



Background Information for Advocates on the Premature Closure of the Cellulose Sulfate trials

Since the closure of the CS trials, the Global Campaign for Microbicides (GCM) and the African Microbicides Advocacy Group (AMAG) have been collecting questions from advocates and seeking answers from site investigators, sponsors, microbicide experts and information publicly available about the trials. This document summarizes what we have learned so far (as of February 5, 2007).

If you have questions that are not addressed in this brief, please forward them to info@global-campaign.org and we will do our best to track down the answer. The latest version of this evolving document is available at: www.global-campaign.org.

Why were the Cellulose Sulfate (CS) trials closed?

Two organizations were conducting separate, Phase III clinical trials of the same candidate microbicide, cellulose sulfate, also known as Ushercell. CONRAD, a reproductive health research organization, was conducting a trial among women in Benin, India, South Africa, and Uganda. Family Health International was conducting a trial in two sites in Nigeria. Both sponsors are not-for-profit research groups dedicated to advancing health in developing countries.

CONRAD halted its Phase III trial following a meeting of its independent data monitoring committee*. The Committee concluded based on a review of preliminary data that CS might be contributing to an increased risk of HIV infection among the study participants.

The Data Safety Monitoring Board (DSMB) of the FHI trial subsequently reviewed data from the CS trial in Nigeria, but did not find any evidence of increased risk among the Nigerian participants.

Study protocol teams, in consultation with the DSMBs, develop “stopping rules” at the start of trials that outline the circumstances under which they will recommend that a trial be stopped either because of compelling evidence of effectiveness or suggestions of harm. Even though FHI’s DSMB did not find any evidence of increased HIV risk in the Nigeria trial, the DSMB decided to stop the trial in order to err on the side of caution (given the findings in the CONRAD trial).

* Each microbicide trial has its own data safety monitoring committee that is charged with protecting participant safety and making recommendations to the Principal Investigators and trial sponsors regarding whether a trial should continue. This group, composed of individuals with expertise in statistics, medicine, clinical trials, and community issues, meets regularly to review the “un-blinded” data emerging from a trial (the investigators, participants and study staff remain “blind” to which women have received the experimental product).

The composition of the DSMB and its Terms of Reference (or scope of work) is a part of the trial protocol which is reviewed and approved by the Institutional Review Boards (IRBs) of the trial sponsor and the countries where the trial is conducted.

How many women sero-converted during the Phase III CS trials?

35 women sero-converted before the CONRAD trial was discontinued (including women in both the experimental and the control groups, although we do not know yet how many were in each group). This number may increase as the final results become available. There were 1,333 women included in the interim DSMB analysis of CONRAD's trial. In Nigeria, 21 women seroconverted among 1,644 participants enrolled in both groups.

While every single infection is a human tragedy, we must also bear in mind that these trials were done in countries and communities hard-hit by the HIV epidemic. In South Africa, for example, 48% of the women who volunteered for trial participation were unable to participate because they were already HIV positive at the time of their screening visit. In Uganda, the rate was 32% at screening. Thus, each new infection that occurred during the trial must also be viewed in the context of a truly devastating pandemic.

Isn't this what happened with the N-9 trials?

Nonoxynol-9 (N-9) is the active ingredient in spermicides that have been available without prescription for family planning since the 1950s. In the 1980s, it was shown that this product also killed HIV and research began to see if an N-9 containing spermicide might be safe and effective as a microbicide. In July 2000, data from a large scale Phase III trial were released showing that even a low dose N-9 gel, if used with high frequency, caused sufficient vaginal irritation to increase a woman's risk of HIV infection. At this point, research on N-9 as a potential microbicide stopped completely and the product is no longer used in situations of HIV risk.

But the Phase III N-9 trial was different from the CS trials. For one thing, previous trials on N-9 had produced conflicting data. Some suggested that it might increase risk and some suggested that it might protect against HIV infection to some extent. By contrast, none of the existing data regarding CS had suggested that it might increase risk.

A second difference was that N-9 spermicides were already widely accessible. Prior to 2000, some people believed N-9 would provide some protection against HIV (based on data that N-9 killed HIV in the laboratory) and they were already promoting it for HIV prevention. This made it critically important for research to establish clearly whether or not N-9 worked as a microbicide. Thus, the stopping rules for the N-9 trial were set so that the trial would stop prematurely only if it came to a clear conclusion in favour or against the product.

CS gel, on the other hand, is a new product, which is not available except in research settings and clinical trials. The CS trials stopping rules required the DSMB to recommend halting the trial as soon as there was evidence of a negative effect. All microbicide candidates now in the research pipeline are being tested under stopping rules designed to protect participant safety. This approach minimizes risk to participants.

Why were Phase III trials of cellulose sulfate initiated if its safety wasn't assured?

Scientists scrutinized the safety data from 11 clinical studies that had been done on CS before the Phase III trials started. These 11 studies were done in Africa, India, the US and Europe. None of the data suggested that the product could cause harm. In particular, there was no evidence of vaginal lesions, as occurred with Nonoxynol-9. CS acts in different way against HIV than N-9 and seemed to have a good safety profile.

Nevertheless, safety evaluation of candidate microbicides is an evolving science. As data from human effectiveness trials become available, they will improve researchers' ability to predict possible harm because scientists will know which laboratory and animal tests are good predictors of how the product may affect humans. For more information on how scientists evaluate safety, please see the GCM issue brief: Evaluating Microbicide Safety (Available for download at: www.global-campaign.org/cellulose-sulfate.htm).

Did cellulose sulfate cause any other safety problems in either the CONRAD or the FHI trials?

In the *preliminary data*, there were no differences experienced or reported between women receiving the CS gel and women receiving the placebo (a gel that looked and felt just like the CS but did not contain the active ingredient). The rates of minor side effects (such as mild vaginal irritation, soreness, etc.) that could be associated with gel use were similar in both groups and major side effects were not detected in either group. There were also no differences in the rates of sexually transmitted infections other than HIV detected between the two groups.

Why did the CONRAD and FHI studies get different results?

No one knows yet. Only once the final data are available and fully analyzed will a clearer picture emerge. Moreover, while the preliminary results in the FHI trial is different from that seen in the CONRAD trial, this is based on small numbers and may change (additional women may be found to be HIV positive once all women return to the site and are tested).

Both trials followed the same basic research design. The researchers involved have double and triple checked the study records to see if there were any differences in how the studies were done, whether there could have been problems with the randomization, etc. So far they have not located any cause that could explain this effect, but the investigation is ongoing.

Scientists are trying hard not to speculate until more is known. It is likely to be several months before the data analysis will be completed and publicly available.

Could the different infection rates by study group or the divergent results between trials be accounted for by differences in risk behavior or differences in the populations participating in the trials?

Researchers are exploring these factors. It is certainly possible that a closer examination of the participant data will suggest something, but no one can draw any conclusions until the analysis is done. Even if there were differences, any viable microbicide would need to be safe and effective for a very diverse range of women to use. It will have to be safe and effective for women regardless of the frequency with which they have sex or the number of partners they have.

What will happen to the CS trial participants now?

All the women enrolled in both the CONRAD and FHI trials are being contacted and asked to return to the clinics so that study staff can explain what has happened and answer any questions that they may have. During these closeout visits, study staff will collect all unused gel supplies and provide counseling; testing for HIV, sexually transmitted infections, and pregnancy; and referrals for medical care. The study clinics will remain open for at least two months to ensure that all participants receive the information they need and to complete the necessary study follow-up and safety monitoring. Longer term follow up is planned for women who became HIV positive during the trial (see below).

What about the women who became HIV positive?

Before the trials started, the trial sponsors developed written agreements with local HIV/AIDS treatment and care providers to assure that any women who sero-converted while enrolled in the trial would get ongoing care and treatment, including anti-retroviral drugs as needed.

FHI worked with local investigators and community representatives to identify facilities that offer HIV-related psychological, social, and medical services, and infected participants will be counseled and referred to those sites. The site investigators have written agreements in place to provide care to HIV-infected study participants in Lagos through programs supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria. In Port Harcourt, where such programs are not available, all participants are referred to HIV care and treatment centers that are heavily subsidized by the Nigerian government. Similarly, CONRAD-funded investigators established linkages at each trial site to local organizations that will provide care for women who become HIV-infected during the trial. CONRAD also set aside funding for women who become HIV-positive during the trial to ensure them access to adequate health care, including HIV antiretroviral treatment when needed.

In all HIV prevention trials some volunteers will become infected despite the intensive counseling, support, and prevention services they receive to help minimize their risk (see below). Care for sero-converters is necessary whether the final results provide clear evidence of a protective effect, a negative effect or no effect of the study product.

Did women sero-convert in all the sites?

There were sero-conversions in the sites in Benin, Nigeria, South Africa and Uganda. There were no sero-conversions in either site in India at the time of the DSMB analysis. One site in India had only started enrolling women in September 2006.

What was done to help women stay uninfected during the trial?

Extensive measures were taken at all trial sites to help women understand that they should not rely on the test product to protect them from HIV. All participants went through comprehensive informed consent procedures in their own languages. Key messages were reinforced at every visit, including the fact that they should not count on the gel for protection, that half were receiving the placebo gel (known to be ineffective), and that they had the right to withdraw from the trial at any time. All participants received monthly HIV prevention counseling, free condoms, and prompt diagnosis and treatment for any curable sexually transmitted infections.

When did the CS trial start? How long had it been going before it was stopped?

Recruitment for the CONRAD trial began in July 2005 and 1,333 women were included in the interim data analysis. Overall the trial was discontinued about midway through.

Recruitment for FHI's cellulose sulfate study in Nigeria began in December 2004. A total of 1,644 women had been enrolled. Follow-up of all currently enrolled participants had been expected to be completed in late October or early November 2007.

Was this the first DSMB review for this trial?

This was the first review for the CONRAD trial. The FHI Nigeria study had had an earlier DSMB review on September 5, 2006. The FHI DSMB found no safety concerns and the trial continued.

Have interim results of the other three effectiveness trials been reviewed by independent Data Safety Monitoring Boards?

PRO 2000 is currently being tested in two different effectiveness trials. The Microbicide Development Programme (MDP) is conducting a PRO 2000 trial in four African countries. Its DSMB reviewed the trial data on January 10, 2007, and found nothing to warrant early cessation of the trial.

A second trial sponsored by the Microbicides Trial Network (MTN) is evaluating PRO 2000 and BufferGel. A DSMB conducted its third review of the data from this trial in October 2006 and likewise found no evidence of safety concerns.

The Population Council's trial of Carraguard is scheduled to end in March and to report results by the end of 2007. A DSMB reviewed the Carraguard data at three interim points during the trial – most recently in September 2006 – and at all points allowed the trial to continue.

What is the process from here and when will we know more about the analysis of results?

According to the investigators, their first priority is to notify the women and ensure that they get appropriate follow-up counseling and care. Efforts are also being made to inform the wider community of the decision and to answer questions and concerns. The volume of data generated by such trials is immense and it will take 4 to 6 months to analyze and interpret.

We at the Global Campaign for Microbicides will continue to try to get answers to advocates questions and create opportunities for dialogue and debate. We hope to work with our partners to develop an advocacy agenda that prioritizes participants' rights, enhances scientific transparency, and encourages deep scientific reflection.