



# POWER DIFFERENCE AND RISK PERCEPTION: MAPPING VULNERABILITY WITHIN THE DECISION PROCESS OF PREGNANT WOMEN TOWARDS CLINICAL TRIAL PARTICIPATION IN AN URBAN MIDDLE-INCOME SETTING

GEERTE C. DEN HOLLANDER, JOYCE L. BROWNE, DANIEL ARHINFUL, RIEKE VAN DER GRAAF AND KERSTIN KLIPSTEIN-GROBUSCH

## Keywords

vulnerability,  
 pregnant women,  
 clinical trials,  
 low- and middle-income  
 countries (LMICs),  
 decision process,  
 cultural competency,  
 research conduct

## ABSTRACT

To address the burden of maternal morbidity and mortality in low- and middle-income countries (LMICs), research with pregnant women in these settings is increasingly common. Pregnant women in LMIC-context may experience vulnerability related to giving consent to participate in a clinical trial. To recognize possible layers of vulnerability this study aims to identify factors that influence the decision process towards clinical trial participation of pregnant women in an urban middle-income setting. This qualitative research used participant observation, in-depth interviews, and focus group discussion with medical staff and pregnant women eligible for trial participation, at a regional hospital in Accra, Ghana. Besides lack of familiarity with modern scientific concepts, specific factors influencing the decision-making process were identified. These include a wide power difference between health provider and patient, and a different perception of risk through externalization of responsibility of risk management within a religious context as well as a context shaped by authority. Also, therapeutic misconception was observed. The combination of these factors ensued women to rely on the opinion of the medical professional, rather than being guided by their own motivation to participation. Although being a (pregnant) woman per se should not render the label of being vulnerable, this study shows there are factors that influence the decision process of pregnant woman towards trial participation in a LMIC context that can result in vulnerability. The identification of context-specific factors that can create vulnerability facilitates adaptation of the design and conduct of research in a culturally competent manner.

## BACKGROUND

After lifting the ban on participation of fertile and pregnant women in clinical trials by the Food and Drug Administration in 1993, the debate on necessity versus ethical limitations of clinical research with pregnant women continues.<sup>1</sup>

<sup>1</sup> Cotton P. FDA lifts ban on women in early drug tests, will require companies to look for gender differences. *JAMA* 1993;269:2067; Macklin R. Enrolling pregnant women in biomedical research. *Lancet* 2010;375:632–3; Allesee L, Gallagher CM. Pregnancy and protection: The ethics of limiting a pregnant woman's participation in clinical trials. *J Clin Res Bioeth* 2011;2(108).

The fear of harming the foetus has been one of the reasons for underrepresentation of (pregnant) women in clinical trials, which inevitably results in deprivation of benefiting from knowledge acquired by clinical trials.<sup>2</sup> Fortunately, to address the burden of maternal morbidity and mortality, research activities with pregnant women are increasingly common. Especially in low- and middle-income countries (LMICs), where the number of affected

<sup>2</sup> Baylis F. Pregnant women deserve better. *Nature* 2010;465:690; Mattison D, Zajicek A. Gaps in knowledge in treating pregnant women. *Gend Med* 2006;3:169–82; Lyerly AD, Little MO, Faden RR. Pregnancy and clinical research. *Hastings Cent Rep* 1994;38(6):inside back cover.

Address for correspondence: Kerstin Klipstein-Grobusch, P.O. Box 85500, 3508 GA Utrecht, The Netherlands. Email: K.Klipstein-Grobusch@umcutrecht.nl.  
 Conflict of interest statement: No conflicts declared.

women remains the highest worldwide, the necessity of research for tailored context-specific solutions is more and more part of the global health agenda.<sup>3</sup> However, questions surrounding the ethical limitations of research with pregnant women, and even more so pregnant women in the LMIC context, remain.

Pregnant women, alongside specific categories of sub-populations like suppressed minorities and children, have often been identified as vulnerable. This categorizing approach to vulnerability has been severely criticized over the past years for not encompassing context-specific factors affecting vulnerability.<sup>4</sup> Alternative approaches to vulnerability, for example the approach of Tavaglione and colleagues, are gaining more ground.<sup>5</sup> Tavaglione and colleagues define vulnerability as the likelihood of being 'wronged, that is - being denied adequate satisfaction of certain legitimate claims to physical integrity, autonomy, freedom, social provision, impartial quality of government, social bases of self-respect or communal belonging'.<sup>6</sup> Also the layered approach of vulnerability that Florencia Luna has proposed, moves away from a categorical approach and considers not a single feature to be definitive of vulnerability.<sup>7</sup> Instead, according to her, a set of layers renders a person vulnerable, which can interact with each other and a person's environment.<sup>7</sup> Although being pregnant or a woman per se should not render the label of vulnerability, according to Luna, low education and low literacy, as well as poverty and a lack of access to good healthcare including safeguarding of reproductive rights,

might play a part in making a pregnant woman vulnerable for research participation within the LMIC context.<sup>8</sup>

In an attempt to alleviate potential vulnerability of study populations, there has been a focus on good quality of informed consent procedures and the ability of persons to protect their own interests.<sup>9</sup> Even though informed consent is broadly accepted as the way to secure autonomy and respect of persons, throughout the years there has been much discussion on how to practically implement this, especially within the context of research in developing countries.<sup>10</sup> Many consent procedures are based on implicit assumptions for a research subject to be mature, moderately well-educated, clear thinking, most likely literate, self supporting, and to have a familiarity with certain concepts of health and research. These are assumptions that may be challenged especially within the context of research with women in LMICs.<sup>11</sup> Hence, to be able to use the informed consent procedure to minimize potential vulnerability of research participants, researchers must be committed to develop context specific and culturally appropriate strategies for obtaining ethically sound informed consent.<sup>12</sup> To prevent the danger of stigmatizing and stereotyping possible research participants, it is argued that ethical

<sup>3</sup> United Nations. 2015. *The Millennium Development Goals Report*. New York: United Nations: 5-9, 28-43; Barreto ML. Health research in developing countries. *Br Med J* 2009;339:b4846; Glickman SW, McHutchison JG, Peterson ED, Cairns CB, Harrington R A, Califf RM, et al. Ethical and scientific implications of the globalization of clinical research. *N Engl J Med* 2009;360:816-23.

<sup>4</sup> Cotton, *op. cit.* note 1, p. 3; Macklin R. Bioethics, vulnerability and protection. *Bioethics* 2003;17:472-86; Kipnis K. Vulnerability in research subjects: abioethical taxonomy. 2001. In: *Ethical and policy issues in research involving human participants*. Bethesda, Maryland: National Bioethics Advisory Commission; G1-13; Levine C, Faden R, Grady C, Hammerschmidt D, Eckenwiler L, Sugarman J. The limitations of "vulnerability" as a protection for human research participants. *Am J Bioeth* 2004;4:44-49; Kipnis K. Seven vulnerabilities in the pediatric research subject. *Theor Med Bioeth* 2003;24:107-20; Wilson D, Neville S. Culturally safe research with vulnerable populations. *Contemp Nurse* 2009;33:69-79; Luna F. Elucidating the concept of vulnerability: layers not labels. *Int J Fem Approaches to Bioethics* 2009;2:121-39; Hurst SA. Vulnerability in research and health care; describing the elephant in the room? *Bioethics* 2008;22:191-202; Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling Pregnant Women: Issues in Clinical Research. *Womens Health Issues* 2013;23:e39-e45.

<sup>5</sup> Tavaglione N, Martin AK, Mezger N, Durieux-Paillard S, François A, Jackson Y, et al. Fleshing out vulnerability. *Bioethics* 2013;29:98-107.

<sup>6</sup> *Ibid*: note 5.

<sup>7</sup> Luna, *op. cit.* note 4, p. 4.

<sup>8</sup> Barreto, *op. cit.* note 3, p. 3; Macklin, *op. cit.* note 4, p. 4; Kipnis, *op. cit.* note 4, p. 4; Wilson & Neville, *op. cit.* note 4, p. 4; Luna F, Vanderpool S. Not the usual suspects: addressing layers of vulnerability. *Bioethics* 2013;27:325-32; 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* 2009;360:816-23; Pace CA, Emanuel EJ. The ethics of research in developing countries: assessing voluntariness. *Lancet* 2004;365(9453):11-12; Benatar SR. Reflections and recommendations on research ethics in developing countries. *Soc Sci Med* 2002;54:1131-1141; 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;189:930-937.

<sup>9</sup> Council for International Organizations of Medical Sciences. 2002. *International ethical guidelines for biomedical research involving human subjects*. Geneva: Council for International Organizations of Medical Sciences (CIOMS): 17-18, 64-66; Mandava A, Pace C, Campbell B, Emanuel E, Grady C. The quality of informed consent: mapping the landscape. A review of empirical data from developing and developed countries. *J Med Ethics* 2012;38:356-65; Kiguba R, Kutuyabami P, Kiyuwa S, Katabira E, Sewankambo NK. Assessing the quality of informed consent in a resource-limited setting: a cross-sectional study. *BMC Med Ethics* 2012;13:21; Valley A, Lees S, Shagi C, Kasindi S, Soteli S, Kavita N, et al. How informed is consent in vulnerable populations? Experience using a continuous consent process during the MDP301 vaginal microbicide trial in Mwanza, Tanzania. *BMC Med Ethics* 2010;11:10; Lema VM, Mbondo M, Kamau EM. Informed consent for clinical trials: a review. *East Afr Med J* 2009;86:133-42; Marshall PA. "Cultural competence" and informed consent in international health research. *Camb Q Healthc Ethics* 2008;17:206-15; Marshall PA. 2007. *Ethical challenges in study design and informed consent for health research in resource-poor settings*. Geneva: World Health Organisation.

<sup>10</sup> *Ibid*: note 9.

<sup>11</sup> Luna, *op. cit.* note 4, p. 4

<sup>12</sup> Kiguba et al., *op. cit.* note 9, p. 5; Marshall, *op. cit.* note 9, p. 5; Sanchez S, Salazar G, Tijero M, Diaz S. Informed consent procedures: responsibilities of researchers in developing countries. *Bioethics* 2001;15:398-412.

international research conduct is reached by implementing a (mini)ethnography in the study approach.<sup>13</sup> Especially in potential vulnerable populations, this can create a situation of 'cultural safety', where the researcher works with those researched to understand their socio-cultural reality to guide preparation and conduct of the study.<sup>14</sup>

Altogether, although categorizing (pregnant) woman as vulnerable is severely critiqued, in the LMIC context individuals can be at risk of being vulnerable when included in clinical research, especially if study procedures fail to address layers of vulnerability. By performing a qualitative study at a possible research site we aim to identify factors that influence the decision-making process for clinical trial participation in pregnant women in an urban middle-income setting to recognize possible layers of vulnerability, and to provide focus points for a tailored and ethical study design for including these women in clinical research.

## METHODS

### *Study design*

This qualitative study used participant observation, semi-structured in depth interviews, and focus group discussion and was conducted from January to April 2013.

### *Research setting and participants*

To study the Ghanaian hospital setting, specifically in gynaecology and obstetrics, the classic method of anthropologic ethnography was used, i.e. participant observation by the interviewing researcher through a medical internship of three months and shadowing of the midwives actively involved in admission of new clients to the Antenatal Clinic (ANC) of Ridge Hospital and the Adabraka Out-Patient Department (OPD) of Ridge Hospital, Accra, Ghana.

Participants for the individual and group interviews were recruited among pregnant women visiting the ANC in February 2013. Also both the midwives in charge of ANC admissions were interviewed. The inclusion and exclusion criteria of the sample of pregnant women were based on the hypothetical clinical trial description to prevent hypertensive disorders in pregnancy, and aligned to an existing trial protocol for a study planned to commence at the same hospital (ClinicalTrials.gov NCT02007837). Inclusion criteria were first antenatal care attendance, a gestational age of less than 16 weeks, and the intention to have both subsequent antenatal visits and delivery at the same clinic. Exclusion criteria were pre-existing hypertension and an

age below 18 years. None of the women coming for the first time during the period of inclusion fit either of the exclusion criteria. Eighteen women in total were eligible to be interviewed. Four women declined participation due to not wanting to stay longer or having to return for the interview.

Every fourth woman was included for the focus group discussion. The group interview was performed at the end of the inclusion period and included three women previously interviewed, and three women additionally included for the group interview due to a too low turnout of previously included women.

### *Individual and group interviews*

During the semi-structured interviews four topics were discussed with participants: medical research and clinical trials familiarity and knowledge, pregnancy, decision-making in health and wellbeing of mother and foetus (in the interviews referred to as 'the unborn child'), and decision-making in (hypothetical) trial participation.

All the interviews with pregnant women took place in the hospital in a different room than the treating room of the midwife. One investigator conducted all interviews. Depending on the preferred language of the respondent, interviews were done in vernacular (Twi or Ga) with a translator, or in English without a translator present. All interviews were audio recorded digitally.

### *Data analysis*

All audio recordings were translated, transcribed, and coded using NVivo 10 (QSR International). After initial coding, coded transcripts were grouped into themes and embedded in previous literature using Grounded Research Theory.<sup>15</sup> Data from participant observation, interviews with the pregnant women, interviews with the medical staff, and from the focus group discussion were triangulated with existing literature to minimize bias.

### *Ethical approval*

The study was approved by the Ghana Health Service Ethical Review Committee in the Greater Accra Region (Protocol ID Number: GHS-ERC 07/01/13), the ethics committee responsible for research at the chosen study site. All participants were asked to provide informed consent for the interviews, the recording thereof, and storing of the data until completion of the study. The process was conducted by the research assistant in Twi or English,

<sup>13</sup> Macklin, *op. cit.* note 4, p. 4; Wilson & Neville, *op. cit.* note 4, p. 4; Kleinman A, Benson P. Anthropology in the clinic: the problem of cultural competency and how to fix it. *PLoS Med* 2006;3(10):e294.

<sup>14</sup> Wilson & Neville, *op. cit.* note 4, p. 4.

<sup>15</sup> Strauss AL, Corbin JM. 1990. *Basics of qualitative research: grounded theory procedures and techniques*. 5th ed. Newbury Park, Cal: Sage Publications.

Table 1. Characteristics of respondents

Respondent	Age	Occupation	Occupation Husband	Religion	Gravidity*	Education	Care Access**	Marital Status
R 01	29	Unemployed	Driver	Christian (Pentecostal)	G1P0	Vocational Schooling	Good	Not-married
R 02	41	Trader (panties)	Trader (Aluminum)	Christian (Charismatic)	G4P3D2	Senior High School	Good	Married
R 03 (FGD)	32	Unemployed	Electrician	Muslim	G3P1	None	Good	Married
R 04	29	Unemployed	Police man	Muslim	G1P0	Senior High School	Good	Married
R 05	39	Trader (fish)	Trader (Charcoal)	Christian	G5P4	Junior High School (F1)	Good	Married
R 06	30	Trader (cooked rice)	-	Muslim	G1P0	Primary School	Good	Not married
R 07 (FGD)	37	Trader (fabric)	Teacher	Christian (Catholic)	G3P2	Senior High School	Good	Married
R 08	38	Hair dresser	Private driver	Muslim	G4P2	Junior High School	Good	Married
R 09	25	Cleaning lady	Technician	Muslim	G3P2	Senior High School	Good	Married
R 10	20	Trader (millet drink)	Driver	Muslim	G4P0	Junior High School	Good	Married
R 11 (FGD)	24	Trader (water)	Carpenter	Christian (Presbyterian)	G1P0	Senior High School	Good	Married
R 12 (FGD)	35	-	-	-	G2P1	-	-	-
R 13 (FGD)	26	-	-	-	G1P0	-	-	-
R 14 (FGD)	32	-	-	-	G2P0	-	-	-
Staff 1	59	Midwife	-	Muslim	P2	Midwifery training	NA	Married
Staff 2	53	Midwife	Transport director	Muslim	P4	Midwifery training	NA	Married

\*Gravidity is indicated with the number of pregnancy including a current pregnancy (G) and the number of deliveries of a child (P). If a child has died after birth it is indicated with a D. \*\*Health Care access is indicated as 'good' if the respondent has indicated herself that she can easily access health care if necessary and if she is in possession of a Health Insurance Card. [-] Unassigned, [NA] Not applicable, [R] Respondent, [FGD] Participant of the Focus Group Discussion.

depending on the participants' preference, and documented by signing (with signature or fingerprint) a written form in Twi or English.

## RESULTS

Thirteen women between 20 and 41 years participated, of whom the majority multiparous (n=8, 62%) and married (n=11, 85%). All but one had completed some form of education, with the highest being secondary or high school completion. The majority of the women were in informal employment (n= 8, 72%) (Table 1).

The analysis of the data resulted in three main themes that influenced individual decision-making in trial participation and introduced potential layers of vulnerability within the consent process: understanding of pregnancy and research, religion and risk perception, and authority and power.

### *Understanding of pregnancy and research*

Medical research appeared to be an unfamiliar concept to the participants and ANC staff. With the exception of two participants, many women did not really understand the necessity of evaluating medication in a large group of people and did not know that this is how medicines are developed. They were unfamiliar with randomization, placebo-controlled practice, and the general idea that research with human beings is essential to gaining knowledge on the effect and the side effects of medication. Most women argued that the way research could help, and the role they could play in it, was if they would take some new medication and if they *personally* would not

be affected by it (or they *personally* benefitted from it) they could tell their friends about it and promote the medication.

During observation and the personal interviews with midwives it became apparent that the concept of medical research was not integrated in the delivery of care. Also, the midwives had no experience in recruiting for trial participation.

Various notions concerning pregnancy were explored. First of all, women saw their pregnancy as part of their purpose in life, and an investment for the future (children can take care of parents). Discomfort associated with pregnancy should be endured. Being pregnant was indicated as something a woman does by herself and together with other (experienced) women. At the same time, the responsibility of the well being of the foetus was often put outside the women herself, namely with God, the husband, or health workers.

Women seemed to think that the foetus mainly has an effect on the mother's lifestyle but not that the mother's lifestyle influences the development of the foetus to the same extent, with an exception of the possibility of an abortion due to actions of the mother. For example, the use of 'medication' was often associated specifically with being pregnant, due to the antenatal care program that includes nutrition supplements and anti-malaria prophylaxes. Most women were not aware of the potential dangers associated with general medication use during pregnancy.

### *Religion and Risk*

Pregnancy, well being of the foetus and decision-making in general was strongly influenced by their believe in God and religion.



Respondent 06 (R06): 'Is it not God? Would you depend on human beings before taking any medicine? If you would do that, then you would surely not take it. [...] It is a matter of accepting it and praying first before taking it because it is only God who can protect you.'

Not only did women bring their religious scriptures to read while waiting, regularly there was also a preacher singing, preaching and praying with the women. Especially bad outcomes were connected to (the will of) God, both in general with pregnancy, as well as when taking medication. By involving God in the decision to trial participation or medication use, the women appeared to remove the possibility of any unwanted outcome by making the outcome God's outcome, which is a *good* outcome whether wanted or not. The concept of 'risk' as the chance of an unwanted outcome was outweighed by religious determinism that removed the negative connotation that is essential to an experience of risk.<sup>16</sup> Within the religious context displayed by the pregnant women, the responsibility of risk management showed to be externalized.

R10: 'Everything is in the hands of God.'

Nevertheless, most of the women did portray a certain responsibility towards the well being of the foetus, indicating that religiosity might change the way the individual determines risk perception.

### *Authority and Power*

Authority and power-distance were themes repeatedly present during antenatal care consultations. Distance in power was illustrated by strong body language: pregnant women often almost whispered to the point where responses were hardly heard, and often casted their eyes down during consultation.

When the pregnant women were asked why they would participate in a clinical trial, quite regularly the request posed by the medical staff was given as the reason for participation:

R05: 'I will take it [the medication of the trial] because it is a health worker that gave it to me. [...] I will consider them [the doctors] in that they will never give me any bad medicine to take.'

Reflecting the general effect of hierarchical structure in Ghanaian society, within the hospital there was also a large influence of (projected) knowledge difference connected to this authority.<sup>17</sup> Both midwives stressed the

necessity of educating the women to allow them to understand the reasons for doing certain things, but they also pointed out that in reality often the women depend on the knowledge and opinion of the midwives.

In addition to the knowledge gap and the midwife's authority, the fear of repercussions with not being treated if one would not follow the instructions was cited as a reason to participate in a trial.

### *Decision-making Towards Trial Participation*

To assess the decision-making process to participate in a clinical trial, women were asked whether they would participate in a hypothetical trial with oral supplementation (nutrients and aspirin) to prevent hypertensive disorders during pregnancy. During the personal interviews, nine of the eleven women decided to participate and two (R01 and R11) refused. One because she was scared for any unwanted effects, and the other because she did not want to take anything that was not tested before. In the focus group discussion, two of the six women refused participation (R11 and R13), one was unsure (R12) and three would want to participate. However, one (R13) was willing to take the new drug if the researcher herself or anyone in her direct surrounding had taken it and not experienced any negative effects. The other woman (R11) changed her opinion later: with a combination of suspected safe components, like in the intervention arm of the hypothetical trial, she would participate, but not with entirely new drugs.

During the interviews, and especially the focus group discussion, the dependence on formulation by the interviewer of risk associated with trial participation, became apparent. If it was said that the risk was small, participation was generally favoured. But when it was underlined that this did not mean that there was no risk at all, women were more hesitant to participation.

For the decision to participate, four women said that they would want to consult their husband (or other family living with them) before agreeing to participation and would not be able to say they would participate without discussing it with the partner. One woman said she would want to talk with her husband about it, but if she had no other option she would decide on her own without consulting him. All other women indicated that they would decide on their own whether to participate in research.

When women were asked what motivated them to participate or why they would want to participate, the seven women who wanted to participate combined reasons described above (depending on authority or religiosity), with expressions of wanting to help other people of the community (sisters, siblings, family). The four other women expressed that the chance of benefitting themselves as a motivator, in combination with mentioning that they would get the medication from the trusted medical staff. The altruism displayed by the interviewed women, was

<sup>16</sup> Giddens A. Risk and responsibility. *The Modern Law Review* 1999;62:1–10.

<sup>17</sup> The Hofstede Centre. 2005. *What about Ghana?* Helsinki: Itim International. Available at: <https://geert-hofstede.com/ghana.html> [Accessed 18 Apr 2016].

primarily confined to the feeling of helping people within their own community or even family. Helping women in general was not cited, and is consistent with their responsibility towards the close community members in other parts of the interview. These two motivations, altruism and personal benefit, are quite generally associated with motivation of trial participation.<sup>18</sup>

Therapeutic misconception, the mistaken belief that trial participation is aimed at direct personal medical benefit, instead of proposed benefit to the community as a whole, was repeatedly heard.<sup>19</sup> Furthermore there was a lack of realization that refusal to participate without influencing regular care was an option.

## DISCUSSION

This research points out several factors that can influence the decision process of pregnant women in Ghana, and possibly other sub-Saharan African settings, to participate in clinical research. Besides lack of familiarity with modern scientific concepts, specific cultural factors influencing the decision-making process were identified. These include a wide power difference between health provider and patient and a different perception of risk through externalization of responsibility of risk management within a religious context as well as a context shaped by authority. Besides these factors, therapeutic misconception was observed to influence the decision to trial participation as well. The combination of unfamiliarity with risk assessment in medical decisions and no previous experience with clinical research resulted in women to rely on the opinion of the medical professional, rather than being guided by their own mentioned primary motivation to research participation.

Even though we suggest further research to test our findings in a larger sample, preferably in a study parallel to a clinical trial, the factors of influence in the decision process displayed in this study point towards several

potential layers of vulnerability, which can be categorized according to the analysis of Kipnis.<sup>20</sup> First, there is cognitive vulnerability, not so much as the mental capacity to deliberate the decision, but because of unfamiliarity with the language and concept of research, risk assessment in medical decision-making, limited education, and (health) literacy. Second, there is seemingly deferential vulnerability because of customary obedience to the medical authority. Third, social vulnerability, being part of a socially undervalued group as a woman, is illustrated by the notions that women's purpose is to bear children without complaining, and is illustrated when the opinion of the husband was pointed out as essential to decision-making. These categories of vulnerability combined with the layered approach of vulnerability show that, as Luna argues, pregnant women are not *essentially* vulnerable but are rendered vulnerable within relations of the presented context. In line with this argument, vulnerability is relational and thus *potential*, and can be minimized when relations and interactions are adapted accordingly.<sup>21</sup> Also, the same factors may cause potential vulnerability for other subpopulations within the same context, for example non-pregnant women or adolescents, but also men.

*The Declaration of Helsinki* states that vulnerable populations involved in research demand 'special protection'.<sup>22</sup> Whereas this statement seems to be a clear basis for ethical research practices, putting it to practice has shown to produce difficulties with defining vulnerability, practical implementation of 'special protection', and seemingly creates a 'vulnerability paradox'; by fear of harming a vulnerable study population, that population remains vulnerable in the scope of medicine. An example of this vulnerability paradox is that many of the prescribed medicines taken during pregnancy are not approved by regulatory authorities such as the Food and Drug Administration to be used in pregnancy, nor is there much data to guide effective and safe dosing – effectively making pregnancy an 'off-label condition'.<sup>23</sup>

In this study with pregnant women in Ghana, the factors influencing the decision process towards trial participation show potential layers of vulnerability but are not reasons to exclude these women from trial participation. These factors indicate a need for creativity in the design and conduct of research to alleviate vulnerability during the informed consent process.<sup>24</sup> Adaptation of the research process instead

<sup>18</sup> Ohmann C, Deimling A. Attitude towards clinical trials: results of a survey of persons interested in research. *Inflamm Res* 2004;53 Suppl 2: S142–7; Dhalla S, Nelson KE, Singer J, Poole G. HIV vaccine preparedness studies in the non-organization for economic co-operation and development (non-OECD) countries. *AIDS Care* 2009;21:335–48; Locock L, Smith L. Personal benefit, or benefiting others? Deciding whether to take part in clinical trials. *Clin Trials* 2011;8:85–93; Madsen SM, Mirza MR, Holm S, Hilstedt KL, Kampmann K, Riis P. Attitudes towards clinical research amongst participants and nonparticipants. *J Intern Med* 2002;251:156–68; Jenkins V, Farewell V, Farewell D, Darmanin J, Wagstaff J, Langridge C, et al. Drivers and barriers to patient participation in RCTs. *Br J Cancer* 2013;108:1402–7.

<sup>19</sup> Appelbaum PS, Roth LH, Lidz CW, Benson P, Winslade W. False hopes and best data: consent to research and the therapeutic misconception. *Hastings Cent Rep* 1987;17(2):20–4; Lidz CW, Appelbaum PS, Grisso T, Renaud M. Therapeutic misconception and the appreciation of risks in clinical trials. *Soc Sci Med* 2004;58:1689–97.

<sup>20</sup> Kipnis 2001 & 2003; Levine et al., *op. cit.* note 4, p. 4

<sup>21</sup> Luna, *op. cit.* note 4, p. 4.

<sup>22</sup> World Medical Association Inc. WMA Declaration of Helsinki. Ethical principles for medical research involving human subjects. *J Indian Med Assoc* 2009;107:403–5.

<sup>23</sup> Mattison & Zajicek; Lysterly, Little, Faden, *op. cit.* note 2, p. 3; McCullough LB, Coverdale JH, Chervenak FA. A comprehensive ethical framework for responsibly designing and conducting pharmacologic research that involves pregnant women. *Am J Obstet Gynecol* 2005;193:901–7.

<sup>24</sup> Marshall, *op. cit.* note 9, p. 5.

of creating a vulnerability paradox is of great importance, especially given that the global burden of maternal morbidity and mortality concentrates in LMICs, and that there is a current global priority to invest in research into new innovations and quality of maternal care improvements.<sup>25</sup>

For culture- and context-specific research design adaptation, the framework presented by Woodsong & Karim is helpful to consider.<sup>26</sup> Their approach, including a pre-enrolment, enrolment and post-enrolment phase, aims to diminish the barrier to access accurate information, and focuses on the need for thoroughly conducted informed consent processes less dependent on the role and authority gap of midwives and obstetricians.

The pre-enrolment phase addresses lack in education and unfamiliarity with research, and includes community introduction of the study and special attention to education about the concept of clinical research.<sup>27</sup> Alternative materials such as a drama skit or an information video presented in public areas (waiting areas, community health centres, etcetera) are examples of possible aids during this phase. Through involving local (in) formal community stakeholders in the development of the material, the material can be adapted to local culture and standards and increase the community support for the research throughout the study.<sup>28</sup> To mitigate the effect of the authority-difference on risk perception and decision-making we suggest that a person similar to possible participants and other than a provider of care introduces the study in public before an individual introduction by the trained research staff. This will create some time for eligible participants to ponder the research and to articulate questions. This active pre-enrolment phase may avoid the therapeutic misconceptions of participants, ensure that potential participants understand they have the right of refusal to participate without influencing regular care, and address responsibility and risk management.

The pre-enrolment phase is followed by the informed consent procedure with specially trained staff. Within this phase, time is provided for reflection, discussion and assessment of the actual understanding of the consent, for example through a brief quiz-like interview. This allows for areas that need additional attention to be highlighted before consent can be provided.<sup>29</sup> In all, these considerations in the enrolment phase may increase the voluntariness of informed consent and the knowledge needed for an informed decision.

Finally, the active post-enrolment stage includes managing rumours, intercepting possible misunderstandings or

questions of participants and their family members, and facilitating continued comprehension of developments and results of the study.

As described above, a context-specific research process that reflects the potential vulnerabilities of a specific population, or in other words a culturally competent process, will require investments in time and effort. However, rather than an ideal that is difficult to operationalize, cultural competency can be actually achieved through a careful process starting from research question identification, including the design and conduct of research until implementation of the findings.<sup>30</sup> Assuring that the decision-making process of participants is truly informed and potential layers of vulnerability are considered, will permit ethically sound research with vulnerable individuals, strengthen enrolment of participants and minimizes drop-outs.<sup>31</sup>

## CONCLUSION

Although being a (pregnant) woman per se should not render the label of being vulnerable, this study shows that there are specific factors that influence the decision process of pregnant woman towards participation in clinical research in the LMIC context that can potentially result in vulnerability. The identification of explicit context-specific considerations that contribute to vulnerability of pregnant women's participation facilitates adaptation of the design and conduct of research in a culturally competent manner. Identification of possible layers of vulnerability should therefore not result in routine exclusion of pregnant women from research participation, but rather provide a stimulator to consider more context specific approaches of research conduct and ultimately improve research quality.

## AUTHORS' CONTRIBUTIONS

Geerte C. den Hollander conceptualized and designed the study, collected and analysed the data, interpreted the data and wrote the first version of the manuscript. Joyce L. Browne contributed to the interpretation of the data and revised the manuscript together with Geerte C. den Hollander. Daniel Arhinful advised on the design of the study and revised the manuscript. Rieke van der Graaf contributed to interpretation of the data and manuscript revisions. Kerstin Klipstein-Grobusch conceptualized the study and advised on the design, contributed to the interpretation of the data and revisions of the manuscript. All authors read and approved the final manuscript.

<sup>25</sup> Bhutta Z A, Cabral S, Chan C-W, Keenan WJ. Reducing maternal, newborn, and infant mortality globally: An integrated action agenda. *Int J Gynaecol Obstet* 2012;119:S13-7.

<sup>26</sup> Woodsong C, Karim QA. A model designed to enhance informed consent: experiences from the HIV prevention trials network. *Am J Public Health* 2005;95:412-9.

<sup>27</sup> Ibid: note 26.

<sup>28</sup> Ibid: note 26.

<sup>29</sup> Woodsong & Karim, *op. cit.* note 26, p. 18.

<sup>30</sup> Kleinman & Benson, *op. cit.* note 13, p. 7.

<sup>31</sup> Woodsong & Karim, *op. cit.* note 26, p. 18.

## COMPETING INTERESTS

The authors declare that they have no competing interests.

### Biographies

**Geerte C. den Hollander** is a medical doctor and resident in International Health Care and Tropical Medicine at the Netherlands Society for Tropical Medicine and International Health. She has a special interest in medical anthropology and international development, in particular concerning maternal health in a global perspective. Her affiliation with the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht is focussed on research conduct in LMICs.

**Joyce L. Browne** is a medical doctor, epidemiologist and assistant professor in Global Health at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, the Netherlands. Her research interests include maternal health, global health, and translation of high-resource generated evidence to low-resource contexts.

**Daniel Arhinful** is a senior research fellow at the Noguchi Memorial Institute for Medical Research (NMIMR), College of Health Sciences of the University of Ghana, Ghana. He holds a PhD in Medical Anthropology from the University of Amsterdam and MA in sociology from the University of Ghana. His research interests include health insurance, maternal and child health, migrant health, and access to medicines and healthcare, particularly in the context of changing demographics and shifting disease burdens.

**Rieke van der Graaf** is assistant professor of Medical Ethics at the Medical Humanities department of the Julius Center of the University Medical Center Utrecht. She has a research interest in the ethics of innovative trial designs, fair inclusion of vulnerable populations, and the integration of care and research.

**Kerstin Klipstein-Grobusch** is associate professor of Global Health at the Julius Center for Health Sciences, University Medical Center Utrecht, The Netherlands and visiting professor of Epidemiology at the School of Public Health, University of the Witwatersrand, South Africa. Her research interests are in maternal and child health and the interface of communicable and non-communicable diseases in low- and middle-income countries.