



Meeting report

**Side Meeting on the Current Global Regulatory and Ethical
Landscape for CHIM Studies including Regional/Global
Collaborative Guidance**

Executive Summary

Conducting controlled human infection model (CHIM) studies in an endemic setting like India can be very valuable and contribute to addressing public health needs by helping to guide the development of products most suited to the populations in need. However, India needs to approach CHIM studies carefully as stakeholders in India are new to this type of engagement in clinical trials. Sustained and transparent public and community engagement are essential for robust outcomes and ethical considerations.

On November 20th and 21st 2019 in New Delhi, a technical meeting on Current Global Regulatory and Ethical Landscape for CHIM studies including Regional/Global Collaborative Guidance was organized as a side-meeting of the 2019 World Conference on Access to Medical Products: Achieving the SDGs 2030. The meeting brought together international and national delegates for two days of focussed discussion and knowledge sharing on ethical, regulatory and scientific aspects of CHIM studies. Participants included international and national experts from the scientific community, representatives from national and international regulatory agencies and ministries of health, ethics community, social scientists, private sector companies with experience in CHIM studies and representatives from WHO and the Wellcome Trust.

The objectives of the meeting were:-

- To discuss the current regulatory and ethical landscapes for CHIM studies globally and discuss the regulatory and ethical aspects including cross regional/global collaborative guidance
- Discussion and inputs for the white paper guidance for CHIM studies developed by the India Volunteer Infection Research Consortium (IVIRC), a grouping of academic researchers and ethicists in India

In the discussion it was emphasized that the India specific guidance should take into consideration global best practice and include the Indian regulatory processes. Important areas that need to be covered in guidance are clear and unambiguous informed consent, participant recruitment and payment and compensation in the Indian context. CHIM studies in India require regulatory and clinical capacity building, training and collaborations (both at regional and global levels).

Key recommendations from the meeting were:

- Regulatory guidance on requirements with regards to challenge agents/strains (stability, reproducibility of data, clarity of GMP and GMP like considerations) need to be clearly defined. Regulators may collaborate for increased clarity on the inclusion of such studies for generating efficacy data and the use of this data for licensure. Dissemination of the

process and methodology taken up by US FDA for market authorization of Vaxchora, the cholera vaccine will promote greater understanding of the processes at NRAs.

- Develop collaboration and engagement between clinician researchers, scientists, ethicists and communications staff. Research sites with experience in CHIM studies can be engaged for capacity building .
- Training of ethics committees, regulatory review committees and researchers
- More cross-regional (AVAREF and SEAR) and global collaborations will promote engagement in CHIM studies
- A defined communication strategy and embedding social science research into the conduct of these studies is recommended.
- Public and community engagement is crucial for all clinical research, including CHIM studies, to build public confidence in clinical research.

The meeting concluded with a discussion on the next steps for India which include consultations with the regulator and policy makers on CHIM studies, a roadmap for CHIM studies in India with a list of future activities, a detailed strategy for communication and outreach on CHIM studies, capacity building of Indian sites to undertake such studies, and, the refinement of the draft white paper guidance based on the inputs received from all relevant stakeholders.

Introduction

Controlled Human Infection Model (CHIM) studies are a method used to study infectious diseases and for the development of interventions for their diagnosis, prevention and treatment. Model establishment requires determination of a dose which consistently produces infection in majority of the volunteers, while challenge studies require the intervention to be given first or just after the 'challenge' to see whether infection can be prevented or inhibited. CHIM studies are conducted using well-characterized strains of an infectious agent under tightly controlled monitoring in healthy volunteers who have undergone rigorous screening and education to ensure safety and an informed understanding of the study. CHIM studies are conducted to prove microbial pathogenicity; to determine host factors that contribute to infection; to define microbial virulence factors; to assess treatment protocols and the efficacy of naturally acquired and vaccine induced responses; and to evaluate potential vaccine candidates. CHIM studies have led to important discoveries in host-pathogen interactions and have been used to accelerate vaccine and drug development.

CHIM studies are a valuable model for the selection of the most promising candidates from an array of available candidates for further product development, and are increasingly being utilized to efficiently bridge safety and immunogenicity testing and phase II/III efficacy studies. CHIM studies not only allow for efficacy data to be generated quickly, they also facilitate the identification of immune correlates of protection, the down-selection of vaccine candidates and early vaccine formulation decisions, thus avoiding unnecessary and costly large-scale trials. There are unique ethical, safety and scientific challenges associated with CHIM studies and hence they are carried out under strict surveillance after independent review and regulatory oversight

CHIM studies are not new and have been carried out since early 1900s, however in the last three decades there has been an increase in their use, driven by the development of new therapeutics and vaccines against a range of organisms. Over 45,000 volunteers have participated in these studies over the last seven decades. In the South East Asian Region (SEAR) human infection studies have been conducted in Thailand for several decades, and have included the organisms causing cholera, shigella, and are more recently being planned for *P. Vivax* malaria. All World Health Organization (WHO) regions, except the Eastern Mediterranean region (EMRO), have countries that conduct CHIM studies, but there is no harmonized guidance as yet for ethical committees or regulators.

In India, the India Volunteer Infection Research Consortium (IVIRC) has been set up with multi-stakeholder representation in July 2019. The IVIRC is comprised of national experts; ethicists, scientists, clinicians, regulators and policy makers and has been working on white paper guidance for CHIM studies in India. In the recently held 3rd Annual Regulators

Conclave for Central and State Regulatory Authorities in India, jointly organized by Central Drugs Standard Control Organization (CDSCO) with WHO, CHIM studies were discussed in one of the sessions. It was recommended that:

(i) A regulatory pathway guidance for CHIM Studies in India needs to be developed by Central Drugs Standard Control Organization (CDSCO), including ethical considerations with the support of the Translational Health Science and Technology Institute (THSTI), Department of Biotechnology (DBT), Indian Council for Medical Research (ICMR) and WHO. A white paper in this regard may be prepared by THSTI and other stakeholders with the support of CDSCO.

(ii) In India, human challenge trials could be considered as an innovative translational approach for certain public health solutions.

Case Example

Typbar TCV® from Bharat Biotech, World's First Typhoid Conjugate Vaccine Prequalified by WHO

Bharat Biotech's Typbar TCV®, the world's first clinically proven Typhoid Conjugate Vaccine against typhoid fever has received prequalification from WHO. This enables the procurement and supplies of this life saving vaccine to UNICEF, Pan-American Health Organization (PAHO) and GAVI supported countries. Typbar TCV® is the first typhoid vaccine, clinically proven to be administered to children from 6 months of age to adults and confers long term protection against typhoid fever. Typbar TCV® has been evaluated in Human Challenge Studies/ CHIM studies at Oxford University and typhoid conjugate vaccines have been recommended by WHO's Strategic Advisory Group of Experts on Immunization (WHO-SAGE).

On November 20th and 21st 2019 in New Delhi, a technical meeting on Current Global Regulatory and Ethical Landscape for CHIM studies including Regional/Global Collaborative Guidance was organized as a side-meeting of the 2019 World Conference on Access to Medical Products: Achieving the SDGs 2030. The meeting was organised by WHO and the Ministry of Health and Family Welfare, Government of India and THSTI, with support from the Wellcome Trust, UK. The meeting brought together international and national delegates for two days of focussed discussion and knowledge sharing on ethical, regulatory and scientific aspects of CHIM studies. Participants included international and national experts from the scientific community, representatives from national and international regulatory agencies and ministries of health, ethics community, social scientists, private sector companies with experience in CHIM studies and representatives from WHO and the Wellcome Trust.

The objectives of the meeting were:-

- To discuss the current regulatory and ethical landscapes for CHIM studies globally and discuss the regulatory and ethical aspects including cross regional/global collaborative guidance
- Discussion and inputs for the white paper guidance for CHIM studies developed by the India Volunteer Infection Research Consortium (IVIRC), a grouping of academic researchers and ethicists in India

The meeting also aimed to discuss opportunities for cross-regional learning and collaborations on CHIM studies and alignment of guidance with the South East Asian Regulatory Network (SEARN), African Vaccine Regulatory Forum (AVAREF), and other countries conducting or considering CHIM studies.

Prior to the start of the meeting on the 20th, a session on CHIM studies was held as a part of the main meeting on 19th November 2019. This session has been captured in the meeting report as many of the points discussed during this session fed into the discussions in the technical meeting.

Parallel Session 4: Controlled Human Infection Model Studies- Regulatory and Ethical Considerations

Panel Discussion Dr Katherine Littler, Dr Jeffrey D' Souza, Dr Diadie Maiga, Dr Christian Ockenhouse, Dr Bernhards Ogutu, Dr Pieter Neels, Dr Melissa Kapulu, Dr Nilima Kshirsagar, Dr Rob Lambkin-Williams

Chair: Dr Gagandeep Kang, Co-Chair: Ms Shobana Balasingam

Two Keynote talks were followed by comments from the panellists and a general discussion. In the first Keynote, Dr Wilbur Chen from the University of Maryland provided an overview of 'Vaxchora' development and licensure. Vaxchora, a cholera vaccine intended for use as a traveler's vaccine was licensed by the US FDA based on efficacy data obtained from a CHIM study, as well as supporting immunogenicity studies. Discussions with the FDA on the use of the challenge model for the vaccine were initiated in 2013, the study was conducted in 2014 and the vaccine was subsequently licensed in 2016. Dr Chen stated that the cholera challenge model is not new and has been used for studies at the University of Maryland since the late 1960s. In the Vaxchora CHIM study, efficacy was determined by challenging the volunteers with cholera at 10 days and 3 months after vaccination. The study was reviewed by the Vaccine and Related Biological Products Advisory Committee (VRBPAC) at the FDA and the lower bounds of the confidence intervals of efficacy were defined and agreed by the FDA *a priori*.

He emphasized that National Regulatory Authorities (NRAs) need to become familiar with CHIM studies and their use in product development. NRAs should understand i) the requirements for standardization and validation for CHIM, ii) the point at which such studies

should be introduced into the product development program, iii) the role of such studies in generating efficacy data and iv) the use of this data for licensure.

In the second Keynote, Ms Shobana Balasingam from the Wellcome Trust discussed the current position of CHIM studies and the next steps for national, regional and global engagement requirements. She provided an overview of the regulatory requirements in different countries with regard to the challenge agent and studies where the CHIM is used alone or as a part of the development cycle of an Investigational New Product (IND). She emphasized the need for clarity in guidance especially with regards to challenge agents (stability, reproducibility, clarity of GMP and GMP like considerations) and for mechanisms of communications between national regulatory authorities (NRAs) globally on CHIM studies. There is a need for clear and internationally consistent guidance from regulatory bodies. She also stated the need for ethics and regulatory guidance at the regional level in addition to a global level and encouraged countries to develop their own guidance consistent with their own needs.

The lectures were followed by comments from the panelists. Dr Katherine Littler from WHO discussed the initiative by WHO towards developing ethical guidance for CHIM studies with support from the Wellcome Trust which is underway. The first meeting towards guidance development was held in June 2019 to understand areas of consensus and divergence on CHIM studies, and the areas of further research. It is important that in Low and Middle-Income Countries (LMICs) the guidance is contextual and therefore the guidance development is a cross WHO initiative with multiple divisions within WHO. WHO is also looking into the possibility of developing global regulatory guidance (one document/disease-specific etc.) however, this is in early stages of discussion. The aim of the guidance is how and when CHIM studies should be conducted. The guidance will have a Q&A section for regulators and ethics committees. A large amount of material with case studies is being developed and is likely to be ready by summer of 2020.

Dr Jeffrey D' Souza from McMaster University, Canada discussed misconceptions around clinical trials in general and CHIM studies specifically and the concerns around deliberate/intentional harm. He clarified that CHIM studies do not violate any of the ethical guidelines including the guidelines issued by the Indian Council of Medical Research (ICMR) as the guiding principle of research ethics is that harms should be minimized and mitigated. It is important to consider the scientific and social value of CHIM studies. While there is no direct foreseeable benefit for all the volunteers in such studies (as is the case in other non-therapeutic trials) ; in LMIC setting, the volunteers may benefit indirectly by developing immunity as a result of exposure to the pathogen.

Dr Diadie Maiga from the African Vaccines Regulatory Forum (AVAREF) mentioned that AVAREF was approached by many countries who were interested in CHIM studies with a

request to develop guidance. Networking provides an opportunity to strengthen the capacity of regulators and ethicists and allows for alignment and harmonization of practices and guidance across countries. He also emphasized the importance of the role of international stakeholders and organizations such as the WHO and Wellcome Trust in supporting regional initiatives.

Dr Christian Ockenhouse from PATH reported on the malaria challenge models and how they are now a routine part of malaria vaccine development and understanding malarial disease pathogenesis. He discussed the need to critical examination of safety, whether the pathogen used for the CHIM and the disease/infection caused is treatable and how important it is to avert the symptoms depending on the model being used. He emphasized that regulators look at the whole package and hence challenge studies are only one part of the dossier submitted for licensure.

Dr Bernhards Ogutu from Kenya Medical Research Institute (KEMRI) discussed the need to shorten drug development timelines and how CHIM studies offer a means to do so. In KEMRI the main constraint was the capacity to conduct Phase I studies and this was resolved by capacity building with scientists from KEMRI visiting Walter Reed Army Institute in the US and understand what a Phase I unit would require. He spoke about the need to build awareness and acceptance for CHIM studies. He also discussed that while conducting CHIM studies in endemic settings is challenging because of infrastructure constraints however, there are many insights that can be gained from such studies such as understanding genetic polymorphism, levels of exposure etc. Legal frameworks for CHIM studies are deficient and need to be addressed. Kenya is working on regulatory guidelines for CHIM studies which will be published in 2020.

Dr Pieter Neels stated that one should be cautious about the generalizability of the results from a CHIM study and be cognizant of its limitations. He also emphasized that since CHIMs are disease specific and vary a lot, therefore having universal guidance even for each pathogen might be problematic and it is perhaps better to think of broad guiding principles.

Dr Melissa Kapulu from KEMRI spoke about the differences seen as you move a CHIM from a naïve to an endemic setting. With the Controlled Human Malaria Infection model in Kilifi, it was observed that since a majority of the volunteers had been exposed to malaria, they do not show parasitemia or show rapidly self-clearing parasitemia. Hence dose-setting in endemic settings is important. Important issues such as the threshold for immunity/marker of immunity in a CHIM study, the expiry date of a challenge agent etc. need clarity and hence there is a need to build capacity of regulators. There is a need for harmonization of guidance as well as local contextualization for guidance. CHIM studies require constant engagement with regulators, ethicists and the communities. She emphasized the value of embedding social science studies into CHIM studies.

Dr Nilima Kshirsagar from ICMR stated that risk-communication is important from an Indian perspective. All relevant stakeholders should be able to understand the need for CHIM studies and their associated risks and benefits. The communication on CHIM studies should be customized to the relevant population and must be clear and easy to understand. Volunteers in CHIM studies need to be able to understand all aspects of the study including the risk for them, the benefit, the degree of discomfort, rescue medication, risk management etc. Continued community engagement around CHIM studies is required.

Dr Rob Lambkin-Williams spoke about his experience with having conducted CHIM studies for RSV. He stated that CHIM studies for Zika are currently being discussed in the US. While CHIM studies do have inherent risks, these can be addressed through rigorous risk management strategies.

This was followed by general questions and discussions with the audience and the following points were emphasized:

- CHIMs can support understanding basic biology, licensure (in some cases) and down-selection of potential interventions (as are now done in malaria vaccine development)
- Need for building capacity for all stakeholders (researchers, community, regulators, policy makers and ethics committee members). Building practical experience requires exposure to research sites that have experience in the conduct of CHIM studies.
- Access and affordability are two critical parameters to ensure that interventions can benefit those in need. CHIM studies have the potential to hasten the access and they should be conducted ensuring that the scientific and ethical concerns have been addressed.
- The harmonization of any guidance for CHIM studies needs to be sensible and flexible based on the risk and the context, however some minimum standards should be set. Guidance should not be too prescriptive and evolve based on communication and deliberations.
- Harmonization of end points for approval by regulators could be considered and regulators should be engaged early in the study.
- A lot of preparatory work is needed by regulators and researchers before such studies can be initiated. CHIM study protocols need careful development and review.
- CHIM studies should look at benefits versus risk (what makes the study valuable? What are critical issues of concern? How should these studies be designed?)
- Transparency, openness and discussions between the various stakeholders are the need of the hour. Public and community engagement are integral both pre-introduction and during and after the study.

Day 1- 20th November 2019

The meeting started with opening remarks by Dr Gagandeep Kang, Dr Manisha Shridhar, Dr Madhur Gupta, Ms Shobana Balasingam and Dr Mandeep Bhandari. It was uniformly agreed that there is a need for greater discussion on CHIM studies in LMICs where few studies have been conducted. Ethical and regulatory requirements need to be laid down for such studies to ensure that they adhere to the highest standards of safety and quality.

Advocacy, transparency and community engagement in CHIM studies, as for all other clinical research studies, is required.

Developing WHO Ethics Guidance for CHIMS

Dr Katherine Littler, WHO

Dr Katherine Littler described the development of the Ethical Guidance and implementation materials for CHIM studies currently being undertaken by WHO. She stated that the guidance will help sensitize ethics committees to CHIM studies as they are often cautious with respect to new areas for research. However, it is important that the guidance is not too prescriptive as the idea is not to exceptionalize CHIM studies. There is a need to build a framework for key issues one needs to consider (ethics normative guidance). The guidance will cover the distinct challenges associated with CHIM studies, highlight areas of further work/consultation. It is being developed through engagement and consultations and builds on existing initiatives.

It is important to recognize that CHIM studies fall within the continuum of clinical research. The guidance aims to address when and how such studies can be conducted and covers several aspects including what differences between CHIM studies and other forms of clinical research are morally significant and how, and, the additional *ethical issues that require attention in CHIM studies*. These include; *justification for CHIM studies* (only way/robust and rigorous/expedient/ cost effective/ fewer number of volunteers /overall lower risk / critical component of the research pipeline); *protocol design*- Strain selection, infection model, diagnosis (timing and method), treatment, in-patient vs outpatient, withdrawal, selection of study populations, addressing competing considerations such as generalizability etc; *risks, benefits and burdens* including risk management strategies; *third party transfer and researcher's responsibility* ; *equity*- if CHIM studies are a part of the pipeline; what is the mechanism for benefit sharing ; *Consent*- How much information is appropriate and how do you work within the current provisions; *engagement*- addressing public concerns and awareness generation; *compensation and inducement*- define clearly reimbursement, compensation and payment and how they should be considered; *research contexts and populations*- naïve versus exposed, pediatric populations etc.; *IP Ownership and Sharing*- Sharing models and infectious agents, centralized reporting requirement,

commercialization; *Governance*-compliance with ethical and regulatory frameworks, *Review mechanisms*- ad-hoc, specialist consultation etc., what conditions should trigger more rigorous governance, gaps in comprehensive oversight.

Many countries have regulations prohibiting intentional infection and these are more aimed biosecurity and public health, rather than research and product development, so in such countries researchers need to engage with legal and regulatory authorities for discussion and modification of regulations.

Points emphasized in the discussion:

- While the pivotal efficacy study for the licensure of Vaxchora was a CHIM study, there was a database for Vaxchora with other studies as well.
- Important for CHIM studies to have an independent medical monitor/ombudsman who acts on behalf of the volunteer.
- Should WHO guidance also include 'whether' CHIM studies should be conducted? You need examples of specific cases where CHIM can and cannot be done, for example diseases in which risk is very unpredictable or unknown.
- Need for transparency and an environment where concerns can be expressed freely while considering such studies.
- How you do it is as important (operational). Watch a CHIM, then do a CHIM and then teach a CHIM.
- Normative guidance is needed. In India there is nothing in New Drugs and Clinical Trial Rules 2019 or the ICMR ethical guidelines that precludes the conduct of CHIM study, but guidance would be useful for all concerned including regulators.
- There is a need for regulators to interact for discussion, knowledge sharing and harmonization.

Controlled Human Infection Models-History of Use at FDA and Regulatory Considerations

Dr Heather Stone, FDA

Dr. Heather Stone described how CHIM studies are regulated by the US Food and Drug Administration. In the US CHIM studies, involving just the challenge agent alone or the challenge agent in combination with a product, are conducted under an Investigational New Drug (IND) application and challenge agents must be manufactured in compliance with GMP. Ethical review by an IRB is also required. The FDA requires a detailed description of possible risk anticipated with challenge strain use and all data from prior clinical studies/studies in relevant animal models conducted with the challenge strain. The totality of evidence is regarded. For instance, for Vaxchora there was data on immunogenicity and earlier trials (~3500 volunteers). Pre-IND meetings for CHIM studies early are strongly recommended. CHIM studies have also resulted in Tafenoquine, an anti-malarial being approved by the US FDA as well as the identification of immune markers that can be used to

support regulatory decisions (e.g. Hemagglutinin inhibition antibody as a marker for influenza immunity). Various considerations are taken into account by the FDA while evaluating a CHIM study including feasibility of conducting field trials, strength and limitations of the CHIM (in terms of clinical end points, role of pre-existing immunity and relevance to the disease being studied), participant selection, strain selection, strain purity, chemistry, manufacturing controls information, dose and stability of the challenge inoculum and its ability to produce a consistent attack rate, risk of environmental transmission, data monitoring and reporting procedures etc. The FDA also maintains that a CHIM study does not always preclude the requirement for large Phase III trials and each study is evaluated on a case by case basis. The role of the FDA is complementary to that of the IRB.

Points emphasized in the discussion after the talk:

- A few of the challenge strains that have been approved by the USFDA as an IND are not categorized as GMP but are **extremely well characterized**. For example, the *P. vivax* model developed by PATH is not GMP as the parasite cannot be cultured under GMP, but it was granted an IND by the FDA.
- One can explore the use of reverse genetics to generate the challenge strain- This is currently being done for the DENV challenge strain by Steve Whitehead's group
- Willingness to share well characterized challenge agents is very important.
- GMP and GMP-like is an important distinction to make and both are acceptable depending on the agent.
- The need for CHIM studies has to be justified very clearly. Immunogenicity is not a good measure of a correlate of protection and if the correlate of protection is well known then you do not require a CHIM study.
- CHIM studies require a public engagement and communication strategy.

US Case Study – Vaxchora[®] licensure

Dr Wilbur Chen, University of Maryland

Dr Chen discussed the CHIM study that led to the licensure of Vaxchora. The cholera CHIM model was developed in the University of Maryland and has been in use for several decades. The model was developed as cholera is caused by a human-host restricted pathogen and there is a lack of animal models. The model uses a very well characterized challenge isolate which has been registered as an IND product, stringent screening criteria, well defined clinical end points, containment of third-party risk and environmental contamination, detailed informed consent process, close monitoring and laboratory testing, and, early treatment. Dr Chen described the use of this model to determine the vaccine efficacy of Vaxchora, however, the model has also contributed to understanding the virulence of the cholera toxin, importance of neutralization of gastric acid, insights into natural immunity and prior infection etc. The challenge inoculum used in the study has been extensively standardized and validated for attack rates and severity of illness consistency and

reproducibility. The use of the cholera CHIM in supporting vaccine efficacy studies was first discussed with the USFDA in 1998. However, at the time the study did not proceed further even though the USFDA agreed with the need to do such studies. The Vaxchora project was later restarted and the pivotal CHIM efficacy study was conducted in 2013 after pre-IND meetings with the USFDA. The study also helped to identify vibriocidal antibodies as a marker of the protective efficacy of cholera vaccination.

Following Dr Chen's talk there was a general discussion on the model and the total volume of diarrhea that a volunteer might experience. This was discussed to be ~18L over days as a worst case, however as volunteers are monitored closely, they are rehydrated with 1.5 times the volume lost after an episode of diarrhea. There were also discussions on compensation, motivation of volunteers to participate and anxiety related withdrawals, if any.

Human Challenge Studies in Endemic Settings: Ethical and Regulatory Issues

Dr Michael Selgelid

Dr Selgelid discussed the findings from his study on the ethical and regulatory issues of CHIM studies in endemic settings. He briefly described the history of CHIM studies and stated that these are often not conducted in endemic settings (LMICs) owing to factors such as lack of capacity, need to avoid vulnerable populations, existing regulations and guidelines etc. His study which looked at 13 different CHIMs carried out in LMICs found that conducting CHIM studies in endemic settings is ethically acceptable and often has strong scientific rationale. Some stakeholders in these countries argued for an ethical imperative to conduct such studies owing to the public health burden of the disease being studied by the CHIM. There was also a uniform felt need for capacity building (scientific, ethical and regulatory), robust risk and burden minimization strategies, careful informed consent process, need for community and public engagement, appropriate payment and compensation, provision of insurance etc. In general, while there was some tension between the safety and scientific value/generalisability, these studies were seen as scientifically and ethically feasible but require very careful and stringent standards to ensure safety, quality and trust. His study also found that there was a need to strike a balance between burdens/risks and benefits, further discussion needed on benefit sharing, upper limits on risk, how to deal with withdrawal of participants, third party risk (given endemic setting), more discussion on payment and compensation, participant selection and governance mechanisms.

Points emphasized in the discussion after the talk:

- It is important to understand the perspective of the ethics committee members and their concerns in endemic settings

- While setting up of CHIM study sites is feasible (NIH funding and other mechanism), you require a pipeline of these studies to ensure sustainability both in terms of capacity and infrastructure
- Insurance mechanisms are important. Dr Selgelid's study found that in some countries, CHIM studies could not be initiated as no insurance mechanisms/compensation mechanisms could be arranged.
- Informed consent timelines are different in the LMICs. For example, in Kenya it took 2 years to prime people and build communication strategies
- Media sensitization is crucial. Needs to be addressed and you need to have a way of addressing lay people's concerns
- Generalizability versus population selection in endemic settings need to be considered
- Need to involve social scientists in LMICs early in the discussions and let them start engaging with the community

Dengue vaccine development and use of the controlled human infection model (CHIM)

Dr Steve Whitehead

Dr Steve Whitehead discussed the role of CHIMs in dengue vaccine development. In dengue, neutralizing antibodies are not predictive of vaccine efficacy as seen by the Dengvaxia trials and there is no animal model that reproduces the clinical and microbiological outcomes, hence, CHIM might be a more efficient way to assess the protective response dengue vaccines at an early stage. A conventional phase III to test efficacy against all serotypes is also difficult owing to the number of volunteers needed.

There are 2 dengue CHIMs; one is an infection model and the other is a disease model. NIAID uses the infection model (viremia as the primary end point) in its studies and has challenge strains for DEN2 and DEN3. The studies can be done in an outpatient setting as the virus is not good at infecting mosquitoes. The challenge model has been used to evaluate the protective efficacy of live attenuated tetravalent dengue vaccines developed by NIAID. The studies involve vaccinating the volunteer and then challenging them with DEN2/DEN3 180 days after vaccination. The results from the study indicate that the vaccine is very protective, but the investigators have been unable to identify a correlate of protection. The model is currently being used to understand whether a homotypic tetravalent immune response is needed for protection.

Regulators in Brazil have stated that licensure for a dengue vaccine can be granted on the basis of antibodies against any of the 4 serotypes. Discussion on dengue CHIMs is underway in Vietnam and Bangladesh. Challenges for this model in endemic areas include; enhanced infection on re-exposure, risk for mosquito transmission and third party infection, the need for catch up vaccination and monitoring for all study participants, impact of pre-existing immunity on vaccine efficacy, differences in legal, ethical and regulatory frameworks etc.

For instance, Vietnam has laws that prohibit the conduct of challenge studies and this is currently being worked on. A Zika CHIM (infection model) has been proposed and is likely to be cleared by the USFDA soon. This required a lot of sensitization of the IRBs, given that a NIH consultation of bioethicists and investigators had previously decided not to consider a Zika CHIM at that time owing to limited available information.

His talk was followed by a general discussion which discussed the need to better understand the legal provisions in India and how they apply to CHIM studies. For example, in India if a dengue CHIM is done, given the endemic nature of the disease it is crucial that all the volunteers are provided with a licensed dengue vaccine at the end of the study if one is available.

Leveraging human infection studies in endemic populations- Immunity and Methodological Considerations

Dr Melissa Kapulu

Dr Kapulu discussed the process of stakeholder engagement undertaken in Kenya prior to the establishment of CHIM studies. She also described the clinical facilities for these studies in Kilifi and some of the learnings from these studies. CHIM studies have been conducted for malaria and will now be extended to Shigella.

The relevant stakeholders were mapped, and several consultations and engagement strategies were used. The stakeholders comprised the regulatory authorities, ethics committees, the Ministry of Health, Ministry of Health Division of Vaccines and Immunization, academic universities and their staff and community representatives. Public engagement was done through the radio, meetings and through Youtube videos.

Kilifi has had a long-standing community engagement program which has been in operation for ~28 years and hence the trust of the community in research is high. The community in Kilifi was engaged through elected KEMRI community representatives. The volunteers had many questions about the study. CHIM as a concept is complicated and requires sustained engagement to help people understand these studies and address their concerns. Developing key messages and talking points with inputs from the community is very beneficial. It is important to embed empirical ethics and social science studies alongside the main study. The social science studies conducted in Kenya provided important insights into what the volunteers felt, their major areas of concern and their motivations to participate all of which contribute to an iterative cycle of making these studies better.

In the malaria CHIM studies, volunteers asked to be kept together in a dormitory style setting however in the Shigella study they preferred individual rooms. Training on clinical and laboratory requirements for such studies in endemic settings is crucial and the staff at

Kilifi were trained at Oxford. Dr Kapulu discussed her work on controlled human malaria infection in semi-immune Kenyan adults. She stated that previous pathogen exposure and modulation of endpoint outcome is required for CHIM studies in endemic settings. CHIM studies in the context of vaccine efficacy and understanding transmission will require considerations of pre-existing immunity. It is important to understand correlates of immunity and how the immunity develops.

In Kenya the pharmacy and poisons board (the NRA) was not previously regulating CHIM studies but now the guidance has been revised. In Kilifi the staff also participated in the study and this further built community trust. CHIM studies in Kenya have strengthened research capacity immensely.

Panel Discussion: Comparative Regulatory Considerations

Moderator: Dr Pieter Neels

The panel discussed the role of regulators in CHIM studies and how these are viewed in different countries. The US FDA views all challenge material as an investigational new drug (IND) and these studies must be approved by the FDA. In the European Union, many member countries conduct CHIMs and in the absence of evaluation of a product, regulatory engagement may not be required at all. The European Medicines Agency (EMA) has conducted a number of meetings to discuss the role of CHIMs in regulatory approvals. EMA has reviewed dossiers for multiple now-approved products that have included data from CHIMs but has no direct role in the approval of clinical trials, including CHIMs, which is seen as a national responsibility.

There is a need for IRBs and regulators to coordinate with each other on CHIM studies. In general, for any country planning to undertake CHIM studies, it was felt that these studies should be within the ambit of the regulator to build confidence and maintain trust. In considering the situation in Africa, Uganda reported a joint review system for complicated protocols which has the regulator, the scientific committee, an independent expert and ethics committee members. Once the joint committee reviews the protocol and provides its recommendations, the protocol is revised and resubmitted to the site ethics committee. Kenya has a mechanism of oversight of the EC by the regulator.

Strengthening the Regulatory Systems through Networks- The AVAREF Experience

Dr Diadie Maiga, AVAREF

Dr Maiga stated that the need to develop a regulatory pathway for CHIM studies was agreed and endorsed by AVAREF in response to a request from in-country NRAs in October 2019. AVAREF was created in 2006 as network of African NRAs and ethics committees to build capacity and achieve consensus on regulatory and ethical questions surrounding R&D of

medical products. This was done as a large number of US trials are now being conducted in Africa especially vaccine trials for many diseases which have a high burden in Africa such as malaria, meningococcal, and Ebola.

AVAREF holds regular meetings of governing bodies and encourages joint reviews and provides technical support to countries to ensure timely regulatory evaluations of clinical trial applications and expedite the availability of safe, effective and quality medical products that meet public health needs.

The operational strategy of AVAREF was revisited in 2016 and a secretariat, governing committee etc. were then put in place. The organization puts forwards guidelines and regulatory tools for use and deployment in members of the network and encourages the use of standardized formats. Joint reviews help building capacity both scientific and ethical and provide an opportunity for sharing information. The network also plays an important role in the context of public health emergencies such as Ebola for establishing collaboration and sustained action in the region.

With regards to CHIM guidance, AVAREF is in very early stages and is in the process of drafting and finalizing the roadmap for guidance development with agreed roles and responsibilities. The roadmap has 4 steps; a) Understanding the current situation, b) Preparation for regulatory tools, c) Development of AVAREF guidance and d) Adoption of AVAREF regulatory tools and guidance. AVAREF is interested in cross-regional collaboration with SEAR.

Clinical therapeutics development through engagement in Controlled Human Malaria Infection studies (CHMIs)- Malaria Perspective

Dr Bernhards Ogutu, KEMRI

Dr Ogutu discussed his experience from having conducted CHMIs in Kenya. He stated that CHMIs in Kenya have characterized the local population better and have the potential to detect un-recognized reactions, streamline the malaria product development pipeline and understand confounders (genetic variability, other concomitant diseases) etc. CHMI framework in Kenya has required capacity building, regulatory and strategic direction, infrastructure strengthening and a health research framework. He stated that the National Commission for Science, Technology and Innovation (NACOSTI) was established under the Science, Technology and Innovation Act 2013 and facilitates the promotion, coordination and regulation of the progress of Science, Technology and Innovation (ST&I) in Kenya. However, this act does not lay down any specifics on the conduct and management of research. Similarly, the Pharmacy and Poisons Board under the Pharmacy and Poisons Act, did not at least initially contain any regulations for clinical trials. These Acts require review and amendments. In Africa, all countries need to work together. More work is also needed

on the legal framework for CHMI studies and other scientific studies in Kenya. The Kenyan government wants to encourage a cadre of lawyers in health law so as to ensure that laws keep abreast of technology improvements. The necessity for such studies and guidance is underlined by the fact that so far in malaria research, no appropriate surrogate markers for vaccine efficacy have been identified, and hence CHMI studies are important.

Dr Ogutu's talk marked the end of the discussion for Day 1.

Day 2- 21st November 2019

The participants were divided into different groups that discussed the initial draft India specific guidance which was developed by the India Volunteer Infection Research Consortium (IVIRC) had been provided to them. Five groups were constituted, to discuss specific sections of the guidance. A summary of the discussions is presented below.

1) Discussion on Risk-Benefit and Facilities for CHIM studies section

- Pre-clinical safety assessment of the challenge strain, what is the data required?
- Are animal toxicity studies required and is it feasible for the challenge agent- The consensus within this group was that for CHIM studies with a well characterized challenge agent not coupled to product development they would not be required. However, for CHIM studies for product development they will be required to be done by the regulatory authorities.
- The need for rescue treatment and its timing related to severity of symptoms or in the absence of symptoms.
- There was also a felt need that this section of the document should be less prescriptive- for example an asymptomatic person with a self-limiting disease may not need treatment.

2) Discussion on the Informed Consent section

- There is a difference between literacy and research literacy and hence educated people cannot always be assumed to be research literate
- There is a need to understand the motivation for participation
- The generalizability of studies and consent processes was discussed
- There was a discussion on the need to include the rescue treatment in the participant information sheet and also a greater need to clarify the freedom/right to withdraw from the study
- Need to clarify the process of removal of data (if any) if someone withdraws from the study
- Test of understanding-How comprehensive can it be made. Insights can be drawn from studies conducted in Kenya and other LMICs
- Back translation requirements

- The need to collate and look at Informed Consent forms and Participant information sheets from other settings where CHIM studies have been conducted (KEMRI, hVIVO etc.) and undertake a workshop to draft informed consent documents with their support if required.

3) *Discussion on Ethics committee training requirements section*

- There is no need to exceptionalize CHIM studies
- While training of ethics committees is crucial it is not possible to train them on everything. Education, orientation and engagement of ethics committees is needed
- Need for external scientific expertise to review studies (will vary depending on pathogen and the CHIM model). Therefore, co-opt experts. However local review is needed and important
- These studies should at least initially only be carried out in a select few sites (tertiary care hospitals with functional Phase I units) which are well-resourced, and, carried out by researchers with experience with clinical trials frameworks. The sites should have ethics committees and facilities that are accredited/ recognized for their quality
- The study site should ideally be located in a region where the disease is prevalent
- Monitoring requirements for CHIM studies and the roles and responsibilities of ethics committees will need to be laid down through SOPs while ensuring that this does not duplicate safety monitoring. Use pre-existing documentation wherever possible. The monitoring committee will be required to have access to all relevant reports and members of the committee should have clearly defined roles
- Explore and build on online training modules for ethics committees and for scientific aspects of conduct of CHIM studies

4) *Discussion on Regulatory section and payment and compensation section*

- The Indian regulator (CDSCO) re-emphasized the need for regulatory guidance in the discussion and refining the draft white paper prepared
- Clarity on import of the challenge agent (process, required documentation) needs to be mentioned in the guidance
- Manufacturing requirements for the challenge agent need to be defined by the regulatory authority
- Need to define all the terms being used- specifically payments, compensation, reimbursement, incentives etc.
- More debate and consensus needed on appropriate payment for participation, so it is not an incentive but acknowledges the burdens imposed on the participant.

5) *Discussion on Public and Community Engagement section*

- There is need to include scientists and other clinicians in the process. Parallel to engagement for CHIM studies, a larger initiative to engage the community with science needs to be initiated.

- A frequently asked questions section should be added.
- Explore a communications strategy that includes engagement with different stakeholders, develop capacity based on models of good practice, learn from institutions that have built communication capacity for CHIM studies especially those in endemic settings.
- A communications flowchart that describes the various channels of communication
- Social science studies to understand community perceptions and how best to engage with them should be embedded within CHIM studies.
- Ask community what they feel is required and important.
- There is a need for a champion for such studies. The fundamental problem is that of trust. Sustained engagement is required, and it should be proactive and transparent.

The discussion section was followed by a talk by Dr Hugh Davies, South Central Research Ethics Committee Health Research Authority, Oxford through video conference on the training needs and ethics of CHIM studies.

The meeting concluded with closing remarks made by WHO.

In the closing remarks, the need for training and sensitization on CHIM studies in India was re-emphasized including the need for regulatory training. An aspect that requires clear process in the Indian context is payment and compensation. The advisory group for the guidance should be expanded to include lay people and lawyers so as to proactively be able to address the various questions that are likely to arise which in turn should be developed as a fact sheet/ FAQ to supplement the guidance. India should carefully consider the CHIM studies that would be most relevant to the Indian context in line with public health needs as and when such studies are considered.

Cross regional and global guidance needs to move in a convergent manner and WHO can look to facilitate more regional interactions in the context of CHIMs. It would be a good idea to look at other emerging technologies such as gene drive to understand how regional and global collaborations and guidance can be fostered.

Summary and Next Steps

CHIM studies are important and valuable in endemic settings but it is important that these are done at a limited number of sites that which can ensure high quality clinical care and the most informative science and product development. As next steps at the national level; the Department of Biotechnology (DBT) and the European Union had issued a joint call for Influenza vaccines where CHIM studies were required to be a part of the application. While the application did not mandate that the Influenza CHIM study should be conducted in India, it is intended to promote the capacity of Indian researchers to conduct CHIM studies.

DBT will hold a consultation on the Influenza project with the Indian regulator by February 2020 where building capacity for CHIM studies in sites in India with oversight from the regulatory authority will be discussed. Following this meeting, a roadmap for CHIM studies in India will be prepared with a list of future activities which will include a detailed strategy for communication and outreach. The draft guidance will be refined based on all the inputs received from all relevant stakeholders.

Internationally, WHO is working on ethical guidance for CHIM studies and the second consultative meeting to discuss the guidance has been planned in February 2020. At the regional level AVAREF is also looking to develop guidance for CHIM studies and the AVAREF plans for the guidance will be discussed further at the SEAR meeting later in the year to ensure regional alignment.



List of Participants

1. Dr Mandeep K Bhandari, Joint Secretary, Ministry of Health & Family Welfare, Government of India
2. Dr. V.G. Somani, Drugs Controller General of India, Central Drug Standard Control Organization (CDSCO), India
3. Dr Gagandeep Kang, Executive Director, Translational Health Sciences and Technology Institute, India
4. Dr Madhur Gupta, Technical Officer-Pharmaceuticals, WHO Country Office for India
5. Dr Manisha Shridhar, Regional Advisor, World Health Organisation South-East Asia Regional Office
6. Ms Shobana Balasingam, Programme Officer, Vaccines, Wellcome Trust, United Kingdom
7. Dr Raj Long, Deputy Director, Global Health, Bill and Melinda Gates Foundation, United Kingdom
8. Professor Aggrey Ambali, Head of Industrialization, Science, Technology and Innovation, New Partnership for Africa's Development (NEPAD) Agency
9. Ms Rubina Bose, Deputy Drugs Controller, CDSCO, India

10. Dr Chandrashekar Ranga, Deputy Drugs Controller, CDSCO, India
11. Dr Rakesh Aggarwal, Director, Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER), India
12. Dr Francis P Crawley, Coordinator, European Fellowship in Research Ethics (EFRE), Belgium
13. Ms Anjali Sharma, Senior Research Technical Advisor, Global Health, Centre for Infectious Disease Research in Zambia (CIDRZ)
14. Dr Stephen Whitehead, Senior Scientist, National Institute of Allergy and Infectious Diseases, National Institute of Health, USA
15. Ms Heather Stone, Public Health Analyst, Foods and Drug Administration, USA
16. Mr Igor Da Silva Barbosa, Premier-secrétaire, Permanent Mission of Brazil to the UNOG and other organizations in Geneva
17. Professor Maria Zambon, Director of Reference Microbiology Services, Public Health England,
18. Dr Rob Lambkin-Williams, Former Executive Scientific Advisor, hVIVO & Virology Consult, United Kingdom
19. Dr Pieter Neels, CEO & Scientific Advisor at Vaccine-Advice, Belgium
20. Dr Nilima Kshirsagar, National Chair Clinical Pharmacology, Indian Council of Medical Research, India
21. Dr Satinder Aneja, Chairperson, Ethics Committee, Translational Health Sciences and Technology Institute, India
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25. Dr Jeffrey D'Souza, Research Associate, Institute on Ethics & Policy for Innovation, McMaster University, Canada
26. Dr Diadié Maïga, Regional Vaccine Regulatory Officer, World Health Organization, Regional Office for Africa
27. Dr Chris Ockenhouse, Director, Medical and Clinical Operations, Malaria Vaccine Initiative, PATH, USA
28. Dr Bernhards Ogutu, Chief Research Officer, Kenya Medical Research Institute (KEMRI) and Director for Centre for Research in Therapeutic Sciences, Strathmore University, Kenya
29. Dr Melissa Kapulu, Research Scientist in Infectious Diseases, Kenya Medical Research Institute (KEMRI), Kenya
30. Professor Michael J. Selgelid, Director, Monash Bioethics Centre, Monash University, Australia
31. Dr Susan Bull, Senior Researcher, University of Oxford, United Kingdom

32. Ms Hellen Opolot, Assistant Executive Secretary, Uganda National Council for Science and Technology, Uganda
33. Ms Winfred Badanga Nazziwa, Head Research Compliance & Quality Assurance, Uganda National Council for Science & Technology, Uganda
34. Dr Hugh Davies, Chair, South Central Research Ethics Committee Health Research Authority, Oxford (Video Conference)
35. Mr Frans Stobbelaar, Chief Executive Officer and Senior Consultant, Pharmaceutical Management Consultants BV, Netherlands
36. Mr Md Abdus Salam Khan, IRB Coordinator, International Centre for Diarrhoeal Disease Research, Bangladesh
37. Prof Vina Ravi Vaswani, Director Centre for Ethics, Yenepoya University, India
38. Dr Vasantha Muthuswamy, President, Forum for Ethics Review Committees in India (FERCI), India
39. Dr Ankur Mutreja, University of Cambridge, United Kingdom
40. Dr Nicolas Noulin, Associate Director, Clinical Science, hVivo, United Kingdom
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49. Dr Nusrat Shafiq, Clinical Pharmacologist- PGIMER, Chandigarh
50. Dr Kadiravan Tamilarasu, Jawaharlal Institute of Postgraduate Medical Education and Research, India
51. Ms Cecilia Chui, Programme Officer, Wellcome Trust, United Kingdom
52. Ms Preeti Kharb, Consultant, WHO India
53. Dr Amrita Sekhar, Consultant, THSTI