Ethics of controlled human infection studies

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Disclosures & thanks

• The views expressed are my own and do not represent the views of the NIH, PHS, or DHHS
• I declare no conflicts of interest
• Thanks to international working group on ethics of controlled human infection studies (PI: Seema Shah)
Overview

1) Background on controlled human infection studies (CHIs): history and scientific basics

2) Ethical framework for controlled human infection studies: SARS-CoV-2 CHIs as case study
Controlled human infection studies (CHIs)

- Studies in which healthy volunteers are deliberately infected with a pathogen in order to study mechanisms of disease and accelerate the testing of vaccines and treatments
- Also called voluntary infection studies, human challenge trials, controlled human infection models etc.
Influenza
Cholera
Malaria
Rhinovirus
Inoculation with smallpox practiced in Africa, China, India, Europe

Smallpox (Edward Jenner) 1796
Yellow fever (Walter Reed) 1900
Hepatitis (Saul Krugman) 1950s
>25 CHI models 2018

Long scientific history of CHIs
Established research paradigm

- >25 CHI models
- Both outpatient and inpatient
- ~25,000 volunteers involved with relatively limited risks
- Rhinovirus, influenza and malaria CHIs most commonly performed
Prominent successes

FDA licensure of cholera vaccine

Proof of concept for malaria vaccine and first proof of efficacy for several antimalarials

Correlates of protection for influenza
Increasing interest

• ... in expanding CHIs to new diseases
Increasing interest

• … in expanding CHIs to new populations
Increasing interest

• … in expanding CHIs to new settings
Why increasing interest

1) CHIs are efficient and cost-effective
   - Require small number of participants (10-100 per study) because highly controlled
   - Can generate basic scientific insights (e.g., mode of transmission, correlates of protection) and preliminary safety and efficacy data on vaccine or treatment candidates—sometimes in the same study
Why increasing interest ctd.

2) CHIs can accelerate research
   - When alternative research methods have important limitations, notably animal models and/or field trials
   - When there is limited interest in certain research areas or investigational products
3) CHIs are ethically interesting because of these features
   – Expose few participants to risks
   – Can lead to fewer participants being exposed to lower risks in later trials
   – Can save lives by accelerating research
   – Can catalyze research investment on disadvantaged populations
Ethical concerns

- CHIs have long raised ethical concerns, even when their scientific contributions were undisputed.

Smallpox
(Edward Jenner, 1796)

Hepatitis
(Saul Krugman, 1950s)
Ethical digressions

- History of CHIs also includes clear cases of ethical digression

- Various infectious diseases (WW II)
- Various sexually transmitted infections (late 1940s)
Ethical analysis

• In the modern era, CHIs have been conducted consistent with recognized ethical and regulatory requirements

• Yet until recently, there has been relatively little specific ethical analysis

The Ethical Challenge of Infection-Inducing Challenge Experiments

Franklin G. Miller and Christine Grady
Department of Clinical Bioethics, National Institutes of Health, Bethesda, Maryland
How should we think about the ethics of controlled human infection studies?
Case study: SARS-CoV-2 CHIs
We advocate for people who want to participate in high-risk, high-reward medical studies.

Are you part of a vaccine trial? Join us to make a difference.

VOLUNTEER FOR CHALLENGE TRIALS
Public debate

Why have 14,000 people volunteered to be infected with coronavirus?

They want to take part in a "human challenge trial," an ethically controversial vaccine test that infects people with a virus doesn't yet have a cure.
Bioethics commentary

Human Challenge Studies to Accelerate Coronavirus Vaccine Licensure

Nir Eyal1,2, Marc Lipsitch1,3, and Peter G. Smith4

1Center for Population-Level Etiology, Rutgers University-New Brunswick, New Jersey, USA. 2Department of Philosophy, Rutgers University, New Brunswick, New Jersey, USA. 3Department of Health Behavior, Society, and Policy, Rutgers School of Public Health, Piscataway, New Jersey, USA. 4Center for Comparative Disease Dynamics, Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA. 5Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA. 6Modern Epidemiology Group, London School of Hygiene & Tropical Medicine, London, UK.

Controlled human challenge trials of SARS-CoV-2 vaccine candidates could accelerate the testing and potential rollout of efficacious vaccines. By replacing conventional phase 3 testing of vaccine candidates, such trials may subtract many months from the licensure process, making efficacious vaccines available more quickly. Obviously, challenging volunteers with this live virus risks inducing severe disease and possibly even death. However, we argue that such studies, by accelerating vaccine evaluation, could reduce the global burden of coronavirus-related mortality and morbidity. Volunteers in such studies could autonomously authorize the risks to themselves, and their net risk could be acceptable if participants comprise healthy young adults, who are at relatively low risk of serious disease following natural infection, if they have a high baseline risk of natural infection, and if during the trial they receive frequent monitoring and, following any infection, the best available care.

Keywords: coronavirus; vaccines; human challenge studies; randomized controlled trials; risk-taking; ethics.

For now, it’s unethical to use human challenge studies for SARS-CoV-2 vaccine development

Jeffrey P. Kahn1,2, Leslie Meltzer Henry3,4, Anna C. Mastrolanza5,6, Wilbur H. Chen7,8, and Ruth Macklin2,3

The prospect of a widely available severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine is an increasingly high priority for an effective response to the coronavirus disease 2019 (COVID-19) pandemic and an area of intense interest and attention for professionals, policymakers, and the public alike. The understandable desire for typically, undertaking HCS in vaccine development requires that the disease for which a challenge would be introduced either has an available rescue therapy to treat those who become infected or the disease is known to be self-limiting. There is no rescue therapy for SARS-CoV-2 infection, and symptoms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) human challenge studies to hasten vaccine development. We have conducted (J. L.) and overseen (L. D.) human challenge studies and agree that they can be useful in developing anti-infective agents. We also agree that adults

To the Editor—Eyal et al [1] have recently argued that researchers should consider conducting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) human challenge studies to hasten vaccine development. We have conducted (J. L.) and overseen (L. D.) human challenge studies and agree that they can be useful in developing anti-infective agents. We also agree that adults...
WHO R&D Blueprint

novel Coronavirus

WHO Advisory Group Tasked to Consider the Feasibility, Potential Value and Limitations of Establishing a Closely-Monitored Challenge Model of Experimental COVID-19 in Healthy Young Adult Volunteers

Technical and ethical guidance

WHO Report

Key criteria for the ethical acceptability of COVID-19 human challenge studies: Report of a WHO Working Group

Euzebiuozz Jamrozik A,1, Katherine Littler d, Susan Bull 1, Claudia Emerson 3, Gagandeep Kang 1, Melissa Kapulu 1,2, Elena Rey 3, Carla Saenz 1, Seema Shah 1, Peter G Smith 1, Ross Upshur 1,3, Charles Weijer 1, Michael J Selgelid 1,3, for the WHO Working Group for Guidance on Human Challenge Studies in COVID-19

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15Universidad ICESI, Cali, Colombia
SARS-CoV-2 CHI landscape

- NIH developed strains for SARS-CoV-2 CHIs and never used them
- Fauci: CHIs are “Plan C or D”

- UK government sponsored dose-finding SARS-CoV-2 CHIs with naïve and previously infected participants

- SARS-CoV-2 CHIs in preparation at University of Leiden
SARS-CoV-2 CHI in UK

- Dose-finding studies completed, but publication of results is pending

SARS-CoV-2 Human Challenge Studies — Establishing the Model during an Evolving Pandemic
Garth Rapeport, M.B., B.Ch., Emma Smith, Ph.D., Anthony Gilbert, M.B., B.Ch., Andrew Catchpole, D.Phil., Helen McShane, F.Med.Sci., and Christopher Chiu, B.M., B.Ch., Ph.D.

UK Research Ethics Committee’s review of the global first SARS-CoV-2 human infection challenge studies
Hugh Davies, On behalf of the HRA Specialist Research Ethics Committee
Ethical foundation

• CHIs are not fundamentally different from other research
  – Aim to generate socially valuable knowledge
  – Expose participants to risks in its pursuit
  – Similar to phase I trials with healthy volunteers

• General ethical principles for research apply to CHIs

Miller F & Grady 2001; Bambery B et al. 2016;
Shah SK et al. 2017; Selgelid & Jamrozik 2018; Jamrozik & Selgelid 2019
Specific ethical challenges

• CHIs raise a unique constellation of unresolved ethical challenges
  – E.g., judgments about social value, risks to third parties, upper risk limits, exclusion criteria

• Ethical analysis complicated by the fact that CHIs can be counterintuitive to the public and foster controversy or distrust
The Greenwall Foundation
Ethical considerations for CHIs

- Sufficient social value
- Reasonable risk-benefit profile
- Fair participant selection
- Suitable site selection
- Context-specific stakeholder engagement
- Robust informed consent
- Proportionate payment

Shah & Rid (Eds.) 2020, Shah SK et al. 2020, Shah SK. et al work in progress
No major substantive differences with WHO ethical guidance
## No major substantive differences

<table>
<thead>
<tr>
<th>WHO Key Criteria</th>
<th>Shah et al. ethical framework</th>
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<tbody>
<tr>
<td><strong>Terminology</strong></td>
<td><strong>Terminology</strong></td>
</tr>
<tr>
<td>• Human challenge studies, controlled human infection studies, human infection challenge studies</td>
<td>• Controlled Human Infection studies (CHIs)</td>
</tr>
<tr>
<td><strong>8 ethical considerations</strong></td>
<td><strong>7 ethical considerations</strong></td>
</tr>
<tr>
<td>• Focus on <em>scientific justification</em></td>
<td>• Focus on <em>social value</em></td>
</tr>
<tr>
<td>• Does not address payment</td>
<td>• Addresses payment</td>
</tr>
<tr>
<td>• Stakeholder coordination and community consultation</td>
<td>• Stakeholder engagement (covers coordination &amp; consultation)</td>
</tr>
<tr>
<td>• Expert review</td>
<td>• Independent review assumed</td>
</tr>
<tr>
<td><strong>Longer and more detailed</strong></td>
<td><strong>Subject to 2000 word limit</strong></td>
</tr>
</tbody>
</table>
Our stance (in May 2020)

• “… we agree on the ethical conditions for conducting SARS-CoV-2 CHIs (see the table). We differ on whether the social value of such CHIs is sufficient to justify the risks at present, given uncertainty about both in a rapidly evolving situation; yet we see none of our disagreements as insurmountable.”
Ethical considerations for CHIs

Sufficient social value
Reasonable risk-benefit profile
Fair participant selection
Suitable site selection
Context-specific stakeholder engagement
Robust informed consent
Proportionate payment

Shah & Rid (Eds.) 2020, Shah SK et al. 2020, Shah SK. et al work in progress
Sufficient social value

- High risks and potential for controversy around SARS-CoV-2 CHIs require rigorous social value judgment (i.e., magnitude, distribution and likelihood of health benefits)
  - Contribution relative to other research
  - Coordination of stakeholders to use CHI data
  - Path from CHIs to health benefits
  - Access to proven interventions
Value of SARS-CoV-2 CHIs

- Social value mainly seen in potential to accelerate *vaccine development*
- Though could be valuable in other ways
  - Accelerate development of treatments
  - Learn about mechanisms of infection and disease that help guide clinical practice and health policy
  - Etc.
Faster vaccine development?

1) Replace vaccine efficacy testing (Eyal et al 2020)
   - Claim: can save millions of people if safe and effective vaccine is identified months earlier than using alternative research methods
Timing of CHIs

- Establishing a CHI model takes at least 4-12 months
  - Characterize potential challenge strains
  - Identify, isolate and culture suitable strain
  - Establish CHI model in animals and humans (e.g., identify appropriate dose)

- Phase 2/3 trials are faster to establish
  - Though transmission can be difficult to predict

Darton et al 2015
Limitations of CHI data

- Data from CHIs generally play a supportive role in regulatory approval
  - Data not generalizeable (e.g., SARS-CoV-2 CHIs involve young, healthy adults)
  - Safety data not robust due to small number of participants
- Perception that approval was rushed can fuel vaccine hesitancy
1) Replace vaccine efficacy testing (Eyal et al 2020)

2) Identify correlates of protection
   - Current correlates are not perfectly accurate (e.g., antibody titers) or complex and costly to measure (e.g., long-term immune response)
   - More accurate, simpler and cheaper correlates could accelerate development of vaccines that meet global need
Faster vaccine development?

1) Replace vaccine efficacy testing (Eyal et al 2020)
2) Identify correlates of protection
3) Select most promising vaccine candidates
   – 127 in clinical development, 194 in preclinical development (WHO 2021)
   – SARS-CoV-2 CHIs could catalyze development of vaccines that meet global need
Value of CHIs in pandemics

• In a global pandemic of an emerging infectious disease, research moves at “warp speed”
• Because CHIs take time to establish, their social value can be difficult to predict
Reasonable risk-benefit profile

- Identify risks and potential benefits (if any)
- Recognize important uncertainties, especially in CHIs on emerging infectious diseases (e.g., mild and moderate symptoms, long-term complications from SARS-CoV-2)
Risks to participants

• Risks to participants should be minimized and below upper limit
  – Enroll young, healthy participants (e.g., QCovid® risk calculator used in UK)
  – Monitor closely, provide prompt treatment & compensate for research-related injury
  – No consensus on upper risk limit, but could analogize to other research or altruistic activities
Risks to participants

- Young, healthy people at lowest risk, though uncertainties remain and available treatments are limited
  - 18-44 yrs: 0.03% risk of death, 1.1% risk of hospitalization (Verity et al 2020)
  - <20 yrs: 0.001% risk of death, 0.2% risk of hospitalization in females (Salje et al 2020)
  - CHI: 0.0025% risk of death, 0.022% risk of hospitalization (Mannheim et al 2021)
Acceptable level of risk?

- Risks slightly higher than in phase I trials, other CHIs and altruistic activities

Table S1. Comparison of mortality risks in altruistic activities and daily life.

<table>
<thead>
<tr>
<th>ACTIVITY</th>
<th>MORTALITY RISK</th>
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<tbody>
<tr>
<td><strong>CLINICAL RESEARCH</strong></td>
<td></td>
</tr>
<tr>
<td>Malaria CHIs with healthy individuals (18-50 years)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Influenza CHIs with healthy individuals (18-49 years)</td>
<td>0.0018%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phase 1 trials with healthy individuals (any age)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>&lt;0.014%</td>
</tr>
<tr>
<td>SARS-CoV-2 CHIs with healthy individuals (20-29 years&lt;sup&gt;4&lt;/sup&gt; and 20-44 years&lt;sup&gt;5&lt;/sup&gt;)</td>
<td>0.03-0.2%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phase I trials, typically with terminally ill cancer patients (≥18 years)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>LIVING ORGAN DONATION</strong></td>
<td></td>
</tr>
<tr>
<td>Kidney (≥18 years)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>&lt;0.03%</td>
</tr>
<tr>
<td>Liver (≥18 years)&lt;sup&gt;8 9&lt;/sup&gt;</td>
<td>0.1-0.5%</td>
</tr>
<tr>
<td><strong>DAILY LIFE</strong></td>
<td></td>
</tr>
<tr>
<td>Riskier car trip (any age)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>0.0002%</td>
</tr>
<tr>
<td>Influenza (&gt;65 years, 2018-2019)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.05%</td>
</tr>
<tr>
<td>SARS CoV-2 infection in healthcare workers (age not specified)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>0.67%</td>
</tr>
</tbody>
</table>

<sup>5</sup>Likely upper mortality risk estimates because the available data report aggregate outcomes for healthy individuals and individuals with pre-existing conditions.

Shah SK et al. 2020
Risks to third parties

- Risks to third parties not enrolled in the research should be low
  - Confine participants in research facility for as long as needed (>2 wks minimum)
  - Minimize risk of withdrawal with appropriate participant selection and robust informed consent process
  - Coordinate with public health authorities
Public engagement is key to avoid common misunderstandings about CHIs. Misunderstandings could foster distrust in clinical research and/or public health measures (e.g., vaccination) -- though it depends on context. Limited evidence to support either concerns or public acceptability of CHIs.
• Public distrust of SARS-CoV-2 vaccination
Take-aways

• CHIs are not ethically distinct from other types of research
• However, CHIs have a complex history and raise a unique constellation of unresolved ethical challenges
• CHIs can also be counterintuitive and might foster public controversy or distrust
Take-aways ctd.

- SARS-CoV-2 CHIs were rightly controversial, but they may have produced considerable value—stay tuned
- CHIs can be ethically acceptable and useful with careful review and planning, as well as understanding of their social value