THE ETHICS OF CONTROLLED HUMAN INFECTION MODEL STUDIES FOR MITIGATING PANDEMIC RISKS

AUTHORS: BRIDGET WILLIAMS, JOSH MORRISON, DOMINIC WILKINSON, JULIAN SAVULESCU

SUMMARY OF RECOMMENDATIONS

RECOMMENDATION 1 - ESTABLISH A CLEAR MECHANISM FOR DETERMINING WHEN A CHIM STUDY WITH A PPP IS IN THE PUBLIC INTEREST

1.1 Establish a process to determine when expected benefits ethically justify expected harms

1.2 Develop models to quantify benefits and risks of CHIM studies with PPPs

1.3 Identify example scenarios where CHIM research would be appropriate (and not appropriate) in an outbreak setting

1.4 Develop processes to understand and monitor public sentiment to CHIM research

1.5 Develop educational materials for policymakers and the public, including resources for the media

1.6 Establish a group who would be charged with making the determination of when a CHIM study during a public health emergency would be justified

RECOMMENDATION 2 - ESTABLISH PROCEDURES TO STREAMLINE ETHICS REVIEW OF CHIM STUDIES WITH PPPS

2.1 Maintain a standing Specialist REC for CHIM research in an outbreak

2.2 Adapt the HRA REC checklist to develop a special checklist for CHIM research with PPPs

2.3 Create template protocols for CHIM studies with PPPs

2.4 Develop informed consent procedures for CHIM research

2.5 Review the approach to compensation for high-risk research in the UK

2.6 Create a template communications plan for CHIM research in an outbreak

RECOMMENDATION 3 - DEVELOP AND MAINTAIN THE INFRASTRUCTURE AND EXPERTISE REQUIRED TO CONDUCT HIGH QUALITY CHIM STUDIES EFFICIENTLY

3.1 Produce a report on the expertise and facilities available to conduct CHIM research in the UK and globally

3.2 Conduct a roundtable discussion to discuss the role of CHIM research in development of medical countermeasures against PPPs

3.3 Review the procedures for manufacturing challenge agent and identify options for accelerating this process in an outbreak

3.4 Investigate the potential for conducting person-person transmission studies

3.5 Develop a roadmap to ensuring CHIM research capacity for pandemic preparedness

CHIM = CONTROLLED HUMAN INFECTION MODEL PPP = PATHOGEN WITH PANDEMIC POTENTIAL REC = RESEARCH ETHICS COMMITTEE

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RECOMMENDATIONS IN MORE DETAIL

Recommendation 1 - Establish a clear mechanism for determining when a CHIM study with a PPP is in the public interest

In our framework, determining when a CHIM study is in the public interest is a key question. It's a question that involves significant empirical uncertainty, especially in the setting of an outbreak of a novel pathogen, and normative uncertainty. It requires an estimation of the expected harms and benefits of conducting a CHIM study and an ethical judgement to be made on whether the expected benefits to the population justify the expected harms to participants. Having mechanisms in place ahead of time to make this decision would help to ensure that decision-making in an emergency is informed, well-reasoned, procedurally fair and efficient. Therefore, we make the following sub-recommendations, which we think will help achieve this aim.

Recommendation 1.1 – Establish a process to determine when expected benefits ethically justify expected harms

A key ethical question in CHIM research is when the expected benefits to society justify the expected harms to participants. We have presented one possible framework for determining when the expected harms to participants are justified by the expected population benefits of the research. However, given the importance of this criterion for ethical research, we recommend further work to develop an explicit, justifiable, reproducible approach to this question that is logically consistent, procedurally fair and informed by all relevant stakeholders. This should include ethicists, members of RECs, scientists, epidemiologists, public health specialists, policymakers and members of the public.

Recommendation 1.2 – Develop models to quantify benefits and risks of CHIM studies with PPPs

Making a judgement on whether a study is in the public interest requires an estimation of its expected benefits and harms. To provide this information, we suggest the development of computational models to assess the impacts of CHIM studies in different scenarios. These should be developed for different types of pathogens (e.g. airborne respiratory viruses, vector-borne viruses, etc.), and for studies in an outbreak scenario and in the inter-pandemic period.

Economic models should also be developed to allow for rapid estimation of the cost-effectiveness of conducting a CHIM study in different scenarios. This would require a costing exercise to systematically estimate the costs of conducting CHIM studies, which could be combined with an estimate of the study impacts to develop a cost-effectiveness estimate.

It would be important to recognize the limitations of these models and avoid putting too much weight on estimates that might seem highly precise but could be very inaccurate. It would also be important to include uncertainty in these models and ensure this was clearly communicated to decision-makers. This might call for results to be presented as confidence intervals rather than point estimates. However, despite their limitations, we believe that quantitative models can aid decision-making, especially when the alternative is to rely on intuitive judgments that might be poorly informed. Models can be helpful to clarify areas of uncertainty and elucidate the implicit assumptions driving intuitive judgements.

Recommendation 1.3 – Identify example scenarios where CHIM research would be appropriate in an outbreak setting

The models described in Recommendation 1.2 should then be used to identify scenarios where CHIM studies are likely to be in the public interest. Outbreak scenarios and scenarios in the interpandemic period should be considered. Details to include are pathogen and outbreak features, political and social factors, and mitigation measures, such as the availability of current vaccines, or the expected difficulty of developing an effective vaccine. Before conducting this research, careful thought should be given to the potential for malicious use of the results and steps taken to reduce this risk. After understanding the types of scenarios where CHIM studies may be useful, the likelihood of these scenarios occurring should be estimated.

Recommendation 1.4 – Develop processes to understand and monitor public sentiment to CHIM research

One of the key concerns raised about a CHIM study during the COVID-19 pandemic was the possible effect on public trust in vaccines and science. Being able to understand how public sentiment is changing in a dynamic situation like a pandemic would enable more informed estimates of the potential effect of a CHIM study on public trust. Understanding public sentiment may also be helpful for decision making. Although it ought not to play a deciding role in the decision of whether a study should go ahead, public sentiment should be one input into the decision.

This should build on existing structures to understand opinions of the UK public on health research, such as the NIHR Centre for Engagement and Dissemination. It may

also build on processes used by the team responsible for the SARS-CoV-2 CHIM study to understand public sentiment. These procedures should be able to be used to monitor changes in public sentiment over the course of an outbreak.

Recommendation 1.5 – Develop educational materials for policymakers and the public

To ensure that decision-making is informed and minimise the risks of impairing public trust, policymakers and the public should have an understanding of the nature of CHIM research. Educational materials should be developed to inform the public of the nature and history of challenge studies, and their potential benefits. This may include comparison of the risks with other altruistic activities, such as organ donation, firefighting and military service.

Recommendation 1.6 – Establish a group who would be charged with making the determination of when a CHIM study during a public health emergency

As outlined in Section 5, public health emergencies present special situations that call for changes to standard procedures. Due to the close involvement of research with government policies and the need for coordination across actors in this setting, we recommend that the determination of whether a CHIM study is in the public interest should be made by a group composed of representatives from relevant government agencies including the HRA, funders, ethicists, and scientists. This composition of this group and procedures for its conduct should be established ahead of time.

Recommendation 2 - Establish procedures to streamline ethics review of CHIM studies with PPPs

While the ethics review process for the SARS-CoV-2 CHIM studies did not delay the research, we think additional measures could be taken to reduce the risk of CHIM research with PPPs being unnecessarily delayed, or of being conducted unethically. Therefore, we make the following sub-recommendations to help to streamline the ethics review of CHIM studies with PPPs.

Recommendation 2.1 – Maintain a standing Specialist REC for CHIM research in an outbreak

For the approval of the SARS-CoV-2 CHIM studies a Specialist Ad-hoc REC was assembled to ensure thorough and timely ethics review of the studies. We recommend that this Specialist REC be maintained as a standing group to ensure the relevant expertise is available to review proposals for a CHIM study in an outbreak. The composition of the standing group may change over time, and members should receive additional training on considering CHIM studies and the ethical issues they raise. The group should include ethicists, infectious disease experts, epidemiologists and modellers.

Recommendation 2.2 – Adapt the HRA REC checklist to develop a special checklist for CHIM research with PPPs

The HRA has a checklist for RECs to use when reviewing research proposals. We recommend adapting this checklist for CHIM research with PPPs. This would include adding additional questions on the involvement of policymakers, funders and regulators in determining whether the study is in the public interest, as well as details on special consent procedures, communications with local health authorities and plan for rapid release of results.

Recommendation 2.3 – Create template protocols for CHIM studies with PPPs

Template protocols should include plans for deciding on sample size, statistical analysis, recruitment procedures, informed consent procedures, study procedures including inoculation, monitoring, treatment, follow-up, management of adverse events and participants wishing to withdraw from the study.

Recommendation 2.4 – Develop informed consent procedures for CHIM research

CHIM studies with PPPs are likely to involve greater amounts of uncertainty in risks and benefits than most other types of research studies. In some instances, they may also carry greater risks of death or serious injury. Therefore, there should be special procedures developed to ensure that the participants understand the risks they are volunteering to accept and the uncertainty in the risk estimates. This may include educational materials and a test for understanding, particularly for a quantitative understanding of risk and uncertainty.

Recommendation 2.5 – Review the approach to compensation for higher-risk research in the UK

Currently HRA recommends against including payment for risk in compensation for research participants. For reasons described above we believe that providing payment for risk is an important component of ensuring fairness in CHIM research. Therefore, we recommend the policy on compensation in research be reviewed.

A system of payment for CHIM research participation should be developed ahead of time. This should have an agreed upon approach to payment for study participation that includes the time, discomfort and pain

of study participation, payment for risk, and a system of compensation for harms that may occur as a result of the study. Appropriate rates of payment for risk could be informed by rates of hazard pay in other types of employment in the UK, including the military.

Qualitative research should be conducted with prospective CHIM study participants to ensure that the rate of payment is considered fair but not unduly coercive.

Recommendation 2.6 – Develop a template communications plan for CHIM research in an outbreak

A communications plan should be developed. This should include plans for communication with national and international policymakers, other members of the CHIM research community, the local public health authority responsible for a CHIM site, and members of the public, including through media releases and social media communications.

The communications plan should include plans for publishing study results and data accessibility. Although open access to data and study materials should generally be encouraged, thought should be given to potential misuse of data and publication plans should be adjusted to mitigate this risk if relevant.

Recommendation 3 - Develop and maintain the infrastructure and expertise required to conduct high quality CHIM studies efficiently

A key finding of our analysis was the importance of enabling CHIM research to happen efficiently in an outbreak. As we learned through COVID-19, in a rapidly spreading outbreak, delays can influence whether thousands of people die, and whether thousands of others lose their jobs or experience significant financial hardship. Therefore, there is important benefit from gaining information that could improve the pandemic response as quickly as possible.

Major factors influencing the speed with which a challenge study could be conducted were the speed with which sufficient amounts of challenge agent could be produced, the availability of appropriate facilities and expertise to conduct CHIM studies. Our discussions with experts also highlighted the role the CHIM studies could play in developing medical countermeasures for PPPs ahead of time, which would also help to maintain readiness in a pandemic. Therefore, we make the following sub-recommendations that aim to improve the speed at which a CHIM study could be conducted.

Recommendation 3.1 – Produce a report on the expertise and facilities available to conduct CHIM research in the UK and globally and the feasibility of maintaining this capacity

The report should include information on the investment needed to conduct CHIM studies and the feasibility of sustaining the necessary investment. This should include the investment required to maintain readiness to conduct urgent CHIM studies upon detection of an outbreak with pandemic potential.

The report should include an analysis of the current CHIM research capacities in the UK and the impacts of increasing CHIM research on the research and clinical workforce. It should also include analysis of the requirements for manufacturing challenge strain and the impacts of diverting laboratory resources to this task during a major infectious disease outbreak.

Recommendation 3.2 – Conduct a roundtable discussion to discuss the role of CHIM research in development of medical countermeasures against PPPs prior to another pandemic

Several groups have highlighted the potential role of developing vaccines for prototype pathogens in reducing pandemic risk. The speed with which the COVID-19 vaccine was developed was partly due to previous research aimed at developing vaccines for the coronaviruses responsible for MERS and SARS-1.

We recommend a roundtable discussion be held with key figures in the efforts to develop such prototype pathogens to discuss the role that CHIM research in the UK could play in these efforts. This should include scientists leading relevant research, CEPI and the WHO, as well as representatives from the UKgovernment and major research funders.

Recommendation 3.3 – Review the procedures for manufacturing challenge agent and identify options for accelerating this process in an outbreak

Our analysis highlighted that the development of sufficient stock of challenge agent is one of the key determinants of how quickly a CHIM study could be conducted, and a key limit on the value of studies.

Procedures should be developed to ensure that challenge agent manufacture can begin as soon as there is an indication of an outbreak with a PPP or novel agent that may have pandemic potential. This should occur immediately and before any decision has been made on whether a CHIM study would be helpful. Options for speeding up the production of challenge agents should be

explored, including the use of reverse genetics or synthetic biology. These options should be reviewed by biosecurity experts to assess their dual-use potential.

Consideration should also be given to when, if ever, it might be appropriate to use a challenge agent that is not developed to GMP standards. It seems plausible that this would be appropriate in some circumstances, e.g. where the agent posed an urgent and significant threat to large numbers of people.

Recommendation 3.4 – Develop a roadmap to ensuring CHIM research capacity for pandemic preparedness

A plan should be developed to ensure that capacity is developed to conduct research to a high standard and in a timely manner in the inter-pandemic period and at the onset of an outbreak with pandemic potential. A roadmap with necessary steps and timelines should be developed. This should integrate with existing pandemic preparedness plans.

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