

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/329778860>

The willingness to participate in biomedical research involving human beings in low- and middle- income countries: a systematic review

Article in *Tropical Medicine & International Health* · December 2018

DOI: 10.1111/tmi.13195

CITATIONS

0

READS

28

8 authors, including:



Joyce L. Browne
Utrecht University

72 PUBLICATIONS 273 CITATIONS

[SEE PROFILE](#)



Irene Agyepong
Ghana Health Service

125 PUBLICATIONS 2,872 CITATIONS

[SEE PROFILE](#)



Kerstin Klipstein-Grobusch
University Medical Center Utrecht

235 PUBLICATIONS 4,420 CITATIONS

[SEE PROFILE](#)



Rieke van der Graaf
University Medical Center Utrecht

54 PUBLICATIONS 278 CITATIONS

[SEE PROFILE](#)

Some of the authors of this publication are also working on these related projects:



Migration and cardiovascular disease risk; the RODAM study [View project](#)



Tuberculosis in Urban Zambia [View project](#)

Article Type: Systematic Review

The willingness to participate in biomedical research involving human beings in low- and middle-income countries: a systematic review

Joyce L Browne^{*1}, Connie O Rees^{*1}, Johannes J. M. van Delden², Irene Agyepong^{3,4}, Diederick E. Grobbee¹, Ama Edwin⁵, Kerstin Klipstein-Grobusch^{1,5}, Rieke van der Graaf²

*Joint first authors

¹ *Julius Global Health, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands*

² *Department of Medical Humanities, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands*

³ *Ghana Health Service, Research and Development Division, Accra, Ghana*

⁴ *Ghana College of Physicians and Surgeons, Public Health Faculty, Accra, Ghana*

⁵ *Department of Psychological Medicine and Mental Health, School of Medicine, University of Health and Allied Sciences, Ho, Ghana*

⁵ *Division of Epidemiology & Biostatistics, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/tmi.13195

This article is protected by copyright. All rights reserved.

Abstract

Objectives: To systematically review reasons for the willingness to participate in biomedical human subjects research in LMICs.

Methods: Five databases were systematically searched for articles published between 2000 and 2017 containing the domain of 'human subjects research' in 'LMICs' and determinant 'reasons for (non)participation'. Reasons mentioned were extracted, ranked and results narratively described.

Results: 94 articles were included, 44 qualitative and 51 mixed-methods studies. Altruism, personal health benefits, access to health care, monetary benefit, knowledge, social support, and trust were the most important reasons for participation. Primary reasons for non-participation were safety concerns, inconvenience, stigmatization, lack of social support, confidentiality concerns, physical pain, efficacy concerns, and distrust. Stigmatization was a major concern in relation to HIV research. Reasons were similar across different regions, gender, non-patient or patient participants, and real or hypothetical study designs.

Conclusions: Addressing factors that affect (non-)participation in the planning process and during the conduct of research may enhance voluntary consent to participation and reduce barriers for potential participants.

Keywords: health, low- and middle- income countries, willingness to participate, barriers to participate, reasons for participation, reasons for non-participation, informed consent.

Introduction

Ample studies have addressed the willingness of human subjects to participate in biomedical research. Some studies focused on ethical aspects, looking into voluntary informed consent and the relation between participants' motivations and the level of voluntariness that they display. Others looked into practical aspects in an attempt to understand barriers for research participation and improve recruitment and retention rates.(1–4) Studies on the willingness to participate include research in specific populations such as pregnant women or children with cancer, ethnic minorities, and in varying contexts in high as well as low- and middle-income countries (LMICs).(2,5–9)

Systematic reviews on willingness to participate are rare,(7,10) and do not exist for research participation in LMICs specifically. At the same time, these reviews are highly relevant for research conducted in LMICs since social determinants such as poverty, limited health care access, illiteracy, and linguistic or cultural aspects may influence the willingness to participate and affect the understanding of research concepts such as randomization, research risks and voluntariness.(11–15) A better understanding of the motives of those who participate could improve informed consent processes, incorporating a culturally competent approach, and inform ethical guidelines for the design and conduct of health-related human subjects research. We therefore aim to systematically review reasons for the willingness to participate in human subjects biomedical research in LMICs.

Methods

Eligibility Criteria

Articles were eligible for inclusion in this systematic review if they related to the domain of biomedical research involving human beings in LMICs (as defined by the World Bank) and addressed 'reasons to (not) participate'.(16) Articles were included if published after the year 2000, following amendments in the guidelines for research ethics in low-resource settings.(17) Articles were excluded if they concerned secondary analysis or were not published in English or Dutch.

Data Search

A systematic search of the electronic databases PubMed, Embase, Cochrane Library, Popline and GHIL (Global Health Library) was conducted to include all articles up to June 27th, 2017. A search string involving relevant key words and possible variations was constructed based on the domain (human subjects research in LMIC) and determinant (reasons for (non-) participation, see Supplementary File 1).

Study Selection

Studies were screened for title and abstract based on the eligibility criteria independently by two reviewers (CR and JB). Reasons for exclusion were registered. Discordance of article relevance between reviewers (CR and JB) was discussed and resolved, with full-text articles being assessed and a third reviewer (RvdG) consulted if necessary. If the full-text article was not available online, one attempt was made to contact the author, and if no response was received the article was excluded.

Data Collection

Data extraction of the articles was performed by two reviewers (CR and JB) for the following items: authors, year of publication, original study design, indication (disease), country, participants, study design of the nested study, aim of derived study, reasons identified and generic reasons identified. 'Original study design' referred to the type of research of which the willingness to participate was investigated, 'nested study' referred to at which point the 'willingness to participate' in research was investigated (hypothetical, prospective or retrospective). 'Generic reasons' were the groupings of individually different reasons given in relevant articles.

Data Items

The various reasons for and against participation were classified into categories as defined in Table 1. Categories were defined by the authors (JB, CR, RvdG) after data extraction, based on themes derived from previously published similar reviews (18).

Data synthesis

The analysis aimed to provide an overall ranking of frequency of reasons for participation and the relative importance of reasons compared to others in two steps. First, it was assessed whether a reason was listed in an article. Subsequently, for the papers that provided ranking information with regard to relative importance of reasons, the order of the top three reasons was determined. Given the heterogeneity of methods to determine relative ranking of reasons across studies, the ranking as reported in each of the studies was used.

Thus, three rankings were created: (1) the absolute frequency a reason was listed in the articles, (2) the frequency a reason was ranked in the top three, (3) and how many times a reason was ranked as most important. A descriptive composite ranking of importance was subsequently created based on these three categories, in an attempt to globally suggest which reasons may be most important.

For papers that did not provide information on the relative importance of a reason compared to others, the article was only considered for the absolute number of times a reason was mentioned.

Accepted Article

Ranking of reasons were stratified for the following categories, if available in more than one article: World regions (as defined by the World Bank, with the regions of 'South Asia' and 'East and Asia & Pacific' combined into 'Asia'), male versus female, non-patient versus patients, HIV research versus non-HIV research (due to the hypothesis possibility that stigmatization could influence research participation, particularly in HIV research) and hypothetical (i.e. empirical studies that ask participants about potential participation in studies that do not (yet) exist or enroll participants) versus 'real' studies.⁽¹⁶⁾ 'Real' studies (i.e. empirical studies nested in research for which participants were recruited/enrolled in) could either be prospective or retrospective. An article was categorized into a specific region by study location. If a paper concerned multiple countries or regions, the information specific to individual regions was extracted.

Quality Assessment

Owing to the nature of the research question for this review the risk of bias for included studies was not investigated. The protocol for this systematic review was registered in the PROSPERO database (CRD42015017126).

Results

The search across all databases yielded a total of 1243 results of which 987 unique articles remained after removal of duplicates. 144 articles were screened in full-text, resulting in ninety-four articles included in this systematic review. Figure 1 presents study selection flow diagram. Supplementary Table 1 presents an overview of included articles, the characteristics of which are summarized in Table 2. The majority of articles (n=54) reported both reasons for and against participation in research. Most were hypothetical (n=64), and all were qualitative (n=44) or mixed methods (n=50). The majority of articles reported on studies about specific diseases, most commonly infectious diseases. Most studies were conducted in sub-Saharan Africa (n=45), followed by Asia (n=27, Latin America and the Caribbean (n=11), the Middle East and North-Africa (n=4) and Eastern Europe (n=2)."

Table 3 presents the frequency a reason for (non-)participation was mentioned in studies, the number of times ranked as a reason in the top three, and the number of times ranked as top reason. 55 studies included information on the relative importance of reasons mentioned. Table 4 provides the composite summary of relative importance. Supplementary Table S2 provides ranking of reason

per article, Table S3 the number of times a reason was listed, and Tables S4-8 ranking by different population characteristics. Supplementary graphs S1-S13 visualize the data provided here.

Reasons most frequently mentioned and indicated as relatively most important within studies in favor of participation, were altruism, personal health benefits, access to health care, monetary benefit, knowledge, social support and trust. Overall, these were common across LMICs in different regions, real and hypothetical studies, for both HIV and non-HIV research, for men and women and for non-patient and patient participants (Tables 3,4; Figures S1-13).

Altruism

Altruism was mentioned in 46 of 94 articles and thus the most often cited reason for study participation. (1,19,28–37,20,38–47,21,48–57,22,58–64,23–27) It was ranked in the top three 30 times,(1,19,37,40,41,44–48,50,51,20,52–59,61,65,21,66,23,27,30–32,36) and the top reason for participation 20 times.(1,19,45,48,52,54,56,58,59,61,66,20,21,23,30–32,36,37) Altruism was ranked first in all regions, except for Eastern Europe, where it was ranked third, in both HIV and non-HIV research, among non-patient and patient participants, for hypothetical and real studies and for male participants.

Personal health benefits

Personal health benefits were mentioned as a motivator for research participation in 40 papers, (22,25,40–44,46–48,50,51,26,52–54,56–60,62,63,27,64,67–74,28,30,31,33,36,39) ranked in the top three in 21 papers,(30,31,51–54,56–58,65,67,68,36,71,40,41,44,46–48,50) and reported as the top reason for participation nine times.(40,46,47,51,53,57,65,67,68) This category ranked second for the regions of Sub-Saharan Africa, Asia and South and Latin America, HIV research, for non-patient participants, male participants and real and hypothetical studies, and was ranked first overall in articles involving female participants.

Access to health care

Access to health care was mentioned as a motivator to participate in research 42 times, (3,19,33,34,38,40,41,49,50,53–55,20,57,58,60,62–64,67,71–73,21,75–84,24,85,86,25,27,29,31,32) ranked in the top three 20 times, (19,21,55,57,58,67,71,77,78,80,81,86,27,31,32,40,41,50,53,54)

This article is protected by copyright. All rights reserved.

and was ranked first in four studies.(41,71,78,80,86) It ranked third overall in articles for Sub-Saharan Africa, Asia, South and Latin America and in articles concerning both male and female participants and for hypothetical studies and second in Eastern Europe. It was ranked as second for non-HIV research and real studies, fourth for HIV research, and third and second for non-patient and patient participants respectively.

Monetary benefit

Monetary benefit was mentioned as a reason 31 times, (3,19,33,35,37,41,45,48–50,53,54,20,55,58–60,69,71,81–83,86,21,87,22–24,27,31,32) ranked in the top three ten times,(19,21,27,37,45,48,59,69,71,86) and ranked as the top reason twice.(27,69) Several studies stated that monetary benefit was one of the less important influencing factors in participation,(35,38) it being ranked fourth overall in importance. This was ranked as the third most important reason in HIV and non-HIV research, was ranked fourth for the regions of Sub-Saharan Africa, Asia and Eastern Europe, and for patient and non-patient participants, male and female participants and for real and hypothetical studies. It was ranked fifth for South and Latin America, and ninth for North Africa and the Middle East.

Knowledge

The gaining of knowledge through research participation was mentioned 16 times overall, (25,27,76,81,82,87–89,41,44,54,59,60,62,67,73) ranked in the top three reasons four times, (44,59,67,89) and was given as the top reason in one paper to participate.(44) Knowledge was ranked fifth in Sub-Saharan Africa and Eastern Europe, in HIV research, by male and patient participants and for hypothetical studies. It was ranked sixth for research conducted in Asia.

Social support

Social support as encouragement or approval to participate in research by family members, community or friends was mentioned 18 times, (20,22,69,75,78,85,86,89–91,23,32,35,36,42,53,59,63) in the top three reasons in six studies,(20,32,36,69,78) and ranked sixth overall. Social support seemed to play a larger role in Asia than in other regions. Furthermore, it appeared to be slightly more important for HIV research than non-HIV research (being ranked sixth

and seventh in these categories, respectively). There was no difference between male and female participants' perspective (or between real and hypothetical studies) of social support as a reason for participation, but was more important for patients than non-patient participants. However, a few articles suggested that the influence of family and friends was more important for women. (78)(46) Furthermore, social support was ranked higher in North Africa (ranked third) and the Middle East in comparison to other regions.

Trust

Trust was mentioned in 17 articles, (1,30,72–74,78,86,88,53–56,60,62,63,69) and was ranked in the top three in six papers. (1,30,56,69,78,86) While the reason of 'trust' was ranked seventh overall, it was ranked higher (fourth) for research in South and Latin America and North Africa and the Middle East, as well as for non-HIV research, patient participants and for real studies (ranked fifth).

Other reasons for participation

Additional reasons for participation mentioned were: ability to withdraw,(92) advice from physician, (20,27,77,86) community involvement, (34,61–63,66) cultural acceptability, (63,92) creating a feeling of community,(44) low pressure decision,(75) need for treatment,(77) research involving a non-invasive procedure,(46,81) peer enrolment, (33,44,85) low perception of risk,(54,70) result availability,(20) guarantee of confidentiality, (23,33,34,62) being unaware of voluntariness of participation,(46) research outcome, (60,62,66,85) and finally seeing research participation as motivation to avoid risky behavior.(59)

The most important reasons for non-participation were safety concerns, inconvenience, stigmatization, lack of social support, confidentiality concerns, physical pain, efficacy concerns and distrust. Overall, these were common across different regions, real and hypothetical studies, HIV and non-HIV research, men and women and non-patient and patient participants (Tables 4-5, S1-13).

Safety concerns

Safety concerns were the most often mentioned reason for non-participation. This was a particular issue for vaccine or drug trials, but not for observational studies. Safety concerns were mentioned in 45 papers, (1,20,34,36,37,39–42,45,47,48,21,50–53,55,56,58,59,61,62,22,67–69,71,76,77,89,93–

95,23,96–100,26,28,30–32) ranked in the top three reasons 32 times,(1,20,41,45,47,48,50–53,55,56,21,58,61,65,67–69,71,77,94,95,23,97–99,30–32,36,37,40) and identified as the top reason for non-participation 16 times.(31,32,68,71,77,94,95,97,99,40,45,47,48,55,58,61,65) Safety concerns were consistently ranked as most important in all categories, with the exception of North Africa and the Middle East, where they ranked second. In some articles, it was explicitly mentioned that women were generally more ‘worried about complications’.(27)

Inconvenience

Inconvenience was mentioned in 25 articles as a reason for non-participation, (20,28,50,51,54,58,67,69,71,101–103,30,104–107,31,32,34,37,42,44,46) ranked as the top three reasons fourteen times,(31,44,103,105,107,46,50,54,67,69,71,101,102) and ranked first in four articles.(67,102,103,105) Examples of inconveniences included not having enough time to participate in research, transport issues, or a long distance to the research site.(67,71)

Stigmatization

Especially in trials about HIV and other STIs, stigmatization was named a barrier. Despite being ranked third overall, stigmatization was consistently ranked higher for HIV research, specifically in Sub-Saharan Africa and Asia, among non-patients, and female participants. Stigmatization was in fact only mentioned once in relation to non-HIV research, suggesting that despite being mentioned 20 times overall,(22,23,52,53,68,69,75,87,94,95,99,108,31,32,36,37,41,42,47,50) being ranked in the top three five times,(23,32,41,50,95) and as the top reasons thrice,(23,41,50) it is not one of the more important reasons for non-participation when looking at human subjects research in general.

Lack of social support

Lack of social support was mentioned as a reason for non-participation 23 times, (32,41,77,85,86,89,90,94,95,99,103,106,44,109–111,48,53,54,68,72,75,76) ranked in the top three eleven times,(32,41,109,48,50,53,77,94,95,103,106) and given as the top reason three times.(53,106,109) Lack of social support was found to be ranked higher (third) for research being conducted in Asia, involving HIV and women, whilst playing a smaller role in the regions of Sub-Saharan Africa, North Africa and the Middle East and Eastern Europe. Furthermore, it seems to be slightly less important for non-patient participants over patient participants.

Confidentiality concerns

Confidentiality concerns were mentioned 12 times, (20–22,43,44,46,58,87,92,108) ranked in the top three, four times,(21,44,46,92) and ranked first, three times.(44,46,92) Confidentiality concerns were ranked highest by research participants in North Africa and the Middle East (second), even though it was ranked fifth overall. This reason was not assigned the same importance for Eastern Europe or South and Latin America, or for HIV research. Furthermore, they seemed more important for male participants than female participants, and were also more important for patient participants over non-patient participants and hypothetical over real studies.

Physical pain

(Fear of) physical pain was mentioned as a reason 13 times,(19,20,76,83,106,28,31,44,47,50,53–55) ranked in the top three five times,(19,20,31,47,106) and given as the most important reason twice.(19,47) It seemed to be slightly more important for male participants, patient participants, for non-HIV research, and research participants in Sub-Saharan Africa. For South and Latin America this reason was least cited.

Efficacy concerns

Efficacy concerns were mentioned 12 times, (36,40,98,99,45,47,51–53,59,77,93) ranked in the top three ten times,(36,40,45,47,51,52,59,77,98,99) and ranked first twice.(59,98) This was of the most importance for research conducted in Asia, and in HIV research. For men and studies conducted in Eastern Europe, South and Latin America and North Africa and the Middle East, it was a less important reason.

Distrust

Distrust was mentioned in 14 articles, (21,34,58,62,83,37,39,41,42,45,53,55,56) and given as a top three reason four times.(41,56,58,61) Distrust was an important factor mostly in Eastern Europe, and was ranked as the eighth most important reason overall.

Other reasons for non-participation

Additional reasons given for non-participation were costs,(44,58,69,104,112) cultural insensitivity,(37,102) fear of false-positive test results after participation in HIV research,(36,44,45,50,59,87,94,95) fear of knowledge of health status,(19,28,30,54,68) insufficient compensation,(21,43) invasive procedures, (1,20,30,39,54,78,88,107) lack of interest, (30,34,37,61,87,96,103,105,106,110) lack of clarity,(1,30,37,51,52,92,112) not willing to comply to terms of research,(55,68,94,107,109) no perceived need,(29,53,55,65,99) feeling overwhelmed,(110) placebo concerns,(29,40,52–55) having had a previous negative experience,(75,112) not wishing to be re-contacted,(92) feeling tempted to unsafe behavior,(43) lack of perceived benefit,(93) effect on lifestyle,(20,53) worsening medical condition, (100,101,103) and having a lack of knowledge about research.(26,55,56,75,89,96,102)

Discussion

This systematic review shows that the most important reasons for willingness to participate in research (altruism, personal health benefits and access to health care) or not (safety concerns, inconvenience, stigmatization and lack of social support) are common across LMICs in different regions, for both HIV and non-HIV research, for men and women and for non-patient and patient participants. Research professionals and ethics committees addressing the interests of LMICs (study) populations can use the results from this review to prepare for and conduct research in these environments.

Some of the reasons identified in this review could influence the voluntary decision to participate in research. For example, (expected) personal or community health benefits, access to health care, (dis)trust or community pressure could affect autonomy in the consent to participate in research, or *de facto* constitute controlling influences affecting autonomy.(15,113)

As many of the reasons to (not) participate are linked to socio-economic factors relatively common in LMIC contexts (such as poverty and illiteracy), the complete removal of these influences seems unrealistic for study investigators. Literature and international ethical guidelines for research conduct (14) mention a number of ways that could help to mitigate the potential threats of these reasons to participate to voluntary informed consent. Simultaneously, barriers to research identified in this review, such as need for/lack of social support, fear of stigmatization, inconvenience and therapeutic misconception can also be addressed using these approaches.(114)(113)

Accepted Article

First, community engagement, in which the role of the family and community (leaders) in decision making is acknowledged and incorporated.(113) Community engagement addresses the importance of (expected) personal and/or community benefit in the decision to participate in research, and can enhance the understanding of research.(113) The 2016 CIOMS International Ethical Guidelines for Health-related Research Involving Humans similarly recommend to engage communities when conducting (clinical) research in low-resource settings to ensure ethical and scientific quality. (14)

Second, the potentially inappropriate influence of reasons to (not) participate on voluntary consent could be attenuated by balancing the decision to participate in research against a person's expressed values in the consent process.(15) This 'threshold inquiry' assesses whether the (potential) participant would also have participated in the absence of these influences and as such not persuade, coerce or manipulate a person into participation. Importantly, these influences are *potentially* -but not by definition inappropriate. Thus, a threshold inquiry allows for an assessment of whether the inducement for trial participation (e.g. access to health care) is sufficiently weighted against the risk the person assumes, and as such does not result in 'poor judgment which makes us take unnecessary, unreasonable, and excessive risks of harm, whether physical harm or the harm of violating important values' – as there is nothing 'unethical or wrong when individuals considering entering a trial weigh the inducement against the risk they will assume'.(115)

Therefore, the third manner in which potential influences could be addressed is to incorporate procedures in informed consent processes that safeguard the understanding of the nature and implications of the research. Various existing strategies can be employed, including sufficient time for subjects to consider their participation and discuss it with family and friends; and provision of adequate information about what research entails (about research in general and the specific research in particular) from someone without a dependency relationship (such as between physician and patient).(4,15)(113)

Previous reviews of reasons for research participation have been conducted for specific LMIC populations, healthy volunteers in predominantly high-resource settings and specific subpopulations in high resource settings. Reviews summarizing studies conducted in Brazil, India and China, similarly identified the importance of altruism, personal benefit and access to health. (2,9) Overall, participation in human subjects research seems an effort of subjects to improve their personal or community's circumstances, and this effort generally outweighs monetary gain in importance. (7,9,116–118) This contrasts with a review of reasons among healthy volunteers to participate in clinical trials in mainly high-resource settings (United States (n studies=6), Portugal, Spain, the

Netherlands, Croatia, Germany, United Kingdom and Malawi (all n=1), in which financial rewards were reported a primary motivation to participate - albeit altruistic motives informed the decision as well.(119) For specific (patient) populations in high resource settings - children and their parents participating in drug research, women with breast cancer, cancer patients, and minority populations in the United States - altruism and access to health care were (more) important considerations in the decision to participate in research. (5–8,119)

The major reasons for non-participation – concern for safety; distrust of research or health professionals; privacy concerns, and a fear of social consequences – were also reported by previous reviews in LMICs, high resource settings and among specific subpopulations.(7,9,116,120)

To the best of our knowledge, this is the first systematic review to investigate motivations that influence willingness to participate across LMICs as a whole. As we stratified our results by various study characteristics, the results can be generalized to a wide scope of human subjects research. The comprehensive inclusion of study designs, both qualitative and quantitative methods, is a strength of this study.

This review, however, has limitations that should be considered when interpreting the findings. First, the method by which the importance of reasons for participation was determined may not yield indisputable results, as a standardized methodology of ranking of reasons of (non-) participation is not available. We aimed to provide a structured overview with a ranking of relative importance, a quantitative improvement over previously published reviews.(9) Second, the majority of studies included were hypothetical (64 out of 94), and the extent to which these reflect real life situations may vary. Nonetheless, the ranking of reasons for (non-)participation between hypothetical and ‘real’ studies yielded similar results. We did not look specifically into the difference in reasons to participate based on the method of data collection (e.g. interview vs. self-administered questionnaire) or study design (e.g. observational vs. interventional research). It is possible that differences in reasons for (non-) participation could be found between these groups. Furthermore, the paucity of data of studies from North Africa, the Middle East, and Eastern Europe, as well as from non-infectious disease research, limits the generalizability of the results to these domains. The same can be said about the fact that we limited relevant articles to those written in the Dutch or English language, meaning literature written in other languages common to LMIC (i.e. French, Spanish) was not taken into account in this review.s

This review identified a number of research needs for global health (research) ethics. First, a standardized way to collect data on reasons for (non-)participation in research and synthesis of preferences would allow for better comparison and analysis of data across studies. This would

This article is protected by copyright. All rights reserved.

eliminate many of the limitations identified for this review. Ideally, these tools could help researchers to assess motivators and barriers to conduct of the study in the feasibility or piloting stage. Second, given potential similarities in the reasons to (not) participate between LMICs populations and disadvantaged populations in high-income countries resulting from socio-economic disadvantage, further research into the reasons for (non-) participation in these groups may be of value, including systematic synthesis of the body of literature up to now. Similarly, very few reviews included (potentially) marginalized or hard-to-reach populations in LMICs such as (ethnic) minority groups or members of the LGBT community.

The main motivations to participate in human subject research in LMICs are altruism, a desire for personal health benefits, and access to health care. Safety concerns, inconvenience, a lack of social support and - for HIV-related studies - stigmatization are the major reasons for non-participation in these populations. In order to ensure voluntary consent to participation and reduce barriers for potential participants, these reasons for (non-)participation should be considered in the planning and conduct of research.

Acknowledgments

We gratefully acknowledge Rob Scholten PhD (Dutch Cochrane Center) for his advice on the approach for analysis and Tessa Pronk PhD (Utrecht University Library) for her help in setting up the search strategy.

References

1. Khalil SS, Silverman HJ, Raafat M, El-Kamary S, El-Setouhy M. Attitudes, understanding, and concerns regarding medical research amongst Egyptians: a qualitative pilot study. *BMC Med Ethics*. 2007/08/31. 2007;8:9.
2. Shah JY, Phadtare A, Rajgor D, Vaghasia M, Pradhan S, Zelko H, et al. What leads Indians to participate in clinical trials? A meta-analysis of qualitative studies. *PLoS One*. 2010/05/28. 2010;5(5):e10730.
3. Mfutso-Bengo J, Manda-Taylor L, Masiye F. Motivational factors for participation in biomedical research: evidence from a qualitative study of biomedical research participation in Blantyre district, Malawi. *J Empir Res Hum Res Ethics*. 2015/03/06. 2015;10(1):59–64.
4. Dekking SAS, Van Der Graaf R, Van Delden JJM. Voluntary Informed Consent in Paediatric Oncology Research. *Bioethics* [Internet]. 2016 Jul [cited 2016 Sep 14];30(6):440–50. Available from: <http://doi.wiley.com/10.1111/bioe.12237>
5. Tromp K, Zwaan CM, van de Vathorst S. Motivations of children and their parents to participate in drug research: a systematic review. *Eur J Pediatr* [Internet]. Springer; 2016 May [cited 2016 Sep 14];175(5):599–612. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27041121>
6. Luschin G, Habersack M, Gerlich I-A. Reasons for and against participation in studies of medicinal therapies for women with breast cancer: a debate. *BMC Med Res Methodol* [Internet]. BioMed Central; 2012 [cited 2016 Sep 14];12:25. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22405127>
7. Limkakeng A, Phadtare A, Shah J, Vaghasia M, Wei DY, Shah A, et al. Willingness to participate in clinical trials among patients of Chinese heritage: a meta-synthesis. *PLoS One*. 2013/01/26. 2013;8(1):e51328.
8. Spears CR, Nolan B V, O'Neill JL, Arcury TA, Grzywacz JG, Feldman SR. Recruiting underserved populations to dermatologic research: A systematic review. *Int J Dermatol* [Internet]. 2011;50(4):385–95. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L361460559>
9. Zammar G, Meister H, Shah J, Phadtare A, Cofiel L, Pietrobon R. So different, yet so similar: meta-analysis and policy modeling of willingness to participate in clinical trials among Brazilians and Indians. *PLoS One*. 2010/12/24. 2010;5(12):e14368.

- Accepted Article
10. White C, Hardy J. What do palliative care patients and their relatives think about research in palliative care?-a systematic review. *Support Care Cancer* [Internet]. 2010 Aug [cited 2016 Sep 23];18(8):905–11. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19705165>
 11. Emanuel EJ, Wendler D, Killen J, Grady C. What makes clinical research in developing countries ethical? The benchmarks of ethical research. *J Infect Dis*. 2004;189:930–7.
 12. Luna F. Elucidating the concept of vulnerability: Layers not labels. *Int J Fem Approaches Bioeth* [Internet]. 2009;2(1):121–39. Available from: <http://inscribe.iupress.org/doi/abs/10.2979/FAB.2009.2.1.121>
 13. Glickman SW, McHutchison JG, Peterson ED, Cairns CB, Harrington RA, Califf RM, et al. Ethical and Scientific Implications of the Globalization of Clinical Research. *N Engl J Med* [Internet]. 2009 Feb 19 [cited 2016 Jun 7];360(8):816–23. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMs0803929>
 14. CIOMS. International Ethical Guidelines for Biomedical Research Involving Human Subjects [Internet]. 2015 [cited 2015 Oct 22]. Available from: http://www.cioms.ch/images/stories/guidelines_demo/AllGuidelines-1-25.pdf
 15. Nelson RM, Merz JF. Voluntariness of Consent for Research: An Empirical and Conc... : *Medical Care* [Internet]. *Medical Care*. 2002 [cited 2016 Sep 14]. p. 69–80. Available from: http://journals.lww.com/lww-medicalcare/Abstract/2002/09001/Voluntariness_of_Consent_for_Research__An.10.aspx
 16. The World Bank. Countries [Internet]. [cited 2015 May 20]. Available from: <http://www.worldbank.org/en/country>
 17. Levine RJ. Some recent developments in the international guidelines on the ethics of research involving human subjects. *Ann N Y Acad Sci*. 2000;918:170–8.
 18. van der Zande ISE, van der Graaf R, Hooft L, van Delden JJM. Facilitators and barriers to pregnant women’s participation in research: A systematic review. *Women Birth* [Internet]. Elsevier; 2018 Jan 17 [cited 2018 Mar 18];0(0). Available from: <http://www.ncbi.nlm.nih.gov/pubmed/29373261>
 19. Abrams A, Siegfried N, Geldenhuys H. Adolescent experiences in a vaccine trial: A pilot study. *South African Med J* [Internet]. 2011;101(12):884–6. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L363024066>

20. Al-Amad S, Awad M, Silverman H. Attitudes of dental patients towards participation in research. *East Mediterr Heal J*. 2014/06/20. 2014;20(2):90–8.
21. Burt T, Dhillon S, Sharma P, Khan D, Mv D, Alam S, et al. PARTAKE Survey of Public Knowledge and Perceptions of Clinical Research in India. *PLoS One* [Internet]. 2013;8(7). Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L369423899>
22. Chakrapani V, Newman PA, Singhal N, Jerajani J, Shunmugam M. Willingness to participate in HIV vaccine trials among men who have sex with men in Chennai and Mumbai, India: a social ecological approach. *PLoS One* [Internet]. 2012;7(12):e51080. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3514227/pdf/pone.0051080.pdf>
23. Chu Z, Xu J, Reilly KH, Lu C, Hu Q, Ma N, et al. HIV related high risk behaviors and willingness to participate in HIV vaccine trials among China MSM by computer assisted self-interviewing survey. *Biomed Res Int*. 2013/12/29. 2013;2013:493128.
24. Copenhaver C, Ding D, Mortimer JA, Zhao Q, Guo QH, Galasko D, et al. Perception of stigma and willingness to participate in a cohort study among proxy respondents and controls in Shanghai, China: Scobhi-pilot. *Alzheimer's Dement* [Internet]. 2009;5(4):410. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L70109737>
25. de Bruyn G, Skhosana N, Robertson G, McIntyre JA, Gray GE. Knowledge and attitudes towards HIV vaccines among Soweto adolescents. *BMC Res Notes*. 2008/09/02. 2008;1:76.
26. Dong X, Wong E, Simon MA. Study design and implementation of the PINE study. *J Aging Heal*. 2014/03/29. 2014;26(7):1085–99.
27. Doshi MS, Kulkarni SP, Ghia CJ, Gogtay NJ, Thatte UM. Evaluation of factors that motivate participants to consent for non-therapeutic trials in India. *J Med Ethics* [Internet]. 2013;39(6):391–6. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L52488387>
28. Evangeli M, Kafaar Z, Kagee A, Swartz L, Bullemor-day P. Does message framing predict willingness to participate in a hypothetical HIV vaccine trial: An application of Prospect Theory. *AIDS Care - Psychol Socio-Medical Asp AIDS/HIV* [Internet]. 2012; Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L52351189>
29. Fede AB, Miranda MC, Lera AT, Prestes P, Schaffhausser HL, Matushita D, et al. Placebo-controlled trials (PCT) in cancer research: Patient and oncologist perspectives. *J Clin Oncol*

[Internet]. 2010;28(15). Available from:

<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L70261398>

30. Gitanjali B, Raveendran R, Pandian DG, Sujindra S. Recruitment of subjects for clinical trials after informed consent: Does gender and educational status make a difference? *J Postgrad Med* [Internet]. 2003;49(2):109–13. Available from:
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L36950065>
31. Jaspan HB, Berwick JR, Myer L, Mathews C, Flisher AJ, Wood R, et al. Adolescent HIV prevalence, sexual risk, and willingness to participate in HIV vaccine trials. *J Adolesc Heal* [Internet]. 2006/10/19. 2006;39(5):642–8. Available from: http://ac.els-cdn.com/S1054139X06001960/1-s2.0-S1054139X06001960-main.pdf?_tid=9be5fede-c5c7-11e4-9aa6-00000aab0f26&acdnat=1425842363_f2ce36132d1846bd02ff28af2caec85c
32. Jenkins RA, Torugsa K, Markowitz LE, Mason CJ, Jamroentana V. Willingness to participate in HIV-1 vaccine trials among young Thai men. *Sex Transm Infect* [Internet]. 2000;76(5):386–92. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1744201/pdf/v076p00386.pdf>
33. Karim QA, Kharsany ABM, Naidoo K, Yende N, Gengiah T, Omar Z, et al. Co-enrollment in multiple HIV prevention trials - Experiences from the CAPRISA 004 Tenofovir gel trial. *Contemp Clin Trials* [Internet]. 2011;32(3):333–8. Available from:
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L51291281>
34. Kiawi E, McLellan-Lemal E, Mosoko J, Chillag K, Raghunathan PL. “Research participants want to feel they are better off than they were before research was introduced to them”: engaging cameronian rural plantation populations in HIV research. *BMC Int Heal Hum Rights*. 2012/06/26. 2012;12:8.
35. Kruse-Jarres R, Rodman A, Mahlangu J. Regional factors influencing participation in clinical trials in hemophilia in the United States of America and South Africa. *J Thromb Haemost* [Internet]. 2013;11:1071. Available from:
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71209471>
36. Li Q, Luo F, Zhou Z, Li S, Liu Y, Li D, et al. Willingness to participate in HIV vaccine clinical trials among Chinese men who have sex with men. *Vaccine*. 2010/05/11. 2010;28(29):4638–43.
37. Lindegger G, Quayle M, Ndlovu M. Local knowledge and experiences of vaccination: implications for HIV-preventive vaccine trials in South Africa. *Heal Educ Behav*. 2006/06/03. 2007;34(1):108–23.

38. Macphail C, Delany-Moretlwe S, Mayaud P. "It's not about money, it's about my health": determinants of participation and adherence among women in an HIV-HSV2 prevention trial in Johannesburg, South Africa. *Patient Prefer Adherence*. 2012/09/01. 2012;6:579–88.
39. Mahomed H, Shea J, Kafaar F, Hawkrigde T, Hanekom WA. Are adolescents ready for tuberculosis vaccine trials? *Vaccine* [Internet]. 2008;26(36):4725–30. Available from: http://ac.els-cdn.com/S0264410X08007974/1-s2.0-S0264410X08007974-main.pdf?_tid=952e5654-c5c7-11e4-afb5-00000aab0f01&acdnat=1425842352_0d79a3d3341dfa99d8c88d9da499eab9
40. McGrath JW, George K, Svilar G, Ihler E, Mafigiri D, Kabugo M, et al. Knowledge about vaccine trials and willingness to participate in an HIV/AIDS vaccine study in the Ugandan military. *J Acquir Immune Defic Syndr*. 2001/07/27. 2001;27(4):381–8.
41. Mensch BS, Friedland BA, Abbott SA, Katzen LL, Tun W, Kelly CA, et al. Characteristics of female sex workers in southern India willing and unwilling to participate in a placebo gel trial. *AIDS Behav* [Internet]. 2013;17(2):585–97. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L369476779>
42. Meque I, Dube K, Bierhuizen L, Zango A, Veldhuijzen N, Cumbe F, et al. Willingness to participate in future HIV prevention trials in Beira, Mozambique. *Afr J AIDS Res*. 2015/01/03. 2014;13(4):393–8.
43. Nyamathi AM, Suhadev M, Swaminathan S, Fahey JL. Perceptions of a community sample about participation in future HIV vaccine trials in south India. *AIDS Behav*. 2006/10/04. 2007;11(4):619–27.
44. Okall DO, Ondenge K, Nyambura M, Otieno FO, Hardnett F, Turner K, et al. Men who have sex with men in Kisumu, Kenya: comfort in accessing health services and willingness to participate in HIV prevention studies. *J Homosex*. 2014/08/05. 2014;61(12):1712–26.
45. Perisse ARS, Schechter M, Moreira RI, Do Lago RF, Santoro-Lopes G, Harrison LH. Willingness to participate in HIV vaccine trials among men who have sex with men in Rio de Janeiro, Brazil. *J Acquir Immune Defic Syndr* [Internet]. 2000;25(5):459–63. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L32055576>
46. Rodrigues RJ, Antony J, Krishnamurthy S, Shet A, De Costa A. "What do I know? Should I participate?" Considerations on participation in HIV related research among HIV infected adults in Bangalore, South India. *PLoS One*. 2013/03/06. 2013;8(2):e53054.

47. Ruan Y, Qian HZ, Li D, Shi W, Li Q, Liang H, et al. Willingness to be circumcised for preventing HIV among Chinese men who have sex with men. *AIDS Patient Care STDS*. 2009/04/02. 2009;23(5):315–21.
48. Sahay S, Mehendale S, Sane S, Brahme R, Brown A, Charron K, et al. Correlates of HIV vaccine trial participation: an Indian perspective. *Vaccine*. 2005/01/22. 2005;23(11):1351–8.
49. Shaffer DN, Yebei VN, Ballidawa JB, Sidle JE, Greene JY, Meslin EM, et al. Equitable treatment for HIV/AIDS clinical trial participants: A focus group study of patients, clinician researchers, and administrators in western Kenya. *J Med Ethics [Internet]*. 2006;32(1):55–60. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L43085477>
50. Smit J, Middelkoop K, Myer L, Seedat S, Bekker LG. Willingness to participate in HIV vaccine research in a peri-urban South African community. *Int J STD AIDS [Internet]*. 2006;17:176–9. Available from: <http://std.sagepub.com/content/17/3/176.full.pdf>
51. Suhadev M, Nyamathi AM, Swaminathan S, Suresh A, Venkatesan P. Factors associated with willingness to participate in HIV vaccine trials among high-risk populations in South India. *AIDS Res Hum Retroviruses*. 2009/02/26. 2009;25(2):217–24.
52. Suhadev M, Nyamathi AM, Swaminathan S, Venkatesan P, Sakthivel MR, Shenbagavalli R, et al. A pilot study on willingness to participate in future preventive HIV vaccine trials. *Indian J Med Res [Internet]*. 2006;124(DEC.):631–40. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L46592103>
53. Tharawan K, Manopaiboon C, Ellertson C, Limpakarnjanarat K, Chaikummao S. Women's willingness to participate in microbicide trials in northern Thailand. *J Acquir Immune Defic Syndr*. 2001;28(2):180–6.
54. Thienkrua W, Todd CS, Chaikummao S, Sukwicha W, Yafant S, Tippanont N, et al. Prevalence and correlates of willingness to participate in a rectal microbicide trial among men who have sex with men in Bangkok. *AIDS Care*. 2014/05/07. 2014;26(11):1359–69.
55. Udrea G, Dumitrescu B, Purcarea M, Balan I, Rezus E, Deculescu D. Patients' perspectives and motivators to participate in clinical trials with novel therapies for rheumatoid arthritis. *J Med Life [Internet]*. 2009;2(2):227–31. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L358723424>
56. Vieira de Souza CT, Lowndes CM, Landman C, Szwarcwald CL, Suttmoller F. Willingness to

participate in HIV vaccine trials among a sample of men who have sex with men, with and without a history of commercial sex, Rio de Janeiro, Brazil. *AIDS Care*. 2003;15(4):539–48.

57. Woodsong C, Alleman P, Musara P, Chandipwisa A, Chirenje M, Martinson F, et al. Preventive misconception as a motivation for participation and adherence in microbicide trials: evidence from female participants and male partners in Malawi and Zimbabwe. *AIDS Behav*. 2011/08/25. 2012;16(3):785–90.
58. Wu E, Wang T, Lin T, Chen X, Guan Z, Cao C, et al. A Comparative Study of Patients' Attitudes Toward Clinical Research in the United States and Urban and Rural China. *Clin Transl Sci*. 2015/01/16. 2015;
59. Yin L, Zhang Y, Qian HZ, Rui B, Zhang L, Zhu J, et al. Willingness of Chinese injection drug users to participate in HIV vaccine trials. *Vaccine*. 2008/01/15. 2008;26(6):762–8.
60. Akazili J, Chatio S, Achana FS, Oduro A, Kanmiki EW, Baiden F. Factors influencing willingness to participate in new drug trial studies: a study among parents whose children were recruited into these trials in northern Ghana. *BMC Res Notes* [Internet]. 2016;9:139. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26936043>
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4776433>
61. Boudia W, Grissa MH, Zorgati A, Beltaief K, Boubaker H, Sriha A, et al. Willingness to participate in health research: Tunisian survey. *BMC Med Ethics* [Internet]. 2016;17(1):47. Available from: <http://bmcomedethics.biomedcentral.com/articles/10.1186/s12910-016-0131-3>
62. Doshi M, Avery L, Kaddu RP, Gichuhi M, Gakii G, du Plessis E, et al. Contextualizing willingness to participate: recommendations for engagement, recruitment & enrolment of Kenyan MSM in future HIV prevention trials. *BMC Public Health* [Internet]. 2017;17(1):469. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/28521748>
63. Den hollander GC, Browne J I., Arhinful D, van der Graaf R, Klipstein-Grobusch K. Power Difference and Risk Perception: Mapping Vulnerability within the Decision Process of Pregnant Women towards Clinical Trial Participation in an Urban Middle-Income Setting. *Developing World Bioethics*. 2016;
64. Meneguín S, Aparecido Ayres J. Perception of the informed consent form by participants in clinical trials. *Invest Educ Enferm* [Internet]. 2014;32(1):97–102. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L606862200>

65. Dong Y, Shen X, Guo R, Liu B, Zhu L, Wang J, et al. Willingness to participate in HIV therapeutic vaccine trials among HIV-infected patients on ART in China. *PLoS One*. 2014/11/06. 2014;9(11):e111321.
66. Groth SW, Dozier A, Demment M, Li D, Fernandez ID, Chang J, et al. Participation in Genetic Research: Amazon's Mechanical Turk Workforce in the United States and India. *Public Health Genomics*. 2017;19(6):325–35.
67. Asiki G, Abaasa A, Ruzagira E, Kibengo F, Bahemuka U, Mulondo J, et al. Willingness to participate in HIV vaccine efficacy trials among high risk men and women from fishing communities along Lake Victoria in Uganda. *Vaccine*. 2013/09/12. 2013;31(44):5055–61.
68. Deschamps MM, Zorrilla CD, Morgan CA, Donastorg Y, Metch B, Madenwald T, et al. Recruitment of Caribbean female commercial sex workers at high risk of HIV infection. *Rev Panam Salud Publica*. 2013/10/08. 2013;34(2):92–8.
69. Fincham D, Kagee A, Swartz L. Inhibitors and facilitators of willingness to participate (WTP) in an HIV vaccine trial: construction and initial validation of the Inhibitors and Facilitators of Willingness to Participate Scale (WPS) among women at risk for HIV infection. *AIDS Care*. 2010/02/11. 2010;22(4):452–61.
70. Kiwanuka N, Robb M, Kigozi G, Birx D, Philips J. Knowledge about vaccines and willingness to participate in preventive HIV vaccine trials. *J Acquir Immune Defic Syndr [Internet]*. 2004;36(2):721–5. Available from: <http://graphics.tx.ovid.com/ovftpdfs/FPDDNCGCOBNLIA00/fs035/ovft/live/gv010/00126334/00126334-200406010-00009.pdf>
71. Newman PA, Chakrapani V, Weaver J, Shunmugam M, Rubincam C. Willingness to participate in HIV vaccine trials among men who have sex with men in Chennai and Mumbai, India. *Vaccine*. 2014/09/01. 2014;32(44):5854–61.
72. Shanks L, Moroni C, Rivera IC, Price D, Clementine SB, Pintaldi G. “Losing the tombola”: a case study describing the use of community consultation in designing the study protocol for a randomised controlled trial of a mental health intervention in two conflict-affected regions. *BMC Med Ethics [Internet]*. 2015 Dec 2 [cited 2017 Aug 19];16(1):38. Available from: <http://bmcmedethics.biomedcentral.com/articles/10.1186/s12910-015-0032-x>
73. Zvonareva O, Kutishenko N, Kulikov E, Martsevich S. Risks and benefits of trial participation: A qualitative study of participants' perspectives in Russia. *Clin Trials [Internet]*. 2015;12(6):646–

53. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26062594>
74. Gonzalez-Saldivar G, Rodriguez-Gutierrez R, Viramontes-Madrid JL, Salcido-Montenegro A, Carlos-Reyna KEG, Treviño-Alvarez AM, et al. Participants perception of pharmaceutical clinical research: A cross-sectional controlled study. *Patient Prefer Adherence*. 2016;10:727–34.
75. Dietrich J, Maesela P, Kagee A, Gray G. Are adults in soweto still willing to participate in future vaccine trials? A qualitative study. *AIDS Res Hum Retroviruses* [Internet]. 2011;27(10):A82. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L70554521>
76. Kaljee LM, Pham V, Son ND, Hoa NT, Thiem VD, Canh do G, et al. Trial participation and vaccine desirability for Vi polysaccharide typhoid fever vaccine in Hue City, Viet Nam. *Trop Med Int Heal*. 2007/01/09. 2007;12(1):25–36.
77. Li JY, Yu CH, Jiang Y. Participation in cancer clinical trials as viewed by Chinese patients and their families. *Oncology*. 2011/03/25. 2010;79(5–6):343–8.
78. Lobato L, Gazzinelli MF, Gazzinelli A, Soares AN. [Knowledge and willingness to participate in research: a descriptive study of volunteers in a clinical trial]. *Cad Saude Publica* [Internet]. 2014/08/08. 2014;30(6):1305–14. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L602154245>
79. Mfutso-Bengo J, Ndebele P, Jumbe V, Mkunthi M, Masiye F, Molyneux S, et al. Why do individuals agree to enrol in clinical trials? A qualitative study of health research participation in Blantyre, Malawi. *Malawi Med J*. 2009/06/23. 2008;20(2):37–41.
80. Pare Toe L, Ravinetto RM, Dierickx S, Gryseels C, Tinto H, Rouamba N, et al. Could the decision of trial participation precede the informed consent process? Evidence from Burkina Faso. *PLoS One*. 2013/11/22. 2013;8(11):e80800.
81. Qiu X, He J, Qiu L, Larson CP, Xia H, Lam KB. Willingness of pregnant women to participate in a birth cohort study in China. *Int J Gynaecol Obs*. 2013/06/12. 2013;122(3):216–8.
82. Ramjee G, Coumi N, Dladla-Qwabe N, Ganesh S, Gappoo S, Govinden R, et al. Experiences in conducting multiple community-based HIV prevention trials among women in KwaZulu-Natal, South Africa. *AIDS Res Ther*. 2010/04/27. 2010;7:10.
83. Reynolds J, Mangesho P, Vestergaard LS, Chandler C. Exploring meaning of participation in a clinical trial in a developing country setting: Implications for recruitment. *Trials* [Internet].

2011;12. Available from:

<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L70627039>

84. González-Saldivar G, Rodríguez-Gutiérrez R, Viramontes-Madrid JL, Salcido-Montenegro A, Carlos-Reyna KEG, Treviño-Alvarez AM, et al. Participants' perception of pharmaceutical clinical research: A cross-sectional controlled study. *Patient Prefer Adherence* [Internet]. 2016;10:727–34. Available from:
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L610346068>
85. Kamuya DM, Theobald SJ, Marsh V, Parker M, Geissler WP, Molyneux SC. “The one who chases you away does not tell you go”: silent refusals and complex power relations in research consent processes in Coastal Kenya. *PLoS One* [Internet]. 2015 Jan [cited 2015 Sep 13];10(5):e0126671. Available from:
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4433355&tool=pmcentrez&render type=abstract>
86. Mamotte N, Wassenaar D. Voluntariness of consent to HIV clinical research: A conceptual and empirical pilot study. *J Health Psychol* [Internet]. 2016; Available from:
<https://www.ncbi.nlm.nih.gov/pubmed/26929170>
87. Ogendo A, Otieno F, Nyikuri M, Shinde S, Nyambura M, Pals S, et al. Persons at high risk for HIV infection in Kisumu, Kenya: identifying recruitment strategies for enrolment in HIV-prevention studies. *Int J STD AIDS*. 2012/05/15. 2012;23(3):177–81.
88. Kivouele TS, Bitemo M, Linguissi LSG, Ntoumi F. Perception, knowledge and practices on malaria of the congolese population and its willingness to participate in clinical trials. *Am J Trop Med Hyg* [Internet]. 2011;85(6):203. Available from:
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71042832>
89. Mbunda T, Bakari M, Tarimo E, Sandstrom E, Kulane A. Factors that Influence the Willingness of Young Adults to Participate in Early Vaccine Trials and Contraceptive Practices in Dar es Salaam, Tanzania. *AIDS Res Hum Retroviruses* [Internet]. 2014;30 Suppl 1:A247. Available from:
<http://online.liebertpub.com/doi/pdfplus/10.1089/aid.2014.5550.abstract>
90. Montgomery ET, van der Straten A, Stadler J, Hartmann M, Magazi B, Mathebula F, et al. Male Partner Influence on Women's HIV Prevention Trial Participation and Use of Pre-exposure Prophylaxis: the Importance of “Understanding.” *AIDS Behav* [Internet]. 2015;19(5):784–93. Available from:

<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L615102993>

91. Téguété I, Dolo A, Sangare K, Sissoko A, Rochas M, Beseme S, et al. Prevalence of HPV 16 and 18 and attitudes toward HPV vaccination trials in patients with cervical cancer in Mali. *PLoS One* [Internet]. 2017;12(2). Available from:
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L614522431>
92. Ahram M, Othman A, Shahrouri M, Mustafa E. Factors influencing public participation in biobanking. *Eur J Hum Genet*. 2013/08/08. 2014;22(4):445–51.
93. Chalamilla GE. Preparation of a young adults' cohort for HIV vaccine trials: Experience from Dar es Salaam, Tanzania. *Trop Med Int Heal* [Internet]. 2012;17:20–1. Available from:
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71014526>
94. Djomand G, Metch B, Zorrilla CD, Donastorg Y, Casapia M, Villafana T, et al. The HVTN protocol 903 vaccine preparedness study: lessons learned in preparation for HIV vaccine efficacy trials. *J Acquir Immune Defic Syndr*. 2008/04/09. 2008;48(1):82–9.
95. Farquhar C, John-Stewart GC, John FN, Kabura MN, Kiarie JN. Pediatric HIV type 1 vaccine trial acceptability among mothers in Kenya. *AIDS Res Hum Retroviruses*. 2006/06/27. 2006;22(6):491–5.
96. Idika N, Datong C, Adesanmi A, Austin-Akaigwe P, Faneye A, Awoderu T. HIV vaccine and microbicide preparedness among youths in Lagos, Nigeria. *AIDS Res Hum Retroviruses* [Internet]. 2010;26(10):A98. Available from:
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L70300409>
97. Kiwanuka N, Ssetaala A, Mpendo J, Wambuzi M, Nanvubya A, Sigirenda S, et al. High HIV-1 prevalence, risk behaviours, and willingness to participate in HIV vaccine trials in fishing communities on Lake Victoria, Uganda. *J Int AIDS Soc*. 2013/07/25. 2013;16:18621.
98. Kufa T, Chihota V, Charalambous S, Verver S, Churchyard G. Willingness to participate in trials and to be vaccinated with new tuberculosis vaccines in HIV-infected adults. *Public Heal Action* [Internet]. 2013;3(1):31–7. Available from:
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L368600442>
99. Ye L, Wei S, Zou Y, Yang X, Abdullah AS, Zhong X, et al. HIV pre-exposure prophylaxis interest among female sex workers in Guangxi, China. *PLoS One*. 2014/01/28. 2014;9(1):e86200.
100. O'Neill S, Dierickx S, Okebe J, Dabira E, Gryseels C, D'Alessandro U, et al. "The importance of

blood is infinite”: Conceptions of blood as life force and fear of trial participation in a Fulani village in the Gambia. *Trop Med Int Heal* [Internet]. 2015;20:360. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L72055100>

101. Anjos SM, Cohen LG, Sterr A, De Andrade KNF, Conforto AB. Translational neurorehabilitation research in the third world: What barriers to trial participation can teach us. *Stroke* [Internet]. 2014;45(5):1495–7. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L53060650>
102. Boniphace Y. Willingness and participation toward prevention of mother to child transmission among males of reproductive age. a study from Kilimanjaro-Tanzania. *Dar es Salaam Med Students’ J* [Internet]. 2010;16(1):23–6. Available from: <http://www.ajol.info/index.php/dmsj/article/viewFile/53348/41926>
103. Loh SY, Lee SY, Quek KF, Murray L. Barriers to participation in a randomized controlled trial of Qigong exercises amongst cancer survivors: lessons learnt. *Asian Pac J Cancer Prev*. 2012/01/01. 2012;13(12):6337–42.
104. Martinez-Andrade GO, Cespedes EM, Rifas-Shiman SL, Romero-Quechol G, Gonzalez-Unzaga MA, Benitez-Trejo MA, et al. Feasibility and impact of Creciendo Sanos, a clinic-based pilot intervention to prevent obesity among preschool children in Mexico City. *BMC Pediatr*. 2014/03/22. 2014;14:77.
105. Murthy V, Awatagiri KR, Tike PK, Ghosh-Laskar S, Gupta T, Budrukkar A, et al. Prospective analysis of reasons for non-enrollment in a phase III randomized controlled trial. *J Cancer Res Ther*. 2012/02/15. 2012;8 Suppl 1:S94-9.
106. Rohra DK, Khan NB, Azam SI, Sikandar R, Zuberi HS, Zeb A, et al. Reasons of refusal and drop out in a follow up study involving primigravidae in Pakistan. *Acta Obs Gynecol Scand*. 2008/12/25. 2009;88(2):178–82.
107. Ruzagira E, Wandiembe S, Bufumbo L, Levin J, Price MA, Grosskurth H, et al. Willingness to participate in preventive HIV vaccine trials in a community-based cohort in south western Uganda. *Trop Med Int Heal*. 2009/02/12. 2009;14(2):196–203.
108. Nyblade L, Singh S, Ashburn K, Brady L, Olenja J. “Once I begin to participate, people will run away from me”: understanding stigma as a barrier to HIV vaccine research participation in Kenya. *Vaccine*. 2011/10/04. 2011;29(48):8924–8.

109. Bakari M, Munseri P, Francis J, Aris E, Moshiro C. Experiences on recruitment and retention of volunteers in the first HIV vaccine trial in Dar es Salam, Tanzania - the phase I/II HIVIS 03 trial. *BMC Public Health* [Internet]. 2013;13(1149):[8]p. Available from: <http://www.biomedcentral.com/content/pdf/1471-2458-13-1149.pdf>
110. Sexton KR, Wiggins SN, Bondy ML. Reasons for refusal to participate in an epidemiologic study of minority women. *Cancer Epidemiol Biomarkers Prev* [Internet]. 2011;20(10). Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L70707209>
111. Smit J, Middelkoop K, Myer L, Lindegger G, Swartz L. Socio-behaviour challenges to phase III HIV vaccine trials in sub-Saharan Africa. *Afr Heal Sci* [Internet]. 2005;5(3):198–206. Available from: <http://www.bioline.org.br/toc?id=hs>
112. Mfutso-Bengo J, Masiye F, Molyneux M, Ndebele P, Chilungo A. Why do people refuse to take part in biomedical research studies? Evidence from a resource-poor area. *Malawi Med J*. 2009/06/23. 2008;20(2):57–63.
113. Bhutta ZA. Beyond informed consent. *Bull World Health Organ*. World Health Organization; 2004;82(10):771–7.
114. Ahmed S, Palermo A-G. Community Engagement in Research: Frameworks for Education and Peer Review - ProQuest [Internet]. *American journal of public health*. 2010 [cited 2015 Sep 23]. p. 1380–7. Available from: <http://search.proquest.com/openview/2cf5a349a74b911de0d393d35e80f827/1?pq-origsite=gscholar>
115. Emanuel EJ. Undue inducement: nonsense on stilts? *Am J Bioeth* [Internet]. 2005 Sep [cited 2017 Aug 28];5(5):9-13; discussion W8-11, W17. Available from: <http://www.tandfonline.com/doi/abs/10.1080/15265160500244959>
116. Spears CR, Nolan B V., O'Neill JL, Arcury TA, Grzywacz JG, Feldman SR. Recruiting underserved populations to dermatologic research: A systematic review. *International Journal of Dermatology*. 2011. p. 385–95.
117. Nappo SA, Iafrate GB, Sanchez ZM. Motives for participating in a clinical research trial: a pilot study in Brazil. *BMC Public Health* [Internet]. 2013 Jan [cited 2015 May 14];13(1):19. Available from: <http://www.biomedcentral.com/1471-2458/13/19>

118. Porteri C, Pasqualetti P, Togni E, Parker M. Public's attitudes on participation in a biobank for research: an Italian survey. *BMC Med Ethics* [Internet]. 2014 Jan [cited 2016 Mar 21];15:81. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4258254&tool=pmcentrez&render_type=abstract
119. Stunkel L, Grady C, Agrawal M, Grady C, Fairclough DL, Meropol NJ, et al. More than the money: a review of the literature examining healthy volunteer motivations. *Contemp Clin Trials* [Internet]. Elsevier; 2011 May [cited 2016 Sep 14];32(3):342–52. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/21146635>
120. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to Participation in Randomised Controlled Trials. *J Clin Epidemiol* [Internet]. Elsevier; 1999 Dec 1 [cited 2016 Mar 21];52(12):1143–56. Available from: <http://www.jclinepi.com/article/S0895435699001419/fulltext>
121. Sikateyo B. Understanding participants' consent in an entero-toxigenic vaccines trial in the Misisi Township in Lusaka, Zambia. *Trop Med Int Heal* [Internet]. 2012;17:67. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71014682>

Correspondence: Joyce L. Browne, Julius Global Health, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands. Email J.L.Browne@umcutrecht.nl

Table 1: Categorization and Definitions of Reasons

Reasons Category	Generic Reason	Explanation
Participation		
Personal Benefit	Access to health care	Receiving free access to medical treatment in the form of ancillary care, 'access to quality care', 'free medical treatment', etc.
	Personal health benefits	A benefit associated specifically with the disease/condition being addressed in the research. For instance 'protection for HIV' in an HIV vaccine trial, or 'HIV testing and counseling' in an HIV prevention trial.
	Need for treatment	Participant would rely on research to obtain specific treatment, particularly in the case of patient participation.
	Monetary benefit	Financial and/or material gain.
	Knowledge (existing/expanding)	Having previous knowledge of the indication/research, or participating in research in order to 'gain knowledge' or 'receive education' about a certain disease, or alternatively to 'satisfy curiosity'.
	Perception of being at risk	Perceiving oneself of being at high risk of contracting the disease covered by the research (e.g., HIV vaccine).
	Feeling of community	Social group forming between participants
Benefit for Others	Altruism	'Doing something good for community', 'ability to help others', 'solidarity with sufferers', 'helping to further research', 'benefit society' and other similar sentiments.
	Community involvement	The research benefits/involves specifically the community of the participant in some way.
Agreeable Research Aspects	Guarantee of confidentiality	Being assured of adequate confidentiality with regard to participation/personal details.
	Allowing withdrawal	Participants free to withdraw from study
	Convenience	Taking part does not take up much time/is accessible.
	Result availability	Results made available to participants at research conclusion
	Researcher attitude	Positive attitude of researchers
	Non-invasive procedure	Procedures done in the research are not extensively/at all invasive.
Social Acceptance	Cultural acceptability	Participation is considered appropriate according to local cultural/religious norms.

	Trust	Trust in researchers, regulations, medicine.
	Social support	Society's, family members', and/or friends' approval or encouragement for participation in the research.
	Peer enrolment	Friends or peers have (previously) enrolled in the research
	Research outcome	Participants are supportive of the research objective, e.g., vaccine development.
	Advice from physician	Following advice of health professional (doctor, nurse, health worker, etc.).
Non-Participation		
Physical Harm	Safety concerns	Fear of side effects, sero-conversion, fear of gaining a disease from vaccination, fear of physical harm, not wanting to be used as a guinea pig.
	Invasive procedures	Lack of willingness to undergo invasive procedures.
	Physical pain	Fear of specific procedures, repeated blood draw/vaccinations.
	Worsening of medical condition	Recurrent illnesses/conditions
Social Harm	Confidentiality concerns	Concerns about personal details/details of participation.
	Cultural insensitivity	Aspects of research do not comply with aspects of participant's culture.
	Lack of social support	Friends/Peers/Family members/Partner do not approve of participation, or discourage participation.
	Stigmatization	Social disapproval/discrimination for participation.
Practical Inconveniences	Inconvenience	Research site too far, participation takes up too much time, not compatible with schedule.
	False-positive test results	Receiving a false- positive test results as a result of a vaccination (e.g., for HIV, comparable to reaction to Mantoux test after BCG vaccination).
	Non-compliance to terms of research	Lack of willingness to comply to terms of research, e.g. child-bearing, or cessation of current treatment
	Personal costs	Unwilling to spend money on transportation costs etc.
Disagreeable Research Aspects	Lack of clarity	Lack of proper explanation or understanding of specific aspects of research, e.g. 'lack of information', 'inadequate information', 'lack of

		understanding'.
	Insufficient compensation	Compensation (material or monetary) offered for research participation deemed insufficient.
	Efficacy concerns	Skepticism of efficacy of (e.g.) vaccine.
	Placebo concerns	Unwilling to receive placebo
	Re-contact	No desire of being re-contacted.
Personal Opinions/Assumptions	Distrust	Distrust of researchers, drug companies, governments, regulatory bodies, physicians (misconceptions).
	Previous negative experience	Previous negative experience with research/indication.
	Lack of knowledge	Lack of sufficient or accurate knowledge about general research aspects, thereby not feeling at ease about participation.
	Lack of interest	No interest in area of research, or research participation.
	No perceived need	Satisfaction with available drugs/treatments, or denial of existence of problem, no wish for further treatment
	Overwhelmed	Other ongoing (social, emotional) issues (e.g., dealing with a dramatic diagnosis)
	Fear of health status	Fear of positive test results, health concerns
	Temptation to unsafe behavior	Treatment gives participants a false sense of security to undertake more risky behavior (e.g., unsafe sex after HIV vaccine)

Table 2: Summary of characteristics of included studies (n=94)

Characteristic		N=, references
Type of reasons	Reasons for participation	21, (3,24,60,64,70,73,74,79–82,91,25,121,27,33,35,38,49,57,59)
	Reasons against participation	19, (93,94,103–110,112,95–102)
	Both	54,(1,19,32,34,36,37,39,40,42–45,20,46–48,50–56,21,58,61–63,65–69,71,22,72,75–78,85–89,23,90,92,28–31)
Study nature	Hypothetical study	64,(3,20,31,32,34–37,39–42,21,43–52,22,53–56,58,59,61–63,65,23,66,67,69–72,75,77,80,81,24,87–89,91,92,94–98,25,99,102,107,112,28–30)
	'Real'/embedded study	
	Prospective	21,(1,19,83,86,90,93,100,101,104,105,108,110,27,121,38,57,64,68,73,76,78)
	Retrospective	9,(33,60,74,79,82,85,103,106,109)
Study methods	Quantitative	
	Qualitative	44,(3,19,38,39,42–44,48,49,57,61,64,20,66,71–73,75,79,81,83,85,87,22,88,90,91,96,98,100,101,109,112,121,23,24,28,29,33,34)
	Mixed Methods	50,(1,21,45–47,50–56,25,58–60,62,65,67–70,74,27,76,77,80,86,89,92,94,95,97,99,30,102–104,106,107,110,31,32,35–37)
Types of studies reasons were assessed for	Clinical trials	5,(19,30,74,78,121)
	Non-therapeutic trials	1,(27)
	Bio-banks	1,(92)
	Dental research	1,(20)
	(Medical) research in general	7,(1,3,21,58,61,79,112)
	Genomics Research	1, (66)
Disease/disorder focus	Infectious diseases	
	HIV	40,(22,23,38,40,42–49,25,50–54,56,57,59,62,65,28,67–71,75,82,83,86,87,31,89,90,93–96,99,102,107,108,32,109,33,34,36,37)

	Malaria	6,(60,80,83,85,88,100)
	Tuberculosis	2,(39,98)
	Sexually transmitted infections	3,(41,53,57)
	Typhoid fever	1,(76)
	RSV	1, (85)
	Non-infectious diseases	
	Cancer	6, (29,77,91,103,105,110)
	Stroke	1,(101)
	Dementia	1,(24)
	Haemophilia	1,(35)
	Childhood obesity	1,(104)
	Pre-eclampsia	2,(63,106)
	Rheumatoid arthritis	2,(55,74)
	Mental Health	1, (72)
	Cardiovascular Disease	3, (64,73)
Regions	Sub-Saharan Africa	45,(3,19,40,42,44,49,50,57,60,62,63,67,25,69,70,72,75,79,80,82,83,85,86,28,87-91,93-97,31,98,100,102,107-109,112,121,33,35,37-39)
	Middle-East and North-Africa	4,(1,20,61,92)
	Latin-America and the Caribbean	11,(29,45,110,56,64,68,74,78,94,101,104)
	Asia	27,(21,22,46-48,51-54,58,59,65,23,66,71,76,77,81,99,103,105,106,24,27,30,32,36,41,43)
	Eastern Europe	2,(55,73)

Table 3: Frequency reasons for and against participation in human subjects research were mentioned in included studies (n=94)

Reasons for Participation				Reasons for Non-Participation			
	x Mentioned (n=73)	x Top 3 (n=41)	x Top Reason (n=41)		x Mentioned (n=71)	x Top 3 (n=47)	x Top Reason (n=47)
Ability to withdraw	1	1	0	Confidentiality concerns	12	4	3
Access to Health Care	42	20	4	Costs	5	3	1
Altruism	46	30	20	Cultural insensitivity	2	2	0
Advice from physician	4	2	0	Distrust	14	4	0
Community involvement	5	2		Efficacy concerns	12	10	2
Convenience	3	0	0	False-positive test results	8	4	1
Cultural acceptability	2	1	1	Lack of social support	23	11	3
Feeling of community	1			Fear of health status	5	3	0
Personal health benefits	40	21	8	Inconvenience	25	14	4
Knowledge	16	4	1	Insufficient compensation	2		
Monetary benefit	31	10	2	Invasive procedures	8	6	4
Low pressure decision	1			Lack of interest	10	3	0
Need for treatment	1	1	1	Lack of Clarity	7	4	3
Non-invasive procedure	2	2	1	Non-compliance to terms of research	5	3	1

Peer enrolment	4			No perceived need	5	2	0
Low perception of risk	3	0	0	Overwhelmed	1		
Personal benefit	5	1	1	Physical pain	13	5	2
Result availability	1	1	0	Placebo concerns	6	4	1
Social support	18	6	0	Previous negative experience	2		
Trust	17	6	0	Re-contact	1	1	0
Guarantee of Confidentiality	4	1	0	Safety concerns	45	32	16
Unaware of voluntariness	1	0	0	Stigmatization	20	6	2
Motivation to avoid risky behavior	1	0	0	Temptation to unsafe behavior	1		
Research Outcomes	5	1	0	Lack of Perceived Benefit	1		
				Effect on lifestyle	2	0	0
				Worsening of Medical condition	3	2	1
				Lack of Knowledge	7	3	1

Table 4: Ranking of Reasons

	Top Reasons for Participation	Top Reasons for Non-Participation
1	Altruism	Safety Concerns
2	Personal Health Benefits	Inconvenience
3	Access to Health Care	Lack of Social Support
4	Monetary Benefit	Stigmatization
5	Knowledge	Confidentiality Concerns
6	Social Support	Physical Pain
7	Trust	Efficacy Concerns
8		Distrust

Figure 1: Flow diagram of review process

