Chapter 4
Community Engagement, Ethics Review, and Regulation

4.1 Community Engagement

Community engagement is ethically important for many types of research. Given that HCS represent a particularly complex, sometimes unfamiliar, and potentially controversial type of research, engagement may be especially warranted in the context of HCS (World Health Organization 2017). Since different issues may arise in different communities, and since HCS may be particularly unfamiliar in LMICs, community engagement is arguably an essential part of setting up and maintaining HCS capacity in LMICs (El Setouhy et al. 2004; Njue et al. 2014; Hodgson et al. 2015). The LMIC HCS case studies reviewed below generally occurred within long-established research institutions, some of which had teams specifically appointed to engage with local communities. The group in Kenya has a particularly significant track record of community engagement regarding research in general and, more recently, HCS in particular (Gikonyo et al. 2008; Njue et al. 2014, 2018).

Several interviewees noted that, ideally, engagement does not merely entail researchers informing communities about planned or on-going research, but should be a two-way process from which researchers could also learn about community perspectives, suggestions, or concerns etc. (see Box 4.1). Engagement activities might also involve consultation with other institutional staff, including ethics committee members. Indeed, several stakeholders identified engagement with, and capacity building of, local ethics committees as a key area that had been necessary for the conduct of some HCS (in both HICs and LMICs), especially where those committees had little previous experience of HCS designs (see Box 4.2).

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Box 4.1 Community engagement for HCS

[Our trials have a significant] community engagement component … [O]ne of the first things is to set up a website and … map up stakeholders … [W]e have [participants, and] the research ethics guidelines [for them] are quite comprehensive. What about the stakeholders? … [W]e have … ethics committees … and then we have friends and family [of participants], including social media, for instance … it can go crazy, you know, [and] you need to manage it from the beginning and then you have the media and the wider public … [A]ll these stakeholders … they have their interest[s] … and they would want certain types of information. [Scientist, Asia]

[Regarding community engagement] I'd have more rather than less information. I think that often we have this bad reputation because we create a vacuum of information, a void. And that void gets filled by misunderstanding. So … I think we ought to be proactive and avoid that void by filling it with information for the community. And openly … I think that for a number of reasons, not just, you know, pragmatically getting involvement but also for people to understand what is it that comes out of these studies, what the risks are. I mean we say so little about the benefits from research in lower/middle-income countries, in general. [Ethicist, North America]

We are lucky we have … a group that is called the KEMRI [Kenya Medical Research Institute] Community Representatives. These are people elected. We have two hundred and twenty people that we are interacting with every three months. Just to talk about the work of the KEMRI but also to hear comments from the community … [T]hose become key people whom community members can go to, ask questions, get clarifications, you know, complain too, if they want to complain, and so they give us this information. [Scientist, Africa]

I think with something like challenge studies where … there is a potential if messages are half heard, or shared, you know, out of context … there is a potential [for] rumours, or worries, or, you know, issues to flare up. And so, if you don't have the sort of mechanisms and relationships that allow people to say, "Hold on, I'm actually worried about this or that," or "No, I don't like the fact that this or that is happening." And you're able to discuss it, and do so in a way that isn't defensive or dishonest, I think that's the only way, really, that you can get this kind of complex information discussed, and that there can be mutual learning. So I think it's important for all kinds of studies because I think it's remarkable what kind of activities can lead to concerns that you don't necessarily predict. [Scientist, Africa]

Box 4.2 Engagement with ethics committees and by ethicists

[Wh]at we did in Kenya was to possibly spend a couple of years before we did a challenge study to sensitise the scientific community why we wanted to do challenge studies and [what] we think they [are] really warrant[ed] for, at this point in time, and there was a back and forth. Initially, people were very sceptical; but … we explained to them more [and] then were able to meet with the ethics committees and explain

to them about this technology, why we wanted to go through this route, what … it bring[s] to the table for everybody. [Scientist, Africa]

One of our key stakeholder groups here in Thailand, is ethics committees. Not just our own ethics committees, and obviously we have to engage with them properly because they need to look at our protocol and all that. But also making an effort to engage with other ethics committees … because we have a reputational risk, right? The reputational risk for our ethics committee: 'You what? You approve[d] this study?' Other committees might say 'You're crazy!' – so we should engage with them. [Scientist, Asia]

[F]or ethicists in particular, engaging with the community becomes kind of like 'Of course it must be done, yes it must be done', but I don't see them doing it very often. So, it requires a lot of effort; social scientists tend to do a better job than biomedical ethicists. But I think it is something we're going to increasingly need to think about, not just for challenge studies but for all of clinical research. [Gagandeep Kang, scientist, India]

4.2 Ethical Review

HCS are sometimes perceived to be an unusual and/or particularly sensitive type of research, and thus some commentators have recommended policies of special ethics review procedures, for example by a specialised and/or national committee (UK Academy of Medical Sciences 2005; Bambery et al. 2015; Shah et al. 2018). In contrast, some have argued for maintenance of the *status quo*—i.e., that HCS should be reviewed according to normal procedures for research with healthy volunteers—since other kinds of research involving similar levels of risk are adequately handled via ordinary ethics review committee oversight processes (and even though HCS might be particularly complex and/or specialised, committees are generally empowered to appoint experts to assist with review of highly specialised research) (Hope and McMillan 2004) (see Box 4.3).

Box 4.3 Standard ethics review of HCS

[A]t the end of the day, the requirement[s] for a trial just like any other trial are the same … I think the main thing is building the capacity of the ethics committees to know what are the issues around challenge studies, what are the salient issues and what are the emerging issues. [Scientist, Africa]

I think the important thing is that they're reviewed by a committee with sufficient capacity to perform the review, full stop. It doesn't need to be a national committee. But there may be some settings where they don't really have that capacity. They would need to be able to really understand this, and it actually relates to … a general issue about this review, which is how the scientific aspects are reviewed. [Importantly,] somebody needs to be able to look at the scientific basis for the risks and the benefits

> … [The committee] needs to have adequate capacity [to review] both the scientific and the ethical … considerations … I would say that's the same for all clinical research. [Scientist, UK/Europe]
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> I would recommend against [specialised ethics review]. I think we would be creating red tape. I think the … fundamental concept of an IRB applies to any research study … I don't think there's anything special about a human challenge trial … any phase I study almost by definition is not going to benefit the participants. [Scientist, North America]
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> [Y]ou can imagine [that], in science, we'll always have new things coming up … 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[ing] 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]

4.2.1 Ethical Frameworks for Human Challenge Studies

One option for enhancing the review of HCS would be the development of specific ethical principles/guidelines/frameworks for HCS (and/or, for example, for HCS with particular pathogen) (Miller and Grady 2001; Selgelid 2013; WHO Expert Committee on Biological Standardization 2016; Davies 2019). Some stakeholders were in favour of such ethical frameworks, whereas others argued that specific considerations related to particular pathogens were more important, and thus that the scientific expertise of ethics committee members (e.g., regarding the pathogen in question) would be more important to ensure the ethical conduct of HCS (see Box 4.4). Among those who favoured the development of specific ethical guidelines/frameworks for HCS, certain ethical issues were identified as potential candidates for inclusion (and/or as issues not covered satisfactorily by existing research ethics frameworks), including (i) limits to risk to participants, (ii) third-party risk management, and (iii) risk-benefit assessments of HCS as compared with alternative study designs (see Box 4.4).

Box 4.4 Ethical frameworks/guidelines for HCS

> I think we do need more frameworks and guidelines for human challenge studies because I think they do raise [particularly salient] questions … and, therefore, require more careful thinking than we've done in the context of other types of trials. [Ethicist, North America]
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> I wouldn't make it a special framework specific to challenge studies. There are things that arise in challenge studies that might also arise in other contexts that I think call for a different framework. [For example,] bystander risks come up in challenge trials

> but also come up in other types of research like HIV cure studies. And [bystander risks] are not something that IRBs or the US regulations cover. So you do need a different framework to think about bystander risks. [Ethicist, North America]
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> [HCS are] a challenge for our [standard research ethics] benefit framework. Is it really the case that, if the question is socially important enough (and [diseases] like malaria and dengue and Zika, are pretty damn socially important), an adult can consent to, in effect, an unlimited amount of [or at least] a very high degree of risk? I think that can't be right. So, I think there has to be a line there somewhere … What that line is to me, is really the hard question of CHIM. [Ethicist, North America]
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> I think the principles are largely the same as with other types of studies but there are these additional questions that we've actually been debating like [for example] if there's a perfectly good animal model or you've got a very high attack rate in the field and you only need to recruit twenty people in the field, why would you deliberately expose healthy people to the pathogen? So I think there are issues around understanding challenge studies [and] the scientific process which leads into the ethical questions is quite important. [Scientist, UK/Europe]
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> [Ethics committees reviewing HCS] generally [have] some expertise in the disease that you're working with and [disease-specific expertise] is, I think, more important than having a general framework for all the different challenge models. So I would rather put my protocol in front of a malaria specialist than a generalist in … challenge models … There are different risks for *Shigella*, for *Salmonella*, [and] for malaria – and to generalise those into one framework I think you run the risk of trivialising some of those risks or [by trying to] make a level playing field for everyone you'll [make], say, *Shigella* [on par with] malaria when they're really not on a par. [Scientist, North America]
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> I think it would probably be useful to have special guidance for low resource settings. I think there are just enough issues around how much infrastructure is enough infrastructure, payment issues, community consultation issues, [etc.]. So I think the idea of guidance that's directed at low resource settings would be useful. [Ethicist, North America]

As discussed earlier (see Chap. 3), the bioethical literature includes examples of ethical frameworks, principles, and/or criteria for HCS (and/or specific issues related to HCS) (Miller and Grady 2001; Bambery et al. 2015; Shah et al. 2018). One framework for HCS review (drawing on such literature and prior experience of ethics review more generally) has been proposed by Hugh Davies as part of the online resource 'Reviewing Research' (Davies 2019). In addition to more general research ethics considerations, Davies highlights the importance of (i) "public consultation, involvement in design and public access to study details" (i.e., community engagement and transparency), given the sensitivity of HCS designs, and (ii) assessment of "harms to possible contacts and the environment" given the risk of transmission of challenge strains (Davies 2019). Given the growing number of HCS in multiple countries, the growing ethics literature on HCS, and the controversial and/or unresolved issues highlighted in this report, there may be a role for ethical frameworks for HCS. Among other related developments, the WHO Global Health Ethics Unit is in the process of developing guidance on ethical issues related to HCS.

4.2.2 *Potential Models for Special Ethical Review*

Regarding potential special review procedures for HCS, different models have been proposed, including: (i) the appointment of a special committee (e.g., a national committee) or sub-committee for review of all HCS (e.g., with additional infectious disease expertise) (UK Academy of Medical Sciences 2005; Bambery et al. 2015), (ii) special review for *new* challenge models in particular (e.g., with two independent experts, perhaps followed by more usual review for future use of that model, once it is shown to be safe and scientifically valuable) (Bambery et al. 2015; Shah et al. 2017), or (iii) usual review with particularly strict requirements for a prior systematic review, publicly available rationale, and well-defined compensation for harm (all of which might be required for other kinds of studies, but could perhaps be more strictly required in the case of HCS) (Bambery et al. 2015).

Ultimately, policymakers in any given jurisdiction will need to adopt a policy regarding HCS review that is apt for the local context. Ethically, the important outcomes (regardless of the policy chosen) might include that burdens, including risks (to both participants and third parties), are appropriately minimised; that public trust in research is maintained; and that scientifically valuable, acceptably low-risk studies are not unduly impeded by excessively costly or slow review procedures (Eyal et al. 2018).

As noted in other sections of this report, public controversies have the potential to undermine support/acceptance of (other) research and/or public health endeavours—domestically and/or internationally. Thus, in some cases, international consultation and/or appeal to international agencies (e.g., WHO) may be appropriate. Whether or not a particular jurisdiction decides on specialised or standard review, international agreement on an ethical and regulatory framework for HCS may help to improve review and ensure that relevant issues are consistently addressed (WHO Expert Committee on Biological Standardization 2016). Stakeholders interviewed in this project held a range of different views, with some in favour of standard review procedures (see Box 4.3 above) whereas others favoured some form of specialised review (see Box 4.5). Finally, some raised potential problems with specialised review (see Box 4.6).

Box 4.5 Advantages of specialised ethics review for HCS

> IRBs work really well for fairly routine … garden variety research, but I think when you're at the vanguard, you want some sort of specialised mechanism and … I think there are substantive reasons for that, that get to the quality of the expertise that you get – and specialised review, the ability to pick through and second guess the scientific rationale, is really key. [Jonathan Kimmelman, ethicist, Canada]
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> I think the most important thing is to be transparent. So whatever process you set up – and perhaps having a central high-level review mechanisms for all such studies is the way to go – … to make it clear that there is nothing being hidden from anybody is

the important thing. To some extent, having a centrally mandated committee would also be helpful because it would provide some distancing and protection from the investigators and their institutions. [Gagandeep Kang, scientist, India]

[T]here may be some cases where having an extra layer of review that the researcher either voluntary agrees to or that the sponsor puts in a place can help make sure that everything is done as rigorously and carefully as possible and then … reassure the existing levels of review that we already have. [Ethicist, North America]

Box 4.6 Potential problems with special review for HCS

[S]pecial challenge ethics committees … can give you clearance to do stuff which nobody else can and [that] doesn't sit right with me … [I]t should be … the general ethics committee and … they should have training and they should understand the issues and … of course, also I think investigators [should] make sure that the issues are clearly articulated. [Scientist, Asia]

I suppose you could [have a specialised IRB for HCS] but they're so rare in a given place … and to set up something separate just for one study a year for challenge [studies] is a bit over the top I feel. It's an over-response to a problem that doesn't exist. [Scientist, North America]

I'm not sure that having a panel of experts will speed anything up! … [W]e had difficulty enough just explaining the host country [i.e., LMIC] processes to [those involved in] the US regulatory review process … I would think that kind of requirement should probably come from the host country. If the host country wants to have [an] additional advisory [body] or ask the WHO, or ask some other group … it's really up to them to decide what level of review they think is necessary. [Carl Mason, scientist, USA]

4.3 Regulation

HCS are governed by standard regulations related to the scientific conduct of research (including the need for ethical review procedures, etc.) and those related to the development and use of investigational interventions (e.g., where vaccines or drugs are tested during HCS). More specifically, HCS may be subject to particular regulations related to the development and use of a challenge organism (and, in some cases, additional regulations if the organism is genetically modified) (Academy of Medical Sciences 2018). Since the general regulations governing research and the use of investigational vaccines are not specific to HCS, this section focuses particularly on (i) the regulation of challenge organisms, and (ii) the role of HCS in regulatory development pathways towards the licensure of new vaccines (and/or treatments).

4.3.1 International Regulations

In 2016, the WHO Expert Committee on Biological Standardisation published a short guidance document entitled 'Human Challenge Trials for Vaccine Development: Regulatory Considerations' (WHO Expert Committee on Biological Standardization 2016). The Working Group involved in the preparation of this document included representatives from HIC regulators and research institutes as well as similar bodies in Sub-Saharan Africa. The guidance document does not contain binding requirements but is intended to provide general advice to regulators and manufacturers of biological products in WHO Member States. Overall, it is suggested that HCS should be conducted in a similar way to a (non-HCS) vaccine study—i.e., following standard requirements for clinical research (e.g., International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (CGP) procedures and local regulatory Clinical Trial Authorisation (CTA) procedures for the conduct of a study)—although the document notes potential variations in local regulations, for example those governing genetically modified organisms.

Among other points, the guidance document notes that HCS have been conducted in LMICs, and that, where this occurs, "the same standards apply as in more developed countries" (WHO Expert Committee on Biological Standardization 2016), including compliance with local regulations (with a recommendation for the establishment of an appropriate framework for challenge studies if none exists), and ethics review with a particular emphasis on risks to participants and third parties. Further, the document recommended that ethical considerations regarding HCS should be thoroughly evaluated. As of 2019, WHO has initiated a process to review relevant considerations with the goal of developing ethical guidance related to HCS.

4.3.2 Regulating Challenge Strains

The majority of HCS have been conducted in HICs, particularly in the UK/Europe and USA. Challenge studies in LMICs have also frequently involved collaborators from HICs and, with the exception of the Colombian vivax HCS program (see Chap. 5), it has usually been the case that the challenge organism has undergone part or all of its development in an HIC before being used in an LMIC HCS (although this may change with future capacity building). Nevertheless, many challenge strains originated in LMICs (particularly for pathogens primarily endemic to LMICs): for example, although the NF54 malaria parasite used in the African challenge studies was first obtained from a patient in the Netherlands, and subsequently developed primarily in the USA, there is evidence that it originated in Africa (Eldering et al. 2016).

In cases where a strain (wherever it originated) undergoes preparation in a HIC before use in an LMIC HCS, the challenge organism will usually be subject to regulatory oversight in both countries—as occurred for the African studies reviewed below (which involved a strain prepared in the USA). Thus, we review US, UK, and European regulatory requirements below before discussing the regulation of challenge strains in LMICs.

4.3.2.1 US, UK and European Regulatory Requirements

The US Food and Drug Administration (FDA) requires that challenge organisms comply with current Good Manufacturing Practices (cGMP) regulations, a set of controls that aim to ensure the safe production, monitoring, and use of investigational agents (including drugs, vaccines, and challenge organisms) for use in humans.[1] The situation for genetically modified challenge strains (which, to date, have not been used in LMIC HCS) is more complex, requiring review by the local USA Institutional Biosafety Committee (IBC), and—in some cases—the Recombinant DNA Advisory Committee (RAC). Of particular importance for LMIC HCS, the FDA also has jurisdiction over challenge strains exported from the USA to other countries (with the exception of a short list of countries with national regulatory authorities (NRAs) recognised by the FDA[2]) (Academy of Medical Sciences 2018; Baay et al. 2018).

The US FDA is relatively unique in its regulation of challenge strains—with the norm in many other jurisdictions being more ad hoc and/or responsibility for the quality of a challenge strain devolving to the (usually academic) institution where the organism is prepared. As the 2016 WHO document on regulations governing challenge studies noted, "in many countries, because the challenge stock … itself is not considered to be a medicinal product, [challenge studies without the use of an investigational drug or vaccine] would not come under the NRA's review and authorization. Thus, much less clarity exists on regulatory expectations and quality matters in such cases" (WHO Expert Committee on Biological Standardization 2016).

For example, the UK Medicines and Healthcare products Regulatory Agency (MHRA) does not currently require that challenge organisms are prepared according to the kind of stringent regulations applied to vaccines and drugs, nor does it require a CTA for a particular HCS unless it also employs an investigational drug or vaccine (e.g., to be tested against an infection challenge). This largely reflects the international "default" where there are no specific regulations for challenge strains (perhaps because of the relative novelty of HCS and small number of sites conducting such studies). Thus, in the UK and in many other countries,

[1] See https://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm. [Accessed 29 March 2019].

[2] EU/EEC, Australia, Canada, Japan, Israel, New Zealand, Switzerland, South Africa—see FDA 21 CFR 312.110.

Table 4.1 Regulatory bodies and/or specific regulations relevant to challenge organisms

International		
Regulatory agency	Relevant regulation	Comments
WHO (ECBS)	Human challenge trials for vaccine development: regulatory considerations (2016)	General advisory document, no specific requirements for challenge strain. Recommended for implementation in WHO member states
National/regional (HIC)		
Country/region regulatory agency	Relevant regulation	Comments
United Kingdom MHRA	Nil specific challenge strain regulation	ACRE and DEFRA (if genetically modified)
United States of America US FDA	cGMP (for both challenge strain and other investigational products)	plus IBC and/or RAC (if genetically modified)
Europe European Medicines Agency (EMA)	Auxiliary medicinal products in clinical trials (2017)	EMA guidance is non-binding and requires member state ratification

ECBS Expert Committee on Biological Standardisation, *FDA* Food and Drug Administration, *cGMP* current Good Manufacturing Practices, *IND* Investigational New Drugs, *IBC* Institutional Biosafety Committee, *RAC* Recombinant DNA Advisory Committee, *ACRE* UK Advisory Committee on Releases to the Environment, *DEFRA* Department for Environment, Food, and Rural Affairs

HCS are conducted largely within academic institutions and these institutions are de facto responsible for the development and use of challenge strains (see Box 4.7). For genetically modified organisms (GMOs), additional requirements apply, similar to those in the USA. For example, the UK Advisory Committee on Releases to the Environment (ACRE) and the Department for Environment, Food, and Rural Affairs (DEFRA) have (sometimes-overlapping) responsibilities for GMOs (whether or not scientists intend to release such a challenge strain beyond the laboratory) (Academy of Medical Sciences 2018) (see Table 4.1).

Box 4.7 Regulating challenge strains

> [In the UK, challenge strains such as] malaria parasites are not a regulatory product. So we have ethical approval but no regulatory approval, and so the stringent assessments of the quality of products and storage and all those other things, we just don't have anyone who controls that and so you don't have that added reassurance that you might do with the GMP. That's one thing that could come in that could really help control the field and give some reassurance about the whole process. [Scientist, UK/Europe]

> When we're talking about the challenge strains, the manufacturing quality, purity, and reproducibility from batch to batch… all of these things are really important considerations but they're not, at least in the UK, currently subjected to the same level of regulatory scrutiny [as, for example, vaccines]. So it's a little bit of a grey area, and it benefits us because it makes it easier to do the challenge studies but also there's potential risk there, I think, and maybe it is touching some ethical issues as well because actually you know, we make all of our challenge strains to a GMP standard; it's very time consuming, very costly, but it has benefits: a fair amount of stability, reproducibility from batch to batch, and also we can have a degree of confidence that we're happy with what is given to our volunteers. [The volunteers] assume that what you're challenging them with is going to be safe. [Malick Gibani, scientist, UK]
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> I think from a regulatory point of view they do need special handling because there are issues like understanding a non-GMP manufacturing process that is still safe enough—because [not all challenge strains are] manufacturable to GMP. Probably those [GMP] standards are excessive for something which is never going to be a final product. You can have very tight systems around producing a challenge agent but [that] are not as [extensive] as GMP, and defining what those are, I think, is difficult to do in the abstract; you have to talk about individual agents... but I think, from a regulation point of view, there has to be enormous expertise in looking at those agents to make sure that they are as safe as possible and that protocols include information to show the limitations of that. [Scientist, UK/Europe]
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> [W]e could reconsider how we're requiring the production and the characterisation of the challenge product because that sometimes … is limiting because … if there's only so many products that have been made in this GMP manufacturing style, you're limited [with respect] to the study questions that you can ask and the relevance of that. And … it's limiting in a way because of that huge amount of scrutiny/oversight of that product. At the same time, you want to make sure that you're delivering a product that's safe. [Scientist, North America]
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> As an investigator I would say [that regulating challenge strains is] not necessary or I would say it's very cumbersome. But, on the other hand, it is also very important that there is an independent review of the GMP aspects of the challenge strains because … there is risk. Maybe it's not so high, but there is quite a bit of risk. But I think it's a good [mechanism] at the European level, what they call [an] "auxiliary medicinal product" [because] the set-up of preclinical investigations may be quite different for something that you only use … for such a purpose in clinical [challenge] trials, compared to something [like a vaccine] that you readily release [for use in] the health system. [Benjamin Mordmüller, scientist, Germany]

The European Union, via the European Medicines Agency (EMA), does have GMP requirements similar to those of the FDA—but these procedures typically apply to *facilities* that produce agents for human use, rather than to individual *products*. However, each product must have a Qualified Person who is uniquely responsible for each and every release of a clinical trial lot of material for research. These requirements potentially extend to challenge organisms—which are covered by EMA regulations as Auxiliary Medicinal Products (AMPs); however, these regulations do not include detailed requirements for infection challenge strains in particular and, in any case, all EMA regulations must be implemented by each EU

Member State and (as of early 2019) they have not yet been widely ratified (Baay et al. 2018).

Some pathogens that cannot currently be maintained in a laboratory (e.g., vivax malaria) may not be able to be prepared according to strict GMP requirements. Several investigators interviewed for this project indicated that they nevertheless routinely follow GMP requirements to the extent that this is possible within current scientific limits. Overall, many stakeholders felt that clear and (ideally internationally) consistent guidance from regulatory bodies would be useful to researchers, although there were unresolved issues regarding the optimum regulatory model for challenge strains and for HCS more generally (see Box 4.7 above). With recent increases in HCS in both HICs and LMICs, there will be opportunities for regulatory agencies to develop appropriate national, regional, and international norms specific to challenge strains and other aspects of HCS, including their role in licensure of new interventions (discussed in Sect. 4.3.3).

4.3.2.2 Low- and Middle-Income Country Regulatory Requirements

Given the relatively small number of challenge studies performed in LMICs to date, many LMICs may not yet have specific regulations related to HCS and/or challenge strains—although, similar to countries like the UK, there are usually local regulations governing investigational drugs and vaccines (which may be used in some HCS). Nevertheless, challenge strains have sometimes been reviewed and approved for use in research by relevant LMIC pharmaceutical regulators (see Table 4.2), generally after approval by a HIC regulator (e.g., US FDA) for international collaborative studies (Hodgson et al. 2014, 2015; Shekalaghe et al. 2014). Likewise, researchers in some countries are required to obtain clearance from other agencies (generally Ministry of Health or similar) for certain types of

Table 4.2 LMIC regulators

Country	Regulator	Approval of challenge strains	Other relevant agencies
Colombia	Instituto Nacional de Vigilancia de Medicamento	N/A	
Gabon	Direction Médicament et de la Pharmacie	Yes	Ministry of Health
Kenya	Pharmacy and Poisons Board	Yes	
Tanzania	Tanzanian FDA	Yes	
Thailand	Thai FDA	N/A	Ministry of Public Health

Note No specific regulations govern challenge strains in these jurisdictions; African regulators listed above have approved challenge strains in conjunction with US FDA

research (e.g., research with potential public health implications such as third-party risks).

This pattern of prior approval of a challenge strain in a HIC prior to use in LMICs may be due to a combination of multiple factors (see Box 4.8), including (i) lack of laboratory capacity for the development of challenge strains in many LMICs, (ii) lack of regulatory capacity for thorough review of challenge strains (meaning that LMIC regulators may defer to HIC regulatory review) in part due to the low number of HCS so far conducted in LMICs, and/or (iii) de facto or more formal requirements from LMIC regulators and/or other institutions that HIC sponsors test investigational agents (whether vaccines, drugs, or challenge strains) in HIC populations prior to testing in LMICs (see Box 4.8).

Box 4.8 Regulatory norms and practices in LMICs

> [S]ome regulators may not be comfortable taking a model into their country until it's been used in the US, and that can be for a number of reasons. [First, regulators might not like] their people being experimented on as 'guinea pigs', and so they want data from the US first. [Second,] some of it is just this idea … that if something goes first to an endemic setting it's ethically suspect and it's something that wouldn't have been allowed in the US, and so it's like an ethical double standard. [Third,] some of it may be just the people want some preliminary data before they're comfortable with allowing a study to go forward. But whatever it is … I've noticed that sometimes there is this resistance by regulators to having a study be conducted in their [LMIC] setting if it hasn't first been done in a [HIC] non-endemic setting. [Ethicist, North America]
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> [O]n the GMP side of things, how this is produced and how [it] is ensured that no contaminations are there, and release criteria, [and so on, are things] that we have not discussed with the regulators in Gabon … [I]t is also because these assessors there, they are not … trained like those at the FDA for example … but there are now programs to improve this regulatory environment and capacities in Africa … I know there's one, for example, between these German regulators and these African regulators, because they've seen that this is a problem and they have to rely really on the judgment of others. [Benjamin Mordmüller, scientist, Germany]
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> [There is a] concern that developing countries don't have the regulatory infrastructure to really evaluate these studies and they don't have the clinical trial [infrastructure] or [other important] infrastructure to do these studies. So [LMIC regulators] want to make sure that, before a challenge study goes to an endemic area, it's been thoroughly [tested] in the United States, because it gives regulatory authorities in the developing countries confidence that they're not the first to see this. I'm hoping that as we build up the regulatory infrastructure in some of these developing countries, that they will feel more confident in being first, but I don't think they're there yet and... I don't necessarily think challenge studies have to be done in developed countries first. [Anna Durbin, scientist, USA]
>
> Some of the regulators in Malawi [said] 'What regulations do you have?' and we [said] 'Oh in the UK we have this, and in the US they have that and in France they have this' and so, for setting it up, the regulatory considerations are really important in an endemic setting but there's nothing that you can copy and paste; there's no

> gold standard that you can refer to, and that's a potential problem, and you know, will the government of Uganda decide to take a liberal view on challenge studies whereas the government [of] Malawi decide to take a more conservative view on that? [It would help to have] a bit more clarity and … consistency [internationally]. [Dr. Malick Gibani, scientist, UK]

Stakeholders interviewed in this project identified regulation of research (and HCS in particular) in LMICs as an area that might benefit from capacity building. Fortunately, there are a number of on-going LMIC regulatory capacity building initiatives, particularly in Africa (Ndomondo-Sigonda et al. 2017), although these are usually focused on regulation of vaccines and therapeutics, rather than challenge strains. Likewise, there are opportunities for communication between HIC and LMIC regulators, although these tend to be ad hoc rather than usual practice according to formalised procedures (personal communication, expert stakeholder). This review focused on the five LMICs in which HCS have been conducted and published since 1992; a wider review of the regulatory environment in other countries considering or conducting HCS could help to inform future regulatory guidance and international collaborations.

4.3.3 Challenge Studies and Licensure of New Interventions

A key unresolved question related to regulatory approval of new interventions (e.g., vaccines) is the role of HCS in the development pathway towards approval/licensure. HCS can play a role at multiple steps in development pathways, for example in the context of (i) basic science and very early phase research (e.g., exploring infectious disease pathogenesis, immune correlates of protection, and developing models of infection), (ii) phase IIB studies (i.e., providing preliminary estimates of efficacy to enable the selection of candidate interventions for prioritised investigation in field trials), and (iii) phase III studies (i.e., more definitive estimates of efficacy intended to obviate the need for field trials) (Sauerwein et al. 2011; Chattopadhyay and Pratt 2017; Shah et al. 2017; Baay et al. 2018; Roestenberg et al. 2018a).

The degree to which phase 2B HCS can be used to predict (phase 3) field trial efficacy (which is sometimes sufficient to support licensure of a vaccine) and, similarly, the degree to which phase 3 HCS can support licensure decisions will depend in part on whether the findings of the HCS are generalisable to the disease epidemiology in the target population for the intervention (see Sect. 3.2.1.1). For example, (i) results from HCS in US volunteers were used to support licensure of a cholera vaccine for travellers (but not for those living in endemic settings because the results were not considered generalisable to these populations—in whom higher doses of the vaccine were required to generate a similar immune response

(Sow et al. 2017))[3] and (ii) results from HCS in UK volunteers were used to support WHO prequalification (which endorses the product for licensure in WHO member states) of the first typhoid vaccine (which is manufactured by an Indian company) (Jin et al. 2017; World Health Organization 2018). The latter HCS used a wild-type typhoid strain (making it more generalisable to natural infection than attenuated strains) and HCS results with this strain were found to correlate with immunogenicity in (non-HCS) field trials in children in endemic areas, thus supporting using this vaccine in such settings/populations (Feasey and Levine 2017; Jin et al. 2017).

HCS designs have also been used to provide preliminary (Phase 2B) estimates of vaccine efficacy for malaria vaccines that have subsequently entered clinical trials (e.g., the PfSPZ vaccine (Hoffman et al. 2002; Olotu et al. 2018)) and/or been licensed for use (e.g., the RTS, S vaccine (Ballou 2009; RTS 2015)) and to 'deselect' vaccines that showed no efficacy against malaria challenge (Spring et al. 2009; Roestenberg et al. 2018b) including in a Gabonese HCS reviewed below (Dejon-Agobe et al. 2018). Safety and/or efficacy trials of at least two malaria vaccines using HCS designs have taken place in Sub-Saharan African countries (Dejon-Agobe et al. 2018; Olotu et al. 2018). The degree to which current falciparum malaria HCS designs can be used to supplant field trials, however, remains controversial. This is in part because few falciparum malaria strains are available for use in HCS, and some doubt that efficacy measured against this limited number of strains would be generalisable to diverse malaria infections "in the wild" (see Box 4.9 and also Box 3.3 in Sect. 3.2.1.1) (Chattopadhyay and Pratt 2017).

Box 4.9 The role of HCS in licensure of new interventions

> [A] couple of years ago [in 2016] we approved a cholera vaccine [for travellers to endemic countries] where the efficacy data was based entirely on a human challenge study. So that sort of creates a new paradigm or it establishes a precedent for a new paradigm. [Although] this is not something FDA did in isolation. We had … public advisory committee meetings to discuss this pathway toward approval … and there was agreement from our [external] advisory committee [made up of infectious disease experts with no declared conflicts of interest] that this would be a reasonable way to proceed. [Regulatory representative, North America]
>
> [T]he regulatory authorities as far as I can see … tend to be extremely wedded to the way they've always done things, so I think somebody should, people should, be making … the case for looking [at the role of HCS in licensure pathways] from first principles and looking at what is the evidence that this is likely to predict future benefit. [Scientist, UK/Europe]
>
> [F]or malaria the problem is: Can you licence a product on the basis of a few human challenges done with a few different strains and say that that provides coverage for

[3]For details of FDA licensure, see https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM509681.pdf. [Accessed 1 March 2019].

> the diversity of parasites out there in the world? That's the biggest regulatory hurdle … [North American Scientist]
>
> I think a clearer, better lined regulatory pathway would be helpful. WHO does not rule the regulators of … the European Union, the U.K., Japan or the U.S. but certainly does influence very heavily the regulators in low- and middle-income countries. It would be nice to see more from WHO [regarding] how such studies should be done. [Gagandeep Kang, scientist, India]

4.3.4 Regulation of Over-Volunteering

Since HCS often attract high levels of payment, they may be one area of research that could be particularly likely to be undermined, scientifically and ethically, by over-volunteering. The underlying ethical concerns are that participation in too many studies, too frequently, may (i) lead to excessive risk to volunteers and/or (ii) distort research results (or interpretation thereof) when a participant is not representative of the general/study population due to past interventions, possibly including relevant vaccines and/or other challenge strains. Some interviewees identified concerns related to over-volunteering, particularly in LMICs (see Sect. 3.6.2); however, few empirical data are available to assess the extent and effects of this phenomenon in particular countries.

In the UK, The Over-volunteering Prevention System (Allen et al. 2017), governed by the MHRA, requires that participants enrolled in (predominantly phase I) studies of healthy volunteers are registered to prevent overly-frequent research participation. It is unclear whether HCS participants are always required to be enrolled in this system. Similar systems exist in France, Germany, the Netherlands, Belgium, and Switzerland, although to our knowledge these systems are optional rather than required. In any case, it is widespread common practice to exclude those known to have recently participated in other research involving exposures that could interfere with the results of subsequent studies. In the absence of a formal regulatory system, this relies on potential HCS participants to declare such information—but they may be especially reluctant to do so in cases where study participation is motivated by monetary payment. Thus, this may be an area in which other national regulators and/or policymakers may be able develop systems that reduce risks to participants and support safe, efficient, and transparent research with healthy volunteers.

4.3.5 Laws Criminalising Intentional Infection

In the background of specific regulations governing research, some countries may also have laws prohibiting the intentional infection of individuals with pathogens. For

example, the UK only repealed a law of this kind in 2010 (Brazier and Gostin 2016). Thus, researchers and regulators in each country must also be mindful of local laws (beyond specific research regulations) that may be relevant to HCS, including those that criminalise infecting others. Depending on how such laws are interpreted, they may, in some cases, preclude conducting HCs in a particular country. There are ongoing debates regarding the ethics of criminalising infectious disease transmission (Stanton and Quirk 2016) and relevant future work in this area could include a review of international laws regarding infectious diseases, especially in countries considering conducting (more) HCS.

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