. This would preserve the scientific validity of the study, but acceptability to the proxy in certain instances may be unpalatable and is unknown. A possible mitigating strategy could be ensuring that delayed consent is conducted in a quiet and private environment where bereavement counselling and support are available.

Nevertheless, the ethical principles of autonomy, non-maleficence and justice once again come head to head: does collection of specimens after death for the 'greater good' of research to inform the treatment of future patients supersede the autonomy of the deceased? This is a difficult area, especially in the era of COVID-induced limitations of personal contact with relatives. Where collection of samples does not jeopardise the scientific process, or other unnamed ethical factors (e.g. delay in turning around a critical care bed), then delayed proxy consent would appear best. However, where timeous collection of specimens is required, obtaining immediate consent exposes the proxy to the trauma of having to simultaneously process news of death and consider the societal importance of obtaining such samples. On the other hand, a waiver of consent may appear to override the wishes of the proxy regarding the posthumous integrity of their relative. This is an unprecedented situation. Future patients need to be protected from unnecessary mortality by a better understanding of disease. Does this need supersede the individual rights of those unfortunate individuals who have succumbed to the infection?

### Engaging communities as part of consent processes

In general, early and continuous community engagement (CE) is an integral part of regular research projects.<sup>[56]</sup> The FDA regulations only allow for a limited waiver of the need for consent when additional protections of the rights and welfare of participants are in place. These include consultation with representatives of the communities in which the clinical investigation will be conducted and from which participants will be drawn; public disclosure of the research, including potential risks and benefits; and public disclosure of the results and the demographics of the study after its completion.<sup>[31]</sup> CE is also promoted by the Nuffield Council on Bioethics, which has called for investment into such mechanisms in emergency research 'to make them a reality'.<sup>[57]</sup> As part of the eight-step approach for CE described and strongly encouraged in the Tygerberg Research *Ubuntu*-inspired Community Engagement (TRUCE) Model, co-creation of knowledge production and co-development of CE material with communities are important.<sup>[58]</sup>

However, in emergency or urgent research conducted during COVID-19, when access to communities is limited during lockdown under the Disaster Management Act owing to the highly contagious nature of the disease, contacting community members, creating

community advisory boards and engaging early with communities is challenging. At best, CE can be attempted using social media and community newspapers in areas where these are still operating. For example, CE educational videos on research in general can be developed to assist communities to better understand the importance of research during this pandemic, including the possibility that samples of blood and tissue will be taken to learn more about COVID-19 and will be approved by an REC.

## Conclusions

While a waiver of consent is reserved for extraordinary circumstances involving emergency research in global and SA research ethics guidance, none of these documents speaks to the unique scenario created by the current COVID-19 pandemic, where ICU research and histopathological diagnosis are critical to inform current and future care and are in the public interest. Given the challenges outlined above, it is clear that obtaining written informed consent in the context of critical care research during COVID-19, either before or after a patient has died, will not be feasible. Proxy consent when the family is contacted telephonically to inform them of the death of the patient would not only be impractical but, worse still, insensitive, especially if linguistic and cultural differences exist regarding end-of-life beliefs and etiquette. This dilemma leaves researchers with little choice. Interpretation of the existing guidance in combination with SA legislation around notifiable diseases and obtaining biological samples for research after death provides some justification for a waiver of consent for the intended research, followed by deferred proxy consent at a later stage, as the most ethical route to follow.

**Declaration.** None.

**Acknowledgements.** We thank the Tygerberg ICU team for insights into the practicalities of conducting research during COVID-19, and Dr Anke Nitzsche, medicolegal advisor, Western AllCape Health, Cape Town, for legal insights into the Disaster Management Act and regulations related to the National Health Act.

**Author contributions.** KM wrote the first draft and conducted an initial and continual literature search. BWA conceived the idea for the research project, assisted with the literature search, read and approved all versions and checked references. TMR contributed to early discussions around national guidance, contributed to the article, added references and read and approved all drafts.

**Funding.** None.

**Conflicts of interest.** None.

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Accepted 18 May 2020.