Malaria vaccinology: from the development of a new malaria vaccine to the ethics of clinical trial participation

Lamers, O.A.C.

Chapter 5

Risk in healthy volunteer studies: Does it matter if the agent is a drug or a bug?

O.A.C. Lamers, I.M.C. Kamerling, M. Roestenberg, M.C. de Vries, M. Hoogerwerf

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Abstract

Clinical research, involving healthy human participants, has, because of its very nature, been the subject of extensive discussions, as adverse events can be minimized yet never completely avoided. Controlled human infection (CHI) studies where participants are exposed to infectious agents in a controlled setting have received additional scrutiny being perceived as particularly risky.

In the following we analyzed whether, and if so how CHI studies differ from phase 1 clinical trials in matters of risk to participants themselves and risks to others through disease transmission. We found CHI and phase 1 studies to be generally comparable, with risk to others may be the potentially most consequential difference between CHI and phase 1 studies. Finally, we propose a set of guidelines to facilitate the evaluation of CHI studies by medical ethical committees in the future.

Introduction

Phase 1 clinical trials are characterized by the administration of novel pharmacological compounds to humans to determine safety and tolerability profiles and pharmacodynamics and -kinetics. Without phase 1 clinical trials much of the current medical and pharmacological knowledge would not have been possible, as testing in humans is a prerequisite for the approval of any new drug[1,2].

CHI studies, involving the exposure of healthy participants to pathogens in a controlled setting, have been implemented for a long time [3] and are a generally well-established and accepted scientific tool[4]. Recent discussions have focused on CHI studies for novel pathogens (i.e. the Zika and the Sars-CoV-2 virus)[4,5]: it could be argued that CHI studies are most useful in these settings, accelerating both our understanding of new diseases as well as vaccine and therapy development. However, novel diseases may be unpredictable with no rescues treatment, thereby making potential risks to participants difficult to mitigate or counteract [6-8]. Additionally, CHI studies with infectious agents may not only involve risk for the participants themselves, but also affect bystanders through disease spread. While phase 1 clinical trials are never completely devoid of risk, they do not generally affect anyone other than the participants themselves[7]. Risk may therefore be seen as a factor a distinguishing CHI studies from phase 1 clinical trials.

In the following we will discuss the (perceived) risks of CHI studies compared to more traditional phase 1 clinical trials, focusing on the risks to the participants themselves and risk to bystanders.

Risks and burdens to participants

Despite extensive safety measures, clinical research always entails a risk of adverse events. However, healthy individuals should not suffer irreversible long-term sequelae from participating in research and this holds true for both phase 1 clinical trials and CHI studies[9-11]. In some publications risk is defined to include the burden to participants[12], whereas in others risk and burden are considered separate concepts[13]. For a more accurate comparison between studies, risk and burden will be discussed as separate entities in this paper.

Risk, defined as the danger to incur serious harm, is based on objective, measurable criteria. This has also been described as the “risk of harm”, a serious, but rare occurrence, which could be considered the “worst-case scenario” and needs to be mitigated as much as possible[13].

Burden or “risk of discomfort” refers to any negative experience of transient nature that is part of trial participation. Some degree of burden is inherent to trial participation and any study procedure can, in this definition, be considered as such. However, the subjective experience of burden will vary from person to person[13,14].

Phase 1 clinical trials assessing novel pharmacological compounds in humans generally have a low risk. Not all phase 1 clinical trials are necessarily first in human trials as well. In trials assessing different doses of a new compound, only the very first administration is considered as first in human. Similarly, testing the effectiveness of an old drug for a new disease may also be considered as a phase 1, yet not a first in human, clinical trial[15]. While symptoms may vary, and some participants may not experience any symptoms at all, systematic meta-analyses have shown that the most common adverse events in phase 1 clinical trials with healthy participants are mild to moderate and include headache, drowsiness and diarrhea[16,17]. Dosing of a novel compound is calculated based on the minimum anticipated biological effect level (MABEL) and no observed adverse events levels (NOAEL) and derived from animal experiments[18,19]. However, for some compounds there still can be a small factor of uncertainty in translating preclinical findings to clinical research as animal models may not always be representative, causing risks to humans to be overlooked[20]. Phase 1 clinical trials, where previously healthy participants have suffered irreversible consequences, have been reported in the past[21-23]. These incidents mostly stem from inaccurate translation from animals models to testing in humans or from the occurrence of serious unexpected adverse events[21]. Additional safety measures, such as careful dose-escalation and sentinel exposure of one participant prior to dosing others, are put in place to further reduce the risks of adverse events[21,24].

Prior to execution of a CHI study, information about the mechanisms of action and possible risks to participants are gathered: the course of disease and related adverse events are usually well-known and predictable[25]. In some CHI studies symptoms may even be used as outcome measures, such as in challenge models for gastro-intestinal pathogens[26-28]. It could nevertheless be argued that there are instances in which risks remain high, such as CHI studies involving highly pathogenic micro-organisms, for example Ebola or Anthrax. However, just like pharmacological compounds tested in phase 1 clinical trials undergo extensive screening prior to administration to humans, we argue that the same is true for pathogens. In theory, both pathogenic micro-organisms and highly toxic substances could be tested in humans in phase 1 clinical trials without prior risk assessment through preclinical research. Yet holding onto the principle of not causing irreversible damage to participants, neither drugs nor pathogens that are known to be harmful or even deadly to humans should go into clinical testing, no matter the scientific or social benefits[9-11]. An

exception are chemotherapeutic agents which may have potentially serious side effects and are therefore frequently tested in patient populations rather than healthy participants [29]. The argument that one would be more easily tempted to conduct high risk CHI studies rather than high risk phase 1 clinical trials is also null because both are equally possible and there is no intellectual nor practical incentive to prefer the one over the other.

The burdens of phase 1 clinical trials and CHI studies are variable: they can include lifestyle and dietary restrictions to optimally monitor pharmacokinetics and pharmacodynamics as well as more invasive procedures, such as such as lumbar punctures or pain stimuli[30]. For many trials, participants are expected to remain at the study facility for a period of time, ranging from a couple of hours to one or two weeks, to ensure safety and accuracy of measurements.

When comparing different trial types, it is helpful to consider the objective risk of harm and burden as separate concepts, which can be visualized as a spectrum of two intersecting axes, ranging from high to low in both directions (**Fig. 1**). Clinical research can then be localized on this matrix, according to the perceived consequences of any given study on its participants.

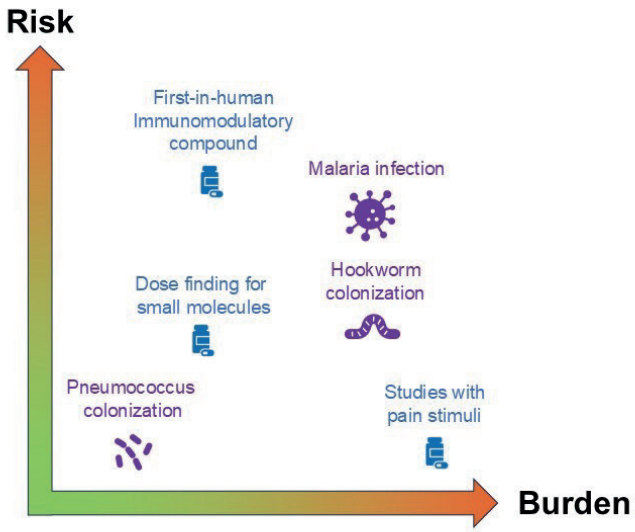

Figure 1. Risk and burden in phase 1 clinical trials and CHI studies
A first-in-human phase 1 clinical trial with a first in class immuno- or neuro-active compound will always, despite extensive pre-clinical studies, involve some degree of uncertainty simply because of its novelty. If such a study also includes invasive procedures, such as a lumbar puncture, it would classify as high risk and relatively high burden (upper right quadrant). In contrast, a dose-finding study for small molecules belonging to a class of compounds already tested in humans, has a low chance of mild adverse events and limited number of study visits, therefore classifying as low risk and low burden (lower left quadrant).

Pneumococcus colonization, which has been introduced to investigate vaccine efficacy[31] and to study factors that influence colonization[32], is a CHI model associated with a small chance of mild adverse events[33]. After being nasally instilled with *Streptococcus pneumoniae*, participants are monitored for symptoms and evidence of colonization [31]. Pneumococcal colonization itself is a natural occurrence and with a very small chance of treatable complications in healthy young individuals[34], therefore considered low risk. Burden is also low as except for recording potential symptoms, there are no lifestyle restrictions for participants [35]. In contrast, controlled human malaria infections (CHMI), consisting of the infection of healthy participants in a controlled setting[36], involve a higher risk to participants because, if left untreated, it is a potentially fatal disease[37]. Burden is also higher as participants are required to undergo blood draws on several occasions[38].

In conclusion and in line with the current WHO's stance on the matter[4], we argue that the risk to which CHI study participants are exposed is not inherently different from that of phase 1 clinical trials, as both risks and burden depend on individual study characteristics rather than their classification as phase 1 clinical trials or CHI studies. While this reasoning does not exclude the possibilities of specific subcategories of high risk and high burden, there is no reason to assume that these are more likely to belong to the larger CHI or phase 1 grouping. Both highly pathogenic organisms as well as highly poisonous chemical compounds exist and both could theoretically be tested in humans. To prevent harm to study participants a set of rules and regulations have been set in place, which apply in equal measure to clinical trials and CHI studies[9-11].

Risk to others: the right to withdraw, bystander risk and quarantining

Linked to the risks to the participants themselves are the risks to others. Bystander risk refers to third parties experiencing harm without participating in clinical research themselves and is often overlook by ethical regulations[39,40].

There are examples of phase 1 clinical trials with risks to others, such as studies involving potentially teratogenic substances. These clinical trials entail a risk for an unborn child, but may also be seen as burdensome as female partners of male participants are required to use double contraception[40]. However, the risks to bystanders are more prominent in CHI models[41,42] and it has been previously argued that some degree of bystander risk may be acceptable if justified by the social value of the research[7].

Closely linked to bystander risk is the necessity for quarantine. The right to withdraw from a clinical trial at any time is one of the fundamental stipulations of voluntary participation[9-11]. However, in CHI studies immediate withdrawal is not always possible, as treatment and follow-up visits may be necessary for the safety of the participants themselves but also to protect others[4].

Both phase 1 clinical trials and CHI studies occasionally require participants to stay in an in-patient facility. In phase 1 clinical trials, permanence in a facility serves to carefully monitor participants for both scientific and safety purposes. Withdrawal and refusal to remain in the research center could impact the quality of the collected data, but, from a safety perspective, it would affect the participants only[43]. Restrictions imposed on phase 1 clinical trial participants are therefore more practical in nature and good management, exhaustive informed consent and adequate monitoring during the study can limit early withdrawal. Most importantly, the right of the participants to withdraw at any time takes precedence over other matters, leaving them in charge of deciding whether and for how long they want to be part of research. In contrast, in certain CHI studies, quarantine may be necessary to prevent an infection from spreading beyond the boundaries of a controlled setting[44], resulting in risk to bystanders.

When evaluating bystander risk, it is important to determine risk of transmission, severity of transmission and background risk of contracting the disease[7,40]. Risk and severity of transmission vary per studied pathogen. *Vibrio cholerae* CHI studies are an example where the pathogen can be transmitted in the absence of proper hygiene and sanitation. Additionally, some patients may become severely ill and require intravenous rehydration[45]. Hence, if an infected participant were to leave the research center prior to study conclusion, this could, potentially, initiate a cascade of transmission and have negative consequences for bystanders.

However, it is important to realize that there are also many CHI models that either do not involve transmissible pathogens or that, when they do, have a low risk of transmission which only becomes problematic in specific instances[46,47]. For instance, hookworm colonization studies have a very low risk of transmission: eggs derived from feces can only hatch if they are inoculated in soil at warm temperatures, making transmission highly unlikely in areas with moderate climates and universal access to adequate sanitation[48] (**Fig. 2**).

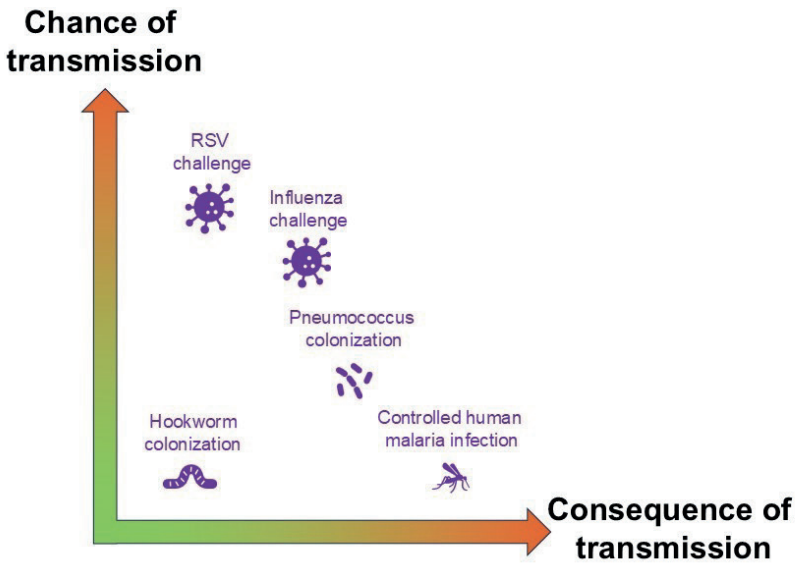

Figure 2. Chance and consequence of transmission without mitigating factors in CHI studies
When analyzing risk to bystanders through transmission in CHI studies, it is important to determine the chance of transmission of any disease and the consequence of such transmission occurring. For instance, hookworm colonization studies have a very low risk of transmission as long as adequate sanitation is present. The consequences of transmission are also limited as hookworm infection is not life-threatening. CHMIs are another example with a low chance of transmission (as long as the vector is not present), but with potentially fatal consequences if the transmission were to happen. Controlled infections with respiratory pathogens (*Pneumococcus,* influenza or respiratory syncytial virus) all have a higher chance of transmission, yet consequence are either treatable or generally mild. It should be noted that in all instances appropriate precautions are taken to prevent transmission to others[31,46,49].

Another factor that needs to be considered is the background risk of contracting a disease, that is, the chance of becoming ill independently of participation in clinical research. An example where background risk is applicable are CHI studies with respiratory viruses: especially in the winter months incidence increases among the general population meaning that the background risk of transmission is also higher[50]. However, the endemicity of an illness does not exonerate from identifying susceptible populations and devising strategies to protect them. In some studies involving respiratory viruses, such as rhinovirus or respiratory syncytial virus outpatient challenges, risks to third parties can be mitigated by implementing precautionary measures and specific hygiene rules (e.g. distancing and wearing a face mask)[51].

Despite the above exceptions, it has been argued that maintaining the quarantine until participants are no longer infectious in some CHI studies is pivotal for the safety of society and becomes a priority which may conflict with the right to withdraw of the single

participant. The fact that CHI study participants may be required to give up part of their autonomy, even if willingly so, distinguishes this type of research from phase 1 clinical trials[9-11].

However, it should be noted that the right to withdraw is never formally compromised in such cases. In other words, individuals are still allowed to interrupt participation at any desired timepoint, yet it is the dismissal from isolation that may be postponed, for their own and others' safety. Hence, one must distinguish between violations of the participants' autonomy as such and a delay in the physical freedom of movement. Another way to mitigate the infringement of personal freedom of movement is to allow participants to quarantine in their own home[52]. Extensive informed consent to explain the risks and consequences of CHI participation and the consequent requirement for quarantining can further alleviate the pressure on participants. Previous studies, investigating CHI participants' opinion on the matter, found that the majority understood and agreed with the need to treat a disease before allowing for definitive withdrawal[53].

Summarizing, there is a small subset of CHI studies that differs from other clinical research because there is a possibility of transmission to third-parties. Quarantining may be put in place to protect bystanders, affecting the ability of participants to withdraw at any desired timepoint. Medical ethical committees should carefully consider CHI studies with these characteristics, making sure that the risks do not exceed the benefits and that the measures imposed on participants remain reasonable. However, even in cases where quarantine may be necessary and participants may experience temporal limitations to their physical freedom, the integrity of the right to withdraw and personal autonomy is guaranteed.

Based on our risk analysis and the extensive comparison between phase 1 clinical trials and CHI studies, we have identified a set of key questions that researchers may consider prior to initiating a CHI study and which we have summarized in **Table 1**. This tool is meant to facilitate risk assessment of CHI studies with new and old pathogens. While this does not replace assessment by a qualified medical ethical committee, it may help researchers to enhance both the safety and overall risk analysis of CHI protocols.

Table 1. Guidance for potential questions to be added to the risk analysis of CHI studies

Risk to the participants
Have other CHI studies with the same type of pathogens been conducted in the past and, if so, what were the outcomes?
What are the expected symptoms and/or adverse events and how will they be mitigated?
What are the long-term effects of the pathogen under study?
Is there an effective treatment for the pathogen under study? Is the disease under study self-limiting?
Has a certain dose of the pathogen been tested before and with what outcomes?
Have participants been selected to minimize risks to their health?
What are the side effects and duration of treatment for the pathogen under study?
Risk to bystanders/risk of transmission
How infectious is the pathogen under study?
Is there a risk of transmission for bystanders?
What are the chances of transmission, should the infectious agent be released in the environment?
Are there susceptible members of the population that need to be protected from the disease under study?
What steps can be taken to protect these susceptible populations from infection?
What is the background risk of infection for this particular disease in the general population?
What measures need to be put in place in general to avoid transmission?
Are quarantine measures for participants necessary and if yes, how long and how much will quarantine measures affect participants?
Is the informed consent and participant information clear about which measures (e.g. quarantine) are put in place to protect bystanders and how this will affect participants' ability to retire from the study at any time?

Conclusion

Clinical trials have been and will remain invaluable for scientific innovation. CHI studies are likely to become even more important in the future given the rise of new pandemic and the necessity to quickly respond to them. In this paper we have extensively analyzed the differences and similarities between phase 1 clinical trials and CHI studies as far as risks to participants and risks to bystanders are concerned. While some of these points have been made earlier[7,8,54], we provide a comprehensive review risk assessment of CHI studies compared to phase 1 clinical trials.

Although we state that CHI studies are comparable to other research with healthy participants, we acknowledge that bystander risk and risk of disease transmission require additional scrutiny. Based on our analysis in this paper, we provide guidance to analyze the ethical acceptability of CHI studies. **Table 1** lists a number of questions that could be answered prior to conducting a CHI study. While this is not meant as a replacement of the local regulatory authorities, it is supposed to complement them and encourage reflection on behalf of the researcher. The guidelines provided in **Table 1** could facilitate and improve safety evaluation and risk analysis of CHI studies.

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