RESEARCH ETHICS SUPPORT IN COVID-19 PANDEMIC (RESCOP): PROPOSED RAPID REVIEW PROCESS FOR SOUTH AFRICAN RECs

Background

The World Health Organization characterized COVID-19 as a pandemic on March 11, 2020. The number of cases and the mortality rate outside its starting point in China have increased exponentially, including in South Africa where the first case was diagnosed on the 5th March. The doubling time in South Africa has been in the region of 3 days, but could very soon reach 24 hours. Its immediate effect amongst vulnerable communities and individuals give rise to grave concerns. Not only must the speed of transmission be reduced, but appropriate scientifically proven therapies are essential to allow for health services in the country to be able to care for people with the disease.

International scientific partnerships leading to multicenter and multinational COVID-19 Research and clinical trials have become necessary. In the face of the COVID-19 public health emergency, the usual timeframes for research ethics review must be reduced without undermining the substantive protections provided by the review process. Mechanisms need to be developed to ensure that urgency is not used to circumvent standards for the ethical conduct of research; safety and respect for human rights of the participants that are to be enrolled in COVID-19 studies. Moreover, research conducted during this time must take into consideration other public health interventions and at no time should these studies compromise the public health response to the pandemic or the provision of appropriate clinical care. Mechanisms will also need to be established to restrict conflicts of interests, in particular those of a political nature; timely and wide dissemination of information including results; and relations with sponsors including drug companies. The research community must comply with established ethics guidelines before, during and after the conduct of this research. Quarantined individuals are particularly vulnerable, hence special care is required when enrolling them in proposed studies. This must reflect in the informed consent procedures and follow-up.

In South Africa, the National Health Act, section 72 mandates the establishment of the National Health Research Ethics Council (NHREC) whose functions include *inter alia* to set norms and standards for the conduct of research in humans [72(c)]. The NHREC has published binding national guidelines, *Ethics in Health Research: Principles, Processes and Structures* (DoH, 2015, 2nd ed.) as the norms and standards for ethical conduct of health-related biomedical and social science research in South Africa.

Section 3.4.1 of these guidelines describes a major incident as any sudden event that occurs where local resources are constrained, making urgent response difficult. Unusual and sudden demands on local resources could have ethical implications for patient care. Research in these contexts could be critical for advancing emergency health care interventions and treatments. While the guidelines emphasise that patients in these contexts would be extremely vulnerable, RECs are cautioned not to be overly restrictive and recommend that the ethics clearance process must occur very rapidly and that related research proposals should be rapidly processed without compromising rigour. For example, minimal risk studies could undergo rapid expedited review, while more than minimal risk studies could undergo rapid full committee review. RECs should innovate in developing such rapid review processes in line with DoH (2015) 3.4.1.

Regarding consent in major incident research the guidelines state that, proxy consent may be ethically permissible "where no statutory proxy is available if the risk of harm to knowledge ratio justifies it." (DoH, 2015, 3.2.4.3). The REC may approve delayed consent in certain circumstances (3.2.4.3).

Section 3.2.4.4 describes the minimum conditions for research involving adults who are incapacitated as follows:

"Research involving incapacitated adults should be approved only if

i. *The research, including observational research, is not contrary to the best interest of the individual;*
ii. *The research, including observational research, places the incapacitated adult at no more than minimal risk (i.e. the 'everyday risk standard' which means the risk is commensurate with 'daily life or routine medical, dental or psychological examinations and in social or education settings activities' – referred to as 'negligible risk' in some guidelines); or*
iii. *The research involves greater than minimal risk but provides the prospect of direct benefit for the incapacitated adult. The degree of risk must be justified by the potential benefit; or*
iv. *The research, including observational research, involves greater than minimal risk, with no prospect of direct benefit to the incapacitated adult, but has a high probability of providing generalizable knowledge; i.e. the risk should be justified by the risk-knowledge ratio;*
v. *Greater than minimal risk must represent no more than a minor increase over minimal risk;*
vi. *The legally appropriate person (treatment proxies as stipulated in NHA s 7 or s 27(1)(a) of the Mental Health Care Act 17 of 2002) gives permission for the person to participate; and*
vii. *Where appropriate, the person will assent to participation. Note that the incapacitated person's refusal or resistance to participate, as indicated by words or behaviour, takes precedence over permission by a proxy.*

The National Health Act specifies the sequence of legally appropriate treatment proxies as spouse or partner; parent; grandparent; adult child; brother or sister. The Mental Health Care Act provides, in no particular sequence, that legally appropriate proxies are spouse; next of kin; partner; associate (defined as 'a person with a substantial or material interest in the well-being of a mental health care user or a person who is in substantial contact with the user'); and parent or guardian. "

RESCOP is of the view that where there is no proxy, and the patient passes on without being able to provide delayed consent, the relevant REC should be provided with motivation for retention and use of the data in the study. It is imperative that all valuable data is utilised in societal interests.

Section 3.2.6 of the guidelines describes the approach to be taken when reviewing research involving patients who are highly dependent on medical care. Because of their medical vulnerability, and the fact that their decision-making and communication skills may be compromised, special attention needs to be paid when considering their participation. The guidelines (3.2.4.3 & 3.2.6) also allow for the REC to approve delayed consent in particular circumstances in this context. However, it is emphasised that this **does not mean that consent is waived**. Clear and full justification for delayed consent must accompany the research proposal. It is also important to carefully consider the individual circumstances of the patient so as to avoid violating personal or cultural values.

The following criteria must be satisfied when approving delayed consent:

- *"the research is based on valid scientific hypotheses that support a reasonable possibility of more benefit than that offered by standard care; and*

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

Section 4.5.1.4 of the DoH (2015) guidelines allow RECs to recognize prior review and approval by another registered REC at their discretion to avoid duplication of effort. Where two or more RECs recognize each other's prior review, this is termed "reciprocal recognition". It is for the REC to determine the nature of the documents to be filed locally. At minimum, this should include a copy of the approval letter from the other REC. The decision to recognize prior review and approval may be revised by the REC if justifying circumstances arise for such revision. The reasons for such reversal of decision will need to be documented.

RECs and RESCOP should also keep abreast of rapidly evolving international guidance documents that address ethical issues and procedures for research in emergency situations, including COVID-19. These are being collated in a shared RESCOP Dropbox folder and in a new WHO open access COVID-19 resources website see (Pending – RESCOP will circulate URL as soon as it goes live)

RESEARCH ETHICS SUPPORT IN COVID PANDEMIC (RESCOP)

RESCOP is an informal, voluntary research ethics support group. Its 'membership' is currently chairs of RECs, members of SAHPRA and other research ethics role players and interested parties with research ethics expertise. RESCOP in principle supports the rapid review and recognition of prior review by another REC as per the NHREC guidelines, provided that the rights and interests of research participants being safeguarded at all times and that National and International ethics norms and standards will be adhered to al all times (RESCOP meeting notes 24 March 2020).

If requested to advise on the ethics of clinical trials and other COVID-19 related research, a possible process to be followed is outlined below.

1. RESCOP could advise on and track the rapid review process.
2. For multi-site, multi-institution proposals, the primary rapid expedited or rapid full review (depending on risk level) will be conducted by the institutional REC of the National PI of the study in question.
3. The rapid review should take at minimum 48 hours for a minimal risk study and ideally no longer than 72 hours for a clinical trial.
4. The primary REC or PI may consult RESCOP for informal advice.
5. The National PI may share the review outcome of the review to RESCOP.
6. The REC's concerns, comments and recommendations may be reviewed by RESCOP and the National PI.
7. On request, RESCOP is available to support and advise the National PI and local PIs and related RECs during this process as and when the need arises.

ACKNOWLEDGEMENTS:

RESCOP meeting minutes 24 March, 2020.

REFERENCE:

Department of Health (2015). *Ethics in Health Research: Principles, Processes and Structures (2nd ed.).* Pretoria: Author.

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