Chapter 6
Conclusions

6.1 Lessons Learned to Date

Perhaps the most significant lesson learned in LMIC HCS to date is that HCS can be conducted safely and to a high scientific standard in LMICs where pathogens such as malaria, cholera, and *Shigella* are primarily endemic. As one stakeholder in Africa noted:

> I think [an important] lesson people have learned is that [although] a number of the partners from the [global] North were very skeptical that this could be done in Africa, now it has been proven that it can be done in endemic countries and it can work well. It's a good way to see that possibly we can start having the whole development process start fairly early in the region and possibly moving this forward. And I think, for me, the feeling is that, we need to sustain doing this so the competency further develops and then we move to the next level and also start getting involved in the entire process of vaccine and even drug development, using the same platform. [Scientist, Africa]

Conducting such research in endemic settings enables HCS that address basic science research questions that would be difficult or impossible to address in non-endemic HICs (e.g., the pathogenesis of infection in partially immune individuals) and the testing of new interventions in a study population from which the results may be more generalisable to the eventual target population for an intervention, with 3 vaccine trial HCS already conducted in LMICs. Furthermore, preparing LMIC institutions to conduct HCS (often in collaboration with HIC institutions) can help to build capacity for infectious disease research and the ethical review of complex HCS designs. As more LMIC institutions are able to conduct HCS for pathogens that are primarily endemic in LMICs, it may arguably become appropriate to prioritise such HCS in LMICs over those in HICs—at least where doing so would improve the generalisability of results and thus facilitate realisation of the ultimate goal of reducing infectious disease burdens in endemic settings.

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Many of the unresolved ethical and regulatory issues are common to both LMICs and HICs (see Sect. 6.3), but the particular implications thereof may vary at a local or national level. For example, the optimum models of ethical review of HCS and regulatory review of challenge strains are yet to be determined and may need to be adapted to different settings. However, there are generally much greater funding and capacity constraints for scientific institutions, regulatory bodies and ethics committees in LMICs as compared with HICs, and these should be addressed to assure the quality of HCS conducted in such settings. The success of the studies above has been partly attributed to significant capacity building efforts (Hodgson et al. 2015).

In terms of the burdens of research, HCS in endemic populations with innate or acquired immunity to the challenge pathogen often entail (on average) less risks for participants than those in non-endemic populations with low prevalence (or absence) of such protective factors. Some other burdens of participation were increased in certain settings: for example, relatively long periods of inpatient isolation have been used in endemic settings because of weak local infrastructure that might mean that risks to participants and/or third parties would be unacceptably high with outpatient designs. On the other hand, outpatient HCS were successfully conducted in Colombia (in a non-endemic area) as well as in Tanzania and Gabon (in endemic areas). While the latter involved a (perhaps very low) probability of transmission of malaria to third parties, it is contentious whether such small increases in high (endemic) background risk are of public health importance and/or ethically problematic.

Involving social scientists and community engagement workers in LMIC HCS has been a successful strategy in terms of informing and learning from volunteers and the local community. Such work has generated rich additional data regarding controversial questions (such as whether to recruit by education level and how individuals respond to payment for HCS participation) that will help to inform future HCS design (Njue et al. 2014, 2018). Further (ethical and scientific) improvement of LMIC HCS is particularly important given that such studies constitute unique opportunities for improving scientific knowledge regarding, and developing new interventions to reduce the burden of, neglected diseases primarily endemic in LMICs. Researchers, ethics review committees, and regulators should arguably continue to pay careful attention to HCS design in particular contexts since the success of LMIC HCS partly depends on community acceptance of such research designs, which in turn depends on an acceptable level of burdens for participants (and third parties) and a thorough and transparent review process.

6.2 Points of Consensus

Based on a review of relevant literature and interviews with stakeholders with expertise in LMIC HCS, there is widespread consensus that LMIC HCS can be ethically acceptable if they have a sound scientific rationale and burdens to participants (and third parties) are minimised (although the appropriate weightings

of particular burdens and the optimum strategies for minimising them may be contentious). While the majority of the stakeholders we interviewed were actively involved in LMIC HCS, scientists and ethicists not involved in such studies also agreed that they could be ethically acceptable—i.e., that infecting research participants with pathogens is sometimes justifiable, including where such participants are recruited from LMIC populations. Where a research question with particularly important implications for public health can only be feasibly (and/or efficiently) addressed by HCS that recruits from an LMIC population, there may be particularly strong ethical grounds for LMIC HCS. In addition, capacity building associated with HCS may lead to other benefits, including improvements in local scientific research and ethical review.

Nevertheless, there was widespread agreement that HCS can be particularly burdensome for participants, and that they sometimes involve risks to third parties. Given the burdens to participants, the need for particularly stringent informed consent processes (e.g., involving tests of understanding) is widely recognised, and such processes are already established practice in LMIC HCS. Likewise, payment of HCS participants is widely accepted; even stakeholders from Latin America, where payment is not the norm, did not think that payment was unacceptable. However, the appropriate model of payment remains contentious, and may vary in different cultural and economic settings. Given the potential for the imposition of excessive burdens (including third-party risk in particular) to undermine public trust, the need to gauge and maintain public acceptance of HCS designs is widely seen as an important reason for robust community engagement and/or social science research to occur in parallel with LMIC HCS.

There was also consensus that HCS researchers must not only be scientifically well informed, but also exceptionally careful in the conduct of HCS, particularly regarding the safety of participants. As one interviewee noted:

> No matter how careful we are in our regulations or ethical frameworks, ultimately conducting a human challenge study in the right way will come down to a conscientious, compassionate, careful investigator … perhaps even more fundamentally than other types of research because there's such an intensive component of involvement between the researcher and the subjects, because there is this fact that the researcher is intentionally infecting people. [Ethicist, North America]

6.3 Controversies and Unresolved Issues

Our review and qualitative interviews also identified a number of controversial and/or unresolved issues in need of further empirical data and/or ethical analysis. Broadly, these relate to (i) burdens and benefits, (ii) participant selection and payment, and (iii) issues of governance.

6.3.1 Burdens and Benefits

Regarding the burdens and benefits of (LMIC) HCS, further work will be needed to (i) explore how requirements to share the benefits of research should apply to LMIC HCS (e.g., those that explore the natural history of disease and thus lead to few near-term benefits as compared with those testing a new intervention), (ii) clarify what, if any, should be considered the upper limit of risk (and/or other burdens) to which HCS participants should be exposed, (ii) determine whether a small probability of irreversible or long-term harm is an acceptable risk of HCS participation and/or how such risks should be weighed against benefits, (iii) determine how small third-party risks should be weighted in the context of background risks of infection in the community (e.g., in endemic settings), (iv) clarify the degree to which limits to risk (including third-party risk) should depend on implications for community trust and/or acceptance, (v) determine the conditions under which exposing HIC populations to the burdens of HCS with pathogens endemic only in LMICs can be ethically justified. In addition, the design and review of HCS (in LMICs and elsewhere) could be improved by more systematic risk-benefit assessment, including comparisons to alternative study designs (e.g., field trials). Such risk-benefit assessments would ideally include methods for (i) assessing controversial issues (such as those listed above), (ii) dealing with situations of uncertainty (e.g., first-in-human HCS), and (iii) making ethically acceptable trade-offs between risks to participants and public health benefits (e.g., using low risk strains in HCS might reduce risks to participants but also compromise generalisability to wild-type infection).

6.3.2 Participant Selection and Payment

Current controversies regarding participant selection and payment surround questions related to (i) the appropriate models of payment for highly burdensome HCS in different settings, (ii) whether, or when, less educated individuals should be excluded from HCS, (iii) the generalisability of adult HCS results to children (e.g., under what conditions, if any, would HCS in HIC adults be more generalisable to at-risk children in LMICs than HCS in LMIC adults?), and (iv) the conditions under which, if any, it would be acceptable to involve children in HCS. One area of consensus related to (iv) was that significant community engagement should be conducted and/or international consensus should be sought before the further planning of HCS in children.

6.3.3 Governance

The ideal model(s) of ethical and regulatory governance of HCS are yet to be determined. In particular, further work is needed to clarify (i) the appropriate model of regulatory governance of challenge strains (including in LMICs) and whether this can be standardised (to a greater degree) at an international level, (ii) the role(s) of HCS in regulatory pathways for the development of new interventions, (iii) the conditions under which HCS protocols should be reviewed by standard ethics committees and/or specialised committees, (iv) the (potential) need for a specialised ethical framework and/or principles/guidelines for HCS in general and/or HCS in LMICs—and the specific content thereof.

6.4 Future Directions

Challenge studies are a growing area of research that has the potential to advance science and lead to improvements in public health, especially in LMICs. They involve ethically sensitive research practices, however, and raise numerous controversial issues. Further work is needed by biological scientists, social scientists, community engagement experts, and bioethicists in order to establish norms of best practice for HCS that ensure the safety of participants and promote public trust and acceptance of this type of research so that its potential benefits can be realised in the long term. Further research and/or related activities regarding ethical and regulatory issues related to (LMIC) HCS could include (i) more detailed analyses of the controversial and/or unresolved issues identified in this report, (ii) broader surveys of other stakeholders (including HCS participants and members of the general public as well as policymakers in different settings), (iii) workshops with policymakers and regulatory representatives (including in endemic regions), (iv) multidisciplinary collaborations regarding HCS study design, (v) the development and refinement of risk-benefit assessment tools to compare HCS designs with one another and compare HCS with alternative designs from both ethical and scientific points of view, (vi) further research capacity building in LMICs (including the strengthening of existing ethics review mechanisms for HCS), (vii) a more extensive review of international regulatory requirements and laws regarding intentional infection, (viii) education and awareness-raising regarding HCS (including their scientific importance, ethical issues, and sharing of insights from past HCS) with stakeholders at institutions where future HCS are being considered or might be appropriate or called for, and more general public community engagement.

References

Hodgson, S.H., E. Juma, A. Salim, C. Magiri, D. Njenga, S. Molyneux, P. Njuguna, K. Awuondo, B. Lowe, and P.F. Billingsley. 2015. Lessons learnt from the first controlled human malaria infection study conducted in Nairobi, Kenya. *Malaria Journal* 14 (1): 182.

Njue, M., F. Kombe, S. Mwalukore, S. Molyneux, and V. Marsh. 2014. What are fair study benefits in international health research? Consulting community members in Kenya. *PLoS ONE* 9 (12): e113112.

Njue, M., P. Njuguna, M.C. Kapulu, G. Sanga, P. Bejon, V. Marsh, S. Molyneux, and D. Kamuya. 2018. 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. *Wellcome Open Research* 3.

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