Detail for DoH 2015 Guideline 3.4.1

Major incidents and research, including public health emergencies

(Text to be incorporated into DoH 2015 when revision completed)

Contents

3.4.1.1 Preamble

Major incidents include any sudden event that occurs where local resources are constrained, making responding urgently and appropriately challenging. Major incidents include acute disasters – natural or man-made – such as floods, tornados, earthquakes, **outbreaks of deadly disease**, or political violence and armed conflict with resulting injuries to humans. They may also take the form of an unusual and sudden demand on local resources or other emergencies with consequent ethical implications for patient and health care. Research in major incidents is important for advancing emergency health care interventions and treatments, and refining resource allocation, policymaking and implementation. 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.

In the process of responding rapidly to the public health emergency driven by COVID-19, methodological and ethical dilemmas emerged for researchers and clinicians. The previously acceptable ways of generating and synthesising evidence are no longer feasible. Many challenges arose for researchers, such as forced self-isolation, the government ordering site closures, regulatory restrictions on travel, which affected whether and how ongoing clinical trials and other community-based research could proceed. In addition, the possibility of community-based infection by the virus increased the vulnerability of field workers and participants, many of whom chose to stay home rather than to report for clinic visits.

Conducting research in major incident contexts requires certain adjustments, for example, planning of the research and ethics review processes usually must occur very rapidly. However, it is vital that the research is still conducted in a manner that complies with the acceptable principles that underpin the scientific and ethical integrity of research with human participants. It should be noted that not all research about or during the major incident is urgent, and as such, does not have to follow an expedited pathway. The REC should carefully assess the nature of the research to determine the appropriate review process. Careful ethical reflection is essential, albeit the urgency.

Researchers and Research Ethics Committees (RECs) found the information provided in 3.4.1 of DoH 2015 to be insufficient in the challenges faced in some contexts during the COVID-19 pandemic.

The additional guidelines focus on strengthening some key elements of the ethico-legal framework for research that are central to ensuring that participants' moral agency is respected. The key elements include research ethics review, informed consent, community engagement, use of placebo in clinical trials, information sharing, and sharing of collected biological material and associated data for knowledge generation. None of the key elements is new but understanding and interpretation of each benefit from focused attention through the lens of major incident research.

The intention of this guideline is to provide contextualised guidance to researchers and RECs in light of a public health emergency. However, it is equally important to note the context of uncertainty related to public health emergencies and that such guidance could also evolve as new information becomes available. Although the guideline has been drafted based on the COVID-19 pandemic, this may not strictly apply to all public health emergencies.

Public health emergencies require a public health ethics approach. It is therefore imperative that the theoretical framework used by RECs be broadened to consider public health principles, which focus on solidarity, mutuality and reciprocity, among others.

For specific guidance on conducting clinical trials during a pandemic, please refer to section 10.11 of SA GCP 2020.

3.4.1.2 Multinational collaborative projects

International scientific partnerships leading to multi-centre and multinational research, have become necessary to ensure rapid evidence-based decision-making to support clinical management of COVID-19 related cases as well as to ensure sufficient funding. Such research should, however, be mindful of both local and international priorities. It should be responsive and sensitive to local realities, needs, values, and the national ethico-legal framework. Researchers should engage with the local communities and all relevant supportive social/healthcare individuals working within said community, from the initiation of the research, very early-on and at all stages, if feasible. Collaboration with international partners should undertake joint decision-making to prioritize the challenges faced in the pandemic/outbreak, to choose the research project that will best address those challenges, and to ensure that the research conducted enhances the likelihood of benefit for the participants and participating local communities. While solidarity and reciprocity are crucial for dealing with a public health emergency, the rights and interests of participants should not be compromised. International collaborations should be based on the principle of fairness (see Montreal Statement on Research Integrity in Cross-Boundary Research Collaborations 2013 and the Global Code of Conduct for Research in Resource Poor Settings 2020).

3.4.1.3 Research conducted during a pandemic

While the scientific and ethical rationale to conduct research during public health emergencies is well established, research must not impede emergency medical responses. In other words, research should not be conducted if the effect would be to divert personnel, equipment, facilities and other resources from the response to the public health emergency. Additionally, this means that resources allocated to research should not compromise routine delivery of health care and public health services required notwithstanding the public health emergency.

Where clinicians treat patients in health facilities and conduct research with their patients as research participants, great care must be exercised to avoid therapeutic misconception as an outcome of their dual role (see sections 3.2.5 and 3.2.6 of DoH 2015 and 10.10 of SA GCP 2020). A therapeutic misconception prevails when a patient/participant believes that the primary purpose of a trial procedure or intervention is to confer therapeutic benefit rather than generate generalisable knowledge, thus confounding the purpose of research and treatment. In a therapeutic context, clinicians must act in the best interests of their patients. When a patient become a trial participant, this obligation becomes more complex. Of necessity, the trial context has a different focus, i.e., the systematic generation of new knowledge within a paradigm that may or may not include direct benefit/s for individual participants. This implies that the best interests of individual participants may not be the focus as the researcher/s may not be able to change the trial protocol to best suit an individual participant's interests. In research, the study protocol is designed to answer a research question, without any objective to meeting the needs in the best interest of individual patient

Researchers and clinicians are reminded that it is never necessary for a patient to be a research participant, especially under the assumption that a patient will be better off by being enrolled in a trial. If it is certain that the trial-related interventions will benefit patients, then the interventions should be administered as part of treatment, **not** research. In the context of COVID-19, nobody has been certain about how best to treat patients leading to the justification for doing research involving very sick patients. Thus, the ethical principles governing enrolment must prevail, including informed consent. It is irresponsible and unethical to enrol patients in clinical trials if there is failure to meet all the legal and ethical requirements.

3.4.1.4 Placebo-controlled clinical trials in a pandemic

As a general principle with clinical trials, the benefits, risks, burdens, and effectiveness of a new intervention must be tested against the best proven intervention(s) (SA GCP 2020). This principle is applicable irrespective of whether the proposed new intervention is preventive or therapeutic (curative) based. In a case where no proven and registered intervention exists, every participant in a clinical trial should receive the standard care available in the context, as a minimum level of care. Standard of care in the context of a clinical trial, refers to the formal diagnostics and treatment processes that study participants can access should they present with symptoms or a specific illness. These identified diagnostics and treatment processes should be aligned with the existing local best practices.

Where there is no best proven intervention, and the research is ongoing, it might be difficult to define the standard of care. Such is the case with the COVID-19 pandemic, where durable vaccine immunity has become questionable especially with the emergence of new variants of SARS CoV2. As a result, it is difficult to clearly identify the standard of care ***{Standard of care has to be the best available treatment at the time}.*** Clinical trial governance imposes limitations on flexibility which adds to the complexity. Rather than naming a standard of care, it may be more useful to apply continuous assessment of emerging scientific and clinical data to determine an intervention with good clinical data.

However, at the same time, it is not ethically prudent to use a placebo arm or a non-intervention study arm in clinical trials, where such enrolled study participants would not receive the minimum standard of care and could thus face risks of serious or irreversible harm. This is particularly problematic when some proven interventions that can be considered as standard of care, do exist. Although the currently available vaccines (approved and new candidate vaccines) might not be ideal, they ought to be considered for use as long as they protect against severe illness, prolonged hospitalisation, and death. The Regulator, Government or appropriate authority must advise the public through official communications on which intervention(s) should be regarded as the standard of care.

It is not ethical to conduct a clinical trial with completely vaccine naïve study participants and have a placebo control arm, if vaccines with proven efficacy are available. Researchers developing new vaccines should consider a trial design with the control arm being a different currently approved vaccine. At the same time, researchers and RECs should consider the following: The challenge of developing new preventive and therapeutic agents without a placebo arm should be balanced against the possible risk participants could be exposed to should a placebo arm be used. Thus, a careful risk-benefit assessment should be conducted.

The COVID-19 pandemic has demanded a re-look at how researchers and RECs engage with risk assessments in clinical trials. From a REC perspective, this requires heightened scrutiny of protocols for ethics review and a careful analysis of the foreseeable risks to study participants. While this is the norm in the ethics review process, greater care must be exercised, given the potential for additional risks of harm to study participants and researchers, such as secondary social stigmatization.

3.4.1.5 Ethical Principles in research

While all ethical principles must be upheld, some require special attention during a pandemic. Some of these are captured below:

Scientific Validity and Social Value

An outbreak can necessitate the use of alternative study designs to yield meaningful data. Study designs must be feasible, appropriate, and scientifically valid. Methodological and ethical merits of study designs must be carefully assessed prior to the research being conducted. Where the science is deficient, the research will lack social value and should not be conducted. For research to have social value, it must be responsive to the health needs and priorities of those communities in which the research is being conducted (CIOMS, 2016). The DoH 2015 guideline states that r**esearch should be relevant and responsive to the needs of the people of South Africa (see 2.3.1.)**. However, in a pandemic situation, the social value of research should extend beyond the South African context. In a pandemic situation, social value would apply also to the global community and in terms of the response, the considerations could have global implications, for e.g., equitable access to vaccines developed from research (CIOMS, 2016). Research conducted in SA also contributes to the global public health good. RECs should therefore consider the social value of the research at a global level and not just at the local context, in the review of such studies.
At the same time, 'rigorous ethical safeguards should be in place', especially in respect of 'externally sponsored research, to prevent the exploitation of those who take part in the research' (Nuffield Council on Bioethics undated).

In cases where some interventions have features that would make them difficult to implement locally, local contexts must be considered, and designs be modified to ensure successful implementation within available resources.

Distributive Justice: Equitable Distribution of Risks and Benefits

Burdens and benefits of participation must be equitably distributed among all role players where possible.

Interventions developed during emergency infectious disease outbreaks, when being implemented, are usually limited initially. Fair selection of participants is requisite, and there is an ethical obligation to ensure that privileged, well-off or well- connected individuals are not further privileged, nor is selection politicised. Where vulnerable populations are excluded, there must be sound justification for this.

It may be acceptable to prioritise certain populations when enrolling into the study based on the principle of utility. An example is frontline healthcare workers. If experimental interventions have been proven to be effective, healthcare workers could be prioritised for enrolment in, for instance, an implementation study so they are readily available to help patients.

The lack of available preventive or therapeutic health products authorised for use creates an opportunity to rapidly translate evidence of efficacy emanating from early phases of research into practice, to enable prioritised groups early access before emergency use authorisation. Extensive emergency use with inadequate data collection on patient outcomes must be avoided.

When reviewing research proposals aimed at developing preventive or therapeutic health products, ethics committees and regulatory authorities should ensure that the issue of access to developed products is addressed. No segment of population should bear the burden of research but be denied access to the benefits resulting from the research. If we are to contribute to global good, then at minimum, there should be shared benefits accrued from the research.

Beneficence and Nonmaleficence: Safety, Risks, Emergency Use of Investigational Interventions

In the context of infectious disease outbreaks research, reducing risks of harms includes providing participants with non-pharmaceutical prevention methods that have already been proven to be effective. Preliminary research could inform the standard of prevention proven to be effective in reducing transmission of the contagious agent, the risk of acquiring the agent, or severity of the disease, and mortality. The standard of prevention refers to the package of comprehensive tools provided or made available to participants in the trial. The components of the prevention package will vary with the degree of risk of exposure. The standard of prevention should be practically achievable in the local setting and should be reasonably accessible to those at risk of infection.

The principle of beneficence places an obligation on researchers and sponsors to minimise risk to participants in the trial. Determining what level of prevention a trial will offer, requires deliberation with relevant stakeholders on how best to achieve the highest level of protection possible and what ethical justifications are required to support a trial providing a higher or a lower standard of protection that is aligned with that available to others in the population.

The ongoing accumulation of safety reports following interventions after emergency use authorisation highlights the need for ongoing pharmacovigilance and safety evaluation. While the mandate of the regulatory authority is recognised, RECs must act rapidly to evaluate the reported side effects and decide on whether to pause or terminate the use or recommend amendments to the information leaflet or make other interventions to minimize the risks of those involved in the studies.

Autonomy: Informed Consent

Infective disease outbreaks cause enormous amounts of anxiety, distress and even mental ill health in populations at large. This could result in a challenge to the informed component of informed consent as many would not be in the proper frame of mind to make well-informed choices. Nevertheless, the principle of autonomy requires that both the liberty and agency elements are satisfied for consent to be truly informed. Hence, being under duress cannot be used as an excuse for people not making voluntary decisions. Therefore, potential participants must be assisted in understanding the study and the true implications of their enrolment in it. The notion that informed consent is a process does not change just because the research is being conducted in a pandemic. Where individuals are incapable of giving informed consent, for example patients in intensive care units on ventilation, special protections apply in that RECs could be approached to allow for proxy or deferred/delayed consent to be obtained.

3.4.1.6 Informed consent

Infectious disease outbreaks can cause enormous anxiety, distress and even mental ill health in populations at large. This could result in a challenge to the informed component of informed consent as many would not be in the proper frame of mind to make well-informed choices. Nevertheless, the principle of autonomy requires that both the liberty and agency elements are satisfied for consent to be truly informed. Hence, being under duress cannot be used as an excuse for people not making voluntary decisions. Therefore, potential participants must be assisted in understanding the study and the true implications of their enrolment therein.

Informed consent is a necessary element of responsible conduct of research and in line with good clinical practice in a public health emergency. Special protections should be applied in cases where individuals

are incapable of giving informed consent, for example, patients in intensive care units on ventilation, or some patients experiencing incapacitating symptoms or are cognitively impaired secondary to either the disease or its treatment, and therefore could lack sufficient decisional capacity (see 3.2.4 of DoH 2015). In all contexts, severely ill patients' participation in research should be carefully measured and well justified, considering the ethical requirements for enrolment (see 3.2.5, 3.4.2 & 3.4.3 of DoH 2015). Thus, the ethical principles governing enrolment must prevail, including informed consent. The NHA (Act 61 of 2003) requires prior written consent for research. Enrolling patients despite meeting all legal and ethical consent requirements is in principle unlawful and unethical. Critically ill or incapacitated people may benefit from innovative treatments or yield important data for future application. It may be ethical to include them in research. In principle, research involving incapacitated persons should be approved only if: 1) enrolment would not be contrary to the best interests of individual patients, 2) the study benefits outweigh the foreseeable risks and 3) a legally authorised person (otherwise known as statutory proxy decision-makers, such as a **spouse or partner; parent; grandparent; adult child; brother or sister as outlined in the NHA)** can provide proxy consent where possible (see 3.2.4.3 & 3.2.4.4 of DoH 2015). However, it should be noted neither the NHA nor the Mental Health Care Act 17 of 2002 makes provision for proxy decision makers for **research purposes** specifically. However, the list of statutory proxy decision makers provided for in the NHA (s 7) and the Mental Health Care Act (s 27, s 33) for **treatment purposes** could be applied to the research context.

Proxy informed consent

The necessity for proxy consent and enrolment of a patient in research should be weighed against the requirement to uphold the principle of autonomy. Furthermore, research participants should be informed of the contact details of the local research ethics committee as a potential recourse in case concerns or complaints arise.

Statutory proxy consent is when a legally authorised person provides consent on behalf of the patient (see 3.2.4.3 & 3.2.4.4 of DoH 2015). Regarding consent in major incident research, such as research during a pandemic, the scope of proxy consent as highlighted in DoH 2015 can apply. The DoH 2015 guideline states that consent from a decision-maker other than the statutory proxy may be ethically justifiable where the statutory proxy is unavailable or cannot be located. Such a surrogate decision-maker should, depending on the participant's context, include a person who is socially accepted, such as an informal caregiver, trusted friend, pastor, or a relative *other* than a statutory proxy. It should be noted that proxy consent or consent from a surrogate decision-maker is the only possible means of obtaining consent to include a participant in research, provided the risk of harm to knowledge ratio justifies it. Informed consent should still be sought once a participant regains decisional capacity.

It is the responsibility of the REC to review and approve the surrogate decision-maker when the statutory proxy is not available. When reviewing and approving the surrogate decision-maker, a REC should ensure that the surrogate decision-maker, when consenting on behalf of a research participant, considers a participant's previously formed preferences and values (if known), and in case of research that offers a prospect of clinical benefit to the participant, the extent to which participation would promote the participant's own clinical interests.

In cases where the nature of the pandemic necessitates restrictions in the movement of people and physical contact with proxies or surrogate decision-makers to obtain consent is not possible, e.g., where these persons would not be permitted into a healthcare facility, effort must be taken to contact them in ways other than direct contact in a healthcare facility. Where a statutory proxy or a surrogate decision-maker may not be available for prospective permission to enroll a participant, or in situations where a

research intervention or investigation is time-sensitive, requiring permission on or soon after emergency department arrival or critical care admission, *and* it is highly unlikely that a proxy or surrogate permission would be obtainable, delayed consent, without prospective proxy permission would be the last resort, based on a clear, comprehensive, and clinically sound justification.

a) Delayed informed consent

With appropriate ethical justification (not just urgency), which is clearly described in the research protocol, it may be acceptable for the REC to consider approval of delayed consent (see 3.2.4.3 of DoH 2015), where obtaining prior participant consent may not be possible. Delayed informed consent or deferred consent **is not equivalent to** waived informed consent. Delayed informed consent is informed consent volunteered by the participant but is obtained after the research has begun. It should be emphasised that informed consent should always be sought first and that delayed informed consent may only be considered in exceptional circumstances where the likelihood of a obtaining informed consent after the research has begun is highly probable.

In instances where a patient, as prospective participant, is temporarily incapacitated, proxy permission for inclusion of the patient in the research should be obtained prior to enrolment, followed by delayed consent when the patient/participant regains the decisional capacity to consent. However, where incapacity results in death of the participant/patient before delayed consent can be obtained, the continued use of the patient's data and/or samples would depend on the individual circumstances, taking into consideration the wishes of the patient's/participant's statutory proxy or surrogate decision-maker. Irrespective of these provisions, the necessary data oversight processes should be in place. Here again, the REC is the appropriate body to review the provisions put in place for type of oversight.

Furthermore, with reference to the situation where a patient dies before delayed consent may be effected, an objection by the patient's proxy or surrogate decision-maker to the continued use of the patient's data and/or samples, will render the further use of the data and/or samples potentially unethical and/or unlawful. However, if the data has been anonymised, its further use may be justified on the basis of its benefit in promoting the public interest and the common good. However, RECs should show sensitivity to the participants' prevailing cultural and value systems when considering the future use of samples and data, specifically in instances where the further use of the data and samples may be difficult to discern. RECs should also consider provisions of relevant material transfer agreements and data transfer agreements that may contain provisions regarding the further use and destruction of donors' data and samples.

b) Consent for post-mortem research following natural death

Researchers initiate research on deceased persons in order to advance scientific knowledge into the pandemic in the public interest. In South Africa, deceased persons are not protected by the Constitution (Constitution 1996) and are only partially protected by the common law crime of interfering with a corpse (S v Coetzee 1993) and statute law governing the removal of tissue (National Health Act 2003).
Consent for postmortem research following natural death (refers to death that occurred as a result of the pandemic), and the need for consent to autopsies, may be dispensed under the common law doctrine of 'necessity' (Neethling et al 2001) during pandemics.

Such information is in the public interest because it will inform critical care facilities on how to save lives of future patients and assist government in responding to a pandemic by adequate planning. It is also reasonably justifiable in the public interest to ascertain the health status of deceased persons who have

been exposed to the risk of the pandemic, in order to protect their family, their friends, healthcare practitioners, undertakers and their staff members, and members of the public with whom they have been in contact. However, it is also important that RECs take into consideration the participants' and communities' cultural, value and belief systems.

c) Electronic or telephonic consent

The unique circumstances presented by the pandemic shifted the context of several aspects of research including the ideal of direct researcher-participant, face-to-face interaction, towards the virtual online data collection methodological approaches. This shift has affected ways in which informed consent can be obtained from participants. Research conducted electronically or telephonically to collect the desired data uses methods of obtaining the equivalent of informed consent that have become settled in social and behavioural science research (see chapter 6 of DoH 2015).

Electronic signatures are defined according to the Electronic Communications and Transactions Act 25 of 2021 (ECTA) as "data attached to, incorporated in, or logically associated with other data and which is intended by the user to serve as a signature". It represents an electronic functional equivalent of paper-based signatures with the same legal authority if it meets legal requirements, and can include

•a typed name at the end of an email.

•a scanned image of a handwritten signature embedded into a Word document.

•a digital signature.

In addition, in terms of section 13 of the ECTA, where the signature of a person is required by law and such law does not specify the type of signature required, an advanced electronic signature must be used. It must be noted that a written signature is still applicable. Only when an electronic signature is the preferred option would a person be obliged to use an advanced electronic signature

A range of alternatives to deal with the challenge of obtaining **prior written** informed consent, have been proposed. Some international regulators have formally endorsed telephonic and electronic informed consent as an alternative to paper-based informed consent. Reviewers on Ethical Research Committees must insist on a proper, decisive description of how informed consent of participants will be regarded as authentic.

The following guidelines recommend alternative ways of obtaining informed consent where prior written consent is not possible:

- **Consent obtained telephonically**: A witnessed audio record of the informed consent process; from the time when the study is introduced to the participant to when the participant confirms willingness to participate, should be kept as evidence of the informed consent process. The recorded audio can where possible, be followed by a signed written consent document. For example, participants can be sent the Participant Information Sheet (PIS) via electronic means and consent can be recorded verbally. However, telephonic consent is not advisable for moderate to high-risk studies or where the type of research is contentious or of a sensitive nature. Authenticating the identity of the participant is important. Considerations on how best to preserve participants' anonymity and confidentiality must be retained when alternative electronic platforms are used.
- Obtaining informed consent via electronic platforms e.g., electronic mail, Google Forms, SurveyMonkey, WhatsApp, MS Teams and other virtual platforms, should be considered, provided there is adequate motivation to use this alternative. Electronic signatures may also be considered, where applicable, provided security and authentication measures are in place. Additionally,

researchers should note the importance of recording the evidence of consent obtained via these platforms. This method of consent, however, has the potential to exclude participants with no access to electronic platforms or electronic signatures. Researchers should explain how inclusivity will be pursued.

- Compliance to the stipulations of the POPI Act should be always observed.
- The capacity to consent should not be assumed but independently and carefully assessed by the researchers. Safeguards should be built into the process to protect the incapacitated patient while balancing the risk of harm with the proposed research benefits. Researchers should note that any form of telephonic consent carries some degree of risk in terms of authenticating identity or misunderstanding the purpose of the research. It is important that the type of study and the nature of the research question is carefully considered. In all cases, researchers should provide SOP delineating the way they will approach informed consent in each instance.
- When using electronic/online means for your research projects, please consider issues such as connectivity, online accessibility, and data costs. This issue is relevant to both researchers and participants.

3.4.1.7 Expedited ethics review

Expedited review applies to minimal risk research, however expedited processing does not equate to curtailing deliberation time. The expedited processes therefore ought to be specific to administrative processing of the ethics application.

3.4.1.8 Rapid ethics review

The usual requirements for independent ethics review remain in place for research in public health emergencies (see 3.4.1 in DoH 2015). There is no provision in the ethico-legal framework in South Africa for a national health research ethics committee that reviews research protocols. In particular, the NHREC does not review research proposals and is not authorised to engage in joint regional or multi-national reviews. Instead, the ethico-legal framework falls upon the National Health Act which requires that each institution that conducts health research to establish or have access to a registered HREC (see 1.4 of DoH 2015). In principle, therefore, ethical clearance for any human-related research study, should be obtained for each site in the case of multi-site research. No single South African HREC has the authority to review and/or approve a research protocol for multiple sites unless all these sites fall under the same HREC, e.g., as in the case of university RECs including satellite sites. This principle is supported by the fact that a local REC would be in the optimal position to consider the local circumstances of the given site within its jurisdiction, in providing ethical approval inclusive of the local capacity, constraints and challenges that pertain in conducting the research at that specific site.

However, because preparations for research in a public health emergency must usually occur very rapidly, research proposals may require expedited processing. This means that fewer REC members review the proposal and that the time for deliberation by the REC is reduced. It is possible in appropriate circumstances to review and approve a proposal without undermining the substantive protections provided by the full review process of an REC in about five days, provided that REC's operational systems are in good working order and that the REC members are experienced. Urgency however, can never justify circumvention of the established ethics guidelines and statutory standards for a thorough review, ethical conduct of research, and adequate consideration of the safety and well-being of participants, researchers,

fieldworkers and communities at large. RECs must develop clear mechanisms and procedures, to ensure that rigor and integrity of the review process, are not compromised. Additionally, there should be proper REC monitoring and ethics oversight, so that the REC can respond quickly, should new information necessitating a review of the risk-benefit of the approved study become available.

Given that all registered RECs undergo a robust process of registration and subsequent quality assurance audits, when NHREC-appointed auditors scrutinize and examine the documentation relating to Terms of Reference, Standard Operating Procedures (SOPs), and records of operational processes of each HREC, it follows that reciprocity of review is possible (see 4.5.1.3 of DoH 2015).

A combination of expedited review (see 4.5.1.5 of DoH 2015), which shortens the review process, and reciprocal recognition of the review of another registered REC serves to avoid duplication of effort. The ability to use this operational shortcut requires that RECs have put the appropriate planning and robust processes in place. The REC should have a review SOP that allows the combination of expedited review and reciprocal recognition of reviews of other registered RECs, and that there are measures in place to ensure consistency in the review and oversight processes of the REC. The possibility of reciprocal recognition of reviews should occur in a collaborative, harmonious manner, bearing in mind that each REC bears the responsibility of protecting the safety, rights and interests of participants enrolled in their sites.

The roles and responsibilities of each REC involved in the reciprocal review process should be clearly described and agreed upon in writing by the participating RECs. DoH 2015 deliberately does not impose use of reciprocal recognition of reviews on any REC; nor is there a prescribed method for agreeing to reciprocal recognition. The expectation is that REC Chairs should communicate with each other and agree on a way forward regarding review of a multi-site research protocol when it is desirable to avoid duplication of effort. It is expected that common sense should inform the decision-making process, since the objective is to share resources, achieve standardisation as appropriate, and avoid unnecessary duplications.

There is a need to harmonize the review processes so that trustworthiness can be built into the reciprocal review. RECs are encouraged to engage in joint reviews in the case of research conducted in public health emergencies. However, the independence of the participating RECs should not be compromised through this process and each local REC should consider the local circumstances inclusive of local constraints and challenges that pertain in conducting the research at that site. Matters to be considered include which RECs are participating in the particular reciprocal recognition arrangement, how protocol amendments will be managed e.g., a site-specific logistical amendment may not lead to amendments at all sites, but only noting by the others, how adverse events or unanticipated problems will be managed e.g., it might be decided to report AEs in the usual way to own REC and SAHPRA but Serious Adverse Events (SAEs) notify the other participating HRECs. It is important that SA GCP 2020 be followed consistently. It is possible that some RECs already have SOPs in place for reciprocal recognition of reviews. The agreement might be reached by sharing the SOPs to ensure that all participating RECs understand and can participate on the basis of a shared SOP.

The REC may revise the decision to recognise prior review and approval if justifying circumstances arise for such revision. The reasons for such reversal of decision should be documented.

3.4.1.9 Information sharing

In a public health emergency, rapid sharing of information generated during research is seen to be desirable so that evidence-based decision-making can inform the response to the emergency. Sometimes, researchers might forget about the necessary cautionary restrictions of ethical requirements such as

maintaining confidentiality and privacy of personal information. Researchers should also bear in mind that early results might be misleading and should proceed cautiously when publicising interim results. Sharing results with research participants is important and should be carefully balanced with considerations of the participants' best interest.

Evidence and knowledge that emerges from research during the pandemic should be disseminated and in other widely spoken local languages in addition to English, especially when addressing the public at large. The media must be enabled to deliver accurate messages about new methods of clinical management or the availability of new treatments and preventive measures such as vaccines.

3.4.1.10 Conflict of interests

The dual role of the clinician-researcher is an important consideration in research, but more so in a public health emergency. Researchers are reminded to separate these roles so that potential conflicts of interest can be managed. Conflicts of interest can occur at various levels and at different time points of the research process and may change in a pandemic. Such conflicts of interest could be for financial gain in cases of industry-sponsored research involving drug companies, first to publication etc., which could introduce possible researcher bias in how the study is conducted, analysed and reported.

However, conflicts of interest could also exist without any financial gain, such as researchers driving a research agenda that could lead to personal career advancement or promoting strongly held social views. Likewise, there could be political pressure for researchers (at national or local levels) to drive a particular research agenda.

All conflicts of interest, including disclosures of such conflicts should be documented and declared by the researcher and then managed by the REC in accordance with the DoH guidelines (Section **4.5.1.7)**. Apart from the disclosure of conflicts of interests, there should be institutional policies and processes for the management of these conflicts of interest (see 10.1 of SAGCP 2020).

3.4.1.11 Community engagement

Research during a public emergency requires fair and meaningful community engagement and inclusive decision making. The most inclusive level of engagement is one in which local stakeholders take part in decision-making processes with respect to research design, implementation and evaluation. It requires that all reasonable steps be taken to ensure that all potential role players, including those who are vulnerable and/or marginalized, are included.

Established community engagement processes may be challenging during a pandemic. When switching to electronic/online means for the research projects, researchers should take issues such as connectivity, online accessibility, and data costs, into account. The use of virtual platforms such as social media may exclude community members without access to such platforms, with poor internet connectivity or without data bundles for use with mobile phones. The local context of research must be considered. This requires the researcher to a re-look at how community engagement can still occur despite these challenges. Researchers are advised to seek permission to access the fieldwork locations from the appropriate authorities ahead of time to avoid delays.

3.4.1.12 Field work

It is important that researchers adhere to incident-specific prevention and control national regulations, guidelines, and protocols in the collection of data during this time, to limit transmission of the pathogen and reduce risk for both the researcher and the research participants. Face-to-face meetings (e.g., door to door surveys in a community, focus groups, or handing out a hard copy questionnaire or doing face-to-face interviews) should be limited, and could be replaced by internet-based research processes whenever possible.

However, where the electronic/online consent process and data collection are not feasible and some populations may not be reachable via these means, and the research methodology cannot be adapted, then the researcher should carefully weigh up the risks to the researcher and participants. Furthermore, the researcher should ensure that all fieldwork adheres to prevention and control measures such as:

- Requiring masks to be worn properly i.e., covering both nose and mouth,
- Hand hygiene: frequent washing of hands with soap and water or use of 70% alcohol-based sanitizer
- Frequent cleaning of the working environment
- Adherence to cough etiquette: coughing or sneezing into a tissue or elbow
- Social distancing (1.5m between people) must be maintained and number of participants per day or at any one time can be limited
- Ensuring proper ventilation, and sufficient space in indoor venues. Wherever possible, consideration to meet outdoors rather than indoors should be made, but allow for privacy, as required.
- Symptom monitoring, screening and testing.
- Keeping a daily register with contact details of any individual entering the workspace/venue so that everyone can be contacted should one of the researchers or participants be infected, leading to the need to either quarantine those individuals or advise them to be tested for the pathogen concerned.

It is important that the study protocol being submitted to the REC has identified the possible risks that both the researchers and participants might face. The protocol must include detailed precautionary measures and strategies in place to mitigate the risks. The researcher must ensure that the risks to the participants and researchers are justified by the potential benefits to the participants, society and/or science. The researcher must provide all the necessary information to the REC to allow proper assessment of the risk: benefit ratio of the study. The researcher should identify possible hazards, evaluate the potential to mitigate the hazards, and indicate how the hazards will be eliminated/mitigated and who will be responsible. Additionally, the researcher is encouraged to develop a research specific SOP covering all the Pandemic-related aspects. The REC should prioritize safety over productivity.

In principle, the following should apply:

‣ Delay fieldwork where COVID-19 safety rules cannot be upheld.

‣ Consider the age and co-morbidities of researchers, as well as of research participants, prior to providing approval for fieldwork

Team leaders of fieldwork must ensure planning for emergency or unexpected circumstances in the field, for instance: communication procedures if no cell phone coverage/service is available, preparation of a

field safety plan and, where appropriate, availability of a map to required support systems, such as a nearest hospital.

All proposals that involve fieldwork must adopt the National Disaster Management Act Regulations and other applicable national guidelines and protocols and adhere to the restrictions imposed by the risk-adjusted approach (Alert Levels) from government. It is the responsibility of each researcher to be aware of the information from health authorities on COVID-19, and their institutional guidelines of what is permissible.

3.4.1.13 Responsibilities of institutions conducting research

All research institutions should take responsibility to have institutional protocols to assess major incident related research risks and the prescribed precautionary measures to be taken to mitigate these risks for staff, students, volunteers and participants.

The research team leader must ensure the training, preparation and evaluation of the team for fieldwork (see above). Processes must be put in place to ensure that a team member will immediately report any unsafe or unhealthy situations to the fieldwork team leader or research study/project supervisor.

The researcher must ensure every member of the research team and each participant are wearing the necessary personal protective equipment (PPE) and sanitizer, and supply these items where there is a shortage, if face-to-face interactions are envisaged.

APPENDIX

Appendices are not related to research ethics but are practical considerations to help protect researchers and participants.

A. COVID-19 Safety Toolkit for fieldwork

Once staff and students are permitted to undertake fieldwork involving activities in close proximity to each other or participants, each member of the team should ensure that they have a personal "COVID-19 fieldwork Safety Toolkit" when interacting with other members of the team and, if relevant, with human participants in research. The safety Toolkit consists with at least one of the following items: face masks, alcohol-based sanitizer (70% alcohol), thermometer for use with the whole group for daily screening, A4 size zip-lock plastic bags to store documents, and bag with ties for disposal of any waste materials e.g., used masks.

B. Travelling TO AND FROM the field

General guidance for travel

Care must be taken to minimize congestion and ensure adequate ventilation. A detailed plan for exposure prevention must be outlined in the fieldwork plan.

Consideration in the fieldwork Risk Assessment must also include transportation availability should any individual need to leave the site of the fieldwork for any reason and specifically if she/he falls ill. All fieldwork staff must conduct daily self-monitoring for symptoms and should be encouraged to use the Higher Health screening app.

If any member of staff or student is feeling unwell in any way or is advised to initiate further medical follow-up on completion of the self-assessment tool, the fieldwork Team Leader should ensure that the

individual immediately refrains from fieldwork and returns home to self-isolate and to obtain a COVID-19 test if indicated.