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)

3.4.1.1 Preamble

Major incidents include any sudden event that occurs where local resources are constrained, so that responding urgently and appropriately is difficult. 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 resultant injuries to humans. They may also take the form of an unusual and sudden demand on local resources or other emergency with consequent ethical implications for patient care. Research in these contexts is important for advancing emergency health care interventions and treatments, and for 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 were no longer feasible. Many challenges arose for researchers, such as forced self-isolation, government ordered 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 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 has to follow an expedited pathway. The REC should carefully assess the nature of the research to determine the appropriate review process.

Researchers and Research Ethics Committees (HRECs) found the information provided in 3.4.1 of DoH 2015 to be insufficient in the face of 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.

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 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 the 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 also 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 & 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 to generate generalisable knowledge, thus conflating the purpose of research and the purpose of treatment.

Researchers and clinicians are reminded that it is never necessary to be a research participant and especially that thinking a patient will be better off through 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 which formed the justification for doing research with very sick patients. Necessarily, thus, the ethical principles governing enrolment must prevail, including informed consent. It is irresponsible and unethical to enrol patients despite the failure to meet all the legal and ethical requirements.

3.4.1.3 In a therapeutic context, clinicians must act in the best interests of their patients. When a patient becomes 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 for individual participants. This implies that the best interests of individual participants may not be the focus as researchers may not be able to change the trial protocol to suit an individual participant's interests. In research, the protocol is designed to answer a research question, not to meet the needs of individual patients. Multinational collaborative projects

International scientific partnerships leading to multi-centre and multinational research, including COVID-19 research and clinical trials, 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, the national ethico-legal framework, and should ensure that the research engages with communities and researchers from the local context early-on at all stages if feasible. Collaboration with international partners should undertake joint decision-making to prioritize the challenges faced in the outbreak, to choose the research project that will best address those challenges, and to ensure that the research conducted holds out the likelihood of benefit for the participants and participating communities. While solidarity and reciprocity are critical for dealing with a public health emergency, the rights and interests of participants should not be undermined. International collaborations should be based on the principle of fairness (see Montreal Statement on Research Integrity in Cross-Boundary Research Collaborations 2013).

3.4.1.4 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 is that the National Health Act requires each institution that conducts health research to establish or have access to a registered HREC (see 1.4 of DoH 2015). In principle, therefore, ethics clearance should be obtained for each site in the case of multi-site research. No one South African HREC has authority to review and 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.

However, because preparations for research in a public health emergency usually must occur very rapidly, proposals may require expedited processing, which means that fewer REC members review the proposal and that the time for REC deliberation is curtailed. It is possible in appropriate circumstances to review and approve a proposal without undermining the substantive protections provided by the review process in about three to five days if the REC's operational systems are in good working order and committee members are experienced. Urgency can, however, never justify circumvention of the established ethics guidelines and statutory standards for thorough review, ethical conduct of research, and adequate consideration of the safety and well-being of participants. RECs must develop clear mechanisms and procedures, to ensure rigor and integrity of the review process is not compromised. Additionally, there should be proper REC monitoring and ethics oversight, so that the REC can respond quickly, should new information that necessitates 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 deliberation time, 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 HREC 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 are 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 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 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, to achieve standardisation as appropriate, and to avoid unnecessary stipulations.

There is a need for 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 public health emergencies however the independence of the participating RECs should not be compromised through the process. 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 too 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 decision to recognise prior review and approval may be revised by the REC if justifying circumstances arise for such revision. The reasons for such reversal of decision should be documented.

3.4.1.5 Informed Consent

Informed consent is a necessary element of responsible conduct of research in a public health emergency. Nevertheless, given the severity of COVID-19, some patients will be experiencing incapacitating symptoms or be cognitively impaired secondary to either the disease or its treatment, and will therefore lack sufficient decisional capacity (see 3.2.4 of DoH 2015). In all contexts, severely ill patients' participation in research should be carefully considered in light of the ethical requirements for enrolment (see 3.2.5, 3.4.2 & 3.4.3 of DoH 2015). Necessarily, thus, the ethical principles governing enrolment must prevail, including informed consent. It is irresponsible and unethical to bend the rules so that patients can be enrolled despite failure to meet all the legal and ethical requirements. In principle, research involving incapacitated adults should be approved only if enrolment would not be contrary to the best interests of individual patients, if the risk of harm is appropriate and if a legally appropriate person can provide proxy consent where possible (see 3.2.4.3 & 3.2.4.4 of DoH 2015). This necessity for proxy consent and enrolment of a patient in research should be weight against the requirement to uphold the principle of autonomy.

a) Delayed consent

Delayed consent **is not** waived consent. Delayed consent is provided by the participant but after the research has begun. In some circumstances, the incapacity of the patient may be temporary, although this may not be known at the onset. With appropriate ethical justification (not just urgency) clearly described in the protocol, it may be acceptable for the HREC to consider approval of delayed consent (see 3.2.4.3 of DoH 2015), where obtaining prior participant consent may not be possible. In the case of incapacity that could result in death of the patient before delayed consent may be effected, the continued use of the patient's samples would depend on the circumstances, taking into consideration the wishes of the patient's next of kin. See also waived consent below. Should the patient's next of kin object to the continued use of the patient's samples, the further use of the samples is not legally and ethically justified.
Proxy consent

Proxy consent is when an 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 under pandemic, DoH 2015 state that proxy consent may be ethically permissible where no statutory proxy is available, and proxy consent is the only possible means of obtaining consent to include a participant in research, provided the risk of harm to knowledge ratio justifies it

b) Waiver of consent

While other international guidelines such as the US Common Rule make provision for consent to be waived under certain circumstances, in South Africa the possibility of a waiver of consent is limited and should be reserved for extraordinary circumstances. When, in times of pandemics, obtaining informed consent in critical care or ICU research (either before or after the death of a patient) is impossible or problematical, a waiver of consent will be ethically justified if legally necessitated in terms of the public interest. Where possible, this should be followed by a deferred proxy consent at a later stage. From a research ethics perspective, RECs should ensure that a clear and full ethical justification for the proposed waiver accompanies the research proposal. The ethical principle of autonomy and respect for persons versus solidarity (societal common good) must be carefully assessed.

c) Consent for postmortem research following natural death

Many COVID-19 patients are at high risk of dying. The government issued Guidelines on Postmortem Testing for Natural Deaths in October 2020 to facilitate collection of swab samples immediately after death to obtain diagnostic information. Whilst researchers and clinicians believe it is important to establish the cause of death at histopathological levels to facilitate better understanding the pathogenesis of the disease, unfortunately, the government did not include the possibility of taking biopsies when collecting swab samples. It is suggested that the National Institute for Communicable Diseases (NICD) should be approached to assist with having the October 2020 guidelines (mentioned above) amended to permit collection of biopsies for pathogenesis research. Otherwise, obtaining such samples requires consent from patients or from a legally appropriate proxy (see above). Cultural perspectives on the removal and use of bodily tissues from the deceased should be taken into consideration. The National Health Act chapter 8 s 66 refers to postmortem examination of deceased persons, and s 62(1) read with s 64(1)(b) & (c) refers to the use of proxy consent for permission to obtain and use specific bodily tissues in health research. Note that if no proxy is available, then the patient cannot be enrolled.

It should be noted that other variations of proxy or delayed consent that are not mentioned in DoH 2015 or SA GCP 2020 are not authorised methods for obtaining consent. A complete waiver of consent is not acceptable.

d) Electronic or telephonic consent

There is a shift in a pandemic context from the traditional face to face in person interaction, towards virtual online data collection methodological approaches. This shift has affected ways in which informed consent is obtained. Research that is 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).

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

This guidance recommends alternative ways of obtaining informed consent where prior written consent is not possible:

- **Consent obtained telephonically**: A witnessed audio record of the informed process; from the time the study is introduced to the participant to when the participant confirms willingness to participate, should be kept as evidence of the consent process. The recorded audio can where possible be followed by a signed written consent document. For example, participants can be sent the 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 identification of the participant is important.
- Obtaining informed consent via electronic platforms e.g. electronic mail, WhatsApp, 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. This method of consent however, has the potential to exclude participants with no access to electronic platforms or electronic signatures.
- Compliance to POPIA should be 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.

3.4.1.6 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. Return of results to research participants is important and should be carefully balanced with considerations of the participants' best interest.

Dissemination and knowledge-translation of evidence that emerges from research during the pandemic should be 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.

3.4.1.7 Conflict of interest

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, fist to publication etc, which could introduce possible researcher bias in how the study is conducted, analysed and reported.

However, conflicts of interest could also occur 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 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).

3.4.1.8 Community engagement

Research during an 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 are taken to ensure that all those concerned, including those who are vulnerable and marginalized are included.

Established community engagement processes may be challenging during pandemic. When switching to electronic/online means for the research projects, issues such as connectivity, online accessibility, and data costs should be considered. 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 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.

3.4.1.9 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 survey in a community, focus groups, or handing out a hard copy questionnaire or doing face to face interviews) should be limited, and where possible could be replaced by internet based research processes, but where 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, and ensure 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 environmental cleaning
- Cough etiquette: coughing or sneezing into a tissue or elbow
- Social distancing (1.5m between people) is 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

It is important that the study protocol being submitted to the REC has identified all possible risks that both the researchers and participants might face, and has 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 REC should be provided will all the information to allow proper assessment of the risk: benefit ratio of the study. The researcher should identify possible hazards, evaluate the potential to mitigate the hazard, and indicate how the hazard will be eliminated or mitigated and who will be responsible. Additionally, the researcher may develop a research specific SOP covering all the COVID-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

Staff leaders of fieldwork must ensure planning for emergency or unexpected circumstances in the field, for instance: communication procedures if no cell phone 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 to carry out 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 about COVID-19, and their institutional guidelines of what is permissible.

3.4.1.10 Responsibilities of institutions conducting research

An assumption is made that all research institutions will have institutional protocols to assess major incident related research risks and the precautionary measures to be taken to mitigate these risks for staff, students, volunteers and participants.

The research team leader must ensure training, preparing and evaluation of the team for fieldwork (see above) and put processes in place to immediately report any unsafe or unhealthy situations to the fieldwork team leader or research study/project supervisor.

The researcher must ensure every one of the research team and participants are wearing the necessary personal protective equipment (PPE), supply it where there is 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 etc.

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.