Consent in health research with incapacitated adults in a time of pandemic: The National Health Research Ethics Council needs to urgently reassess its guidelines

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In most instances, health research involves patients who are capable of giving informed consent, a statutory and ethical requirement. A smaller subset of patients lacking this capacity owing to their condition present an ethical problem, particularly because both the Bill of Rights of the Constitution of South Africa, and the National Health Act, require adult participant consent, without exception. Local research ethics guidelines, as a way of facilitating such research, suggest the use of a strategy combining proxy and delayed consent. Under conditions of a pandemic, research involving possibly large numbers of critically ill, incapacitated adults is likely. However, with lockdown restrictions, proxy decision-makers will not be available much of the time. Currently, local guidelines do not address the problem of what ought to be done in situations where incapacitated research participants die before being able to provide delayed consent for use of their research data. Under such circumstances, retention and use of such data is ethically justifiable based on the resultant public health benefits. The National Health Research Ethics Council needs to urgently reassess its consent guidelines in this respect.

S Afr J Bioethics Law 2020;13(1):29-33. https://doi.org/10.7196/SAJBL.2020.v13i1.727

Health research usually involves the participation of individuals who have the capacity to give informed consent, as both a statutory and ethical requirement. In South Africa (SA), both section 12 of the Bill of Rights of the Constitution[1] and section 71(1) of the National Health Act No. 61 of 2003[2] make prospective informed consent mandatory for all adult participation in health research. Research ethics guidelines published by the National Health Research Ethics Council (NHREC)[3] reinforce the primacy of informed consent as a requirement for research participation, but at the same time suggest a variety of strategies to facilitate research in situations where individuals do not have the capacity to give informed consent.

The importance of informed consent in research participation stems from its embodiment of the principle of respect for autonomy – one of the three ethical principles arising from the Belmont Report,[4] and later developed by Beauchamp and Childress[5] in their seminal text on bioethics. Autonomy is dependent on the conditions of liberty and agency, the latter implicitly recognising the importance of an individual's decision-making capacity. Capacity, in turn, is determined by an individual's ability to understand and evaluate the consequences of research participation, to make a decision and to communicate this. Capacity may be legally determined by age or, if age is not a factor (i.e. in those ≥18 years in SA), by the above abilities, and researchers' judgement of the extent to which a given individual possesses them. This can be a difficult task in some cases, where individuals may be in states representing subtle transitions between normal cognition and conditions that interfere with the understanding of information, evaluation of consequences and decision-making. Such states may be caused by pathological alterations in consciousness, behavioural disorders, medication and other substances, anxiety or pain.

Some individuals, suffering from a broad cross-section of conditions, may present less of a challenge when evaluating capacity for informed consent, because their level of consciousness is obviously depressed beyond a point where understanding and decision-making would reasonably be possible. The critically ill, who frequently experience significant derangements of normal physiology interfering with cognition, represent a small proportion of possible research participants in any healthcare system, but also an important one because of their vulnerability. Yet it is often in this same population that innovations in patient care are most needed, and stand to have significant benefits in reducing mortality and suffering.

The COVID-19 pandemic, while beginning deceptively slowly wherever it has taken hold, invariably leads to a very sharp increase in the number of cases and of those requiring hospitalisation, including critical care. This potentially severe burden on the healthcare system, together with movement restrictions imposed by lockdown regulations, poses a unique problem for research participation in the subset of patients who are incapacitated.

Informed consent and incapacitated adults as research participants: the current approach

Statutory requirements regarding informed consent for research participation in SA effectively rule out the possibility of including adults lacking the capacity to give informed consent. The NHREC

guidelines argue in section 3.2.4.3 that to apply this literally, and thereby exclude participants who may benefit from research, is unethical.[3] This argument is put forward on the basis that both the National Health Act and the Mental Health Care Act No. 17 of 2002 make provision for proxy decision-makers in cases of factual incapacity due to mental illness for treatment decisions. It is therefore suggested that 'an ethical argument can be made' for adopting a similar approach regarding proxy decision-makers as granters of permission for research participation in situations where adults do not have the capacity for informed consent (section 3.3.4.3) or in major incident research (section 3.4.1). The list and order of acceptable proxies are further recommended as those specified in either of the above Acts.

The NHREC guidelines also suggest the possibility of delayed consent as a strategy in research involving incapacitated adults, in section 3.2.4.3 (and in relation to major incident research, in section 3.4.1). Delayed consent, also sometimes referred to as deferred consent,[6] is consent obtained after the inclusion of participants in research and collection of data. Although the term is used widely, it is doubtful that this can correctly be referred to as consent, because in order to truly align with the principle of autonomy, informed consent must be given prospectively. It has therefore been suggested that the word 'consent' is inappropriate to describe this process.[7] Regardless of the terminology used, the practice of including incapacitated patients in research processes first and asking for permission later is an attempt to honour the principle of autonomy. Arguments supporting this approach rely on the assumption that these patients will at some point later in their clinical course be in a position to reasonably and meaningfully consider the question of further participation, and make an informed decision.

In suggesting proxy and delayed consent as strategies to facilitate the inclusion of incapacitated adults in health research, the NHREC guidelines specify a number of minimum conditions to be considered by research ethics committees (RECs). These conditions deal with four main aspects of the research: (*i*) that it should not be contrary to the best interests of the patient; (*ii*) that it should be associated with an appropriate level of risk; (*iii*) that a legally appropriate treatment proxy gives permission; and (*iv*) that the patient will in future assent to participation (meaning that delayed consent will be sought after inclusion). Inconsistencies and lack of clarity with the above conditions in the guidelines are discussed below.

- It is unclear whether prospective proxy permission for inclusion in research is an absolute requirement or not, and whether delayed consent alone (without the involvement of a proxy) is envisaged. In section 3.2.4.3, which deals with delayed consent, there is no direct reference to a proxy decision-maker, but an indirect reference to 'the participant and her relatives' being informed of the research retrospectively. In section 3.2.4.4 (iv), there is explicit reference to the requirement for permission from a proxy decision-maker in addition to a requirement in 3.2.4.4 (v) for 'assent to participation', which presumably means delayed consent. The situation where a proxy decision-maker may not be available for prospective permission is not dealt with explicitly.
- The definition of acceptable risk is unclear and of doubtful practical value for RECs to use in decision-making. Section 3.2.4.3 establishes conditions for delayed consent. The acceptable risk level is described as being equivalent to 'no more risk of harm than that inherent in the patient's condition or alternative methods of treatment'. However, in section 3.2.4.4 that follows, several other different descriptions of acceptable risk levels are given in situations where researchers wish to include incapacitated adults (including situations where delayed consent may be acceptable). The risk level suggested is minimal risk (described as an 'everyday risk standard') for research with no participant or future benefits, and 'greater than minimal' risk for research with possible benefits for either participants or future patients through the creation of generalisable knowledge. The acceptable increase of risk to 'greater than minimal' is described as only allowable if this is a 'minor increase', without defining what this means. Thus, the guidelines suggest two quite different levels of acceptable risk for application of what appears to be the same or a very similar consent strategy. In addition, vague and arbitrary terms to describe incremental increases in acceptable risk above minimal are used.

Notwithstanding the contradictory information above, the NHREC guidelines suggest a strategy for including incapacitated adults in health research involving permission from proxy decision-makers, together with delayed consent.

Limitations of proxy and delayed consent for health research in a pandemic

The existence and rapid evolution of a pandemic such as COVID-19 requires an equally rapid public health response, a key component of which is health research. While this research may cut across a broad spectrum of designs and methods, not all of which involve critically ill patients, it is conceivable that answers to some of the most important clinical scientific questions will necessitate the study of patients who lack the capacity to give informed consent. Given that severe forms of COVID-19 may progress rapidly, typically lead to severe pulmonary dysfunction requiring critical care admission and have no proven, effective treatment other than cardiorespiratory support, some of these incapacitated patients may be at a significantly increased risk of mortality. It is this subset of patients, who may benefit from innovative treatments or yield important data for future application, that are the focus of considerations in this section.

Limitations of proxy consent

Within the context of a pandemic such as COVID-19, reliance on proxy decision-makers is very limited in application. Under the restrictions of the lockdown, proxies would not be permitted into a healthcare facility. While it may be possible to contact proxies in ways other than direct contact in a healthcare facility, this would probably be complicated and take longer than the normal approach of direct contact. In situations where a research intervention or investigation is time-sensitive, requiring permission on or soon after emergency department arrival or critical care admission, it is highly unlikely that proxy permission would be obtainable (this is also often true under normal conditions). Therefore, of necessity, emphasis is likely to be placed on delayed consent, without prospective proxy permission, as a means of facilitating research under lockdown conditions.

Reliance on delayed consent in those who die

In a subset of critically ill patients who do not have capacity for informed consent, and where proxy permission is unlikely under

pandemic conditions of lockdown, delayed consent might seem to offer a viable consent strategy. While such a strategy is not in alignment with section 71 of the National Health Act, it is in alignment with the NHREC guidelines. However, the adoption of such a strategy is complicated by the understanding that some of these patients may die or not recover capacity to make a decision about further participation. The NHREC guidelines are silent about the legal and ethical position regarding further use of data obtained prior to such a death.

The ethical justifiability of delayed consent in the critically ill based on the principle of autonomy

Beauchamp and Levine[7] pointed out 40 years ago that the word 'consent' should not be used to describe this process. This was in response to the proposed use of deferred consent for research in a critical care unit. While the deferred consent referred to was proxy consent for incapacitated adults delayed by 48 hours due to the perceived psychological trauma of approaching proxies immediately for consent, this point is equally applicable to the concept of delayed consent referred to in the NHREC guidelines. Beauchamp and Levine highlight the meaning of consent as the refusal or acceptance by the individual affected by an activity or intervention in advance of its occurrence, with proxy 'consent' basically describing proxy permission. Thus the chronological order of events is absolutely fundamental to the meaning and conceptual validity of consent.

The focus here, however, is not merely the use or meaning of a particular word. It is the question of whether delayed consent allows research participants to adequately express their autonomy, which is the ethical principle underlying the process of informed consent. After all, it is the desire to uphold this principle in the face of an inability to know what the decision of an incapacitated patient might be that has produced the trade-off of delayed consent. If the answer to this question is that delayed consent does not allow participants to adequately express their autonomy, then the rationale for offering delayed consent as a viable consent strategy in guidelines, and for following this strategy in practice, must be questioned.

In considering the question above, it is necessary to reflect on what it means for a research participant to adequately express autonomy. Several different conceptions of autonomy exist, reflecting a range of viewpoints of autonomy as embedded either in healthcare practice (clinical patient care or health research) or in social interactions.[8] Conscientious, libertarian and relational conceptions tend to focus on autonomy as a global, long-term interaction of individuals with a healthcare system, and as an embodiment of personal values, such as critical reflection, judgement and accountability, with an important social justice component. Decisional autonomy, on the other hand, focuses on autonomy as a moral framework for decision-making located at a particular point in time when a clinical or research-related decision needs to be made by a research participant. While all of these conceptions offer important insights, the decisional conception of autonomy is best suited to application in a clinical research environment such as the one considered here, as it most closely maps to the process of informed consent in this context.

Decisional autonomy assumes a competent individual who is provided with adequate information to make a decision, free of external (and internal) influences. It is claimed that the obligation of researchers to respect the autonomy of participants does not extend to those unable to act autonomously, including those lacking capacity.[9] Despite this, incapacitated participants enjoy moral status, and researchers have a duty to protect them and optimise possible benefits to them arising from research. Thus, the inclusion of incapacitated patients in research without their informed consent should not constitute a moral dilemma, provided that their immediate wellbeing is protected by careful consideration of the applicable risk-benefit ratio, and reasonable efforts are made to maximise benefits of the research. This responsibility falls to RECs and the researchers responsible for patient care.

It would be prudent for RECs to bear in mind that delayed consent, despite sounding as though it somehow supports or furthers the autonomy of incapacitated participants, actually has no effect on it, apart from moving forward in time beyond a point when an incapacitated participant regains capacity. It therefore follows that delayed consent should not be presented by researchers as a consent strategy, unless this is with reference to the period after regaining of capacity – which is uncertain in critically ill patients. Many would probably see proxy permission as a way of showing respect to a participant who is not capable of making his or her own decision.[10,11] But it should not mistakenly be seen as showing respect for *autonomy*, which implies its enabling. By initially including incapacitated patients in research without their informed consent, the negative obligation of removing controlling influences over a patient's decision-making is ignored – an act that cannot be undone.

What happens when the participant dies?

The death of an incapacitated research participant prior to the availability of a proxy decision-maker represents a predicament when the assumptions that proxy permission will be available and that the participant will regain capacity do not materialise. The point at which death occurs may vary, but it is likely that at least some, a substantial amount or all of the research data will have already been collected. The question now arises whether or not it is acceptable to include these data in the research without having obtained the participant's consent, or a proxy's permission, to do so. This predicament exists because it would seem wrong to use the data where autonomy over their use is not exercised. Current SA research ethics guidelines are silent on how to proceed in this situation.

Given the importance of autonomy as an ethical principle, and the universal emphasis on informed consent, together with the legal position and absence of direction from guidelines, RECs could make a decision not to allow the use of these data. While this position may potentially be seen as ethically and legally correct, it still raises serious ethical problems, as well as methodological ones. From a methodological perspective, the exclusion of such data is likely to introduce bias, as the most seriously ill participants, who may be the population of interest, will be excluded from any further analysis. From an ethical perspective, there are several problems. The possible future benefit of using such data is lost. While choosing to exclude such data may be seen as upholding the principle of autonomy, it could also be argued that the loss of future benefits is unjust. Although the participant will have been treated justly at the outset by not being excluded from participating, and thus being exposed to possible benefits of the research, his or her participation would be disallowed from conveying any future benefits, compared

with participants who survive. While this is admittedly a weaker argument than one centred on justice related to personal benefit, it does identify an inequality in the balance between risk and benefit (both personal and future) that disadvantages participants who have died.

Should the principle of beneficence be given more weight in the consideration of how to proceed?

Current research ethics guidelines weigh a number of factors and ethical principles when suggesting approaches to the problem of research involving incapacitated adults. While risks and benefits are considered and balanced in determining whether or not it may be justifiable to include such patients as research participants, a focal point of decision-making for RECs is the matter of informed consent, and what the implications may be of deciding to include incapacitated adults in research without it. However, considerations of autonomy are not the only ones, or even necessarily the most important ones, to guide our actions. Beneficence and non-maleficence require that incapacitated patients, because of their moral status, must be protected and, as far as possible, benefit to some degree from the research that they participate in. Decisions related to the participation of incapacitated adults in research are deliberated on by RECs weighing up the relative risks and benefits of the research, including future benefit to others for the public good, when deciding whether or not research data should be retained and used in the future.

Is there a communitarian argument in support of the use of data without consent motivated by an argument for the public good, in certain circumstances?

Beginning in the immediate post-war period, and gaining momentum through the rights movements of the 1960s and 1970s and to the present time, individual autonomy as an ethical principle has been on the ascent.[12] It was cemented into the Nuremburg Code in non-negotiable form,[13] and enjoyed prominence in the Declaration of Helsinki,[14] ethical guidelines[3,15] and statute. Indeed, it is easy to see how the National Health Act, for example, with its absolute requirement for written informed consent, has been influenced by these sentiments, when in many situations, both clinical and research, this ideal is simply not possible. More recently, beginning around the early 1990s, the supremacy of individual autonomy – coupled with its overarching need for informed consent – has been questioned on both philosophical and practical grounds.[16]

Opposition to the long-standing supremacy of individual autonomy takes several forms, but perhaps the most frequent is on the grounds of more prominent roles for beneficence and justice, and particularly the public good.[17] The objective should be to identify a balance between autonomy and these two principles, and not favour one over any of the others.[16] Referring to an Aristotelian conception of the common good, Sutrop[16] proposes that the public good is not merely the sum of individual goods, but that it transcends these, while its benefits are shared individually. O'Neill[18] proposes that research involving public health outcomes must of necessity be in the public good, and contends that this is so because such outcomes apply to whole populations (or smaller subpopulations), and therefore cannot be tailored to individual choice.

In situations where critically ill research participants die without regaining capacity and without an accessible proxy decision-maker, consideration should be given to the data being retained and used for research based on the public good, counterbalancing autonomy-based arguments to disallow such use. This is of particular pertinence in the midst of the current COVID-19 crisis.

The position in other guidelines

The Declaration of Helsinki makes provision in article 30 for the inclusion of incapacitated adults in research, but emphasises the important role of a proxy decision-maker.[14] In situations where a proxy decision-maker is not available, inclusion of incapacitated adults may proceed provided that the research protocol (which sets out in detail why proceeding without a proxy decision-maker might be necessary) has been approved by a REC. Delayed consent must be obtained as soon as possible. There is no explicit guidance regarding use of research data in cases where delayed consent is not possible.

International research ethics guidelines from the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization also underscore the importance of proxy decision-makers in situations where research is considered with incapacitated adults, and they also require delayed consent when possible.[15] The CIOMS guidelines also, in guideline 10, allow for waivers of the requirement for informed consent to be considered with incapacitated adults if: (*i*) it would not be possible to carry out the research without such a waiver; (*ii*) the research has significant social value; and (*iii*) the risks involved are minimal. There is no specific guidance regarding situations where a waiver is not in operation, a proxy decision-maker is not available and delayed consent is not possible because a participant dies.

Deferred consent is provided for in legislation from the UK, Europe and the USA.[19] None of these countries have legislation or research ethics guidelines that explicitly deal with the question of whether data should be retained and used if a proxy decision-maker is not available and delayed consent is not possible because a participant dies. New Zealand legislation requires the permission of a proxy decision-maker; however, this must be an individual legally appointed as such, and not merely a family member or an individual in a close personal relationship.[20] There appears to be no provision made for delayed consent. In Australian research ethics guidelines, the role of proxy decision-makers and delayed consent appears to be minimal, while provision is made for waivers of informed consent based on conditions similar to those in the CIOMS guidelines.[21] The Netherlands recommends that research data are retained and used, and that proxy decision-makers are informed when they eventually become available, but their availability after the death of the patient does not influence the decision to retain and use the data.[22]

Conclusion

Under the conditions of a pandemic, such as are now unfolding globally and in SA, participation of critically ill patients in health research is complicated by a lack of capacity to give informed consent. Under such circumstances, local research ethics guidelines suggest the use of proxy and delayed consent. Because of the lockdown strategy in an attempt to control spread of the SARS-CoV-2 virus, proxy consent is unlikely to be possible much of the time. Under these conditions, researchers must rely primarily on delayed consent. While this approach may be supported by current guidelines, in a subset of cases, participants will

die before regaining the capacity required for delayed consent, raising questions about whether or not research data collected up until that point ought to be retained and used – a question not addressed by local research ethics guidelines. Concerns about the need for informed consent need to be balanced by considerations of the public good. In order to avoid situations where researchers are uncertain of how to proceed, the NHREC guidelines require clarification on how to deal with such cases as a matter of urgency, particularly where delayed consent may not materialise and proxy consent cannot be obtained.

Acknowledgements. None.

Author contributions. CS conceived the research and drafted the manuscript. AD critically revised the manuscript.

Funding. None.

Conflicts of interest. None.

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Accepted 31 May 2020.