

## **Report on Webinar: Pandemic Research: Drawing from Lessons Learnt During the Sisonke Study**

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### **Introduction**

The SA Medical Research Council's Bioethics Advisory Panel held a webinar on 8<sup>th</sup> September 2021 to explore lessons learnt from the Sisonke Study. Understanding both the positive encounters and challenges could assist with research planning and implementation that responds to scientific, ethical and regulatory dynamism going forward in the current and future pandemics. COVID-19 has been associated with high mortality and a lack of safe and efficacious interventions. Experience from pandemics in the past and the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak allow for the recognition of the many challenges to conducting research in this context. A pandemic itself puts pressure on the need to conduct research, especially where the mortality rate is high and treatment options are limited. Ethically conducted research needs to be supported and promoted and the risk of unethically conducted health research during these emergencies must be rigorously curtailed. All people during this time deserve their health to be promoted and protected. Hence there is an ethical imperative for the meticulous collection of robust and good data. This must be coupled with respecting dignity and upholding rights. Expedience does not justify unethical practice. What is required is balance, and this balance must be informed by the voices of relevant stakeholders (O'Mathúna, Siriwardhana, 2017). This Report starts off with an introduction to the ethical issues considered when planning the webinar, the objectives of the webinar and an outline of the program. The content and discussions at the webinar are detailed thereafter.

### **Relevant Ethical Principles**

All ethical principles must be upheld when conducting research during a pandemic. However, some principles require special attention during this time (CIOMS, 2016). Certain relevant principles pertinent to vaccine research and the Sisonke Study include scientific and social value; distributive justice; and protectionism.

#### ***Scientific Validity and Social Value***

Lessons learnt from the SARS-CoV-2 outbreak is that it has rapidly evolved necessitating the use of alternative study designs to yield meaningful data. Study designs, while feasible must also be appropriate in order to ensure scientific validity. 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). While the randomised-controlled trial design is often considered the gold standard for obtaining robust data in clinical trials, alternate trial designs that may increase efficiency while still maintaining scientific validity must be explored. It is essential that the methodological and ethical merits of these designs be carefully assessed prior to the research being conducted.

### ***Distributive Justice: Equitable Distribution of Risks and Benefits***

As has been seen with COVID-19, it may be acceptable to prioritise certain populations when enrolling into the study. An example is frontline healthcare workers who put themselves at risk during infectious disease outbreaks while attending to infected patients. If experimental interventions have been proven to be effective, they could be prioritised for enrolment in, for instance, an implementation study so they are readily available to help more patients (CIOMS, 2016).

### ***Protectionism: Ethics Review and Oversight***

Soon after COVID-19 was declared a pandemic by the World Health Organisation (WHO), there was an explosion of research activities including clinical trials with the objective of finding cures and vaccinations. Standard mechanisms for ethical review have been found to be too time consuming and procedures have been developed to facilitate and accelerate ethics review and continued oversight where significant ethical concerns are raised by the research (CIOMS, 2016). Rapid review and approval of novel approaches are necessary to avoid delays in research during this time. When the nature of the global threat is considered, it becomes understandable that new practices will be embarked upon in the emergency context (Nuffield Council of Bioethics, 2020). Nevertheless, any such decisions will require ethical justification, and it is important to bear in mind that ethical principles cannot be transgressed but can be adjusted to exceptional circumstances. The urgency to find a cure or prevention cannot be used as a justification to preclude responsible research practice. (UNESCO, 2020). Research Ethics Committee (REC) over-reach may also be a concern as it could lead to delays in the implementation of studies or amendments to protocols.

### **The Sisonke Study**

In January 2021, emerging evidence of the lack of efficacy of the ChadoX/astrazenica vaccine against the dominant beta (B1.351) variant strain circulating at that time curtailed the roll-out of this vaccine to health care workers that had been prioritised to receive it in the national rollout programme. The lack of available vaccines authorised for use in South Africa and the emerging evidence of the efficacy of the Ad26 SARS-CoV-2 vaccine created an opportunity to rapidly translate this evidence into practice utilising a phase 3B open label study design, the Sisonke Study, which thus enabled health care workers early access to an efficacious vaccine before emergency use authorisation. This rapid translation of evidence into practice is instructive of the speed required in emergency or pandemic situations. The speed also meant that the relevant stakeholders (researchers, the South African Health Products Regulatory Authority (SAHPRA) and the RECs that reviewed the Sisonke Study) were confronted with a number of scientific, regulatory and ethical complexities and considerations. Regarding vaccine development, the primary ethical requirement is to ensure that safe, effective and affordable vaccines are made available to all people globally during a

pandemic. To this end, studies must comply with sound, scientific methodology. Despite the enormous pressure to develop an effective vaccine as soon as possible, the primacy of the safety and well-being of each trial participant and the quality of the research results should not be undermined by these time constraints. In addition, regulators should not compromise the quality of their evaluations and follow-up, in particular during the transition from research to production and distribution (UNESCO, 2021).

In the lead-up to, and the implementation of the Sisonke Study, researchers, regulators and RECs laboured through challenging, novel and uncharted terrain in an attempt to respond to the demanding requirements of science, ethics and the law while at the same time working against the clock to ensure that healthcare workers could be vaccinated before the expected third wave set in. Dedication and commitment coupled with the rigorous application of scientific, regulatory and ethical principles by all the stakeholders resulted in over 450 000 healthcare workers being vaccinated in time.

### **Objectives of Webinar**

1. To reflect on the complexities and challenges associated with Sisonke Study
2. To discuss the strategies drawn upon by researchers, regulators and RECs when dealing with the challenges
3. To consider how lessons learnt during this study could assist when planning pandemic research.

### **WEBINAR PROGRAM**

**Date:** 08 September 2021

**Time:** 13.00 – 15.30

**13.00** Welcome and Overview: Professor Ames Dhai

**Session 1: Reflections from Researchers:** Session Chairs: Professors Mariana Kruger & Jerome Singh

**13.05 – 13.20:** Principle Investigators: Professors Glenda Gray, Linda-Gail Bekker, Ameena Goga

**13.20 – 13.35:** Researchers on the Ground: Drs Rebone Molobane Maboja, Erica Lazarus, Fareed Abdullah.

**13.35 – 14.00:** Panel Discussion

**Session 2: Ethico-Regulatory Reflections:** Session Chairs: Dr Mantoa Mokhachane, Professor Danie du Toit

**14.00:** SAHPRA and REC Submissions: Dr Fathima Mayet

**14.10:** The SAHPRA Perspective: Dr Boitumelo Semete

**14.25:** The REC Perspective: Professor Marc Blockman, Ms Marzelle Haskins

**14.45:** Panel Discussion

**15.20: Closure and Future Directions:** Dr Cathy Slack, Professor Joseph Mfutso Bengo

## **SESSION 1: RESEARCHER PERSPECTIVES**

The first session focused on perspectives from researchers as they set about preparing for, and then implementing the study. It included presentations from the national principal investigators (Professor Glenda Gray, Linda-Gail Bekker and Ameena Goga) and investigators at the sites who were responsible for the implementation of the study (Dr Rebhone Maboja, Erica Lazarus and Fareed Abdullah).

### **Presentations from the National PIs**

Professors Gray, Bekker and Goga narrated the process from conception to implementation of the Sisonke Study. The Sisonke study was dubbed “Plan B” by the researchers as they swiftly veered into action from the 1<sup>st</sup> February 2021 when data became available that the Astra Zenica (AZ) vaccine demonstrated very little vaccine efficacy against the Beta variant of concern, which was the predominant variant in South Africa at that time. This information became available just as the AZ doses were about to land in the country for vaccination of health care workers (HCW). The then Minister of Health was alerted, and a meeting convened with him where all options on how to address this impediment were examined. Professor Gray contacted Paul Stoffels, Vice Chairman of the Executive Committee and Chief Scientific Officer of Johnson and Johnson (JNJ) and a meeting between JNJ, the National Department of Health (NDoH) and researchers was convened on 2<sup>nd</sup> February to explore access to the Ad26 COVID-19 vaccines. Evidence that it was efficacious was available from the ENSEMBLE trial. By 3<sup>rd</sup> February, JNJ commenced on recalling the investigational vaccine from throughout the world, to Belgium, and started an inventory of all the investigational vaccines that were available globally. On the 4<sup>th</sup> February, at a meeting to discuss the process of delivering the vaccine to HCWs without an Emergency Use Authorisation. (EUA), it was determined that the most optimal way forward was via a phase 3B study. The South African Medical Research Council (SAMRC) was charged with executing the study. The South African Health Products Regulatory Authority (SAHPRA) was consulted urgently on 5<sup>th</sup> February for regulatory guidance. Despite it being a Friday evening, SAHPRA took the call and advised the team accordingly. Between the 5<sup>th</sup> – 7<sup>th</sup> February, the Sisonke Study Team assembled, drafted the protocol and had it reviewed by international experts and the NDoH. By Monday 8<sup>th</sup> February, the protocol was finalized, budgets were drafted and the regulatory application was submitted to SAHPRA. On Tuesday 9<sup>th</sup> February, a workshop was convened with NDoH, NICD and the Study Team to engage on how to implement Sisonke. In addition, funders were presented with the budget and the shipment of vaccine explored. It was realized that the vaccines could not be brought in without regulatory approval. On Wednesday 10<sup>th</sup>, the research team received the review from SAHPRA, and the Human Research Ethics Committees (HREC), the protocol was redrafted and resubmitted. A meeting was held with National Treasury on Thursday 11<sup>th</sup> and on Friday 12<sup>th</sup>, SAHPRA approved the Sisonke Study and different teams met to operationalize the project. The researchers continued working against the clock and late into the nights. They met with the vaccine roll out sites on Saturday 13<sup>th</sup> and on Sunday 14<sup>th</sup>, investigators met to finalise the implementation plan. On the night of Monday 15<sup>th</sup>, the vaccines were packed into planes in Belgium and they arrived in South Africa on Tuesday 16<sup>th</sup> at mid-night. Biovac moved into action and packed the product the rest of the night. The vaccines were shipped at 4am on Wednesday, 17<sup>th</sup> and the President and Minister of Health were vaccinated at 13h00 that day.

The researchers illustrated how, within 14 days they were able to deliver the vaccines to HCWs. They described all the work that went into this emergency operation and how flexible SAHPRA and the HRECs were. They stressed their appreciation for this flexibility, as it was necessary to make timely implementation possible. The national rollout planned by the government was to have started on Monday 15<sup>th</sup>. Sisonke started just 2 days later and in time to get HCWs vaccinated before the 3<sup>rd</sup> wave.

The national PIs then went on to present the lessons that they had learnt from the Sisonke process from two perspectives: lessons learnt during the Sisonke and lessons learnt with implications for research.

## The 10 lessons learnt during Sisonke:

1. Advocacy
2. Registration
3. Electronic capture system
4. Communication between staff at vaccination site
5. Health assessments at vaccination centres
6. Guides for vaccine storage, pharmacy staff and vaccinators
7. Transparency about adverse events
8. Real-time support to vaccinees post vaccination and national AE surveillance system,
9. Monitor and investigate breakthrough infections
10. Flexibility and Team work across all levels and between public and private sectors

### **1. Consistently advocate for vaccination to reduce public hesitancy and facilitate access to a choice of vaccination sites such as religious and community centres, schools, shopping malls and drive-through centres.**

- There were many concerns regarding severe adverse events to vaccines, resulting in researchers rapidly putting together a key message at both local and national outlets: severe adverse reactions to vaccination are rare and can be managed, but severe COVID-19 is not easily managed.
- Appropriate, clear messaging and peer education using webinars, posters/ leaflets, social media engagements and interviews on local, national and international news outlets are critical.

### **2. Let digitally literate people help elderly and marginalised people register for vaccination.**

- Registration for vaccination occurred mainly through a web-based portal. Researchers learnt that registration for vaccination should be allowed through various portals and systems including WhatsApp and short message systems so that the digital divide does not exclude people.
- During national vaccine rollouts, it is important to allow walk-ins to maximise vaccine uptake (many HCWs had not refreshed their details or had missed SMS notifications).

### **3. An electronic vaccination data system (EVDS) is critical.**

- An EVDS is an important tool for scheduling, real-time communication with vaccinees, recording vaccinee characteristics, ensuring standardisation of implementation, ensuring data quality and for monitoring and reporting vaccination progress and programme effectiveness.
- JNJ consent had to be built into the EVDS
- Busy vaccination centres should use EVDS scheduling to avoid over-crowding; and queue marshals could be employed to ensure vaccinees abide by their EVDS appointment time, and to assist with social distancing.

**4. a. Instant messaging platforms like WhatsApp are vital for quick communication amongst staff at vaccination centres.**

**4.b. Communication between researchers and the pharmacy is essential to ensure adequate vaccines being supplied on time.**

- Getting factual and useful information to vaccination sites is key to enhance efficiency at the vaccine centres and to allay concerns.
- The WhatsApp groups enabled principal investigators to rapidly implement changes on the ground, redistribute vaccine doses to avoid wastage and enabled investigators and vaccination centre staff to support each other through long days and weeks.

**5. Health Assessments at vaccination sites.**

- Although severe allergic reactions to COVID-19 vaccines are rare, rapid assessments are needed at vaccination centres to identify people at risk of severe reactions.
- These assessments are important to identify people with a history of severe allergic reactions/ anaphylaxis. These individuals will need to be vaccinated at specialised centres under medical supervision and with pre-medication.

**6. Develop clear 'how to' guides for vaccine storage, pharmacy staff and vaccinators and ensure the protocol is implemented consistently at all sites.**

- Never before has there been a vaccine campaign of this scale and complexity, therefore, allocating this process to dedicated trained teams and expanding the capacity of these teams optimised efficiency at vaccination centres.
- This process should also be implemented during the rollout.

**7. Transparency about adverse events to the public.**

- In the Sisonke study, the rate of reported non-serious and serious adverse events with vaccination was low.
- There was a need to differentiate between normal reactogenicity and study related adverse events. This had to be communicated to the public honestly.
- Education and communication about these adverse events are required early in the process. This needs to be conducted regularly, frequently and honestly. Both the benefits versus the risks of vaccination are to be included in the communication at the same time and as one activity. Often risks were communicated separately from the benefits of vaccination, generating fear and confusion.
- Ensure that all communications frame this as a research study – HCWs and the public were confused as to the status of Sisonke and it was seen as many as a phase 1 roll out of the national program.

**8. Provide real-time, responsive support to vaccinees post vaccination.**

- Adverse event reporting systems that are easily accessible, easy to use and data-free are needed to maximise adverse event reporting and follow-up.
- In the Sisonke study adverse event reporting included text message based electronic reporting, 24-7 toll-free call centres, web-site links, health facility-based reporting as well as encouraging spontaneous case reporting.

**9. Develop efficient systems to monitor and investigate COVID-19 breakthrough infections and deaths post vaccination.**

- During and after vaccination, monitoring and investigating breakthrough infections (BTI) and deaths are critical to understand the emergence of new variants.
- The Sisonke national BTI consortium ensures complete documentation of disease, hospitalizations and deaths, as well as viral genetic information.

- Each severe BTI and death needs investigation and review by a team of experts to confirm the occurrence and establish temporality (in relation to vaccination) and whether disease or death are associated with COVID-19. For the national rollout, similar systems are required, and should be led by key national stakeholders and experts.

#### **10. Flexibility and teamwork are essential within vaccination centres, across national, provincial and district levels and between public and private sites.**

- Sisonke's mandate to reach as many HCWs as possible within three months with the 500,000 doses of the Ad26.COVS vaccine was achieved through public private partnerships in many sites, with the private sector either serving as vaccination centres or providing staff as vaccinators, pharmacists or syringe fillers.
- Flexibility should include site opening times after working hours and on weekends. This could certainly be key to realising the country's goal to vaccinate 40 million people in 2021.
- Central coordination and tracking of all approvals received is also essential and is also a lesson for research per se.

### **Presentations from Researchers Implementing Sisonke**

Dr Rebone Maboja started off the discussions on the Sisonke implementation with a description of the implementation process on the ground. After self-registration, there were 3 SMSs sent to the potential participant in rapid succession. The first one confirmed registration, a second one invited participation and enrolment via e-consent and once this was done, a third one was sent with a voucher number. The participant then awaited an SMS with the date for the vaccination.

She highlighted some of the lessons learnt with the voucher system that had been used. She raised a concern that it inadvertently resulted in some form of discrimination because of its complexity. It was used as a means to provide proof of informed consent and to a degree, it allowed centralised risk prioritization. The majority of highest risk staff did not receive timely vouchers as they had categorised themselves incorrectly or their area/institution had not been opened by then. Vouchers were delayed or no voucher had been received. Incorrect vouchers were received due to sharing of cell phones in the family. Other challenges included internet access was limited or not available. At times, sites went offline. There were errors during registration especially to key identifiers (name, ID, cellphone number). These were unable to be corrected and needed escalation. The solution for this was to have "super users" (uber users) and a help desk, of senior protocol team support available. Informed consent is usually the most time-consuming process in a clinical trial and yet very critical. To optimize efficiency in this process, the e-consent system was used. The e-consent also provided self-control privacy to the participants when answering medical questions. Centrally a system was in place. However, many health care workers had trouble using the system. The lesson learnt was that while e-consent is a useful tool to optimise consent process without compromising GCP expectations, there were challenges in communities with limited access to online systems and hence verification systems needed to be considered.

Dr Erica Lazarus described how balance within the study was managed. While it was important to leave the definition of frontline HCW relatively broad so that all HCWs at high risk of exposure to COVID-19 would be eligible for enrolment, there was a need for risk stratification within the eligible population, particularly at the commencement of the study, so that those at highest risk would be vaccinated first. Research sites worked with their partnered NDoH vaccination facility to determine risk based on on-the-ground experience. Site teams identified staff working directly with patients as highest risk, especially those in COVID-19 wards, ICUs, Emergency departments and the vaccine sites. This was followed by other wards, and then those with indirect/minimal clinical contact but still exposed through other mechanisms e.g. HCWs in laboratories and hospital security staff. This internal risk stratification led to some conflict initially but having dedicated gatekeepers to prioritise participants by risk and also ensure eligibility was important. A central strategy that was implemented a few weeks into the trial was the release of vouchers based on registration answers to facility, ward and front-facing status. Dedicated gatekeeper strategies to implement these

decisions mirrored processes within a clinical trial: confirmation of identity; confirmation of informed consent (voucher number); and confirmation of employment, including role at work. Release of invitation to participate was then based on the registration questionnaire. This too came with its own challenges. If the need and urgency had not been so critical and there had been more time, sms communication in the registration sms to explain stratification briefly may have helped. Nevertheless, the lesson learnt was that adhering to basic GCP principles is possible in complex, large scale implementation studies but methods to stagger enrolment appropriately need to be brainstormed.

Dr Fareed Abdullah, a clinician researcher, shared his experiences and insights from a clinician's perspective and highlighted that HCWs are now less anxious when working in COVID-19 wards. When Sisonke was announced, there was a celebratory mood by HCWs. What helped was that the study was approved by SAHPRA; it was being managed under clinical trial conditions; and the JNJ vaccine had been shown to be efficacious against the beta variant. Prioritizing frontline workers was a form of recognition of their role and the risks and dangers that they faced. Seeing the first vaccines getting into arms was the first tangible sign that there was an end game to this pandemic. Many (not all) frontline health workers had reduced anxiety when entering the COVID-19 wards after being vaccinated. Many of the clinicians who had had a bad experience with COVID-19 were quite nervous about the side effects they may experience with the vaccine. Most frontline clinicians wanted their families to be vaccinated as them infecting their families had always been a great source of stress and anxiety. However, there was some relief in the knowledge that if they were vaccinated, their risk of transmission to their families was also lowered. Overall, most of the clinicians were highly appreciative of the SAMRC and the Sisonke vaccination drive.

Dr Abdullah stressed that government owes a duty of care to HCWs. This is fundamental to any employment and contractual relationship. The Sisonke study was able to assist the state in delivering on this duty of care. This is valued both by HCWs and society for which they work and give themselves to.

### **Session 1 Panel discussion**

1. **Question:** Because Sisonke was plan B, was it primarily a host country post trial access initiative or a public deployment of locally established efficacious vaccine in context of public health emergency?

**Response:** It was neither. There was already evidence that the vaccine was efficacious. JNJ had applied for rolling submission with SAHPRA and other regulators. No commercial lots of vaccine were available. There was only investigational product available. Given there was no regulatory approval, Sisonke had to be conducted under study conditions.

2. **Question:** Did participants on the ground understand the difference between the nature of an open label phase 3 b trial and a roll out? Did they understand they were research participants and not recipients of the rollout vaccine program?

**Response:** Researchers tried on many platforms to explain the difference to the public. The team on the ground also tried to clarify this confusion. Technical aspects of it being a phase 3 b may have been lost on a public that did not understand. Research sites had staff to conduct information sessions. Individuals were instructed to use electronic informed consent. This was not always possible. Additional strategies were embarked on and GCP was adhered to for these as well. All available means were used to disseminate information on the study. These included various types of media. At site, potential participants were requested to read the consent forms, understand the voluntary nature of participation, and that it was an open label study. Hard copies of forms were also available and trained counselors were on site to explain all the different terms and any other question that participants may have had. However, assessment of understanding to the degree required in clinical trials was not possible with all the participants. But they did have the opportunity to ask questions and get them answered. Given the pressures of the pace, satisfying the requirements for informed consent may not have been perfect in all instances. However, all attempts were made to meet GCP requirements under all circumstances. The team did its best under the circumstances. However, the team is open to criticism and to admit that they could have done a better job.

3. **Question:** What could have been done differently regarding messaging? Are participants aware that for the next 2 years they should inform the study team about any adverse events?



**Response:** Messaging and information on adverse events were done by SMS and at different times. The team is involved in passive and active surveillance and they examine all databases, the DATCOV registers, etc. The team is aware of who the Sisonke participants are from the EVDS. This is used to identify participants with adverse events that may come to hospitalisation, etc. In addition, members of the team receive direct reports from participants. These individual are referred to the safety desk.

**4. Question:** How did the EVDS work with enrolment in rural areas? How effective was it?

**Response:** Infrastructure was developed by the team including provision of computers for data collection, etc. The researchers were able to use mobile data systems and had developed relationships with mobile networks who supplied the data to support sites. All rollout sites were part of government appointed sites. Government was also to ensure connectivity and computers were available. Where they were not, researchers supported the infrastructure.

## SESSION 2: REGULATORY AND ETHICS PERSPECTIVES

The objective of session 2 was to hear what the experiences from researchers, SAHPRA and HRECs were as they worked against the clock with rapid reviews and how collaboration was achieved to ensure rapid turn-around times without compromising ethical and regulatory requirements.

The session started with Fatima Mayat, researcher from the team handling the SAHPRA and HREC submissions and requirements, deliver a presentation entitled “The Good, the Bad and the Ugly”. She described how the team navigated the regulatory and ethical terrain in a pandemic situation to implement Sisonke. She categorized her experience as the good, the bad and the ugly, as everything about Sisonke was unprecedented. She aptly called Sisonke “the crazy beautiful study”. What was achieved together was phenomenal. Because of the urgency, the protocol team, research staff, HRECs, SAHPRA and many other role players had to be innovative, flexible, nimble and passionate. She was confident that all of them were exactly that.

She described Sisonke’s conception, gestational period and delivery as all being just 2 weeks in February 2021. Data from the ENSEMBLE 1 study had been released in late January 2021 and FDA, EMA and WHO applications had or were about to be submitted. The first Sisonke submission to SAHPRA materialised just a week after its conception. The “Good” was explained as: given all involved were thrown into deep end, they had to make things happen for the country. It soon became evident that all had the ability to respond in an accelerated fashion in this emergency because of unprecedented meaningful collaboration in line with Sisonke’s true meaning, “TOGETHER”. Collaborators included HRECs, SAHPRA, the Protocol Team, NDoH, the Sites and the Private Sector. The turnaround times from submission to approval was exemplary. With SAHPRA, it was just 4 days.

### • Turnaround times from submission to approval

|                  | SAHPRA    | Wits HREC | Pharma Ethics | SAMRC Ethics | UKZN-BREC | SMUREC-MECRU | UCT-HREC  | Stellenbosch |
|------------------|-----------|-----------|---------------|--------------|-----------|--------------|-----------|--------------|
| Application date | 08-Feb-21 | 09-Feb-21 | 09-Feb-21     | 08-Feb-21    | 08-Feb-21 | 09-Feb-21    | 08-Feb-21 | 08-Feb-21    |
| Approval date    | 12-Feb-21 | 15-Feb-21 | 16-Feb-21     | 12-Feb-21    | 16-Feb-21 | 18-Feb-21    | 16-Feb-21 | 17-Feb-21    |
| <b>#Days</b>     | <b>4</b>  | <b>6</b>  | <b>7</b>      | <b>4</b>     | <b>8</b>  | <b>9</b>     | <b>8</b>  | <b>9</b>     |

*\* Initial protocol submitted to SAHPRA and ECs was protocol V1.0. Following SAHPRA queries, this was updated to protocol V2.0 dated 11 Feb 2021 and approved by SAHPRA & all ECs*

The “Good” was achieved because of the responsive environment which included:

- Availability - SAHPRA committees, and HREC chairs would make themselves available to the protocol team to discuss queries at nights, weekends, on short notice.

- Clinical Trial Form (CTF) 1 submission deferment for administrative documents - SAHPRA allowed the team to amend the initial ENSEMBLE CTF1 to facilitate researchers focusing on the science of the application. Documents were submitted and updated in due course but this process allowed was highly efficient for an emergency situation.
- Capacity Building – Collaborations between sectors lead to upskilling of staff and introduction of many new people to Good Clinical Practice (GCP) and basic trial process. This is fundamentally driven by the stringent legislative requirements in South Africa.
- Continual process optimization - Covid and Sisonke forced SAHPRA and HRECs to think of new ways of doing things, to optimise efficiencies and to enhance the clinical trial framework in SA.
- Electronic Informed Consent Forms (ICF) – this was a novel approach in many settings and its approval was necessary to make Sisonke work. Practically paper copies were available at sites as a back-up.
- Oversight and reaction – Committees became flexible and maintained oversight at a time when there were just so many new terms and findings. They had to make quick decisions while weighing up risk/benefit aspects sometimes in a data free zone.
- Pharmacovigilance - Researchers established a safety desk, a Protocol Safety Review Team (PSRT) and a panel of experts to facilitate and support the study safety. The Sisonke pharmacovigilance system was a combination of a passive surveillance system with an active reporting domain. It set a model for National roll-out to follow. It was extensive and more thorough than usual surveillance systems. A collaborative approach with SAHPRA and NDoH allowed for adoption of a reporting system that met the needs of the regulator. This was further refined as the study progressed.

The 'bad' was described as:

- Lack of harmonization between HRECs resulting in duplication of queries. One HREC had word for word the exact same questions as SAHPRA. To mitigate delays the team submitted all queries from everyone to everyone. Hence a central HREC should be considered in emergency outbreaks like the current pandemic.
- HRECs had at times to be reminded that the Sisonke was a Phase 3b pragmatic real-world study. Much data from phase 1-3 trials was already available. The study aimed to evaluate field effectiveness and support scale up strategies. The sub-study would evaluate in more detail the immunogenicity, durability and neutralization activity of the vaccine regimen. At times, it was felt that by the types of questions received from HRECs, they may not have understood the nature of the study.
- A prolonged safety pause occurred related to clotting and investigations into vaccine-induced immune thrombotic thrombocytopenia (VITT). This cost time when SA was one of the countries where no other vaccine option was available.
- Mixed messaging on vaccination of pregnant and breastfeeding women. A Version 3.0 amendment at the beginning of April requested inclusion of pregnant and breast feeding women. When the study pause was lifted, SAHPRA directed that the protocol team remove vaccination of pregnant and breastfeeding women from the updated protocol despite there being no data indicating lack of safety of the vaccine in these women. The team was subsequently re-instructed to add on this allowance later in April by which time they were at Version 4.3 and only had a few of weeks left on Sisonke. The mixed messaging created confusion for the public. This sequence of events occurred possibly because of SAHPRA being over cautious, but it resulted in controversy around the issue of pregnancy and breastfeeding. Furthermore, there was little time to implement the inclusion when finally instructed to do so.

Ms Mayat articulated the "ugly" as being:

- Misunderstandings – at times there was a lack of understanding of how the study was being operationalized, e.g., interplay between research staff and rollout vaccination sites.

- Study conduct and participant safety was a primary concern of all the researchers. This was always tantamount on numerous trials conducted successfully previously by the investigators on Sisonke. Everyone seemed to be watching the team that literally committed themselves to working 7 days a week on this study. They took complaints very seriously and needed to understand and act rapidly to dispel untruths or misunderstandings and try to rectify any inadvertent non-compliance if it did exist.
- Complaints were submitted to SAHPRA and the National Health Research Ethics Council (NHREC) at times prior to sponsors or investigators being made aware of concerns so that they could be clarified. There were concerns as to whether this was a research study or rollout. This may have led to confusion around the informed consent. The teams spent quite a bit of time clarifying the difference. It must be underscored that it was not possible to receive the vaccine without participants going through the e-informed consent process. Additionally this was reiterated at the time of vaccination. A complaint was received by NHREC regarding undue pressure applied to a HREC. This may call into question the capabilities of HRECs to respond in times of emergency where speed is of the essence.
- This study also highlighted the lack of clarity on governance issues regarding who has absolute jurisdiction over research conducted in a hospital. For example in one hospital there were 3 research groups all with approved HREC clearance. But a HREC that did not have researchers working in the study also wanted the study to be approved by them.

What is clear is that South Africa definitely has a robust and ethical regulatory and clinical trial framework. Mechanisms exist for concerns to be addressed. All stakeholders from experienced research teams to established ethics and regulatory bodies were navigating uncharted terrain. Something this urgent, this important and this big is unprecedented and has not been done in SA before. The study teams worked throughout the day and night to execute this study and took responsibility for everything that occurred.

Ms Mayat informed the delegates of some of the statistics related to implementation that were not commonly known.

#### **Some implementation Statistics**

- Participants enrolled nationally: **477 102**
- Sisonke Sub-study participants: **1297**
- Research teams approved: **38**
- Investigators approved: **246**
- Pharmacists submitted: **237**
- Ethics Committees: **7**
- Vaccine Wastage: **~1 %**
- Adverse Events reported: **12 414**
- Serious Adverse Events reported: **550**

There is active case investigation for all SAEs.

- Call center inbound calls: **> 11 000**

She concluded her presentation by stating that vaccine research and development brings hope and a solution to combat a global pandemic. Sisonke showed that even in an emergency, regulatory and ethical standards could be

upheld. South African clinical researchers, regulators and HRECs have in the main, displayed evidence of research, regulatory and ethics maturity as proven by the successful execution of this study.

Dr Portia Nkambukle from SAHPRA presented on perspectives from the regulatory authority. She commenced with an explanation of the process followed by the regulator when a clinical trial is submitted for review. There is a submission date that applicants abide by. The application is screened and if it does not meet regulatory requirements, it is sent back and not accepted. Where it meets all requirements at screening it is allocated for review and the review report is submitted to the Clinical Trials Committee (CTC) where it is peer reviewed at a CTC meeting. If it meets all requirements, it is approved. In short, there are 3 steps in the process: complete application submitted, then reviewed and outcome arrived at.

With COVID-19 trials, the submissions are made at any time and do not to follow the submission dates. The application forms were revised to accommodate this amendment to timelines. In the Sisonke Phase 3b study, Efficacy and safety were already established, and it was conducted under study conditions to provide additional information. It was clarified that with the national roll out, vaccines are given section 21 authorization / registered with conditions prior to recommendation for rollout by the National Department of Health

SAHPRA guidelines were revised to respond to the pandemic so that expedited and rapid reviews could be conducted.

#### **SAHPRA Guidelines Revision as Response to COVID-19**

- 25 March 2020: SAHPRA Policy on Conduct of Clinical Trials of Health Products During the Current Covid-19 Pandemic
- 13 April 2020: GCP Training and Expedited Review of Clinical Trial Applications During Covid-19 Pandemic
- April 2020: Clinical Trial Application Form – Guidance in conditions of a Public Health Emergency
- March 2021: Oversight and Monitoring in Clinical Trials - Revised

Lessons Learnt by SAHPRA were as follows:

- Collaboration between SAHPRA and the applicants is pivotal as a joint efforts to expedite the review and respond to SAHPRA recommendations/queries.
- Frequency of meetings had to be increased to expedite review of Covid-19 CTA. Sisonke was approved within 4 days.
- SAHPRA stipulated tighter review and response period.
- Responses were typically received before the expected due date.
- Dual review by experts with efforts to expedite review in a public health emergency was necessary.
- Capacity of sites (resource) - Public Health Emergency or consideration for condition of approval was granted and capacity was to be built on an ongoing basis with applications for additional investigators and sites. All sites had to comply with GCP.
- Improved communication between Investigators and SAHPRA was necessary.
- Improved engagement with the media and the public was necessary.

- 4 weekly progress reports were required for Sisonke. The applicant provided reports/feedback timeously.
- Safety concerns reported in the USA (blood clotting disorder) resulted in an urgent meeting and collaboration with the Applicant (April 2021). Meetings were held round the clock including weekends. Internal collaborations between the committees within SAHPRA also improved. Recruitment was placed on hold while investigations and mitigating issues were considered.
- To speedily address the safety concerns, collaboration between various internal experts in SAHPRA (Clinical Trials, Pharmacovigilance and COVID-19 working group) was required.
- SAHPRA participated in the USFDA engagements on the safety review.
- Modification of reporting time frames was necessary to ensure more regular updates (4 weekly progress reports - safety and futility reporting to 2 weekly submissions). Protocol and informed consents were updated as outcomes of these measures.

The HREC considerations were presented by Professor Marc Blockman and Ms Marzelle Haskins.

Prof Blockman provided an overview on the experiences at HREC; some thoughts on REC challenges during the COVID 19 Pandemic and he also touched on whether HRECs are a burden or benefit to research during these times. He commenced with a reminder of the benchmarks for ethical research in the seminal publication by Emanuel et al., JAMA, 283, 2000: What Makes Research Ethical?

- Social or scientific value
- Scientific validity
- Fair subject selection
- Favorable risk-benefit ratio
- Independent review
- Informed consent
- Respect for potential and enrolled subjects
- Collaborative partnership

He stressed the need to be true to the above even in a phase 3b pragmatic study during the pandemic.

He discussed grappling with the challenge of how studies could be conducted ethically in the midst of a global pandemic given the requirements for rapid review, rapid communication, sharing of information and due diligence to patient and participant safety.

When pausing research/restarting research, general considerations included:

- Balance between looking after participants with prospect of direct benefit vs stopping the study and forfeiting benefits.
- How to follow up safety.
- Issues with follow up - videos/telephonic.
- When to restart - essential vs "non-essential" research and at what level? What should PPE look like? What should the environment look like?
- Post-Graduates-career risk.

Considerations for Rapid Review included:

- How do we facilitate accelerated clinical trials to get treatments that may work, ie., evidence based, that informs improved standards of care; and guides management and relates to policy changes?
- How do we navigate fast review and turn-around times and balance this with the inevitable reviewer fatigue?
- HREC was asked to meet regularly, often every second week to discuss studies. In addition, external reviewers were used.
- Benefit-risk in an unknown disease entity was of concern. HRECs, just like all others involved were learning about pandemic “on the run” and also reviewing and developing risk benefits on the run.
- Premature data was used to assess the applications.
- With global master protocols it was necessary to make sure issues were relevant/contextualised to our population and that there was local investigator involvement.
- What is standard of care?
- Can placebo be used if there was no standard of care?
- With adaptive clinical studies, HRECs need to be flexible as data or risk changes as was seen by the Hydroxychloroquine applications.
- With the vaccine research, there was a massive pressure to approve with limited phase 1 data. Concerns as to how to push back despite this pressure arose. There was pressure to have a vaccine and perhaps HRECs may have been over rigorous with their oversight role, ie., risk/benefit-beneficence vs maleficence. *While effective treatment for severe COVID-19 would be beneficial, an effective vaccine is needed for there to be any prospect of return to normal life (Dawson, 2020).* This has been the mantra and HRECs ensured facilitation of such studies.
- The placebo question applied to vaccine research as well.

Questions on informed consent revolved around issues of:

- Vulnerability
- Therapeutic misconception
- Delayed vs deferred vs waiver
- Proxy - difficult as family not available and worse still, they cannot visit
- Safe consent practices: cellphone-video-tablets are available. It remains unclear as to how safe these consent practices are.

Confidentiality considerations include:

- How to protect confidentiality adequately as COVID-19 is a notifiable disease.
- Risk of stigma – for participants and the community.
- Risk of discrimination.

PPE concerns were:

- PPE as standard of care.
- Should we insist that all preventative studies supply PPE to the participants?
- What would this PPE look like?

- How much and how often should it be provided

#### Community Involvement:

- Is necessary especially with preventative studies.
- Who is the community is often at question when eg. many healthcare workers groups are being accessed?

Marzelle Hazkins discussed the administrative challenges related to COVID-19 review. She grouped these into submission challenges and review process challenges.

#### On submission challenges she stated that:

- Many RECs found it challenging when dealing with manual paper-based systems, which result in administrative challenges such as tracking of studies, assigning reviewers and generating reports. HRECs need to be prepared going into the future for e-submissions and e-reviews.
- Proposals submitted for expedited review are often rushed and incomplete (i.e. informed consent documents do not comply with HREC requirements). This delayed the approvals. Getting it right the first time goes a long way to expedite the review process. Researchers should follow standard operating procedures and templates developed from the different RECs.
- Researchers do not provide sufficient information on sites, researchers and research capacity to evaluate the site's ability to effectively conduct the research (i.e. where participants are to be hospitalised, current GCP certification, GCP certificates expired, etc). With the vaccine studies, there were many sites but these sites were also doing lots more of other type of COVID-19 research. RECs need to have the assurance that the site has the capacity to effectively do the research and researchers should provide this assurance. When studies are conducted on hospitalised patients, researchers did not submitted adequate information, e.g., which hospitals were used, whether the hospital had given permission, etc
- There is an increase in the volume of documents/submissions which results in increased workload and undermines optional functioning of administrators. HRECs have limited budgets and staff. They are not equipped to manage the influx of work during this time especially as they are expected to do all this within short periods.

#### Considerations with the review process were as follows:

- It is sometimes challenging to secure reviewers on short notice and obtain feedback on an expedited basis. The administrators are under pressure and often have to follow-up with reviewers or find alternatives.
- High volumes of submissions for expedited review makes it difficult for reviewers to provide feedback within expedited timelines. There are additional pressure on reviewers as well resulting in relevant concerns being missed or unnecessary irrelevant questions sent to researchers. This further delays the process.
- Administrators and reviewers are often overwhelmed with queries or unreasonable requests from researchers who do not respect the boundaries of the review process. Examples include working at night, over weekends, etc. and receiving WhatsApp messages at odd times. Researchers should respect the boundaries of the review process and should also remember that decisions are combined committee decisions and not something that one HREC member can respond to immediately to solve the researcher's problem. There are unrealistic expectations from researchers. Timelines need to be respected.
- The logistics surrounding expedited review procedures/meetings on short notice is challenging because this does not fall within the normal SOPs of RECs and requires constant flexibility from administrators.
- Reviews of non-COVID19 related submissions are neglected or postponed to facilitate expedited reviews. Because RECs and reviewers can "only do so much" with the staff and support they have and without additional staff and reviewers some applications are bound to fall by the wayside.

## Session 2 Panel Discussion

1. **Question:** Was every ethics committee in SA involved in approval of the Sisonke?

**Response:** Wherever investigators of record were situated, those HRECs were used. Difficulties arose with multiple HRECs doing the reviews. In some hospitals there were 3 different group of investigator teams hence this required 3 different HRECs. At Steve Biko there were 4 different teams and 4 different RECs reviewed and approved the protocol.

2. **Question:** Did the research team collaborate when they applied? Was there one protocol submitted to all committees?

**Response:** One submission was sent to all HRECs. These were sites that had been approved for ENSEMBLE1 – this explains how sites were chosen.

3. **Question:** What were the communication issues between HRECS and SAHPRA in that they asked the same questions?

**Response:** In a pandemic consideration needs to be given to centralised HREC review. Early on in the pandemic the chairs of HRECs formed a loose group called Research Ethics Committee Support during the Pandemic (RESCOP). Reciprocal review was difficult because the NHREC did not exist at that time. A central body for review is currently being considered. There is a need to streamline the reciprocity process so as to avoid repeating the reviews and processes can be fast-tracked. The MRC REC considered comments from other HRECs and this was helpful in terms of expediting the process.

4. **Question:** Is the regulator capacitated to keep up its momentum for future studies. SAHPRA has done a great job thus far.

**Response:** This is very challenging. SAHPRA reviewers and staff can be commended for availing themselves to assist with the expedited processes. Going forward, SAHPRA is looking into working on reviewing capacity and processes in place for CT approvals. SAHPRA is taking reviewer fatigue seriously therefore it is committed to building and improving capacity.

5. **Question:** How did HRECs handle the fact that most its members would be participants in study?

**Response:** This was recognised at the outset. HREC members who would not be in Sisonke took the responsibility in the meeting to keep the HREC potential Sisonke participants in line and should they veer off, especially with the therapeutic misconception, they would be brought back in line. The review process was still very rigid.

6. **Question:** Can the NHREC be a solution in case of pandemic reviews?

**Response:** There was minimal discussion/ interaction with the NHREC because it was not functional for a considerable time.

7. **Question:** Explain the confusion when breastfeeding, pregnant women were removed and then put back in.

**Response:** FDA and CDC paused the use of JNJ because of the rare VITT event. Sisonke was going to start enrolling breastfeeding and pregnant women at this stage. But this was paused in Sisonke because of decreased information and limited data on Ad26. They were included in a sub-study. Currently, there exists adequate information at a global level that allows for inclusion of pregnant women. Generally, pregnant women are at high risk of morbidity and mortality should they contract the virus.

8. **Question:** What were ethical issues or impact of the halt? Were vials lost? Should something like this happen again – should we act differently?

**Response: Researcher response:** 4,500 vials were lost. There was also a negative impact on trust. HCWs post the pause became hesitant and hence a slowdown in enrolment leading to an extension of the definition of HCW to that used by the WHO. The regulator and HREC did their job to optimise safety. Being in data free zone, RECs and SAHPRA needed more international data and also required to work with other regulators to inform their decisions.



Rollout and the implementation study were going well. However, halting did result in a lot of vaccine hesitancy and uncertainty. Researchers get frustrated, but it is possible that if researchers were on the HREC or SAHPRA, they would have done the same thing.

Pregnant women were never part of protocol to start off with hence, they were not really effected by pause. An application was being amended to include them. When the study was paused, pregnant women were invited to be part of sub-study and when Sisonke was over, they were able to get onto the national rollout. With breast feeding women, the situation was different as they had been vaccinated on Sisonke, but with the pause had to be removed from the protocol. After removing them within a 24-48 hour period researchers received ethics approval to include them again. Going back to re-include them meant another set of submissions to HRECs. This whole halting process caused lots of confusion, concern and dissatisfaction among breast feeding women. The quick succession of events and changes highlighted the difficulties in the pandemic situation when things move so quickly. It is a logistical nightmare to be sending documents for submission to HRECs every 2 days. For this reason, breastfeeding women were encouraged to join the sub study.

**HREC response:** stopping was a correct thing. Looking at it broadly – the objective of Sisonke was implementation and to teach the national program about implementation. What it did teach, was how to get people together very quickly and to understand this adverse event. It also made sure that may people that had clotting problems were not excluded. There was a small group of people only with clotting concerns. The national PIs set up a panel to study this and council them. While it was a prolonged period, and may have caused some vaccine hesitancy, it assisted with some learnings and teachings and brought the regulator, HRECs and investigators together. On the whole, more good resulted from that.

**9. Question:** Do people with thromboembolic disease vaccinate in the national rollout?

**Response:** there are very few contraindications to vaccines. This should be celebrated.

Thromboembolic phenomenon is not an exclusion. However it should be discussed with the treating practitioner and there should be more intensive follow up. This was also a lesson learnt from the halting process.

Sisonke developed an algorithm to guide research sites with assessing participants. This was kept simple, with color coding, etc. There were very few contraindications. Most of the time people were afraid. They needed assurance and needed to know which participants required more rigorous follow up.

**10. Question:** Were researchers also given a chance to be in Sisonke? If so, would this not have been a conflict of interests?

**Response:** Anyone meeting the criterion of HCW was able to be vaccinated.

It was discussed at MRC and taken to the Bioethics Advisory Panel (BAP) as an ethical issue. The BAP also held a webinar on this. The decision was that all vaccinators were vaccinated first before they started vaccinating at sites. Investigators of record were also vaccinated upfront because of the fact that they visited sites daily. Many other researchers waited until all front liners were vaccinated and they were vaccinated later in the program. Researchers vulnerable to exposure were vaccinated.

**11. Question:** Comment on what was learnt as a scientific community on the ability to communicate with public. Are there ways in which this can be improved, especially in light of the huge impact of misinformation on social media?

**Response:** Researchers and scientists are terribly poor communicators and can do a lot better than currently done. They are often so busy rolling out the work they do that they forget to communicate. There is a need to have people supporting them to communicate.

One of lessons is: how do we make sure doctors, scientists and other HCWs are better communicators? Should we run workshops to teach us?

It is important to be mindful of the context and the needs of people that want to vaccinate and their impediments to getting access to vaccinations.

**12. Question:** Will there be a booster ?

**Response:** The research team are currently working with NDoH on this. About 30% doctors have had the Pfizer boost – but safety data on this is not yet available. There will need to a study for this. Government will require being guided by scientific data and should not rush into this. Companies may not allow off-label use. When vaccines get registered there is a risk management plan, a pharmacovigilance plan and issues around their use. There is a need to adhere to the regulatory requirements of use, and government must be able to monitor safety rigorously when it comes to mix-and-match.

### **Themes that emerged from the discussion and questions in the Q/A facility**

1. **Research Governance**
2. **Public relations, communications** – national PIs agreed that more could have been done. Researchers were very focused on delivery of the study within the short timeframe, and this important aspect was not given the attention that it should have.
3. **Lessons learnt were shared with NDoH to enhance public roll out:** maximising EVDs as no voucher system was used. Training were given to healthcare workers during and before the implementation study. These HCWs rolled over to the country program. Knowledge was imparted theoretically and practically.
4. **Adhering to basic GCP principles and consenting process.** Researchers feel this was achieved.
5. **Coercion – as no other option was available?** Participating in the study was a voluntary process and researchers tried to ensure understandability. As 477000 were vaccinated only, it is clear that many chose not to participate.
6. **How did research participants in Sisonke engage as promoters and advocates of vaccine – enhancing vaccine confidence through messaging from users is an effective strategy** – done to some extent but more needs to be done.
7. **Accuracy of breakthrough infections tracked?** Researchers have access to NICD/NHLS and private lab reporting through data-sharing agreements.
8. **Lessons learnt to inform public messaging to hesitants?** Researchers need to find ways to improve trust – if only adverse events are disclosed, then only half the story is being shared. It's a risk-benefit ratio and it's important for us to communicate accurately that for almost 100% of the population eligible for vaccination the benefit of vaccination outweighs the risk. Individual circumstances should be considered - hence the need for assessments at vaccination centres to identify those few people who need special care during vaccination/ observation post vaccination
9. **Information needed on follow up:** all Sisonke participants will be in the study for long term follow up. There is a sub-study as well with more intense follow up and blood draws
10. **Since COVID-19 vaccine development has differed from traditional vaccine development which usually takes 10-15 years, how has this impacted the Sisonke Trial?** Vaccine developers were able to leverage the history, expertise and experience of developing vaccines for other diseases such as HIV and Ebola, to develop vaccines for COVID-19. This meant that we had data from a phase 3 research study (ENSEMBLE) showing efficacy of the Ad26.COV2.S vaccine by Jan 2021. These results were used to write the Phase 3B Sisonke implementation study - the latter aimed to assess the real world effectiveness of the Ad26.COV2.S vaccine. This initiative was critical for health workers in SA, for SA as a country and for the world as data on real world effectiveness of COVID-19 vaccines is sparse. Additionally it provided protection for consenting HCW before the 3rd wave.
11. **Re: Lack of harmonization of RECs** - 1) there is at present no national requirement for RECs to harmonise on multisite trials 2) there was nevertheless unprecedented voluntary cooperation between many SA RECs and SAHPRA to facilitate rapid review 3) this opens the conversation about whether multisite trials should have a single REC of record, possibly based at the National PI's site. This is currently under informal discussion.
12. **What did the Sisonke trial put in place regarding dissemination of results to participants?** Dissemination is ongoing. The first dissemination occurred on public platform with MOH on a Friday briefing platform that was televised. Further dissemination plans will occur once data is published.

13. **Multisite trials should consider the Reciprocal Review application process**
14. **Queries on ethics and regulatory clearance for use of left over vaccines for Olympic team, etc.** all necessary clearances were obtained.
15. **Was there consideration given to using reciprocal REC review mechanisms where one REC would be the REC of record?**
16. **Going forward there is need for centralised review processes.**

## CLOSURE WITH KEY LEARNINGS

- Social Value & Scientific validity: Learning about implementation of vaccination at a site/ facility level and not just about efficacy & safety at an individual HCW level enhances the social value of the study
- Stakeholder Engagement – The importance of collaboration amongst multiple stakeholders, and in a compressed timeframe was emphasised. Also highlighted was the importance of messaging this as a study versus rollout in the minds of the public & enhancing understanding of concepts such as open label, phase 3 B, implementation study in the minds of the public, and those that will interact with them.
- Fair Selection – the importance of a strong registration system to avoid exclusion of those HCWs at a digital disadvantage was underscored. Strong systems are necessary to prevent rigging and to ensure that most at risk HCWs were prioritized. It was also important to engage with pregnant and breastfeeding persons across the length of the study given changes in their eligibility across the study.
- Risk-Benefit – the importance of sound systems for assessing serious adverse reactions, for reporting Adverse Events and monitoring breakthrough infections was highlighted. Communicating risks in relation to benefits was important and necessary, that is not communicating about risks alone but rather sufficiently minimized and sufficiently outweighed risks.
- Informed Consent – The importance of participant understanding of key concepts such as ‘implementation study’ was stressed. Also that it is important to consider how to supplement e-consent forms with additional strategies when face to face encounters will allow it e.g. at the vaccination site.
- Ethics & Regulatory Review – The importance of SAPHRA and RECs doing substantive reviews in demanding time-frames, and the importance of amending forms and processes to allow this was recognised. It is important to clarify the jurisdiction of an REC’s approval for example when no investigator from the affiliated institution will collect data at a site that falls in an area geographically located near to the REC. It is also important to refine reciprocal review processes given South Africa’s de-centralized REC system. Reciprocity of review can offer opportunities for efficient review.
- Fair inclusion and participation of pregnant women, especially after phase 2 studies should be presumed and exclusion of pregnant women should be justified. Unfair and unjustifiable exclusion is unethical and can impact on post-trial access for pregnant women.
- Sisonke means togetherness. Sisonke has shown that togetherness and unity of purpose of regulatory bodies and ethics committees and researchers were crucial for timely and speedy review and approval during the pandemic. Speedy review is possible in public health emergencies while complying with GCP and ethics guidelines.

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