

Title:

Informed consent, community engagement, and study participation at a research site in Kigali, Rwanda

Abstract:

People enroll in medical research for many reasons ranging from decisions regarding their own or family members' health situation to broader considerations including access to health and financial resources. In socially vulnerable communities the choice to participate is often based on a risk-benefit assessment that goes beyond the medical aspects of the research, and considers the benefits received. In this qualitative study, we examined the motivations of Rwandan women to participate in a non-commercial collaborative research study examining the safety, acceptability, and adherence of a contraceptive vaginal ring in Rwanda juxtaposed with the perceptions of the research within the community.

351 women attended the screening visit, four were excluded because they were not able to complete the assessment of understanding. The remaining participants' ages ranged from 17 to 38 and 80% had primary level of education or below. 120 were enrolled. Findings highlighted motivations for joining the study that were relayed both formally by the clinic (e.g. testing and treatment) and informally by the community including the positive aspects of the ring. There were also some negative rumors circulating regarding the research site, likely from excluded participants who faced potential stigma

based on that exclusion. It was understood by most participants that they were enrolled in a research study and participants actively sought out enrollment in the research for a variety of reasons. The experiences demonstrate that although inequalities in access to health care may create conflicting situations around the study, it is possible to form partnerships between a research center and participants/their partners, for research about reproductive health.

## INTRODUCTION

People enroll in medical research for a variety of reasons ranging from personal decisions regarding their own or family members' health situation to broader considerations. For instance, desperately ill patients may see trial participation as a last "best hope of rescue"<sup>1,23</sup>. Others may decide to enroll based on different factors, such as altruism, personal benefit or convenience, financial incentives or monetary reimbursement, recommenda-

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<sup>1</sup> Fisher H, McKeivitt C, Noaz A. Why do parents enroll their children in research: a narrative synthesis. *J Med Ethics*. 2011;37:544-551.

<sup>2</sup> Bosk C. Obtaining voluntary consent for research in desperately ill patients. *Med Care*. 2002;40:64-68.

<sup>3</sup> Kuehn B. Patients' unrealistic hopes for cancer trial benefits may hinder consent. *JAMA* 2011;305:1186-7.

tions of others, advertisements, among other reasons<sup>4,56</sup>. Common in both low to middle income countries (LMICs) and high income countries (HICs), trial participation may also be triggered by “therapeutic misconception”, that is, the failure to appreciate the distinction between research and individually-tailored treatment<sup>7</sup>, and, in disaster research, by “humanitarian misconception”, that is, an overlap between the notion of medical research and the notion of aid. Specifically, people may decide to participate believing that the research is directly linked to the provision of humanitarian aid<sup>8</sup>. The notion

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<sup>4</sup> 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;5:e14368.

<sup>5</sup> Limkakeng A, Phadtare A, Shah J, Vaghasia M, Wei DY, Shah A, Pietrobon R. Willingness to participate in clinical trials among patients of Chinese heritage: a meta-synthesis. PLoS ONE. 2013;8:e51328.

<sup>6</sup> Luchtenberg M, Maeckelberghe E, Locock L, Powell L, Verhagen AA. Young people’s experiences of participation in clinical trials: Reasons for taking part. Am J Bioethics. 2015;15:11:3-13.

<sup>7</sup> Lidz C, Appelbaum P. The therapeutic misconception: problems and solutions. Med Care. 2007;40:55-63.

<sup>8</sup> O’Mathuna D. Research ethics in the context of humanitarian emergencies. J Evid Based Med. 2015;8:31-5.

of “humanitarian misconception” shows that those made vulnerable by natural or man-made disasters may feel “pushed” to enroll in research by the fear of losing other benefits. Something similar has been observed in socially vulnerable individuals and communities. Social vulnerability is common among research communities in low- and middle-income countries (LMIC), and previous research shows that it may play a critical role in altering voluntariness in informed consent, in particular when quality health care is not freely available outside clinical studies. Paré Toe and colleagues showed in a social science study carried out in Burkina Faso that most parents/guardians wanted their child to be enrolled *a priori* in a malaria trial, based on factors unrelated to the research purposes, (i.e. free and better quality health care and reimbursement of travel expenses)<sup>9</sup>. Similarly, free access to medical care has been mentioned as an inducement, and sometimes as undue inducement, to trial participation for children and families in LMICs<sup>10</sup>.

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<sup>9</sup> Toe LP, Ravinetto RM, Dierickx S, Gryseels C, Tinto H, Rouamba N, Diallo I, Cissao Y, Bayala K, Hausmann S, Muela J, D’Alessandro U, Grietens KP. Could the decision of trial participation precede the informed consent process? Evidence from Burkino Faso. PLoS ONE. 2013;8:e80800.

<sup>10</sup> Pasquali SK, Burstein DS, Benjamin DK, Smith PB, Li JS. Globalisation of pediatric research: analysis of clinical trials completed for pediatric exclusivity. Pediatrics. 2010;126:e687-92.

Over the years, clinical research in these contexts has increased and facilitated delivering healthcare solutions to address health disparities on some levels<sup>11</sup>. At the same time, the so-called “globalization of clinical trials” also brings an inherent risk of exploitation, since it might be driven by the opportunity of lower costs, easier ethical and regulatory review, and easier availability of participants whose choice to participate in research studies is often informed by the access to health care not the risks and benefits of the research<sup>12</sup>. For individuals and families in a disadvantaged socio-economic situation, in fact, trial participation may become a strategic choice to secure otherwise unavailable health and non-health resources<sup>13</sup>. This is well illustrated by some cases reported by a research team in the Democratic Republic of Congo, for example, a mother trying to ‘shift’ respiratory symptoms on her child enrolled in a malaria study in order to get free medicines for another

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<sup>11</sup> Lang T, Siribaddana S. Clinical trials have gone global: is this a good thing? PLoS Med. 2012;9:e1001228.

<sup>12</sup> Lidz C, Appelbaum P, *op. cit.* note 7.

<sup>13</sup> Ravinetto R, Afolabi MO, Okebe J, Van Nuil JI, Lutumba P, Muhindo Mavoko H, Nahum A, Tinto H, Addissie A, D’Alessandro U, Grietens KP. Participation in medical research as a resource-seeking strategy in socio-economically vulnerable communities: call for research and action. Trop Med Int Health. 2014;20:63-6.

sick child of hers<sup>14</sup>. This does not imply the inability to understand the nature of the research and of its medical risks and benefits: the potential participants may have a good understanding of these elements, but still choose to participate, for the overarching aim of securing access to healthcare.

The informed consent process was designed to implement the ethical principles of respect for persons (i.e. individuals should be treated as autonomous entities, and persons with diminished autonomy should be protected) and to ensure that research participants are aware of the benefits and risks of the research so that they may make a fully informed and free decision. However, as noticed above, in socially vulnerable communities the choice to participate may be based on a risk-benefit assessment that goes beyond the medical aspects of the research, and considers the benefits represented by the services and benefits received<sup>15</sup>. Despite the challenges related to social vulnerability, research in these communities remains highly needed.

Non-commercial, collaborative research is especially fit to address the unanswered health needs of these populations, and it often benefits the communities by building local research and medical capacity. In addition, it may contribute to bringing the benefits of the research programs into these areas. However, differently from commercial sponsors, non-commercial research groups are not the owner of the products tested in research studies and they are generally not in the position to decide on distribution and pricing.

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<sup>14</sup> Kalabuanga M, Ravinetto R, Maketa V, Muhindo Mavoko, H, Fungula B, Inocencio da Luz R, Van Geertruyden JP, Lutumba P. The challenges of research informed consent in socio-economically vulnerable populations: a viewpoint from the Democratic Republic of Congo. *Developing World Bioeth.* 2015;16.

<sup>15</sup> Toe LP, et al. *op. cit.* note 9.

ing policies; still, they have a moral obligation toward the host communities, and they should strive to facilitate future access to the interventions tested in research. For this, a comprehensive translation to policy strategy may be needed, including prior dialogue with national and international health authorities and an explicit advocacy toward an “access” plan (e.g., preferential prices, intellectual property rights measures, etc.)<sup>16</sup>.

To gain a better understanding of the decision-making mechanisms in the setting of a clinical study in a socially vulnerable community, we examined the motivations of Rwandan women for participation in a research study juxtaposed with the perceptions of the research within the wider community.

Rwanda is a small landlocked country located in the Great Lakes region of Africa with a population of around 11.3 million people<sup>17</sup> with 84% of the population living in rural areas<sup>18</sup>. The Rwandan economy is supported

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<sup>16</sup> Ravinetto R, Alirol E, Mahendradhata Y, Rijal S, Lutumba P, Sacko M, El-Safi S, Lim K, van Loen H, Jacobs J, Peeling RW, Chappuis F, Boelaert M. Clinical research in neglected tropical diseases: the challenge of implementing Good Clinical (Laboratory) Practices. *PLoS Negl Trop Dis*. 2016;10(11):e0004654.

<sup>17</sup>World Bank Rwanda [home page on the internet]. No date [cited 2016 April 06]. Available from: <http://www.worldbank.org/en/country/rwanda>.

<sup>18</sup> National Statistics Institute of Rwanda (NSIR). Rwanda Demographic and Health Survey, 2016. Kigali: NSIR, Ministry of Finance and Economic Planning, Rwanda Ministry of Health, DHS Program; 2016.

primarily by the agricultural industries and 63% of the population lives below the international poverty line (i.e. less than \$1.25 US per day)<sup>19</sup>. The illiteracy rate in Rwanda has been declining in recent years and estimates show that 80% of Rwandan men are literate and 77% of Rwandan women are literate. The first official language spoken by nearly all Rwandans is Kinyarwanda, however both English and French are also considered official languages and are used in the education system<sup>20</sup>. Rwanda has a community based health insurance scheme that provides basic health coverage to 80.9% of the population for an annual premium of about \$5 US per family member<sup>21</sup>.

## METHODS AND ANALYSIS

The data for this analysis were drawn from both qualitative and quantitative data collected at Rinda Ubuzima Research Center during The Ring Plus Study (ClinicalTrials.gov Identifier: NCT01796613), a study examining the safety, acceptability, and adherence of a contraceptive vaginal ring in Ki-

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<sup>19</sup> Human Development Report 2016: Human Development for Everyone Rwanda. c 2016 [cited 2016 September 08]. Available from: <http://hdr.undp.org/en/countries/profiles/RWA>.

<sup>20</sup> NSIR, *op. cit.* note 18.

<sup>21</sup> Rwanda Ministry of Health. Ministry of Health Annual Report, July 2012 - June 2013. Kigali: Rwanda Ministry of Health; 2013.



gali, Rwanda<sup>22</sup>. The study took place from June 2013 to December 2014 and was an open label, single center, randomized controlled trial with a large qualitative research component integrated throughout the study. The primary objective of the clinical trial, which will be reported elsewhere, was to evaluate the safety and acceptability of intermittent and continuous contraceptive vaginal ring use in Rwandan women between the ages of 18-35. The primary objective of the social science component of the study was to understand the acceptability of and adherence to the ring. The secondary and exploratory objectives of the social science component were to examine context specific attitudes regarding ring use, family planning, and participation in the study itself. The analysis for this paper focuses on the latter only and the other objectives will be published with the clinical trial's results.

We recruited HIV-negative women who were interested in using a contraceptive method, excluding those with a history of complications with hormonal contraceptives and/or contraindications for hormonal contraceptive use. The population recruited into the study was women who did not define themselves as sex workers but they were at high risk of HIV and other urogenital infections, as was evidenced by an HIV prevalence of 21% at

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<sup>22</sup> Schurmans C, De Baetselier I, Kestelyn E, Jespers V, Delvaux T, Agaba SK, van Loen H, Menten J, van de Wijgert J, Crucitti T, RING PLUS study group. The ring plus project: safety and acceptability of vaginal rings that protect women from unintended pregnancy. BMC Public Health. 2015; 15(348).

screening. All participants were tested and treated (as necessary) for chlamydia, gonorrhea, syphilis, herpes simplex virus type 2, symptomatic bacterial vaginosis, candidiasis, and trichomoniasis at the baseline visit. Participants were also tested for pregnancy, HIV, and cervical cancer and referred to care as needed. Treatment was also provided for partners of participants, if the participant requested it. At enrolment and if participants met all the eligibility criteria and wished to be part of the study, they were randomized into one of the two ring use groups. Those in the intermittent group subsequently attended two Regular Study Visits, two Ring Insertion Visits, and a Final Visit, while those in the continuous group attended three Regular Study Visits and a Final Visit (see Figure 1). The visits were timed around ring removals and insertions, and the total study duration was a maximum of 14 weeks. The study was approved by Rwanda National Ethics Committee, National Health Research Committee (Rwanda), the Institutional Review Board of the Institute of Tropical Medicine (Belgium), and the University of Liverpool Committee on Research Ethics (United Kingdom).

[INSERT FIGURE ONE HERE]

Figure 1: Schedule of Clinical and Social Science Assessments

Analyses were drawn from several different data sources including focus group discussions (FGD) and in-depth interviews (IDI) with participants of the study, IDIs with a selection of participants' partners, and excluded participants, key informant interviews with community members, obser-

vations at recruitment sessions and at the research center, and informed consent documents from the study. Participants for FGDs and participant IDIs were selected from those who attended at least the screening visit, partner IDIs were conducted with partners of participants of the study, and the key informant IDIs were conducted with community leaders. We used purposive sampling to select the participants to invite to the FGDs and IDIs, based on quantitative data collected in the clinic. The male partners were first selected purposively based on information captured from their partner during study visits. After this list was exhausted, we randomly selected the partners using a random number table. In order to contact the partner, we first contacted the participant and asked her if it was okay to interview her partner and, if she agreed, we obtained his phone number from her. Then we called the partner and asked if he was interested. All participants and partners, underwent an informed consent interview and, if they agreed to participate, they were required to sign a separate form for the social science component. The community leaders were also required to sign informed consent prior to the interview.

The qualitative data were analyzed using closed and open techniques. A set of codes was derived from the literature and all the transcripts were coded. As the coding progressed, emergent codes were added and after multiple readings of the data, the codes were grouped into themes. Quantitative data, including basic demographic information, were analyzed using descriptive statistics.

The informed consent process for this study was extensive and preceded by community sensitization activities. It was designed based on the general approach to informed consent that has been developed at Rinda Ubuzima since 2006 when the research center opened. Before the individual informed consent process, there were general education and study specific information sessions in the communities presented in Kinyarwanda by the Outreach Manager, Study Nurses, and Physicians that provided an overview of health topics, as well as created a presence in the community. This team was trained and skilled in presenting study related information in the community, as well as in conducting informed consent with potential participants. Following the sessions, interested women were invited to the research center and the onsite informed consent process was initiated, which entailed both group and individual activities. Women had the opportunity to watch a group informed consent video, consisting of a study nurse reading the patient information sheet in Kinyarwanda, while they were waiting to be seen individually. Next, there was an individual literacy assessment; this was added after Rinda Ubuzima staff realized that participants perceived literacy in different ways. For example, someone who could write her name stated she was literate because she was proud that she could write her name but yet she could not read a document about the research study. There were two separate informed consent discussions, one before the Screening Visit and a second before the Enrolment Visit. After the participant had the opportunity to discuss the information in the patient information sheet, a nurse conducted

an assessment of understanding with the participant by asking her direct questions about the study. Once all the pending questions were answered and the assessment of understanding was completed, the informed consent form was reviewed and, if she had made a decision to participate, the woman confirmed the decision by signing or thumb printing the consent form. The consent form was also signed by the person obtaining the consent and, in case of illiterate participants, by the independent witness. At the time of the research, in Rwanda, the age of consent was 21 therefore if a participant was between 18-21, then a legally authorized guardian had to sign the consent form as well<sup>23</sup>. Women who failed to reach an adequate understanding of the study after repeating the assessment of understanding two times, despite the nurse's/counselor's attempts to tailor the explanation, could not be enrolled in the study. This tool for assessment of understanding has been used at Rinda Ubuzima since 2006 but it has never been formally validated. The next step was the informed consent for enrolment, which included the same steps as above except the literacy assessment was not repeated. Therefore, each enrolled participant underwent two separate informed consent interviews before formally enrolling in the study.

The main study benefits as described in the informed consent interview included free access to a new contraceptive method (i.e. a contraceptive vaginal ring) for the duration of the study and testing and treatment of sex-

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<sup>23</sup> In 2016, this law changed and now the age of consent is 18.

ually transmitted infections, while the main risks included potential discomfort during the pelvic exam and phlebotomy and potential psychological discomfort when asked questions about sexual health and other personal information during clinic visits and during the social science component.

## RESULTS

In the study, we screened 351 women of reproductive age wishing to use a contraceptive method and enrolled 120 women in the intervention study. Of the 351 participants who attended a screening visit, 25 were excluded at the screening visit and 35 did not come for the baseline visit. Of those participants excluded at the prescreening visit, four failed the assessment of understanding and could not continue with the study. Five participants had to repeat the assessment of understanding twice but passed the second time so they were able to attend subsequent visits. The age range of the remaining participants (n=347) was between 17-38 with 79% having completed primary school education or below. 75 participants (21%) were illiterate as assessed at the prescreening visit and of those, 22 illiterate participants were enrolled in the study. 291 participants attended a baseline visit and 120 were enrolled in the study. Those not enrolled were either excluded after screening (n=25) or baseline visits (n=116) or did not come to the baseline visit (n=35). 175 potential participants were invited to the enrollment visit: 49 did not attend the visit and six were excluded at the enrollment visit.

104 participants of the 120 (see table 1) who were enrolled in the study participated in at least one IDI and/or FGD. The remaining 16 were either not selected or were not available to attend. In addition, we conducted one interview with an excluded participant specifically about the informed consent process and the impact of being excluded. We also interviewed three community leaders about the perception of research in their local communities.

[INSERT TABLE ONE HERE]

Table 1: Total number of participants in social science component

#### Motivation for Joining the Study

In the IDIs and FGDs conducted after study participation had ended, we asked women for the primary reasons for joining the study. We grouped the responses into items that were likely relayed to participants by study staff at information sessions in the community or during the informed consent interview, and items that were likely relayed informally in the community.

Women mentioned the free testing and treatment most often as a motivation for wanting to be screened for the study including testing for HIV and other sexually transmitted infections, free treatment of sexually transmitted diseases, and especially cervical cancer screening.

*“You would look if we had a chance of having cervical cancer...Yes, they tested us, do you know how much this test costs? But here, we were tested for free and in addition, any diseases that they find in you are treated for free.”* (Georgette<sup>24</sup>, married 35 year old participant)

Travel reimbursements were mentioned as a reason for joining the study during discussions but the talk was about others who were later excluded as coming only for the reimbursement:

*“The majority heard that you also give the participant tickets [reimbursement] and they came rapidly... We have been told that people who are pregnant or breastfeeding are not eligible in the study, we told them that, but they refused, they would say, even if we breastfeed, we will go there...”* (Umutoni, 29 year old married participant).

Finally, other participants joined to try a new family planning method but a great deal of information about the vaginal ring that was used in the study was circulated informally throughout the communities after the information sessions. Participants joined because they heard the ring was good and that it did not cause perceived negative side effects like other family planning methods and they wanted to try or test it. Women complained that other family planning caused headaches, vaginal dryness, among other side effects. Participants also heard that the ring caused increased sexual desire and in-

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<sup>24</sup> All names used in the paper are pseudonyms.



creased lubrication. During discussions, the women compared the ring to other methods such as the injection that supposedly made women dry. The increased wetness from the ring improved their sexual relationships.

*“She [current participant] told me how sex was going well at home and she added that with the ring she has satisfied her husband with sex...When she talked about sexual desire I felt excited and that was the right point! I told her that I am interested to use the ring.”* (Umutesi, 25 year old participant living with partner).

We also asked the women why they decided to remain in the study. Most agreed that because they had no problem with the ring, they stayed in the study. Others enjoyed participating and were proud to be engaged in the partnership with the research staff. The solid partnerships built between the research team and the participants also encouraged women to remain in the study.

*“I willingly participated in the study, every time I had discussions with you, it made me enjoy being in the study more. There was no way to stop in the middle, as it was important to me. I was seeing the benefits I had from the ring, it was great! I had no problem that would make me feel like hating the study.”* (Daniella, 31 year old married woman)

However one person stated that it was an obligation to remain in the study while another said that it was her right to remain in the study.

## Rumors in the community

While women provided these positive reasons for joining the study, there were also negative rumors spreading in the community while enrolment was still going on. We wanted to understand why, amidst rumors, some still joined the study. We probed about the rumors during FGDs and IDIs and women elaborated about their own communities and experiences. The rumor heard most often was that at Rinda Ubuzima, during the pelvic exam, we remove the uterus and ovaries, some said it was for sterilization purposes while others thought we sold them. Others added on that our site is affiliated with Illuminati, a secret organization rumored to run the world.

*“Some say that it is about Illuminates, they want to bring our ovaries to foreign countries and sell them so they get money. They also say, ‘how do you think they get all that money they provide you? It is because they sell your ovaries so they get a lot of money.’”* (Alice, 21 year old participant living with partner for four years)

Participants heard from community members that the pelvic exam and the use of the speculum causes cancer, sexually transmitted diseases, and other problems with the cervix, despite the fact that others joined the study specifically for the cancer screening.

*“You go yourself and they will inject you with cancer and manipulate your uterus, nothing else they will give you except those diseases...”* (Genoveva, 24 year old participant living with partner for seven years)

Current participants told us that others did not join because they feared the pelvic exam. Other participants spoke about how the ring itself could potentially cause problems including bleeding, cancer, or even death.

After further probing, participants thought that it was the excluded participants who spread the negative rumors in the community. Not all communities had negative rumors circulating but rumors of some sort were mentioned by participants in all end trial FGDs and several IDIs. Because of the information sessions in the communities, the exclusion criteria were known, one of which was HIV infection. The participants who were enrolled in the study thought that those who were excluded started these rumors to avoid being assumed to have HIV because they could not continue in the study after the screening. Participants also thought that the excluded participants spread rumors because those who were excluded were jealous that they were not in the study. Some current participants even lied to their neighbors about their active participation because of the rumors.

*"They know that I did not participate. When they asked if I participated, I said, "Why should I die?" (Immaculee, 28 year old single participant)*

#### The impact of informed consent

During the end of study IDIs with women, we asked if they came to the study site with the decision already made to participate. Of the ten interviewees, eight stated that they had already made the decision but that the information provided during informed consent confirmed their decisions to

participate. Other women in FGDs said they came to the site to verify if the rumors, whether positive or negative, they heard in the community were true and/or to test the ring but also decided to join prior to coming to the site. Again, when they arrived at the site, they confirmed their decision to join after going through the informed consent processes. With one exception, participants also explained very well how they knew they had a right to withdrawal from the study and that it was voluntary. However, the concepts of rights and voluntariness were not elaborated in discussions.

It was understood by participants, for the most part, that Rinda Ubuzima was a research center and not a family planning clinic. This was not the case for male partners: we interviewed ten partners and over half (6 of 10) thought their partner was going to a family planning clinic for the ring, not a research center. However, according to both quantitative and qualitative data, the male partners were very involved or at least informed regarding the decision to use the ring (or not). For example, at the last study visit, 119/120 (99.2%) participants stated that their main sex partner knew she was using the ring and 118/120 (98.3%) reported that her partner knew she was in the research study. There were at least eleven women who did not attend the baseline visit because their partners did not want them to join the study and/or use the ring.

## DISCUSSION

One issue that is apparent from this small qualitative study on informed consent is that there are always impacts on the communities in which research is conducted, for better or worse, and the community perceptions regarding specific research studies/topics impact participation in the studies. For instance, another research group reported that rumors about research and the associated medical processes may circulate communities and even hinder participation in research studies: fear of blood collection, for example, has been circulating communities in Gabon since colonization<sup>25</sup>. Similarly, the local meaning of blood may have impacted the successes of a more recent Ebola trial<sup>26</sup>.

One unintended consequence of the Ring Plus Study was the potential of HIV status disclosure, to community members through exclusion from the study. As a way to avoid potential health disclosures or health suspicions, women who did not meet all the inclusion criteria may have started spreading rumors in their communities about the study. If excluded participants,

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<sup>25</sup> Grietens KP, Ribera JM, Erhart A, Hoibak S, Ravinetto RM, Cryseels C, Dierickx S, O'Neill S, Muela SH, D'Alessandro U. Doctors and vampires in Sub-Saharan Africa: ethical challenges in clinical trial research. *Am J Trop Med Hyg.* 2014;91:213-215.

<sup>26</sup> Bannister-Tyrrel M, Cryseels C, Delamou A, D'Alessandro U, van Griensven J, Grietens KP. Blood as medicine: social meanings of blood and the success of ebola trials. *Lancet.* 2015;385(9966):420.

whether HIV positive or negative, were spreading rumors about the study to avoid being labeled HIV positive, this would be very different than community members fostering negative perceptions of research and the Rinda Ubuzima research site. Some women came to the study site to verify if the rumors were true but these same women also had their minds made up to join the study. Overall, we observed some level of tension. Women were primarily interested in joining the study, because of the direct and indirect benefits, i.e. access to an innovative contraception method, free testing and treatment for STDs – and this may be seen as an expected finding, based on existing literature from sub-Saharan Africa. But failure to be recruited caused, in addition to the disappointment for missing such benefits, also the risk of stigmatization at community level, and prompted a negative attitude toward the research. The responses from the community regarding this particular study also demonstrate, in line with what observed in other studies in sub-Saharan Africa, the deep seated inequalities that may be caused by medical research in the community regarding access to quality health care. Community members who participated in the research accessed healthcare, i.e. diagnostic procedures, that was inaccessible to others, as well as received some financial benefits, i.e. reimbursement for travels to the clinic. Although the national ethics committee approved the specific reimbursement amounts, it may have still represented a financial benefit for some participants. Researchers should be aware of these risks and try to prevent conflict in the community

although it is not that simple when there are longstanding inequalities existing in the community.

In many research settings in sub-Saharan Africa, comprehension in informed consent is complicated by low literacy, local cultural beliefs and by the difficulty of translating research concepts into local languages<sup>27,28</sup>. Mandava and colleagues showed that research participants in LMIC appear to be less likely to say they can refuse participation in a trial or withdraw from it and are more likely to worry about the consequences of refusal or withdrawal<sup>29</sup>. Tam and colleagues also showed that participants from developing countries were less likely, compared to participants in high-income countries, to understand the voluntary nature of participation, the freedom to

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<sup>27</sup> Marshall PA. Ethical Challenges in Study Design and Informed Consent for Health Research in Resource-Poor Settings, in Social, Economic and Behavioural Research. Special Topics No. 5. Geneva: WHO; 2007.

<sup>28</sup> Afolabi M, Okebe JU, McGrath N, Larson HJ, Bojang K, Chandramohan D. Informed consent comprehension in African research settings. *Trop Med Int Health*. 2014;19:625-42.

<sup>29</sup> 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 countries. *J Med Ethics*. 2012;38:356-365.

withdraw at any time and the notion of randomization<sup>30</sup>. Conversely in our study, the women understood that they were enrolled in research, not attending a family planning clinic. We hypothesize that the information obtained during the informed consent process, administered by skilled and ad hoc trained health staff, and the proximity of the research group to the community contributed to the understanding that Rinda Ubuzima was a research site, and with one exception they all were aware that participation is not an obligation. Despite these findings, there is still a need to validate the tool for the assessment of understanding that is currently in use at the research center, to get more solid data on participant's understanding. Unfortunately, lack of validation of such tools is a commonly noted issue in sub-Saharan African research contexts<sup>31</sup>.

One surprising finding from this study was the possible contradiction between what some women said in the clinic (e.g. being proud to participate, enjoying the discussions) and what they said in their communities (e.g. lying about participation) which led us to a hypothesis that women viewed the research center as a safe and confidential environment, as opposed to their

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<sup>30</sup> Tam NT, Huy NT, Thoa, LTB, Long, NP, Trang, NTH, Hirayama K, Karbwang, J. Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. Bull World Health Organ. 2015;93:186-98H.

<sup>31</sup> Afolabi M, et al. *op. cit.* note 28.



communities where a façade needed to be put up. A clear example was one participant who told her sister she participated because her sister was open to the idea and told another sister that she did not participate because she had a negative perception of the research. This somehow echoes the observations of Kalabuanga et al (2015) who noticed in the Democratic Republic of Congo that the tension between poverty and research-related benefits may create competition for enrolment, with potentially disruptive effect at societal or household level<sup>32</sup>. Even if based on few cases, this ‘negative effect’ of trials at household level may need further *ad hoc* research. Alternatively, the contradictory information between the clinic and the community may also demonstrate social desirability, that is, people say what they think others want to hear or even a silent refusal to discuss certain things as a way to safeguard their close relationships, both at the clinic and in the wider community.

Making a decision to join a study prior to receiving information about the risks and benefits might not mean that the informed consent process does not work but it certainly reveals deeper social injustices and inequalities where a woman seeks a research site instead of a local health center for cancer screening or STI testing and treatment. Similar to research conducted by Toe et al (2013), we found that our potential participants were active actors in the process and tried to become enrolled in the study, some fully

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<sup>32</sup> Kalabuanga M, et al, *op. cit.* note 14.

knowing that they were not eligible. It is difficult to state that these women did not understand they were enrolling in research. Many of the participants claimed to know that the Ring Plus Study indeed involved research but still joined for the STI testing and treatment and cervical cancer screening. Their attitude does not reveal poor comprehension of “research”, but rather a good awareness of the importance of prevention and treatment of STI/cervical cancer and of safe family planning. This awareness resulted in an active search of pragmatic ways to access these things, for example by enrolling in a low risk clinical trial.

One major limitation of the study was that we spoke primarily with participants who were enrolled in the study, except one IDI with an excluded participant. In addition to the women who came to the site for the screening but were not eligible for enrolment, we also “missed” women who did not come to the site for screening after attending the information session in the community. There were 461 women who attended the community sessions but 351 made their way to the clinic for a screening visit. We also spoke with participants after they were enrolled in the study, not before. Their reasons and views about participation could have changed over the course of the study as they became more familiar with the ring and study procedures. Our sample was also limited to women with ages between 17-38 in Kigali city. The women in the research-naïve, rural areas likely have different views about research and family planning in general, as well as different perceptions and rumors circulating regarding research. The study itself was low

risk as it tested a contraceptive vaginal ring which had already been proven to be safe and effective in Europe, the US, and South America<sup>33</sup>.

The experiences from the Ring Plus Study demonstrate that even though inequalities in access to health care may create conflicting situations around the study (e.g. competition for access, frustration, rumors), it is also possible to form an optimal partnership between a research center, enrolled women and their partners, for research about reproductive health. Further, researchers should be attuned to the rumors that circulate regarding the research and not only acknowledge these rumors but try to understand what deeper issues exist in the community and aim to address those issues before implementing research that could enhance unintended consequences in the community. If qualitative research on community perceptions and expectations for research studies could be conducted prior to the clinical trial, researchers would have a better idea of the context and issues that exist in that particular community. Additionally, researchers should work to develop and build a sustained engagement not only with those enrolled in the study but also with women who are interested but not eligible.

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<sup>33</sup> Shimoni N, Westhoff C. Review of the vaginal contraceptive ring (NuvaRing®). J Fam Plann Reprod Health Care. 2008;34(4).

## FUNDING

The main study has been funded by The European & Developing Countries Clinical Trials Partnership (EDCTP) through a project entitled ‘Preparing for clinical trials with vaginal rings that protect women from HIV and unintended pregnancy’ (grant code SP.2011.41304.043); the University of Liverpool and the ITM.

## ACKNOWLEDGEMENTS

We would like to thank EDCTP, ITM, UoL, the RING PLUS study group, and study participants for making this study possible.