Chapter 3
Ethical Issues

3.1 Intentional Infection

For members of the public, and perhaps many scientists and ethicists, who may be surprised to learn that HCS involving intentional infection (still) take place, the first ethical question may be whether intentionally infecting healthy volunteers as part of research is ever acceptable (Lynch 2012; Evers et al. 2015). Intuitions that such research practices should not be permitted may rest on presumptions that intentional infection with pathogens would involve unacceptably high levels of risk (see Sect. 3.3.1) and/or that physicians should be curing diseases rather causing them to occur among research participants (i.e., that intentionally causing disease is a moral wrong over and above the risks involved) (Hope and McMillan 2004). In an early paper on ethical aspects of HCS, Hope and McMillan provide an extensive philosophical analysis (summarised in the following paragraphs) of the question of whether intentional infection of participants is worse, morally speaking, than imposing other kinds of risks on participants (Hope and McMillan 2004).

Acts resulting in harm are often viewed as less morally acceptable where the harm was intended, rather than merely foreseen. To explore the application of the distinction between intended and foreseen harms to HCS, Hope and McMillan compare infecting a research participant (with a potentially harmful disease) with performing a lumbar puncture on a participant (with the aim of testing the person's cerebrospinal fluid, or CSF) which might generally be considered an acceptable part of research involving human participants. Supposing that both acts might lead to similar risks and/or harms (a lumbar puncture can cause a severe headache, for example, as can many infectious diseases), one might think that only in the HCS case is the harm intended—in the lumbar puncture case, the small probability of severe side-effects might be considered foreseen, but not intended.

There are several possible ways of drawing distinctions between intended and foreseen harms. First, one might argue that foreseen harms are those that occur when the ultimate aim of an act is to bring about a beneficial outcome but there is no (other) way of bringing about this beneficial outcome without bringing about the harm in

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question. This way of drawing the distinction might assume that in such cases the (only) *intent* is to produce a good outcome, and any harm that occurs is a *foreseeable but unintended* side-effect. For example, in the lumbar puncture case, there is usually no less harmful way to test research participants' CSF other than by performing a lumbar puncture (i.e. puncturing the lining of the spinal cord with a needle, which itself leads to the risk of side-effects). However, Hope and McMillan note that on this way of drawing the distinction, the harms associated with HCS could also be considered 'merely' foreseen:

> [I]f there were less harmful means of bringing about the testing of the putative vaccine they would be adopted: the risk of harm resulting from infecting the research participants is foreseen but not intended. (Hope and McMillan 2004)

Hope and McMillan further argue that the view that the moral acceptability of an action depends on whether any resulting harms are intended versus (merely) foreseen, where the intention/foresight distinction is drawn in this way, ultimately fails because this would lead to counterintuitive judgements in other scenarios. For example, this view would suggest that it would be acceptable to kill one innocent person if this were the only way of saving more than one other person.

On a second way of drawing the distinction between intended and foreseen harms, one might argue that harms are merely foreseeable when an act that causes a harm in the process of causing a beneficial outcome is more closely causally related to producing the good outcome than it is to producing the harm (Hope and McMillan cite Frances Kamm as articulating a similar idea with her "Principle of Permissible Harm" (Kamm 1989)). However, even if it were the case that this distinction identified an ethically salient difference,[1] it is not clear that the causal connections between intentional infection and harm are any closer than those between a lumbar puncture and the harms of a known side-effect of such a procedure (Hope and McMillan 2004).

Ultimately, Hope and McMillan conclude that such distinctions fail to support ethically relevant differences between the harms of challenge infections and other kinds of harms imposed on healthy volunteers in the pursuit of socially valuable research. Thus, the intentional infection of participants involved in (carefully conducted) HCS can, under certain conditions, be ethically acceptable. The authors note that modern HCS researchers typically take great care to minimise risks to participants (e.g. through the choice of challenge strain and close monitoring, early diagnosis, and treatment of participants). If the risks of HCS are thus within acceptable limits (i.e. such risks fall within widely accepted limits to research risks), and arguments regarding the unacceptability of intentional infection (as compared with other types of research risks) ultimately do not succeed, then there is no *prima facie* reason to rule out the ethical acceptability of intentional infection as a research practice.

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[1] Hope and McMillan note that intuitions regarding the ethical salience of such 'causal intimacy' might actually arise because of the *probability* of certain harms and benefits arising from an act (since close causal relations between an act and particular consequences are often correlated with a higher probability of those consequences occurring), rather than any other meaningful difference in causation.

Moreover, in the limited ethics literature on HCS to date, there appears to be a consensus that intentional infection per se (and the risk associated with it, once appropriately minimised) can be permissible so long as certain ethical conditions are met (Miller and Grady 2001; Hope and McMillan 2004; Pollard et al. 2012; Bambery et al. 2015; Shah et al. 2017; Selgelid and Jamrozik 2018). As one ethicist from North America noted during an interview for the current project, HCS are not the only kind of research that involve risks to participants without the prospect of benefit:

> There are these arguments [that challenge studies are] contrary to physicians' obligations, [that] *primum non nocere* [the ethical principle that doctors should first do no harm] rules it out and so on. I don't buy those arguments. I think that would rule out most of all research. Research puts people at risk, in part, for the benefit of others.

HCS are nonetheless ethically sensitive and raise important questions, some of which are similar to issues in other areas of research although there may be specific implications of such questions for HCS in particular. Such questions (discussed in the following sections) include those regarding (i) the kinds and level of benefits that would justify exposing healthy volunteers to risk, (ii) how the eventual benefits of HCS should be shared with participants and relevant communities, (iii) the acceptable limit of burdens (including risks) to which healthy volunteers may acceptably be exposed, (iv) the need for protection of third-parties from infection (by participants), (v) fair participant selection/exclusion, especially when considering recruitment or exclusion of vulnerable individuals, (vi) appropriate financial payment of participants, (vii) the potential need for special ethical principles/guidelines/frameworks and/or review procedures (e.g. special committees), (viii) appropriate selection, development, and regulation of challenge strains, (ix) the role(s) of HCS in the licensure of new interventions (e.g., vaccines), and (x) the need for community engagement to raise awareness of challenge studies and ensure that such studies are publicly acceptable to the communities in which they take place.

3.2 Benefits

3.2.1 Scientific Rationale and Social Value

There is a general consensus in research ethics that although research participants may be exposed to risk without the prospect of individual benefit, such risks are only justified to the extent that the study is designed according to a valid scientific rationale that is plausibly expected to lead to significant social value (over and above other study designs involving less risk to human volunteers) (Wikler 2017). The social value of HCS research might include improved scientific knowledge and/or public health benefits, with a key example of the latter being the (accelerated) development of new interventions that reduce the harms caused by the infectious disease being

studied (Savulescu 1998; Miller and Grady 2001; Hope and McMillan 2004; Pollard et al. 2012; Bambery et al. 2015).

Thus, where HCS involve particularly significant burdens (e.g., risks to participants and third parties), they arguably require a particularly strong scientific rationale. *Inter alia*, proposed HCS should be compared with other study designs to (insofar as possible) ensure that similar benefits cannot be achieved with research involving fewer burdens. Alternative study designs could include (i) animal models[2]—thus the rationale for HCS might be stronger in cases where the pathogen in question only infects humans and/or (ii) studies of natural history or novel treatments in patients diagnosed as having been naturally infected with the pathogen in question (although natural history studies might sometimes involve withholding proven effective treatment, to which patients might not consent, or which might be ethically problematic for other reasons), and/or (iii) field trials (e.g., where large numbers of individuals are given an investigational vaccine or placebo (or an existing vaccine) and followed until a sufficient number of each group are exposed to the infection in question to make accurate estimates of vaccine efficacy).

With respect to testing interventions, field trials are arguably the most important comparator for HCS designs. Compared to field trials, HCS may often be shorter, less costly, and involve fewer participants—thus allowing a more efficient 'selection' of potentially effective interventions which could (if this results in faster development, licensure, and implementation of such interventions) lead to public health benefits being achieved sooner (Sauerwein et al. 2011; Roestenberg et al. 2018b, c) (see also Sect. 4.3.3). Where this is the case, there may thus be a strong ethical rationale to pursue challenge studies as part of vaccine development.

Furthermore, other things being equal, there may be a stronger scientific and/or ethical rationale to conduct challenge studies where (i) field studies are impractical (e.g., where a pathogen is often asymptomatic and/or currently causes few cases but is likely to cause sporadic epidemics in future (Shah et al. 2017)) and/or (ii) immune correlates of protection are unknown (since, if it is already known that a certain measurable immune response to a vaccine is correlated with a certain level of clinical protection, then there would be arguably be less rationale for infecting participants in order to measure vaccine efficacy), and/or (iii) there is a clear pathway from HCS to licensure (discussed later in Sect. 4.3) (Chattopadhyay and Pratt 2017).

Thus far, the advantages of challenge studies in terms of reduced time and reduced costs (etc.) have rarely been quantified. However, there are clearly quantifiable advantages in terms of the number of participants—challenge studies typically enroll less than 100 participants (see the Case Studies reviewed in Chap. 5. of this report) or sometimes up to a few hundred, whereas field trials of vaccines typically enroll thousands (or sometimes many tens of thousands) of participants. To take one comparison, the recent HCS that supported WHO pre-approval of a new typhoid vaccine challenged 103 participants with typhoid (Jin et al. 2017), whereas previous field trials of other typhoid vaccines have

[2] Animal models, including animal challenge studies (perhaps especially in non-human primates), may raise ethical issues of their own, although these are not the focus of this report.

involved between tens of thousands and up to around 100,000 participants (Wahdan et al. 1980; Levine et al. 1987). On the other hand, although vaccine field trials involve risks for participants, including risks of exposure to the pathogen in question (perhaps especially among groups who receive a placebo vaccine in cases where the investigational vaccine is shown to provide individual protection), they typically involve less burdens per participant than HCS (which, for example, generally require much closer monitoring of participants, especially during inpatient HCS), and do not necessarily involve a high probability of infection (whereas HCS participants are intentionally exposed to infection, usually in such a way as to ensure that most, if not all, become infected). Thus, risk-benefit assessments comparing HCS with other designs will require both scientific and ethical analysis. Ideally, researchers and funders would be able to specify the expected benefits, expected burdens, and expected costs of all plausible potential research programs (e.g., HCS vs. field trial) aimed at particular scientific knowledge and/or public health benefits, so as to permit the rational and efficient design of research programs and the efficient allocation of resources. This can be difficult, especially when the results of different scientific investigations, and the probability and/or benefit of eventual implementation of a new intervention, are difficult to estimate *ex ante* (and often overestimated even by experts (Kiwanuka et al. 2018)) in part because of uncertainties regarding the outcomes of scientific research (see Box 3.1), and in part because of uncertainties about the translation of (early phase) results (including via regulatory development pathways) into the licensure and deployment of novel interventions leading ultimately to public health benefits. Yet recent analyses of the role of HCS in vaccine development have suggested developing systematic algorithms that could help to determine the optimal development strategy and/or series of studies required (Roestenberg et al. 2018). Stakeholders interviewed for this project were optimistic regarding the potential for well-designed HCS to accelerate the development of interventions while involving fewer participants,[3] although some were more cautious regarding efficiency and/or cost-effectiveness comparisons between HCS and field trials (see Box 3.1).

Box 3.1 Rationale for HCS

> [I]f you have a good model … then I think it can be very useful in streamlining vaccine development and … eliminating candidates that [are] not that great, and ensuring [that] those candidates that have the best safety and efficacy profile move forward … [You] could also translate that to therapeutics … if you have a model that can be used for therapeutics, you can down select candidates in a much more efficient and less costly manner. Prof. Anna Durbin, scientist, USA

[3]N.b. the interview sample for this report was potentially biased by the preferential inclusion of scientists active in HCS research—see Sect. 1.2.

> [HCS] will try to mimic as best as they can what happens when you've got a real infection with the pathogens in order to detect … the ability of your vaccine to protect, and you could do this with a limited amount of subjects … involved and not requiring very large field trials in order to get information on the effectiveness of your vaccine. [Regulatory representative]
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> [T]he essential question that needs to be asked is: If we pursue infection challenge studies, how much marginal value are we getting from that pursuit against the [alternative] of pursuing that same acquisition of knowledge by another means? … It can be really, really hard to know which scientific method is going to be the most expedient in arriving at a given state of knowledge … and often we're not as good at making those predictions as you would think … and I think part of the reason why we're not good at that is [that] there are a lot of different conditions that need to hold in order for a particular research study to yield the kind of social benefits that [the] research study is directed towards. [Jonathan Kimmelman, ethicist, Canada]
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> [T]he point about cost effectiveness is really interesting … undoubtedly doing a challenge trial of a vaccine is going to be quicker and cheaper than doing a large phase 3 field trial that runs over several years—but it doesn't mean that [challenge studies are] as quick or as cheap as you might like …
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> [T]here are large costs associated with [them] financially and in terms of time, but yeah they can certainly accelerate that process through but that relies on people actually believing the data in the challenge model. [Malick Gibani, scientist, UK]

3.2.1.1 Generalisability

A key link between the scientific rationale and the social value of a study is the generalisability of the findings (whether these consist of knowledge of disease pathogenesis or estimates of the efficacy of a novel intervention) to the population and context for which the eventual benefits of a research program are intended (Wenner 2015, 2017). The ethical acceptability of LMIC HCS might thus be contingent on such studies generating scientific knowledge that is particularly relevant to LMICs (i.e., more relevant than knowledge that could be generated by HCS in HIC study populations) and/or testing interventions that would (if found to be effective) be particularly beneficial to communities in LMICs (Selgelid and Jamrozik 2018, Wenner 2015, 2017).

Certain choices in study design (e.g., regarding the selection of participants, choice of challenge strain, method of challenge, etc.) might lead to results that are more or less generalisable to the populations most at risk of a particular disease. For example, it would be ethically preferable to conduct HCS in LMICs if/when these can provide results that are more generalisable to (LMIC) populations at risk than results generated by HIC HCS. This might often be the case because of features shared by potential (LMIC) study participants and the (LMIC) population(s) most at risk of

the infection in question (e.g., in terms of naturally acquired immunity, co-infections, genetics, microbiome, nutrition, etc.). LMIC HCS in such circumstances would, other things being equal, arguably have a stronger scientific and ethical rationale than a similar HCS design conducted in a (non-endemic) HIC population (see Section "Potential Ethical Imperative for Challenge Studies in Endemic Settings"). Yet there may be exceptions to this general pattern; such inferences are complex and require careful assessment—especially, for example, where HCS in adult volunteers are intended to be generalisable to children in endemic settings (see Sect. 3.5.4.1).

The choice of challenge strain is another element of study design that might influence generalisability and thus give rise to ethical tensions. Using an attenuated challenge strain (or a single well-characterised strain whereas natural infection involves multiple strains), for example, might reduce the risks to participants. If using such a strain means that the findings are not generalisable to wild-type infection (i.e., do not accurately predict the efficacy of a vaccine) in the relevant population and/or epidemiological context, however, then this could undermine the ethical rationale for using HCS rather than an alternative study design (Chattopadhyay and Pratt 2017; Selgelid and Jamrozik 2018). Thus, although the risks to participants associated with the use of wild-type strains in HCS (such as those used in the Colombian vivax program reviewed below or those used in the pivotal trial supporting recent WHO approval of a typhoid vaccine (Jin et al. 2017)) require careful justification, the use of such strains may sometimes be more ethically justifiable than the use of attenuated strains (or a strain that does not adequately reflect the complexity of natural infection) (see Boxes 3.2 and 3.3). Many stakeholders interviewed were well aware of these complexities, although it was often acknowledged that more data are needed (e.g., comparing HCS findings with subsequent field trials) to inform judgements regarding generalisability. In at least one case, concerns regarding a lack of generalisability (from the challenge strain to local malaria strains) reportedly led to the abandonment of a proposed HCS in India (see Box 3.3).

Box 3.2 Generalisability of HCS

> [A] challenge trial … produces information that's very controlled and so translating that to actually knowing about a vaccine's efficacy … in a population that's previously been exposed to other infections or people who are infected by mosquitoes instead of … intravenously, those things can be difficult … [J]ust knowing what the value is of a challenge trial and how likely it is to lead to licensure is sometimes complicated. [Ethicist, North America]

> Challenge studies are a model for real infections. They are not real infections, in the sense that you generally have to manipulate the dose to get higher attack rates, [and] you [often] do a different type of monitoring than would happen in the field and so you are dealing with a very different setting from wild infections. [Scientist, UK/Europe]

The problem is that [HCS are] a bit artificial in the sense that … you cannot really give the right type organism because it will be too virulent and it will be ethically challengeable, so the [end result] is that you end up [attenuating] your [challenge] pathogen [to the point] where it is [not very] virulent [and then] you may wonder what is the value [of the result of the study], what is the real efficacy of your vaccine? The trade-off between these two extremes … is one of the key factors that will tell us whether a human challenge can be helpful in the beginning of the development [of a] vaccine. [Regulatory representative]

If that challenge is not really giving you a good readout on who that end target population is, [then] you're potentially putting people at risk [without a good justification and] getting an answer that's not going help you decide whether it works or not in that target population. [Scientist, North America]

I think what the [dengue HCS] community is saying is that they're developing attenuated strains [for use in HCS] … but then, what is the relevance? How, how can you justify [it] if it's attenuated to the point it's so different to [wild-type] dengue infection? How do you know that it's relevant to protection against dengue? [Scientist, UK/Europe]

Box 3.3 Generalisability of malaria HCS

Each strain of each malaria species is different, so if we show [vaccine-induced] protection against [a particular] HCS strain this might not lead to natural protection [against wild-type strains]. [Scientist, Asia]

[With vivax malaria HCS] you're using natural strains. That's …a problem and it's an advantage. [It is] a problem because you don't really know exactly which parasites you're giving to the volunteers, at least in the first instance, if you're doing mosquito challenge, because you have to [feed] the field mosquitoes on patients [who have] a natural infection. [On the other hand, using such] wild type [parasites from natural infection] is an advantage in terms of how you test your vaccine. The results of your vaccine [trial] are much more real world [because] you're exposing your vaccinated volunteers to the same challenge as if they were walking through a jungle in an endemic area. [Scientist, Asia]

[A] malaria challenge study … was taken to a committee constituted by the Indian Council of Medical Research. That committee told them that, you know, in principle, all of this is fine but to make this study more epidemiologically relevant you must use a challenge strain from India. I don't think they understood what it takes to make a challenge strain. And how difficult it would be for the vaccine developers to come up with the challenge strain. That did not move forward because it was just too complicated. [Gagandeep Kang, scientist, India]

3.2.1.2 Potential Ethical Imperative for Challenge Studies

Given that HCS are often expected to lead to significant public health benefits more efficiently than alternative research designs, some commentators have argued that there is an ethical imperative to conduct HCS if (or when) no other (less burdensome) feasible research design could obtain similar results and/or if (or when) *not* performing HCS could lead to greater net harms including (i) longer delays to the development and implementation of beneficial new interventions for (neglected) infectious diseases and/or (ii) the exposure of more participants to potentially greater risks in alternative study designs (e.g., field trials involving larger numbers of participants exposed to risks associated with experimental vaccines, where similar vaccine efficacy estimates could have been more efficiently obtained with fewer participants in a challenge study) (Bambery et al. 2015; Selgelid and Jamrozik 2018). Assuming useful HCS can be conducted safely (and other general ethical requirements are satisfied), they might, in such circumstances, be arguably not only ethically permissible, but ethically required or obligatory (i.e., there would be an ethical imperative to conduct such trials) (Bambery et al. 2015; Selgelid and Jamrozik 2018). While few interviewees endorsed such a claim without qualification, there was widespread agreement that the ethical (and scientific) rationale for certain HCS designs in particular circumstances (including in LMIC populations) could be particularly strong, and that pursuing alternative study designs in certain circumstances might be less ethically acceptable (see Box 3.4).

Box 3.4 Could HCS sometimes be ethically obligatory?

> There may be a case where it is impossible to test a vaccine for some disease that we can anticipate will arise and it is within the bounds of reasonable risk to do a human challenge study. Then I think it might be pretty close to something I'd call ethically obligatory, if not using that exact terminology. [Ethicist, North America]
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> I think where it … almost ethically would be obligatory is if you had a disease where the conventional, old way of doing the testing was going to take five years and then the placebo control group people were going to get sick and die, but you could do a human challenge study [and] it'd be done in a month instead of recruiting people over a long haul. [Scientist, North America]
>
> we actually thought that *Shigella* was an example of a case where… human challenge studies are essentially the only responsible way to proceed with vaccine development. To think that… one could immunise thousands of toddlers and then await disease occurrence and incidence [in a field trial with] an experimental vaccine that hasn't been well characterised, you know, that's also hard to justify when you can do a challenge model in a handful of consenting adults [so that] some other issues can be addressed before you take it out to the target population for its final efficacy studies. I almost think it's obligatory to do challenge studies. [Carl Mason, scientist, USA]

Potential Ethical Imperative for Challenge Studies in Endemic Settings

The vast majority of HCS have been conducted in high-income countries. Over 40,000 people have participated in HCS in the ~70 years since World War II (Evers et al. 2015), yet the 13 LMIC case studies we review below enrolled a total of around 400 participants—i.e., less than 1% of the global total. Even HCS research on pathogens that are primarily endemic in LMICs has been largely conducted in non-endemic HICs. Potential reasons for this include: (i) the presence of more/better funded research infrastructure and researchers in HICs (Baay et al. 2018), (ii) the availability of healthcare resources in HICs that can be devoted to caring for HCS participants, thus providing greater assurance of risk minimisation (Gordon et al. 2017), (iii) the view that recruitment among vulnerable populations should be restricted to types of research that are likely to lead to novel medical interventions that could be shared, ideally in the near future, with the local population—this would thus rule out HCS except where these involve or (in the case of HCS aimed at infection model development) facilitate testing drugs or vaccines (Macklin 2003; Pratt et al. 2012; Wenner 2017), and (iv) regulations and/or norms in LMICs that sometimes require prior testing (e.g., early phase studies) of an intervention or research model in the country of the sponsor of the research (usually in a HIC) before testing in an LMIC (Malaria Vaccine Initiative 2016).

The relative current research capacities of HICs and LMICs, including capacity for HCS, are arguably the result of longstanding injustices in the global distribution of wealth and thus funding for research. This has in turn contributed to a relative neglect of research regarding pathogens that are mainly endemic in LMICs and the perpetuation of large inequities in the global burden of disease. There have thus been calls for more HCS in LMICs (Gibani et al. 2015; Gordon et al. 2017; Baay et al. 2018). Furthermore, If there is an ethical imperative to conduct HCS (in general) that is grounded (in part) in the need to relieve significant burdens of infectious disease, then there is arguably an even stronger ethical imperative to conduct (appropriately designed) HCS in LMICs in particular because, *inter alia*, (i) LMIC infectious disease research (including HCS) could lead to significant public health and/or research capacity-building benefits where they are most needed, (ii) HCS may be more efficient and thus lead to such public health benefits more quickly and/or cost-effectively than other study designs, (iii) HCS performed in HIC populations (and estimates of efficacy of any interventions tested there) may not always be generalisable to LMIC populations, and (iv) studies of acquired immunity (which, it is hoped, will improve vaccine development for neglected pathogens) must recruit previously infected individuals who (for many relevant pathogens) live predominantly in LMICs (Selgelid and Jamrozik 2018). In some cases, the ready availability of pathogen strains from locally infected patients may also be an advantage (e.g., for vivax malaria, which currently cannot be maintained in a laboratory culture), as compared with the logistical complexity and costs of exporting these strains to HICs for HCS and other research (Malaria Vaccine

Initiative 2016). Interviewees for the current project raised multiple reasons why it might be advantageous to conduct HCS in LMICs (see Box 3.5).

Box 3.5 Rationale for HCS in LMICs

> [I]t makes sense to bring a challenge model to evaluate … an intervention in the population where it will ultimately be used because you'll get the best handle of whether it's going to work or not … and, even if it doesn't work, being able to analyse the reasons why it failed might help you to do better the next time around. [Gagandeep Kang, scientist, India]
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> [T]he main scientific justification for doing it in endemic regions [is] that you are testing vaccines in the population where they will be deployed. [I]t's just the correct model, which always [involves doing the research in] the correct study population. Because it is actually the population where you'll be using the vaccine. [Scientist, Asia]
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> I don't think it's in the best interest of low-resource countries [to require that HCS are first conducted in HICs before moving to LMICs] because, if we start with those stipulations, many of the things that are needed by low-resource settings will never be studied. [Ethicist, North America]
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> If you do a challenge study in an endemic setting, it's viewed as responsive to the health needs of the people in that country in addressing a problem they understand and think is important. There may be a baseline risk of transmission that people already accept or just are aware of, and so introducing an additional risk doesn't change the risk profile for them greatly in their estimation. So I think these are the types of reasons people give as saying it might be better, ethically, to do a study in an endemic setting. [Ethicist, North America]
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> Not only are we opening up research possibilities for African institutions, we're actually [now] able now to address research questions that were off the table before this happened … because you can only ask these questions in a malaria-exposed population. [Scientist, North America]
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> Most of the malaria challenge models have been conducted in non-endemic settings and that's problematic from a scientific point of view, in that you don't necessarily know whether or not the volunteers are representative of the likely final beneficiaries of a vaccine … either in terms of genetics or in terms of acquired immunity. [Scientist, Asia]
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> Much malaria vaccine work was also done using human challenge studies in the US and … you can set up a perfectly competent, capable study group in sub-Saharan Africa that would be able to do it in endemic areas and answer many of the questions that you really need to have answered much more quickly. [Scientist, North America]
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> I think [challenge studies in endemic settings are] great idea and… I think, in fact, maybe justice demands it. … the notion of … distributive justice in research … says that as early as it's … reasonably safe to do so, we ought be doing these studies in the population that stands to benefit. I mean … that's what justifies the burden it seems to me, in part. [Ethicist, North America]

Some interviewees even questioned whether continuing to conduct HCS in HICs for pathogens primarily endemic in LMICs could (still) be scientifically and/or

ethically justified (see Box 3.6).[4] On the other hand, some participants noted that both HIC and LMIC HCS could be justified, depending on the scientific question being investigated. For example, as discussed above, some HCS aim to test vaccines intended for use among young children who often have no immunity to the pathogen in question (see Sect. 3.5.4). In such cases, even if the eventual target population for the vaccine were children living in endemic areas of LMICs, adult HCS participants in HICs may be a useful model, at least in respect of their level of pre-existing immunity, since (like young children in LMICs) they have no immunity from prior exposure, whereas many of the adults living in endemic areas will already be (semi-)immune, and thus efficacy trials in the latter group would not necessarily be highly generalisable to children (see Box 3.7).

Box 3.6 On-going justification of HCS in HICs

I don't understand why you wouldn't … do challenge studies in endemic countries? I mean I would turn it around and say – why are we doing them in non-endemic countries? [I think] research should be focused in the settings in which those health problems are occurring and I think this is a colonial history that we have which has been propagated by institutions [in high income countries]. The current situation is that they're the ones who have the facilities to do these. They have more funding to do this kind of work, so they just do it where they are as opposed to where it's needed. [Scientist, UK/Europe]

[Starting HCS research in HICs was the most] pragmatic way but I'm starting to question why we haven't stopped. [C]onducting research in Oxford with all those students, giving them so much money? I wonder if that's a good thing to do. I would question that. So rather than questioning: why here [in] an endemic setting? – Why Bangkok? – I want to question: why Oxford? [Scientist, Asia]

I think it is, it's almost unethical to conduct [HCS] in non-endemic settings because those subjects do not benefit at all. They aren't going to be exposed to the disease. Their immune responses aren't typical. The genetic makeup is different. For a whole variety of factors. If you have a viable vaccine or you think it's a viable vaccine, it should be evaluated in endemic settings and, and brought to market as quickly as possible to benefit those people. And conducting studies, non-endemic studies only delays things. [Scientist, North America]

[F]or years, we've been doing CHIM studies in Maryland and Oxford where as it turns out there isn't a lot of malaria … I get the reasons to do that, that you need facilities with all kinds of sophisticated technology and you need the expertise … [but] morally there's an argument for doing these studies in low resource settings as soon as possible and indeed [the same argument] suggests that perhaps there's something even more problematic about doing them in settings where nobody's … going to be exposed the risk of disease. [Ethicist, North America]

[4] Although note again that the interview sample was potentially biased by the preferential inclusion of researchers with an interest in LMIC HCS.

Box 3.7 The need for both LMIC and HIC HCS

> [T]here are certainly scientific arguments why one might choose different populations but I don't think, as some people have argued, that, scientifically, it is, by definition, better to be in an endemic setting. I don't think that's true. I think, scientifically, there are good arguments for doing things in developing countries but … the case isn't always in my view adequately made, for why that is better, or not, [than in] a developed country. [Scientist, UK/Europe]
>
> [Testing interventions for which LMIC children are the target population] is the one area [in which it might be justified to do] the challenge studies in non-endemic countries because … the most practical way of providing data that is relevant to young children, at least in the case of malaria, is [to conduct studies with] adults [in non-endemic settings], because [like children] they're non-immune. [Scientist, UK/Europe]
>
> [Y]ou could argue that … testing vaccines in malaria naïve adults in Oxford is more predictive of the vaccine efficacy in … endemic regions … but we already know that children growing up in endemic regions are exposed to other parasites [and] those infections modulate their immune responses, there's lots of other factors that impact their immune response so even in that setting you can't predict the efficacy on the ground. [Scientist, UK/Europe]

3.2.2 Benefit Sharing

The topic of benefit sharing has been a prominent focus of international research ethics discourse during recent decades (El Setouhy et al. 2004; Njue et al. 2014; Wenner 2015). The sharing of benefits with study participants and/or local populations is commonly cited as an ethical requirement for international research involving human participants, but controversy surrounds questions regarding the nature, content, and weight of such a requirement (El Setouhy et al. 2004; Wenner 2015, 2017). How such a requirement is understood has important implications for the ethical justification of HCS conducted in LMICs.

For example, a requirement for tangible benefits, such as drugs or vaccines approved as a result of a study, to be made available to the local population can lead to a reluctance to conduct basic science and/or *early phase* research (including some HCS designs) in LMICs because such research is not intended to lead to the immediate development or approval of such interventions (Macklin 2003; Wenner 2015, 2017). Nevertheless, such research can lead to benefits in terms of scientific knowledge that is necessary for the development of such interventions in future. In particular, it can lead to knowledge that is of particular relevance to the population in question (Wenner 2015, 2017). Indeed, many of the LMIC HCS reviewed later in this report were focused on model development (where such models may be used later for the testing of interventions) and/or understanding locally relevant aspects

of host-pathogen interaction. It may thus be more relevant to consider the overall long-term expected benefits of a program of research as a whole (rather than a single study in isolation) (London and Kimmelman 2019) so long as there is reasonable confidence that the program can/will continue—and this is unfortunately not always the case, because a lack of funding or other issues may delay or entirely halt a proposed research program (see Box 3.8).

Box 3.8 Benefit sharing

> [T]hose subjects who are involved in these studies should be able to benefit from the vaccine that is eventually licensed. So you should be focusing on doing the studies in the target population. [Scientist, North America]
>
> Often I find [that] much of … research ethics is preoccupied with a synchronic view of clinical research looking merely at a single clinical trial as opposed to the relationship of that investigation with subsequent investigations, and/or investigations that preceded it. [Jonathan Kimmelman, ethicist, Canada]
>
> I wish we had been part of a larger development plan … because of our bureaucracy, our trials were slow and [because funding was no longer available] we were unable to really conduct the studies that we needed or probably should have conducted or would have been of important value … [O]nce we had established a good challenge model, it would have been helpful and probably more ethical … to be able to continue working [and to test (more) vaccines]. [Carl Mason, scientist, USA]

On the other hand, if benefit sharing requirements apply to vulnerable populations in HICs, and these populations are being recruited for HCS with pathogens that are not locally endemic, then there might be no benefits that could meaningfully be shared with such populations, which implies that it may be more ethical to conduct such studies among vulnerable populations in LMICs than among those in HICs (see Sect. 3.5.1).

3.2.3 Capacity Building

Research may lead to other kinds of ancillary benefits (not directly related to the social value of answering a research question), including (i) research capacity building, (ii) other assistance to the local community, (iii) ancillary benefits to individual participants (e.g., healthcare, provision of testing, etc.), and (iv) payment of participants (discussed in Sect. 3.6). Ethics committees usually exclude these benefits from the risk-benefit assessment of individual studies but whether that is appropriate is controversial and in any case it has been argued that such benefits at least be considered as part of the justification for research programs in LMICs (El Setouhy et al. 2004).

Research capacity building might include contributions to relevant infrastructure, equipment, training of scientific staff, and training of ethics review and/or regulatory body members. Many of those interviewed as part of this project saw building capacity for HCS (and other research) in the countries in which relevant diseases are endemic as important. In addition to technical/scientific capacity building, participants identified ethics capacity building as a particular area of need because many ethics committee members (in LMICs) were not familiar with HCS designs and required significant training and engagement (see also Sect. 4.1) to facilitate review of recent LMIC HCS (see Box 3.9).

Box 3.9 Capacity building

> [W]e've been receiving vaccines and drugs developed from other places, so some other people have gone through this to enable us to have what we have now. Now that we are building our capacity, it is also our time now to possibly start … helping and building the next generation of vaccines and drugs. [Scientist, Africa]
>
> [E]ngaging the investigators in developing countries, and having them involved at the beginning, at the ground level of things, and having some of those research resources distributed into places … where the research can be done locally [is] beneficial to the local research community and … can sometimes be a source of pride for the country itself. [Scientist, North America]
>
> I do think capacity-building in endemic settings and making sure that other countries have the ability to do research that they value and that their communities value is really important, and that, … just having collaborations that are global is not sufficient, that we really do need to be thinking more about building capacity. And so it could be that building capacity in human challenge studies will be important to help countries do things … they really value and think are important. [Ethicist, North America]
>
> The issue is how do we capacity build the ethics of your committees to address the new changes that are coming in … proactively, not wait for things to happen, for them to catch up with how they review … I think there's a lot of experience in ethical review, there's a lot of capacity building that has been going on. [Scientist, Africa]
>
> One of the things we did when we are setting up the platform was to [hold] joint meetings between the scientists and the ethics committees, so that people are [able to] share their experiences and possibly anxieties and I think this helped build capacity and people, having seen more of these protocols, now they have a better understanding and now we have several teams that are now able to do this challenge study. [Scientist, Africa]

3.2.4 Potential Individual Benefits of Participation in Endemic Settings

Being infected with a pathogen during HCS often entails few, if any, benefits to research participants. However, if a person is at high risk of infection with the

relevant pathogen in day-to-day life, in some cases being infected in the course of research will (i) entail less risk than being infected 'in the wild' (e.g., because of more immediate diagnosis and comprehensive medical care) and (ii) confer a benefit in terms of immunity (whether partial or complete/'sterile') similar to that of vaccination (albeit achieved with a comparatively higher risk intervention) (Selgelid and Jamrozik 2018), that will reduce the risk and/or severity of future bouts of infection (Herrington et al. 1990). Such considerations of individual benefit have not been widely discussed in the ethics literature, perhaps because HCS have, for the most part, taken place in HICs with pathogens that are not locally endemic and/or confer low risks of severe disease. In a recent exception, the 2017 Report on Ethical Considerations for Zika Virus Challenge Trials does mention possible benefits of this kind for challenge study participants recruited in endemic-regions during periods of significant transmission (Shah et al. 2017), and the possibility of such benefits was also noted by Michael Selgelid in a presentation at the 2013 Wellcome Trust Scientific Conference on Controlled Human Infection Studies in the Development of Vaccines and Therapeutics (Selgelid 2013).

HCS might also entail benefits for individual participants in endemic settings if they involve the testing of a vaccine candidate that provides protective immunity against wild-type infection (although the demonstration of protection—or the lack thereof—may be one of the goals of the study and thus be uncertain at the time of enrolment). Such benefits would not arise from the challenge infection itself (and would, for example, also arise in vaccine field trials in endemic settings), yet they may nevertheless (in at least some cases) provide an additional ethical reason in favour of conducting HCS in endemic, rather than non-endemic, settings.

Still, most HCS to date impose a *net* risk on participants (whether or not there are any direct benefits), and it would be unusual if infection as part of a challenge study entailed an expected *net* benefit. Exposure to attenuated pathogens is a vaccination strategy that has been used for some diseases (e.g., live attenuated vaccines for measles, yellow fever) and is being explored, for example, for malaria. However, the benefits of attenuated malaria challenge in endemic settings are the subject of on-going research and hence as yet uncertain (Arévalo-Herrera et al. 2016; Olotu et al. 2018). Thus, although HCS participation in an endemic setting may be less risky and/or more beneficial than participation in a non-endemic setting, participants would still (usually) be accepting a net risk in order to contribute to a research program, the main goal of which is to lead to future public health benefits (as opposed to immediate direct benefits to participants). As Prof. Jonathan Kimmelman suggested in an interview for this project, if we had adequate confidence that people would actually benefit from infection, then we should arguably institute a public health program (rather than a research study) that deliberately infects people with the pathogen in question. Other interviewees did acknowledge a potential for individual benefit in endemic settings that would not occur in non-endemic settings, although it was usually seen as a relatively minor consideration, and one that was contingent on there being a high background risk of infection in the local community (see Box 3.10).

Box 3.10 Benefits of HCS participation in endemic settings

> [The] rationale for participating in research is that … you may help yourself and you may help your community and you may help the world and if you do it in … a non-endemic country, then it's just the last one of those; whereas here it's probably all three because, maybe, there is a small chance that an individual volunteering here for a[n HCS] may benefit, in terms of enhanced immunity … when they go back into their malaria endemic homes. [Scientist, Asia]
>
> [Whether an individual participant can be said to benefit] depends on the attack rate where you are and what the probability is [of being infected in daily life, as compared with participating in HCS]. [I]f you [participate in a] challenge [study] you've got a definite risk of infection and an unknown risk of severe complications. [Scientist, UK/Europe]

3.3 Burdens for Participants

Research participation can involve a range of burdens of varying significance, and some HCS designs could, overall, entail relatively high levels of burdens for participants. In research ethics, distinctions are sometimes drawn between risks and other types of burdens, although it has been argued that risks and other burdens should be considered together since, despite apparent differences, they are both (sets of) adverse consequences in the lives of study participants (Rid 2014). On the other hand, study participants may distinguish between what they take to be risks and burdens in various ways (Kraft et al. 2019). Here, we will bracket these debates and use 'burdens' to capture all adverse aspects of research for participants—including exposure to risk (and thus sometimes harm), privacy infringements, restrictions of freedom of movement (e.g., being isolated in an inpatient unit), and/or other reductions in well-being etc.

3.3.1 Limits to Risk

Among other burdens, research often involves risks to participants, although infectious disease research (in particular) also sometimes involves potential risks to third parties (discussed in the next section). HCS may involve varying degrees of risk to participants depending on the study design. Level of risk may depend upon decisions regarding pathogen/challenge strain, study population, whether participants will be inpatients (with close monitoring) or outpatients (with less monitoring), etc. Risks consist of two components: the probability of a harm occurring, and the magnitude of that potential harm (Rid 2014). Furthermore, the

magnitude of a harm is a function of its severity and average duration (with more severe and longer duration harms being of higher magnitude and thus more concerning—See Sect. 3.3.4).

HCS have been identified as a group of studies that can, at least sometimes, pose significantly more than minimal risks to participants (Miller 2003), raising questions regarding the upper limit of permissible risk imposition in research among healthy volunteers, and in HCS in particular. Reviews of recent challenge studies have found no deaths or lasting harms among participants (Roestenberg et al. 2012; Darton et al. 2015), however accurate estimates of the risks associated with a particular challenge study (or programme of studies) may not always be explicitly quantified.

As a comparator in healthy volunteer research, one review of phase I non-oncology drug trials performed by one pharmaceutical company found a risk of serious adverse events (those that result in hospital admission, persistent or major disability, life threatening event, birth defect, or death) of up to 0.3% (with no deaths) and a rate of severe adverse events (those that interfere in a major way with a participant's basic daily functioning) of up to 1%; a second review of publicly available phase I trial data found similarly that severe and serious adverse effects comprised less than 1% of all adverse events (Emanuel et al. 2015; Johnson et al. 2016). However, these reviews did capture all phase I (or similar) studies. Rare cases of severe harm among healthy volunteers have included multi-organ failure requiring intensive care admission (in a phase I immunotherapy drug trial) (Goodyear 2006), brain damage and death (in a phase I neurological drug trial) (Moore 2016), and respiratory distress leading to death (in a chemical challenge study where healthy volunteers inhaled an active agent to simulate the pathophysiology of asthma) (Moore 2016).

HCS taken together could be associated with a range of risks, from very low (e.g., studies with low virulence pathogen and/or inpatient studies of treatable pathogens with very early diagnosis and treatment) to significantly higher risks (e.g., infection of immune-naïve individuals in outpatient studies with highly virulent pathogen). Lower risk HCS (e.g., many study designs in current use) might well be safer than many phase 1 drug trials, whereas higher risk challenge designs (and first-in-human HCS) might expose volunteers to significantly greater risk and/or uncertainty. Two questions arise: firstly, should very low risk HCS be classified as minimal risk research?; secondly, if more than minimal risk HCS are in-principle ethically acceptable, what should be the upper limit of risk to which HCS volunteers should be exposed?

3.3.1.1 Minimal Risk

While it is sometimes held that research with healthy volunteers (including HCS) should entail no more than 'minimal risk', or a minor increase above minimal risk, the definition of minimal risk is contentious, and (as above) at least some challenge designs would plausibly exceed such a threshold (as drawn by common definitions) (Hope and McMillan 2004; Resnik 2005). On the one hand, if 'minimal risk' is defined as no more than the usual risks encountered in daily life, then this fails

to take into account the fact that some people regularly encounter higher levels of risk in daily life than others, either due to their appetite for high risk activities (e.g., motorcycle riding) or because of the prevailing conditions where they live (e.g., being exposed to endemic infectious diseases, or not having access to adequate sanitation—see Sect. 3.3.3) (Hope and McMillan 2004; Resnik 2005; Wendler 2005; Wendler and Emanuel 2005; London 2006; Shaw 2014). Likewise, setting the standard at the level of the risk that a risk-averse person would encounter in daily life is arguably too strict (Hope and McMillan 2004), and would certainly rule out many HCS—since a risk-averse person would not usually deliberately infect herself with a pathogen. Anecdotally, many individuals volunteering for HCS have a significant appetite for risk. As one scientist describes them: "These were the same young people who would go down the hairiest parts of rivers on rafts" (Cohen 2016).

Alternatively, minimal risk might be specified numerically, for example minimal risk research might be limited to studies involving a less than 1 in a million chance of lasting harm (which would exclude at least some HCS designs—see Sect. 3.3.4) or no more than a 1 in 1000 chance of severe adverse effects to participants.

3.3.1.2 Upper Limit to Risk

Propositions for an upper limit to acceptable risk in research with healthy volunteers include (i) no limit (since consenting adults should be able to decide on the level of risk they will accept) (Shaw 2014), (ii) the risks of high-risk, socially beneficial occupations like fire-fighting (since, similar to research, such jobs involve some individuals taking on net risk to benefit society) (London 2007), or (iii) the risks of kidney donation (since norms in non-research contexts permit this to be done from a sense of altruism, which may also motivate some research participants) (Miller and Joffe 2009).

There is, in any case, no universally agreed upon upper limit for the degree of research risk permissible in HCS. Some argue that it is more justifiable to pursue higher risk research where there is a high likelihood that a given study will produce significant benefits—but most commentators agree that easily imaginable HCS with very high risks[5] would not be justifiable (Hope and McMillan 2004; Miller and Rosenstein 2008; Miller and Joffe 2009). In part, this is for pragmatic reasons, since the public reaction to a case of severe harm in high risk HCS research could lead to a moratorium on other lower risk but potentially beneficial studies (Hope and McMillan 2004). Thus, the need to avoid such an outcome provides (additional) reasons for (i) community engagement around HCS, (ii) careful review of higher risk studies and/or HCS in general, and (iii) enhanced safety monitoring practices during the conduct of HCS (Hope and McMillan 2004; UK Academy of Medical Sciences 2005; Bambery et al. 2015).

[5]Consider HCS involving HIV for example.

Many interviewees agreed that an absolute upper limit to risk for would be difficult to define, and some suggested that limits in particular contexts should be partly defined through community consultation, with this in turn being partly with a view to maintaining public trust in research—meaning that even if a higher risk study were judged acceptable under a given ethics framework (e.g., because of high expected benefits), there might be good reasons to find out whether relevant communities would actually accept such a study design (e.g., through community engagement activities) (see Box 3.11).

Box 3.11 Limits to risk and public acceptability of research

> [T]he way I understand [limits to risk in the context of ethics review] … is that … we're not just trying to make sure that this specific study is done well and it's ethical – we're also, to some extent, trying to protect the institution of research. [Ethicist, North America]
>
> I also think that those limits ought to be dictated by public perception, to a certain degree … [I]t's not merely a question … [of] how much can we ask an individual to put their lives at stake; it also really bears on how much is the public willing to view this as a kind of legitimate and sanctioned activity, if we put people at this level of risk. [Jonathan Kimmelman, ethicist, Canada]
>
> [W]hat we've learned in my [African] setting, and this is also looking back at some of the studies done here (which we thought were very safe) and how they became problematic … [W]e've learnt that we don't take anything for granted … in the community. We just have to be very careful about it, because it's got the potential to be misunderstood … in all different ways. It doesn't matter whether it is the most safe procedure you thought you were introducing; as long as it is unfamiliar in the community, it is likely to flare up all kinds of rumors. [Scientist, Africa]
>
> [O]n the essential question of 'Can the study proceed from a regulatory perspective?', what are we looking for in terms of ensuring it's safe? And the criteria that we hold to is 'Are there unreasonable risks?' And admittedly that is somewhat of a judgment call about what's reasonable and unreasonable, but the regulatory bar is, is 'Are there unreasonable risks?' [Regulatory representative]

3.3.2 Minimising Risks

It is widely held that risks to participants should be minimised. A key consideration is whether exposing participants to a given risk is necessary to answering an important research question. If not, then such (unnecessary) risks should arguably be eliminated, thus minimising the quantum of risk for a given expected social benefit (US Department of Health and Human Services 1979; Savulescu 1998; Miller and Grady 2001; Hope and McMillan 2004; World Medical Association 2008; Rid et al. 2010; Bambery et al. 2015).

Minimisation of risks to participants during HCS might involve, *inter alia* (i) selection of study populations at lower risk of severe disease, (ii) use of pathogens and/or strains that produce less severe disease, (iii) early diagnosis and/or treatment, (iv) keeping participants as 'inpatients' to enable particularly close monitoring for at least part of the study, (v) close monitoring of (any) outpatient participants, and (vi) careful follow-up for long term outcomes of infection and treatment. Risk minimisation might be considered particularly important in the context of HCS; as one North American scientist argued:

> [Y]ou're completely responsible [from] the moment you … give that injection until that person is clear, either doesn't get it and you've documented that or you've diagnosed it and treated it. So that's different [from] other … non-therapeutic interventions … you have total responsibility and, if you can't be certain that you can take that total responsibility, you have no business doing this. [North American Scientist]

3.3.2.1 Early Diagnosis and Treatment

For HCS with pathogens (such as malaria) where effective treatments are already available, the diagnostic strategy used in a given HCS may significantly influence the risk of symptoms and/or disease as well as the need for inpatient isolation. The potential to reduce such risks will often be particularly important where curative (as opposed to merely supportive) treatments are available. As one North American scientist stated:

> [D]iagnostics [drive] the whole study design in malaria – because if you can't diagnose [participants] until they're pretty sick, then you have to keep them in a hotel. And, if you diagnose them really early, then all that hotel stuff … gets eliminated. And so … we're almost not interested in doing any studies that require hotel phases for malaria anymore because … you don't need to have a whole wing of a hotel when you could just have a more sensitive test. [North American Scientist]

Such observations reveal the ways that study design involves practical and ethical trade-offs. While inpatient studies (and the especially close monitoring these permit) reduce risks for participants, for example, they also increase the burdens related to isolation and close monitoring. Early diagnosis can mitigate both risks and other burdens. Thus, except in situations where there is a strong rationale in terms of the research question that requires delaying treatment, there is arguably a strong ethical case for early diagnosis and curative treatment during HCS for pathogens for which such treatments exist, although thresholds for treatment initiation remain controversial (see Box 3.12).

Even the use of very sensitive microbiological tests and early effective treatment, however, does not always preclude the development of significant symptoms during HCS. One reason that symptoms might occur despite the use of very sensitive diagnostic testing is that some individuals develop symptoms at lower levels of pathogen concentration in the body than others. Unless the threshold for treatment selected as a part of the design of the study is set at or below

the level at which the most "sensitive" individual develops symptoms (which might be unknown or difficult to estimate with certainty prior to the conduct of such studies) some individuals may develop symptoms whereas others may not. Investigators may be able to set very low thresholds for treatment in cases where this would not compromise the scientific rationale of the study. In other cases there may be (ethical and scientific) trade-offs between the burdens to participants (experiencing symptoms) and additional important scientific information gained by allowing infections to continue past the point where symptoms develop. Such additional burdens would presumably only be ethically justifiable where similar scientific information could not be gleaned by less burdensome methods (see Box 3.12). For malaria in particular it may be possible to employ treatment(s) against the form of the pathogen that causes symptoms (thus reducing the burdens associated with symptoms among participants) while allowing progression of, and observing, development of other forms of the pathogen (see Sect. 3.4.1).

A second reason that symptoms might occur despite the availability of highly sensitive tests is that there may be trade-offs between a higher frequency of testing (so as to diagnose an infection as early as possible) and the burdens that such close monitoring entails for participants. Since diagnostic tests cannot usually be administered continuously (e.g., 24 hours a day), and since participants have an interest in retaining some privacy and freedom of movement (whether in the context of inpatient or outpatient HCS), the availability of highly sensitive tests and a low threshold for the initiation of treatment might not prevent symptoms from developing in all cases, since there will be a certain amount of time between administrations of the diagnostic test and/or a certain amount of distance between participants and the testing centre (in outpatient studies)—see also Box 3.18 (in Sect. 3.3.7.2) for an example of the development of symptoms in an outpatient.

Box 3.12 Early diagnosis and treatment during HCS

> [Some HCS designs are] pushing the boundaries. I know [some scientists] would make [a] case for why they would want to see the severe symptoms in the participants. That is where I would draw some lines and say at the end of the day, in as much as it's about science and new knowledge and benefit for everyone else, but how much are we making people bear the burden and the risk. Is there a level to which we find we are crossing a very thin line between what is ethical and what is not? What is allowable and what is not? And for me severe symptoms are crossing that line very quickly. [Scientist, Africa]
>
> I think it's really inappropriate [to delay] treatment … [S]ome people said … if we delay it for another forty-eight hours then … we'll get more interesting data and we can plot pretty curves of the PCR quantitatively and this kind of stuff. And, for drugs, the longer you leave it the better. I'm very uneasy about that because it seems to me that scientifically, the longer you leave it … even for one hour [or if] you leave it for longer after you confirm infection, there has to be an increased risk of some complication and we know you can get severe malaria. [Scientist, UK/Europe]

> So there's like two camps and everything in-between. The one camp is: we need all the data. We should just let them go all the way to become blood-smear positive [with relatively high burden malaria infection], then we can do PCR on everything and get beautiful curves, and it'll tell us everything. The other camp is: any of these suckers in the blood means it failed so we should treat at the first sign of smoke, right. And doing either extreme isn't great. [Scientist, North America]

3.3.3 Risks to Participants in Endemic Settings

Conducting HCS in LMICs might influence the potential risks to participants in several ways. On the one hand, where local health and related infrastructure is fragile, HCS participants may encounter higher risks due to delays to treatment during outpatient studies if/when they develop symptoms of the challenge infection. It may sometimes be possible to mitigate risks such as these via capacity building of treatment centres and/or inpatient study designs.

On the other hand, HCS in LMICs could involve lower risks of severe disease if they recruit individuals who have (partial) acquired immunity due to prior infection and/or innate forms of resistance to particular pathogens—e.g., genetic conditions affecting red blood cells such as sickle cell that reduce the severity of malaria, an effect demonstrated in one LMIC HCS reviewed below (Lell et al. 2017). It may also be ethically important to purposefully recruit individuals with such traits for HCS that involve testing interventions that (if licensed) would be intended for use in such (sub-)populations, since the safety and efficacy of a given intervention may be different in certain groups.

Furthermore, where participants in a challenge study are at risk of being infected with a pathogen in daily life (e.g., because they live in an endemic area[6]), one might think that, in some cases, this background risk reduces the marginal risk an individual would take on by participating in a challenge study[7] (c.f. Sect. 3.2.4). It may thus be more ethically acceptable, from the point of view of balancing the risks and benefits of a study, to enrol those who already face higher background risk (other things being equal). There was widespread agreement among interviewees that such considerations could be ethically relevant in terms of minimising risk in HCS study design, and might often favour of conducting HCS in endemic populations (see Box 3.13). Research ethics literature regarding background risk more generally (Rothman 1982; Robinson and Unruh 2008), however, provides reasons for being wary about the sentiment that risk imposition

[6]Importantly, it should not be assumed that anyone living in a country in which a pathogen is being actively transmitted (in part of the country) is at risk of infection on a day-to-day basis (note, for example, that the malaria HCS in Kenya and Colombia reviewed below actually took place in cities in which malaria is not endemic).

[7]With the exception of pathogens such as dengue, for which the sequence of infections with different strains influences the probability of severe disease (see Selgelid and Jamrozik 2018).

on participants might be more acceptable where background levels of risk are higher when/if (i) higher levels of background risk (e.g., in LMICs) themselves reflect injustices and/or (ii) research participation would significantly increase risk to participants who already face high background risks (while it should be kept in mind that *the absolute magnitude of net/marginal risk increase is a key consideration*, independent of background risk magnitude).[8]

Box 3.13 Background risks of infection and risk to participants

> [I]t's less ethically difficult in recruiting volunteers [in endemic areas], considering that you're giving someone an infectious disease, to use volunteers drawn from a population that's at risk anyway, rather than a population that would never be at risk, in terms of justifying the balance of risk. [Scientist, Asia]
>
> [I]f you are already exposed, if you're at a greater risk, [the risk] you're being asked to accept as a result of your … participation in the study is lower and the benefit is going to be the same. So the benefit versus risk profile [is better]. [Ethicist, North America]
>
> [T]here are some compelling reasons [to conduct endemic-region HCS], and that's one of them, that … the background prevalence means there is less of a differential … between the [alternative] of not participating and … deliberate exposure. [Jonathan Kimmelman, ethicist, Canada]
>
> [Y]ou get into all of these questions about whose daily life is the right comparator. Is it a local standard? Is it a universal standard? And so that makes me think it's preferable to do the challenge trials in endemic settings because there's an argument that it's actually lower risk in those contexts. [Ethicist, North America]

3.3.4 Long-Term Risks and Lasting Harms

Most commentators have argued that, as a general rule, HCS should involve infectious diseases that are treatable and/or self-limiting (i.e., resolving without treatment) (Miller and Grady 2001; Miller and Rosenstein 2008; Bambery et al. 2015; Roestenberg et al. 2018a). Some have added the criterion (or interpreted

[8]Part of the point of (ii) is that those who favour a Rawlsian account of ethics/justice, which requires making the worst off groups of society as well off as possible, might conclude that it is more acceptable to impose higher marginal research risks on well off participants in HICs (with lower background risks) than to impose lower marginal risks on less well off participants in LMICs (with higher background risks)—because we should avoid worsening the situation of those who are already worst off. A second point of (ii) is that if the net/marginal increase of risk resulting from HCS participation is high enough for those who already face high background risks, then HCS may not be justified even if the net/marginal increase in risk for such participants is lower than would have been the case for participants elsewhere: a comparatively lower level of net/marginal risk increase does not entail an acceptable level of net/marginal risk increase (if the lower level of net/marginal risk increase is itself quite high).

'self-limiting' in such a way) that there be "no lasting consequences" (Miller and Rosenstein 2008) or no "irreversible pathology" (Roestenberg et al. 2018a).

Requirements that there be no lasting consequences or harms are potentially important since (i) some infections can (after partial treatment) reactivate from a latent or dormant form (e.g., vivax malaria), (ii) certain pathogens are sometimes more severe on subsequent infection (e.g., dengue), and (iii) some post-infectious syndromes can lead to lasting morbidity even after the acute infection has resolved or been "cured" (e.g., post-infectious irritable bowel syndrome, post-infectious 'reactive' arthritis, Guillain-Barré syndrome, etc.).

Regarding (i), the dormant form of vivax can usually be definitively treated, although certain individuals are at higher risk of adverse effects of treatment and/or treatment failure, and are thus sometimes excluded from vivax HCS (Bennett et al. 2013). Regarding (ii), the risk of severe dengue (either during or after HCS) can be mitigated via careful participant and/or strain selection, although dengue HCS nevertheless require particularly careful study design (Thomas 2013; Mammen et al. 2014; Larsen et al. 2015; Selgelid and Jamrozik 2018). Regarding (iii), while some post-infectious syndromes have known risk factors (see Table 3.1), meaning that individuals known to be at higher risk can be excluded from HCS, such strategies often cannot prevent these outcomes entirely. The fact that lasting harms have not been documented among HCS participants for these pathogens may reflect careful selection practices and/or relatively low numbers of total participants (in whom, by chance, a rare event has not been observed) and/or publication bias (i.e., events that may have occurred might not have been published).

One HIC researcher interviewed was aware of at least one case of presumed post-infectious arthritis occurring after HCS with an enteric pathogen (the case remains confidential and unpublished, consistent with publication bias mentioned above). More generally, interviewees agreed that such lasting harms were particularly concerning and, at a minimum, require (i) careful risk mitigation strategies, (ii) systems to compensate any participants who experience harm, and, in some cases, (iii) long-term follow-up of participants.. However, there was no clear consensus about what level of residual risk of such outcomes, if any, should be considered acceptable. Some experts noted that several pathogens already used in HCS are (rarely) associated with lasting harms (see Box 3.14 and Table 3.1). Of note, many of the LMIC HCS reviewed later in this report were carefully designed to reduce such risks, usually by exclusion of those with known risk factors for such outcomes.

Box 3.14 Lasting and/or irreversible harms

> I'm very uncomfortable with the idea that you might leave somebody with irreversible harm when they haven't been given any possible benefit. [Scientist, UK/Europe]
>
> [A] healthy volunteer … has no expectation of incurring Guillain-Barré syndrome or … a major infection and so … the risk is really … quite pronounced in the healthy

> volunteer because of the fact that the counterfactual [the risk of not participating] … is virtually no risk at all. [Jonathan Kimmelman, ethicist, Canada]
>
> Would I give somebody something that [would cause] long-term risks? … I know that there's been controversy about Zika [which] can cause Guillain Barré syndrome … And who knows how many? One in a million. One in a hundred-thousand. That's a risk … that has to be taken into consideration. [Scientist, North America]
>
> [I]f there's irreversible harm, I think most people would say that that's unreasonable risk … [T]here may be risk of severe injury in some human challenge studies; but, if the risk is very low – one in a million, one in a hundred-thousand – perhaps then that might be considered a reasonable risk. But that's where it does get into judgement. [Regulatory representative]

Table 3.1 Potential long term risks and lasting harms

	Pathogen	Reported in HCS	Mitigation strategy	Strategy used in LMIC HCS
Lasting harm				
Guillain-Barré syndrome	Multiple—campylobacter, influenza, Zika, *Shigella spp.* etc.	No	Early diagnosis and treatment	Unknown
Post-infectious arthritis	Multiple—particularly enteric pathogens incl. *Shigella spp.*	No (possible unreported case)	Exclude those with risk factors (e.g., HLA-B27), early diagnosis and treatment	Yes
Post-infectious irritable bowel syndrome	Enteric pathogens incl. *Shigella spp.*	No	Exclude those with risk factors	Yes
Long term risk				
Relapse	Vivax malaria	Yes	Long follow-up, early diagnosis and treatment, exclude those with risk factors for treatment failure (CYP 2D6)	Yes
Severe dengue (if first infection during HCS)	Dengue	No	Avoid travel to dengue-endemic areas, Vaccination post-HCS	N/A

HLA-B27: human leukocyte antigen B27, a genetic risk factor for post-infectious arthritis. CYP 2D6: Cytochrome P450 2D6, a genetic risk factor for primaquine treatment failure (identified in previous HCS research) leading to vivax relapse. N/A: no dengue HCS have been conducted in LMICs to date

> [S]ome of these infections or some of these infection models [involve] risks that you don't know about and you can develop chronic consequences after these infections. And so I think … we need to fully inform [potential participants] that it's not just … this acute infection, that it could lead to something chronically. [Scientist, North America]
>
> [M]ost of the models will have their very rare risks, [just] like [natural] infections. Like we know many [natural] infections [are associated with] a rare risk of something … exotic occurring, which we rarely see, but … if [natural] infections have that, then challenge models for sure will have that. And obviously you should try to limit that as much as possible, but you're not going to get to 100% safety. [Meta Roestenberg, the Netherlands]
>
> The borderline cases [ethically speaking] are [firstly, challenge studies] where the diseases are serious and people get really sick … and the second kind is where there are these long term effects that aren't entirely predictable. To me those are kind of like two features of the borderline cases. [Ethicist, North America]

3.3.5 Uncertainty

Even for pathogens where the natural history of infection is thought to be well characterised, the fact that HCS allows for a closer examination of pathogenesis from the moment of infection means that not all risks will be known, particularly at the beginning of a research program with a novel HCS design (and/or new challenge strain) when few (or no) people have yet been challenged. Indeed, HCS research has revealed new and/or unexpected aspects of certain diseases, and these findings have led to refinement of HCS exclusion criteria as well as further research (see Table 3.2).

Furthermore, HCS trials of new vaccines may also lead to unexpected adverse effects, given the potential for unexpected interactions between the pathogen, the vaccine, and the host immune system (for example, vaccines for RSV and dengue have in some cases been shown to increase the risk of severe disease upon exposure to infection after vaccination (Acosta et al. 2016; Wilder-Smith et al. 2018)). In any case, such uncertainties are not unique to HCS. First-in-human trials of new drugs have sometimes lead to severe harms among healthy volunteers, such as the infamous first-in-human phase 1 TGN1412 immunotherapy trial that lead to several healthy participants being admitted to intensive care (Kenter and Cohen 2006). One interviewee for the current project specifically cited the TGN1412 trial and made an analogy with first-in-human challenge studies on this point:

> [W]hen you put something into a human being for the first time you really don't know what's going to happen, right? You could kill them. … So you just have a pilot individual or two … You put in a low dose. You have very close observation. You've done toxicology studies. I mean it's so gingerly done. And then you build your way up. [Scientist, North America]

Such uncertainties have implications for consent of HCS participants and ethical review of HCS, particularly new designs (or designs that have as yet enrolled only

Table 3.2 New and/or unexpected findings in challenge studies

Pathogen	Finding	Reference(s)	Impact
Falciparum malaria	Myocarditis/myocardial infarction with non-obstructive coronary arteries	Nieman et al. (2009), van Meer et al. (2014)	Individuals with cardiac risk factors excluded from malaria HCS
Vivax malaria	Pharmacogenetic factors (CYP 2D6) influencing risk of relapse	Bennett et al. (2013)	Further research regarding this polymorphism; potential exclusion of carriers from vivax HCS; public health implications
Dengue	Serositis (a supposed marker of disease severity) in asymptomatic first infections	Mammen et al. (2014)	Further research regarding dengue pathogenesis

small numbers of participants). As a given challenge strain infection and/or HCS design has been conducted in increasing numbers of participants, researchers (as well as reviewers and regulators) can have greater confidence that estimated risks are increasingly accurate and uncertainty reduced. However, since one of the virtues of HCS is that they involve fewer participants than field trials, larger studies (and/or post marketing surveillance of vaccines) may still reveal rare adverse effects (e.g., interactions between the vaccine, the pathogen, and the human host) that were not observed in the small number of HCS participants in earlier phase studies.

In the 2017 NIH Report on Zika HCS, uncertainties regarding the risks to participants and third parties (e.g., due to sexual transmission) were appealed to as considerations (among others) against conducting of Zika HCS (Shah et al. 2017). However, as better estimates of relevant risks are now available and greater understanding of the underlying mechanisms may allow for mitigation strategies, these considerations might now be considered less weighty (by some). More generally, first-in-human HCS in particular will always involve a significant degree of uncertainty. Although this does not preclude novel HCS, it does justify an especially thorough review of prior evidence regarding the pathogen in question (see Box 3.15).

Box 3.15 Uncertainty

> I think with most [HCS designs] you know if you do your screening properly, you hope that nothing will go wrong, but here are people who have conditions that are unrecognized and unrecognizable by the screening tools that we use. For example, this isn't a challenge study, but, for the flu vaccine and narcolepsy, who would've

known to screen for HLA-type before giving a flu vaccine, right? So I don't think you could predict everything. [Gagandeep Kang, scientist, India]

I think there are types of challenge studies or models that … are completely safe if not more safe than other types of trials we do all the time. I think what's hard is when we don't have a good sense of the disease and what all of its longer-term effects might be. With those trials it's very difficult to even evaluate what the level of risk would be. And that's where it's not clear to me whether their level of risk is fully in-line with what we already permit. [Ethicist, North America]

[T]housands of people have been in [malaria] studies over the years, and they must have been a lot more nerve-racking [back when] less than a 100 people [had] been in these studies. [Scientist, North America]

3.3.6 Other Burdens for Participants

Almost all clinical research entails multiple burdens (other than risks) for participants. These can range from minor burdens, such as filling out a short questionnaire or being subject to standard medical examinations, to potentially more significant burdens such as the privacy infringement of revealing one's medical or personal information, to major burdens such as a long duration of hospital stay and/or isolation. Certain study interventions will be more burdensome for some individuals/populations than for others. Due to cultural beliefs regarding the value/importance of blood, for example, blood draws (especially of larger volumes) may be especially worrisome, and thus burdensome, to research participants in sub-Saharan Africa, as compared with other groups who may be less concerned regarding blood draws (Saethre and Stadler 2013; Njue et al. 2018).

Since HCS frequently involve multiple study visits, blood draws, and monitoring by study staff—and since inpatient HCS in particular involve significant time away from normal activities—many HCS designs are potentially associated with a level of burdens that would be high compared with most studies conducted in healthy volunteers. There are other analogous cases in non-HCS research, although infrequent, such as metabolic chamber studies (in which participants sometimes spend days in a tightly controlled, isolated environment, for precise measurement of metabolic parameters), which, when they are conducted in HICs, frequently attract high levels of payment (see Box 3.16). Likewise, major burdens for participants in HIC HCS typically attract significant payment of participants; and this has sometimes been the case in LMIC HCS, often because payment for one night in an inpatient facility is indexed to local wages and participants spend 1–4 weeks of confinement during the study (see Sect. 3.6).

Recent social science work with participants has suggested that HCS participation, particularly in inpatient studies, can lead to a wide range of burdens and/or secondary effects on the families of participants. In one LMIC study, for example, the children of participants were unable to attend school while a parent was participating in HCS

(Njue et al. 2018). One HIC study found that outpatient HCS participants often encountered significant disruptions to their daily lives as a result of participation (Kraft et al. 2019). Many stakeholders we interviewed for this project felt that the burdens of participation (i.e., burdens other than risk imposition) raised ethically important issues for HCS design in need of further analysis.

Box 3.16 Burdens of participation

> [HCS protocols often] keep people in residence for a long period of time. I think that's pretty unique. I don't think we do that for many other studies … just that phenomenon of saying to people – you know, you might need to be in residence for a month or even longer, six weeks, you'll need to stay here and you will not be able to leave, under any circumstances … I don't think we fully understand what the ethical implications of that are. [Scientist, Africa]
>
> [T]here's physical risk, which I think for [some HCS] is quite small, but there is also the emotional risk … but the bigger thing is the burdens. [In some HCS designs] you have to be in residence for fourteen days, minimum, [and] being in residence means that you have to make sure that other parts of your life … and kids, and jobs [are taken care of] … so that's quite a big commitment, and a sacrifice, I would say. [Scientist, Asia]
>
> How can we make [participation a good] experience good for them? What kind [of] residence would that be required to be? … If we are curtailing their freedoms of movement, how does that then balance against the risk? … We are telling them not to go to endemic areas, even when they do get out of there – they're still within the study. In other words, we're interfering with their freedom, and how do we take account for that? [Scientist, Africa]
>
> [Y]ou pay a lot of money for someone to stay as an inpatient. [For example, in a] metabolic chamber study … people were getting paid $6,000 for that, because you're in a chamber for a month. [Ethicist, North America]

3.3.6.1 Mental Health

Since challenge studies often involve significant burdens for participants, these burdens could plausibly include and/or lead to deterioration in mental health (whether or not the participant had a prior history of psychiatric illness). Such risks may be particularly significant during prolonged inpatient studies involving social isolation, and some research groups have adopted careful psychological screening of potential participants to inform judgements about their ability to tolerate periods of isolation (sometimes of several weeks' duration) (Pitisuttithum 2018). Even with careful recruitment practices, one previous LMIC HCS recorded a serious adverse effect related to a participant who was briefly admitted to hospital due to an anxiety crisis (by comparison, in the same study, no physical serious adverse events occurred from the challenge infection) (Herrera et al. 2011). The mental health of

participants is thus potentially an area warranting further social science work and/or ethical analysis; the exclusion of any potential participant with a psychiatric history may be overly restrictive and/or unfair, thus a nuanced approach is needed. As one stakeholder noted:

> [In] Oxford we have a very high proportion of volunteers who have a known psychiatric diagnosis: anxiety, depressive. The majority of those are managed … it doesn't affect their activities of daily living. As to working, maybe they take antidepressants. So it's not as simple as just saying 'Anyone with any psychiatric history is not suitable.' [Scientist, UK/Europe]

3.3.7 Participant Behaviour

All research with human participants involves the possibility of unexpected human behaviours. In the context of HCS, certain participant behaviours might lead to greater risks than those anticipated in the study protocol—for example, participants (i) choosing to withdraw from the study and/or refusing to be treated after challenge infection, and/or (ii) leaving the study site and/or becoming uncontactable after being infected. Since researchers are exposing healthy volunteers (and sometimes third parties) to potential severe harms (e.g., if an infection with malaria were to go untreated), investigators arguably have especially weighty ethical responsibilities to ensure that the risks entailed by such human behaviours are minimised. It is perhaps also the case that participants who consent to be infected have an ethical responsibility to abide by monitoring, treatment, and/or social distancing requirements during and/or after the study (especially where not complying might entail risks being imposed on others). We discuss the right to withdraw and the risk of participants absconding (i.e., leaving the study without informing research staff) below.

3.3.7.1 Participants' Right to Withdraw

The right of participants to withdraw from a study—at any time, for any reason, and without having to give a reason—is widely endorsed in theoretical research ethics and in practice, although the practical implications of this right have been a matter of debate in particular contexts (Edwards 2005; Helgesson and Johnsson 2005; McConnell 2010; Schaefer and Wertheimer 2010). If a challenge study participant were to exercise this right after being infected with certain pathogens and before the infection has resolved (with or without curative treatment) then this might increase risks to participants themselves and/or risks to third parties. Many HCS researchers interviewed for this project recognised the difficulties that might arise in such contexts and the potential for adverse outcomes that could undermine public trust in research, including (in some cases) a higher potential for third-party risk in LMICs. Investigators have tried to account for this in study protocols;

however it was seen as an unresolved issue in need of further analysis and guidance for researchers (see Box 3.17).

Box 3.17 Participants' right to withdraw

> [T]hese are adults and … their participation in the study is voluntary. They could always withdraw their informed consent. They could walk even though that is a risk to the community at large. We can't hold them against their will. And that was a concern. And so we spent a lot of time emphasising to them … early on in the trial, how important it was that they complete the treatment and they complete the follow-up. And that we understand that it's a long time. [Carl Mason, scientist, USA]
>
> [I]n our consent forms, we [advise participants that] in the event that you wish to leave the study, of course you're allowed to do this, but we would expect you to complete a course of treatment … But I think if there was a scenario where somebody left and they wouldn't take the treatment, we didn't have a protocol to follow in that scenario. I think we would have to let them go. We did say if somebody went missing … we would notify the local authorities to search for them because there would be a concern about their mental and physical health. And we would contact their next of kin to try and locate them … Of course, in the UK, the concern [in malaria HCS] is not about transmission, it's about wellbeing of the patient. But, you know, in Nairobi [given the nearby presence of vector mosquitoes] there's a potential to have onward transmission as a result of not having treatment. [Scientist, UK/Europe]
>
> Another issue I see as more complicated in the context of challenge trials is the right to withdraw … [W]ithin the context of the US regulations it's considered a right that people have, that they can exercise at any time. There are other trials where you still can't quite just leave when you want to leave because it may not be safe for you, but challenge trials are trials where that issue becomes difficult. And I think it would be helpful to know more, to have a better public health framework maybe similar to what we think about for quarantine, to understand what [are] the limits of measures to restrict someone's liberty, if they're in a challenge trial, like when is that even acceptable and to what extent. [Ethicist, North America]
>
> [W]hat we have in these consent forms [in Gabon], and what we also explained to them, is that they can leave anytime – but when they have been infected … they need to come back to be treated. [Benjamin Mordmüller, scientist, Germany]
>
> [T]here are reviews of the data on informed consent [but] the right to withdraw is less well-understood in low-income countries. And if that's right the rates of withdrawal are something that is really tricky in the context of challenge studies because there may be times when it's not safe for someone to leave the research. [Ethicist, North America]

3.3.7.2 Risk of Absconding from Studies

Participants have occasionally absconded from HCS after being challenged, including one high profile case of a participant in a UK malaria HCS who was

eventually located in the Netherlands.[9] Absconding from a study might in some scenarios be a special case of the right to withdraw (i.e., participants exercising the right without notifying study staff), or, in others, it might reflect impaired decision-making by a participant due to physical or mental illness. Many of the scientists we interviewed identified the possibility of such events as a significant concern that had (in some cases) led to revisions of study design and procedures (see Box 3.18). One solution might be closer monitoring of participants. However, the more closely participants are monitored during the study (whether on an inpatient or outpatient basis), the more this monitoring may be burdensome for them. Thus there are important ethical trade-offs to be made in study design between post-challenge monitoring that is sufficiently close to minimise risk but not so intrusive as to be overly burdensome.

Box 3.18 Risk of participants absconding and risk mitigation strategies

> [W]e had someone in one of our typhoid studies who absconded because he was an actor and had an audition, which he hadn't been expecting, for a lead role in a play … [W]hilst he was developing typhoid he went to do his audition, and we lost touch with him and we were very worried about him and in fact he got the role … and he actually had positive blood cultures for typhoid at the time. [Scientist, UK/Europe]
>
> [W]e had one volunteer leave from one of our studies … [H]e'd been challenged as part of that study and he decided he'd go and see his uncle [in another country]. And fortunately we caught him and we made sure he took [treatment for his infection], and so on. [Scientist, North America]
>
> There was talk of once in a while somebody sneaking out and going to the shops but not much of like, somebody being away in terms of going home and putting others at risk … Somebody will sneak out of the gate of the university and go to the shops nearby and come back. [Scientist, Africa]
>
> [A]s a result of our lost volunteer … we wrote into our consent document and our volunteer information sheet and our protocol, actions that we would undertake if a volunteer went missing. [Scientist, UK/Europe]

3.4 Risks to Third Parties

Many types of research with infectious diseases can pose risks of infection to those not directly participating in the research (i.e., third parties) (Kimmelman 2005; Battin et al. 2008; Eyal et al. 2018; Shah et al. 2018). In the case of HCS, the principle risks to third parties are related to transmission of the challenge strain(s) from infected participants to others—and potentially onwards to many more people. Third-party

[9] https://www.theguardian.com/society/2010/oct/19/malaria-trial-nurse-found [Accessed 29 March 2019].

risks are sometimes referred to as 'bystander risks'; we eschew this term here, because an infectious disease can, via a chain of transmission (sometimes of great distance and/or duration), harm distant others, not only bystanders (i.e., those who happen to be present when the research is taking place although not themselves participants).[10] Risks to third parties include the possibility of transmission (and/or harm) to unborn children, providing a reason to exclude pregnant women from HCS (Shah et al. 2017). Other third parties at risk can include participants' family members, but also members of the general public (Miller and Grady 2001; Hope and McMillan 2004; Bambery et al. 2015; Shah et al. 2017).

Other effects on third parties may be relevant for certain HCS designs. Where live-attenuated vaccine strains are tested in HCS (particularly vaccines for enteric pathogens such as *Shigella*), for example, there is sometimes a small probability of transmission of the vaccine strain to third parties (Kimmelman 2005) (although, given adequate attenuation, the potential harms are low, at least for immunocompetent individuals, and there may even be a net benefit of such transmission (Paul 2004)). Where challenge with vector-borne pathogens is administered by mosquito bite, furthermore, the potential introduction of a new vector species (imported from elsewhere for the purposes of HCS) could alter local ecology[11] (were the vectors to escape from the study facility) and, in endemic settings, the epidemiology of vector-borne diseases transmitted by this vector (Orjuela-Sanchez et al. 2018).

Some have argued that researchers have extensive ethical duties to third parties where there is a risk that infection will be transmitted to them from research participants. In the context of infectious disease research more generally (though not focused specifically on HCS), Battin et al. have argued that, where it is possible to identify specific people at risk, researchers should obtain individual informed consent from these third parties before commencing a study and/or, where the risks are significant but particular third parties are not readily identifiable, some form of community consent should be sought (Battin et al. 2008).

One way to obviate the need for such additional consent procedures is to reduce third-party risks to near zero by (i) rigorous infection control and biosafety procedures at HCS research centres, and, in some cases (ii) strict isolation of participants (e.g., by keeping them in an 'inpatient' setting for the period in which they are potentially contagious), although this in turn entails significant burdens for participants. Alternatively, where such third-party risks are not reduced to near zero they could in some cases be monitored and/or quantified by (enhanced) public health surveillance in the local area including genotyping of strains detected to assess the degree to which the challenge strain is transmitted to the local population. For example, one recent paratyphoid HCS design by UK investigators explicitly included provisions for the institution of such public health surveillance

[10] Others have opted for 'risks to nonparticipants' (see Eyal et al. 2018).

[11] This risk is not unique to challenge studies, as other types of (vector-borne disease) research sometimes involve maintaining colonies of vector species and, in some cases, the importation of such species.

measures in the event of presumed or suspected transmission of infection from participants, including the provision of the challenge strain to local public health microbiological laboratory for comparison with any clinical isolates (e.g. those detected during a public health outbreak occurring around the time of the proposed study) so that it would be possible to make accurate assessments of whether third-party transmission from study participants had occurred (McCullagh et al. 2015). This, however, might significantly increase study costs and require capacity building of local public health laboratories in LMICs.

In any case, while some may debate whether such strict duties (to obtain consent from any third parties at risk) always apply, the potential risks (even if small) may vary in different contexts depending on the mode of disease transmission. For vector-borne diseases such as malaria, if there are no local vectors then there are minimal risks of third party transmission (apart from blood donation by participants while infected) (Herrera et al. 2009; Hodgson et al. 2014; Hodgson et al. 2015). The risks of transmission of diarrhoeal pathogens via sewerage systems have been considered in reviews of HCS protocols (Cohen 2016; Pitisuttithum 2018). Such risks may be low in HICs with adequate sanitation, but could be higher in communities with poor access to sanitation (e.g., in LMICs), suggesting a strong rationale for inpatient studies and/or robust biosafety procedures in such settings (Pitisuttithum 2018).

Conducting HCS in endemic LMICs may affect the potential third-party risks of such studies in multiple ways. On the one hand third parties with pre-existing immunity (and/or other forms of resistance to the infection in question) may be at lower risk of severe disease were they to be infected as a result of third-party transmission from study participants. On the other hand, other third parties might be at higher risk, including children (especially those who are malnourished, unwell for other reasons, etc.), those with health issues including other chronic infections (e.g. HIV), and/or those with poor access to healthcare. More generally, since populations in LMICs often have higher levels of ill health partly because of inequities in the social determinants of health, some might consider it less ethically acceptable (and/or potentially more unjust) to impose third-party risks of infectious disease in such contexts, even if the background risk of the infection in question is already relatively high[12] (e.g., where HCS are conducted in an endemic area—see related discussion of background risk in Sect. 3.3.3).

Thus, the potential for higher third-party risks in certain contexts can lead to controversial questions. How important, for example, is a small third-party risk and/or single episode of transmission (e.g., from a study participant to a third party) in the context of high local endemic transmission (and/or high average local levels of immunity)? Some individuals and communities may consider this additional risk negligible, while others may see each additional episode of transmission as highly significant –stakeholders interviewed for this project held widely divergent opinions

[12] A further relevant consideration, depending on the disease in question, is whether the challenge strain is already prevalent in a given endemic area (since participants and third parties may have immunity from prior infection with locally prevalent strains that would not necessarily protect against severe disease when infected with a different challenge strain).

on this matter (see Box 3.19). Given this potential controversy, and given the potential for third-party risks to undermine public trust in research (see Box 3.20), the potential for such risks would constitute an additional reason for community engagement (to assess community views on the importance of such risks and/or to seek community consent for the research to proceed) and for carefully designed research procedures that reduce transmission risks.

Box 3.19 Third party risk and background risk

I think [the risk to third parties of a malaria HCS in a highly endemic area] is a very, very small risk only if you can even, or should even, call it a risk –[because] eighty per cent and more [of the local population] harbour malaria parasites at any given time point. [Scientist, UK/Europe]

I think it really depends on the background transmission rate … [I]f you're working in a hyper endemic setting, I just don't think there's any quantifiable increased risk to the population … [P]eople are being infected every week, all the time, so … I don't think that's a risk, a real increase[d] risk for the population. [Scientist, UK/Europe]

[If] there is not much greater risk [to third parties, compared to background risk] and you are not using a strain that is resistant to any of the drugs that are available, then people [once they understand this] will be much more comfortable I think … most of the risk that we see are much more academic than real [or] practical. [Scientist, Africa]

[In Thailand, even if a participant were able to leave the isolation ward, local population] antibody levels were much higher than the antibody levels that were seen in volunteers in the previous studies in the US. So for [*Shigella*], and probably for some other diseases as well, such as malaria in challenge studies in endemic areas, you're going to have people [in the general population] that have partial immunity. And the risk [to third parties] might actually be a little less. [Scientist, North America]

[C]ontainment is possible. It's expensive. Not so expensive in developing countries as it is in developed countries, but it's possible and if you can minimise risk [to third parties] you should do so, and remember that it's a drop in the ocean, but it's a drop in the ocean that can result in death. [Scientist, UK/Europe]

I think of the response if an individual is inadvertently infected. A third party individual is going to [feel] different[ly about it] if they later learn that it's because they came into contact with someone who was in a scientific experiment, than if it's [just] because of a mosquito … [R]isk is, or has, these … moral layers … that we all … bracket when we talk about risk … in a quantitative way. [Jonathan Kimmelman, ethicist, Canada]

Box 3.20 Third party risk and public acceptance of research

> [T]hird party risks are a very, very important component, both on … first principle research ethics that … if there are third party risks there are risks that are being born involuntarily by other individuals but also from the standpoint of public perception … [W]hen the public perceives a risk that is enduring, [and] as having been involuntarily endured, then there tends to be much more acrimony and controversy than when the public feels that … there's a voluntariness and an awareness … and so I think those kind of third-party risks are the kinds of risks that you worry about in terms of destabilising or undermining … public support for research. [Jonathan Kimmelman, ethicist, Canada]
>
> We just need someone with typhoid on the Oxford study to go and not tell them they're working in a food van and have an outbreak in Oxford and that will be it [for the whole field of challenge studies]. [Scientist, UK/Europe]

3.4.1 Third-Party Risks and Studies of Transmissibility

Some HCS are designed to investigate the transmissibility of the pathogen in question. For example, such studies might involve measuring the number of microbes in the blood and/or stool of an infected participant (the idea being that the number of microbes present is in many cases correlated with the risk of transmission to others). Investigation of transmission was one of the goals of several historic yellow fever and malaria HCS (see Sect. 2.2) and was also identified as an area potentially in need of further work by malaria HCS researchers based in Kenya (Hodgson et al. 2015). HCS that specifically aim to investigate the transmissibility of the challenge infection warrant particularly careful design with regards to third-party risk (e.g., because studies not investigating transmissibility can be designed with early curative treatment, whereas transmissibility studies will often be required to leave participants infected with the challenge strain for longer periods of time, during which they may be able to transmit the infection to others).

Australian investigators recently conducted a falciparum malaria HCS assessing the transmissibility of falciparum malaria in malaria-naïve Australian volunteers who were treated post-challenge so as to reduce symptoms among participants (since malaria symptoms are caused by a particular form of the parasite, amenable to specific treatment) without affecting the transmissible forms of malaria (gametocytes). These transmissible forms were then measured by feeding mosquitoes on the blood of participants so as to provide a model of transmissibility against which transmission-blocking interventions could be tested (Collins et al. 2018). To our knowledge the only similar HCS testing transmissibility in an LMIC is a vivax malaria study in Colombia that was based on secondary analysis of samples from one of the HCS case studies reviewed below (Arévalo-Herrera et al. 2014). Both the Australian and Colombian

studies were performed (using mosquitoes in tightly controlled laboratory settings) in non-endemic areas lacking malaria vector mosquitoes in the wild, meaning that there would be effectively no risks to third parties. Were such transmissibility studies to be conducted in malaria-endemic settings and/or areas with local vector mosquitoes, study design and review would arguably require careful assessment and/or mitigation of third-party risks.

3.5 Participant Selection

Since the formalisation of ethical principles for research, there have been debates regarding how fairness should be understood in the context of selecting participants for research and the extent to which special considerations apply to recruitment from vulnerable populations (National Commission for the Proptection of Human Subjects of Biomedicaland Behavioral Research 1978; Meltzer and Childress 2008).

Individuals and populations can be vulnerable in different ways, and the term 'vulnerability' is generally used in research ethics to identify those who are more likely to be exploited and/or harmed as a result of participation in research (Macklin 2003; Luna 2009; Rogers et al. 2012; Lange et al. 2013). Individuals might be physiologically vulnerable (e.g., at higher risk of severe harm as a result of participation in research), socio-economically vulnerable (e.g., perhaps more likely to be influenced by payment for research participation—see Sect. 3.6), and/or vulnerable in terms of being unable to provide autonomous consent (e.g., children—see Sect. 3.5.4) or because of dependence on others (e.g., children, institutionalised individuals) (Goodin 1986; Luna 1997; Macklin 2003).

A particular concern regarding exploitation of vulnerable populations is that relatively privileged populations may be the primary beneficiaries of research conducted in more underprivileged populations (Macklin 2003). However, conducting HCS in LMICs may be less exploitative in this regard if (i) the findings from such studies are thus more relevant to the (LMIC) populations in which the pathogen being studied is endemic and (ii) scientific knowledge and/or new interventions produced by HCS are ultimately made available to those populations (Wenner 2015, 2017).

An increasingly recognised problem is that excluding vulnerable populations from research as a way of protecting them from further burdens can ultimately lead to these same populations being excluded from the benefits of research (Sheffield et al. 2018). It may sometimes thus be ethically important to include vulnerable populations (with appropriate measures to minimise burdens), especially where the results of research in other populations are not likely to be generalisable to the vulnerable populations in question. This is one consideration that is sometimes in favour of conducting (more) HCS in LMICs.

3.5.1 Vulnerable Populations in Human Challenge Studies

Since many pathogens for which HCS might be considered occur at higher rates in poor LMIC communities that are particularly vulnerable (in multiple ways), fair participant selection for HCS may be especially complex (World Health Organization 2017). Concerns regarding the potential for exploitation of, or harm to, individuals from vulnerable populations might thus explain why more HCS haven't been conducted in LMICs to date. However, there are several countervailing considerations. First, in cases where the results of HCS in non-endemic HIC populations are not likely to be generalisable to LMIC populations where a given pathogen is primarily endemic, there may be both scientific and ethical reasons to recruit HCS participants from an endemic population (Hodgson et al. 2015) (see Sect. 3.2.1.1). Second HCS in endemic LMICs might sometimes entail relatively lower risks and/or potential for direct benefits to participants (e.g., related to immunity) as compared with those in non-endemic settings—meaning that HCS in some 'vulnerable' populations might (perhaps counterintuitively) involve less risk to participants (Selgelid 2013; Lell et al. 2017; Selgelid and Jamrozik 2018) (see Sect. 3.3.3). Thirdly, undertaking HCS (and/or other kinds of research) only in HICs might undermine efforts to build research capacity in endemic settings and exacerbate the research neglect of certain pathogens (Selgelid and Jamrozik 2018). Finally, recruitment in HICs might still end up disproportionately selecting vulnerable individuals, especially since HCS often involve large time commitments and/or isolation from other social activities, meaning that, for example, unemployed people and/or students might be overrepresented in HIC study populations (see Box 3.21) (Elliott and Abadie 2008).

Many of those interviewed for this project supported conducting HCS in LMICs because the results may then be more relevant/generalisable to the eventual target population for novel interventions. Some noted that although the rates of poverty and some other vulnerabilities are often higher (on average) in LMICs, LMIC populations should not be labelled as vulnerable *en masse* and thus excluded from research. Each community, in HICs as well as LMICs, includes a range of individuals with different levels of various vulnerabilities. Whether HCS are conducted in HICs or LMICs it is thus important to evaluate the specific vulnerabilities of the (potential) study population and design studies in ways that reduce the chance of harm and/or exploitation accordingly.

Box 3.21 Participant selection and vulnerable populations

> I do think location matters. I understand the concern about exploiting populations that are already vulnerable because they're living in an endemic setting, and, like, "Oh well, now you're adding to their risks." But I, I think there are reasons to do it in endemic settings first. [Ethicist, North America]

> [O]ccasionally I see people … neglect the fact that in low income and middle income countries you have islands of affluence, and in high income countries you have islands, if not continents, of disadvantage. [Jonathan Kimmelman, ethicist, Canada]
>
> I'm completely committed to the value of fairness. But I think we, as a result of that, should not act as if persons in low- and middle-income countries were incapable of altruistically participating in research that benefits others. [Ethicist, North America]
>
> [HCS participants are] usually younger people because we need healthy people, and they tend to be people who have enough time to manage this. So … sometimes it's so demanding in terms of time that people who have high-stress jobs or very busy families can't really participate. And so it's generally people who just really care about contributing something and feel good about contributing something to science and biology. [Scientist, North America]
>
> I wouldn't say all of them but a significant proportion are people that are unemployed, you know. And so … you're giving them a nice opportunity for income. And whether they understand … And then that needs to be balanced with them fully understanding the risks. [Scientist, North America]

3.5.2 Consent

Informed consent for research participation involves a potential participant with adequate cognitive capacity who is adequately informed regarding the details of a study, understands this information, and makes a voluntary, uncoerced decision to participate. Among those interviewed, there was widespread agreement that HCS per se did not need a special consent process. However, many supported the notion that (in research in general, and in HCS in particular) the higher the burdens (including risks) of a given study, the greater the responsibility of those conducting the study to ensure that participants are able to give fully informed consent. HCS that involve new or particularly complex models, higher risks, and/or those recruiting individuals with little prior experience and/or understanding of research may thus warrant an especially careful consent process (see Box 3.22). Our review of LMIC HCS case studies found that consent processes in HCS frequently involved multiple information sessions and/or tests of understanding, suggesting that investigators recognise the importance of more stringent consent processes in such studies.

Box 3.22 More stringent consent requirements

> [W]hen you have elevated risk … that expectation for understanding and for voluntariness is much more enhanced than when you have low levels of risk, and so under those circumstances there ought to be a much more demanding and exacting consent process. That really seems straightforward but that also seems embedded in the standard notion of … how we do informed consent so [it] doesn't seem that

> claim is a radical departure from what we already believe and practice. [Jonathan Kimmelman, ethicist, Canada]
>
> [T]he greater the risks of study participation, the greater your duty to really be sure that your subjects are fully understanding what's at stake. [Ethicist, North America]
>
> [T]he things that do actually improve understanding are giving people more time to think about a consent document and then testing their understanding, and then re-educating them on the things they don't get right. So those things I think probably should be more universally implemented than we do right now. And they would also be useful for challenge studies. [Ethicist, North America]
>
> CHIM studies might be a good example of a circumstance where you'd actually want to build in some comprehension checks and that's definitely not just an issue for low resource settings [Ethicist, North America]
>
> So [in Gabon] we explained [the risks of the study] but we also have a quiz afterwards, so they actively have to answer these questions by themselves … [W]e have a quiz with multiple choice answers, and they have to pass this quiz [so] that we can somehow have evidence that they really understood. [Benjamin Mordmüller, scientist, Germany]

3.5.3 Education Level

It is sometimes thought that it would be more ethical to recruit those with higher levels of education as research participants because this may improve informed consent (if educated participants more easily understand information about the study). Some HCS (including in LMICs) have thus aimed to recruit tertiary-educated individuals and/or university students (especially medical students) in particular (Hodgson et al. 2014; Shekalaghe et al. 2014). Despite these apparent advantages, there are also several ethical disadvantages of such a recruitment strategy: (i) excluding less well-educated individuals might be unjustified if they are able to understand a study well enough to provide adequate informed consent, (ii) university students (or those who have received university education) may not be representative of the eventual target population for an intervention (e.g., because they are more likely to be affluent and/or to live in cities and less likely to live in highly endemic parts of LMICs and/or because in some countries women are much less likely than men to receive university educated), (iii) excluding less well educated individuals from HCS research may thus be unfair, especially where poor and/or less well educated individuals are at higher risk of the disease in question and/or where women are underrepresented in tertiary education (leading to the exclusion of such individuals from research), (iv) students may feel pressure to participate (e.g., from academics within the faculty with an interest in the study) making consent less voluntary (Bonham and Moreno 2008), (v) educated individuals (e.g., healthcare workers) may sometimes actually be less compliant with study protocols than other potential participants. Two anecdotal cases support

the latter point: (1) the participant who absconded from one falciparum malaria HCS (discussed below) was a healthcare worker, and (2) in a Colombian malaria HCS discussed below, one participant who worked as a paramedic was strongly suspected to have self-treated with antimalarials after challenge, thus undermining the scientific value of his or her participation in the experiment (Herrera et al. 2009).

3.5.3.1 Education Level in Low- and Middle-Income Countries

In practice, LMIC investigators have sometimes been successful in recruiting enough tertiary-educated individuals for HCS (Shekalaghe et al. 2014; Jongo et al. 2018), whereas others have found it difficult to recruit as many students as planned (and thus recruited others with lower average education levels (Hodgson et al. 2015)). Social scientists embedded with more recent challenge studies have suggested that many less educated individuals appeared to be able to provide adequate informed consent, especially with well-designed community engagement and multiple opportunities for careful explanation of the study (Njue et al. 2018). Including less educated individuals can help researchers to recruit more people from rural, highly endemic areas, and thus learn more about acquired immunity and the efficacy of interventions in those at particularly high risk of the infection in daily life (Hodgson et al. 2014; Hodgson et al. 2015). More work will be required in other settings to assess the quality of informed consent and whether the presumption in favour of recruiting especially well-educated individuals is justified.

There may be one additional way in which recruiting those who live in or near highly endemic areas, even if they are less educated, is ethically preferable (so long as adequate informed consent is assured): such individuals may be more likely, on average, to have an interest in the goals of the research because prior experience of the infection in question (e.g., in themselves or those close to them) may lead to greater understanding of the need to reduce the harms of such familiar infections and thus motivate participation in research, above and beyond a more general sense of altruism that may motivate individuals in non-endemic areas (see Box 3.23) (London 2005; Njue et al. 2018).

Box 3.23 Consent in LMICs where HCS pathogens are endemic

> Some people worry that, if you do a challenge study in an endemic setting, you have to do more education because people would be less likely to understand what the study actually involves. And there … the data on informed consent actually are somewhat reassuring … [T]he data on informed consent suggests that there isn't a systematic difference in terms of geography, in terms of what people understand. [Ethicist, North America]

> [In] a country like Brazil, where Zika has been a problem … there are people who are willing to … be soldiers against the disease that they see afflicting … their peers, as opposed to … a low income person in Baltimore, who is unlikely to get Zika exposure, unlikely to know someone who has Zika, and is [participating in research] to pay the rent. [Jonathan Kimmelman, ethicist, Canada]
>
> [W]e had [one paticipant] who'd never been to school, but he passed the test of understanding … and we had a few [with] really the low primary level kind of education … So, there were all kinds of education levels. [Our work with these participants] helped us to … realise it does not necessarily have to be the level of education that mattered, it's about understanding what the key elements … of this study are. [Scientist, Africa]
>
> I wouldn't call [consent practices in LMIC HCS] special … [E]verywhere we go the informed consent is adapted to the local setting. And some places are better-educated than others. Some have two or three different languages that you … need to translate into … The informed consent doesn't change hugely between different sites, and we have had steers in the past by the IRBs to say … 'You can make this a bit more simplified,' or, 'You could clarify that.' So we rely heavily on the advice of the [LMIC] IRBs to help us with that as well and get some excellent feedback from them in that regard. [Scientist, North America]
>
> If you're developing a vaccine, and you're planning to actually deploy that in super rural areas where the majority of the population is illiterate, obviously you would want to move that controlled human infection model to that population also because that population for lots of scientific reasons might respond differently so you need to … research whether it's going to work in that population as well. [Meta Roestenberg, the Netherlands]

3.5.4 Children

One of the most controversial questions regarding HCS is when, if ever, it might be ethically acceptable to recruit children as participants in studies that could cause significant symptoms/disease among (child) participants. On the one hand, many pathogens of interest (e.g., falciparum malaria, *Shigella*) predominantly harm young children in endemic settings who would thus stand to benefit most from new vaccines (and thus the research in question). There would thus be a *scientific rationale* for HCS in children. On the other hand, (i) HCS in carefully selected adult volunteers might be sufficiently generalisable to children at risk (and thus obviate the need to recruit children), (ii) children lack the capacity to provide informed consent to participation, which is especially important given that the consent of participants arguably matters more for burdensome and/or higher risk studies (as discussed above), (iii) challenge infection might sometimes be higher risk in children, and (iv) public perceptions of the enrolment of children in HCS could undermine trust in HCS and/or research more generally.

For these and other reasons, the only HCS performed with children have used (live-attenuated) vaccine strains of micro-organisms as the challenge agent (Groome et al.

2017)[13]; recent/modern HCS have thus avoided the use of disease-causing challenge organisms in children (WHO Expert Committee on Biological Standardization 2016; Baay et al. 2018). Among those interviewed for this project, there was widespread consensus that, even if HCS in (involving disease-causing organisms) in children could be conducted safely, there should be a presumption against enrolling children in HCS (involving disease-causing organisms) with HCS in adults and/or field trials in children as plausible alternatives to be tried first. Many suggested that a very carefully described rationale and wide consultation would be required before any such study were considered. A particularly strong theme was the issue of public and/or community acceptance and the risk of undermining trust in research (see Box 3.24).

Box 3.24 HCS in children

> [T]o do these challenge studies for some of these diseases that occur so early in life, you know … a child with diarrhoea … in order for you to really get a good readout on the value of vaccine for child diarrhoea, you can't do it in an adult. You have to do it in a child. But … I don't think we're talking about doing human challenges in children, because I think that there's a lot of issues there in terms of consent. [Scientist, North America]
>
> [A]s a researcher, I would say you could do [a malaria HCS in children with early treatment] safely, but getting it past an ethics committee would be a massive challenge. Certainly, you know, giving kids malaria … the optics of it are not good. So, it would have to be preceded by a massive public and stakeholder engagement campaign. [Scientist, Asia]
>
> I think we might be able to justify [a *Shigella* HCS vaccine trial in children] but it would … definitely be on a case-by-case basis and there would have to be tremendous consensus both in the host country probably as well as globally. That's something you would have to take to [a] body like WHO and really try to build a consensus. [Carl Mason, scientist, USA]
>
> [T]here are certain kinds of risks and certain kinds of incidents that tend to, more than other kinds of incidents, galvanize public opposition campaigns and among those I mentioned is involuntary exposure but among those is risk to children. [Jonathan Kimmelman, ethicist, Canada]
>
> [Y]ou know the difficultly of doing vaccine research in children and you just have to have a few things, coincidently, go wrong and you can destroy a whole program of research or public health implementation. [Scientist, UK/Europe]
>
> I think … in general most people would say that it's just … unacceptable to do challenge studies in children. I think that's most people's starting point, and I think before we move away from that position, we'd have to be on really very solid ground … I hope nothing like that proceeds without all sorts of very extensive consultations and discussions. [Scientist, UK/Europe]

[13] In such cases, exposure to the live-attenuated vaccine strain as a challenge agent would entail an extremely low risk of harm and perhaps even a net benefit to participants.

> [T]here's already, to me, a serious public relations issue about challenging people with a pathogen … and if you were then to translate that to doing that in a group who can't provide consent and something goes wrong I think is obviously a disaster for that family but perhaps for the whole challenge community an even bigger disaster and it starts to feel like [the unethical HCS] around the time of the Second World War. [Scientist, UK/Europe]

3.5.4.1 Generalisability of Adult Challenge Studies to Children

If children are excluded from HCS aimed at understanding and preventing infections that predominantly cause harm to children, then, for pathogens that mainly affect this population, researchers should arguably select participants such that the findings (e.g., regarding vaccine efficacy in the target population) can be generalised to children in endemic settings as reliably as possible (even if there remain important differences between children and adults with respect to the infection in question and/or vaccine efficacy estimates). This raises a further difficulty: children in endemic settings share certain characteristics with adults in similar endemic settings (e.g., genetics, microbiome, etc.); but, with respect to immunity, they may actually be more similar to adults in non-endemic settings (since both young children in endemic settings and most adults in non-endemic settings will be non-immune to the pathogen in question).

Because many adults in endemic settings will have (partial) immunity to the pathogen in question, it may be difficult to recruit non-immune adults locally. Thus it may not always be clear whether it would be (ethically and scientifically) preferable to conduct a given HCS design with adult volunteers from a LMIC in which the pathogen is endemic or in those from a non-endemic (LMIC or HIC) population. An ideal approach, with respect to the scientific aim of generalisability, would be to recruit non-immune (ideally never exposed) adults from a population in a non-endemic area of a LMIC (rather than, for example, from a geographically distant and genetically different HIC population) that would also be closer to a population of children in an endemic area in other respects (e.g., genetics, microbiome). From a pragmatic point of view, it may sometimes be difficult to identify and/or recruit a sufficient number of such individuals (especially if non-immune adults are a rarity in areas near endemic settings), in which case HIC HCS might be more justifiable (see Box 3.25).

Box 3.25 Alternatives to HCS in children

> [D]oing something in children with a challenge model, when you could do that in adults, or in naive individuals in [a] developed country, to me, doesn't feel justifiable. [Scientist, UK/Europe]

> [S]cientifically, the advantage of working in a developing country is where the relevance of the challenge model is increased by working in the relevant population; and, so, in the context of a disease which primarily affects children, studying adults in an endemic setting, in a developing country, may not be a very good model for understanding the disease in children and it could be that studying healthy volunteers in Australia or in the UK, who are naive to that disease, may be more relevant to children. [Scientist, UK/Europe]
>
> I think [enrolling children in HCS] is really quite likely to have a major adverse effect on the public perception of research … even if you could find parents that would consent … I would be very concerned about that. I think, this is the one area [for] which [there] might be some justification for doing the challenge studies in non-endemic countries … [T]he most practical way of providing data that is relevant to young children, at least in the case of malaria, is with non-endemic adults, because in both cases they're non-immune. [Scientist, UK/Europe]

3.5.4.2 Recent Example of a Low Risk Challenge Study in Children

One recent study of a rotavirus vaccine in South Africa used an HCS design, although the authors do not refer to it as a challenge study (Groome et al. 2017). The study recruited healthy children aged 2–3 years with the aim of testing the safety and immunogenicity of an inactivated injectable rotavirus vaccine; the injectable vaccine contained rotavirus proteins (in contrast to live-attenuated rotavirus vaccines that contain a complete virus potentially capable of replication). After vaccination (or placebo), the children were challenged with a live-attenuated rotavirus vaccine strain, and investigators tested (among other outcomes) whether the inactivated injectable vaccine reduced the shedding (in stool) of the live-attenuated rotavirus vaccine strain. There was some evidence that the inactivated vaccine reduced such shedding (thus, if such an effect were generalisable from the live-attenuated rotavirus strain to wild-type strains, this would suggest that the injectable vaccine might reduce replication of and/or disease resulting from and/or the transmissibility of wild-type rotavirus in those vaccinated and subsequently exposed) (Groome et al. 2017).

It is interesting that the authors did not refer to the above study as a challenge study, although other researchers have identified it as an example of HCS in children (Baay et al. 2018). One might think that it was not considered an HCS design because the challenge agent was not a disease-causing strain of rotavirus (i.e., it was attenuated to a degree that, like other live-attenuated vaccines, it would be expected to lead to immunity to the infection in question without itself causing symptoms/disease). However, HCS need not always be designed to result in symptoms/disease in volunteers (See, for example, Sect. 3.3.2.1), and HCS using (asymptomatic) infection/viraemia as the goal/endpoint of challenge (i.e., an 'infection model' involving few or no symptoms among participants as opposed to a 'disease model' involving significant symptoms) have been proposed and/or conducted with arboviruses such as dengue and Zika (Larsen et al. 2015; Durbin and Whitehead 2017).

In any case, the rotavirus study discussed above does not set a precedent for disease-causing HCS in children since the challenge agent used (a live-attenuated vaccine strain) would (i) entail minimal, if any, risk to participants, and (ii) potentially provide direct benefits to participants if the live-attenuated vaccine strain provided/increased immunity against wild-type infection.

HCS with such highly-attenuated strains (whether designed as vaccines or not) might not be especially generalisable to wild-type infection, which would in some cases undermine the scientific rationale for the use of such designs (see Sect. 3.2.1.1) (Selgelid and Jamrozik 2018). However, if it were shown that an attenuated strain that is incapable of causing disease among participants nevertheless provided useful generalisable knowledge regarding infection with wild-type strains, such a strain could potentially be ideal for use in HCS (in children or in adults) with respect to the assessment of the relative burdens and benefits of such a design.

3.6 Payment of Participants

Enrolling in a challenge study often entails (i) potential financial costs for participants (e.g., travel costs, childcare, and time away from usual activities, including paid work), (ii) potential burdens during participation (including, for example, exposure to risk and/or harm and potentially long periods of isolation—see Sect. 3.3). Since research participants endure these costs and burdens contributing to projects that primarily aim to benefit others (e.g., future people at risk of the disease being studied), it has been argued that payment is often ethically appropriate—although payment of research participants remains controversial, especially in the contexts involving (economically) vulnerable populations and/or high levels of payment (Macklin 1981; McNeill 1997; Savulescu 2001; Cryder et al. 2010; Gelinas et al. 2018). Importantly, payment may be intended as (i) reimbursement for costs incurred, (ii) compensation for harms (if they occur), (iii) compensation for other burdens, (iv) an incentive for participation, or some combination of all of these goals (Gelinas et al. 2018).

Attitudes toward the payment of research participants vary across individuals and across different cultures/countries, as do payment practices. Small reimbursements (e.g., for travel costs) are relatively uncontroversial and quite common across jurisdictions. The need for compensation for research-related harms (if they occur) is also relatively uncontroversial, and was widely supported among interviewees for this project, although legislation and current practices regarding such payments vary considerably in different countries (Chingarande and Moodley 2018). For example, LMIC researchers may sometimes have difficulty obtaining the necessary insurance to cover such compensation for harm, which can be one factor that undermines local research capacity (see Colombian vivax HCS reviewed in Sect. 5.3).

Payment intended to compensate for other burdens and/or incentivise research participation, however, are more controversial (Gelinas et al. 2018). Such payments, and even high levels of payment, are widely viewed as appropriate in

some countries (e.g., UK and USA (Savulescu 2001; Cryder et al. 2010)) but they are less accepted in other countries and are sometimes even proscribed by local regulations and/or norms (e.g., in some Latin American countries). Recent HCS have sometimes involved high levels of payment; for example, an HIC influenza HCS offered participants USD $4,000 (Cohen 2016). Among HCS in LMICs reviewed below, participants were paid (i) in Kenya, up to approximately USD $500 (depending on duration of infection and other factors) (Hodgson et al. 2015; Nordling 2018), (ii) in Thailand, amounts indexed to local wages (Thai minimum wage is equal to approximately USD $10 per day,[14] meaning that payment for participation in a one month inpatient study might amount to approximately USD $300 or more), and (iii) in Colombia, no payment apart from reimbursement for costs (travel etc.). Stakeholders interviewed for this report generally agreed that payment for participation in (LMIC) HCS was ethically acceptable, and that it was particularly appropriate to pay individuals who participate in particularly burdensome HCS designs (e.g., inpatient studies). However, determination of the appropriate method(s) for titration of payment according to the burdens of participation was an area that was considered contentious and/or unresolved (see Box 3.26).

Arguments in favour of payment of participants have focused on (i) reciprocity (because participants take on burdens and risks in order to benefit others) (Njue et al. 2018), (ii) analogies between research participation and other forms of labour (Gelinas et al. 2018), (iii), payment for taking on risk as for other types of high-risk socially beneficial activities (e.g., fire-fighting) (Savulescu 2001), (iv) evidence that payment may be a signal that reminds potential participants that studies in healthy volunteers are usually not beneficial for them and may impose a net risk of harm (Cryder et al. 2010), (v) a potentially important incentive to increase participant enrolment numbers (in socially valuable, appropriately low-risk research) (Macklin 1981). As mentioned above, it has also been argued that there should be a system to compensate those who suffer (rare but potentially significant) harms as a result of HCS participation, even if risks have been minimised and fully disclosed to participants (Bambery et al. 2015).

Box 3.26 payment in LMICs

> [T]he current situation is … for whatever reason, [that] somebody says it's not appropriate to pay people in developing countries … and sometimes that didn't come from developing countries themselves, it comes from somewhere else and it's

[14] Current Thai minimum wage was 325 THB at time of writing, see https://tradingeconomics.com/thailand/minimum-wages [Accessed 30 March 2019].

also perfectly clear that the amounts that are paid in some US settings are grossly inappropriate. [Scientist, UK/Europe]

[I]n endemic countries I think … when you're asking people to give up ten days of their life, to stay in an inpatient unit … I think they should be compensated. That's … a lot of their time and freedom. Certainly it's time away from how they could be making other money – and it's difficult, frankly, to find people altruistic enough [to] say 'Sure, I'll stay in your inpatient unit for ten days, for the betterment of science.' Prof. Anna Durbin, scientist, USA

[F]or a long time, in a [low-income] setting [the standard view has been that] people should not be compensated, so that they can make a voluntary decision not driven by gains that might accrue from participating in the study … [A]s much as people get worried about [payment in LMICs], it is the same as what you are seeing with people who are doing the phase one studies in Europe … [T]he students end up doing that [i.e., serving as participants], because they want some extra money [and] because they want to be a part of something. [Scientist, Africa]

[We]'re thinking [that] because we need a population that … has a better chance of understanding the study, it would be people around [the research institution] – so either hospital staff, students, lecturers, so people who are in the campus probably … so they won't go for minimum wage, it's crazy right? Ah, so that's compensation for burdens and then there should be incentives. I mean this is a challenge study, no incentives, forget it. No-one's going to come and I think we should incentivise people properly. [Scientist, Asia]

[H]ow do we appropriately compensate for all these inconveniences? And I think tied to that is, and this is what we struggle with, is are we compensating for the risk? Are we compensating for the fact that the inmate actually gets sick and feels all the discomfort that comes with the sickness? How do you even know what to compensate for that? You can compensate for time stayed, you can compensate for expenses, you can fund expenses, but how do you compensate for someone being sick? [Scientist, Africa]

I don't want to underpay people because it's not fair to underpay people. If I take two weeks out [to participate in research], committing this amount of time and sacrificing my social life, [and] probably [drinking] no alcohol for two weeks, [that would constitute a significant burden]. Come on, you have to pay people! [Scientist, Asia]

Often the procedures for challenge studies are really quite onerous compared to other studies so if you just add all that up together, just logically, the amount that they should be paid is more than for other studies. How much that should be, should probably be linked to local purchasing parity. That makes sense to me. [Scientist, UK/Europe]

3.6.1 Undue Inducement

Many researchers and ethicists might be concerned that payment of participants (particularly high levels of payment, and/or among economically disadvantaged populations) may result in 'undue inducement' to enrol in research. This presupposes that some payments or inducements may be appropriate or 'due' (for

example, reimbursements of travel costs or payments *in lieu* of lost wages) whereas others are inappropriate (Macklin 1981). Undue financial inducement might (or might be perceived to) (i) undermine the understanding and/or voluntariness components of informed consent by impairing decision-making (leading, for example, to participants accepting more risk than they would usually accept and/or forsaking responsibilities to children and family members) (Grady 2001; Njue et al. 2014, 2018), and/or (ii) lead participants to conceal important details of their medical or psychiatric history resulting in increased risks to them and/or perhaps compromising the scientific validity of the study (Gelinas et al. 2018; Taylor and Morales 2018), and/or (iii) lead participants to 'over-volunteer', e,g., participate in multiple studies simultaneously, which could have similar deleterious effects (see Box 3.27). In contrast, some have argued that—because each of these ethical concerns can be appropriately remedied without removing financial payment—payment per se is not ethically problematic, and even very high levels of payment may be acceptable (Savulescu 2001; Emanuel 2005).

Many of our interviewees were concerned about the potential for undue inducement to participate in HCS (in both HICs and LMICs) and acknowledged that higher levels of poverty, as well as cultural norms, could alter local perceptions of payment for research participation. However, some also argued that this should not necessarily preclude the payment of participants in LMICs, especially for highly burdensome (and/or highly socially valuable) research including some HCS designs. Several noted the potential for undue inducement among economically vulnerable participants in HICs, emphasising that this potential issue was not unique to LMICs, but one that required further work in different settings to determine and review fair levels of payment (see Box 3.27).

Box 3.27 Undue inducement and vulnerable populations

> [O]ur ethics committees are very worried about compensation and inducement … But if you look at challenge studies in the West, you look at challenge studies in Africa, whoever is [participating in] the study always says, 'My main motivation is the money.' But, has anybody set a price on what is enough, and what is insufficient? … [I]f I paid someone $100 a day in Baltimore would they participate? If I paid them $1000 a day in Baltimore would they participate? Where do you set the price? … In India or in Africa or anywhere else, I think you should compensate people who are volunteering, and I think you should compensate them well. Inpatient studies should definitely be compensated more than outpatient studies but … I don't think we've done enough work on what's right, and what is actually inducement. [Gagandeep Kang, scientist, India]
>
> [Concerns about undue inducement of vulnerable participants] very rarely came up … in [a research site conducting HCS in UK/Europe]. We mainly had excessively educated, sort of, philosophy students and that kind of thing who found it very interesting, and I think [to] a lot of them … the amount of money we paid really didn't make much difference to them … whereas in [a research site conducting HCS in North America], I've been there and witnessed how they do things there … [and]

> it's some of the most vulnerable people in that society [who end up participating]. [Scientist, UK/Europe]
>
> I don't have anything against what they are doing in the States. [The] situation might be completely different; [the] country is completely different. So I don't, I don't think the payment is harming anybody; and … from the volunteers that I have seen in the States, I think that they accept the money because they like the money, but not because they need it … It's not that you are influencing them by—possibly, I mean, who knows? It's very difficult to know. [Sócrates Herrera, scientist, Colombia]
>
> [T]he one worry I have is that if you pay people a lot of money that you could have a higher increase in people not revealing certain information to the study team and lying about inclusion criteria, exclusion criteria, or what they did in the course of the trial, or what side effects they're experiencing. And all of those things could have a detrimental impact on safety. So I think we probably need more data on whether higher payments induce people to conceal information that would relate to their own protection. [Ethicist, North America]

3.6.2 Other Ethical Issues Related to Payment

In addition to undue inducement, there may sometimes be other ethically concerning effects of (high levels of) payment. Firstly, payment may lead to the disproportionate recruitment of impoverished individuals and groups, which would in some cases arguably be unjust, for example if the disease under study did not primarily occur in similar populations (see 'Participant selection') (Macklin 1981; Elliott and Abadie 2008). Secondly, high payment may undermine sustainable research practices and fair availability of research opportunities, an effect to which institutions in resource-limited settings may be particularly susceptible; for example, if certain types of research involve much greater payments, it may be more difficult for other studies (with lower levels of payment) to enrol participants; in the longer term, some worry that this could jeopardise participation in research more generally (Njue et al. 2014). Finally, some worry that payment may change the way that researchers treat research participants and/or that participants will view themselves as being akin to employees as opposed to volunteers (Njue et al. 2014) (see Box 3.28).

There are already fears of creating an 'underclass' of research participants in HICs (drawn from underprivileged groups in society) (Elliott and Abadie 2008) and/or of 'over-volunteering' (i.e. participating in research too frequently in order to receive payment, see Sect. 4.3.4). These patterns of participant selection could in some cases undermine the safety of participants (e.g., because compounds used in one study interact with those used in another study) and/or scientific analyses (e.g., because data generated with the research 'underclass' are not generalisable to the eventual target population) (Shamoo and Resnik 2006; Allen et al. 2017). Such concerns could be magnified in LMIC settings and/or impoverished communities in HICs, especially where there are large populations of unemployed individuals and a fragile social support system. Further social science research on potential

inducement of participants and/or over-volunteering as well as transparent longitudinal data (e.g., regarding the level of payment in different studies and the sustainability of research with variable levels of payment over time) would help to clarify the practical importance of such concerns (see Box 3.28).

Payment in both HIC and LMICs is a significant motivator for participation, often rated by participants as more important than the altruistic motives of contributing to important science (though such motivations commonly co-exist) (Njue et al. 2018; Kraft et al. 2019). In endemic settings, where many members of the local population may be more likely to be poor (and/or vulnerable in other respects), even carefully considered levels of payment have caused controversy. For example, in June 2018 a Kenyan media article expressed concern regarding payment of participants in a malaria HCS, despite prior community engagement and thorough consideration of appropriate levels of compensation of appropriate levels of compensation (Gathura 2018; Kenya Medical Research Institute (KEMRI) 2018). In the interviews for this project, payment of HCS participants was identified as a complex issue in need of further analysis (see Box 3.28).

Box 3.28 Sustainability, over-volunteering, and relationships between researchers and participants

> There are institutions that are involved, and look at what should be acceptable … [W]ithin our setting, what can we possibly keep up with, and what can we sustain? … [O]nce you start compensating people at a … certain level, they will expect that to continue. And when it comes to another study they will not [have the same levels of compensation], so I think it's one way [of] looking at what would be acceptable within our frameworks, I think, if you are driven by local institutions [and their views on sustainable payment levels]. [Scientist, Africa]

> [T]here are several … phase one trials that are happening in India where we have these professional trial participants. They make a livelihood out of trial participation … [T]here is a washout period of 45 days or something and … after every … 45 days, they just go and participate in one trial after another; and these people, if there is no trial, if they are not eligible to participate in a trial, they go hungry. [Vijayaprasad Gopichandran, ethicist, India]

> [Overvolunteering] will undermine the science, but I think the primary thing is … thinking from a more society than science perspective … [w]hat it winds up doing is giving all of research a bad name. So the fact that your own research got ruined is bad enough, but you are ruining then research for a number of different areas. [Gagandeep Kang, scientist, India]

> [O]ftentimes people think entirely in terms of how paying people might change a person's decision to go into the research, losing sight of the fact that the person that's doing the paying is also altering his or her relationship with that individual by paying them … If you feel like … you can … retain a person in a trial by paying them more, you probably are … feeling much less pressure to treat that person with respect and to try and do various things [to] keep their motivations aligned with your own. [Jonathan Kimmelman, ethicist, Canada]

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