15

Research ethics support during the COVID-19 epidemic:

a collaborative effort by South African Research Ethics Committees

Authors

Theresa M. Rossouw[i,ii,iii]
Douglas Wassenaar[iv,v]
Mariana Kruger[vi]
Marc Blockman[vii]
Alistair Hunter[viii]
Theresa Burgess[ix,iii]

For results to have maximum impact and relevance in a public health emergency, ethics review and approval must be rapid and timeous, without compromising the rigour and quality of the review.

The COVID-2019 pandemic caused disruption of health services globally due to increased need for critical care facilities and collateral damage to routine healthcare services. Global and local research into disease pathogenesis and management strategies is central to a public health emergency response. South African legislation mandates that no health research may be conducted without approval from a registered Research Ethics Committee. For results to have maximum impact and relevance in a pandemic situation, ethics review and approval must be rapid and timeous, without compromising rigour and quality of review. This chapter argues that South African Research Ethics Committees were under-prepared for this task, largely due to gaps in national ethics guidance and the critical absence of the National Health Research Ethics Council. Although ethics guidance documents contain enabling clauses, no specified procedures for rapid review in emergencies exist. Consequently, and in an unprecedented initiative, several Research Ethics Committee chairpersons and members formed a spontaneous informal, *ad hoc* group, 'Research Ethics Support in COVID-19 Pandemic' (RESCOP), to share resources and support for managing the review of research related to COVID-19.

The chapter outlines the processes put in place and mechanisms introduced by RESCOP in the interest of responsible and accountable, but rapid, ethics review. We describe good practices for rapid full ethics review of COVID-19 health research, including clinical trials.

RESCOP's innovative collaboration enabled rapid but thorough ethics review of research protocols during the epidemic. The processes established can serve as a good-practice model that could be adopted and adapted by other committees and future versions of national research ethics guidelines.

i Department of Immunology, University of Pretoria
ii Research Centre for Maternal, Fetal, Newborn and Child Health Care Strategies, University of Pretoria; South African Medical Research Council
iii Centre for Medical Ethics and Law, Stellenbosch University
iv Biomedical Research Ethics Committee, University of KwaZulu-Natal
v South African Research Ethics Training Initiative, University of KwaZulu-Natal
vi Department of Paediatrics and Child Health, Stellenbosch University
vii Department of Medicine, University of Cape Town; Groote Schuur Hospital
viii Division of Radiation Medicine, University of Cape Town
ix Division of Physiotherapy, University of Cape Town

Click to navigate to Contents

Introduction

The COVID-19 pandemic caused unprecedented disruption of health services globally. Not only was there a dramatically increased need for hospital and critical care facilities due to the large number of people presenting with SARS-CoV-2 infection, but it diverted attention and resources from routine healthcare services with consequent collateral damage, especially to maternal and child health, HIV, and tuberculosis (TB) services.[1,2,3]

When faced with a devastating infectious disease with no preventive or curative treatment, the public health response relies heavily on urgent local and global research into disease pathogenesis and management strategies. Nevertheless, research, however urgent, should comply with applicable legal and ethical frameworks. South African legislation mandates that all health research with human participants must receive prior ethics review and approval from a National Department of Health (NDoH)-registered Research Ethics Committee (REC). For results to have maximum impact and relevance in a public health emergency (PHE), ethics review and approval must be rapid and timeous, without compromising rigour and quality of review. South African RECs were relatively under-prepared for this urgent task. Despite many decades of formal, well-structured ethics review in the country[4], it appears that no REC had standard operating procedures (SOPs) facilitating the rapid review of research in PHE. This situation was exacerbated by having no national ethics guidance documents that specified procedures for rapid review of research in PHE.[5,6]

This chapter explores the need for ethically responsible and accountable research during a PHE, the possible reasons for RECs being under-prepared, and the response of South African REC chairpersons and members to form a spontaneous informal, ad hoc group, 'Research Ethics Support in COVID-19 Pandemic' (RESCOP), to share resources and support for reviewing research related to the COVID-19 epidemic, including clinical trials. This chapter details the processes and mechanisms introduced by RESCOP to support rapid full ethics review of clinical trials, reflects on lessons learnt, and concludes with a proposed good-practice model that could be adopted and adapted by other RECs and future versions of national research ethics guidelines.

Research ethics regulation and guidance in South Africa have been well structured and resourced since the revision of the National Health Act[7] and the first formal South African NDoH research ethics guidance issued in 2004[8], accompanied by the formation of the Health Research Ethics Council (NHREC) which, inter alia, registered and audited all South African RECs for compliance with the national guidance. A second revised and updated version of the national guidelines was published in 2015[5] after a process of wide consultation and expert input. Prior to the 2004 guidelines and NHREC formation, research ethics review was largely an institutional prerogative, using local guidance from the South African Medical Research Council or international guidance as needed. However, research guidance, in general, always lags behind real-world developments in the field, and should be revised periodically to accommodate innovations in science and research design. This chapter describes such pressures and a response arising from nationally and internationally urgent COVID-19 research.

Key findings

Impact on health systems and research during COVID-19

The COVID-19 pandemic has had a major impact on health care as most countries opted to focus on COVID-19-related and emergency health care. Similarly, many patients were reluctant to visit healthcare facilities due to the risk of contracting COVID-19. Of note, routine healthcare utilisation decreased to a third, especially for patients with mild to moderate illnesses.[9] Drawing from expert advice formulated by the COVID-19 Ministerial Advisory Committee, the South African government closed non-essential services, including routine and elective healthcare services, implemented physical distancing with self-isolation, closure of schools, travel restrictions and national lockdowns to limit the spread of SARS-CoV-2.[10,11]

The South African COVID-19 epidemic was associated with an increased mortality rate, a surge in mental health problems, substance abuse, and gender-based violence. Deaths in the country increased, with a national excess death rate of 262 per 100 000 population by 24 April 2021 and a COVID-19 case fatality rate of 2.2%.[12] The increased deaths were attributed to COVID-19 infections, as well as limited access to healthcare, especially for antenatal and postnatal services, HIV and TB testing and treatment, and non-communicable diseases such as cancer.[8] The mental health problems included avoidance behaviours, depression and anxiety, worsened by job losses and financial insecurity.[13,14] Psychosocial support services were stretched while the psychosocial consequences led to stigmatisation, racism, xenophobia and discrimination.

The COVID-19 epidemic also affected the general health of the population as existing gaps and healthcare constraints worsened.[10] Restriction of movement and exercise led to weight gain with increased obesity, aggravation of hypertension and other cardiovascular diseases, as well as substandard management of other non-communicable diseases. Child development was also affected as schools closed and normal social interaction and exercise were limited.

Other challenges included a deficit of adequately trained healthcare workers and personal protective equipment. Disproportionate distribution of healthcare workers between

urban and rural areas amplified inequity in health service delivery. Detection, contact tracing and monitoring of patients were seriously limited. Added to these problems were issues of misinformation and fake news, which exacerbated stigmatisation, anxiety, and xenophobia.[10]

Healthcare research in general suffered during the COVID-19 epidemic, as all research activities were paused during certain phases of national lockdown.[15] This effect was especially debilitating for clinical trials. Researchers and RECs were inadequately prepared for dealing with this sudden blanket cessation of recruitment and management of participants. Clinical trials are essential foundations of evidence-based health care to provide future patients with new prevention technologies and therapies. Existing national guidelines provided no direction for RECs and researchers on how and when essential research could safely continue, especially where existing participants should continue their treatment, for example, in trials for multidrug-resistant TB.[16] At the same time, there was a rapid increase in COVID-19-related research, including preventive and therapeutic clinical trials, where researchers requested rapid ethics review and appealed to RECs not to delay approval of their research, given the lack of known effective prevention and treatment modalities.

Informed consent was often a complex issue, as knowledge regarding COVID-19 was still evolving and full risk/benefit disclosure was not always possible due to lack of evidence-based information. Paper-based consent forms posed risks of transmitting COVID-19, while incapacitated patients' family members could not provide consent in person as they were not allowed into healthcare facilities – all of this challenging the respect for persons necessary in research. Proxy consent, delayed proxy consent and waivers of consent are all complicated alternatives that require careful consideration of practicality as well as potential harms and benefits.[15] These debates are especially complicated in the presence of incomplete contextual information and suboptimal interaction on online platforms. This caused great discomfort for researchers and RECs alike. In effect, all research that could not be conducted via online systems was stopped, creating inequity for participants in need of in-person follow-up.

Ethically responsible and accountable research during a pandemic

During a PHE, such as the COVID-19 pandemic, priorities may change, and some research may become urgent. However, while regulatory and administrative processes may be adapted to meet the demands, ethical principles remain essentially unchanged.[18,19] RECs must carefully review research protocols to ensure that the principal investigator (PI) has designed the research to minimise potential harms and maximise potential benefits to participants and their communities, and that scientific validity and social value are upheld while urgent evidence-based solutions to the PHE are found. The challenge is to facilitate important research while maintaining uncompromised ethical oversight. In a PHE, RECs come under increased pressure while researchers may rush to construct urgent protocols in the context of potentially severe resource constraints due to the burden of COVID-19 patients.

Many of the studies submitted to RECs are also multi-national studies, adapted and customised for local conditions. Issues such as methods of recruitment, disparities in health care, ancillary care and post-trial access are considerations that may require negotiation before studies can be ethically implemented. This is not peculiar to the COVID-19 era but, in the COVID-19 space, issues may be more acute and complex and consequently may require additional scrutiny by RECs.

Tension between urgency and due diligence

Striking a balance during a PHE between urgency and uncompromised ethics review and oversight can be challenging. Some therapeutic studies in PHE adopted adaptive designs to accommodate rapid shifts in direction as some approaches proved ineffective. There is the risk of signing 'blank cheques', as in many cases there may be little evidence for the efficacy of medicines against SARS-CoV-2, many of which have been repurposed for use in COVID-19 treatment. Thus, extra vigilance by RECs is required along with urgency as a parallel pressure. Weaker justifications for studying new treatments may have to be weighed up accordingly and, if allowed, approved with suitable safety monitoring and stopping rules to protect participants. The frequent lack of relevant peer-reviewed data is also problematic during a PHE, as global research occurs rapidly and non-peer-reviewed data (such as is found in pre-publication papers) must often be considered. Assessing the integrity of preliminary, non-peer-reviewed data is a source of concern for RECs.

The shifting ethics debate around vaccine trials

Vaccine trials, which are clearly a priority during COVID-19, should be considered in terms of their strategic importance for disease prevention. Despite the absence of long-term safety data related to certain new technologies, vaccines are recognised as a key strategy in the management of COVID-19 with the potential benefits of reduced morbidity and mortality and increased population immunity. New vaccine studies are essential, especially with the development of COVID-19 variants which may be more virulent, infectious or resistant to initial vaccine responses.

Many questions arose, such as, at what point does a placebo-controlled vaccine trial become unethical?[18] Once the efficacy of vaccines has been established and products become freely available in the public sector, it might be argued that a new standard of care has been developed which should thus form the control arm of any further vaccine trials. However, given the emergence of variants of concern, and slow roll-out of approved vaccines (as is the case in South Africa and elsewhere), a case may be made to continue trialling new vaccines against placebos. The

extent to which older vaccines will still work against new variants is a point of debate and mostly informed by *in vitro* data to date.

Given the global shortage of COVID-19 vaccines and the urgent need for such prevention, trials present an opportunity for researchers, supported by RECs, to negotiate fair post-trial access for the community. Unfortunately, due to the urgency of the situation and, once again, the absence of operational guidance in this regard, this ethical aspect was initially mostly neglected in South Africa.[21]

In the fast-moving landscape of COVID-19 vaccine development, it is difficult for RECs to remain current. Facts upon which decisions are based may soon become outdated. Indeed, it may be difficult to define precisely what the standard of care should be during a PHE where the therapeutic and prevention landscape is continually changing.

Implementation of pragmatic trials oversight difficulties for RECs

The first large-scale vaccination programme in South Africa, aimed at healthcare workers (the Sisonke Trial), was performed as part of a formal phase IIIb implementation trial, despite being billed by some as a roll-out. RECs were under pressure to rapidly review and weigh the risks and benefits and possible imperfections of such a large-scale exercise. Some RECs found it challenging to negotiate and oversee the implementation of such large-scale pragmatic approaches within the traditional research paradigm. While it is necessary to initiate such programmes during a PHE, there are nevertheless risks of harm, as there are in all clinical trials. Therefore, it is particularly important that RECs maintain close communication with researchers and the South African Health Products Regulatory Agency (SAHPRA) for close monitoring of progress and adverse event reports.

Risks of over-researching

International collaboration has facilitated the rapid development of new vaccines as well as treatment strategies. Sharing of samples to facilitate their optimal use is therefore of clear benefit in PHEs. However, when large diverse populations become available for research, RECs must be wary of opportunism occurring under the guise of crucial public health research.[16] The intense interest in COVID-19 has spawned a plethora of studies, with competition between several research groups for the same patient data or samples. RECs must ensure that fair, non-repetitive and minimally disruptive access to samples can occur. This may require formal custodianship and sharing of research databases and repositories, which can become valuable resources but require due consideration of protection of personal information.

Increased burdens on RECs, reviewers and researchers during COVID-19

In addition to therapeutic trials, observational research with COVID-19 patients during the pandemic increased exponentially. Apart from the potentially increased complexity of studies, the number of studies requiring urgent review also increased. Hence, some RECs committed to rapid full committee reviews with the result that several full committee meetings, over and above scheduled meetings, also took place. In addition, there were many minimal-risk expedited studies that required review outside of full committee meetings. Many RECs switched to virtual meetings, enabling rapid full committee processes between scheduled meetings. REC members were thus subjected to significant additional workload during the pandemic, with increased pressure on REC members and administrative staff. Moreover, reviewer fatigue may become prevalent after performing multiple reviews in quick succession. This is in addition to the heavier workloads and long hours that many COVID-19 experts (who in many cases also review studies, care for COVID-19 patients and serve on high-level government COVID-19 advisory committees) invested. Many of these people may also be researchers themselves, feeling the weight of their research responsibilities. A unique related conflict-of-interest situation arose in that many eligible REC members also enrolled in the Sisonke vaccine trial after approval.[a] How RECs managed this conflict warrants careful future study.

Doing research differently under COVID-19

Standard research ethics guidance requires RECs to ensure that research is conducted appropriately during a PHE. In addition to the issues associated with COVID-19 research, it is important to consider practices and risks of viral transmission generally among participants and researchers during research. Depending on the risk and stage of the pandemic, research projects may have to be justified and measures for mitigation of transmission risk described before approval. Appropriate handling of biohazardous material and other potential sources of infection may have to be addressed. Face-to-face interactions may have to be avoided, reduced, or substituted with online contact where possible. Any in-person interactions require formal COVID-19 prevention protocols to reduce the risk of transmission. RECs may be more inclined to allow face-to-face studies where research is combined with already scheduled clinical visits.

Given that research is ultimately beneficial for mankind in advancing evidence-based health solutions, a balance must be struck between limiting and facilitating research. Recently, pauses on research in key areas relevant to South Africa (such as HIV and TB prevention and treatment) were lifted because ongoing interruption of such studies may lead to long-term harms that are potentially greater than the COVID-19 threat. As a result, after initial shutdown of many research studies under early lockdown restrictions,

a Enrolment in the Sisonke trial was open only to registered healthcare workers.

TB and HIV clinical trials were allowed to resume by RECs. As lockdown levels have eased, most other studies have also restarted.

With so many issues to consider during the COVID-19 pandemic, ethical rigour nevertheless remains paramount. RECs with heavy and complex workloads had to remain vigilant and, while cognisant of urgency, not be pressurised into making rushed decisions in the interests of expediency.

Why South African RECs were initially under-prepared to review public health emergency research during COVID-19

As mentioned, the NHREC is the regulatory authority for RECs in South Africa.[7] In accordance with section 72 of the National Health Act, the mandate of the NHREC entails setting norms and standards for health research in South Africa, developing guidelines to facilitate best practice for South African RECs, and adjudicating complaints about research ethics.[5] The NHREC was established in 2006 and the National Minister of Health appoints members to serve on the NHREC for three-year cycles. However, from November 2019 to December 2020, the NHREC was not reconstituted. This resulted in RECs being left without active formal NHREC support during the first and second waves of the COVID-19 epidemic.[22]

In addition to general research ethics guidance, the NDoH 2015 research ethics guidelines provide some direction for major incidents and research. The guidelines highlight the importance of research in these contexts, including disease outbreaks, specifically for the development of emergency healthcare interventions and treatment to improve survival rates and quality of life. Resource allocation research to refine policies is also encouraged. The guidelines caution RECs against being "overly restrictive about the type of research that may be conducted" (section 3.4.1), while recognising that research participants and their families may be highly vulnerable. RECs are also encouraged to consider alternative approaches to informed consent.[5]

The NDoH guidance also permits reciprocal recognition of review decisions, to avoid duplication of effort in REC review. However, the guidance states that this is at the discretion of individual RECs, and that RECs can independently determine the nature of documentation that should be submitted for reciprocal review.[5] Anecdotally, prior to COVID-19, RECs that recognised prior review by other RECs indicated that this was typically considered only for minimal-risk research, where prior review was conducted by a REC in relatively close proximity and mutual understanding of the research context. In addition, it emerged that prior to COVID-19, RECs did not have formal procedural standard operating procedures for reciprocal review in place.

While the NDoH guidance is sufficiently broad to facilitate the autonomy of RECs in reviewing and approving PHE research, operational guidance is lacking. Differences in interpretation of appropriate restrictions for PHE research and informed consent processes by individual RECs may lead to disparate review procedures during the independent, asynchronous review of multi-site clinical trial protocols. The absence of clear guidance to operationalise mutual recognition of ethics review, especially for more-than-minimal-risk research, meant that RECs were under-prepared to reduce duplication of effort in urgent research and in conducting urgent reviews to maximise reliable and safe conduct of clinical trials during COVID-19. The broad, non-specific nature of the PHE section of national research ethics guidelines may therefore have had the unintended consequence of potentially slowing down COVID-19 research in South Africa. This was also compounded by the absence of the NHREC itself to advise, interpret and update guidelines for urgent COVID-19 research.

Table 1 describes some of the issues that made ethics review of research protocols unique during the COVID-19 and added to the sense that RECs were ill-prepared for the task.

Table 1: Issues and experiences highlighting the uniqueness of REC reviews during COVID-19

Issue	REC experiences during COVID-19
Remote, electronic REC functioning	Many REC members and administrators were working from home, requiring rapid online systems development which importantly considered the Protection of Personal Information Act and other aspects of confidentiality. Working online was novel for REC members, administrators and ad hoc reviewers, and required agility and adaptation to process flows for many RECs.
Rapidly constituted REC meetings	All REC meetings moved online and, in some cases, these meetings became weekly or bi-weekly – all to ensure timeous review and collaboration with COVID-19 investigators. In addition, the medicines regulator (SAHPRA) only approves clinical trials subject to parallel REC approval, so rapid review was essential.

Issue	REC experiences during COVID-19
Immature, multi-national, multi-centre protocols with adaptive study designs	RECs also had to deal with some immature COVID-19 protocols that were either trialling novel agents or repurposing old medicines. The majority of these COVID-19 clinical trial protocols were multi-national and multi-centred with adaptive study designs. This meant that for treatment or prophylactic trials, trial arms would either continue or be dropped, depending on interim analyses. This entailed flexibility in review and the ability for RECs to adjudicate on immature data or, at times, without full pre-clinical data to facilitate early treatment or prophylactic protocols that may have benefited very vulnerable individuals or sick patients.
Community engagement	Challenges with community engagement were twofold. RECs were required to ensure appropriate community representation during deliberations due to challenges with online platforms and digital means. This required additional resourcing and capacity development. In addition, ensuring appropriate community engagement during the planning and execution of research was challenged by the urgency of COVID-19 research, lockdown constraints, lack of access of many community members to online platforms, and determining the relevance and appropriateness of community representation during pandemics.
Informed consent	With the very high risk of COVID-19 spread and limitations placed on research staff engaging face-to-face with potential participants, RECs had to urgently establish ways for participants to provide informed consent, both electronically and remotely. In addition, although the NDoH 2015 guidelines provide helpful input regarding the approach to obtaining deferred and proxy consent, COVID-19 introduced additional challenges 'on the ground'. A significant issue was the difficulty in accessing family members to provide proxy consent, as hospitals prevented family members from entering facilities. Other issues around remote, electronic consent processes were highlighted, including establishing the digital literacy of participants or their proxies, the protection of individual privacy and confidentiality of data, justice issues associated with data costs and research participation, and challenges with establishing the veracity of electronic or remote methods of providing informed consent.

REC=Research Ethics Committee; NDoH=National Department of Health

The South African Research Ethics Councils' response

The escalating international COVID-19 pandemic started to raise concerns during early (2020) routine meetings of some South African RECs. Questions were asked about whether adequate contingencies were in place to conduct review of emergency COVID-19-related treatment research protocols without undue delay, given anecdotal reports from PIs and RECs about the generally slow (two to four months) turnaround time of final approvals for multi-site clinical trials at some RECs. After COVID-19 attained international status as a pandemic on 11 March 2020, early treatment protocols began to be submitted to RECs with requests from PIs that these be reviewed without delay so that treatments could be tested and developed. Despite guidance encouraging REC chairpersons to consult on difficult issues, RECs typically operate independently. However, in this case, because of the unprecedented urgency to conduct rapid ethics review of complex multi-site clinical trials and the lack of procedural/operational specificity in the current guidelines described earlier (and because standard expedited review procedures for minimal risk research were clearly inapplicable for complex clinical trials), one REC chairperson (DRW) reached out to another REC chairperson (MB) to discuss contingencies for minimising delays in reviewing urgent COVID-19 treatment and prevention research. MB's response was positive and indicated that he was similarly about to seek support and collaboration from other REC chairpersons on the same question. A forthcoming multi-site COVID-19 treatment trial also warranted discussion among the REC chairpersons of collaborating sites.

As noted, the NHREC appointed for the period 2016 to 2019 had left office in November 2019. While many former Council members continued to serve on various RECs across South Africa and could provide unofficial guidance and advise to their respective RECs, there was an absence of formal, national-level guidance. In addition, given the magnitude of research ethics issues and the challenges associated with reviewing and conducting research during the COVID-19 epidemic, REC chairpersons recognised the importance of a collaborative and inclusive approach by RECs to COVID-19 research. Therefore, the two chairpersons initiated and co-ordinated RESCOP as an informal national network of biomedical REC chairpersons.

A snowball approach was used and within less than three weeks, a network had been formed with over 80 members, comprising mainly REC chairpersons, co-chairpersons, REC members and support staff representing most RECs in South Africa, especially those active in the review of clinical trials. It was encouraging to note that the South African medicines regulator, SAHPRA, had also committed to rapid emergency review processes to assist in testing suitable products to address the escalating morbidity and mortality associated with the epidemic.

RESCOP performed two main functions: provide a network of support and ad hoc consultation among REC chairpersons facing requests for urgent review of treatment and prevention trials, many of which were to be run at multiple sites, requiring some consistency of procedures across sites; and provide access to relevant recent scholarly ethics

resources and advisories on the ethical but accelerated conduct of full committee ethics review of clinical trials during the COVID-19 epidemic. To this end, one member (MK) opened an open-access Dropbox folder in which recent relevant COVID-19 research ethics resources were stored for access by interested parties. This folder currently houses over 160 resource documents, most of which are dated 2020 and later. An early set of RESCOP resources was also requested and used by the World Health Organization (WHO) when starting the international Public Health Emergency Preparedness and Response (PHEPREN)[23] initiative to offer similar support to stakeholders internationally.[b]

Significantly, in the early weeks of the epidemic, RESCOP also posted a specific procedural guidance document in the open-access folder, entitled *Rapid Full Committee Review of COVID-19 treatment and prevention trial procedures*, designed to be aligned with and supplementing the NDoH 2015 guidelines. The RESCOP advice stated: "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 NDoH ethics and health research guidelines (section 3.4.1).[5]

In this statement, the term 'rapid full review' was used to emphasise that the proposed review process was not analogous to expedited review, which typically applies to minimal-risk research (section 4.5.1.5)[5], and that this was a rapid but full review process, identical to the process ordinarily used to review more-than-minimal risk studies that require full committee ethics review, with the key difference being that instead of waiting for each scheduled monthly meeting to finalise outcome decisions, special full committee processes were initiated to shorten the decision intervals, using either online meetings, round-robin e-mail decisions, etc. All the processes recommended turned out to be compliant with those recommended by WHO guidance[19] for such circumstances.

Other later RESCOP activities involved efforts to implement 'reciprocal' review of multi-site studies, mainly to reduce significant duplication of REC effort and achieve consistent review outcomes in multi-site studies. The RESCOP advisory stated that "Section 4.5.1.4 of the DoH (2015) guidelines allow RECs to recognise prior review and approval by another registered REC at their discretion to avoid duplication of effort". However, after some attempts it became clear that there was no uniformity among RECs on how reciprocity (sometimes referred to as 'centralised review')[24] should be operationalised. In attempts to implement this with neither a clear definition nor operational steps (except for the enabling phrase in NDoH guidelines), several possible meanings emerged without clear consensus or recognition of what was being negotiated. These meanings included:

- One national REC takes over the entire oversight of all sites of a national clinical trial, with the agreement of all parties (PIs and affected REC chairpersons).
- One REC makes their review and recommendations available to other RECs to adopt or amend locally as required, but multiple RECs remain involved as ethics oversight bodies for their respective PIs and research sites.
- One REC conducts the review and approval but all site RECs remain responsible for all the downstream post-approval oversight of study activities and PIs in their local domain.

Other complex variations emerged and are also under consideration by the United States-based Office for Human Research Protections (OHRP).[25]

Another minor RESCOP activity was the regular forwarding of notices of online research ethics webinars to all RESCOP members via a group e-mail, thereby maximising South African REC stakeholders' access to current local and international topical resources and discussions on ethical aspects of COVID-19 research.

Lessons learnt from RESCOP

Firstly, RESCOP created an unprecedented level of active engagement, co-operation and support between South African RECs. This active informal network could continue to function usefully around future issues other than the COVID-19 drivers already described. Synergies were created and duplication of effort was reduced in multi-site protocol review in many cases. Sharing protocol reviews in other cases, along with pooling of resources and materials, helped to align reviews and facilitated rapid and thorough review by sharing comments on protocol weaknesses and strengths. A procedural guideline on how to implement rapid review was also generated and circulated. Such active, non-competitive co-operation is unprecedented in South Africa, apart from a former network of REC chairpersons co-ordinated by Professor Cleaton-Jones of the University of the Witwatersrand that dissolved after the NHREC was initiated around 2003/2004. RECSOP provided advice and support that turned out to be congruent with international guidance that emerged in parallel.[19] Potential risks and benefits to participants were always carefully foregrounded, while simultaneously promoting potential public health benefits to the country.

Efforts to implement reciprocity (single review of multi-site studies) did not work well in all cases, flagging the need for our local ethics guidance to develop clear procedural guidelines to facilitate this effectively in future, as is being done in America. As a caveat, no formal evaluation of RESCOP members and outcomes has been conducted to date, so this description remains subjective and anecdotal.

b Personal communication: K. Littler, World Health Organization, 2020.

Recommendations for a good-practice model

Table 2 summarises the principles of a proposed good-practice model for ethics review in PHE, based on lessons learnt from RESCOP.

Table 2: Principles of a proposed good-practice model

Principles	Practical examples
Shared vision	Fairness in research is paramount. Ethics review should be rapid, but thorough and fair.
Values	Scientific validity, social value, fair recruitment strategies, favourable risk–benefit relationship, informed consent, respect for communities and independent ethics review.[25]
Collaboration	Building on strengths of RECs and individual members Building trust and active collaboration between RECs
Inclusivity	Involvement of all national RECs
Informed decision-making	Open-access folder containing academic resources Sharing notices of online research ethics webinars
Rapid review	Sharing reviews Implementing rapid but thorough alternatives to scheduled monthly meetings
Reciprocity	Developing formal processes and guidelines for reciprocity of ethics review
Fairness	Considering the fairness of research collaborations and partnerships Ensuring that post-trial access has been considered
Reflection	Frequent evaluation of what is working
Adaptation	Adapt and document processes and guidance as required.

Source: Emanuel et al., 2004[26]; Lavery and IJsselmuiden, 2018.[27]

Conclusion

RESCOP arose as a support network of REC chairpersons and stakeholders to support and advise each other in meeting the country's urgent research needs in an ethically sensitive, innovative, guideline-compliant and responsible way during the COVID-19 PHE, without compromising review thoroughness or diligence, but minimising avoidable administrative delays. RESCOP achieved this by providing *ad hoc* discussions, guidance and support as well as sharing an open-access folder of relevant, recent research ethics COVID-19-related papers, comments and guidelines with the community of REC chairpersons and national stakeholders. It is believed that RESCOP's informal guidelines to South African RECs during the epidemic greatly assisted RECs in conducting meaningful rapid full ethics review, which enabled important COVID-19 treatment and prevention trials to start much sooner in South Africa. This was all the more notable in the absence of the statutory NHREC that was re-appointed only early in 2021, by which time most South African RECs had developed and implemented RESCOP support and guidance through two local waves of the COVID-19 epidemic.

Acknowledgements

The authors acknowledge comments and support from RESCOP colleagues during the processes described in this article.

References

1. Ongole J, Rossouw T, Fourie B, Stoltz A, Hugo J, Marcus T. MDRTB in South Africa – Sustaining Primary Healthcare Essentials in the COVID-19 Pandemic. Int J Tuberc Lung Dis, 2020; 24(6):643–645. URL: http://dx.doi.org/10.5588/ijtld.20.0214

2. Ahmed T, Rahman AE, Amole TG, et al. The effect of COVID-19 on maternal newborn and child health (MNCH) services in Bangladesh, Nigeria and South Africa: call for a contextualised pandemic response in LMICs. Int J Equity Health, 2021: 20(77). URL: https://doi.org/10.1186/s12939-021-01414-5

3. Jewell BL, Mudimu E, Stover J, et al. for the HIV Modelling Consortium. Potential effects of disruption to HIV programmes in sub-Saharan Africa caused by COVID-19: results from multiple mathematical models. Lancet HIV, 2020; 7(9): E629–640. URL: https://doi.org/10.1016/S2352-3018(20)30211-3

4. Cleaton-Jones P, Wassenaar DR. Protection of human participants in health research: A comparison of some US federal regulations and South African research ethics guidelines. S Afr Med J, 2010; 100(11):710–716. URL: http://www.samj.org.za/index.php/samj/article/view/4525/2993

5. South African National Department of Health. Ethics in health research: Principles, processes and structures. 2nd edition. Pretoria: NDoH; 2015.

6. South African National Department of Health. Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa. 2nd edition. Pretoria: NDoH; 2006.

7. South African National Department of Health. Republic of South Africa: National Health Act 61 of 2003. Pretoria: NDoH; 2003. URL: https://www.gov.za/documents/national-health-act#

8. South African National Department of Health. Ethics in health research: Principles, structures and processes. Pretoria: NDoH; 2004

9. Moynihan R, Sanders S, Michaleff ZA, et al. Impact of the COVID-19 pandemic on utilisation of healthcare services: a systematic review. BMJ Open, 2021; 11: e045343. DOI:10.1136/bmjopen-2020-045343

10. Mbunge E. Effects of COVID-19 in South African health system and society: An explanatory study. Diabetes Metab Syndr, 2020; 14(6):1809–1814. DOI:10.1016/j.dsx.2020.09.016

11. South African National Department of Health. South Africa COVID-19 Experiences to Date. 25 August 2020. URL: https://sacoronavirus.co.za/2020/08/25/slideshow-south-africa-covid-19-experiences-to-date-25th-august-2020/

12. South African Medical Research Council. Report on Weekly Deaths in South Africa. 2021. URL: https://www.samrc.ac.za/reports/report-weekly-deaths-south-africa?bc=254

13. Dubey S, Biswas P, Ghosh R, et al. Psychosocial impact of COVID-19. Diabetes Metab Syndr, 2020; 14(5):779–788. DOI: 10.1016/j.dsx.2020.05.035

14. Gould C. Gender-based violence during lockdown: looking for answers. Servamus, 2020; 113(7):56–57. URL: https://journals.co.za/doi/10.10520/EJC-1e76d4d50f

15. Vissers MFJM, Cohen AF, Van Gerven JMA, Groeneveld GJ. The impact of the global COVID-19 pandemic on the conduct of clinical trials: Return to normalcy by considering the practical impact of a structured ethical analysis. Br J Clin Pharmacol, 2021; 87(3):837–844. URL: https://pubmed.ncbi.nlm.nih.gov/32668047/

16. Pai M. Covidization of research: what are the risks? Nat Med, 2020; 26(1159). URL: https://doi.org/10.1038/s41591-020-1015-0

17. Moodley K, Allwood B, Rossouw TM. Consent for critical care research after death from COVID-19: arguments for a waiver. S Afr Med J, 2020; 110(7):629–634.

18. Nuffield Council. Research in global health emergencies. 2020. URL: https://www.nuffieldbioethics.org/publications/research-in-global-health-emergencies

19. World Health Organization. Guidance for research ethics committees for rapid review of research during public health emergencies. 2020. URL: https://www.who.int/publications/i/item/9789240006218

20. Singh J, Upshur R. The granting of emergency use designation to COVID-19 candidate vaccines: implications for COVID-19 vaccine trials. Lancet Infect Dis, 2020; 21(4): e103–109. URL: https://doi.org/10.1016/S1473-3099(20)30923-3

21. Moodley K, Rossouw TM. South African COVID-19 vaccine trials hold key lessons for future partnerships. The Conversation, 29 February 2021. URL: https://theconversation.com/south-african-covid-19-vaccine-trials-hold-key-lessons-for-future-partnerships-154676

22. Moodley K. Research imperialism resurfaces in South Africa in the midst of the COVID-19 pandemic – this time, via a digital portal. S Afr Med J, 2020; 110(11):1068–1069. DOI:10.7196/SAMJ. 2020.v110i11.15285

23. Epidemic Ethics. Research, Preparedness & Response. 2021. URL: https://epidemicethics.tghn.org/

24. Ferguson A, Master Z. Multisite Research Ethics Review: Problems and Potential Solutions. Bioéthique Online, 2016; 5/7. URL: http://bioethiqueonline.ca/5/7

25. Office for Human Research Protections. Practical and ethical considerations for single IRB review. 2021. URL: https://www.hhs.gov/ohrp/sites/default/files/2020-exploratory-workshop-summary-irb.pdf

26. Emanuel EJ, Wendler D, Killen J, Grady C. What makes clinical research in developing countries ethical? The benchmarks of ethical research. J Infect Dis, 2004; 189(5):930–937. URL: https://doi.org/10.1086/381709

27. Lavery JV, IJsselmuiden C. The Research Fairness Initiative: Filling a critical gap in global research ethics. Gates Open Research, 2018; 2:58. URL: https://doi.org/10.12688/gatesopenres.12884.1