Building bridges: a multidisciplinary approach to controlled human hookworm infection

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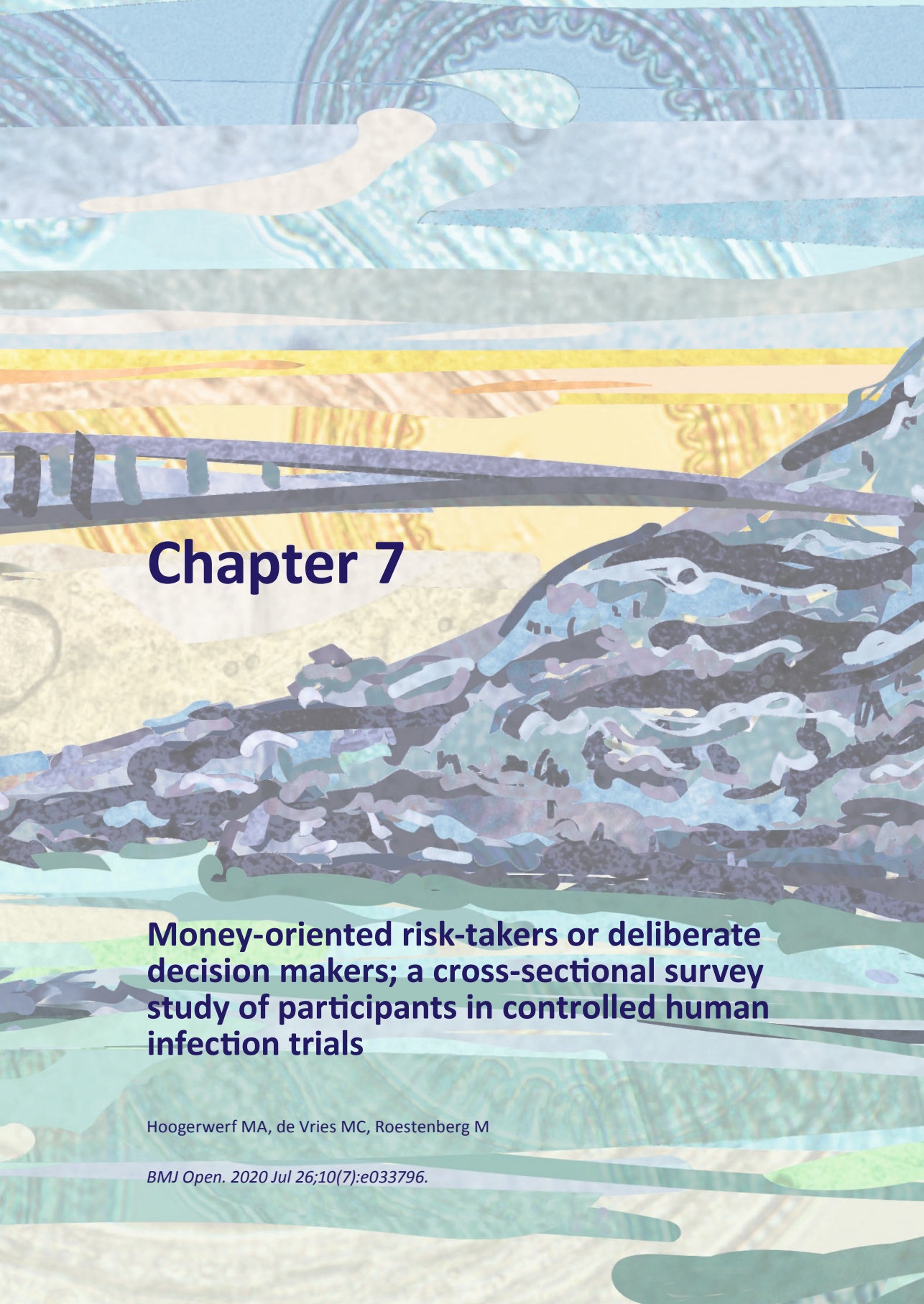

Chapter 7

Money-oriented risk-takers or deliberate decision makers; a cross-sectional survey study of participants in controlled human infection trials

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BMJ Open. 2020 Jul 26;10(7):e033796.

Abstract

Objective
To quantitatively investigate the motivations, decision-making and experience of participants in controlled human infection studies.

Design
Cross-sectional descriptive survey study.

Setting
Previous participants of controlled human infection studies at the Leiden Controlled Human Infection Center, control group of students from Leiden University.

Participants
61 previous participants and 156 controls.

Measurements
Ranking of motivational and decisional factors, risk-propensity score and multiple-choice questions on experience of trial participation and ethical aspects of controlled human infection studies.

Results
Motivating factors for participants were contributing to science (80%), contributing to research that may benefit developing countries (72%) and the financial compensation (62%). For 51% of participants a reason other than financial compensation was the most important motivational factor. Participants considered trust in the study team (70%), time investment (62%), severity of symptoms (52%), chance of developing symptoms (52%) and whether it is an easy way to make money (52%) in their decision to participate. Most controlled human infection participants (84%) were proud of their participation, would advise others to participate (89%) and would participate in a similar trial again (85%). Controlled human infection participants had a higher risk propensity score than students (4.37 vs 3.5, $p<0.001$).

Conclusions
Although financial compensation is important, the motivations for participants in a controlled human infection study are diverse and participants make a balanced appraisal of risks and burden before participating.

Introduction

Controlled human infection (CHI) trials are increasingly used in the development of novel vaccines and drugs against a variety of pathogens.[1] In these trials, volunteers are purposely infected with a pathogen in order to test the efficacy of new vaccines or medicines and to study host-pathogen interaction.[2] CHI trials have boosted vaccine development against for example malaria[3] and cholera,[4] and generated valuable information on host-pathogen interactions in many other diseases.[2] Currently over 40 000 volunteers have participated in these studies,[1] with exponentially increasing numbers over the past decades. Like phase 1 drug trials also including healthy volunteers CHI-studies lack individual benefit to the volunteer, requiring a thorough review of the balance of risks and burden to the participant versus the social and scientific benefits. Literature on the ethical debate of CHI-trials is growing, with particular emphasis on informed consent, undue influence by financial compensation and the right to withdraw.[5-7]

Like the debate concerning phase I drug trials[8] there is suspicion that volunteers are only driven by money[9,10] and as a result do not adequately weigh the risk and burden of participation[11], the 'money-orientated risk-taker'. Participants in phase I trials score higher on questionnaires examining sensation-seeking behaviours compared to age- and sex-matched controls, adding to the notion that these volunteers are more prone to take, possibly ill-considered, risks in their lives.[12,13] However, recent research shows that phase I participants consider other arguments besides the financial compensation, such as curiosity, contributing to medical research, helping future patients and the risks involved[14,15]. In response to a recent publication[16] public discussion, particularly on social media, scrutinised voluntariness of participation, since studies often include medical students as participants who were presumed to have felt pressure to participate, next to the ongoing discussion about acceptability of risks and burdens. Qualitative data on motivation of participants was recently collected in two studies with volunteers in controlled human malaria infection trials in the United States and Kenya. These showed that participants had other motivations next to the financial incentive.[17,18] However, these studies only included small groups of participants (16 and 36 respectively) in a malaria trial, and quantitative data on motivations and experiences is lacking. Given the ongoing debate on the ethics of CHI-trials, a more quantitative assessment of the experiences and motivation of participants in a broader group of volunteers is needed to gain better insight into the profile of the CHI-volunteer, their motivations and experiences.

In order to investigate whether participants in CHI-trials are different from the general population it is valuable to compare the participants to a control group. This also enables a longitudinal comparison of motivations and thought-processes of potential participants with those who have actually participated, providing a better insight into how volunteers come to their decision. An additional benefit of a control group from the general population is there will be a proportion unwilling to participate. These controls provide a comparator

in decisional factors and can give information on the acceptance of aspects of controlled human infections even by those unwilling to take part.

The Leiden Controlled Human Infection Center has conducted multiple CHI-trials in malaria, schistosomiasis and hookworm. This unique setup offers an ideal opportunity to fill the abovementioned knowledge gaps. We therefore conducted a survey study in former participants of these trials, using students from the local university as a control group. The aim of this study is to quantitatively investigate the motivation, decision-making process and risk propensity of participants in CHI-trials compared to a control group. Furthermore, this study explores participants' views on ethical questions in CHI-trials.

Methods

This cross-sectional descriptive survey was conducted amongst participants of CHI-trials performed at the Leiden Center for Controlled Human Infections and students of the Leiden University in October 2018.

Participants

Participants of previously conducted CHI-trials with malaria, hookworm or schistosomiasis were invited to participate in an anonymous survey. Inclusion criteria were having undergone controlled human infection and previous consent to be contacted again for further studies. There were no exclusion criteria. All 66 previous participants were eligible for inclusion. CHI-trials were conducted between November 2016 and September 2018. Surveys were distributed and collected via e-mail through data management program Castor EDC. [19] Participants who did not respond to the e-mail were sent one reminder. CHI-participants received a 10€ voucher as reward.

As control group students from the local university were included. This group has been selected as the majority of participants in CHI-studies at the study centre is recruited from this population. Before lectures at the medical faculty the anonymous paper survey was distributed to all students present and collected afterwards. Surveys were furthermore distributed during two meetings of local (non-medical) student societies, where the researchers handed students present the survey and collected them after completion. Controls did not receive compensation.

With an expected response rate of 80% we estimated that around 50 previous participants would return the survey. Based on experiences in recruiting we estimated that one-third of students would be willing to participate in a CHI-trial, so in order to include an equal number of controls willing to participate to actual participants we aimed to include 150 controls.

Survey

The survey was designed by the researchers, based on previously published research[14 15] and topics of ethical debate.[5] Motivational and decision-making factors were chosen based on the research by Grady et al[15] and by identification of potential motivational factors through discussion with researchers involved in screening and recruitment of trial participants. Participants were allowed to add their own factors. Motivational factors in the survey were "curiosity", "contributing to science", " contributing to developing countries", " financial compensation", " interest in the subject" and " personal experience". Factors in the decision making process were " Severity of possible symptoms", "chance of developing symptoms", "time investment", " an easy way to make money", " trust in the study team" and "it's research about parasites". Questions on ethical acceptability were formulated based on issues identified in literature as key concepts in CHI-trials [5-7] (surveys in supplement A).

CHI-participants (from here referred to as PP) reflected on their own experiences, whereas the control group (CC) were asked to consider participation in a malaria trial and a trial with hookworm to reflect the different types of studies conducted. CC were provided descriptions of the trials detailing study procedures, possible adverse events, number of visits and sample collections and the financial compensation (descriptions in supplement A). PP and CC were asked to rate motivational factors and factors considered in their decision about participation. Each factor could be rated as not important, slightly important, considerably important or very important. Next to this ranking CC and PP were also asked to identify the single most important factor.

Attitudes towards risk-taking were investigated using the Risk Propensity Scale (RPS)[20], a seven-item questionnaire consisting of statements on taking risks in daily life that are rated between 1 and 9 (supplement B). Higher scores represent a higher propensity to take risks. This questionnaire was selected as this is a concise questionnaire focussing on general risk-taking propensity in daily life.

Experiences of PP and opinions on ethical issues were examined using multiple-choice questions. Wherever relevant, CC were presented with similar questions.

Statistical analysis

A ranking order of motivational and decision-making factors was compiled, ranking from the factor with the highest percentage of 'important' or 'very important' to the lowest. Differences between CC and PP were calculated using a Fisher's exact test.

RPS scores were analysed as described by Meertens.[20] Differences in mean scores were analysed using a linear regression model, adjusting for age, sex and health-care related education or job Frequencies were calculated for the multiple-choice questions on the experiences of PP and ethical issues. Differences in demographical characteristics were calculated using a Chi-square test, differences between CHI-models were calculated using a

one-way ANOVA for continuous parametric data and Kruskall-Wallis test for non-parametric data, and a Chi-square test for categorical data. A p-value <=0.05 was considered statistically significant.

Calculations were made using SPSS v23.[21] The institutional review board of the Leiden University Medical Center where the study was performed reviewed the protocol and provided ethical approval (P18.203).

Patient and public involvement

No patients were involved in this study. This study was designed to investigate healthy volunteers' opinions and preferences. Volunteers were not involved in the design or recruitment process. Interested participants were presented the results during a meeting, participants will be provided the research article after publication.

Results

61 of 66 CHI-participants and 156 of 156 students returned the survey. There were no missing answers in the questionnaires of PP, although many CC did return incomplete questionnaires. Nevertheless, since all questions were answered by at least 85% of controls, all questionnaires were included in the analysis (All survey outcomes are provided in Supplement C).

Baseline characteristics and demographics for both PP and CC are in Table 1. The majority of PP (67%) were students while participating in their trial. Most PP had not previously taken part in medical research (72%) and 53% were employed or studying in a healthcare-related field. In both groups the majority were female. CC were younger than PP (p<0.0001) and most were recruited from the medical faculty.

Of the CC, 69% would not participate in any of the CHI-trials (referred to as CN), 22% would only participate in the malaria trial, 3% only in the hookworm trial and 6% in both trials (CP).

Table 1. Demographic characteristics of study participants

	CHI participants (n=61)	Controls (n=156)
Participation in trial for:		
Schistosomiasis (n=17):	16 (26%)	N/A
Hookworm (n=26):	22 (36%)	
Malaria (n=23):	23 (38%)	
Sex		
Male:	24 (39%)	35 (22%)
Female:	37 (61%)	98 (63%)
Missing:		23 (15%)

Table 1. Demographic characteristics of study participants *(continued)*

	CHI participants (n=61)	Controls (n=156)
Age		
< 18 yrs	0	3 (2%)
18-24 yrs:	38 (62%)	145 (93%)
25-30 yrs:	11 (18%)	8 (5%)
>30 yrs:	12 (20%)	0
Employment		
Student:	41 (67%)	156 (100%)
Working:	19 (31%)	
Other:	1 (2%)	
Previously participated in research		
Yes:	17 (28%)	N/A
No:	44 (72%)	
Employed in healthcare or healthcare related study?		
Yes:	32 (53%)	126 (81%)
No:	29 (47%)	30 (19%)
Would you participate in one of these controlled human infection trials?		
Yes, both	N/A	9 (6%)
Yes, only malaria		35 (22%)
Yes, only hookworm:		4 (3%)
No:		108 (69%)

Motivation

Motivation was investigated both by ranking factors of importance and by identifying the single most important factor. PP considered "contributing to science" as an important (43%) or very important (38%) motivating factor, followed by "contributing to developing countries" (41% important, 31% very important) and the financial compensation (25% important, 38% very important) (figure 1). However, when asked the single most important motivation, PP most often noted the financial compensation (49%) followed by "contributing to developing countries" (29%) . There were no apparent differences in motivation for participants from different CHI-models.

For CP the financial compensation was most often important (39% important, 52% very important, p=0.001 for comparison between PP and CP), followed by "contributing to science" (33% important, 39% very important, p=0.48) and "contributing to developing countries" (46% important, 26% very important, p=0.9). The single most important motivation was financial compensation for 41% of CP and "contributing to science" and "interest in the subject" for 15% each. The single most important factors were not distributed significantly different between PP and CP.

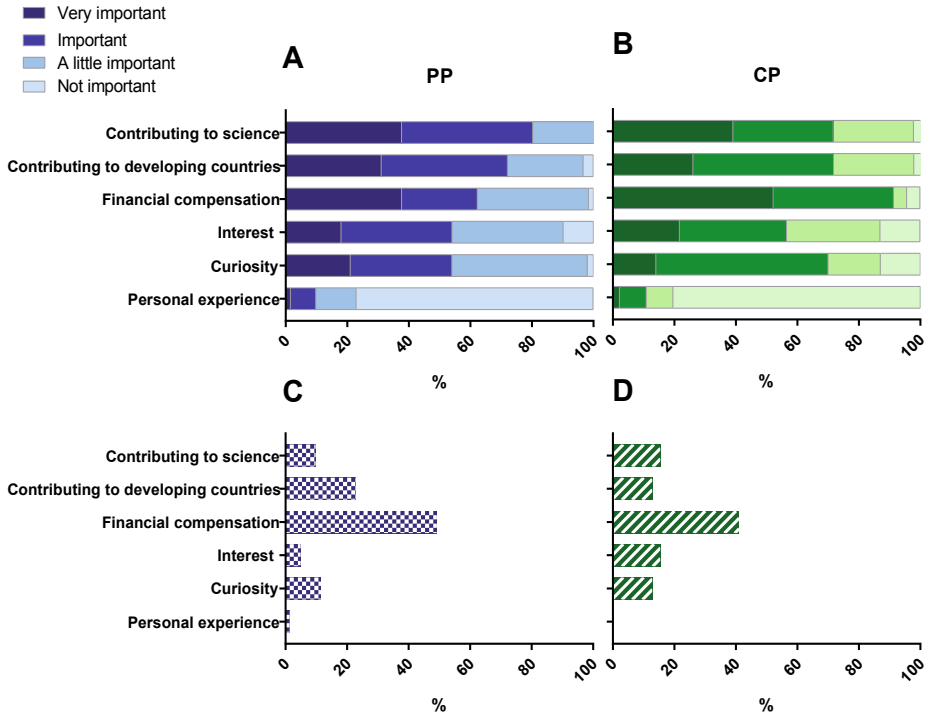

Figure 1. Ranking of motivational factors to participate in a CHI trial for PP (panel A) and CP (B). Single most important motivation factor for PP (C) and CP (D).

Decision to participate

PP most often found trust in the study team important in their decision to participate (34% important, 36% very important) followed by the time investment (43% important, 20% very important), severity of symptoms (36% and 18%), chance of developing symptoms (31% and 23%) and "an easy way to make money" (31% and 23%). The single most important factor in the decision to participate was highly variable, including the chance of developing symptoms (23%), severity of symptoms (21%) and time investment (20%).

CC most often considered the chance of developing symptoms and severity of symptoms important ($p<0.001$ for comparison between PP and CC), with CP also considering the time investment and "an easy way to make money". The severity of symptoms was the single most important factor (47% for CP, 53% for CN) (Figure 2), which is significantly more often than for PP ($p<0.001$).

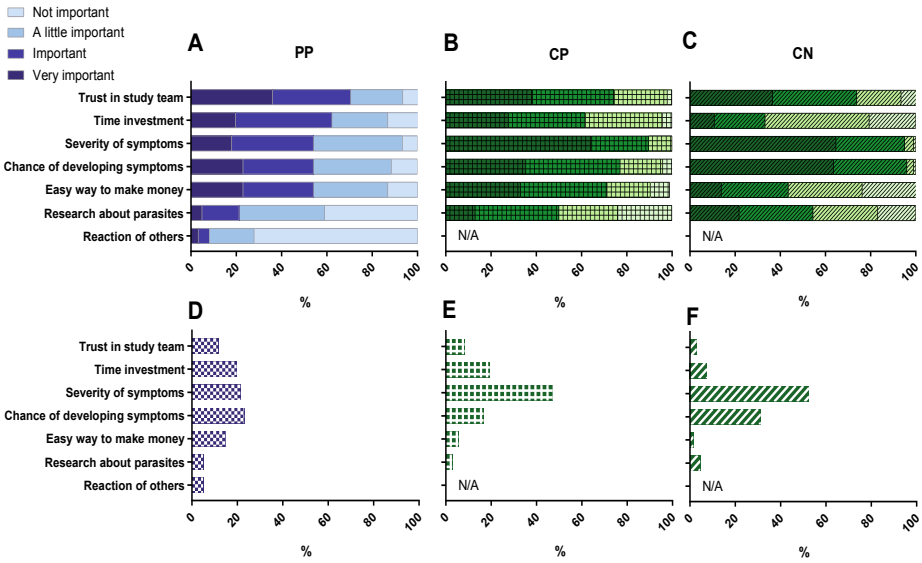

Figure 2: Ranking of factors considered in the decision to participate by PP (A), CP (B) and CN (C). The single most important factor in the decision to participate for PP (D), CP (E) and CN (F).

Assessment of symptoms and risks

The majority of PP (57 out of 61, 93%) considered the trial to be of no or little risk and the majority were not afraid of symptoms before the start of the trial (49 of 61, 80%). For 10 PP their fear of symptoms increased during the trial, mainly because they saw other volunteers with symptoms or as one volunteer stated "we were working each other up the day of the malaria infection about the mosquito bites and what would happen". For the others, fear of symptoms declined (n=8) or remained the same (n=43). PP scored the symptoms they experienced during the trial on a scale of 0-10, with 0 being no complaints at all, 10 complaints so severe they had to withdraw from the trial. The mean score was 2.85 (SD 2.7, range 0-10) for all models, with no significant differences between CHI-models (p=0.228).

Reaction of others

Many (80%) PP reported negative reactions about their trial participation, quoting reactions like: "Are you getting worms in your body?" or "You are taking a risk with your health". However, 64% also received positive reactions, such as "That's an important thing to support", "That is very interesting research to participate in" and "That's good money for little effort". The responses of third parties largely did not influence their decision to participate (93%). All PP but one reported no outside pressure to participate in the study; the one exception was a participant who, while describing no pressure to initially participate, reported some during the study when the participant was unable to meet some of the logistical demands of the study. In response, the participant was offered the option of missing out on certain follow-up procedures in order to remain in the study for the primary

endpoint, rather than dropping out altogether. This participant described being glad to have been offered that proposition and was proud to have completed the study after all.

Opinion on ethical issues

PP and CC were asked their opinion about the concept of deliberate infection and the right to withdraw. For 77% of PP it was considerably or very important to always be able to withdraw. However, 95% replied that they found it understandable that in a CHI-trial immediate withdrawal is not always possible if this was done for their own safety or that it was acceptable if explained during the informed consent procedure. PP also found it acceptable for a physician to deliberately make them ill for the benefit of the trial (100%). Some added that this was what they voluntarily signed up for, as long as possible symptoms were explained before the trial. CC generally had similar views: 94% felt it was understandable that it is not always possible to withdraw and 82% found it acceptable for a physician to deliberately make a person ill for the trial.

Financial compensation

Of the PP, 10 out of 61 would have participated without any financial compensation. The majority of PP (84%) considered the compensation as good, and 3 considered it too high. PP most often spent the financial compensation on a holiday (41%), followed by costs of daily life (20%) and savings (18%). PP view the compensation as an incentive to participate (56%), compensation for costs (50%) and payment for risk and burden (49%). The majority of CN could not be convinced to participate for double the compensation (86%) and only 3 (3%) would change their mind about participation if both the compensation and the risks were doubled. CP were also unwilling to take more risk: only 5 of the 44 (11%) would still participate if the risk was twice as high but compensation also twice as high (Figure 3).

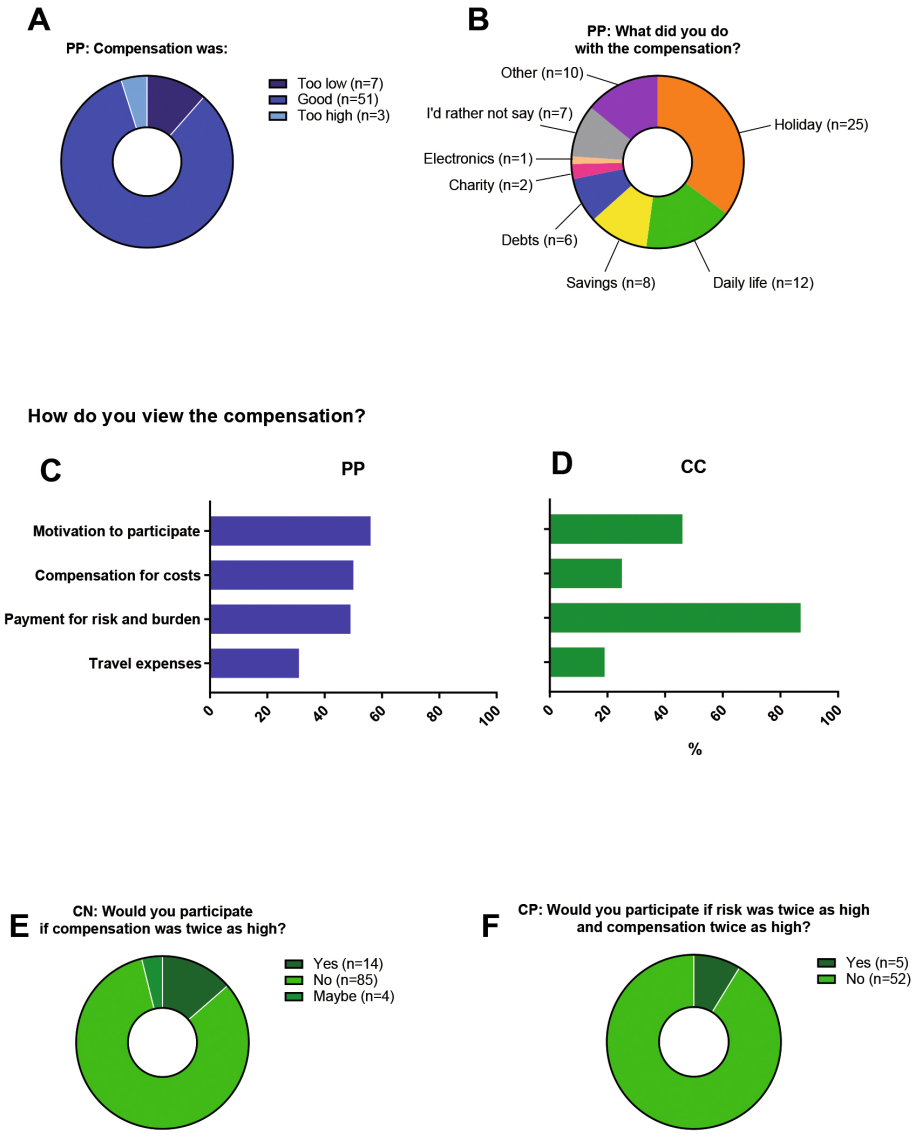

Figure 3. Opinion of PP (n=61) on the amount of financial compensation (A) and how they used the compensation (B). View of PP (C) and CC (D) on why financial compensation is offered (multiple answers could be given). Opinion of CN (n=103) to change their mind if compensation was twice as high (E) and opinion of CP (n=57) if the compensation was twice as high and risk was twice as high (F).

Looking back at participation

Remarkably, a large proportion (59%) of PP felt they had gained benefits from their participation other than the financial compensation, like increased knowledge about the conduct of clinical trials or the disease for which they participated, the pride of having contributed to important research and the experience of going through a trial with the other participants and the study team. One volunteer stated that he had 'learned to get up early in the morning and improve my daily rhythm'. Most (84%) were proud of their participation, would advise others to participate (89%) and would participate in a similar trial again (85%) (Figure 4A). In retrospect, 80% felt that the benefits of the study outweighed the burden they experienced, and of the 20% who did not, 3 out of 12 stated they had experienced so little discomfort they did not have any burden. For 46% of volunteers the symptoms met their expectations, 36% experienced fewer symptoms than expected and 20% experienced more (Figure 4B). Even those participants who had more symptoms than expected evaluate their participation positively: 8 out of 12 felt proud of their participation and would advise others to participate, 10 out of 12 would themselves participate again (Figure 4C).

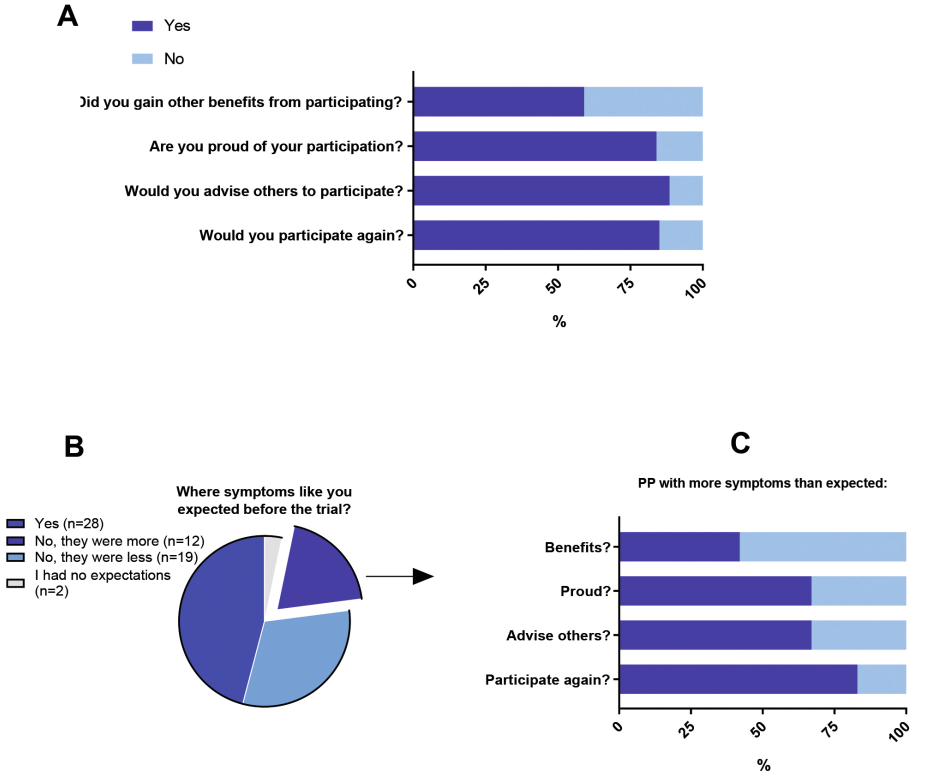

Figure 4. General evaluation of PP (n=61) looking back at their participation (A), assessment of symptoms when looking back (B) and general evaluation of PP who experienced mores symptoms than expected (C).

Risk propensity scale

PP had a significantly higher risk propensity score than CC (estimated difference 0.9, p<0.001)) (Figure 5). CP also scored significantly higher than CN (estimated difference 0.9, p=0.001). No evidence for differences between participants from different CHI-models, males or females or those with a health-care related job or education were observed.

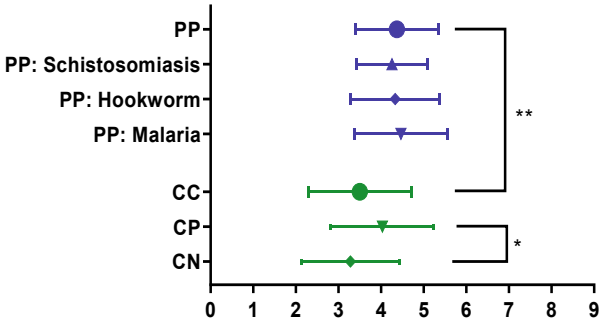

Figure 5: Risk Propensity Scale. Higher scores indicate a higher propensity to take risks. Symbols indicate mean, errors bars indicate standard deviation. ** p<0.001, * p=0.001

Discussion

This survey study is the first to quantitatively investigate the motivations and experiences of participants in CHI trials. These findings shed light onto the experiences and opinions of participants on issues that have been subject of extensive ethical debate.

We have found that, contrary to commonly mentioned fears, [10 22] the largest group of volunteers felt that contributing to science and to research benefitting developing countries was an important motivation. For 51% of PP the financial compensation was not the most important reason to take part. Interestingly, for 38% of PP financial compensation was not or only of little importance, and 10 (16%) would have participated without any compensation. Our data convincingly shows that factors other than financial compensation are important motivators which are considered in the decision to participate.

A larger group of CC found the compensation important compared to PP, although as a single most important motivation for participation proportions were similar. CC also gave more importance to the symptoms compared to PP. Possibly, the compensation is initially most important for a potential participant to be interested in the study, with motivations becoming more diverse after receiving more information about the study and through actual participation. In the decision-making process CC gave more importance to the symptoms, which may reflect that during the first deliberations about participations the symptoms are an important decider, whereas with more information other factors are taken into account.

The motivations of CHI-participants seem to be concurrent with findings in volunteers of phase I drug trials. Stunkel and Grady describe in a 2011 systematic review[8] that although the financial compensation is usually necessary, it is not sufficient for participation, and note that risk is the deciding factor in participation. However, other large-scale studies in phase I drug-research participants, [15] noted that money is the most important motivator in 60% of individuals, which is clearly more than we found. Possibly, the population (students, gender and age) might play a role in motivating factors as well as the nature of the trial. A survey of the motivations of individuals participating in Ebola and influenza vaccines is a good example of the latter, whereby almost 90% of participants found contributing to the health of others important. [23] It is possible that both CHI-trials, especially those researching vaccines for Neglected Tropical Diseases and phase 1 trials for vaccines with similar expected public health benefits may attract volunteers with more altruistic motivations compared to phase I drug research in general.

Differences in population may also be reflected within CHI-studies in different countries. Our Dutch PP were motivated by other factors than Kenyan participants of a controlled human malaria infection (CHMI) trial, who were most often driven by the financial compensation and the health care provided by the trial staff. [18] The Kenyans were rewarded the wage of a day's work for each day of participation to make up for lost income. This was different for the Dutch PP, who have universal access to healthcare and receive compensation for time spent and travel expenses. Participants from both countries, however, showed little concern about trial risks and showed high levels of trust in the study team. In a qualitative study amongst US CHMI participants[17] the participants similarly describe little concerns about the risks, trust in the study team as important and mixed motivations for participation. The differences between the American, Kenyan and Dutch CHI-participants illustrate the influence of cultural differences and healthcare organization that remain important to address and separately investigate.

This study also provides more insight into the presence of undue influence by the financial compensation. We have found that a majority of PP has used their received compensation for leisure activities such as a vacation or put the money in their savings accounts. This indicates they do not have a direct financial need in daily life to take part but could spend the money for more luxury expenses. The control group also provides evidence that potential participants cannot be persuaded to participate for more money if they are not inclined to do so in the first place, or accept more risk for more money, even though the compensation is an important motivation to participate for them. We acknowledge that without any compensation many PP would probably not participate but do conclude that the motivations of participants are varied and that the role of the financial compensation is not as important as presumed.

Another important issue in current debate is the acceptable risks and burden to participants and the risk-taking attitude of trial participants. This survey cannot answer what acceptable

risks and burdens are, but can give important insight into what participants actually consider acceptable.

Both PP and CP scored higher on the RPS as compared to CN. Interestingly, the scores in both groups were lower than those of the original validating study for the RPS who had a mean score of 4.63 (SD 1.23, range 2.00-07.00),[20] suggesting that the RPS varies considerably between different populations. Possible symptoms and risks were an important reason for CN to decline participation, whereas CP and PP apparently weigh the symptoms but find them acceptable. This higher acceptance of possible risks matches the higher risk-taking propensity, but does not mean that risks and burden are not considered. Even the majority of participants who experienced more symptoms than expected look back positively on their participation, are proud of their participation and would participate again. Combined with the finding that the large majority of PP felt the benefits outweighed the burdens of the study, the majority would participate again and would advise others to do so too and that many reported to have gained more benefits than the financial compensation alone, we conclude that at least for these studies the balance of burdens and risks was acceptable to the volunteers.

This study did not specifically assess understanding and informed consent by the PP, however some conclusions on the success of informed consent and voluntariness can be drawn. All participants but one reported no pressure to participate. Although a reporting bias cannot be excluded PP were a heterogenous group of volunteers with diverse backgrounds, none of which connected to the research department. Most participants also indicate that the symptoms experienced were as expected or less, showing they had adequate expectations before starting with the trial. This is confirmed by the fact that most PP reported no change or a decrease in their fear of developing symptoms during the study. We have found no suggestion of pressure to participate and generally conclude PP were well informed about participation, although a more targeted survey would address this question more directly.

This survey also illustrates PP's and CC's views on other issues of ethical debate in CHI-trials. The right to withdraw is considered very important by both groups, however most, including CN, agree that it is acceptable to put restrictions on this if done for the safety of the volunteer and agreed beforehand. The majority of CC did not express ethical concerns about the concept of deliberate infection as they believe that the research will be performed in a safe manner and that risk and benefits are adequately weighed, showing an apparent acceptance of this kind of research even by those who would not participate. This shows that if properly informed, participants are willing to accept some restrictions on the right to withdraw, highlighting the importance of complete and thorough informed consent procedures.

Recall bias may have distorted some of the answers to the questionnaires because of the long lag time between completion of the CHI-trial and filling out the survey for some

volunteers. Some answers to questions in the PP group may also have been influenced by participation in the trial. In addition, social desirability and missing answers may have confounded the results, although surveys were processed anonymously and missing answers were evenly distributed among the questions. Notwithstanding, this study has included a reasonably large number of CHI-participants compared to previous studies and covers several different CHI-models, thereby improving generalizability.

The use of the control group has several limitations. The control group of students may not be a complete representation of the participant population as it is more homogenous in age, education and healthcare background than the actual participants which impairs generalizability. Controls were furthermore offered a hypothetical participation, which may not be comparable to the actual decision to take part. However, participants are largely selected from the same population and this control group represents two-thirds of trial participants. We thus believe that the comparison is still of value.

Conclusion

As the first study to quantitatively investigate the motivations and perceptions of participants, this survey is a crucial addition to the ongoing debate on CHI-trials. This study is amongst the first to add the voice of participants to the current debate. We found that the motivation of CHI-participants is highly varied with significant importance for altruistic motivations. Participants are able to make a balanced appraisal of risks and burdens that results in a mostly satisfactory experience of participation for them. Based on these findings we propose that the current image of the CHI-participant as 'money-oriented risk-taker' is not accurate and may have to be nuanced to the CHI-participant as 'deliberate decision-maker'.

Acknowledgements

The authors are grateful to Jacqueline Janse, MSc for her help in developing the questionnaire and Castor database and to Clarize de Korne, MSc for her fruitful discussions and ideas on this subject. MH was supported by Dioraphte Foundation for another trial. Dioraphte Foundation was not involved in the design, execution or publication of the present study.

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Supplementary material

Supplement A: Surveys

A. Questionnaire for participants in controlled human infection trials

General:

1. In which study did you participate? Malaria/Schistosomiasis/Hookworm
2. Are you male or female?
3. What is your age? 18-24/25-30/>30
4. At the time of your participation in the trial were you: Student/Working/Unemployed
5. Had you participated as a subject in medical research before? Yes/No
6. Do you work in healthcare or do you follow a health-care related study? Yes/No

Motivation:

7. On a scale of 0 to 5 indicate how important the following factors were for your decision to participate (0=not important at all, 5=very important)
   a. Curiosity 0 1 2 3 4 5
   b. Contributing to science 0 1 2 3 4 5
   c. Helping people who are less well-off than me 0 1 2 3 4 5
   d. The financial compensation 0 1 2 3 4 5
   e. I'm interested in the subject 0 1 2 3 4 5
   f. Personal experience with the disease 0 1 2 3 4 5
   g. Other, namely ……
8. On a scale of 0 to 5 indicate how much did you weigh the following factors before deciding to participate?
   a. Severity of possible symptoms 0 1 2 3 4 5
   b. Chance to get symptoms 0 1 2 3 4 5
   c. How much time the study will cost 0 1 2 3 4 5
   d. Easy to make money 0 1 2 3 4 5
   e. Trust in the study team 0 1 2 3 4 5
   f. The fact that this is a study about parasites 0 1 2 3 4 5
   g. Reaction of people around you 0 1 2 3 4 5
9. Did you discuss your participation with people around you? Yes/No
   a. If no: why not (open question)
   b. If yes: with whom? Parents/partner/friends/roommates/class mates/colleagues/others……
   c. Did you receive positive reactions on your participation? Yes/No (space for open answers)
   d. Did you receive negative reactions on your participation? Yes/No (space for open answers)
10. Did you feel pressurised to participate? Yes/No

a. If yes: why? Needed the money/did not want to say no after signing up/pressure from the study team/other……

How was the infection experienced?

11. How did you estimate the risk of this study before participating? (0=very low, 5=very high) 0 1 2 3 4 5
12. Before the infection took place, were you afraid of getting symptoms? Yes/No
13. Has this changed during the course of the trial? Yes/No
    a. If yes, has your fear of symptoms increased or decreased?
14. How did you experience the moment of the infection itself? Positive/neutral/exciting/fearful/other
15. On a scale of 0 to 5, indicate how you experienced being infected for this study (0=not at all, 5=very much)

1. Exciting 0 1 2 3 4 5
2. Interesting 0 1 2 3 4 5
3. Fearful 0 1 2 3 4 5

Symptoms and trust in study team

16. On a scale of 0 to 5 how would you rate your symptoms during this trial? (0=no symptoms, 5=so bad I had to quit the trial)
17. Were the symptoms as you had expected before the start of the trial? Yes/No, space for open answer
18. Did you feel the symptoms and risks of this study weigh up to the possible benefits for you and for science? Yes/No, space for open answers
19. Do you think it is acceptable that a doctor might make you ill as part of research?
    a. Yes, I trust that I will we well taken care of and that the research is safe
    b. Yes, if it contributes to science and to finding a cure or treatment for a severe disease the benefits outweigh the disadvantages
    c. No, this goes against the principle that a doctor should do no harm
    d. Other, namely…….

Informed consent

20. How important was the screening and presentation you received for your decision to participate? (0=not at all, 5=very important) 0 1 2 3 4 5
    a. What's the most important thing you remember from the screening? Possible symptoms/risks of participation/when and how often to visit the trial centre/rules surrounding life style during the trial/other
    b. Did your opinion about the study change after talking to the trial physician about possible risks and symptoms?
4. Yes, afterwards I was relieved, I thought the symptoms would be more severe
5. Yes, I thought the complaints were less severe
6. No, the information in the letter was enough

7. Other …….
    c. Can you briefly describe the purpose of the study you participated in? Open answer

Right to withdraw

21. An important part of a study protocol is that volunteers can always withdraw from a study.
    a. How important do you feel it is to be able to withdraw from a study at all times? (0=not at all, 5=very important) 0 1 2 3 4 5
    b. In a controlled human infection trial it is often not possible to immediately withdraw from the study, because there needs to be a treatment and final check-up even after withdrawal, to ensure the safety of the volunteer. How do you feel about this?
8. That's logical: this is done for your own safety and you know this before participation
9. That feels as a restriction to my freedom to withdraw from the trial
10. Other, namely ……

Compensation

22. Would you participate in this trial is there was no financial compensation? Yes/No
23. How do you view the compensation?
    a. As a compensation for time spent and travel costs
    b. As a compensation for the risk and discomfort of participation
    c. As motivation to participate
24. What did you do with the money you received? (multiple options) Holiday/Electronics/ Paid debts/Used it in daily life/Gave to charity/I'd rather not say/Other…….
25. What did you think of the amount of the compensation? Alright/too high/too low
26. If the risk of severe symptoms was twice as high, but the compensation was also twice as high, would you participate? Yes/No
27. Other than the financial compensation, do you feel you have benefitted from your participation? Yes/No If Yes, how?……..

Concluding

28. Are you proud of your participation?
29. Would you advise others to take part in a trial like this? Yes/No space for open answer
30. Would you participate in another trial? Yes/No
    a. If no: why? Takes too much time/symptoms too severe/compensation too low/ other

A. Questionnaire – version for students

1. What is your age?
    - <18 years old
    - 18-25 years old

- >25 years old

2. I am male/female
3. Would you participate in a study investigating a new drug? Yes/no

Malaria study:

Wanted: healthy volunteers for a study into the efficacy of a new vaccine against malaria. Earlier research has shown that this vaccine can be administered safely to humans. Now, the effect on protection against malaria will be studied. After three vaccinations, volunteers are exposed to bites of a malaria mosquito. After these bites volunteers visit the trial centre daily for 14 days for check-up visits. At each visit volunteers are checked if they have developed malaria. If a volunteer becomes positive he or she is immediately treated. Possible side effects include itching after vaccination and after mosquito bites and headaches, fever, myalgia and a flu-like syndrome if a volunteer gets malaria. Including vaccinations and all check-up visits volunteers have to come to the trial centre 25 times, for 15 minutes each. Compensation: €1200,-

Hookworm study:

Wanted: healthy volunteers for a study into hookworms. Hookworms are parasites measuring 1-2 cm that live in the intestine. In children this infection can cause anaemia, protein deficiency and impaired cognitive and physical development. In order to treat this infection and develop a vaccine more research is needed. For this study volunteers are infected with hookworm. This is done by placing a gauze with water containing the larvae on the skin. The larvae cannot be seen with the naked eye. Possible symptoms are itching and a rash on the site of infection and abdominal complaints, such as abdominal pain and diarrhoea. Volunteers have to come to the trial centre weekly for 16 weeks for a check-up visit of 15 minutes and have to hand in a stool sample every week. After the 16th week all volunteers are treated so the worms go away. Compensation: €1500,-

4. Would you participate in (one of) these studies?
    - No, with neither of these ➜ go to Q5, skip Q6
    - Yes, but only with the malaria trial ➜ go to Q5, then to Q6
    - Yes, but only with the hookworm trial ➜ go to Q5, then to Q6
    - Yes, with both studies ➜ go to Q6
5. If you do not want to participate in this study or these studies, how important are the following factors in your decision? (0=not at all, 5=very important)
    - Takes too much time 0 1 2 3 4 5
    - I think the risk is too great 0 1 2 3 4 5
    - I'm afraid to get symptoms 0 1 2 3 4 5
    - Compensation is too low 0 1 2 3 4 5
    - The idea to be infected with a worm 0 1 2 3 4 5
    - The idea to be infected with a parasite 0 1 2 3 4 5
    - Other, namely ……

6. If you do want to participate in (one of) these studies, how important are the following factors for you? (0=not at all, 5=very important)

- Curiosity 0 1 2 3 4 5
- Contributing to science 0 1 2 3 4 5
- Helping people who are less well-off than me 0 1 2 3 4 5
- The financial compensation 0 1 2 3 4 5
- I'm interested in the subject 0 1 2 3 4 5
- Personal experience with the disease 0 1 2 3 4 5
- Other, namely ……

7. When considering participation, how important are the following factors to you? (0=not at all, 5=very important)

- Severity of possible symptoms 0 1 2 3 4 5
- Chance to get symptoms 0 1 2 3 4 5
- How much time the study will cost 0 1 2 3 4 5
- Easy to make money 0 1 2 3 4 5
- Trust in the study team 0 1 2 3 4 5
- The fact that this is a study about parasites 0 1 2 3 4 5

8. Do you think it is acceptable that a doctor might make you ill as part of research?

- Yes, I trust that I will be well taken care of and that the research is safe
- Yes, if it contributes to science and to finding a cure or treatment for a severe disease the benefits outweigh the disadvantages
- No, this goes against the principle that a doctor should do no harm
- Other, namely…….

9. An important part of a study protocol is that volunteers can always withdraw from a study. How important do you feel it is to be able to withdraw from a study at all times? (0=not at all, 5=very important) 0 1 2 3 4 5

10. In a controlled human infection trial it is often not possible to immediately withdraw from the study, because there needs to be a treatment and final check-up even after withdrawal, to ensure the safety of the volunteer. How do you feel about this?

- That's logical: this is done for your own safety and you know this before participation
- That feels as a restriction to my freedom to withdraw from the trial
- Other, namely ……

11. Would you participate in this trial is there was no financial compensation? Yes/No

12. How do you view the compensation?

- As a compensation for time spent and travel costs
- As a compensation for the risk and discomfort of participation
- As motivation to participate

13. If the compensation was twice as high, would you participate in the trial? Yes/No

14. If the risk of severe symptoms was twice as high, but the compensation was also twice as high, would you participate? Yes/No

Room for additional remarks

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Supplement B: *Risk Propensity Scale*

Adapted from: Meertens RM and Lion R. Measuring an individual's tendency to take risks: The Risk Propensity Scale. *J Appl Social Psychol* 2008;38(6):1506-20.

Risk Propensity Scale

Please indicate the extent to which you agree or disagree with the following statement by putting a circle around the option you prefer. Please do not think too long before answering; usually your first inclination is also the best one.

1. Safety first.

totally disagree	1	2	3	4	5	6	7	8	9	totally agree

2. I do not take risks with my health.

totally disagree	1	2	3	4	5	6	7	8	9	totally agree

3. I prefer to avoid risks.

totally disagree	1	2	3	4	5	6	7	8	9	totally agree

4. I take risks regularly.

totally disagree	1	2	3	4	5	6	7	8	9	totally agree

5. I really dislike not knowing what is going to happen.

totally disagree	1	2	3	4	5	6	7	8	9	totally agree

6. I usually view risks as a challenge.

totally disagree	1	2	3	4	5	6	7	8	9	totally agree

7. I view myself as a . . .

risk avoider	1	2	3	4	5	6	7	8	9	risk seeker

Supplement C: Complete Survey results

Results for motivation and decision to participate are presented in figures 1 and 2 in the original article.

Question		Participants	Students
Did you talk about your participation with other?	Yes No	56 (92%) 5 (8%)	N/A
Did you receive positive reactions?	Yes No	36 (64%) 20 (36%)	N/A
Did you receive negative reactions?	Yes No	45 (80%) 11 (20%)	N/A
Were you influenced by the reactions?	Yes No	4 (7%) 57 (93%)	N/A
Did you feel pressure to participate?	Yes No	1 60	N/A
How did you assess the risk before participation?	No risk Little risk Moderate risk High risk	11 (18%) 46 (75%) 3 (5%) 1 (2%)	N/A
Were you afraid of symptoms before the infection?	Yes No	12 (20%) 49 (80%)	N/A
Did this change during the research?	Yes No	18 (30%) 43 (70%)	N/A
In what way?	Increased Decreased	Increased: 10 Decreased: 8	N/A
How did you experience moment of infection?	Positive Neutral Exciting Frightening Other	15 (24.5%) 16 (26%) 26 (42.5%) 1 (2%) Other: 3 (5%)	N/A
Exciting	Not A little Considerable Very	22 (36%) 28 (46%) 10 (16%) 1 (2%)	N/A
Interesting	Not A little Considerable Very	5 (8%) 16 (26%) 29 (48%) 11 (18%)	N/A
Frightening	Not A little Considerable Very	42 (69%) 19 (31%) 0 0	N/A
Severity of symptoms (scale 0-10) (SD)	All Malaria Schistosomiasis Hookworm	2.85 (2.7) 2.0 (1.7) 2.8 (2.7) 3.8 (3.3)	N/A

Question		Participants	Students
Were symptoms like you expected before the trial started?	Yes No	28 (46%) 33 (54%)	N/A
Did you feel the burden of the study weighs against the possible benefits?	Yes No	49 (80%) 12 (20%)	N/A
Do you think it is acceptable a doctor might make you ill for this study?	Yes No Missing	61 (100%) 0 0	124 (82%) 27 (18%) 5
How important was the screening and information appointment in your decision to participate?	Not A little Considerable Very	11 (18%) 26 (43%) 12 (20%) (12 (20%)	N/A
What was the most important thing you took from the screening? (Multiple answers possible)	Possible symptoms Risks of participation How often are visits Rules for daily life Other	31 (51%) 31 (51%) 28 (46%) 17 (28%) 4 (7%)	N/A
Did your opinion about the study change after the screening?	Yes, I had worries that were answered Yes, I thought symptoms would be more severe No, the letter was sufficient Other	19 (31%) 4 (7%) 35 (57%) 3 (5%)	N/A
How important is it to you to always be able to withdraw from a study?	Not A little Considerable Very Missing	3 (5%) 11 (18%) 25 (41%) 22 (36 %) 0	0 12 (8%) 48 (31%) 94 (61%) 2
In CHI-trials it's not always possible to immediately withdraw. How do you feel about this?	That's logical, it's done for your own safety Feels like hampering freedom to with draw Other	58 (95%) 2 (3%) 1	146 (94%) 7 (4.5%) 1 (0.5%)
If there was no compensation, would you have participated in this trial?	Yes No	10 (16%) 51 (84%)	4 (3%) 150 (97%)
How do you see the compensation? (multiple answers possible)	Compensation for costs Travel expenses Payment for risk and burden Motivation	31 (50%) 19 (31%) 30 (49%) 34 (56%)	38 (25%) 29 (19%) 134 (87%) 71 (46%)
What did you do with the compensation? (multiple answers possible)	Holiday Electronics Debts Daily life Charity I'd rather not say Other	25 (41%) 1 (2%) 6 (10%) 12 (20%) 2 (3%) 7 (11%) 18 (30%)	N/A

Question		Participants	Students
The received compensation was:	Too low Good Too high	7 (11%) 51 (84%) 3 (5%)	N/A
Other than the financial compensation, did you have other benefits from participation?	Yes No	36 (59%) 25 (41%)	N/A
Are you proud of your participation?	Yes No	51 (84%) 10 (16%)	N/A
Would you advise others to participate in a trial like this?	Yes No	54 (88.5%) 7 (11.5%)	N/A
Would you participate again in a similar trial?	Yes No	52 (85%) 9 (15%)	N/A
Would you participate if compensation was twice as high?	Yes No Maybe	N/A	50 (33%) 96 (64%) 4 (3%)
CN	Yes No Maybe	N/A	14 (13%) 85 (83%) 4 (4%)
CP, only malaria	Yes No Maybe	N/A	25 (71%) 10 (29%) 0
CP, only hookworm	Yes No Maybe	N/A	4 (100%) 0 0
CP, both	Yes No Maybe	N/A	7 (87,5%) 1 (12,5%) 0
Would you participate if the risk was twice as high but the compensation also twice as high?	Yes No Maybe	N/A	8 (5%) 143 (94%) 1 (1%)
CN	Yes No Maybe	N/A	3 (3%) 101 (97%) 0
CP, only malaria	Yes No Maybe		3 (9%) 31 (91%) 0
CP, only hookworm	Yes No Maybe		0 4 (100%) 0
CP, both	Yes No Maybe		2 (22%) 7 (78%) 0