PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A Qualitative Study Investigating the Underlying Motivations of Healthy Participants in Phase 1 Clinical Trials
AUTHORS	Manton, Kerry; Gauld, Cassandra; White, Katherine; Griffin, Paul; Elliott, Suzanne

VERSION 1 – REVIEW

REVIEWER	Jonathan Stadler University of Johannesburg, South Africa
REVIEW RETURNED	25-May-2018

GENERAL COMMENTS	Dear authors, This is a well written article, with the primary aim of understanding the motivations for participation in Phase 1 trials. Using the "theory of planned behaviour" as the core framework, the authors interviewed and ran focus group discussions with experienced trial participants. The main findings are that motivation to participate in clinical trials is varied, and not solely based on monetary reward. Overall the paper is clearly argued, well presented and highly readable. The limitations of the paper are the very small number of research participants (4 interviews and 11 focus groups). The authors acknowledge that qualitative studies are often small; however, they also need to acknowledge that interviews and focus groups are very distinct tools of enquiry and generate different types of data. Often in group settings respondents may present quite different views to those articulated in interviews. The authors assert that the literature on participation in Phase 1 trials is rather sparse, but have missed prominent writings on the topic, particularly from medical anthropologists. Indeed, there are several studies that have asked similar questions to those posed by the authors. For example, see Abadie, Roberto. 2010. The Professional Guinea Pig: Big Pharma and the Risky World of Human Subjects. Duke University Press. Abadie argues that trial participants regard their involvement in Phase 1 trials as renting out the body, a necessary form of exploitation in order to be able to enjoy a specific kind of lifestyle. In the conclusion the authors raise the significance of their research with regard to ethical issues. This ought to be a far more prominent issue in the paper overall. As many commentators note, the geopolitical context of pharmaceutical clinical trials has an important bearing on the ethical issues of participation (for

	example, the practice of off-shoring trials to less developed nations to avoid ethical restrictions – as Petryna suggests), see: Petryna, Adriana. 2009. When Experiments Travel: Clinical Trials and the Global Search for Human Subjects . Princeton: Princeton University Press. Specific comments: On Page 6, line 7-8. The sentence suggests that the harm that resulted from involvement points toward the need to understand motivations for participation, but fails to acknowledge that pharmaceutical trials neglected to adequately protect research subjects from harm. For me, this seems to suggest that the blame has been shifted toward the research subjects and not the researchers conduct. Page 6, Line 17-18: in parentheses notes “prisoners” as trial subjects. Further detail is required to explain this comment – it is highly unethical to involve prisoners in medical research and is generally not permitted. No errors were detected.

REVIEWER	Christine Grady NIH Clinical Center, USA
REVIEW RETURNED	15-Jun-2018

GENERAL COMMENTS	Review of Its Not Just about the Money- an Exploration of Underlying motivations… Thank you for the opportunity to review this manuscript. The authors report on a qualitative interview study of healthy participants of phase 1 clinical trials, showing that “…motivations were varied and not solely centered on financial gains” and concluding that flexibility in scheduling and education of family members might be helpful. They used the Theory of Planned Behavior to organize their study. I applaud the researchers for conducting this research and agree that understanding phase 1 healthy volunteer experiences is important, since there is considerable consternation about who these volunteers are and whether their involvement in research is ethically problematic. Although as they note, there are limitations to a small qualitative study (n=31) My primary concern is about their description of the study as “motivations.” The most common meaning of motivations is the reason or reasons one has for acting or behaving in a particular way. But, as far as I can tell, these respondents were never asked why they participated in research or to describe their reasons. Instead they were asked to describe the advantages and disadvantages of participating- which although interesting, is different than motivations. In that regard, I would explain why/how describing advantages/disadvantages translates into motivations? Or else make major changes to the manuscript, including the title, purpose and the assertion that this study is about motivations, the conclusion (p.20) and other parts. The authors also say that there are no prior qualitative studies of motivations. There are certainly some very good qualitative studies of the experiences of healthy volunteers in phase 1 studies that have some similarities to this study. For example, several papers by Jill Fisher explore these issues (see https://www.ncbi.nlm.nih.gov/pubmed/?term=Fisher+JA+AND+volunteers)

	The title also suggests that participating in phase 1 research is about more than just making money, and they list three commonly described advantages from their focus groups as money, altruism, and opportunity for self-development (p. 12 and Table 2). Understanding these as mixed motives is not inconsistent with other existing studies and literature. Interestingly, although it shows mixed views about participation, it still does not lend itself to conclusions about primary motivations. For example, in the study they cite describing motivations of 1194 healthy volunteers (Grady et al 2017), we found that while 58% said money was their primary motivation for participating (which they cite), almost 94% said that money was important or very important to their decision to enroll (which these authors do not cite), while staff competence/friendliness, risks, helping future patients, and the time involved were important or very important to the enrollment decisions of more than 70% of our cohort. Minor points: Page 20. They write – it would be worthwhile exploring differences in motivations for different trial designs, medical procedures etc. See Chen S. et al. Clinical Trials 2017 for a description of willingness to participate in trials of different types, with different procedures, and with different risks Abstract conclusion and manuscript conclusion are different!

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. This is a well written article, with the primary aim of understanding the motivations for participation in Phase 1 trials. Using the “theory of planned behaviour” as the core framework, the authors interviewed and ran focus group discussions with experienced trial participants. The main findings are that motivation to participate in clinical trials is varied, and not solely based on monetary reward. Overall the paper is clearly argued, well presented and highly readable.

Response: Thank you very much for your positive feedback on our manuscript.

2. The limitations of the paper are the very small number of research participants (4 interviews and 11 focus groups). The authors acknowledge that qualitative studies are often small; however, they also need to acknowledge that interviews and focus groups are very distinct tools of enquiry and generate different types of data. Often in group settings respondents may present quite different views to those articulated in interviews.

Response: Thank you for this feedback. A statement has been added to the Strengths and Limitations section to acknowledge the potential difference in responses by participants who were interviewed as opposed to if they were in a focus group:

‘It is also acknowledged that four of the fifteen discussions were interviews in which the participant may have provided different responses to those they may have provided had they been part of a focus group.’

3. The authors assert that the literature on participation in Phase 1 trials is rather sparse, but have missed prominent writings on the topic, particularly from medical anthropologists. Indeed, there are several studies that have asked similar questions to those posed by the authors. For example, see

Abadie, Roberto. 2010. The Professional Guinea Pig: Big Pharma and the Risky World of Human Subjects. Duke University Press.
Abadie argues that trial participants regard their involvement in Phase 1 trials as renting out the body, a necessary form of exploitation in order to be able to enjoy a specific kind of lifestyle.

Response: Thank you for providing this reference which has now been included in the paragraph on financial incentives (page 5) which now reads as follows:

'It has been suggested that, without a financial incentive, recruitment of healthy participants would be a slow process, potentially thwarting the progress of new drug development (Abadie, 2010; Iltis, 2009). Debate, however, surrounds the amount of financial incentive that should be offered. Higher incentives, for example, have been shown to encourage repeat or opportunistic volunteerism (Abadie, 2010; Tishler & Bartholomae, 2003). These sorts of volunteers, who are so heavily motivated by financial reward, can lose their ability to evaluate the risks, are more likely to take part in consecutive trials where the wash-out period is too short, or concurrently participate in more than one trial which increases their exposure to trial risks (Abadie, 2010; Gelinas, Lynch, Bierer, & Cohen, 2017; Iltis, 2009; Tishler & Bartholomae, 2003). Abadie (2010), for example, found that every participant in their study said they had taken part in at least one trial that they considered to be very risky because the financial incentive was very attractive. In addition, financial incentives may encourage a bias towards participants from lower socio-economic classes who may view the reimbursement more favourably than those from higher socio-economic classes'

4. In the conclusion the authors raise the significance of their research with regard to ethical issues. This ought to be a far more prominent issue in the paper overall. As many commentators note, the geopolitical context of pharmaceutical clinical trials has an important bearing on the ethical issues of participation (for example, the practice of off-shoring trials to less developed nations to avoid ethical restrictions – as Petryna suggests), see:
Petryna, Adriana. 2009. When Experiments Travel: Clinical Trials and the Global Search for Human Subjects . Princeton: Princeton University Press.

Response: We agree with the reviewer; the ethical issues surrounding human phase 1 clinical trials are numerous. Unfortunately, due to word and funding limits, a further exploration of the ethical issues was outside the scope of this manuscript. We feel that we have addressed this issue to the best of our capacity within the available word and funding limits.

5. On Page 6, line 7-8.
The sentence suggests that the harm that resulted from involvement points toward the need to understand motivations for participation, but fails to acknowledge that pharmaceutical trials neglected to adequately protect research subjects from harm. For me, this seems to suggest that the blame has been shifted toward the research subjects and not the researchers conduct.

Response: Thank you for this feedback. Several statements have been added to the second paragraph on page 6 to acknowledge the role of the trial companies in these disasters as follows:

'…Independent investigations identified serious deficiencies in both of these trials. The TGN1412 trial, for example, was found to have poor record keeping and an under qualified physician (Attarwala, 2010). The BIA 10-2474 trial was found to have breached the informed consent protocol by not updating the other participants on the status of one participant who was taken to hospital and later died (Enserinck, 2016). While it is acknowledged that the clinical trial companies responsible for conducting these trials did not adequately protect their participants, these tragedies also drew attention to recruitment processes. Specifically, the recruitment processes highlighted the need to

confirm that the information regarding the trial is well understood by potential participants, the impact of payment, and the need to understand motivations for participation (Ferguson, 2008).'

6. Page 6, Line 17-18:
in parentheses notes "prisoners" as trial subjects. Further detail is required to explain this comment – it is highly unethical to involve prisoners in medical research and is generally not permitted.

Response: The article cited (Walsh & Nash, 1978) compared the personality characteristics and motivations of prisoners who volunteered for a clinical trial while incarcerated to those who did not. It also compared the characteristics of those prisoners who volunteered for the trial who had previously volunteered (prior to incarceration) in another clinical trial to those who had not previously volunteered (prior to incarceration). A footnote was added to the bottom of page 7 as follows:
3Please note that while it is unethical today to include prisoners in clinical trials, the study cited in this manuscript was published in 1978, a time with different ethical guidelines.

Reviewer: 2
1. Thank you for the opportunity to review this manuscript. The authors report on a qualitative interview study of healthy participants of phase 1 clinical trials, showing that "…motivations were varied and not solely centered on financial gains" and concluding that flexibility in scheduling and education of family members might be helpful. They used the Theory of Planned Behavior to organize their study. I applaud the researchers for conducting this research and agree that understanding phase 1 healthy volunteer experiences is important, since there is considerable consternation about who these volunteers are and whether their involvement in research is ethically problematic. Although as they note, there are limitations to a small qualitative study (n=31)

Response: Thank you for your positive feedback on our manuscript.

2. My primary concern is about their description of the study as "motivations." The most common meaning of motivations is the reason or reasons one has for acting or behaving in a particular way. But, as far as I can tell, these respondents were never asked why they participated in research or to describe their reasons. Instead they were asked to describe the advantages and disadvantages of participating which although interesting, is different than motivations. In that regard, I would explain why/how describing advantages/disadvantages translates into motivations? Or else make major changes to the manuscript, including the title, purpose and the assertion that this study is about motivations, the conclusion (p.20) and other parts.

Response: Thank you of this feedback. According to the Oxford English Dictionary Online (2018), motivation, within the context of psychology, refers to the (conscious or unconscious) stimulus for action towards a desired goal, especially as resulting from psychological or social factors. As outlined on Page 8 of the current manuscript, the current study is based on the initial underlying salient belief phase of the Theory of Planned Behaviour (TPB; Ajzen, 1991) to determine the various psychological and social factors that may motivate (or stimulate) healthy participants to take part on Phase 1 clinical trials. This study applied the first phase of the TPB to elicit the underlying salient behavioural beliefs (i.e., advantages and disadvantages), normative beliefs (i.e., who would approve of a particular behaviour and who would disapprove), and control beliefs (i.e., what are the facilitators and what are the barriers to enacting a particular behaviour). Each of the beliefs that were elicited could be said to motivate (or stimulate) the participant to take part in a Phase 1 clinical trial. Previous studies that have similarly applied this initial phase of the TPB model to a variety of behaviours also refer to the findings as 'motivations' (e.g., Abdul Hanan, King, & Lewis, 2012; Gauld, Lewis, White, & Watson, 2016; Hamilton, Hatzis, Kavanagh, & White, 2015; Hayden, Obst, & Lewis, 2016; Horvath, Lewis, & Watson, 2012; Lewis, Watson, White, & Elliott, 2013; White et al., 2015). As such, we believe that 'motivation' is the correct term to use for this study and would like to maintain it in the manuscript.

3. The authors also say that there are no prior qualitative studies of motivations. There are certainly some very good qualitative studies of the experiences of healthy volunteers in phase 1 studies that have some similarities to this study. For example, several papers by Jill Fisher explore these issues (see https://www.ncbi.nlm.nih.gov/pubmed/?term=Fisher+JA+AND+volunteers)

Response: Thank you very much for these additional references. A paragraph has been added to the Introduction section (page 5/6) as follows:

'Several qualitative studies based in the United States have investigated the experiences of participants in Phase 1 clinical trials particularly in relation to serial participation and risk perception (e.g., Cottingham & Fisher, 2016; Monahan & Fisher, 2015; Walker, Cottingham, & Fisher, 2018). For example, a longitudinal interview study investigated how repeat participants weighed up the risks and benefits and included questions on their motivations to enrol (Walker, Cottingham, & Fisher, 2018). As most trial participants in the United States are males and from minority groups, the financial incentive was often cited as the main motivation for serial participation. Another interview study examined emotion and risk in Phase 1 participants and found that class and race were key factors in determining the emotional experience of risk (Cottingham & Fisher, 2016). For example, economic insecurity affected the emotional experience of risk when weighed up against the benefits. Monahan and Fisher (2015) suggested that serial Phase 1 trial participants can perceive themselves as entrepreneurs who are cleverly securing their financial futures and, in doing so, downplay the risks.'

4. The title also suggests that participating in phase 1 research is about more than just making money, and they list three commonly described advantages from their focus groups as money, altruism, and opportunity for self-development (p. 12 and Table 2). Understanding these as mixed motives is not inconsistent with other existing studies and literature. Interestingly, although it shows mixed views about participation, it still does not lend itself to conclusions about primary motivations. For example, in the study they cite describing motivations of 1194 healthy volunteers (Grady et al 2017), we found that while 58% said money was their primary motivation for participating (which they cite), almost 94% said that money was important or very important to their decision to enroll (which these authors do not cite), while staff competence/friendliness, risks, helping future patients, and the time involved were important or very important to the enrollment decisions of more than 70% of our cohort.

Response: Thank you for this feedback. The section citing the Grady et al., (2017) article has been amended to include your feedback as follows:

'…The most common motivation was money with 58% of participants saying it was their primary motivation and 94% saying it was important or very important. Other factors were deemed by the cohort as being moderately or very important in their decision-making process. These factors were the staff competence and friendliness (84% and 83%, respectively), the risks (81%), helping the development of new medicines and helping future patients (each 80%), and the time involved (73%)…'

5. Page 20. They write – it would be worthwhile exploring differences in motivations for different trial designs, medical procedures etc. See Chen S. et al. Clinical Trials 2017 for a description of willingness to participate in trials of different types, with different procedures, and with different risks

Response: Thank you for drawing our attention to this article. We have added a sentence to the Future Research section on Page 21 as follows:

‘Building on the quantitative work of Chen at al. (2017), a qualitative study could similarly explore whether there are differences in motivations for the different trial designs, medical procedures and the underlying clinical utility of the trialled drug.’

6. Abstract conclusion and manuscript conclusion are different!

Response: Thank you for picking up on this. As the Abstract has a tight word limit, the conclusion has now been expanded to include all that was written in the Abstract. The conclusion now reads as follows:

‘The current study employed a qualitative approach to explore the motivations of healthy participants taking part in Phase 1 clinical trials. Results showed that the motivations of healthy participants are varied and not just dominated by financial gains, thereby providing valuable information to the ethical debate surrounding financial incentives. Overall, it is anticipated that the results of this study will improve the understanding of factors that influence Phase 1 clinical trial participation. Specifically, practical implications include the need for organisations involved in clinical trials to be mindful of inflexible scheduling and explore the possibility of making educational materials available to family members who may be concerned about the risks associated with participation. These factors may then be used to develop more effective recruitment and retention strategies which will, ultimately, help to develop new vaccines and therapeutics to improve patient health.’

VERSION 2 – REVIEW

REVIEWER	Christine Grady National Institutes of Health Clinical Center, Bethesda MD 20892
REVIEW RETURNED	12-Oct-2018

GENERAL COMMENTS	This revised version of this paper is very clear and complete.