Ethics of Controlled Human Infection Studies in low resources settings, Is the region ready?

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ANREC, Kampala, Uganda
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KEMRI | Wellcome Trust

Outline

- CHIM studies: What?, LMICs, Ethical issues,& Frameworks/guidelines.
- Experience of conducting CHIM studies in Kenya: Role of social science and empirical ethics studies.
- Experience of review and approval of CHIM studies: The case of KEMRI SERU

Controlled Human Infection [Model] (CHIM) Studies

- **CHIM studies / challenge studies –** involve the deliberate infection of healthy volunteers under controlled conditions.
- **Purpose**:

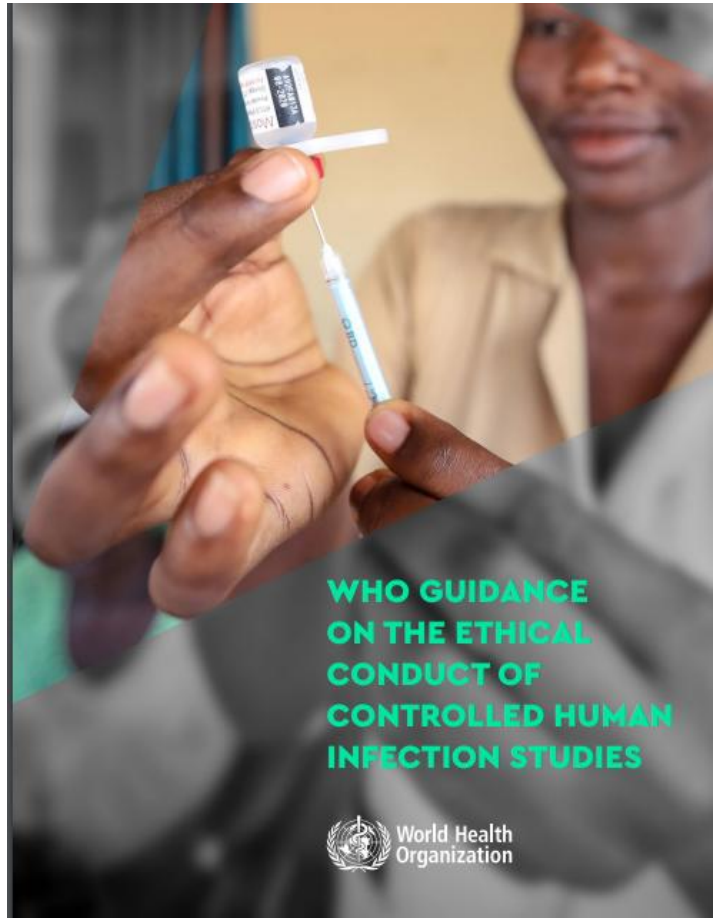
a) developing models of infection or disease – that is, rigorous and reproducible methods of infecting participants with specific pathogens

and/or

a) generating knowledge about host-pathogen interactions (incl. pathogenesis and correlates of infection, transmission and immunity)

and/or

a) testing (novel) vaccines and therapeutics.



CHIM Studies in LMICs (1)

- As of 2015, over 22,000 volunteers had participated in well regulated CHIM studies for a wide range of pathogens of public health importance (Gordon et al, 2017)

- Few, if any, had been conducted in LMICs – potential to benefit most due to the high burden of vaccine preventable diseases

Reasons why?

  - Technical, clinical, ethical and regulatory issues, as well as cultural norms
  - Limited infrastructure and expertise
  - Ethical considerations e.g., informed consent
  - CHIM studies remain relatively unfamiliar with ethics committees and regulatory bodies in LMIC

CHIM Studies in LMICs (2)

- Increasingly, CHIM studies are being conducted in LMICs:
  - In Africa – Kenya, Tanzania, Uganda, Gabon, Malawi, Gambia, Zambia
  - Pathogens – Malaria, Shigella, Schistosomiasis, Pneumonia

- Conducting CHIM studies in endemic countries
  - Potential to generate results that are relevant to the local population;
  - Accelerate vaccine and drug development for prevalent diseases

- However, their **design and conduct, especially in LMIC settings like Africa raises important social, ethical, regulatory, and practical issues that require careful consideration**.

Ethical Issues in CHIM Studies

CHI studies raise important ethical issues*:

- Deliberate infection vs ‘do no harm’ – potential to erode public trust
- Ensuring a valid informed consent (understanding of the study).
- Inadequate guidance on appropriate compensation levels for inconveniences.
- Limited right to withdrawal from the study.
- Risks of third-party infections.

* Bambery et al. 2015; Gordon et al. 2017; Jamrozik & Selgelid 2021; Hodgson 2014

Frameworks for establishing and ethical review of CHIM Studies, Chi et al. 2024 (1)

Table 1. Summary of existing frameworks for establishing and ethical review of HIS.

Gordon *et al.* (2017) & Elliott *et al.* (2018) framework	Bambery *et al.* (2016) framework	Emerson (2018) expanded framework	WHO (2020) COVID-19 HIS framework	WHO (2021b) HIS ethics guidance
1. Issue of national importance, within the research agenda 2. Safety already demonstrated 3. Model quality established by published data 4. Strong scientific case, without alternative approach 5. Promotes capacity development in country 6. Ethical acceptability including issues of understanding consent 7. Governance structure in place (DSMB (data safety monitoring board), sponsor)	1. Scientific rationale 2. Absence of alternative 3. Informed consent 4. Benefits and harms 5. Selection of study participants 6. Independent review 7. Publicly available rationale 8. Protection of public 9. Compensation for harm	1. Rationale for HIS 2. Risks 3. Discomforts 4. Vulnerable subjects 5. Informed consent 6. Financial compensation 7. Right to withdraw from research 8. Independent review 9. Publicly available rationale 10. Protection of the public 11. New model of compensation for harm 12. Knowledge and Data Sharing 13. Community Engagement 14. Governance	**Scientific and ethical assessments** 1. Scientific justification 2. Assessment of risks and potential benefits Consultation and coordination 3. Consultation and engagement 4. Coordination **Selection criteria** 5. Site selection 6. Participant selection Review and consent 7. Expert review 8. Informed consent	1. Research design 2. Risks, burdens and benefits 3. Selecting research sites and populations 4. Consent 5. Reimbursement and compensation 6. Engagement 7. Fair collaborations and sharing 8. Governance, review, and oversight 9. Social science research

Prevailing frameworks and guidelines for establishing and conducting ethical and scientific review of Human Infection Studies. HIS = Human Infection Studies, WHO = World Health Organization, DSMB = Data Safety and Monitoring Boards.

Frameworks for establishing and ethical review of CHIM Studies (2)

- Similar issues across the frameworks

<u>Aspects emphasized in the LMIC frameworks</u>

- ✓Scientific justification of the CHIM study – In LMIC, emphasis is on diseases relevant to the context where the study is conducted
- ✓CHIM Studies design in LMICs should be of ‘ equivalent International standards’
- ✓Safety of CHIM model should be demonstrated from prior studies
- ✓Quality Assurance of the chosen challenge strain; local vs imported
- ✓Promotion of capacity building – technical, infrastructural , regulatory
- ✓Development of localized and relevant regulatory frameworks suited for the context
- ✓Centrality of community engagement; informed consent processes

Progress of CHIM Studies in Africa (1)

Focus on pathogens relevant to the African populations

- Increase in CHIM studies being conducted in Africa; wider scope of pathogens relevant to endemic settings
- Testing of vaccines in CHIM studies e.g., Malaria vaccines
- Potential studies to develop locally relevant strains of pathogens for CHI models e.g., local Malaria strains

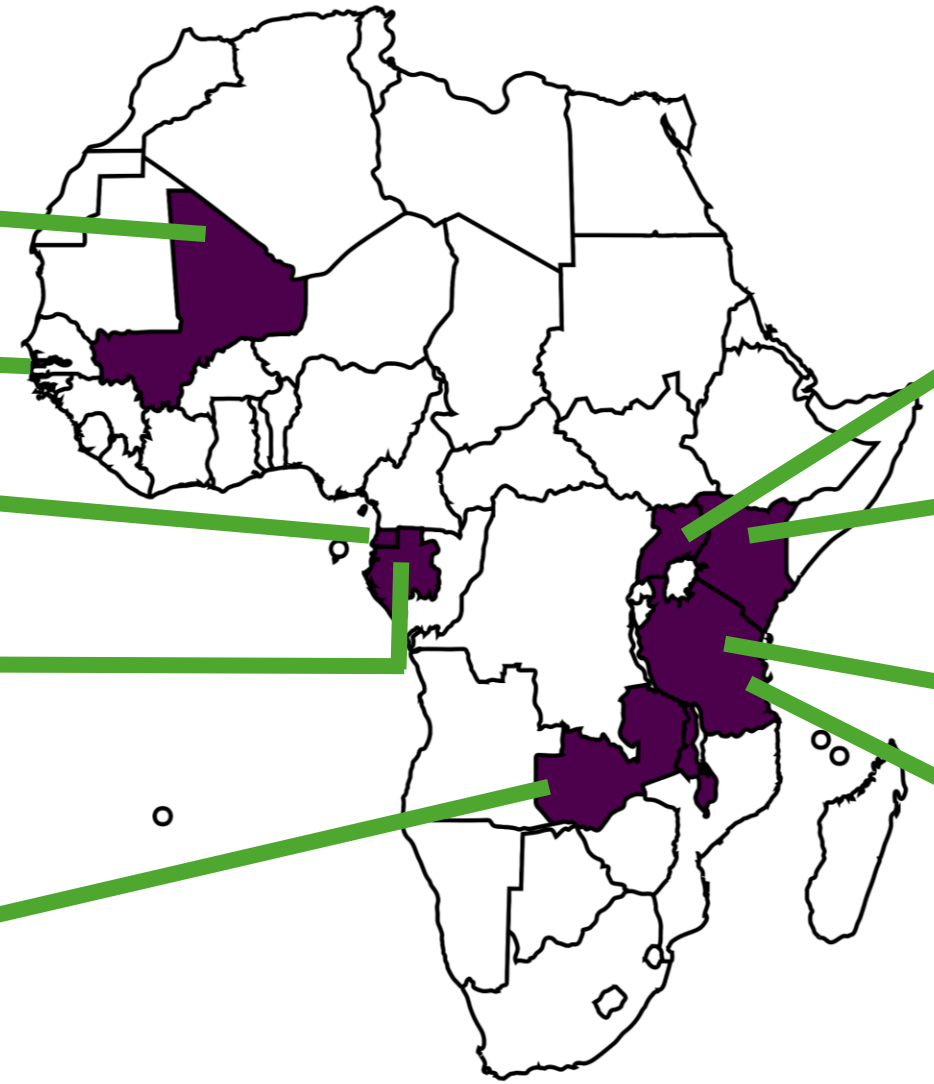
Infrastructure to support CHIM studies

- Increased infrastructural capacity to carry out 'international standard' CHIM studies - Laboratory facilities, improved clinical facilities, personnel

Capacity building – technical expertise

- Building a critical mass of expertise within the continent to establish and manage CHIM Studies
- Increase of African scientists leading collaborative CHIM studies

Human Infection Studies in Africa



Plasmodium falciparum
Neisseria lactamica

Plasmodium falciparum

Plasmodium falciparum

Plasmodium falciparum

Live attenuated vaccines (enteric)

Schistosoma mansoni

Plasmodium falciparum
Shigella sonnei

Plasmodium falciparum

Streptococcus pneumoniae

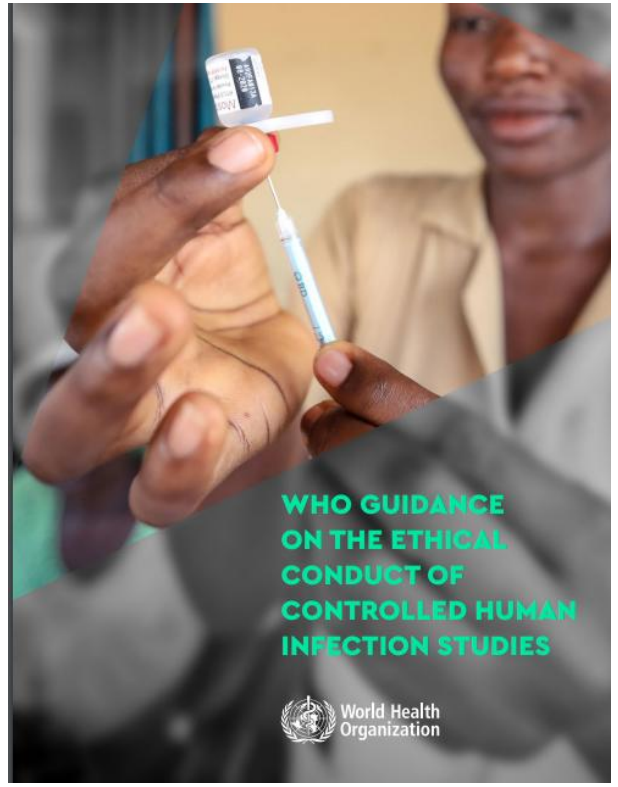
Progress of CHIM Studies in Africa (2)

Governance, regulation and Ethical Review of CHIM Studies

- Increased regulatory and ethical capacity to review CHIM studies – balance between social value and participant protection
- Individual countries continue to develop locally relevant guidelines for CHIM studies. E.g. Pharmacy and Poisons Board (PPB)-Kenya
- Development of guidelines at the continental level – to provide guidance to countries conducting CHIM studies e.g., The African Vaccine Regulatory Forum (AVAREF)
- Cross learning/peer learning opportunities between researchers, regulators and ethics committees
- Capacity building of ethics committees and regulatory bodies regarding CHIM studies

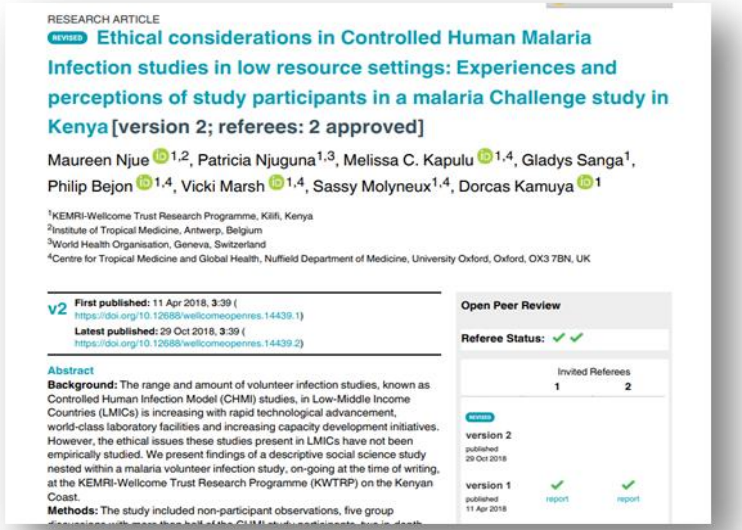
Embedding social sciences in CHIM studies

- WHO (2021b) – Important role of engagement and social science research in ethical acceptability of CHIMs, especially in settings unfamiliar with CHIM studies
- At the **KWTRP,** social science studies have been embedded since 2017 to date – Malaria and Shigella
- Involvement of a wide range of stakeholders: former and current participants, their families, community members, research staff, regulatory bodies, ethics committees



- Studies have given insight into the social and ethical issues of conducting CHIM studies in the Kenyan context
- Issues explored include, participant experiences, levels of compensation, participant benefits and burdens, potential risks and harms

Key outputs: +6 publications & 4 manuscripts



RESEARCH ARTICLE

REVISED **Ethical considerations in Controlled Human Malaria Infection studies in low resource settings: Experiences and perceptions of study participants in a malaria Challenge study in Kenya [version 2; referees: 2 approved]**

Maureen Njue[1,2], Patricia Njuguna[1,3], Melissa C. Kapulu[1,4], Gladys Sanga[1], Philip Bejon[1,4], Vicki Marsh[1,4], Sassy Molyneux[1,4], Dorcas Kamuya[1]

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Open Peer Review

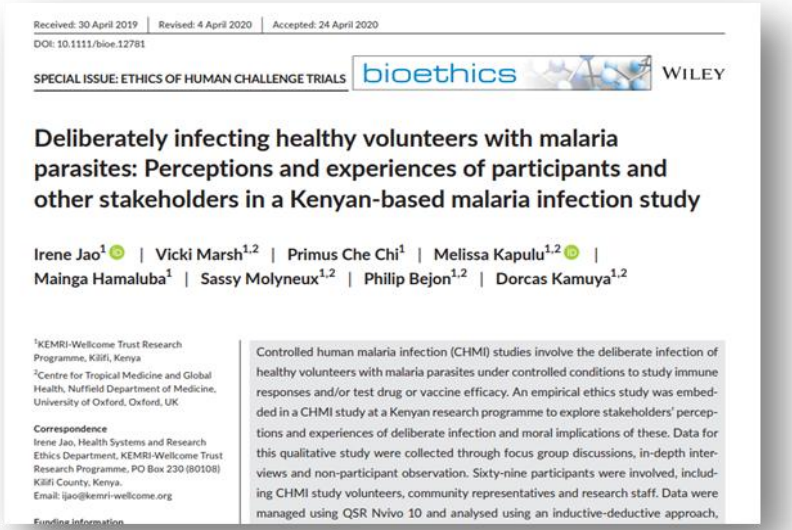
Referee Status: ✓ ✓

	Invited Referees 1	2
REVISED version 2 published 29 Oct 2018		
version 1 published 11 Apr 2018	✓ report	✓ report

Abstract

Background: The range and amount of volunteer infection studies, known as Controlled Human Infection Model (CHMI) studies, in Low-Middle Income Countries (LMICs) is increasing with rapid technological advancement, world-class laboratory facilities and increasing capacity development initiatives. However, the ethical issues these studies present in LMICs have not been empirically studied. We present findings of a descriptive social science study nested within a malaria volunteer infection study, on-going at the time of writing, at the KEMRI-Wellcome Trust Research Programme (KWTRP) on the Kenyan Coast.

Methods: The study included non-participant observations, five group



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SPECIAL ISSUE: ETHICS OF HUMAN CHALLENGE TRIALS bioethics WILEY

Deliberately infecting healthy volunteers with malaria parasites: Perceptions and experiences of participants and other stakeholders in a Kenyan-based malaria infection study

Irene Jao[1] | Vicki Marsh[1,2] | Primus Che Chi[1] | Melissa Kapulu[1,2] | Mainga Hamaluba[1] | Sassy Molyneux[1,2] | Philip Bejon[1,2] | Dorcas Kamuya[1,2]

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Controlled human malaria infection (CHMI) studies involve the deliberate infection of healthy volunteers with malaria parasites under controlled conditions to study immune responses and/or test drug or vaccine efficacy. An empirical ethics study was embedded in a CHMI study at a Kenyan research programme to explore stakeholders' perceptions and experiences of deliberate infection and moral implications of these. Data for this qualitative study were collected through focus group discussions, in-depth interviews and non-participant observation. Sixty-nine participants were involved, including CHMI study volunteers, community representatives and research staff. Data were managed using QSR Nvivo 10 and analysed using an inductive-deductive approach,

Chi et al. Trials (2021) 22:494
https://doi.org/10.1186/s13063-021-05455-7

Trials

RESEARCH Open Access

Understanding the benefits and burdens associated with a malaria human infection study in Kenya: experiences of study volunteers and other stakeholders

Primus Che Chi[1*], Esther Awuor Owino[1], Irene Jao[1], Fredrick Olewe[2,3], Bernhards Ogutu[2,3], Philip Bejon[1,4], Melissa Kapulu[1,4], Dorcas Kamuya[1,4], Vicki Marsh[1,4] and CHMI-SIKA Study Team

Abstract

Background: Human infection studies (HIS) that involve deliberately infecting healthy volunteers with a pathogen raise important ethical issues, including the need to ensure that benefits and burdens are understood and appropriately accounted for. Building on earlier work, we embedded social science research within an ongoing malaria human infection study in coastal Kenya to understand the study benefits and burdens experienced by study stakeholders in this low-resource setting and assess the wider implications for future research planning and policy.

Methods: Data were collected using qualitative research methods, including in-depth interviews (44), focus group

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OPEN PEER COMMENTARIES

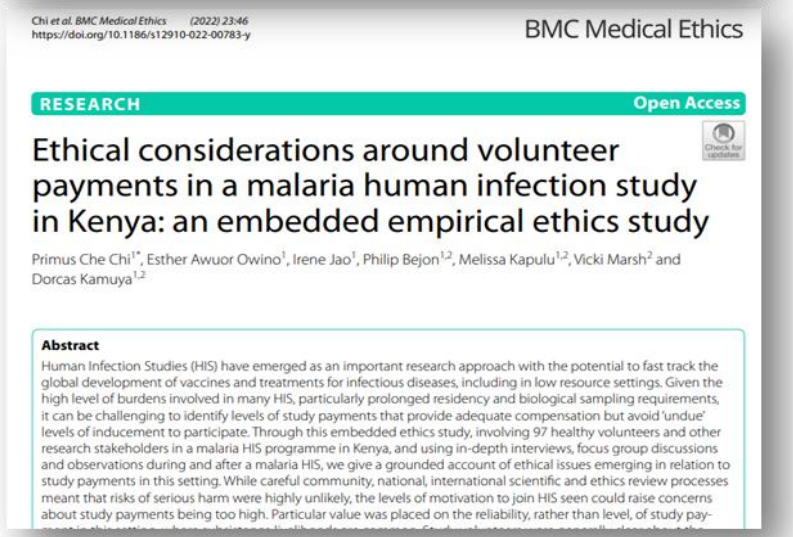
Considering the Importance of Context for Ethical Practice on Reimbursement, Compensation and Incentives for Volunteers in Human Infection Controlled Studies

Primus Che Chi, Esther Owino, Irene Jao, Vicki Marsh, and Dorcas Kamuya

KEMRI-Wellcome Trust Research Programme

The proposed framework by Lynch et al. (2021) for promoting ethical forms of payment in Human Infection Controlled Studies (HICS) in general and SARS-Cov-2 HICS in particular is an important contribution to the literature. It lays out a strong case for having a common framework for payment for all research rather than a unique framework for HICS, whilst still acknowledging the unique features of HICS. By mapping the various forms of payments, their justification and potential ethical issues, issues of context on the analysis of payments to volunteers in HICS from the perspective of researchers working in a low-resource setting in Kenya.

Overall, we would like to emphasize that these wider structural features act as overarching considerations for the ethics of HICS, rather than as components within lists of relevant areas (CIOMS 2016 makes this point clear). In keeping with this wider view, we also strongly agree with the authors that, in planning studies such as HICS in low resource set-



Chi et al. BMC Medical Ethics (2022) 23:46
https://doi.org/10.1186/s12910-022-00783-y

BMC Medical Ethics

RESEARCH Open Access

Ethical considerations around volunteer payments in a malaria human infection study in Kenya: an embedded empirical ethics study

Primus Che Chi[1*], Esther Awuor Owino[1], Irene Jao[1], Philip Bejon[1,2], Melissa Kapulu[1,2], Vicki Marsh[2] and Dorcas Kamuya[1,2]

Abstract

Human Infection Studies (HIS) have emerged as an important research approach with the potential to fast track the global development of vaccines and treatments for infectious diseases, including in low resource settings. Given the high level of burdens involved in many HIS, particularly prolonged residency and biological sampling requirements, it can be challenging to identify levels of study payments that provide adequate compensation but avoid 'undue' levels of inducement to participate. Through this embedded ethics study, involving 97 healthy volunteers and other research stakeholders in a malaria HIS programme in Kenya, and using in-depth interviews, focus group discussions and observations during and after a malaria HIS, we give a grounded account of ethical issues emerging in relation to study payments in this setting. While careful community, national, international scientific and ethics review processes meant that risks of serious harm were highly unlikely, the levels of motivation to join HIS seen could raise concerns about study payments being too high. Particular value was placed on the reliability, rather than level, of study pay-

frontiers | Frontiers in Public Health

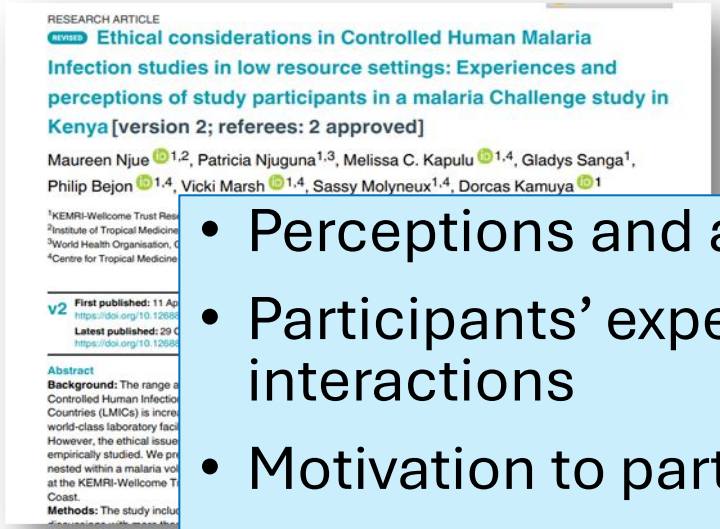
Undertaking Community Engagement for a Controlled Human Malaria Infection Study in Kenya: Approaches and Lessons Learnt

OPEN ACCESS

Noni Mumba[1], Patricia Njuguna[1,2], Primus Chi[1], Vicki Marsh[1,3], Esther Awuor[1], Mainga Hamaluba[1,3], Cynthia Mauncho[1], Salim Mwalukore[1], Johnson Masha[1], Mary Mwangoma[1], Betty Kalama[1], Hassan Alphan[1], Juliana Wambua[1], Philip Bejon[1,3], Dorcas Kamuya[1,3] and Melissa C. Kapulu[1,3]*

Human infection studies (HIS) involve deliberately infecting healthy volunteers with disease-causing pathogens under controlled conditions. These studies are "controlled" by way of using specific types of pathogens, including dose, and the availability of emergency medical facilities to research volunteers. Most HIS involve diseases

Key outputs: +6 publications & 4 manuscripts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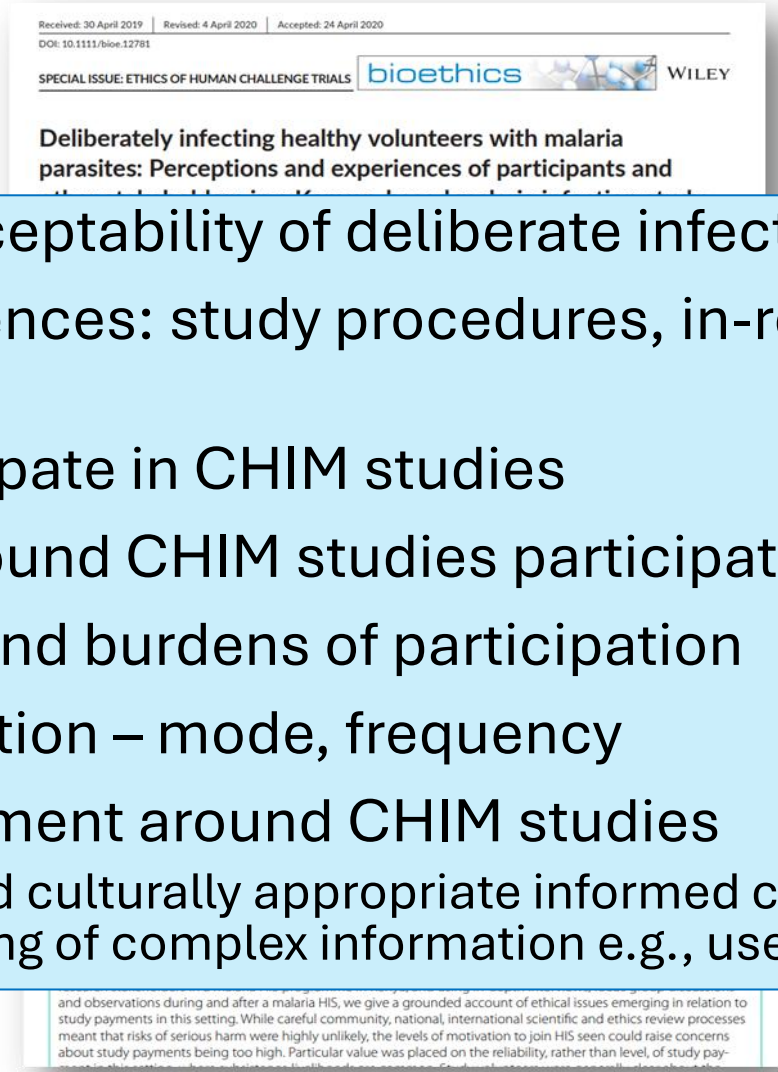
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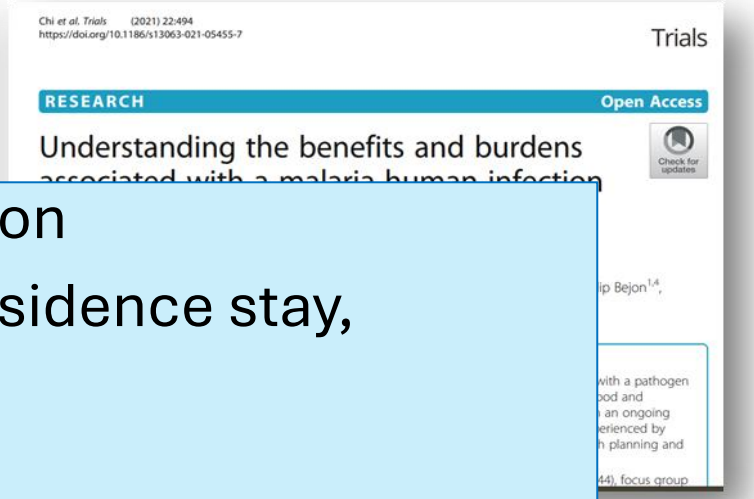
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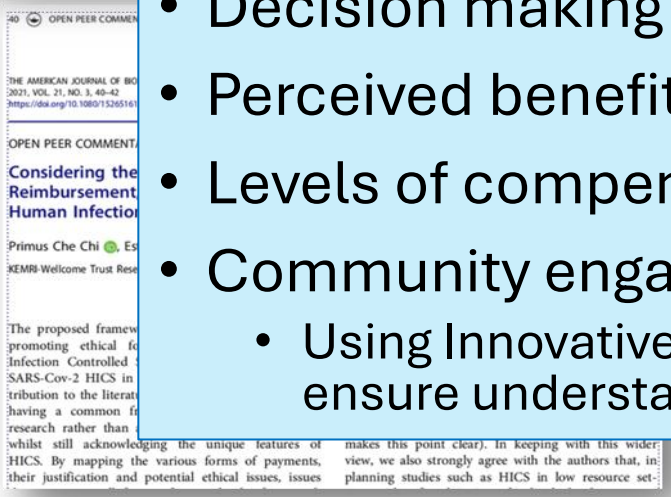
Understanding the benefits and burdens


OPEN PEER COMMENT

Considering the Reimbursement Human Infectio

- Perceptions and acceptability of deliberate infection
- Participants' experiences: study procedures, in-residence stay, interactions
- Motivation to participate in CHIM studies
- Decision making around CHIM studies participation
- Perceived benefits and burdens of participation
- Levels of compensation – mode, frequency
- Community engagement around CHIM studies
  - Using Innovative and culturally appropriate informed consent processes to ensure understanding of complex information e.g., use of participatory videos

Implications: Policy & Practice at KWTRP

Practice of HIS at KWTRP

- Introduction of demonstration tools for the specific volume of blood drawn as part of the IC process.
- Staggering of compensation for participation in future HIS – weekly from end-of –study single payment.
- HIS conducted across pops where high literacy is not a priori criteria – better inclusivity.
- Incorporating the 'uncovered' benefits & burdens in the IC process - ongoing.

Policy (national & international)

- Kenya medicine regulator (PPB) guidance on CHIS (Jan. 2020)
- WHO Ethics Guidance on CHIS (Dec. 2021)
- VolREthics Ethics 'Charter' for the Protection of Healthy Volunteers in Clinical Trials (April 2024)
- AVAREF EWG on CHIS (ongoing)
- WHO guidance on CHIS of pandemic potentials (ongoing)

Acknowledgements

- **CHIM study teams.**

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wellcome

This project is part of the EDCTP2 programme supported by the European Union

EDCTP

World Health Organization

Ethics Guidance for Human Infection Challenge Studies in LMICs: Kenya's Experience

Kebenei Enock, MSC, BSC,

Senior Research Scientist (Research Regulations), & Head

Scientific and Ethics Review Unit (SERU)

Kenya Medical Research Institute (KEMRI)

About KEMRI SERU

- Kenya Medical Research Institute (KEMRI)
- Scientific and Ethics Review Unit (SERU)
- Hosts the locally and internationally accredited IRB.
- The committee was established in 1979.
- Research protocols are increasing in numbers & complexity e.g. CHIM
- Currently, oversighting more than 2,000 ongoing projects countrywide.
- Responded to changes by;
  - ✓Increasing the number of IRB members (multidisciplinary, multisectoral).
  - ✓Continuous ethics education (CEE).
  - ✓Activated active study site monitoring.

SERU

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Ethical Oversight of CHIM Studies at KEMRI

- Relatively unfamiliar research approach in Kenya.
- Currently, KEMRI SERU oversights 5 CHIM studies.
- Common concerns raised:
  1) What is the disease burden?
  2) What is the appropriate rate of reimbursement without inducement?
  3) How will you control community infection?
  4) Dose administration & determination?
  5) What is the rationale for choosing the site?
  6) Biological samples and data handling.
  7) What is the insurance for the volunteers?

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Activities that have Informed CHIM Approvals

- ✓Conferences and workshops on CHIMs in local contexts.
- ✓SERU IRB chairs have taken part in previous CHIM workshops.
- ✓SERU members participated in 4th IABS CHIM conference in May 2023.
- ✓Protocol pre-submission meetings.
- ✓Study kick-off meetings.
- ✓Successful community engagement activities especially in Kilifi, Kenya.
- ✓Social science and ethics studies.
- ✓Site visits to ‘controlled environments’.
- ✓Review of procedures and guidelines for ethical approvals.

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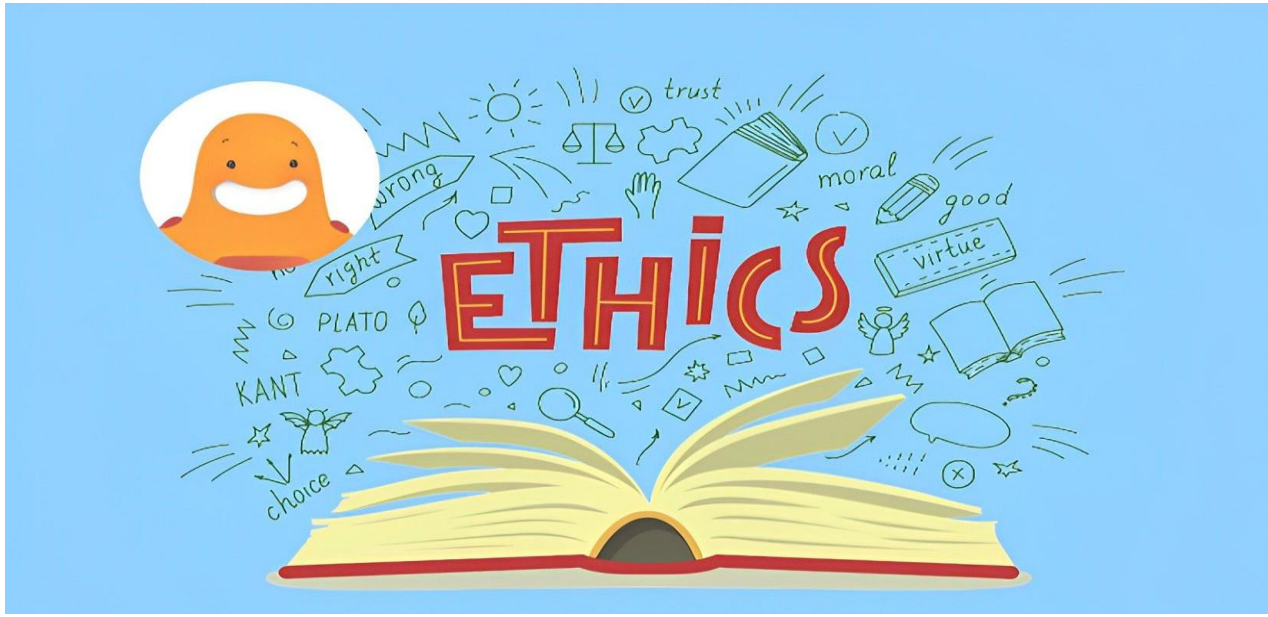
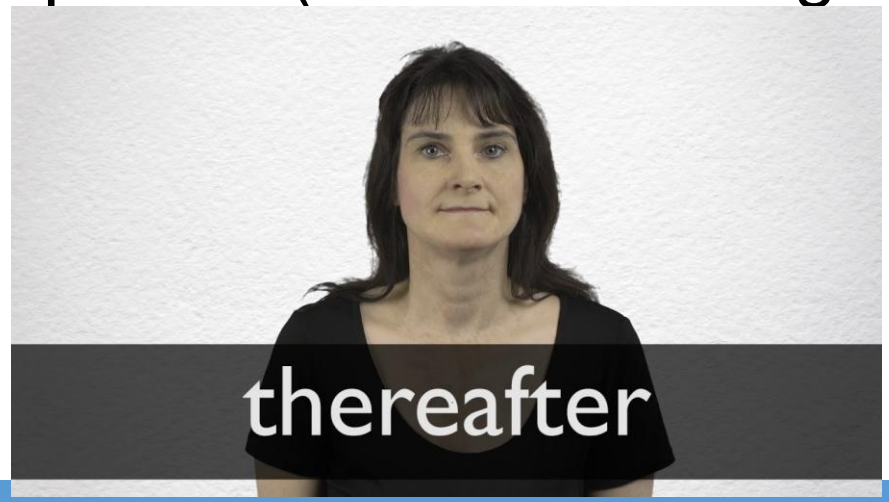
Ethical Concerns on CHIM Studies

- **Informed consent**
  - ✓Sufficiently detailed?
  - ✓Comprehensible?
  - ✓Voluntary?
- **Risk / benefit assessment**
  - ✓Is the ratio favorable or balanced?
  - ✓Is the procedure considered humane?
  - ✓What is the effect on the individual, family, community?
- **Compensation and reimbursement**
  - ✓Is it reasonable?
  - ✓Can it lead to inducement?



Post Trial Ethical Concerns

- Reversibility
- Possible continued shedding of the pathogen.
- Medical insurance cover.
- Guidance and counseling.
- Community acceptance (concerns of stigma).



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Thank You