Using Challenge Trials in Public Health Emergencies: A Roundtable Discussion
11 April 2024

Agenda

- Jake Eberts introduces 1Day and the purpose of this discussion
  - Looking for live feedback on WHO document — discussion here does not represent views of the WHO or anyone’s employer or associated institution
  - Prioritizing fluid discussion and open exchange of ideas
  - Following Chatham House Rule
  - We’ll distribute anonymous notes and summary
- Grateful to have WHO working group representatives, but this is not an official WHO event

- Presenter reviews what the working group has put together and highlights document considerations
- Open discussion

Discussion

Question One

The guidelines note that CHIS may be justified in cases where they could “provide other types of scientific knowledge relevant to public health responses.” — what are some concrete examples of information that might fit into this category?

Person 1: One of the things I liked the most about the guidelines - the discussion about the role of CHIS outside of pure vaccine development. When we embarked on Covid CHIS, the focus was initially on vaccine development (funded by the UK Vaccine Task Force). When the first vaccine was approved, there was a period where we didn’t know what we were going to do. We’re convinced the data generated played a role in shaping PH decision-making about how to get out of the pandemic - de-isolation, rational testing strategies to allow people to come out of self isolation, etc. This was not something we crystallized in our thoughts at the beginning and I see a lot of additional potential values here.

Questions: What would have happened if the first vaccines hadn’t been as successful as they were? People forget how skeptical many people were about when the first gen would be more than moderately effective.

Person 2: Risk reduction. If first gen hadn’t been very effective, having a CHIM to downselect a wider range of candidates would be the value proposition there

Person 3: Report doesn’t have to block… establish a set of circumscribed uses. Could list many uses. Nothing we need to legislate today
Person 4: how much consideration given to eventuality a pandemic may be more severe and lethal in the future? If H5N1 mutated and became H2H transmissible? Or a coronavirus with a 14% mortality?

Presenter: We’re not setting up limits to risks, just asking people to think about them systematically

Moderator: On non-vaccine uses, when we wrote previous documents, we didn’t foresee the importance of accurate testing for PH measures, and how CHIS would help explore that. We’ve tried not to be exhaustive about CHIS implications

Person 5: This is a great document. Exploring the concept of risk benefit - part of it is how rapidly you can establish a model. Benefits greater potentially if established earlier.

Person 5: Something that limited our speed of establishment was time for GMP manufacture - right now it takes 6 months to manufacture a virus. The decision to press go and manufacture to GMP took a while to get to because of risk concerns. Should there be a pandemic, if we can accept the financial risk that we manufacture a virus to GMP (at financial risk) while feasibility, ethical, acceptable discussions happen in parallel - if you got to an answer of yes, you’d have a virus quite quickly.

Presenter: The other thing that happens overtime is that uncertainty about the risk will change.

Person 6: Thank you, I also enjoyed the document. Agree with others on the need to strategize. Guidelines mention how long it takes to set up a CHIS. Clinical trial approvals are seen as a one time application, not an iterative process. In Covid, it was a reiterative process. If we’d waited until everything was clear, we’d miss out on the iterative process with the ethics committee. There may be a pause as you wait for info to make sure of itself. The document could more strongly emphasize that reiterative process and the importance of starting immediately/working in parallel. It may be appropriate to stop.

Person 7: On speed - doing things more quickly even if there is more risk is something that participants may prefer. Oxford studies were more than 1.5 years after Covid took off. I know I as a participant would have preferred to start earlier to make more of an impact.

Person 2: We’ve had numerous discussions with former trial participants. I get the sense from a recent small group discussion - as the people who take on the risks, timing is morally relevant for us. We undertake the risk with trust in medical institutions and researchers that those risks are not in vain and used for maximum benefit. Many of us strongly believe it’s possible to increase marginal risk if there’s a compelling reason to do so to make the risk worth it.

Person 8: In many ways, the issues we see are no different from other studies, including peacetime CHIS. One thing raised is the issue of agent manufacture. The question of timelines is also an ethical question. Only major
obstacle to progression is the one you have on the table: assessment of risk, which will be an issue next time as well.

This document hasn’t addressed how to assess risk, we don’t have a framework for that. We have to have things like war gaming done on the ethics side. Have given lots of advice to the government over the past two years on pandemic preparedness. Governments are focused on the next Covid pandemic. We have to war game the different scenarios. Mortality of 40% would mean a huge benefit for challenge studies - risk benefit is probably favorable. If you’ve done the other work, you could make an argument. But we haven’t war-gamed it ethically. (not just a CHIM question: Have to say to regulators, if there’s 25% mortality, are you going to spend a year doing an RCT vs observational.) Even if we thought that it was ethically acceptable, institutions are then taking the risk of sponsoring the studies, which is a really difficult sell. Others on this call are aware of how hard it is to get institutions to take on the risk.

Person 9: One question for people involved in Covid CHIS: what did you see as the barriers to sending info, publishing the protocol. Beyond sharing with the UK government, sharing took longer. What can we learn?

Person 1: If I boil it down, the problem was we were working with the government. They work the way they work and we had to work in that way. That’s all I can say.

Person 10: Let’s use the term scenario development rather than war games. The next document WHO is planning to produce is the move to do CHIS in the inter-pandemic period on PPP. As they look to produce that guidance - we’ll take longer and look at the families and types of pathogens and where you may or may not be able to do a pathogen. Plan for the ethics and the regulatory questions (how to include the evidence from the challenge studies). That’s the next step. I think that will influence (not fundamentally change this guidance). The last but maybe the most important part of the suite - we will come back to the people on this call.

Person 11: What was said earlier about institutional hesitancy and risk is important. I disagree that any institution would allow for a challenge with a 40% mortality rate (publicity alone). Ours is especially risk averse because of previous history. There’s institutional and public perception limitations. I will say this is a nice document, public perception and engagement is incredibly important and needs to be taken into account. Need to make sure a bad CHIS outcome doesn’t detail other critical pandemic research.

Person 3: Regarding the 40% case, Robert Steel is working on this. Depends on transmissibility, quality of informed consent. Should we create a subgroup to discuss this specifically?

Person 12: On the idea of ethics war gaming: the devil is in the details. Two almost identical studies can have very different decisions based on something not immediately obvious. You can try to produce ever more guidance, but in my experience, too much guidance for ethics committees leads to the next study coming along breaking that guidance. UK CHIS ethics committee: we talked about the general ideas around CHIS, put it together with
those who had previously looked at CHIS, and the committee was ready to have that discussion. Can more be put in the doc about expert review - we don’t have to try to predict everything through wargames, just have experts who are primed for whatever comes through the door.

Person 13: Even if you think high risk challenge studies could be ethically justified in certain situations, we have to think carefully about institutions and public trust. One note on that: it’s important to contextualize trust as broader and affected by many things. Report recommends trials be reviewed by an international committee but seems like national policies have often tremendously larger effects on these things that are not internationally reviewed, like the decision to close/unclose schools, to pause Astrazeneca vaccines. Worry about overinflating the role of trials in impacting public trust during a pandemic.

**Question Two**

Much of the benefit of CHIS depends on their relative speed and efficacy compared to more traditional trials. With that in mind, should this document touch more on what needs to be done today? What sort of things can be done?

Person 5: The length of time it takes to release a GMP virus. Can do manufacturing process development to learn how to expedite the GMP process. Would cost a lot of money but would put us in a much better position going forward.

Person 6: agree with Person 5, we can’t start without funding, as well as underwriting and insurance. There’s probably a governmental response: the decision of who funds, who covers the responsibility to protect researchers isn’t in place right now.

Person 2: Who would need to be some of the actors and institutions involved?

Person 1: There’s a window of opportunity where there is a lot of experience in recent memory of doing this work. We need certain commitments from the government now to undertake these activities, especially related to manufacture and core protocols. (I’m not convinced about core protocols, it would be very bare bones and probably not worth it) I would hope we can develop some pieces of work where there will be concrete outputs and commitments to pivot to start the process early

Person 2: I understand you’re looking at musical immunity through a consortium with CEPI?

Person 1: CEPI has been forward looking, has funded a large international consortium to build capacity to develop optimization processes for GMP manufacturing, to try to increase the speed of agent production, and to increase global capacity for high containment clinical studies. But focusing on coronaviruses, can’t address all the aspects we’re talking about today. Can’t be the only activity in the next five years.
Person 14: Something as a volunteer that I would make a critical issue is that there are a lot of chronicl binds that happened as I progressed toward the idea of a COVID CHIS. Points of restriction that keep the trials locked in place. Cannot overemphasize as a prospective volunteer how frustrating that can be. I take issue with that as time when there is not a consideration for the volunteers who put their time in. Sometimes it does feel as though we are concerning ourselves with things that are going to happen during times of emergencies. This doc puts in place protocols, ideas, suggestions that would be great in peacetime, that would expedite the process. To have agencies discuss these and look at these and prepare before we need them would be invaluable to the people volunteering their bodies. Want to stress the idea that it’s important to me that some of the nuance is understood and regarded and buried through while we are not in times of critical need.

Person 13: So far the discussion has focused on expediting on the funder/science side. Not sure if this belongs in the report, and it’s already being done by 1Day who’s so lovely, but having a highly educated engaged patient cohort who understands methodologies and can credibly claim they know what’s going on, this is of value to me. I’m behind this research, it may be valuable in expediting things and addressing concerns about exploitation. The maintenance of cohorts like that on the participant side can be useful prior groundwork

Person 12: I chair a [relevant scientific] committee, much easier when it’s a study that relies on people who have been pre-recruited. Evidence of engagement with the company, they know what a Phase 1 is, experience, familiarity with the unit. Reassures us that the people volunteering are a good way along in the process even before the study comes along. I understand that’s what 1Day is busy trying to do.

Person 2: This is something we try to do and is very difficult. This segues well into another question on the agenda: to what degree does “professed” altruism play a role in how we assess the balance of risk. There’s the benchmark of kidney donation, which has a significant risk but is widely celebrated. Curious about that thought - if there’s an altruistic and educated cohort, does that change how we approach documents like this? Or assume a median level of understanding?

**Question Three**

To what degree does altruism on the part of prospective participants play a role in how we assess balances of risk? In public health emergencies, the case of COVID showed that there was indeed a sizable contingent of people willing to consider partaking in a human challenge study on purely altruistic grounds. Should the benchmark for risk be more concrete, such as comparison to kidney donation?

Person 12: That’s interesting. One can probably draw parallels to other roles in society with high risk - military, firefighter, police officer, etc. We see participation in research as a different thing from a high risk profession. Should we accept different roles in societies that have a very high level of risk?

Person 13: It can defeat the thought that they’re confused by learning that they’re effective altruists. It’s controversial in research ethics and documents like this shouldn’t put in a limit. One can make various analogies,
ie. being an astronaut. No clear arguments for why one is better than another. Would want a consensus in the ethics community before it went into a document.

Person 12: The benefits of being a firefighter: you potentially rescue people. Wonder if CHIS have an advantage - you can quantify the benefits more effectively than in other types of research. Need to show people the concrete benefits from this type of study. We have to address research waste before asking people to participate in risky studies.

Person 8: Phase 1 is in some ways less foreseeable than CHIS

Person 3: Liver donation is more risky. We know kidney donation is somewhere below the threshold, but we don’t indicate where the threshold is. Difference: specific individual benefit vs inchoate, possibly far greater number of people.

**Next Steps**

**What do people want to see on the agenda?**

Person 6: On the question of whether something is only ethical if you can quantify the risk: CHIS expedites drug or vaccine development, but we have no agreement from regulators that it does expedite. Regulators refuse to give firm commitments on that. Need conversations to understand where they can be used - emergency licensure, pre-authorization - then we can quantify the defined benefit.

Person 14:

1. Looking into , for families that have been identified as highest risk of pandemics in the future, how to tailor guidelines. We’re hoping to do some writing this year, at 1Day, hoping to reach out to folks for their expertise.
2. If we were to conduct pandemic CHIS, what role do regulators play and how would the data be used - hoping to host a 2025 workshop that explores this question in more details

Person : At the Swiss conference last year, I was struck talking to people from other countries about the unique bits of the UK system that enabled us to do it - because of how our system evolved. Worth reflecting on.

Person 15: What I would see here in [Southern African country] is a call discussion with potential participants as well as regulators as we think around how we’d be able to do this. Conversation on disease agnostic approach - may need to think around some level of categorization because of clinical presentation and the risk. Cultural specific conversations may raise risks defined by cultures. For the next meeting, it would be important to be coordinating with regulators, even if it’s a war game. To accelerate running on a trial for an epidemic or any pandemic pathogens.
Person 10: It would be interesting to try to extrapolate what’s unique to CHIS. What are research systemic issues that affect how you do a CHIM - investment, infrastructure, oversight, trust. Commitment in chat about the UK: only place you could have done a challenge study. Becomes a political issue.

Give you the challenge as a community to think through the things that you can influence or work on that are specific to CHIS. It’s my job to work on the systemic ethics and regulatory issues.

We did a piece on adaptive platform trials. Some of the most were the ones that already existed, had partnerships preexisting. Soft skills that we undervalue - relationships of trust. Conversations between researchers and potential participants are really important to build the network, to be able to pivot. A case to make to funders, having the infrastructure in place.