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Ethical (and regulatory) considerations for controlled human infection research

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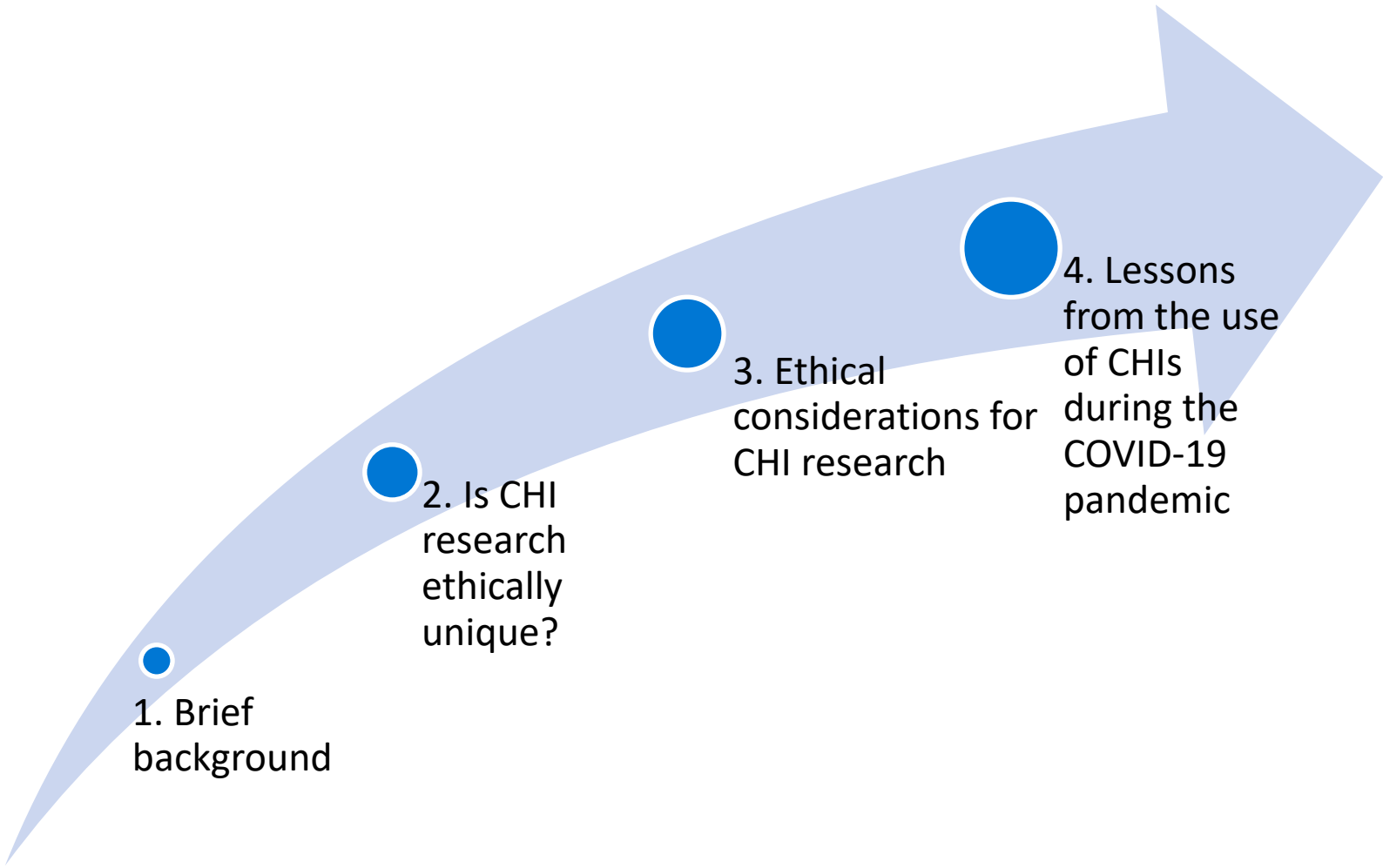
Overview


1. Brief background
2. Is CHI research ethically unique?
3. Ethical considerations for CHI research
4. Lessons from the use of CHIs during the COVID-19 pandemic

1. BRIEF BACKGROUND

Controlled human infection *models* v. *studies*

- First step: Create a safe, reliable model for infecting most participants while not making them too sick
- Several parameters to set:
  - Select a strain, purify it
  - Find the "Goldilocks" dose
  - Determine method of administration
  - Define the goal: infection or disease?
  - Plan how to manage/treat participants after infection
  - Pick facility and level of biosecurity
  - Decide if/how long participants will be confined
- After developing model, can use it in studies

Why CHI research can be ethically important

1) Small (~15-150 participants) and therefore **relatively fast and inexpensive** to conduct once model has been created

2) Capable of rigorously addressing a **wide range of research questions**

- Investigate mechanisms of (early) disease,
- Understand transmission and immunity,
- Gather preliminary efficacy data on investigational vaccines and treatments to prioritize for further study, &
- Provide efficacy data (in combination with Real World Evidence) when phase III trials are not feasible

Prominent successes

- Proof of concept for **malaria vaccine** (Lyke et al 2017)
- Supported FDA licensure of **cholera vaccine** (Chen et al 2016)
- Correlates of protection for **influenza** (Memoli et al 2016)
- Acceleration of approval for **paratyphoid vaccine** (Meiring et al 2019)

2. ARE CHIS ETHICALLY UNIQUE?

Is CHI research ethically unique? Different perspectives

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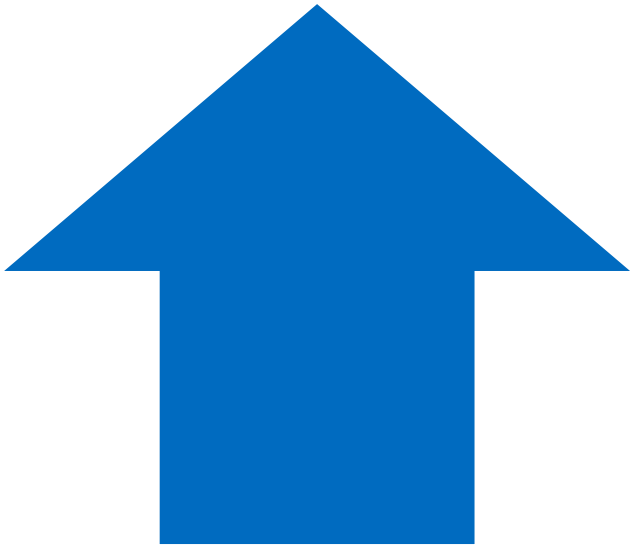
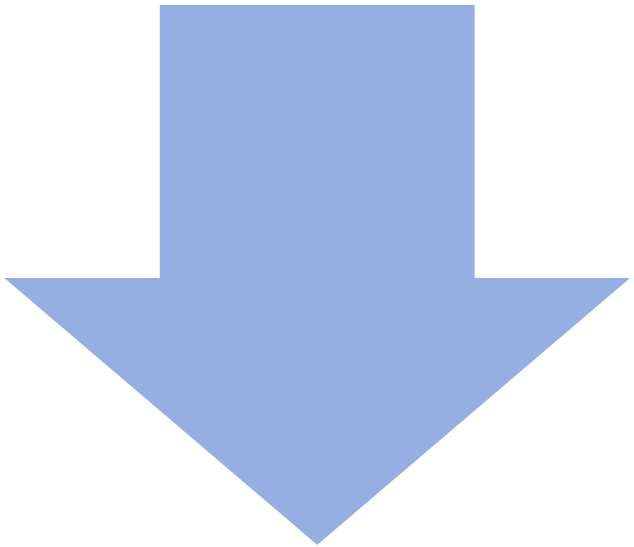


World Health Organization (2021): "[T]his guidance takes the position that CHIS are not, in themselves, an exceptional and morally distinct form of research…."



Indian Council of Medical Research Policy Statement (2023): "[I]ntentional exposure to disease-causing agents or pathogens for developing a human infection model of disease is considered a contravention of the Hippocratic Oath and violates the 'do no harm' ethical code for medical practitioners."

Is CHI research ethically unique?

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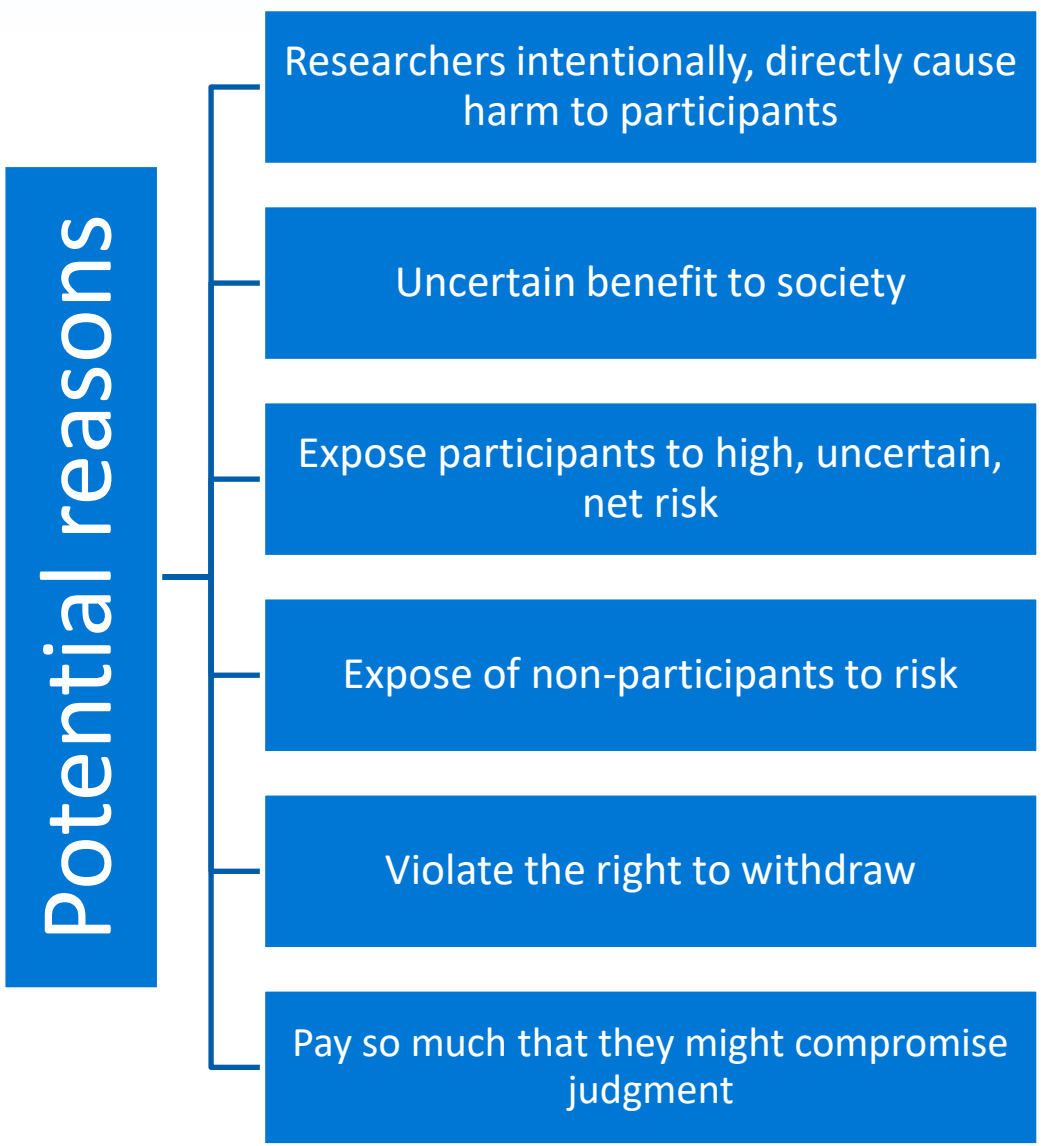


Phase I studies with healthy volunteers + studies with procedures done only for research purposes (e.g., blood draws, liver biopsies)

Studies to address policy informed by politics/ideology (e.g., abortion reversal)

HIV remission studies

Research with digital collection of data through wearables or in homes

Some biobank research with stored samples, research involving deception, some radiation studies

SARS-CoV-2 CHIs: US$6200
Phase I trials: up to US$13,000

1. Deliberate infection by researchers
2. Uncertain benefit to society
3. Uncertain and potentially high risk to participants
4. Risk to third parties
5. Risks related to right to withdraw

While not unique, CHI research can raise a constellation of issues in research ethics that are not fully resolved

And greater ethical complexity when *creating* a CHIM vs. *using* an established one in a CHI study

High levels of uncertainty and ethical complexity inherent in developing a new CHIM

Stronger justification, experience, collaboration, and creativity can help navigate these issues

3. ETHICAL GUIDANCE

Existing ethical guidance

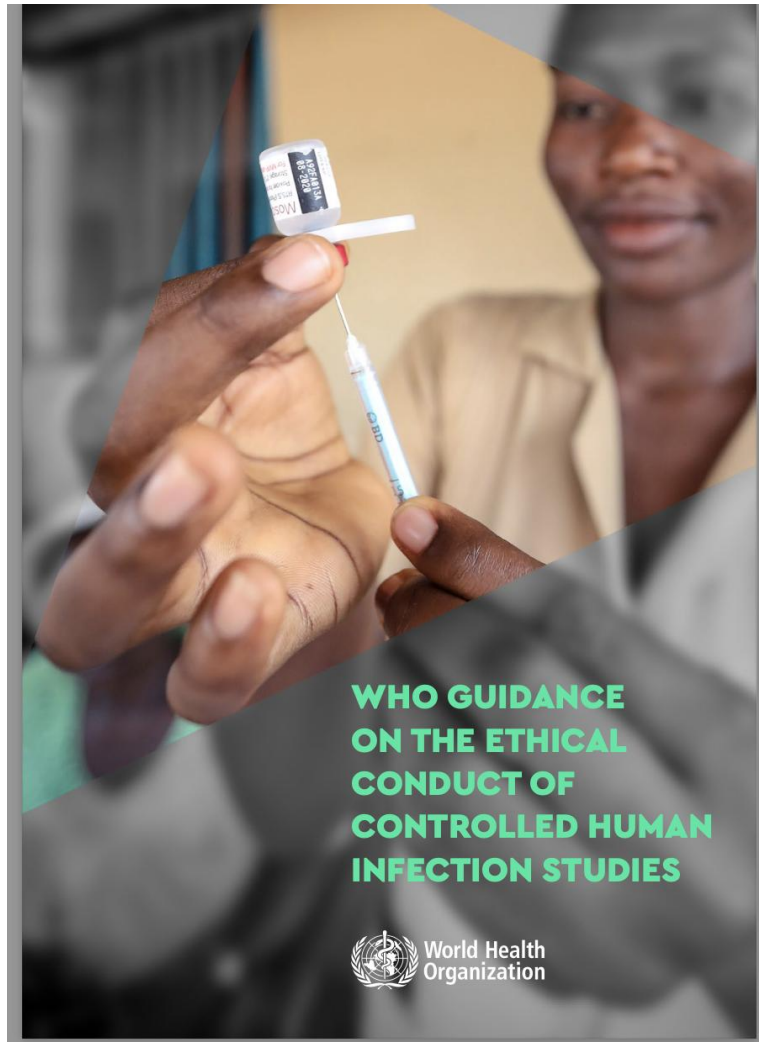
World Health Organization

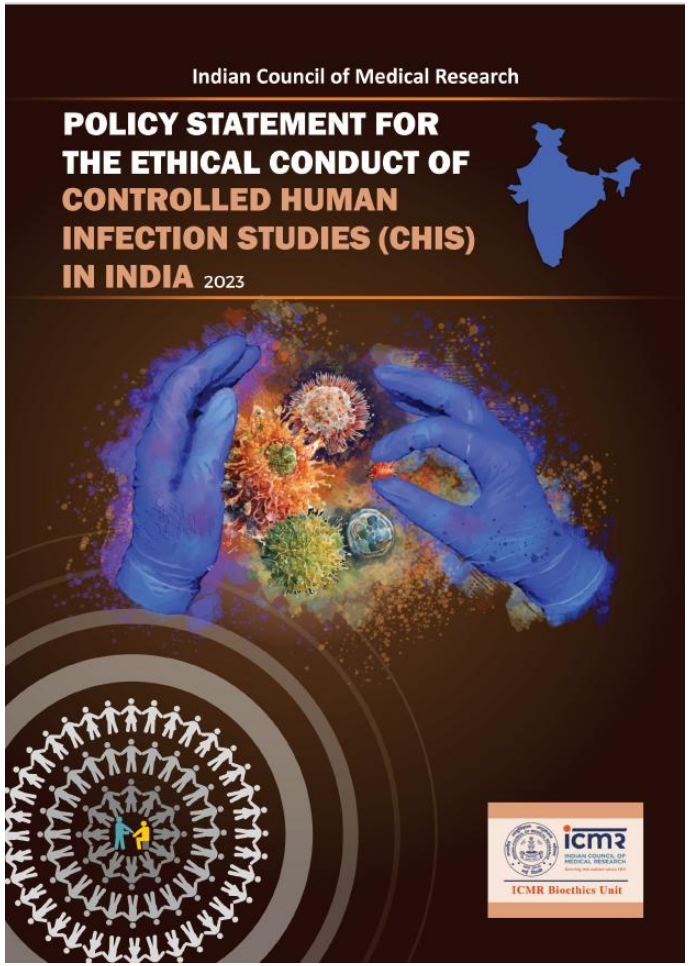
Key criteria for the ethical acceptability of COVID-19 human challenge studies

6 May 2020

1. Preamble

The pandemic of coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, poses an extraordinary threat to global public health, socioeconomic stability, food security and other social goods *(1, 2)*. Left unchecked, COVID-19 would probably claim millions of lives and place extreme strain on health care systems worldwide. While control measures such as physical distancing can help to reduce the spread of COVID-19, these measures come at enormous social and economic costs that may be disproportionately borne by underprivileged groups. Major challenges for the current public health response include (a) a lack of safe, effective vaccines and treatments; and (b) gaps in scientific knowledge regarding pathogenesis, immunity and transmission *(3, 4)*.





Other relevant work

INSIGHTS

POLICY FORUM

RESEARCH ETHICS: COVID-19

Ethics of controlled human infection to address COVID-19

High social value is fundamental to justifying these studies

By Seema K. Shah, Franklin G. Miller, Thomas C. Darton, Devan Duenas, Claudia Emerson, Holly Fernandez Lynch, Euzebiusz Jamrozik, Nancy S. Jecker, Dorcas Kamuya, Melissa Kapulu, Jonathan Kimmelman, Douglas MacKay, Matthew J. Memoli, Sean C. Murphy, Ricardo Palacios, Thomas L. Richie, Meta Roestenberg, Abha Saxena, Katherine Saylor, Michael J. Selgelid, Vina Vaswani, Annette Rid

SUFFICIENT SOCIAL VALUE

CHIs have a long, complicated history. They have contributed to substantial improvements in clinical and public health practice, including the recent licensure of two vaccines (*5*), but also involved some unethical research (*3*). The first step in justifying SARS-CoV-2 CHIs, especially as they would involve major uncertainty and controversy, is to demonstrate their high transparency and promote coordination. Research sponsors should lead by establishing and enforcing standards for rapid data collection, dissemination, and sharing that permit aggregation of results across CHIs. Medical journals should require compliance with these standards before accepting manuscripts. Regulatory agencies should collaborate with sponsors, researchers, and policy-makers to define how CHI data will inform or modify larger trials, licensure, and manufacturing. Finally, sponsors and governments should implement mechanisms to ensure widespread, equitable access to proven products whose development was accelerated by SARS-CoV-2 CHIs. Such wide-ranging stakeholder coordination is difficult but important to demonstrate high social value. Though not achieved for proposed Zika virus CHIs during the 2015–2016 epidemic, it did occur later (*6*).

SARS-CoV-2 CHIs could have high social value in other ways, and individual CHIs could address multiple scientific questions.

bioethics

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You are here: Home Page > Medicine & Health > Medical Ethics > Intentionally Infecting Humans

Overview

Description

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Author Information

Image Not Available

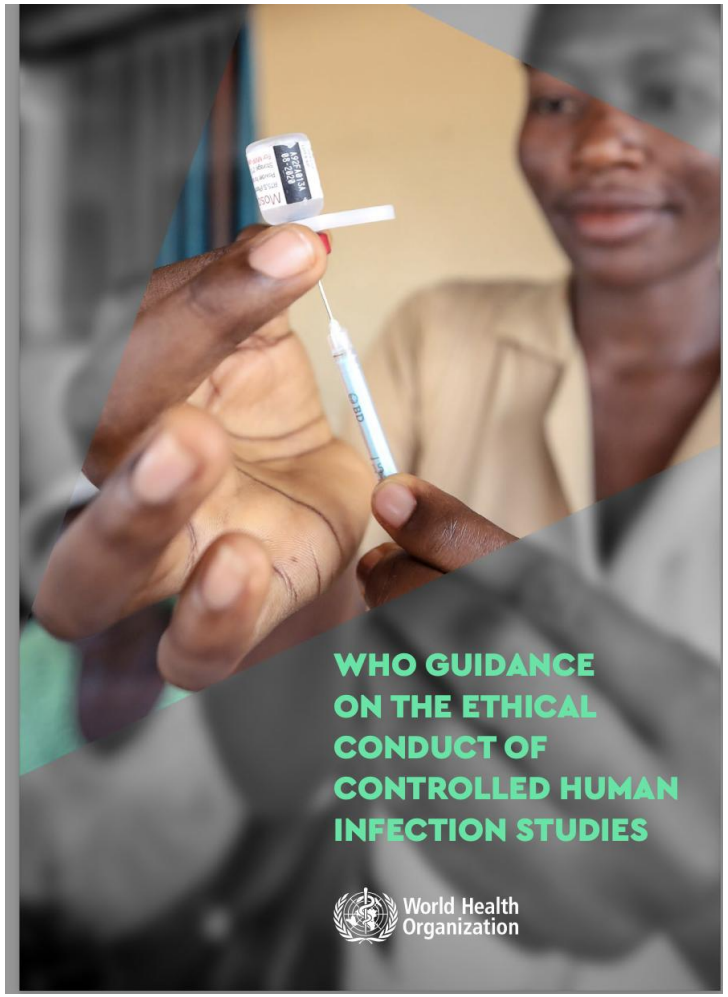
Intentionally Infecting Humans

Is it Ethical?

Seema K. Shah

- Includes an analysis of why this research method is ethically unusual, contrary to the standard view
- Provides an ethical framework that advances beyond existing guidance and regulation
- Reviews debates over the use of CHI research during the COVID-19 pandemic, debunking some claims and showing that this research did not live up to the hype
- This is an open access title. It is available to read and download as a free PDF version on Oxford Academic and is made available under a Creative Commons Attribution-Non Commercial-No Derivatives 4.0 International licence.

World Health Organization guidance



1. Justification
2. Research design
3. Risks, burdens, & benefits
4. Selecting research sites & populations
5. Consent
6. Reimbursement & compensation
7. Engagement
8. Fair collaborations & sharing
9. Governance, review & oversight
10. Social science research

Justification

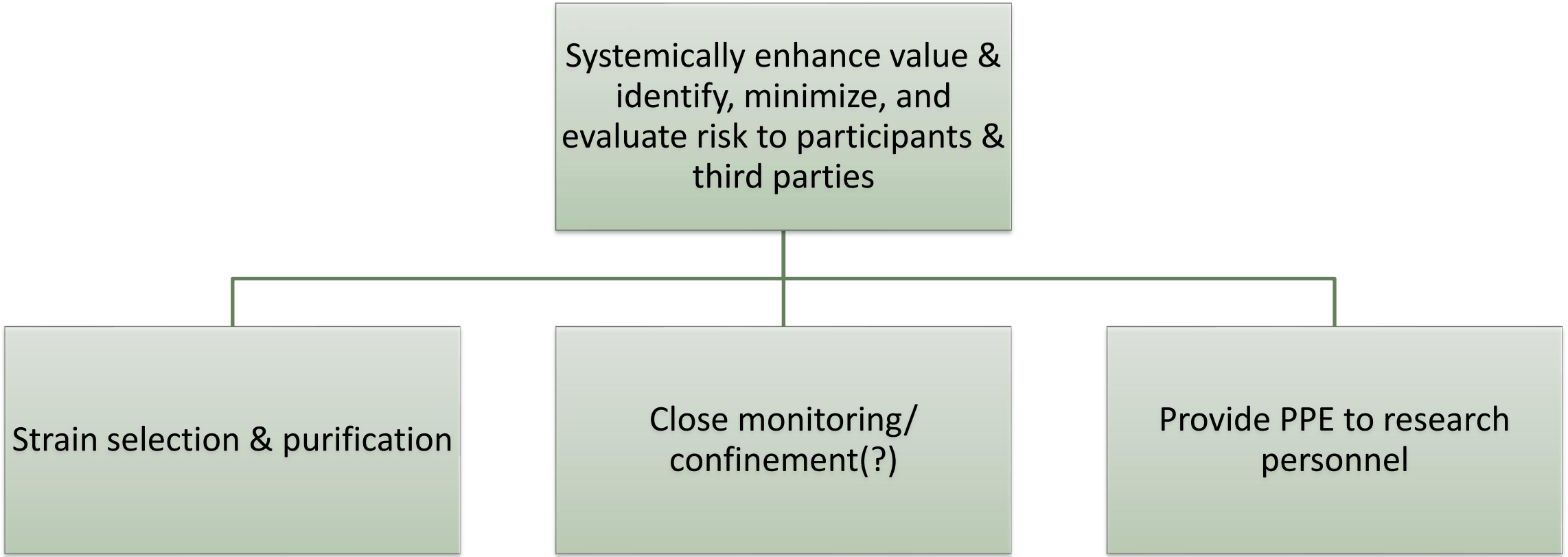
- Consider magnitude, distribution, likelihood of health benefits from research for populations, particularly those that are worst off globally

- Uncertainty requires being more rigorous for new CHIMs:

→Ability to delineate path from CHIM to health benefits

Rid A, Roestenberg M. Judging the social value of controlled human infection studies. Bioethics 2020.

Research design/risks, burdens, and benefits



Selecting sites

Selecting participants

For CHI studies that do not offer prospect of direct benefit, key issues are:

- Fair inclusion of clinically relevant populations
- Excluding participants who would face unacceptably high risks for themselves or third parties
  - Rescue treatment not necessary if enough is known about how to minimize risks

MacKay D, Jecker NS, Pittsuttithum P, Saylor KW. Selecting participants fairly for controlled human infection studies. Bioethics 2020.

Consent

Use evidence-based methods to enhance understanding

- No data to suggest blanket restrictions on populations on basis of low literacy or education are justified

Key elements for CHI research:

- Exposure to infection,
- Burdens and risks for participants,
- Risk to third parties,
- Restrictions on liberty

Vaswani V, Saxena A, Shah SK, Palacios R, Rid A. Bioethics 2020.

Reimbursement and compensation

- Potential for controversy
- Participants should be reimbursed and compensated for time and expenses to avoid exploitation
- Participants should receive treatment, compensation for injury if it occurs (rather than paying for risk up front)
- Can reduce undue inducement & withholding information in other ways

Promoting Ethical Payment in Human Infection Challenge Studies

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Feature article

OPEN ACCESS

Payment in challenge studies: ethics, attitudes and a new payment for risk model

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ABSTRACT
Controlled Human Infection Model (CHIM) research involves the infection of otherwise healthy participants with disease often for the sake of vaccine development. The COVID-19 pandemic has emphasised the urgency of enhancing CHIM research capability and the importance of having clear ethical guidance for their conduct. The payment of CHIM participants is a controversial issue involving stakeholders across ethics, medicine and policymaking with allegations circulating suggesting exploitation, coercion and other violations of ethical principles. There are multiple approaches to payment: reimbursement, wage payment and unlimited payment. We introduce a new Payment for Risk Model, which involves paying for time, pain and inconvenience and for vaccine candidates. This allows the development of effective vaccines to be accelerated, while poor vaccines can be discarded to prevent further expensive, wasteful and unsuccessful trials.[2] CHIMs also require only a small number of participants, which means that fewer people are subjected to the risks involved with taking a novel vaccine.[1] Partly for these reasons, CHIM research has recently experienced a resurgence in popularity with an estimated 22 000 participants involved in CHIMs over the past 70 years.[1] Recent CHIMs have led to many clinically valuable breakthroughs including the proof of efficacy of the new oral cholera vaccine, Vaxchora (CVD 103-HgR),[4] and the proof of efficacy for a Vi-tetanus toxoid conjugate vaccine.[5]

J Med Ethics: first published as 10.1136/medethics-2020-106438 o

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Want cash? Volunteer for a dose of malaria parasite, says Kemri amid ethical queries

Engagement

- Context-specific
  - Urban v. rural settings

- Heightened levels of engagement (+ embedded social science?) if triggers met:
  - Developing a new CHIM
  - Higher risk/uncertainty
  - Special populations enrolled
  - Risks to bystanders

Governance, review and oversight

Ethics literature & WHO guidance suggest no need for specialized regulations

However, WHO ethics guidance to be read in conjunction with existing regulations

And recommended specialized expert review for SARS-CoV-2 CHIs

May need special review to supplement regulations for novel CHIMs

I.e., Uncertainty in risk/benefit, third party risk, right to withdraw

Governance, review and oversight: Procedural protections

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Procedural protections can be a way to address important issues that regulations do not fully address

E.g., strain selection

- GMP is one approach, but it does not work for some models (e.g., schistosomiasis) and may be overkill for others as it was designed for clinical and not research use

Researchers could implement a process for expert review of strain selection and purification

- E.g., use CHIM Data and Safety Monitoring Board

4. APPLICATION: LESSONS FROM COVID-19 CHIM

U.K. was first & only country to conduct CHIM with SARS-CoV-2

- U.S. National Institutes of Health developed strain for SARS-CoV-2 challenge trials
- A "Plan C or Plan D"

* Other countries considered conducting a CHIM for COVID-19, but none did.

In the U.K., use of special review committee (but not new regulations) for SARS-CoV-2 CHIMs

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Conference report

Ethics review of COVID-19 human challenge studies: A joint HRA/WHO workshop

Eloise Williams [a,b,*], Kathrine Craig [c], Christopher Chiu [d], Hugh Davies [c], Stephanie Ellis [c], Claudia Emerson [e], Euzebiusz Jamrozik [f,g,h,*], Monica Jefford [c], Gagandeep Kang [i], Melissa Kapulu [j,k], Simon E. Kolstoe [c,l], Katherine Littler [m], Anthony Lockett [c,n], Elena Rey [o,p], Janet Messer [q], Helen McShane [r], Carla Saenz [s], Michael J. Selgelid [e], Seema Shah [t], Peter G. Smith [u], Naho Yamazaki [v]

Lessons learned:
Engagement & context matter

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1. Groundwork had been laid in U.K. to develop infrastructure and understanding about challenge trials among key stakeholders

2. Universal health care in U.K. meant participants can access care for any long-term health issues from research participation

Lessons learned: Downsides

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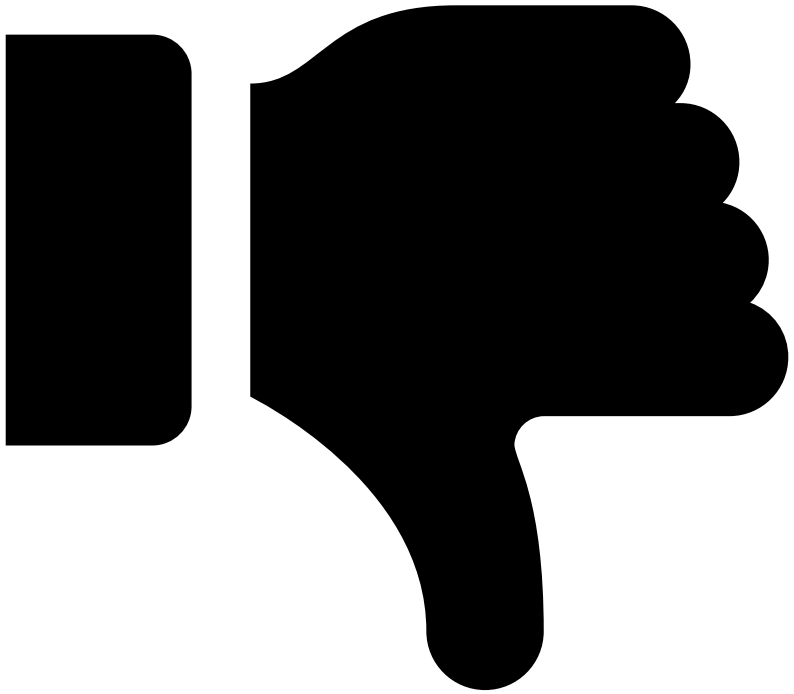
1. Uncertainty was high

2. Value still somewhat unclear

3. Limited generalizability of findings
   - Needed to exclude those at high risk of severe disease
   - Always chasing variants



Lessons learned: When might there be ethical reasons to prioritize CHIMs?

1. CHIMs can have very high social value in several cases
   - When phase III trials are not feasible (e.g., Zika virus)
   - To understand viruses related to those with pandemic potential (e.g., cold-inducing coronaviruses)
   - In non-emergency settings when resources are constrained to de-risk research (e.g., LMIC research on neglected diseases)

Take-aways

- CHI research can offer high social value that is difficult to realize in other ways
- While CHI research is not ethically unique, it can raise unresolved ethical issues
- New CHI models have greater uncertainty & may benefit from special review, creativity in adapting regulatory requirements

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- Tom Darton
- Vina Vaswani
- Zeb Jamrozik

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2c. Risk and the right to withdraw

- CHI studies may involve confinement (e.g., 2-29 days)
  - Minimize risk of withdrawal with appropriate participant selection, robust informed consent process
  - Avoid research if withdrawal is unacceptably risky
  - In event of withdrawal, encourage steps to protect others, abide by legal restrictions under public health authority

Lynch HF. The right to withdraw from controlled human infection studies: Justifications and avoidance. Bioethics 2020.

Shah et al.	WHO guidance	Harmonized criteria	Explanation
(1) Sufficient social value	(1) Justification (2) Research design	**(1) Sufficient Social Value**	Distinguish potential social value from risks before comparing to decide if a study is justified. Research design requires balancing social value and risks.
(2) Reasonable risk-benefit profile	(3) Risks, burdens, and benefits & (2) Research design	**(2) Reasonable risk/benefit profile**	
(4) Suitable site selection	(4) Selecting research sites and populations	**(3) Suitable site selection**	Criteria for selecting sites ≠ selecting participants. Site selection requires consideration of several factors, including capacity and prior engagement.
(5) Fair participant selection	Also (4) Selecting research sites and populations	**(4) Fair participant selection**	Selecting participants primarily requires consideration of fairness.
(6) Robust informed consent	(5) Consent	**(5) Robust informed consent**	Consent should use evidence-based methods to ensure voluntary, informed participation
(7) Proportionate payment	(6) Reimbursement and compensation	**(6) Proportionate compensation & payment**	Payment can include reimbursement, compensation, and incentives.
(3) Context-specific stakeholder engagement	(7) Engagement	**(7) Context-specific engagement with relevant communities**	Engagement with the lay public has value in addition to consultation with other relevant parties & public health officials. The word “stakeholder” has colonialist connotations.