

Development of an Ethical and Regulatory Framework for the Conduct of Controlled Human Infection Studies in Zambia:

Expert Consultation Report

Engagement Workshop

October 14 & 15, 2019 Siavonga, Zambia



CIDRZ

for a healthy Zambia

I. Acknowledgments

On October 14 & 15, 2019, the Centre for Infectious Disease Research in Zambia (CIDRZ) hosted an engagement workshop to discuss the ethical and regulatory frameworks needed for the conduct of Human Infection Studies (HIS) in Zambia. This consultation was conducted as part of CIDRZ's strategy to continually refine its capacity to conduct cutting edge research and establish a platform for HIS in Zambia. The core and overarching objective of the workshop was to contribute to the capacity of ethical and regulatory bodies in governing HIS and, to the development of an ethical and regulatory framework applicable to Zambia and low medium income countries (LMICs) more widely.

The workshop was possible with financial support provided by the Wellcome Trust and the Africa Oxford Initiative (Afox). The contents of this report do not necessarily reflect the views of either grantor, and are the sole responsibility of the attendees listed in Appendix A. Any errors in representation of the rich discussions and events of the day lie with CIDRZ.

We are extremely grateful to Dr. Melissa Kapulu, Mr. Michelo Simuyandi, and Ms. Evelyn Ng'andu for their part in planning and conducting this consultation. We sincerely thank the Session Chairs named in Appendix B who ably facilitated meaningful discussion and kept us on time. Also, we salute our external speakers, some of whom had little notice, for their concise and meaningful presentations. Finally, we are indebted to the CIDRZ team, specifically, Ms. Joyce Chilekwa, Dr. Masuzyo Chirwa, Ms. Matimba Muuka, Mr. Stanley Mwale, and Ms. Hope Mwanyungwi for their exemplary support and note-taking.

The workshop was a great success due to the active participation of all attendees, each an expert and authority in their own right. They generously shared their wealth of knowledge and experience in the areas of research ethics, regulations, community engagement, and the science behind HIS. In particular, we appreciate insights from HIS implementation shared by our delegates from Kenya and Malawi; and by Dr Cecilia Chui from Wellcome Trust, UK, who joined us briefly over Zoom. We are greatly indebted to all attendees for taking the time off their busy schedules and furthering the global dialogue on the ethical and regulatory requirements for conducting HIS.

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II. Abbreviations

Afox	Africa Oxford Initiative
AVAREF	The African Vaccine Regulatory Forum
CHIM	Control Human Infection Model
CIDRZ	Centre for Infectious Disease Research in Zambia
CIOMS	Council for International Organizations of Medical Sciences
DSMB	Data Safety Monitoring Board
ERB	Ethical Review Board
EDVRU	Enteric Diseases and Vaccines Research Unit
GCP	Good Clinical Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
HIS	Human Infection Studies
IND	Investigational new drug
KEMRI	Kenya Medical Research Institute
LMIC	Low Medium Income Countries
MTA	Material Transfer Agreement
NBA	National Biosafety Authority
NCST	National Council of Science and Technology
NHRA	National Health Research Authority
NHREB	National Health Research Ethics Board
PPE	Personal Protective Equipment
SAEs	Severe Adverse Events
SOPs	Standard Operating Procedures
UNZABREC	University of Zambia Biomedical Research Ethics Committee
WHO	World Health Organization
WT	Wellcome Trust
ZAMRA	Zambia Medical Regulatory Authority
ZMA	Zambia Meterology Agency
ZRA	Zambia Revenue Authority

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1. Executive Summary

On October 14 & 15, 2019, the Centre for Infectious Disease (CIDRZ) hosted an engagement workshop on Human Infection Studies (HIS) in Siavonga, Zambia. The 1.5 days engagement workshop documented questions and recommendations arising from the information provided on HIS, a methodology novel in the country. The consultation provided guidance for further activities to engage the public and to develop an ethical and regulatory framework to conduct HIS in Zambia.

The 29 experts who attended the consultation represented bioethicists, research regulators, clinical trialist, social scientists, and funders in sub-Saharan Africa and the UK. Each attendee was invited for their current and anticipated roles in the conduct of HIS in low medium income countries (LMICs) with specific reference to Zambia.

The meeting was divided into eight substantive sessions: 1) benefits and need for HIS in Zambia, 2) methodological issues that impact HIS implementation and outcomes, 3) HIS plans for Zambia, 4) risk and burdens of participation, 5) ethical considerations particularly compensation, 6) participant and community safety, 7) scientific overview of challenge agents, and 8) conclusions and recommended next steps for building a platform for the conduct of HIS in Zambia and the region.

The engagement workshop produced recommendations for implementing HIS in Zambia, and more broadly, in sub-Saharan Africa. Attendees also generated visual data on anticipated methodological issues, risk and burdens, and safety, from professional, HIS participants' and community perspectives.

Main Conclusions

Participants perceived HIS as beneficial because it put fewer people at risk and shortened the time to the development of products and interventions critical to achieving global health goals. However, as HIS requires deliberate infection with a challenge agent/pathogen, they advocated for heightened vigilance to assure participant safety including good ethical and clinical practice with regulatory, ethical, data safety, and community oversight. They suggested extensive screening for inclusion criteria. Additionally, they emphasized the need for adequate infrastructure and personnel to control infection and provide treatment including emergency resuscitation and evacuation if indicated.

The experts agreed that Zambia was well placed to undertake paediatric enteric infection studies that use live attenuated strains because of the strong ethical and regulatory environment in the country. Additionally, CIDRZ's established reputation as a clinical research centre, successful history of community engagement, internationally certified laboratory facilities, and on-going training programs with European and American collaborators, boded well for HIS implementation.

Specific Recommendations for an Ethical and Regulatory Framework for HIS

1. To determine whether the proposed HIS is warranted, the risk-benefit ratio including social harm must be considered.
2. Choice of challenge agent/pathogen must be based on the reversibility of infections, past experience, and certification of Good Manufacturing Practice (GMP).
3. The target population should be drawn from the population at risk of disease; in adult trials, starting with student/college level and with provision for study staff to participate.
4. Researchers must ensure informed consent based on comprehensive understanding of the HIS and its requirements including:
 - a compensation for burden of participation (i.e. wage/reimbursement including for infant/children participation)
 - b access to care and provision for study related injury (i.e. no-fault insurance)
 - c provisions for safety, privacy and comfort if required to be in residence.
 - d withdrawal and exit procedures to preserve individual and community safety
5. Participants should be followed after HIS completion to ensure their safety.
6. Social science studies must be nested within HIS to ensure participant concerns are documented and addressed.
7. Researchers should engage with key gate keepers including civic leaders such as parliamentarians, universities, researchers, potential participants and laypersons to avoid circulation of misinformation.
8. Implementation should build local capacity to conduct HIS and develop scientific products.

Commitments from Regulatory Bodies in Zambia

1. The National Health Research Authority (NHRA) will complete guidance on minimum value of compensation for research participants.
2. The Zambia Medical Regulatory Authority (ZAMRA) undertook to:
 - a Check if challenge agent can be imported under the importation of vaccines as per WHO guidelines;
 - b If not, to see if HIS and challenge agent importation can be incorporated into the submission currently under legal review;
 - c Assess if a third alternative, i.e., to seek Statutory Instrument through the Minister of Health, would be required to guide importation of challenge agents.

Suggested Next Steps for Zambia

1. Review World Health Organization (WHO) and other international/national HIS ethical guidelines and legal frameworks to produce Zambian guidance that while aligned also addresses local concerns including those on fair compensation.
2. Analyze GMP and GMP-like guidelines and propose what might be acceptable for Zambia.
3. Develop an engagement strategy (including for media) for the conduct of HIS in Zambia.
4. Continue engaging with ethical and regulatory bodies to build Zambian capacity to ensure ethical and scientifically sound conduct of HIS.

2. Background

The Centre for Infectious Disease Research in Zambia (CIDRZ) hosted an Engagement Workshop on Human Infection Studies (HIS) on October 14&15, 2019. Held at the Freshview Homes, Siavonga, Zambia, the workshop was designed to contribute to the capacity of ethical and regulatory bodies in overseeing and governing HIS and, to the development of an ethical and regulatory framework applicable to Zambia and in low medium income countries (LMICs) more widely. This report documents the proceedings, discussions, and recommendations from bioethicists, research regulators, clinical trialist, social scientists, and funders on the conduct of HIS in Zambia.

This workshop builds on CIDRZ's history of enteric disease and vaccines research, based on which, it is poised to begin HIS to test enteric disease vaccines, with several possibilities already in the pipeline. HIS often recruit healthy volunteers who are administered viable infectious pathogens to more efficiently test vaccine or drug efficacy and investigate pathophysiology and mechanics of immune response under highly controlled conditions. Conducted almost exclusively in high-income settings, HIS is a new methodological approach in LMICs, where ethical and regulatory frameworks are unprepared to guide HIS implementation especially among children. Though HIS are vital for developing vaccines effective in LMICs, conducting them introduces ethical complexities particular to these settings. Examples include concerns around communal pressure to participate, local language wording in information sheets, beliefs on blood collection, adequacy of infection control measures in the community, and appropriateness of compensation given levels of poverty. Thus, the engagement workshop was planned to provide an opportunity to gather independent opinions from bioethicists, regulators and researchers on requirements for a HIS platform in Zambia. Through the work described in this report, we aim to inform ethical guidance to build a national platform for the conduct of current and future HIS in CIDRZ, Zambia and the wider region. This will accelerate development of next generation vaccines that can help end preventable deaths globally.

2.1. Engagement Workshop Objectives

The core and overarching objective of the Engagement Workshop was to contribute to the capacity of ethical and regulatory bodies in overseeing and governing HIS and, to the development of an ethical and regulatory framework applicable to Zambia and LMICs more widely. In order to do so, we had the following three specific objectives: 1) to understand views, expectations, and experiences of ethical and regulatory bodies, and other stakeholders involved in HIS; 2) identify core ethical issues for HIS implementation in Zambia drawn from the experiences of other LMICs and their implications for HIS in Zambia and; 3) develop modalities to address these issues from the lessons learnt. See Agenda in **Appendix A**.

Attendees made recommendations for implementing HIS in Zambia, and more broadly, in sub-Saharan Africa. They also generated visual data on anticipated methodological issues, risk and burdens, as well as safety, from professional, HIS participants' and community perspectives.

2.2. Consultation Meeting Participants

On the recommendation of Dr. Chilengi and Ms. Shobana Balasingham from the Wellcome Trust, we invited 37 participants - 10 ethicists, 12 regulators, 6 clinical trialists, 3 social scientists, 1 funder, and 5 CIDRZ staff from regulatory department, communications department, and study management. Twenty-nine of those invited or their designees attended the workshop with the funder (Wellcome Trust) joining over Zoom (See **Appendix B**). Unfortunately, 2 African Vaccine Regulatory Forum (AVAREF) staff, 3 regulators from Uganda and Ghana, 1 clinical trialist and 1 social scientist from Gabon, along with 1 ethicist from Zambia were unable to join us. In preparation for the workshop, all participants were invited to read recommended publications, references to which are interspersed throughout the report.

2.3. Consultation Meeting Format

The facilitator, Dr. Anjali Sharma, conducted the meeting in 8 substantive sessions.

Opening Remarks: Dr. Roma Chilengi, Chief Scientific Officer in CIDRZ, opened the meeting with an appreciation of the experts' accommodation of the workshop into their busy schedules. He emphasized the need for effective engagement in developing ethical and regulatory guidance on the conduct of HIS in Zambia with implications for the region. He concluded by stating CIDRZ's expectation that the experts would provide valuable insights on capacity assessment as well as ethical and regulatory considerations which are crucial to establishing a HIS platform in Zambia and the region. He reiterated CIDRZ's commitment to learning from academic, field, ethical and regulatory experts in order to further refine CIDRZ's approach to study design, human subject protections, and compliance with the law of the land.

Session 1: Dr. Roma Chilengi presented the historical perspectives and scientific rationale for conducting HIS. He screened the Wellcome Trust video that explains HIS in simple terms. The presentation and video set the stage for a discussion on the rationale for HIS in LMICs. The discussion centred on balancing the urgent need to alleviate the burden of disease in LMICs against considerations of participant vulnerability, nature of the challenge agent/pathogen, environmental context, and the ethical principles laid out in the Belmont Report, the theory of double effect and that to 'first, do no harm.' Attendees provided suggestions to further a national framework.

Session 2: Dr. Melissa Kapulu presented on methodological considerations based on the Kenyan experience. She shared the long community engagement processes with all levels of society and the research community. She laid out issues of confidentiality, exclusion, safety, risk management, compensation and staff participation that arose during field implementation. Attendees concluded that HIS was less risky than Phase I trials having very well characterized pathogens. However, plans for good communication and to manage misinformation by press should be established.

Session 3: Mr. Michelo Simuyandi presented on planned HIS for Zambia with particular emphasis on the use of rotavirus vaccine (based on a live attenuated strain of rotavirus) as a challenge agent and on LMIC capacity to manufacture challenge agents. This led to discussion on current debates on classifying challenge agents as vaccines and whether challenge agents must be certified as following Good Manufacturing Practice (GMP) or GMP-like. Ms. Cecilia Chiu from Wellcome

Trust contributed a funder's overview of HIS and specific responses to international dialogue on GMP and compensation.

Session 4: Dr. Anjali Sharma facilitated the session on burden of HIS participation and research-related risk using empathy and journey mapping. Imagining a child participant led to questions of autonomy and consent, therapeutic misconception, tolerability of challenge agent and compensation. For adults, informational needs and issues of motivation, compensation vs undue inducement, stigma, and social obligations were raised. For both, considerations of nature of residence, compensation, insurance, safety of challenge agent, and withdrawal were forwarded.

Recap: Dr. Melissa Kapulu opened Day 2 by recapping the main points from the previous day.

Session 5: Mr. Ambrose Rachier, Prof. Mfutso Bengo, and Dr. Sody Munsaka shared Kenyan, Malawian and Zambian perspectives on HIS ethics respectively. Mr. Rachier advocated for detailed independent review of proposed HIS for appropriateness as well as provisions for human protections, local capacity building, and participant comprehension of HIS information sheet. Prof. Bengo added that national guidance can be equivalent if not harmonized to international guidance. Dr. Munsaka explained that Zambian guidance on compensation was based on wage and reimbursement model; however, there was no determination on what constituted fair compensation. These presentations furthered discussions on standards/benchmarks for research ethics application and oversight; community engagement and need for a formula to determine fair compensation.

Session 6: Ms. Evelyn Ng'andu presented community views on HIS from the recent qualitative investigation undertaken by CIDRZ. University students in Lusaka, Zambia, said that they would be willing to participate in HIS provided all their questions were answered and they were allowed to consult trusted elders. Of note, they wanted compensation for the assumption of risk though they could not put a monetary value to putting their person and lives at risk. This led to the clarification of compensation being for the burden of participation and insurance for research related injuries.

Session 7: Mr. Michelo Simuyandi, Mrs. Constance Chisha, and Mr. Lackson Tonga, presented on the requirements for the manufacture of challenge agent, importation of challenge agents, and regulations on contained use of genetically modified materials, respectively. This discussion led to the conclusion that GMP was preferred and that more research was needed on GMP, GMP-like, engagement with media, and managing public sentiment around genetically modified products.

Session 8: Dr. Roma Chilengi offered the view that Zambia was ready for HIS due to existing infrastructure and a strong ethical and regulatory environment for clinical trials. Attendees recommended that the legal environment including for informed consent, health insurance and biosafety be studied; an engagement strategy that segmented the audience across all levels in the political, research and communal arena; as well as further the conversation on GMP/GMP-like, compensation and data protection. Dr. Roma Chilengi closed the meeting with an expression of thanks, along with assurances of reflection and incorporation of the main recommendations into CIDRZ engagement with ethical and regulatory issues that could affect HIS implementation.

3. Proceedings of the Workshop

The workshop agenda covered the following topics: 1) benefits and need for HIS in Zambia, 2) methodological issues that impact HIS implementation and outcomes, 3) HIS plans for Zambia, 4) risk and burdens of participation, 5) ethical considerations particularly compensation, 6) participant and community safety, 7) scientific overview of challenge agents, and 8) conclusions and recommended next steps for building a platform for the conduct of HIS in Zambia and the region. Each session began with a brief presentation followed by group work to initiate discussions to frame the issues and highlight any recent studies or thinking relevant to the topic. Following a group exploration of the topic and any exemplars that should be noted, the group came up with recommendations for next steps.

3.1. Benefits and the Need for HIS in Zambia

Dr. Roma Chilengi opened the discussion with a presentation on ‘Human Infection Studies: Historical Perspective and Scientific Rationale’. He explained that though the nomenclature had evolved to the current ‘Human Infection Studies,’ the World Health Organization definition remains as below:

WHO definition

Human challenge trials are trials in which participants are intentionally challenged (whether or not they have been vaccinated) with an infectious disease organism. This challenge organism may be close to wild-type and pathogenic, adapted and/or attenuated from wild-type with less or no pathogenicity, or genetically modified in some manner.



Dr. Chilengi traced the history of HIS (starting from 1717), started by crude variolations and marked by increasingly rigorous scientific study of inoculates with the passage of time. Many of the earlier experiments usually involved coercive (and even “abusive”) research practices/deception of vulnerable populations such as prisoners, orphans and sex workers. The Nuremberg trials in 1946 & 1947 laid the foundation for research ethics emphasizing protections for individuals, including of their health and autonomy. Persistent unethical research practices have since resulted in various international

Suggested readings:

How One Daring Woman Introduced the Idea of Smallpox Inoculation to England

<https://time.com/5542895/mary-montagu-smallpox/>

Smith KA. Edward Jenner and the small pox vaccine. *Frontiers in immunology*. 2011 Jun 14;2:21.

<https://www.frontiersin.org/articles/10.3389/fimmu.2011.00021/full#B11>

Levine MM, Lagos R. Vaccines and vaccination in historical perspective. In *New generation vaccines 2004* Jan 28 (pp. 19-37). CRC Press.

Williams JR. The Declaration of Helsinki and public health. *Bulletin of the World Health Organization*. 2008;86:650-2.

declarations to protect human participants. Currently, research ethics balance traditional health care ethics with public health ethics to further global health.

Dr. Chilengi emphasized the need to learn lessons from this history to ensure that science can advance life-saving strategies, but without compromising the rights of human participants. Human Infection Studies are important in shortening the time to vaccine development, involve fewer participants and reduce the costs of conducting vaccine research. Additionally, while helpful to understand basic science, animal models do not represent human hosts. Thus HIS provides the opportunity to study both pathogenesis and vaccine immunogenicity mechanisms particularly in human-restrict pathogens. Dr. Chilengi provided the examples of cholera and typhoid HIS that accelerated vaccine development at less cost in time and money that conventional Phase I studies.

Exemplars to study:

Mohan, V.K., et al., 2015. Safety and Immunogenicity of a Vi polysaccharide–tetanus toxoid conjugate vaccine (typbar-TCV) in healthy infants, children, and adults in typhoid endemic areas: a multicenter, 2-cohort, open-label, double-blind, randomized controlled phase 3 study. *Clinical Infectious Diseases*, 61(3), pp.393-402. <https://academic.oup.com/cid/article/61/3/393/490870>

Feasey NA, Levine MM. Typhoid vaccine development with a human challenge model. *The Lancet*. 2017 Dec 2;390(10111):2419-21.

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(17\)32407-8/fulltext?elsca1=etoc](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32407-8/fulltext?elsca1=etoc)

Mosley JF, et al. Vaxchora: the first FDA-approved cholera vaccination in the United States. *Pharmacy and Therapeutics*. 2017 Oct;42(10):638.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5614415/>

Chilengi R. Clinical development of malaria vaccines: should earlier trials be done in malaria endemic countries?. *Human Vaccines*. 2009 Sep 1;5(9):627-36.

<https://www.tandfonline.com/doi/pdf/10.4161/hv.9141>

Hodgson SH, Juma E, Salim A, Magiri C, Njenga D, Molyneux S, Njuguna P, Awuondo K, Lowe B, Billingsley PF, Cole AO. Lessons learnt from the first controlled human malaria infection study conducted in Nairobi, Kenya. *Malaria journal*. 2015 Dec;14(1):182.

<https://malariajournal.biomedcentral.com/articles/10.1186/s12936-015-0671-x>

Dr. Chilengi made the case for HIS to address malaria in LMIC with the first such study published in 2015. Using the case of rotavirus, he suggested that:

There is enough evidence to demonstrate that we need tailor made interventions:

- Environmental factors
- Genetic factors
- Health system factors
- Ethical fundamentals

Dr Chilengi ended his presentation with Wellcome Trust's video: *What are Human Infection Studies* available on YouTube at <https://www.youtube.com/watch?v=FcD7kH5mCLk>.

The presentation triggered discussions on being careful about our underlying prejudices when determining the inclusion criteria for participants, lest history judge us harshly. Attendees noted that HIS should include those most at risk and therefore most in need of tailored interventions. A good example is that of rotavirus vaccine, which was developed in clinical trials among adults in developed, non-endemic countries with sub-optimal outcomes for children in LMICs.

Attendees noted that the context of conducting research had changed with provisions for civic society, ethical and regulatory oversight. In particular, the Belmont Report provided for protections through the principles of respect for persons, beneficence and justice https://www.hhs.gov/ohrp/sites/default/files/the-belmont-report-508c_FINAL.pdf.

For e.g., if the population at risk is particularly poor, then compensation should be commensurate with burden of participation but not unduly induce participation. Of note, the National Health Research Authority (NHRA) was developing guidance on minimum expected compensation albeit not specific to HIS.

Questions arising:

1. What question does HIS answer?
2. What evidence is there that **all** HIS lead to vaccines – for e.g., there is no vaccine yet for gonorrhoea?
3. If these are studies of diseases of poverty, how do we set compensation?
4. Who is the population and how do we safeguard against exploitation of vulnerabilities?
5. What types of pathogens should be considered appropriate?
6. How are we preparing communities?
7. How do people perceive HIS? What are their expectations – expected end results?
8. What does the bigger legal framework allow? What revisions should be considered?

Recommendations:

Following the discussion, the expert participants suggested the following considerations/actions when formulating ethical and regulatory frameworks:

- * Study the platform provided by the current legal framework, research act and guidelines for HIS conduct.
- * Determine what is ‘fair compensation’.
- * Use social science studies to prepare communities to understand the principles guiding HIS and the burden and risks of participation.

3.2 Methodological Issues that Impact HIS Implementation and Outcomes

Dr. Melissa Kapulu presented the ‘Methodological Considerations for HIS - The Kenyan Experience’. She described the long history of public engagement in Kenya starting with stakeholder mapping and consultations on malaria HIS.

Questions asked during engagement differed across those research naïve, research savvy, and from Sub-council Health Management Teams. This previous engagement paved the way for a shorter year-long engagement for enteric HIS. Nonetheless, a recent press release sensationalized compensation. Dr Kapulu recommended public engagement to address concerns and rumours, she also suggested developing informational materials with communities and having a media management plan.

Exemplar to study:

Kapulu, M.C., et al, 2018. Controlled Human Malaria Infection in Semi-Immune Kenyan Adults (CHMI-SIKA): a study protocol to investigate in vivo Plasmodium falciparum malaria parasite growth in the context of pre-existing immunity [version 1; referees: awaiting peer review]. *Wellcome Open Research*.

Dr. Kapulu said the Malaria HIS was conducted among semi-immune adults to understand acquired immunity, accelerate vaccine development, and test vaccine/drug efficacy. The study was designed to prioritize target parasites for vaccine development that protect against infection, disease and transmission stages of malaria (See ClinicalTrials.gov Identifier: NCT02739763 <https://clinicaltrials.gov/show/NCT03947190>).

The study showed that parasite growth was affected by previous exposure to malaria justifying the use of HIS to develop phenotype to 1) evaluate infection doses most suitable for malaria exposed individuals, 2) better understand how malaria immunity develops, and 3) develop vaccine efficacy studies using models in context of immunity. Thus, pathogen exposure & modulation of endpoint were outcome key for human infection studies in LMIC settings.

Social science studies embedded in HIS also deepened understanding of information giving and consenting processes, decision-making for participation, limits of the right to withdraw, experiential evidence to fuel empirical research ethics, perceptions around deliberate infection, and implications of participation on participant's lives.

Dr. Kapulu contrasted the residential arrangements and other requirements of participation in highly controlled malaria and enteric HIS through photographs.

Following the presentation, attendees split into four groups by specialty: Regulators, ethic review board members, scientists, and social scientists/communications experts to provide area-specific considerations for guidance (See **Appendix C**).

The presentation and group work led to discussions on how HIS maybe less risky than Phase I clinical trials as the pathogen/challenge agent is already characterized. While children were not ruled out as participants, college/university students were suggested as a good starting point as they are usually healthy adults who have the education to process complex and abstract ideas. Staff participation increases confidence in HIS.

The time to approval was 4-6 months in Kenya excluding pre-interactions before formal submission. Though HIS raises concerns, in Kenya, closing recruitment or exclusion raised protests. While exclusion criteria maybe clear, participants should not be told reason for exclusion to protect other participants' confidentiality. However, medical or other congenital conditions should be revealed to potential participants.

References:

Hodgson SH, et al. Evaluating controlled human malaria infection in Kenyan adults with varying degrees of prior exposure to Plasmodium falciparum using sporozoites administered by intramuscular injection. *Frontiers in microbiology*. 2014 Dec 12;5:686.

<https://www.frontiersin.org/articles/10.3389/fmicb.2014.00686>

Hodgson SH, et al. Lessons learnt from the first controlled human malaria infection study conducted in Nairobi, Kenya. *Malaria journal*. 2015 Dec;14(1):182.

<https://malariajournal.biomedcentral.com/articles/10.1186/s12936-015-0671-x>

Abdi AI, et al. Plasmodium falciparum malaria parasite var gene expression is modified by host antibodies: longitudinal evidence from controlled infections of Kenyan adults with varying natural exposure. *BMC infectious diseases*. 2017 Dec;17(1):585.

<https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-017-2686-0>

How information is worded is important – for instance, stating compensation was for lost wages incurred Income Tax for Kenyan HIS participants. During the consenting process, issues of confidentiality become blurred as participants may need to consult with spouses, parents and family. In Kenya, some women did not want their husbands to know about the compensation in order to have control on monetary compensation. Detailed and clear guidance on compensation is critically needed particularly for HIS.

Temporary leave from residence should be considered on a case-by-case basis for instance to write an exam or attend a funeral.

Questions arising:

1. Should staff be allowed to participate?
2. What is the best medium of communication?
3. When should the press be engaged?
4. How long should community engagement be? Where should it begin? Who should be included? Which type of audience needs which type of message/information? How should they be told?

Recommendations:

- * Have a press liaison study focal person and engage with editors not just journalists
- * Include ethics and regulatory bodies when dealing with misinformation and other crisis

3.3. HIS plans for Zambia

Mr. Michelo Simuyandi presented the “HIS plans in Zambia”. He began his presentation by introducing the Enteric Diseases and Vaccines Research Unit (EDVRU) at CIDRZ which provides a platform for the development and testing of clinical products including vaccines against *rotavirus*, *V.Cholera*, *Salmonella*, *Shigella*, *ETEC*, *clostridium difficile*, *norovirus* and *cryptosporidium*. The EDVRU works closely with the CIDRZ laboratory which is the only International Organization for Standardization (ISO) certified laboratory in Zambia.

Mr. Simuyandi described how the live oral rotavirus vaccines improved health outcomes for Zambian children but nonetheless performed sub-optimally due to various contextual factors that continue to impact on vaccine efficacy in the country. The EDVRU is actively working towards establishing a HIS rotavirus model to pilot the feasibility and assess the use of routinely administered live attenuated oral rotavirus vaccine Rotarix® as the HIS challenge agent. This model would be used to evaluate the use of minimally invasive procedures such as saliva in assessment of immune responses. The model would also measure vaccine virus shedding as a measure of vaccine induced mucosal immunity as well as a possible correlate of protection.

Mr. Simuyandi noted that HIS has been particularly useful in identifying candidate vaccines for outbreak pathogens and pathogens restricted to humans such as *V.Cholera* which lack suitable animal models, correlates of protection, conditions for traditional clinical trials. Cholera HIS conducted between 1974 and 2001 have used both live-attenuated and non-living oral vaccines.

Mr. Simuyandi also discussed the EDVRU's preliminary work in establishing a HIS Typhoid model by profiling immune responses to active typhoid infections and exploring perceptions around participation in a HIS. Mr. Simuyandi explained that in addition to generating baseline data on immune profiles of individuals living in typhoid endemic countries like Zambia, the model would also explore individual fears and concerns around participating in a HIS, community perceptions and issues of appropriate compensation.

The session ended with a discussion of what would be required to set up HIS Models in Zambia. If new agents are created through genetic modification of pathogens, then there is potential environmental risk. This led into further discussion on GMP and GMP-like requirements. GMP certification is not possible for all pathogens and countries. Such a requirement can exclude African countries from producing challenge agents. There is precedent of HIS using GMP-like with the World Health Organization (WHO) agreeing to local production at safety standards.

Questions arising:

1. In the rotavirus vaccine model described, how many doses would be required for an individual to be considered fully protected before administration of a challenge agent?
2. How does the use of a vaccine as a challenge agent fit into the HIS model concept?
3. When should the press be engaged?
4. How long should community engagement be? Where should it begin? Who should be included? Which type of audience needs which type of message/information? How should they be told?

Exemplars to study:

Chilengi R, et al: Successes, challenges and lessons learned in accelerating introduction of rotavirus immunisation in Zambia. *World Journal of Vaccines* 2015,5(01):43.
https://file.scirp.org/pdf/WJV_2015012616311913.pdf

Bosomprah S, et al: Findings from a comprehensive diarrhoea prevention and treatment programme in Lusaka, Zambia. *BMC public health* 2016,16(1):475.

<https://www.ncbi.nlm.nih.gov/pubmed/27268226>

3. Griffiths UK, et al: Costs of introducing pneumococcal, rotavirus and a second dose of measles vaccine into the Zambian immunisation programme: Are expansions sustainable? *Vaccine* 2016,34(35):4213-4220.

<https://www.ncbi.nlm.nih.gov/pubmed/27371102>

Rudd C, et al: Rotavirus landscape in Africa -- Towards prevention and control: A report of the 8th African rotavirus symposium Livingstone, Zambia. *Vaccine* 2015,33(29):3263-3267.

<https://www.ncbi.nlm.nih.gov/pubmed/25957665>

Beres LK, et al: A preliminary assessment of rotavirus vaccine effectiveness in Zambia. *Clinical Infectious Diseases* 2016,62(suppl_2):S175-S182.

<https://www.ncbi.nlm.nih.gov/pubmed/27059353>

Evans M, et al: Impact of Rotavirus Vaccination on Diarrheal Hospitalizations in Children Aged <5 Years in Lusaka, Zambia

https://academic.oup.com/cid/article/62/suppl_2/S183/2478853

Chen WH, et al. Single-dose live oral cholera vaccine CVD 103-HgR protects against human experimental infection with *Vibrio cholerae* O1 El Tor. *Clinical Infectious Diseases*. 2016 Mar 21;62(11):1329-35.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4872293/>

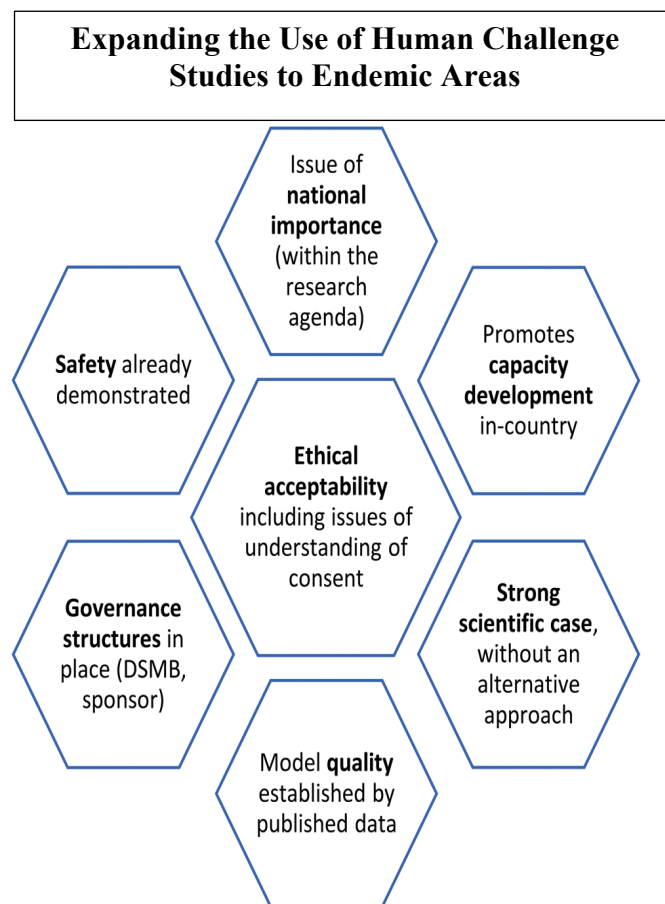
Recommendations: Following discussions, the experts recommended the following in setting up ethical/legal/regulatory frameworks:

- * Need for consideration of GMP versus GMP like certifications in establishing regulatory guidelines in Zambia.
- * While challenge agents could be vaccines, messaging needs to be carefully worded to avoid vaccine naysayers.

3.4. Funder Perspectives on HIS

Dr. Cecilia Chui from the Wellcome Trust presented “Funder Perspectives on HIS” (See <https://wellcome.ac.uk>). Wellcome Trust has a large endowment, £1 billion of which is dedicated to new innovative ideas and the rest, depending on endowment performance, dedicated to advancing science over a 5-10 years period. The vaccines team aims to develop new vaccines and to put existing vaccines to better use.

Wellcome Trust supports HIS to accelerate vaccine development in endemic populations so that vaccines are developed to serve those most in need. HIS can minimize safety risk with self-characterized risks representative of circulating strains that produce infections that are self-curing or treatable with no lasting effects. The infection should be detectable and preferably quantifiable. The potential impact of HIS include higher success rate at later stage of clinical development, early failure and improvement, and acceleration of product development. Sharing findings between donors, scientists, ethicists and communities of practice can help harmonize protocols and pool data as far as reason allows. Currently there is no formalized procedure for global communications between and to National Research Authorities. There is opportunity to create networks with HIS sites currently supported by Gates and Wellcome Trust (See <https://tghn.org>).



[Gordon et al, 2017]

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(17\)32407-8/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32407-8/fulltext)
<https://www.bbc.co.uk/news/health-41724996>

While ethical and regulatory guidance is in place in the US and Europe, more robust guidance is needed for other regions that goes beyond traditional clinical trials, along with recognized regulatory development pathways for licensure of vaccines. Currently GMP-like products are used as long as they meet the highest standards that current science allows though guidance varies on agents that can lead to potential risk on stability and reproducibility. The Medicines and Healthcare products Regulatory Agency (MHRA) can support the development of national regulations. The International Alliance for Biological Standardization (IABS) February 2020 conference will further this dialogue (<https://registration.iabs.org/index.php?id=32>).

The WHO Africa and Asia country offices are developing guidance for regulatory and ethics review to promote regulatory coherence and harmonization. The Wellcome Trust provides ethics support to HIS sites, funds to equip ethics committees to assess HIS and empirical research on ethical issues in LMIC.

Questions arising:

1. When would GMP and GMP-like apply?
2. How do you determine compensation? Do you factor in risk?

3.5. Risk and Burdens of Participation

Dr. Anjali Sharma presented on the 'Risk and Burdens of Participation'. She differentiated between 'risk' as that of bodily harm and 'burden' as infringements on volunteers due to participation.

Attendees sat in four groups to draw an empathy and journey map. In the empathy mapping exercise, attendees created a persona for a HIS participant with attributes that went beyond the socio-demographic to include his/her circumstances, aspirations, and daily concerns. In journey mapping, they visualized the progress of this specific HIS volunteer's experiences, feelings and actions through an enteric HIS from consent to withdrawal/exit. These exercises provided insights into HIS participants' expectations and the complexities they might face during a HIS.

Readings:

Jamrozik E & Selgelid MJ. Human Challenge Studies in Endemic Settings: Ethical and Regulatory Issues (Forthcoming)

Ferreira B, Silva W, Oliveira Jr EA, Conte T. Designing Personas with Empathy Map. InSEKE 2015 May (Vol. 152).

Marquez JJ, Downey A, Clement R. Walking a mile in the user's shoes: Customer journey mapping as a method to understanding the user experience. Internet Reference Services Quarterly. 2015 Oct 2;20(3-4):135-50.

Two groups chose an infant as the HIS enteric volunteer. The other two chose university students, one orphaned and volunteering for a cholera HIS and the other for typhoid. These personas and their journeys through enteric HIS are presented in **Appendix D**.

The group presentations on children in HIS agreed that requirements of consent and autonomy applied as for all clinical trials. However, while one parent's consent was sufficient, customarily, the household head (husband/child's father) could overrule the mother's decision. As such, it was advisable to allow the mother time to consult the family before consenting. The child's assent was

needed where applicable; Zambia does not have provision for emancipated (under 18 living independently) or mature minors (made independent life decisions). Young people may need to consult parents, teachers and siblings. If household heads, they would need to make provision for the care of their siblings.

Compensation and access to health care should be agreed at the time of consent. Consents should have full information including safety profile, tolerability of challenge agent/pathogen, safety measures as well as what happens if a child is sick or dies. Adults would want to understand the severity of symptoms and any previous experience with the challenge agent. In Kenya, they wanted to know that the IRB had approved the study. Adults should know the limits of their right to withdraw and who to contact should anything happen after they withdraw or exit from the study.

As with clinical trials, the possibility of therapeutic misconception was raised. A clean bill of health at no cost could motivate mothers to put their children in trials. The other motive could be to be part of a noble cause. Adults would be motivated by money and perceived benefits for themselves.

If residence was required, then mothers would need leave from work and to make provisions for their household and childcare duties. Confinement also led to discussions around compensation and how wage, opportunity costs and other costs such as childcare should be reimbursed. For adult participants, spouses would have to consult each other before agreeing to being in residence for the duration of a HIS. Residences should be comfortable and allow for privacy. Adult residents would want clean premises.

Stigma also emerged as a possibility for both children and adults due to the nature of the pathogen, being away from home, or associations with being a volunteer in a research study. If there was an infection outbreak, the participants could experience stigma.

Questions arising:

1. Should parent/individual be required to consult spouse? What if husband coerces wife?
2. How do you determine compensation for a child participant?
3. Does Zambian law allow for emancipated or mature minors?
4. At exit, what of loss of health care? What if sick at home?
5. What about other children in the household? Can they enroll? Can they stay in residence?

Recommendations:

- * Conduct ongoing sensitizations so that participants are able to process and contextualize their experiences.
- * If the information sheet is too long, consider group consent and use of cartoons/videos.
- * Include a test of understanding.
- * Have medical and emergency care on stand-by.
- * Follow-up after study completion for any unexpected events.
- * Community engagement was needed to reduce stigma.

3.6. Day 1 Recap

Dr. Melissa Kapulu recapped Day 1 of the workshop. She reiterated the need to have a compelling rationale for undertaking HIS, to utilize treatable pathogens, to model compensation rates, to engage with communities and to incorporate their views through social science sub-studies. There is need to determine who constitute vulnerable populations and the cost-benefit ratio of including them in HIS. She reminded attendees that the first session ended with the recommendation to review current guidelines and guidance in the legal framework for undertaking HIS.

Session two laid the foundation for initiating HIS in the country with students and study staff even though they are less risky than traditional Phase I (first-in-man) studies. Also, the local context was important, for e.g., the taxation laws on compensation. Confidentiality was important to protect study participant rights. Finally, media engagement, particularly with editors, was important. There was need to have a response in hand in case of bad press attention and buy-in from regulators on response to bad press.

Session three asked whether dose vary if live attenuated vaccines are used as challenge agents? The attendees agreed that first use in setting should be a GMP product though there is no harmonised/standardised guidance (even in the UK, Europe or the US) on challenge agent preparation. Autonomy was the main principle justifying participation in HIS. There is need to determine if risk or wage-based model of compensation should be used.

Session four differentiated between 'risk' and 'burden.' It raised the issue of consent and who is empowered to give full consent, compensation for infants/children (under 14 years), residential features, agreement at consent to the compensation and access to care, and consideration of previous experience with challenge agent. In particular, the right to withdraw was limited due to the need to have cleared infection and be treated before exiting the study.

The recap led to a discussion on the right to withdraw which could be seen as analogous to the right to refuse treatment. Here, pathogen selection was important. If the pathogen was a vaccine strain and not wild type, public health ethics and the principle of double effect would apply. In Kenya, participants were allowed to withdraw but still had to be clear of malarial parasite. In the case of Shigella, participants are treated by day 5 but cannot leave until they are cleared of infection. They can also return if they face problems later.

If someone insisted on leaving the premises, then the study could fall back on the informed consent which is legally binding. In Kenya, clinic staff familiar with their communities, screened and consented participants which helped with comprehension and cooperation.

Questions arising:

1. Once you attenuate a pathogen strain, is it a vaccine or a challenge agent?
2. Are residents allowed conjugal and family visits? If not conjugal visits, then why should women be required to be on contraceptives?
3. How do students attend classes if required to be in residence?
4. What if someone is withdrawing due to an AE?
5. Is the informed consent a legally binding instrument in Zambia?
6. What is the reaction of IRBs when they see a HIS protocol for the first time?

Recommendations:

- * Ensure participants understand the limits of their option to withdraw from the HIS.
- * Ensure that participants are treated and are no longer infectious before they leave the study.
- * Use existing HIS ICFs to adapt to Zambian HIS
- * Put guidance for the worst-case scenario of withdrawal from the study; additionally, the protocol must clearly state what will be done.
- * Start with communities used to you
- * Provide for television, books, internet and Sunday church attendance.
- * IRBs should look at what other IRBs have done and be guided by the principle to ‘first do no harm.’ Look at the risk and compensation. Study each ethical point.

3.7. Ethical Considerations Particularly Compensation

Mr. Ambrose Rachier, Dr. Joseph Mfutso-Bengo, and Dr. Sody Munsaka, respectively provided the Kenyan, Malawian and Zambian perspectives on ethics around clinic trials, particularly HIS.

Mr. Ambrose Rachier presented on the ‘Experiences with Controlled Human Infection Model (CHIM) Studies at the Kenya Medical Research Institute (KEMRI)’. He provided some background information about the first CHIM study on Malaria undertaken in Kenya from March 2013 to October 2015. He also spoke on three other KEMRI approved CHIM studies that are ongoing in Kenya. Overall, CHIM should be judged against appropriateness in disease-endemic areas, national importance and alternatives. Detailed independent review is required with an understanding of the context and of ethical review for other studies including HIS. The protocols should include capacity building. The disease should be reversible; for instance, a schistosomiasis HIS was rejected due to concerns about potential irreversible damage.

Principles considered during review:

1. Participation selection
2. Risk/Benefit Ratio
3. Residency requirements
4. Compensation
5. Community sensitization and engagement
6. Adequacy of information sheet including limits of withdrawing
7. Test of understanding
8. Confidentiality/data management
9. Study monitoring
10. Insurance
11. Capacity building

For the first CHIM, other than those usual to clinical trials, considerations included capacity to understand CHIM; for this reason participants were students and staff from four local medical schools. Risks included signs and symptoms of malaria, side effects of drugs used to treat malaria, and allergic reactions. Residency was required to safeguard participant health and safety. The study had a detailed community sensitization plan implemented through formal channels in the community throughout the study. The study was to document and address any concerns raised by the community. Insurance was to cover participants, product manufacturers as well as indemnity

for staff. Products were to be manufactured in a certified and audited Good Manufacturing Practice (GMP) facility and stored in appropriate conditions and monitored daily. The study was to be monitored by appropriate authorities.

Dr. Joseph Mfutso-Bengo presented on the ‘Ethics and Acceptability of HIS in LMIC including Africa’. He emphasized the need to train ethics committees and to have local guidance “equivalent” to, rather than “harmonized” to, international guidance to remain relevant to the local context. Malawi had a formula to estimate local wages to cover transport expenses, loss of income and time required by the study. Participants were to be compensated on completion of challenge period and at each follow-up visit.

Dr. Sody Munsaka presented on the ‘Ethics of Paying Research Participants’. He began his presentation by basing participant compensation on three normative ethical philosophies/theories. Virtue Ethics theories emphasize the actor's moral character/virtue of the actor <https://www.iep.utm.edu/virtue/>. Deontology/Kantian theories examine whether the action itself is right or wrong under a series of rules <https://plato.stanford.edu/entries/ethics-deontological/>. Utilitarian/Consequentialist theories promotes actions that maximize happiness and well-being for the majority of a population <https://plato.stanford.edu/entries/utilitarianism-history/>.

He gave a brief background on the history of research ethics. The 1947 Nuremberg Code introduced voluntarism in research which was consolidated in the 1964 declaration of Helsinki. The 1978 Belmont report contains the three ethical principles guiding research today, i.e., Respect for persons allowing for informed consent; Beneficence which is an assessment of the risk-benefit ratio; and lastly, Justice which promotes the fair distribution of risks, costs, and benefits to potential participants. Compensation was described as payment in cash (value) or in-kind (good) for participating in research and could be for various reasons such as travel, incentive, inconvenience and to reflect risk and/or discomfort. Four models can be used to compensate a participant: Market Model which provides incentives to facilitate recruitment by escalating the payment to meet recruitment; Wage Model which compensates for time, effort and discomfort by standardizing wage-like payments to remove undue influence; Compensation model which is compensation to meet out-of-pocket expenses and; Appreciation model which is a token given for participation in research.

Some ethical questions arise around payments including but not limited to:

How do you compensate child participants when payment is going to the parents who are not the ones bearing the risks?

How do you compensate patient participants who may benefit from the research?

Some issues that may arise from paying a participant are that it may compromise voluntarism, participants may ignore the benefits/risks, harms involved because they value the money more; it may cause participants to hide factors that may compromise the study and that participants may provide information that the researcher wants and introduce bias.

The Council for International Organizations of Medical Sciences (CIOMS): “Subjects may be paid for inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research; they may also receive free medical services. However, the payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgement (undue inducement)”.

The presentations led to discussions on the level of payments offered and undue influence which can cloud participants judgement and/or minimize the risk and discomfort involved, especially among those with no or poor-paying jobs with the time to participate in HIS.

Attendees discussed whether or not to require contraception during an in-patient study to prevent pregnancy and how that affects the women in the study and their spouses.

If countries choose to go the GMP route, then the protocol must provide for local capacity building particularly for laboratories and manufacturing. GMP-like allows for inclusion of more pathogens and countries without lowering standards.

Questions arising:

1. What measures did Kenya put in place for participant compensation?
2. What model of compensation should be used- wage or risk?
3. For those countries that have already reviewed and approved CHIM studies, what general advice would you give Zambian Ethics Committees and Research Authorities?
4. For married participants, are spouses allowed to visit the participants in residence?
5. For students that enrolled in studies what happens to their training programmes?
6. Is there a specific formula used to come up with compensation rates?
7. Should compensation account for the element of risk?
8. Do ethical committees ask for budgets to ensure adequate time allocation for Principal Investigators and for compensation?

Recommendations: Following the discussion, the expert participants suggested the following considerations/actions when formulating the compensation amount:

- * Wage and compensation models are the best suited models for the Zambian setting
- * NHRA to lead this discussion and determine standardized participant compensation for CHIM studies.

3.8. Participant and Community Safety

Deliberations on the safety of the participants began with a presentation from Ms. Evelyn Kunda Ng'andu on willingness of students from institutions of higher learning to take part in HIS. She reported that most of the participants were motivated to participate in a HIS due to altruism, patriotism and risk compensation, provided they had adequate information and assurance of risk mitigation.

Dr. Anjali Sharma reported that students were cognizant of possible side effects and foreseeable risk. She further reported that students wanted to be compensated for time away from their studies and normal activities, getting sick during and after study, and assumption of risk. However, students could not put a monetary value to compensation as it was a matter of human life.

The presentation led to discussion on the need to distinguish between compensation for burden of participation and that for research-related injuries, which follows a different set of rules related to insurance. While many insurance companies in Zambia have been sensitized on no-fault insurance, provision of specific Trial Insurance is still very new in the country. CIDRZ has a corporate liability insurance for its staff and arranges insurance cover for each clinical trial to cover study related injuries as per GCP. However, globally compensation accounts for risk, opportunity cost, lost wages, and time. Generally, high risk studies could bar participation; willing participants should be in residence to permit regular monitoring and access to emergency care and resuscitation. Residency should be as comfortable as possible and include entertainment such as games, internet, library etc.

Following the presentation, attendees split into groups discussing safety and how to assure safety for HIS participants (See **Appendix E**). The groups categorized safety issues by product, process, oversight, infrastructure, personnel, procedure and the community. Product safety measures included those for quality, purity, labelling, stability, reproduction, storage, and manufacturing standards (GMP or GMP-like). Participant inclusion criteria needed to be clearly spelt out with stringent screening procedure for any contraindications or genetic predisposition to the challenge agent. Experienced, competent and multi-disciplinary study teams were needed to meet the requirements of HIS implementation. Also, there should be clear rescue, evacuation and communication plans for effective emergency preparedness and response. The HIS community need to monitor each other and share lessons learned.

The groups also concluded that participants directly benefited from being screened for and educated on the condition of study and having health insurance during the study period. Communities could benefit from improved health facilities, vaccine development, and reduced disease burden.

Questions arising:

1. What would be the barriers to participation for your study when the issues are ranked?
2. How does compensation become a safety issue?

Recommendations:

- * CIDRZ to try the no-fault insurance cover for research related injury
- * Compensation to be clearly set out from the very beginning
- * Processes need to be clearly outlined to assure participant safety
- * The inclusion and exclusion criteria to be well defined in HIS for participants' safety

3.9. Scientific overview of challenge agents

Mr. Michelo Simuyandi gave a scientific overview of pathogen development examining the assumptions and definitions, regulations in development of strains and development of challenge strains. Mrs. Bernice Mwale, the Director General for Zambia Medicines and regulatory Authority (ZAMRA), presented on the importation of challenge agents.

Mr. Simuyandi stated that to be informative of the protective efficacy against natural infection, the HIS model needs to use adequate pathogen strains representative of field strains originating from same geographic region. Homologous challenge agents are genetically/immunologically identical while Heterologous challenge agents are genetically/immunologically different from the vaccine strain. Regulations require challenge strains to be manufactured according to GMP or equivalent standard to ensure an appropriate quality management system. Supporting documents for manufacture and management of challenge agents should include biological properties, qualification and characteristics, labeling, manufacturing control, traceability, storage, return, and destruction.

Mr. Simuyandi indicated that pathogens used in HIS should be characterized by short, acute, self-limiting infection with rapid incubation; moderate morbidity in healthy population; overtly symptomatic but with limited sequelae; predominance as a circulating strain with global distribution, broad antigenic diversity, potential be cultured (i.e. appropriate culture system) and should be able to evoke measurable curative (or prophylactic) immune response to infection. He provided the pros and cons of various vaccine strains used as challenge agents including malaria challenge PfSPZ which covers two strains, the more virulent cholera strain N16961, and CVD103-HgR and Peru-15 strains which though suitable for HIS are not representative of current El Tor strains.

Ishizuka AS, et al.
Protection against malaria at 1 year and immune correlates following PfSPZ vaccination. *Nature medicine*. 2016 Jun;22(6):614.

Shirley DA, McArthur MA.
The utility of human challenge studies in vaccine development: lessons learned from cholera. *Vaccine: development and therapy*. 2011 Oct;2011(1):3.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3904492/>

Mr. Simuyandi laid out a hypothetical plan for validation of a strain starting with strain selection from surveillance (community or hospital based), which might need to be attenuated through genetic mutations to reduce disease severity. The genetic changes would need validation and production of the strains' seed lots (master and working seeds) verified to be under GMP/equivalent procedures costing anything in the region of \$200,000. Frozen vials and the investigational new drug (IND) for challenge studies need to be prepared before conducting volunteer studies to characterize the safety, immune response and excretion of the strain (i.e. genetic predispositions). Therefore costs, related to development and preparation of a challenge agent is not trivial.

Mrs. Bernice Mwale stated that ZAMRA does not aim to hinder but rather facilitate research by facilitating importation permits. ZAMRA is mandated to regulate importation of medicines and

vaccines, but there is no clear legal framework for challenge agents. Currently, ZAMRA follows the WHO guidance to regulate challenge agents as vaccines. She stated that ZAMRA has submitted amendments of their regulations to the Department of Justice which could be the opportunity to add a component of HIS. As a last resort, the Ministry of Health can be requested for a Statutory Instrument to consider all aspects of clinical trials.

Mr. Tonga said that National Biosafety Authority's (NBA) mandate is to regulate the import, transit of goods, and research development. There is no regulation for contained use of genetically modified products. Funding is needed to develop the regulations. He stated that regulators should sit on one platform to harmonize regulations and laws to avoid the overlap of responsibilities. He also said that it is vital for NBA to work on public awareness and work with scientists who are vested in the science of clinical trials or vaccines.

When asked what regulations applied if Zambia was to obtain a clinical isolate, characterize it and attenuate it thereby creating a genetically modified product, Mr. Tonga noted that for public trust, local capacity building was important to assure product quality and safety. For safety review, a scientific committee should be considered with people assigned for and against the product to have a full and fair discussion and recommendation.

During discussions, attendees agreed that producing a challenge agent may take a very long time compared to using already existing agents. Using words such as GMO conjures up the past where people had bad experiences causing distrust. Community engagement and exposure to current and comprehensive information in user friendly language should be used. The press, particularly editors, champions, advocates and those knowledgeable about vaccines should be included.

Questions arising:

1. How can our regulatory and ethics guidance help local researchers to develop local strains?
2. If a researcher has to import a challenge strain, what would be the issues that NBA and ZAMRA need to consider?
3. How is site mutagenesis regulated versus importation given that a GMO product is created after the process of site mutagenesis?
4. Are the organisms being created totally new or it is something very different from the normal product?
5. How do you manage the strains for only the intended purpose?

Recommendations

- * Surveillance systems need to be strengthened for identification of pathogen strain
- * The production of a challenge strain can be done in-country, but the process needs to be taken step by step and consciously
- * Regulators to agree on what regulations and laws should apply when and for what
- * Clarity is needed on GMP and GMP-like requirements for production of challenge agents
- * There is need for capacity building at various levels vital for HIS processes

4. Next Steps

During the Expert Consultation workshop, a number of recurring themes emerged as important to guiding effective HIS implementation and produced recommendations for implementing HIS in LMIC.

Next steps for recurring themes included:

1. **Community engagement strategies** should consider who should be engaged, when, how and with what information. Attendees noted that communities need to understand all aspects of HIS including the nature and characteristics of the pathogen, requirements of participation and limits to participants' rights particularly if in residence. They suggested that after deeper engagement with ethics committees and regulatory authorities, other government bodies should be engaged. These include Members of Parliament (MP) and relevant ministries particularly Ministry of Health, Ministry of Justice, and the Zambia Revenue Authorities – the last to ensure that volunteers are not taxed on their compensation. University leadership, teachers and students along with the National Council of Science and Technology (NCST) need education to understand HIS. Insurance companies also need to understand the nature of HIS to ensure costs of research related injuries as well as corporate and professional liability costs are covered. Among the press, editors were important gatekeepers. In community settings, community leaders (political, traditional, religious and social), neighbourhood health committees and opinion leaders – should be sensitized before reaching laypersons.
2. **GMP/GMP-like** should be compared and contrasted to understand if they are of different or equivalent standard. The ZAMRA is closely following the WHO guidance on acceptable medicines/vaccines for importation. Consideration of pathogen will establish the signs and symptoms to be considered as Severe Adverse Events. The determination of standards acceptable to Zambia should be based on considerations of public safety and to create an environment that is conducive to building the capacity to produce, patent and bring challenge agents to commercial production in Zambia. The Zambia Metrology Agencies evaluates weighting and measuring instruments before they are permitted to be used in health-related measurements.
3. **Participant selection** should represent the population most at risk and therefore most likely to benefit from HIS. However, screening should ensure that participants are not at particular risk of research-related injuries due to genetic predispositions and allergies. Social harm such as family discord and community stigma due to participation should be anticipated and mitigated. While students make good candidates being young adults in good health, other populations that carry the burden of disease should not be excluded.
4. **Risk management** should not be limited to physical, mental and social harm but should also consider protections for confidentiality and privacy. Zambia is in process of

establishing a central data repository and collection of publications under the umbrella of Smart Zambia.

5. Basis and level of **compensation** must be articulated to ensure it is fair but not causing undue inducement. The NHRA is setting the minimum level but cannot specify exact amounts. IRBs/ERCs and scientists would need to determine these, based on demands of participation and context. The Wellcome Trust provides some guidance, while Malawi has formulated a model to calculate fair compensation. The law regarding taxation of volunteers should be considered.

6. **Informed consent** is foundational in HIS and consenting processes should be followed throughout the HIS. It is incumbent upon us to ensure that potential volunteers have complete information, demonstrate understanding of that information, and have opportunity to make decisions based on that information with time to consult persons of their choice. Different audio-visual and print medium should be considered. For long consents, group consenting should be considered. Social scientists should be employed to document participant concerns, and these should be addressed during HIS implementation. The chain of required approvals should be mapped along with the processes required to ensure all approvals are current and in place to provide participant protections.

5. Appendices

A. List of Participants

No.	Name	Institution
1	Dr. Melissa Kapulu	KEMRI Wellcome/Oxford
2	Dr. Ambrose Rachier	KEMRI and National Ethics Review Committee
3	Dr. Edward Abwao	Kenya Pharmacy and Poisons Board
4	Prof. Mfutso Bengo	College of Medicine – University of Malawi
5	Mr. Elled Mwenyekonde	Malawi Health Research Ethics Committee
6	Mr. Billy Nyambalo	Malawi Health Research Ethics Committee
7	Dr. Sody Mweetwa Munsaka	University of Zambia Biomedical Research Ethics Committee
8	Dr. Victor Zulu	University of Zambia Biomedical Research Ethics Committee
9	Dr. Gershom Chongwe	University of Zambia Biomedical Research Ethics Committee
10	Prof. Patrick Musonda	National Health Research Ethics Board
11	Dr. Lornia Mwape	National Health Research Ethics Board
12	Mrs. Sandra Sakala	National Health Research Authority
13	Dr Victor Chalwe	National Health Research Authority
14	Ms. Bernice Mwale	Zambia Medicines Regulatory Authority
15	Mr. Mulubwa Chilambe	Zambia Medicines Regulatory Authority
16	Mrs. Constance Chisha	Zambia Medicines Regulatory Authority
17	Mr. Lackson Tonga	National Biosafety Authority
18	Dr. Lawrence Mwanayanda	EQUIP Health
19	Dr. Roma Chilengi	Centre for Infectious Disease Research in Zambia
20	Dr. Anjali Sharma	Centre for Infectious Disease Research in Zambia
21	Mr. Michello Simuyandi	Centre for Infectious Disease Research in Zambia
22	Ms. Evelyn K Ng'andu	Centre for Infectious Disease Research in Zambia
23	Ms. Hope Mwanyungwi	Centre for Infectious Disease Research in Zambia
24	Dr. Masuzyo Chirwa	Centre for Infectious Disease Research in Zambia
25	Ms. Joyce Chilekwa	Centre for Infectious Disease Research in Zambia
26	Mr. Mwale Stanley	Centre for Infectious Disease Research in Zambia
27	Ms. Matimba Muuka	Centre for Infectious Disease Research in Zambia
28	Ms. Janet Chinyama	Centre for Infectious Disease Research in Zambia
29	Dr. Cecilia Chui	Wellcome Trust, London: Special presentation over Zoom

B. Agenda

Workshop on Ethics and Regulatory Engagement on Human Infection Studies in Zambia October 14 & 15, 2019

Hosted by: The Centre for Infectious Disease Research in Zambia (CIDRZ)

Venue: Fairview Homes, Siavonga, Zambia

Goal: To contribute to the capacity of ethical and regulatory bodies in overseeing and governing HIS and, to the development of an ethical and regulatory framework applicable to Zambia and LMICs more widely.

Objectives:

1. To understand views, expectations, and experiences of ethical and regulatory bodies, and other stakeholders involved in HIS;
2. To identify ethical issues for HIS implementation in Zambia drawn from the experiences of other LMICs and their implications for HIS in Zambia;
3. To develop modalities to address these issues from the lessons learnt.

Outputs: Recommendations for implementing HIS.

Agenda

DAY ONE:14th October, 2019

08:30 – 09:00 - Welcome Remarks and setting the scene – **Dr. Anjali Sharma**

9:00-09:45: Session 1: Benefits and need for HIS in Zambia

Session Chair - Dr. Anjali Sharma and Mr. Ambrose Rachier

9:00-10:30 – HIS - Historical perspective & scientific rationale - **Dr. Roma Chilengi**

09:00 – 09:45 – Historical perspective and scientific rationale

09:45 – 09:50 – Video on Human infection studies

09:50 – 10:30 – Discussion on rationale for HIS

10:30 – 11:00 – **Tea break**

11:00-12:50: Session 2: Methodological issues that impact HIS implementation and outcome

Session Chair – Prof. Joseph Bengo and Dr. Sody Munsaka

11:00 – 11:20 – Methodological considerations based on Kenyan experience – **Dr. Melissa Kapulu**

11:20 – 12:05 – Group discussion on methodological considerations
45 minutes group work by different types of stakeholders-ethics, regulatory, etc.
From their perspectives, what are the methodological issues?

12:05 – 12:50 – Feedback on group discussions

13:00 – 14:00 – **Lunch break**

14:00-15:45: Session 3: HIS plans for Zambia

Session Chair – Mr. Edward Abwao and Ms. Benise Mwale

14:00 – 14:45 – Overview of planned HIS in Zambia- **Mr. Michello Simuyandi**

14:45 – 15:15 – Open discussion on proposed HIS

15:15 – 15:30 – Wellcome Trust – Funders' perspective

15:30 – 15:45 – Q&A

15:45 – 16:15 – **Tea Break**

16:15 – 18:00 Session 4: Burden of HIS participation and risk to participants

Session Chair – Dr. Roma Chilengi and Dr. Lawrence Mwananyanda

16:15 – 16:30: Risks and burdens- Issues around HIS – **Dr. Anjali Sharma**

16:30 – 17:15 - **Journey Map**: Ask each one to reflect and imagine if they were a participant what would they consider as an issue? e.g. ethics issue, regulatory issue

What are the potential risks to participants and third parties (including the degree to which these can/should be minimized)

- a. the acceptable limit of risks to which healthy volunteers may be exposed
 - b. the need for protection of third-parties from infection (transmitted by participants)
 - c. How cured should the participant be to be let go?
 - d. How will the reporting and management of adverse events be done?
 - e. How will the post-trial follow-up of participants be done?
2. Can these studies lead to stigmatization?
 3. How do we deal with the inadequacies in Health systems?

17:15 – 18:00 – Plenary: Get feedback from the group discussions – **Dr. Anjali Sharma**

19:30 – 22:00 – **Dinner**

DAY TWO: 15th October, 2019

08:30 – 09:00 – Recap of Day One – **Dr. Melissa Kapulu**

09:00 – 10:30 – Session 5: Ethical considerations particularly compensation

Session Chair – Prof. Patrick Musonda and Dr. Gershom Chongwe

09:00 – 09:30 – Ethical experiences from LMIC Settings – Kenya - **Mr. Ambrose Rachier**

09:30 – 10:00 – Ethical experiences from LMIC Settings – Malawi - **Prof. Mfutso Bengo**

10:00 – 10:30 - What is UNZABREC position on compensation? How does UNZABREC consider the balance between compensation and risks?- **Dr. Sody Munsaka**

10:30 – 11:00 – **Tea Break**

11:00 – 12:00 – Session 6: Participant and community safety

Session Chairs – Dr. Chalwe and Dr. Melissa Kapulu

11:00 – 11:20 – Willingness to participate: findings from pilot study- **Ms. Evelyn Ng'andu**

11:20 – 12:00 – Open conversation

How is safety monitored and assured?

What are the potential benefits to participants and/or communities?

12:00 – 13:00 – Session 7: Scientific overview of a pathogen

Session Chairs – Mr. Lackson Tonga and Mr. Michelo Simuyandi

Considering issues that may affect scientific outcomes of HIS implementation

Importation of challenge agents from ZAMRA and Biosafety perspective

13:00 – 14:00 - **Lunch**

14:00 – 15:45 – Session 8: Wrap up:

Session chairs: Dr. Roma Chilengi and Dr. Sharma Anjali

14:00 – 14:30 – Q&A

14:30 – 15:45 – Way forward and wrap up

Dr. Anjali Sharma: What issues are we anticipating?

Dr. Roma Chilengi: Where are we as Zambia in terms of capacities?

C. Session 2: Group Work on Methodological Considerations by Specialty

<p>Regulatory Authorities</p> <p>Product: Quality; Purity; Storage/packaging - labelling, stability, reproducibility; Reversibility; Good Manufacturing Practice (GMP) -like; Administration; Material Transfer Agreements (MTAs); Storage and distribution.</p> <p>Processes: Inclusion; Experience (competency); Standard Operating Procedures (SOPs), Protocols; Oversight (Regulatory, Ethics Committees); Research Governance; Severe Adverse Events (SAEs), management; Data Safety Monitoring Board (DSMB); Investigational brochures; Informed consent; Community engagement; Compensation plan (adequate insurance cover); Risk management.</p> <p>Oversight: Governance; Good Clinical Practice (GCP); DSMB; Ethical Review Boards (ERB), regulations; Safety; Information sharing.</p>	<p>Scientists</p> <p>Infrastructure: Clinical facilities update; Emergency drugs, resuscitation supplies, Safe storage and disposal of products; Challenge agent infection control; Accessibility; Security; Fire evacuation procedures and fire-fighting facilities; Ambulance for evacuation; Recreational facilities; Appropriate freedoms.</p> <p>Personnel: Qualified, trained personnel in multi-disciplinary teams of doctors, nurses, pharmacists and nutritionists; Protective clothing; Personal Protective Equipment (PPE); Aseptic techniques;</p> <p>Procedures: GCP; SOP; Recording procedures during participant stay; Community strategy; Sufficient information on ‘dos & don’ts’; Stringent screening procedures to streamline participant selection; Well-characterized product.</p> <p>Community: Awareness, sensitization; Community protection; 3rd party risk.</p> <p>Others: Comprehensive insurance cover; DSMB.</p>
<p>Public Engagement</p> <p>Product: Stakeholder map.</p> <p>Processes: Communication plan to include who, why, when and how.</p> <p>Oversight: Government, ethical and regulatory bodies, communities, media, social scientists and participants/advocates.</p>	<p>Public Engagement</p> <p>Product: formula to model compensation for both risk and lost wages/costs; formula to assess risk; specify standard of care</p> <p>Processes: Engage with ethics to decide compensation amount; engage independent scientists to assess risk; ‘simulate’ proposed study to map stakeholders and to see HIS from their perspective.</p> <p>Oversight: Insurance, rescue facilities.</p>

D. Session 4: Journey Map

Infant HIS enteric volunteer: Two groups envisioned that the mother would learn about HIS. In one case, the mother was a housewife, illiterate, with five children, the last, a 9-months old infant. She was focused on her husband and entertainment (radio/TV) and had money and transport concerns. In the other case, the mother was working, had other children, and was concerned with managing work and family obligations including income, childcare and school runs, and household management. While not the sole or final decision-maker, the mothers were seen as ultimately responsible for ensuring adherence to study protocol and the well-being of the child.

Table 1 The journey when the Infant is the HIS volunteer

Themes	Learning about HIS	Consenting process	enrollment (in/out of residence)	Withdraw	Exit	Follow-up
Actions (Volunteer must take)	Consult husband/ father of child	Availability; Understands and consents	Willingness to reside		Availability	Report to study site
Questions (To be answered before moving to next step)	What if child gets ill or dies? Is it safe? Can child tolerate it? Will I get leave from work? What will people think?	Is it safe? What are the treatment options?	What about privacy and comfort? Will the other children be allowed to stay too?		What happens now there is loss of health care?	Can other children participate?
Happy moments (Positive experiences)	Contributing to a noble cause; Child will get better; Free health care; Compensation	Clean bill of health; Child enrolled; Health insurance; Paid expenses; Compensation	Free health care	Seeing family again (if in residence)	Seeing family again (if in residence)	To continue interacting with study
Pain points (Negative experiences)	Time demand; Long consenting process; Delayed start; Unmet expectations	Poor understanding/ comprehension	Long and painful study procedures (drawing samples); Opportunity cost for resident mother	No autonomy;	Severe Adverse event;	Child has illness
Opportunities (Recommendations)	Ongoing sensitization; Adjustment and reprogramming Group consent; Cartoons, video to explain procedures	Community engagement; Informed consent form (ICF) in local language; ICF comprehension test	Provide treatment	Counseling; Give treatment; Follow-up; Home visits; Community sensitization	Counseling; Give treatment; Follow-up; Home visits; Community sensitization	Collect feedback on how to improve in next trial

Student volunteer: One group envisioned an orphaned student who volunteers for a typhoid HIS. He carries the cares of the world on his shoulders and is focused on caring for his siblings even as he tries to finish his studies. He also is more motivated by personal gain, asking “What’s in it for me?” and being concerned about how he can reassure his siblings about the safety and benefits of his participation. The second group envisioned a student who

volunteers for a cholera HIS. He has no encumbrances and is motivated by novelty, curiosity and rational decision-making based on information. Both groups stopped with the participant withdrawing from the study. Table 2 below presents the journey of a student enteric HIS volunteer.

Table 2. The journey of a student enteric HIS volunteer

Themes	Learning about HIS	Consenting process	enrollment (in/out of residence)	Withdrawal
Actions (Volunteer must take)	Impressions about the study; More information on benefits; Risks	Understand, decide to participate and sign ICF	Reimbursement; Time; Transport; Infection prevention	Intention to withdraw
Questions (To be answered before moving to next step)	Could I die? Is it safe? Who will take care of my siblings? Duration of study? Previous experience with pathogen?	What if there is an outbreak? What of stigma? What's in it for me? How to assure my siblings I will be okay?	Complicated procedures; Worried about getting sick while at home if not in residence	Severe symptoms
Happy moments (Positive experiences)	To contribute to science; Get money; Perceived benefits	Signing consent; Approved by ethics and regulatory bodies; Compensation	If not in residence, of seeing siblings and being given transport reimbursement	No more clinic visits
Pain points (Negative experiences)	Perceived burdens; Who will feed siblings? Symptoms	Understanding the risks; Samples drawn;	Travel fatigue; Stigma from neighbour	Insufficient compensation; Unfinished treatment
Opportunities (Recommendations)	Treatable condition; Minimum risk; Adequate compensation; Provide contacts for further questions	Ask for and address all concerns; Treat adverse events; Provide contact person details	Community engagement; Reassurance of medical attention	

E. Session 6: Participant and Community Safety

Product	Processes	Oversight	
<ul style="list-style-type: none"> ○ Quality ○ Purity ○ Labeling ○ Stability ○ Reproducibility ○ Reversibility ○ Storage ○ Administration ○ Destruction (environment) ○ GMP-like ○ Manufacturing Trade Agreements (MTAs) 	<ul style="list-style-type: none"> ○ SAEs management ○ Investigational-brochure ○ Inclusion criteria ○ Experience and competences of the team ○ SOPs ○ Ethics compliance ○ Oversight ○ DSMBs ○ Research governance ○ Community-engagement/conversation ○ Compensation (insurance to assure risk related injury is covered) ○ GCP ○ Research governance ○ Informed consent 	<ul style="list-style-type: none"> ○ Overall governance ○ Information sharing ○ DSMB ○ Safety ○ Information sharing 	
Infrastructure	Personnel	Procedures	Community
<ul style="list-style-type: none"> ○ Adequate facilities that are up to date ○ Safe storage of pathogen ○ Security of the place ○ Recreational facilities which are appropriate looking at the type of participants that we are going to have in the trial ○ Fire escape ○ Evacuation plans 	<ul style="list-style-type: none"> ○ Multi-disciplinary trained and qualified personnel ○ Staff need PPEs 	<ul style="list-style-type: none"> ○ SOPs ○ GCPs ○ Aseptic techniques ○ Communication plan ○ Stringent screening procedures 	<ul style="list-style-type: none"> ○ Provide awareness and sensitization ○ Provide proper protection ○ Comprehensive insurance cover ○ DSMB