



**GCM Advocates Call on HPTN 035 Results  
Wednesday 11th February at 9:00am EST**

**Speakers**

Salim S. Abdool Karim, Ph.D., University of KwaZulu-Natal, HPTN 035 Protocol Chair  
Neetha Morar, South African Medical Research Council, HPTN 035 Clinical Manager  
Sheena McCormack, PhD, Medical Research Council, MDP 301 Chief Investigator

**Facilitator:** Anna Forbes, Deputy Director, Global Campaign for Microbicides

**Call Participants**

*Please note that the following list is incomplete. We know that 75 people total participated in the call but, due to some technical difficulties, the names of all call participants were not collected by the call operators. If you participated in the call and your name is not on this list, please contact us at [gwolnitzek@path.org](mailto:gwolnitzek@path.org) so that we can add your name to the call list. Thank you.*

**Verified Call Participants (in alphabetical order by first name) = 54**

<b>Name</b>	<b>Organization</b>	<b>Country</b>
Abdullrahman Orosanya	Concern Conscience International	Nigeria
Alan Stone	International Working Group on Microbicides	UK
Alison Ojanen-Goldsmith	Reproductive Health Technologies Project	US
Amy Whalley	Interact Worldwide	UK
Anne Colleti	HPTN	US
Beth Robinson	FHI	US
Bindiya Patel	GCM	US
Chibuike Amaechi	NHVMAG	Nigeria
Chidi Victor Nweneka	Pro-Hope International	The Gambia
Clair Kaplan	Yale School of Nursing	US
Contance Kubwimana	Icyuzuzo	Rwanda
Cynthia Woodsong	RTI International	US
Danielle Altares	PATH	US
David Ngilangwa	Health Research and Communications for Develepment	Tanzania
Deb Baron	MMCI	South Africa
Ellie Papanthasiou	Buchan Consulting	Australia
Eugene Twagirimana	Icyuzuzo	Rwanda
Gary Wolnitzek	GCM	US
Georgina Caswell	GNP+	Netherlands
Jacinta Mulatya	S.A.F.U.A.	Kenya
Janet Frohlich	CAPRISA	South Africa
Jo Robinson	Terrence Higgins Trust	UK
Joel Odondi	Kenya Medical Research Institute	Kenya

Joyce Wood	MDP	UK
Kaijson Noilmar	Legacy Project	US
Kathy Shapiro	Grounds For Health	US
Katie West	GCM	US
Kim Dickson	WHO	Switzerland
Latifa Boyce	AMD	US
Laurie Sylla	Advocate	US
Liz McGrory	GCM	US
Manju Chatani	AMAG	US
Marc-Andre LeBlanc	GCM	US
Mariama Kamara	African HIV Policy Network	UK
Marion Nantukunda	Mama's Club	Uganda
Mary Odhiambo	Nyanza	Kenya
Mialy Clark	GCM	US
Michelle Folsom	PATH	South Africa
Mitchell Warren	AVAC	US
Mitzy Gafos	Africa Centre	South Africa
Nargis Kassam	Advocate	US
Nesha Haniff	LACCASO	US
Num-Sulaporn Chonwilai	Advocate	Thailand
Pat Laphimon	Advocate	Thailand
Paula Akugizibwe	ARASA	South Africa
Pauline Irungu	GCM	Kenya
Rebekah Webb	GCM	Belgium
Rhonda White	FHI	US
Robert Lande	IPM	US
Roger Tatoud	Imperial College London	UK
Ruth Macklin	Albert Einstein College of Medicine	US
Samu Dube	GCM	South Africa
Stephanie Tillman	AMD	US

**Anna Forbes** – Welcomed participants, reviewed the call agenda and itemized “house-keeping” details regarding how the call would be handled, including asking participants to submit their questions to her by e-mail so they could be related to the speakers in order. Then she introduced Dr. Karim

**Dr. Salim Karim** – Provided a brief overview of results of the HPTNO35 trial and invited participants to go to the link to the CROI website (<http://tinyurl.com/dc7dng>) to see a video of his full presentation.

The trial was conducted in five countries; four countries in Africa and the United States. It was a four arm randomized controlled trial, with three of the arms including one of the following -- PRO 2000 gel 0.5%, BufferGel and a placebo gel. The fourth arm was actually a second control arm where women were not using gel. The trial screened close to 6,000 women and enrolled 3,099 women. They were distributed evenly across four arms of the trial. Retention rate within the trial was close to 94%.

The incidence rate of HIV infection in the PRO 2000 gel arm was 2.7/100 (*read this as 2.7 per 100*) person years. In the BufferGel arm it was 4.1/100 person years; the placebo 3.9/100 person years; and no gel was 4/100 person years.

Here's what these numbers mean. If women were not using gel within the study, and if 1,000 women were followed up for 1 year, 40 of them could have been expected to become infected with HIV. In the PRO 2000 arm, on the other hand, one would expect that only 27 would have become infected with HIV.

In other words, the difference between the 27 and the 40 is the 13 HIV infections that could be expected to be prevented per 1,000 women during the course of a year.

Dr. Karim suggested that one could also think about the 13 in another way. It is possible, from these data, to say that if the women in the PRO 2000 arm had not been using the gel, 13 more of them might have become infected than did become infected. There was a 50% difference between the number of infections that occurred (27) and the number of infections that occurred among the women using no gel (40).

That is the basis for the comparison among the arms. The 2.7/100 person years means that 27 infections could have been expected to occur in 1,000 women in a year in the PRO 2000 arm, compared to the placebo arm, where there were 39 infections could have been expected to occur in a year among 1,000 women in a year, and the no gel arm, where 40 could have been expected to occur.

This comparison is how the overall result of the study is calculated. This calculation is done using an "intent to treat analysis" with a hazard ratio of 0.7. It shows that a 30% reduction in HIV infections occurred in the women who used the PRO 2000 gel. There was no protective effect shown among the women using the BufferGel.

PRO 2000 gel did not have any affect on any sexually transmitted diseases (STDs) and was not contraceptive. BufferGel, similarly had no effect on STDs, on contraception or HIV infection.

This 30% reduction in the trial is *not statistically significant*. We look, in the scientific world, for a probability of less than 5% that the effect could, in fact, be a zero effect (that is, due to chance). In other words, we want to be more than 95% sure that the 30% reduction in the trial has not happened by chance.

In order to do this, we look for corroborating evidence. This evidence can be found in what is called a 'sub group analysis'. The sub group analysis is not as compelling as the overall analysis because it is not a randomized comparison. There are certain limitations in undertaking a sub analysis. But if we do the sub group analysis, what we find in low gel users is that the protective effect of PRO 2000 is only 9%. The median rate of gel use was 85% of the time. So "low gel users" were defined as women who used the gel less frequently than that. If we look at women who are high gel users (that is, who used gel more than 85% of the time), the protective effect of PRO 2000 is 44%.

Also, in the sub group analysis, we are most interested in looking at the rate of HIV infection among women who had low levels of condom use and high levels of gel use. Women who use condoms consistently are likely to have low seroconversion rates because condoms are highly protective – but this doesn't tell us anything about the effect of the gel. Among the women in the trial with low condom use and high gel use, we observed a 78% reduction in HIV infection. When women use gel with a higher frequency, they seem to get a larger effect in terms of protection. This is particularly evident when they use it in the absence of condoms, where we observed a very substantial protective effect up to 78%.

*Conclusive remarks*

- BufferGel does not have any impact on HIV.
- PRO 2000 is safe but has no impact on STDs (other than HIV).
- 0.5% PRO 2000 is 30% effective in preventing HIV.
- This effectiveness (above) is similar regardless of which control arm you look at.
- This 30% effect of PRO 2000 is not statistically significant and, therefore, we believe that additional evidence is needed to conclusively determine whether the PRO 2000 is an effective microbicide.
- However, it is important to note that the sub group analyses (where we looked at low condom use and high gel use) corroborate the data that shows the protective effect of PRO 2000.

**Anna Forbes** –thanked Dr. Karim and then read out e-mailed questions submitted for him. Below the questions appear in italics and are followed by the presenter’s response.

*Please provide more information about the pregnancies that occurred during the trial. When will the data on pregnancy outcomes be available?*

613 pregnancies occurred. The pregnancy rate among participants was 11.1%, and was similar across all 4 arms of the trial. Most of the deliveries have occurred so far but we are still waiting for about 30 or so. 65% of the pregnancies resulted in live births. Some still births occurred but, again, the rate of this happening was the same in all of the 4 arms. We see no problems as far as pregnancy is concerned for any of the two gels.

*I am curious about the U.S. site since it is felt that the large number of U.S. cases [of HIV infection] are injection drug use cases. What was the number enrolled? Did it include African-Americans? Is there going to be a write-up on this arm?*

The site was in Philadelphia. The participant population was at pretty high risk, if we look at just the number of sexually transmitted diseases in that group. A detailed description of that study population is included in a “baseline paper” that will be coming out describing all the seven sites and their baseline populations. I can tell you that we had two HIV infections in the Philadelphia site only. The data do not allow us to make any conclusions that would be separate for Philadelphia. All I can say is that Philadelphia showed the same trend as the overall conclusions in the study.

*Do you have any data about anal sex and effectiveness? Did you ask questions about anal sex during the trial?*

At baseline, the anal sex rate on average was 0.4% across the four arms. These are very low levels of anal sex. Interestingly, the Philadelphia site reported the highest level of anal sex. When we asked about anal sex during quarterly visits, the overall anal sex rate was a below 1%. Within that, Philadelphia was again the highest. So anal sex within the trial certainly was not a commonly reported phenomenon and it was balanced across the four arms. We do not see any potential analyses that we would need to adjust for anal sex and it did not feature prominently in this study.

*In your sub-group analysis, didn't you compare similar characteristics across the randomizations? Why then did you say that the analysis does not provide strong evidence? Is it because power calculation did not address this question?*

There are two issues when you do a sub group analysis. When you take out specific outcomes collectively from a randomised arm, you are removing the balance created by randomisation. You are selectively looking at data (in this case women who have low condom use and high gel use). The group selected is very different from the overall group that we have analysed and, therefore, we have lost the benefit of randomisation.

This means that this comparison is now prone to something called confounding. This is a kind of bias. We can adjust for confounding in cases of the number of partners or the frequency of sexual intercourse, (in other words, in cases where we have measured it). But there are some confounders that we cannot measure and, in those confounders, there is nothing we can do to get rid of that bias. That is why there is a potential for bias within the sub group analysis.

In terms of power, the study was not powered to answer questions in the sub group so it doesn't do that. It was powered to answer questions overall. But I can tell you that 18 women became infected in the high gel/low condom sub-group. The incidence rate of HIV infection was 4.6/100 in the placebo arm and 1/100 in the PRO 2000 arm. There were 3 infections in the PRO 2000 arm, 15 infections in the placebo arm. So the sub group itself is not compelling because it is not randomised and not powered. But it is informative in that it corroborates and strengthens our overall conclusion that there is likely to be a protective effect of PRO 2000.

*How safe is pregnancy during these trials?*

This trial included a no gel arm, which allows us to look at safety outcomes in the absence of any gel (including the placebo gel). Almost all markers of safety we looked at, including the pregnancy safety data, were evenly balanced across the four arms of the trial. The placebo gel and the no gel arm had very similar data, which shows us that the placebo has no effect on pregnancy or any other outcomes. We found no differences in these data in the two active gel arms and both control arms. We can safely say that, in the 613 pregnancies, we found no evidence to raise any concerns about the safety of pregnancy in the study.

*PRO 2000's mechanism of action is specific for HIV entry/fusion. Is there any information on its effect on transmission of other STIs? Alternatively, is there information on how effective (or not) this gel would be if STIs are present in the person using it?*

We measured 6 STIs including bacterial vaginosis; chlamydia; HSV2 (herpes simplex 2); gonorrhoea; genital ulcer disease; and trichomoniasis. PRO 2000 had no effect on any of these. Previous testing in animal models showed PRO 2000 as having substantial protective effect against HSV2. Buffer Gel was also shown in animal models to be protective against gonorrhoea and chlamydia. We were taken aback by the fact that neither product seemed to have any effect against any STIs in the 035 trial. This means we need to revisit the data we are seeing in animals and explore whether they apply at all to what we see in humans.

In short, whether a participant had a STI or not, the effect of PRO 2000 still appeared to be the same.

**Anna Forbes** – thanked Dr. Karim and encouraged participants to continue sending questions throughout the call. She then introduced Neetha Morar.

**Neetha Morar** – started her presentation by acknowledging the communities in all the sites who have contributed towards the study, as well as her colleagues in South Africa, Zambia,

Zimbabwe, and Malawi for their contributions. She also expressed her appreciation for the trial site staff, local regulators, MTN and the UD Division of AIDS who shared dissemination plans and materials throughout the whole process.

She explained that HPTN 035 is one of many trials being conducted in South Africa. They started working with the trial communities there last July to prepare them for when and how the trial results would be released. Communities, participants and stakeholders (including regulatory staff) were informed of the different timelines that would be used to respect the embargoes put on this information by CROI conference, NIH and MTN.

The preparation efforts included sharing not only the timeline (when people would know) but also potential scenarios or results that we might expect from this trial. The Principle Investigator for the South African trial sites, Dr. Geeta Ramjee, sent letters explaining the background of the O35 study to colleagues in December 2008. At the beginning of February, we started the process of communicating the results to our regulatory people, then our community and then our participants. Between February 4-6, we shared the results with our regulatory group, the Medical Control Council, governmental bodies nationally and provincially, and our local ethics committee. On February 7, we went to our trial site to give the results to our key community stakeholders and the peer educators who were trial participants in the study. February 8, we provided the results to our Durban-based community stakeholders, trial participants and other key people. With the support of Maropa and MTN, we held a successful media workshop on February 9 at our site which resulted in fairly positive coverage of the trial results outcome.

On February 10, we started the process of giving unblinding information to trial participants (letting them know which arm of the trial they were in). Responses of the various groups overall have been positive and supportive. Except for a few mis-quotes and examples of misunderstanding of the 30% trial result, the media has positively embraced the news, as have the communities and government stakeholders.

One striking example of this support occurred when we gave the results during the embargo period to our community. The community's traditional leader announced that if anyone shared results during the embargo, he would put them on trial in the traditional court. That was heart warming in terms of seeing that the community truly understood the importance of the embargo and the confidentiality of these results. We were also very fortunate in that we had two trial participants who were willing, after counselling and an informed consent process, to speak to the media about their experiences in the trial. One excellent feature article on the trial has already appeared and we are translating it into the local language for broader distribution.

Another notable effect occurred during the unblinding. There was jubilation among the women who found out they had been using PRO 2000 but sadness and concern among the women who had been receiving BufferGel or the placebo gel. We informed everyone that both gels were safe and this was somewhat reassuring to the participants.

The woman who has chaired our Community Working Group for the last four years came to our February 9 media workshop and shared her experiences; specifically the work that HTPN and MTN had been doing to build capacity in the community through trainings on understanding clinical trial ethics and the informed consent process. She said that this has enlightened her as a community working group member. She also talked with the media about the experiences of participants who came to her at the trial site. She expressed that the information, education and

healthcare benefits provided in connection with this trial had really helped women and their partners throughout this process.

Ms. Morar noted that, while her comments here focus on the HPTN 035 experiences in South Africa, there is also a great deal more information she could share about the sites in other countries. The Zimbabwe site has already submitted its report on releasing the trial results and they have had similar experiences. In the HPTN 035 Community Working Group conference call (which concluded just before this call began), members also reported in from Zambia, and Malawi – both reporting positive experiences in response to release of the trial results.

**Anna Forbes** Thanked Ms. Morar and read questions for her sent by e-mail.

*Are all 035 sites following the same process described?*

All had result dissemination plans prepared but the unusual embargo timeline impacted on each site differently. Each site had to work with its local authorities; regulatory processes; and local requirements and constraints.

The trial sponsors provided us with 19 documents to prepare for this including a Q and A, a press release, community flyers, media guidelines and backgrounders, all of which we could tailor for local use at our sites.

*What is the timeline and process for informing staff and participants of other studies at the 035 local sites?*

At our site, Professor Ramjee informed the entire HIV prevention research staff (200 people) at 8:30am on February 9. Then she held a call with local scientists in South Africa at 10:00am. On February 10, we had community meetings at all three of the MDP trial sites informing the communities there. The MDP sites that have not also been involved in HPTN 035 – which are the Africa Centre and the RHRU site – have used similar processes to inform the staff, participants and communities there of the 035 results.

*What was the level of significance if not 0.05%?*

**Dr. Salim Karim**

For a 30% reduction in the PRO 2000 arm compared to the placebo arm, the P value is 0.1. In other words, there is a 10% probability that the 30% could include a zero effect (meaning it could have occurred by chance). What we would traditionally regard as a significant result is a probability of 5% or less. The effect against the no gel arm is 0.06, and that means that there is a 6% chance, which is just outside the 5% that we would regard as statistically significant.

*Will the children born during the trial be followed to see if there were any effects on the children?*

**Ms. Morar**

We have followed and recorded the outcome of every pregnancy in the trial. We have not looked at whether we have the resources to follow the children born to HPTN 035 trial participants. All the new MTN studies started since the formation of the MTN, however, do include a pregnancy study which includes follow up.

*What can you share about the high retention rates, since in the Carraguard trial there was not high retention?*

There was a team effort both at the site level and at the network level. There were regular monthly calls, started by Anne Coletti, where each site shared their retention strategy and sites came together to support each other. Each site came up with its own unique plan for retention which matched the local environment. Staff are currently collecting information on retention from each of the 035 sites as part of the post-trial reporting and documentation.

*What plans have been put in place for the women who were infected during the trial?*

This has been a common question during the trial. Each site had to submit what the local care plans would be and Memorandums of Understanding (MOUs) were developed with local service providers. It's not just a letter that participants are given if they seroconvert. Participants were actually assisted in accessing care. Those who did not want to access care were provided with counselling at the trial site.

*What is your opinion on the communities understanding of 30% effectiveness?*

There appears to be a mixed understanding. In some communities – such as our trial site community -- there is a fairly clear understanding because (in part) of a discussion during a workshop that we held last year. I do believe that, as advocates and community workers, we need to do more work and messaging around what this percentile issue means.

*From your observation, what is the community and policymakers expectation on level of effectiveness that would be embraced for an HIV prevention tool?*

On February 8, we talked with the communities about the 30% effectiveness and many people informed us that they would like something that is more effective - maybe 50%-60%. We are beginning to learn what people would like to see (at what level) before they see the product being marketed.

*Since the trial has now been completed, what will happen to the infrastructure, expertise and knowledge that have been developed at the trial sites?*

At many of the 035 sites, we are fortunate to be able to maintain this infrastructure by engaging it directly in an MTN study. Unfortunately, the Hlabisa site (South Africa) has closed after 10 years because there was no other study for it to take on. We have managed to move staff within RHRU and the Medical Research Council to TB and other programmes, so that their expertise is not lost. We also have a good relationship with CAPRISA and have exchanged staff with them in the past. Scientists locally have been interacting to promote the retention and sharing of knowledge. We need to improve systems to ensure we don't lose staff and infrastructure but it is a challenge and we need more dialogue on this.

*You mentioned disappointment by people who were not on PRO 2000 when they learned which gel they were on. Were participants asked which gel they thought they were on just before they were actually told? We've heard that people often claim to have "known" which gel they were on.*

We still need to get specific information from all sites on this. But, at our site, we observe the therapeutic effect of coming to sites with treatment for curable STIs, monthly check-ups and

pelvic examinations, counselling and healthcare benefits. All this can result in misperception where people think that they are on the 'right' gel and that it works.

*Did participants understand the technical terms very well at the end of the trial?*

Yes, participants who have been in the trial for 30 months have been receiving information, informed consent and have developed an understanding many different terms throughout the trial. (We also had the issue of co-enrollment at our site and that was explained to participants very clearly using lots of different materials.)

When we started preparation for the trial results last July, we discussed scenarios with the Community Working Group and with the participants about what each potential trial result would mean. We are also documenting experiences and responses from the women as we go along so I am speaking from verbal information and experiences.

*A concern with prevention interventions such as these can be that people misunderstand the results and believe that use of the gel negates the need for other preventive interventions e.g. condoms. This is probably more of a concern among the broader community who may not have received as intensive education as participants. Have you encountered such problems and how did you address them?*

When talking with the media, we have fielded a few questions about whether people will be able to use the gel without condoms but these were few and far between, even in our wider communities. This is because our messages have always been very clear and strong on this and they have been around for a while. We have always promoted condoms as the only fully reliable preventive measure and we also always said that any first generation microbicide product should only to be used with condoms as it would not be highly effective.

*How "rigid" is the statistical significance threshold? In other words how to interpret the results? Positive? Good? Promising? Should it be played down? Should we be enthusiastic about it?*

My own view, as a community person and a social scientist, is that the results are promising. The microbicides field for a decade has had very bad news and people were very pessimistic before and were shocked at these results. The results are promising, however we must have the caveat that there should not be a too high expectation placed on the MDP trial. We need to prepare communities that the MDP results could swing either way but I would say these results are 'promising'.

*Did adherence tail off toward the end of the follow-up?*

It's difficult to answer. Adherence was consistent throughout the trial primarily because adherence messages were reinforced on at the site until the very end of the trial. Women did express a sense of being tired due to the long data collection and follow-up period of the study but we will look at the data more carefully.

**Anna Forbes** thanked Ms. Morar and introduced Dr. Sheena McCormick.

**Dr. Sheena McCormick** – started her presentation by thanking all the women who took part in HPTN 035 and the teams that delivered that trial.

The MDP 301 trial is being conducted at 13 clinics in four countries with the help of six partners. In South Africa, these partners are South Africa RHRU in Johannesburg; HPRU in Durban; and the Africa Centre for Health and Population Studies in Mtubatuba. The other three partners are AMREF/NIMR/LSHTM in Mwanza, Tanzania; the MRC Uganda Virus Research Unit in Lusaka, Uganda; and the University of Zambia which is running 2 clinics in Mazabuka, Zambia.

MDP 301 started enrolment in October 2005, with an original recruitment target of was 9,673. At that time, women were randomized to receive one of three gels: 0.5% of PRO 2000; 2%PRO 2000; and the placebo gel. Unlike HPTN 035, MDP 301 does not include a “no gel” control group.

In February 2008, we were advised to discontinue the 2% gel because there was little chance of it working at this strength. So we revised the target enrolment to 9,339 minimum and we completed enrolment with 9,389 in August 2008. We screened 15,730 women and the most common reason for exclusion was being HIV positive at screening. We are due to complete follow up on August 28, 2009.

The MDP 301 participants have experienced a pregnancy rate of 11.6% and it does differ across the clinics. The lowest rate is 7.8% and highest is 16.1% .Of the 917 pregnancies during this trial, 381 of them have occurred in women who were using an effective form of contraception – coil, hormonal method or sterilisation.

At the final week interview (week 52 of their trial participation for most women), 85% of women report using the gel at the last sex act. That is quite consistent across all weeks. We have also seen higher gel use in acts that are not protected by condoms across the whole trial.

Our retention is not as high as in 035 trial; it is at about 87% of women who we have in follow-up at the final visit.

**Anna Forbes** thanked Dr. McCormick and reads questions that have been e-mailed.

*What was the reaction of participants when you told them about the results of 035?*

Anna clarified that, while Ms. Morar had answered this question with regard to participants at the HPTN 035 sites, there are also some trial sites that are doing just the MDP 301 trial (not both trials). She asked Mitzy Gafos of the Africa Centre (one of the MDP 301 sites that did not also do 035) to respond to this question.

**Mitzy Gafos (Africa Centre)**

The MDP 301 participants were asked to come in over the last few days and informed of the 035 trial results. Staff emphasized that it is promising news but not at all conclusive and they feel that they have gotten the message across successfully. Participants’ response has been excited but measured. They have said ‘it makes us more eager to get to the end of our trial’. The first proper participant meeting where we expect larger numbers to attend will occur on February 13.

*What is the expected timeline for MDP results?*

**Dr. Sheena McCormick**

We are working to have the result by the beginning of November. Funding for the current programme finishes on December 31, 2009, so we need to complete them in November in order to disseminate them appropriately.

The last participant visit is August 28. This means we are facing an exceptionally tight timeline in which to wrap up this large trial. We will do a “dummy-run” of the analysis in May. We are also closing out to a “quality suitable for licence” admission but it is a very big task to do this in such a short time.

*How common is anal sex in the MDP trial, do you have any data?*

At enrolment, it was lower than the proportion reported in 035. I think 1-2% of the MDP 301 participants reported ever having had anal sex.

*And could you say a bit more about your plans for studying PRO 2000 as a rectal microbicide?*

We have a phase 1 protocol to look at safety of rectal application in seroconcordant men who have sex with men in two sites in the UK. It has regulatory and ethics approval to proceed but we are putting that on hold until we have results of the phase 3 in October/November. That rectal study is there to support a licensing submission. If our current trial result does not provide an indication to go forward with PRO 2000, then we feel it will be a disappointing result for communities. In that case, we plan to invest that funding in ensuring that the results are well disseminated and understood. So we are keeping that money aside until we know the result.

*At the end of the MDP301 trial, if the effectiveness shows over 33%, what percentage of effectiveness would you be looking at for PRO 2000 to take forward to getting a licence?*

I don't know if I can answer that exactly as it is phrased. A 33% reduction in the HPTN 035 trial would have been statistically significant but that figure is from the protocol which was based on a higher rate of infection in the control arm.

If we observe a 30% reduction in MDP 301, it will be highly significant because we have three times as many HIV infections to put into the comparison as 035. We don't know the rate of infection in our control group but there is no reason to think it will be very different from 035 and on the basis of that, this level of reduction would be significant in our trial.

When looking at the evidence for licensing, regulators focus on the lower level of the confidence interval. With the reduction you saw in 035 of 30%, the confidence interval goes from an 8% risk of increase of HIV infection to a 54% reduction of infection. It is quite a wide range within which the true answer may lie. The reason the range is wide is it is a small number of total infections that happened in the two groups. We will have a much narrower range in MDP, because we have much larger groups.

I hope if we observed 30%, we would have a lower bound of the confidence interval and 15% reduction of infection.

Sorry if this is too technical, it is easier to understand visually.

**Anna Forbes** confirmed that there were no more questions for Dr. McCormick and thanked her. She notes that one more question related to HPTN 035 study had been received.

*When will a report be available on the HPTN 035 results?*

**Dr. Salim Karim**–

The primary manuscript is at an advanced stage – we will submit to one of the major medical journals. It should appear in any one of the major medical journals in 6-9 months. We don't know which journal yet.

**Anna Forbes** read another question just received.

*What are the implications of these results for inclusion of a placebo arm in future trials – has there been discussion of ethics of having a placebo arm?*

**Dr. Sheena McCormick**

Noted that she is attending a meeting in Kampala in March to look specifically into the issue of when and under what circumstances proven new prevention technologies will ethically have to be added to the prevention package provided to all clinical trial participants. This consultation is being convened by GCM in collaboration with UNAIDS and CDC.

She added that, in the past, proven effective products were provided in trials once they were already available to the general public. But there is a huge transition period from licensing to manufacturing to product roll out. Even if we wanted to put PRO 2000 into the standard clinical trial prevention package, it would still take a while to get it.

**Anna Forbes** thanked all speakers and call participants. She noted that 75 people from a wide range of countries had dialed into this call, the highest level of participation ever achieved by GCM on a call of this type. She added that notes from the call would be sent out soon and urged participants to send their e-mail addresses to GCM (if they had not done so already) in order to receive these.