Conceiving contraceptives: the involvement of users in anti-fertility vaccines development
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1. Introduction

In the previous chapter I analyzed the central role of prototype vaccines in safeguarding the scientific development of anti-fertility vaccines from interference by non-experts. Prototype vaccines were mobilized by the scientists to account for the safety and efficacy of the developing product. The safety and efficacy of prototype vaccines are examined extensively in laboratory experiments, in animal studies, and ultimately in clinical trials. Clinical trials are the first occasions on which anti-fertility vaccines are injected into a human body, when a real, embodied user of anti-fertility vaccine is finally constituted.

Controlled clinical trials to test medical therapies and drugs were first introduced in the 1940s. Wartime conditions, and the availability of more science-based medical interventions, such as antibiotics, encouraged the systematic evaluation of treatments. In a clinical trial, a group of people is treated with the new technology or therapy and then compared with another group that receives a placebo or a standard treatment. In the 1970s, the methodology had become standard for clinical practice, and the U.S. Food and Drugs Administration had adopted clinical trials as a core requirement for the registration of a new drug. Currently, clinical trials occupy an important place in the drugs development process (Marks 1998). The clinical trial stage is a time-consuming and relatively expensive element of the research and development process, involving considerable administrative and organizational effort. The research protocol has to be approved by national drugs controlling agencies, institutional review boards, and ethical commissions before a clinical trial can be carried out, and these procedures can last for many months or even years. Clinical trials are generally divided into three or four phases. Phase I trials are to test the safety and the biological effects of the product and to find optimum dosages in 20-50 participants. For new contraceptive products, phase I trials are done with sterilized volunteers to lessen risk. Phase II clinical trials are carried out to assess the efficacy and side effects in 100-200 people. In contraceptive technology development, the
efficacy of the new product is compared with the 95% efficacy of e.g. the Pill. In between phase I and II trials, additional toxicology and teratology studies in animals have to be carried out. In phase III trials the number of participants is greater, and so also the chance of discovering rare side-effects. When the new preparation has been licensed for general use, in some countries the monitoring of side-effects and efficacy continues in phase IV or post-marketing trials (Mintzes 1991). In anti-fertility vaccines development, three different formulations of an anti-hCG vaccine have been tested in phase I clinical trials, and for one of these formulations in addition a phase II clinical trial was completed. Phase I clinical trials also have been carried out with an anti-FSH vaccine and with anti-GnRH vaccines.

In what ways are users represented in clinical trials? Clinical trials are expected to yield results that can be generalized to future users. Trial participants therefore have to represent users at least in a statistical sense. This representation is not straightforward: clinical trial participants differ by definition from end-users, and frequently intentionally so. Trial participants are selected by means of giving their informed consent to the use of an experimental drugs, and on the basis of inclusion and exclusion criteria. The methodological and epistemological limitations of the clinical trial methodology, and of the generalizability of the results, have been comprehensively discussed by medical practitioners, biostatisticians, and social scientists.¹ For example, Hansen and Launso (1989) have shown that there are major differences between the controlled setting of a clinical trial and the future users’ everyday lives. The trial participants are never fully representative of the potential user population at large. The controlled setting of clinical trials is not adequate for predicting problems connected with the daily-life use of the product, such as non-compliance, interactions with other drugs, and abuse. Rare or long-term problems are not detected by clinical trials. In general, the investigators decide which parameters will be monitored. Unexpected or unknown side-effects, or side-effects that are considered irrelevant by the researchers or difficult to measure, are not taken into account (Hansen and Launso 1989). A similar critique has been formulated by Morgall (1991), Hardon (1992), Snow (1994), and Koch (1995). In short, clinical trial participants represent end-users according to certain criteria that always may be disputed. Given the ongoing debates, the issue then becomes: how did the researchers configure the clinical trial participants so as to represent the future users?

There is another sense in which clinical trial participants stand in for future users. Epstein (1995) has described how AIDS activists in the United States successfully countered the roles foreseen for them in clinical trials to test new treatments. They combined methodological and moral arguments to plead that the trial participants should be more fully representative of dif-
ferent groups affected by the disease. Methodologically, they embroidered on the ongoing debate amongst biostatisticians that a more randomly selected group would generate more generalizable data on the safety and efficacy of the experimental treatment, i.e. they contested statistical representativeness. In addition, for the morally informed line of the argument, they presented participation in clinical trials in terms of access to possibly life-saving treatment, "a social good that must be distributed equitably." In other words, according to these AIDS activists, the clinical trial participants should also represent future users in a political sense, to ensure that the health needs of different groups affected by the disease would be taken into account. As Epstein (1995) has indicated, this political sense of representation involves different roles for clinical trial subjects and a more active form of participation, "to become a full-fledged partner in the experimental process". Instead of merely making their bodies available to enable the researchers to produce clean and generalizable data on efficacy and safety, room was created for the goals and ambitions of these "test-users". Viewed from this perspective, other aspects of clinical trial participants than merely those considered relevant for their statistical representativeness come to the fore. In their role as test-users, clinical trial participants also may represent users as early adopters or as the forerunners of those who eventually might use the vaccine. Trial participants typically appear in the scientific reports of the researchers under the heading "materials and methods". But clinical trial participants differ from some of the other materials involved. Characteristically, clinical trial participants - 'subjects' in the words of the scientists - may talk back. These test-users are embodied agents who, like future users, may become co-producers of the technology. One way in which both users and trial participants can be expected to enact agency is by "voting with their feet". Ann Saetnan (2000) has analyzed the introduction of sonographic examination of the fetus as a standard procedure for pregnant women in Norway. She has described how physicians interpret the fact that women visit the clinic for a sonogram as a foot-vote for continuation of the development the technology, regardless of the reasons that might bring these women to the clinic. Conversely, women could simply not use a technology, or not present themselves as clinical trial participants, or drop out after they have been enrolled. Authors such as Nelly Oudshoorn (1994), Inke Klinge (1998), and Lara Marks (1996) have also looked for ways to conceptualize the agency of the sometimes overlapping categories of clinical trials participants, users of medical technologies, and women. The question is how to analyze women's continual participation, or dropping out, without degrading them by portraying them as passive victims of the situation, or by underestimating the constrains placed upon them by their lack of resources and by existing structures.
As I mentioned in the Introduction, no opportunity existed to study the women who took part in the clinical trials. The voices of these participants are absent from my account. Instead, I have examined how the researchers handled the potential agency of clinical trial candidates. What roles were foreseen for the participants in the clinical trials with anti-fertility vaccines? Clarke and Montini (1993) reported how, at a conference of researchers and family-planning organizations in San Francisco that was part of the Planned Parenthood Campaign for New Birth Control, "some speakers seemed to imagine that women would tie themselves to the doors of the local federal building demanding new contraceptives (...) as people with AIDS have done to push for access to particular drugs". This never happened. As the head of the contraceptive branch at the National Institute of Child Health and Human Development (NICHD/NIH), Nancy Alexander, remarked: "There isn't really any constituency that is talking to their congressmen saying 'we need new research in contraception'." (quoted in Service, 1994). As against people with HIV/AIDS, the likely benefits to healthy women of applying for the testing of a new contraceptive are not obvious. Oudshoorn (1994) has also described how the researchers involved in the early development of the Pill in the late 1950s had to work hard to create what she calls "a laboratory in the field" for testing the contraceptive potential of their hormonal preparations. The first field trial was carried out in Puerto Rico, in collaboration with its Family Planning Association. The island guaranteed relatively controlled conditions with little chance that trial participants would be lost for follow-up. An organizational infrastructure was provided by the Family Planning Association, which had a widespread network of family-planning workers and clinics. Trial subjects were found in a new public housing project for poor families, who were used to relying upon the public health system. Oudshoorn concluded that even in this favorable context selected for testing the Pill, researchers encountered many difficulties in trying to discipline the participants to abide by the test protocols. The women had to take the Pill in the prescribed way, submit themselves to interviews and physical examinations, and continue to comply with their appointments to visit the clinic. (Oudshoorn 1994). In other words, clinical trial participants may resist being disciplined in the ways inscribed by the researchers in the technological script. In addition, since the time that the Pill was first tested and introduced, alternative means of family planning had become available, regulatory requirements had become more rigorous, and ethical standards had been raised. To enroll and maintain women in the trials to test anti-fertility vaccines entailed a number of problems.

In this chapter I will examine these problems. I divided the clinical trials into three stages: the recruitment and selection of participants, the actual enrollment and conduct of the trials, and the reporting of the results. How
were clinical trial candidates portrayed in the texts of researchers so as to facilitate their recruitment? When was agency ascribed to the clinical trial participants and when not? What else did the researchers in different countries do to enroll and maintain a sufficient number of women in the trials? Once the researchers had enrolled sufficient and suitable women, they could measure antibody levels in the blood of the trial participants and monitor side-effects. But more than measurements was needed to make the trials successful. The scientists hoped that the anti-fertility vaccines would be effective and safe. What representations of users did they invoke in their scientific reports to portray the testing as successful? What were the effects and the limitations of their representational strategies?

The structure of this chapter is as follows. First, I provide a short overview of the clinical trials that have been carried out with anti-fertility vaccines. The rest of the sections refer to these trials. Next, I analyze the ways in which the clinical trial participants were configured, specifically in the inclusion and exclusion criteria. Subsequently, I discuss how the researchers dealt with the agency of the participants in attempting to recruit and keep them in the trials. Finally, I examine how clinical trial participants were represented in the assessment of the efficacy and safety of anti-fertility vaccines.

2. Clinical trials with anti-fertility vaccines: an overview

Three prototypes of βhCG vaccine have undergone at least phase I clinical trials to test their safety and performance in humans. A whole βhCG vaccine was first tested by Stevens and his colleagues in six female prisoners in the early 1970s (Stevens 1975, personal communication by Stevens 26 December 1996) and in six other women in the United States in 1973 (Stevens and Crystle 1973). The β-hCG-CTP vaccine that Stevens developed for the WHO/HRP Task Force for Immunological Methods for Fertility Regulation was tested in 30 trial participants in the Flinders Medical Center in Adelaide, Australia in 1986-1987 (Jones et al. 1988). In 1994, a phase II trial with this vaccine was started in two hospitals in Uppsala and Stockholm, Sweden. But this trial was suspended after a few months, because the first seven participants all experienced severe and unexpected side-effects. The researchers went back to the laboratory to find out the causes of these side-effects and to do additional animal studies.

Talwar and his colleagues at the All India Institute of Medical Sciences in New Delhi tested a whole βhCG vaccine in four sterilized women in 1974 (Talwar et al. 1976a). This trial was extended by the Population Council to 15 more women in Finland, Sweden, Chile, and Brazil (Nash et al. 1980). In
1990, another phase I trial was carried out with whole βhCG vaccine by The Population Council in Chile, Finland, and the Dominican Republic in 24 sterilized women (Brache et al. 1992).

The researchers at the All India Institute of Medical Sciences extended their 1974 trial to eight non-sterilized women (Hingorani and Kumar 1979). Another trial in 23 non-sterilized women was carried out in Bombay (Shahani, Kulkarni and Patel 1979, Shahani et al. 1982). These trials were sponsored by the International Committee for Contraception Research (ICCR) of the Population Council in New York. In contrast, the Population Council researchers had included sterilization as a criterion in their extension of Talwar's 1974 trial, because of the lack of knowledge of contraceptive effectiveness, and as they fairly add, "the desire to observe antibody response and health effects without the complication of pregnancy" (Nash et al. 1980, 329). The fact that the researchers in Bombay selected fertile women in this stage of research was criticized both in India and abroad. The concerns were not only about the testing in women before adequate safety tests had been carried out, but in particular about the fact that the women were recommended to have abortions in the event they became pregnant. According to the Indian science journalist Jayaraman:

Although Talwar was the first to put hCG vaccine into human trials in 1974, he lost the race because of controversies that cropped up after he jumped the gun. In a hurry to beat his competitors, he vaccinated six unsterilized women with hCG-IT vaccine in 1976 when its efficacy was still in doubt. Two of the women became pregnant, World Health Organization withdrew support, and questions of ethics raised by the Indian scientific community forced him to go back to the laboratory (Jayaraman 1986, 661).²

Next, the Indian research team at the National Immunology Institute in New Delhi proceeded to develop an hCG-based vaccine that was expected to be more effective, called the Hetero Species Dimer-hCG vaccine (HSD-hCG). Three slightly different versions of this vaccine were tested in 101 women in India in a phase I clinical trial in 1988 (Talwar et al. 1990). And in 1991-1992, 148 more women were vaccinated at the All India Institute of Medical Sciences and the Safdarjung hospital in New Delhi, and the Post Graduate Institute of Medical Education and Research in Chanigarh, in a phase II trial to investigate efficacy (Talwar et al. 1994). In 1995, the director and founder of the National Institute of Immunology, Pran Talwar, retired and his successor critically reevaluated the progress of the anti-fertility vaccine development. In 1997, the projects' annual grant from the Indian Department of Biotechnology was halved, and a planned phase III trial was not begun. The
researchers went back to the laboratory to study the long-term safety aspects of the preparation.

Phase I clinical trials were also carried out with an anti-FSH vaccine in men in India (Moudgal et al. 1997a and 1997b), and also with an anti-GnRH vaccine in post-partum women (Talwar 1992) and in men with cancer of the prostate (Ladd et al. 1988, interview with Talwar 22 June 1996). Currently, a phase II clinical trial of the anti-GnRH vaccine is under way in healthy men in Chile (interview with Catterall 18 October 1996).

3. The enrollment of trial participants

The clinical trial protocols for the testing of anti-fertility vaccines were very demanding. Typically, the women would first undergo a thorough clinical examination, including a gynecological examination and a Pap smear. Urine would be collected and blood would be drawn. They were required to keep a menstrual record during the whole test period of about a year. Then they would receive two to four injections in the gluteal muscle, at fortnightly or monthly intervals. Subsequently, the protocol prescribed that they had to visit the clinic monthly for physical examinations, blood and urine tests, and interviews on side-effects. The women in the phase II trial in Sweden were asked to keep "coital diaries". In the 1990 phase II trial in India, eight women visited the clinic for an early morning examination after intercourse in mid-cycle. (Kumar et al. 1976, Talwar et al. 1976b, Nash et al. 1980, Shahani et al. 1982, Jones et al. 1988, Thau et al. 1989, Talwar et al. 1990, Brache et al. 1992, Protocol WHO/HRP 1992 version, Technical Report NII 1991-1996, Talwar et al. 1994). There were no clear rewards for the sterilized participants in phase I trials. The investigators preparing the Swedish phase II trial in fertile women anticipated that the requirements of three injections, close monitoring, and the provision of frequent blood and urine samples may make recruitment difficult and may lead to poor subject compliance in respect to follow up visits (Protocol WHO/HRP 1992 version).

For a successful course of the trials, it was centrally important that enough women would enter and continue to participate. What did researchers do to promote this situation? How could a sufficient number of women be enrolled and maintained in the trials?
3.1 Selection of potential candidates

Clinical trial participants in all the trials were selected on the basis of inclusion and exclusion criteria. These criteria were reflected in the trial protocols. Based on these lists, the research physicians would admit or reject candidates. In this selection the particularities of who might fit the technology was defined, and the process thus entailed the configuring of trial participants. Most of the inclusion and exclusion criteria were medically informed. In general, the trial participants had to be healthy women of reproductive age. For the phase I trials candidates needed to have been surgically sterilized, since the efficacy of the method was unknown. Women with any immunological disorders, such as allergies or a personal or family history of diseases with an autoimmune component, or with sensitivity to the specific components of the vaccine, were excluded. The researchers anticipated that these conditions might interfere with the safety or efficacy of the new vaccine (Griffin and Jones 1991, 181). Other inclusion and exclusion criteria were introduced in order to ensure that the clinical trial population would, in a statistical sense, faithfully represent the intended user population of ovulating women. Candidates had to be pre-menopausal and to have had regular menstrual cycles for at least three consecutive cycles prior to the treatment (Griffin and Jones 1991, 182; Protocol NII 1990).

The inclusion and exclusion criteria were not only medical but also sociocultural. Criteria such as age limits and family situations were based on legal, ethical, and cultural considerations. For example, in the Australian phase I trial in sterilized women, initially a lower age limit of 18 years was proposed by the researchers (Project description WHO/HRP 1984). This was revised and raised to over 29 years, because at that time the researchers reckoned with the possibility that the vaccine might induce irreversible immunity. Irreversibility was considered a potential ethical problem even in sterilized young women, because they might request a reversal of sterilization (Griffin and Jones 1991). Another example of socially informed inclusion and exclusion criteria were family situation requirements. Participants in the phase II trial in India had to be 20-35 years old, of proven fertility, and "exposed to the risk of pregnancy (cohabiting with husband)" (Protocol NII 1990). Also, participants should have at least two living children (Talwar et al. 1992a, 124; Talwar et al. 1993, 210; Talwar et al. 1994, 8533). This last requirement clearly echoed the Indian national population policy of promoting two-child families, and the social importance attached to having children. In contrast, candidates for the Swedish phase II trial were required to "have completed their families" (SC minutes 1991, 5). Not to demand any specified number of children echoed the cultural notion of women’s right of self-determination.
From the lists of inclusion and exclusion criteria we can also learn that certain aspects of the participants were deemed irrelevant in making them representative of future users. Race, ethnicity, class, religion, or educational background did not figure on the lists.

The selection of women on the basis of inclusion and exclusion criteria reduced the number of potential candidates. In Australia, women were recruited by means of press releases in national newspapers and announcements in the medical centers (Press release WHO/HRP 1986, Press release Flinders Medical Centre 1986). The chief investigator in the first clinical trial with the WHO/HRP's anti-hCG vaccine in Adelaide was Warren Jones, Head of the Department of Obstetrics and Gynecology at the Flinders Medical Center at Flinders University. Jones described the Australian phase I trial:

Subject recruitment was initiated in late 1985. There were 181 telephone enquiries from female volunteers of whom 89 were potentially suitable, that is they were surgically sterilised, over 29 years of age and pre-menopausal. Of these 57 were interested in participating in the trial and the final group selected for screening numbered 43 (Jones 1986, 185).³

One way to raise the number of potential candidates was to modify the socioculturally informed inclusion and exclusion criteria, such as age and family situation. In the Australian phase I trial the lower age limit of 29 was changed to over 25 years when additional participants were needed. This was after ten of the selected clinical trial participants had received unstable emulsions, and additional participants had to be recruited to replace them (Press release Flinders Medical Centre 1986, Jones 1986, Jones et al. 1988, 1297).

A similar pattern occurred in the phase II trial with the WHO/HRP's anti-hCG vaccine in Sweden. The original recruitment target for both centers in the Swedish trial was 50 subjects. A total of 61 women contacted the Karolinska Hospital in Stockholm in response to its initial publicity about the trial, and 17 of them remained potentially available after the interview and the screening. In the Uppsala University Hospital, a total of 16 women expressed interest, of whom three passed the interview and the screening stages (SubSC minutes 1994). The representative of one company involved, Mats Ehrnebo, wrote in September 1994 in a progress report to Task Force Manager David Griffin:

There has been a slower than expected patient recruitment.(...) It is planned then for a more extensive patient recruitment. (...) every aspect that could raise the number of patients that could be screened should be encouraged (Ehrnebo 1994).
The researchers involved in preparing this trial had chosen wider age limits: 18-39 years. The selection criteria for the phase II trial in Sweden were discussed at a 1991 meeting of the Steering Committee of the WHO/HRP Task Force. The lower age limit of 18 seemed to be inconsistent with the requirement of "having completed their families". According to the minutes:

It was recommended that if the age range of the subjects was to be kept at 18-39 years, then the requirement that they should have completed their families should be deleted (SC minutes 1991, 5). This requirement was then changed into "having had one proven pregnancy" and being "engaged in a stable relationship with a non-vasectomized male partner of proven fertility", while the age limits were not changed (Protocol WHO/HRP version 1992). Requirements involving completion of the family were no longer specified. In this way the pool of eligible women was maximized. Later, the lower age limit for the Swedish phase II trial was raised to 25, after the Ethics Committee of the hospital in Stockholm received a letter from the women's health advocates involved in the Campaign to Call for a Stop. The Ethics Committee then reexamined the previously approved application in depth and insisted on raising the minimum age (SubSC minutes 1994, Letter by Stemerding 31 March 1994, Letter by Hjemdahl 6 February 1995).

The socially informed criteria had reflected the researchers' ideas of who might be the future users of the method. Initially, because of uncertainty about the reversibility of the method, these were women who had completed their desired family size. At the 1974 Karolinska Symposium in Stockholm, where the first WHO/HRP research programme on immunological contraception was announced, Egon Diczfalusy said:

(...) the present philosophy is (...) that there is a section of population, say, for instance, women who completed their desired family size, who would certainly be willing to accept an immunological method even if it is irreversible, provided it is safe (Diczfalusy 1975, 31).

And in 1982, Jones wrote:

Such a method ideally would provide a 'buffer period' of potentially reversible contraception for the parous woman who no longer wishes to use oral contraception or other methods, but who is not yet ready to undergo surgical sterilization (Jones 1982, 196).

Next, as I explained in chapter 1, the researchers insisted that the method was not meant for any specific category of users: it would be for everybody. The changes in the inclusion criteria to enhance the number of potential candidates made more specified types of users thinkable, e.g. young women.
Now the researchers under the auspices of the WHO increasingly portrayed the new method as "suitable for delaying a first birth, for spacing birth, and for providing a reversible alternative to surgical sterilization after childbearing has been completed" (Griffin, Jones and Stevens 1994, Griffin 1994, Griffin 1996). The changes in the age criteria, prompted by the need to maximize the number of trial candidates, reinforced the representation of future users as women at all stages of their reproductive lives.

In the Indian trials, women were enrolled through the family-planning clinics of public hospitals. The organizational infrastructure of the health-care system in India helped the researchers at the National Institute of Immunology to recruit women in this way. The Indian researchers encountered fewer problems in finding sufficient potential trial candidates than the WHO/HRP Task Force scientists. For the trials with non-sterilized women carried out in India, women’s willingness to participate was seen to be rooted in their need for alternative methods for family planning. In one interview, Talwar spoke about the trial participants as agents who actively sought to become involved. About the enrollment of participants in the phase II trial in the early 1990s, he said:

They were happy. Many of them had problems with IUD’s and other methods. (...) We had no difficulty. In fact whenever you stop the trials, people where coming time and again to the clinics, asking [for the vaccine]. You know the original trials were designed for 750 cycles and it continued to 1224. Because some clinics said: you cannot stop all of a sudden. In recognition of the participation, if people are asking, you have to offer it for a limited period (interview with Talwar 1;25-26).

Also the researchers from the Nair Hospital in Bombay reported that participants in their early phase II trial had a need for alternative contraceptive methods:

These subjects did not desire any more children but were reluctant to undergo surgical sterilization (Shahani et al. 1982, 422).

Next to the prescriptions in the protocols, the array of options available to the potential candidates and country-specific institutional arrangements played a part in selecting and thereby configuring the trial participants. Public hospitals provide care for the poorer part of the Indian population, who have fewer alternatives in planning their families. Apparently aware of the selective effect that this setting might have, Talwar repeatedly stressed that:

The number of literates in our trials is more than one could expect considering the average literacy level in our country (Talwar, in Sunny and Shah 1994, 23).\textsuperscript{5}

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The WHO/HRP Task Force researchers did not comment on the educational background of the participants in Australia and Sweden.

3.2 Portraying women as supportive collaborators

What about the second sense in which women selected for the testing are cast to represent future users: as early practitioners of the new method? Indeed, the researchers did ascribe the role of forerunners of future users to the trial participants. As the researchers at the NII wrote in the information brochure:

These volunteers may be the future users of the vaccine when it is available in the market (Information brochure NII, 3).

The researchers in Sweden, India, and Australia assigned trial participants to the role of supportive collaborators in the technology development process. In Sweden, the information brochure for trial candidates in the phase II trial said:

What are the benefits of participation? (...) By taking part in this trial, participants (...) will be performing an important role in the development of a new method of birth control that may benefit women throughout the world (Information brochure WHO/HRP).

Similarly, in India the information brochure for phase II trial candidates mentioned, among other benefits of participation:

By participating in the trial, the volunteer will benefit from the antifertility effect of the vaccine and she will be involved in an important event in the development of a novel birth control method, which in the future would benefit other women (Information brochure NII, 9).

Two sociologists from Delhi University, Kalpana Viswanath and Preeti Kirbat, conducted fieldwork to study the setting of the phase II clinical trial with HSD-hCG vaccine in New Delhi. They interviewed several of the medical doctors, social workers and participants involved. Viswanath and Kirbat reported that whenever visitors from abroad arrived, certain trial participants were asked to come to the clinic to meet them. The women would dress up with formal sarees and jewelry for such occasions, and the visiting doctors and researchers would take their photos (Viswanath and Kirbat 1997). Thus, the image of women committed to supporting the development of the new birth control technology was confirmed and conveyed to the world.

In Australia, additional participants were needed a few months after the trial had started. In their second press release, the researchers stressed the
commitment and the motivation of the participants who had already been enrolled:

Women volunteers participating in the trial are motivated by a desire to see a more acceptable form of contraception become available for their own and future generations. They have also expressed a wish to help overcome the critical problems of overpopulation in developing countries where a vaccine method is likely to be very acceptable (Press release Flinders Medical Centre 1986).

In other words, here also women participating in the trials were portrayed as agents who actively supported the development of anti-fertility vaccines, if not in their own interest then for the benefit of their children. As in Saetnan’s (1996) study of pregnant women visiting the clinic for sonograms, their many possible motives for participation in the trials were equated with support for the development of anti-fertility vaccines. As the Australian chief investigator Jones wrote in the acknowledgement section of a 1986 article:

The trial subjects were unique in their motivation and commitment to assist in the establishment of a new era of contraception (Jones 1986, 187).^6^

The configuring of trial participants as supportive of the researchers’ project made it easy to understand their readiness to abide by the demanding protocols. This portrayal of the trial participants as distinctively motivated potential users had implications for the researchers’ depiction of future users of anti-fertility vaccines as well. The researchers of the WHO/HRP Task Force mobilized women’s participation in the Australian clinical trial to underscore the acceptability of the method for future users. In 1994, three of the researchers involved wrote:

It is not possible to do meaningful acceptability studies on new methods of fertility regulation until a sufficiently large number of people are actually using the method in question. However, all 200 volunteers for the Phase I clinical trial in Australia, including the 43 women who actually participated in the trial, expressed support for the development of this method largely because of its characteristics (Griffin, Jones and Stevens 1994, 112).

While admittedly speculative in tone, these researchers were suggesting that women’s actual participation in the clinical trial was indicative of the acceptability of anti-fertility vaccines to future users.^7^ They could mobilize the trial participants in this way because of their ascribed role as early adopters.
3.3 Obtaining informed consent

The enrollment of participants followed informed consent procedures. Candidates received information about the experimental drugs and about what their participation would involve. They then could sign an informed consent form to express their voluntary decision to participate. The aim of the informed consent procedures was to enroll women in an ethical manner. Internationally endorsed guidelines to regulate informed consent procedures were recorded for the first time in 1964 in the Declaration of Helsinki, prepared by the Council for International Organizations of Medical Sciences in collaboration with the World Health Organization, and they have been updated several times since then. Worldwide, ethical review committees at research centers and funding agencies scrutinize research proposals, information brochures, and final reports on the basis of these guidelines. Ethical guidelines for biomedical research involving human subjects are centered on the dual purpose of respect for a person’s right to make decisions, and protection of vulnerable persons in biomedical research (Cook and Dickens 1991).8 The provision of comprehensive information to candidates and free decision making were considered essential for ethical enrollment (CIOMS 1993). In other words, to ascribe agency to women in the informed consent procedure was necessary to ensure ethical enrollment.

The women in the Australian phase I trial received verbal explanations from the research physicians and an information sheet (Project description WHO/HRP 1984). The informed consent form stated:

I have read and understood the above information and consent to my inclusion as a subject in the proposed Clinical Trial (Subject Consent Form WHO/HRP 1984).

Women were seen as actively taking the decision to become research subjects and to submit their bodies to the research protocol on the basis of the information provided to them. The informed consent form for the phase II trial under the auspices of the WHO/HRP Task Force in Sweden was accompanied by an extensive information brochure. Again, women were addressed as if they would give their consent or not on the basis of a process of careful communication and individual decision-making. The introduction to the brochure stated that the information was "in order for you to reach a decision". The brochure was written to provide answers to questions likely to be asked by "individuals who volunteer to be in the study", and she was "free to ask questions at any time before and during the study". It was stressed that if she decided to participate in the trial this would be "of your own free will" and that she might "decide to withdraw from the study, for any reason and at any time" (Information brochure WHO/HRP). This mode of addressing
assumed that women had different options for action. Participation in the trial was envisioned as one option for women, the informed consent as a communication process, and women were seen as decision-makers.

A different picture of women’s options for action emerged from the performance of the informed consent procedures in the phase II trial in India. The German documentary-maker and women’s health advocate Ulrike Schaz filmed the recruitment of some women for this trial. The film showed a room in a public hospital in New Delhi where dozens of women were standing in line waiting to see a doctor. The doctor was sitting behind her desk and told a patient:

We have got a new injection. The effect of the injection stops children for one year. You need not be afraid about this. The injection has no side-effects. You see this injection is absolutely 100% effective. We will also put in a copper-T [IUD, jvk]. Continuous copper-T is not very good. If you have it three years, six years, then there is the risk of cancer. That is why we want you to change (Schaz and Schneider 1991).

The information that this doctor gave to the patient diverged from the protocol. The doctor said that the anti-fertility vaccine was a new injection instead of explaining that this was an experimental method. The duration and the efficacy of the vaccine were yet to be established. And there is no evidence to suggest that three or six years of copper-T would enhance the risk of cancer. This documentary was shown to members of the Steering Committee of the Task Force on Immunological Methods for Fertility Regulation of the WHO/HRP at their meeting in August 1992. It was also presented to scientists and staff of the Population Council at their 1992 meeting of the International Committee of Contraception Research, which collaborated with the National Institute of Immunology. These organizations discussed the issue. The research protocol for this phase II trial had been approved by the Drugs Controller of India, the institutional ethics committees, and the Ethics Review Committee of the Canadian International Development and Research Centre, one of the funders of the clinical research at the NII (Talwar 1994 et al., Letter by Maureen Law 28 March 1995). As a part of the international Campaign to Call for a Stop, women’s health advocates discussed the film with the staff at the IDRC (Resistance on the Rise 1995). The film caused concern. This representation of a trial participant differed from the one that the Task Force researchers had been addressing. The woman on the screen was no free-floating agent who could freely decide to consent or not on the basis of her understanding of the complete and accurate information provided to her, but an embodied trial candidate in a specific situation. While the scene underscored the importance of proper infor-
mation, the candidate’s options for action seemed to depend on more than communication processes. Informed consent therefore appeared not as a communication and decision-making process, but as a form of social intervention in a specific context, producing and reproducing power-relations.

At the suggestion of women’s health advocates, some of the researchers from the WHO/HRP Task Force concluded that providing more and better information to women might not be sufficient to ensure her voluntary participation. These researchers proposed that women’s health advocates could play a role in monitoring the conduct of clinical trials. As I described in the previous chapter, women’s health advocates had gained credibility as representatives of an alternative perspective on users in contraceptive development. In the minutes of the August 1992 meeting of the Steering Committee:

The need for involvement of representatives of women’s health advocacy groups at the earliest stages of clinical protocol design and throughout the clinical evaluation of new family-planning methods was recognized and endorsed by the Steering Committee (SC minutes 1992, 6).

But the principal investigators of the forthcoming clinical trial in Sweden felt that there was no need to involve women’s health advocates in their particular trial (SC minutes 1992, 6). Following the proposals of women’s health advocates, the IDRC also suggested to the researchers at the NII that a witness from a local women’s organization should be present at all future clinical trial recruitment sessions (Letter by Maureen Law 28 March 1995). However, the NII did not request any additional funding from the IDRC after their grant expired in 1995, and they did not carry out further clinical studies with anti-fertility vaccines.

The question remained of what the international organizations involved in contraceptive development should do about the obviously unethical situation of providing inaccurate information, as the film demonstrated. As the women’s health advocates had urged in their meeting with IDRC staff in July 1995, the IDRC asked the researchers in India to send them information regarding the longer-term follow-up of the women who had been involved in the study and of any children who were born of these women (Letter by Anne Philips 14 April 1998). The WHO and the Population Council did not publicly undertake any activity. The political sensitivity of criticizing this research partly lay in North-South relationships. In a 1994 guest editorial in the journal Current Opinion in Immunology, Talwar wrote:

In the past, most of the new developments in contraceptive vaccines originated from research in industrially developed Western countries. The BtCG and HSD vaccines have emerged from research in a developing country. Apprehensions have been expressed as to whether trials
can be carried out in a developing country in compliance with the ethical principles enshrined in the Helsinki declaration. Economically developing countries, such as India, are not intellectually and professionally underdeveloped (Talwar 1994a, 702).

In addition, the national character of the Indian achievements was often stressed. For example, the announcement of the launching of clinical trials in India in the News section of Nature starts:

Clinical trials of two locally developed birth control vaccines have started in India (Jayaraman 1986, 323).10

And the researchers involved stated that

The leading work for these vaccines has been done in India, though laboratories in other parts of the world are also engaged in similar studies (Talwar et al. 1992b, 947).

Under the heading 'India's Birth Control Vaccine', an interview with Talwar was introduced with a reference to "the world’s first birth control vaccine, being pioneered at New Delhi’s National Institute of Immunology". A 1991 photo of Talwar at an international congress of immunopharmacology in conversation with Jonas Salk, the inventor of the polio vaccine, is reproduced with the article (Sunny and Shah 1994, 20-27). In this context, to denounce this research of the National Institute of Immunology would imply criticism of the Government of India. India has been an very important partner for the WHO and for the Population Council. As I described in chapter 1, the Government of India was among the first to introduce family planning as an official policy in the 1950s. Contraceptive research was strongly encouraged by the Government.

To be sure, the clinical research in the Indian centers yielded results that were highly relevant to the other contraceptive vaccine developers. The Indian phase II trial for the first time generated information on efficacy, such as the antibody titre necessary to prevent pregnancy (Talwar et al. 1994b). According to the minutes of the Steering Committee meeting of September 1991:

It was recommended that Dr.Talwar and his co-investigators should obtain as much information as possible about the levels and affinities of the anti-hCG antibodies in the serum at the time of implantation in those subjects who got pregnant, as these data would be extremely valuable for estimating the actual efficacy threshold of immunity to hCG (SC minutes 1991, 31-33).
These trials also provided important data for assessing certain safety issues, such as the clinical relevance of potentially harmful cross-reactions. As the chairman of the Steering Committee wrote:

The cross-reactions elicited by the intact β chain vaccine are worrying but that concern diminishes as the number of women who have been vaccinated without adverse consequences increases (Mitchison 1990a, 726).

On the basis of the Indian human trials, the WHO/HRP Task Force scientists also decided to omit some of the safety testing in baboons. As the Steering Committee observed:

The value of a homologuous baboon CG vaccine model becomes less important as the amount of more relevant data from clinical trials increases (SC minutes 1992, 13).

In 1993, Talwar was back in the WHO/HRP Steering Committee.

3.4 Keeping them in the trial

Agency was not solely an attribute that researchers could ascribe or not to clinical trial candidates. Therefore, it cannot be expected that the women actually relinquished their agency by signing a form and becoming research subjects. From the trial reports it turns out that women maintained at least their capacity to foot-vote, and to either continue or stop visiting the clinic after they had been enrolled and selected. Sarah Franklin (1995), who studied women’s determination to undergo In Vitro Fertilization, has also pleaded for a more processual perspective on women’s involvement in ongoing procedures instead of focusing only on their initial motivations. It is therefore important to study the role of clinical trial participants and the agency ascribed to them after their enrollment.

Indeed, women in Australia, India and Sweden continued to drop out after they had been selected. For example, the WHO researchers wrote that of the 37 selected and medically screened subjects for the Australian trial, 11 dropped out. The reasons mentioned by the researchers included one case in which the "husband was opposed" to the trial, and another with "domestic problems". One woman dropped out because of "work commitments". Another, recently returned from south-east Asia, had a recurrence of a parasitic intestinal disorder. Two women dropped out in this stage because they "decided to seek sterilization reversal" (Jones 1986, Jones et al. 1988). Again, the Indian researchers encountered fewer problems in maintaining a sufficient number of women in their trials. In the phase I trial in India with the three HSD-hCG vaccines fifteen of a total of 116 subjects
ceased to participate, among whom were two subjects who were "excluded from the trial due to non-adherence to the study protocol" and one who was "lost to follow-up". Only three of the 116 subjects discontinued "owing to personal reasons" (Talwar et al. 1990). Drop-out was a problem for the researchers. It meant the loss of prudently selected participants, and it rendered useless the work of enrolling them and the measurements done on them. How did the researchers handle women's capacity for foot-voting in order to prevent drop-out? There were important differences between the life and health of women in India and of women in Australia and Sweden. These differences had affected the ways by which they had been recruited, and also influenced their options for action once they had become research subjects. Accordingly, the researchers devised different means to prevent drop-out.

In the Indian trials, the daily life situations of women facilitated their enrollment and perpetuation in the trial. The sociologists Viswanath and Kirbat have described how the most frequently mentioned advantage of participation for clinical trial participants was that it improved their access to medical care. Since they could not afford to go to private clinics, asking for medical treatment meant leaving all work and queueing for hours in long lines outside the public hospitals. As clinical trial participants, they and their families received priority treatment. It might be difficult to overestimate the importance of this benefit for poor women of childbearing age in India. Moreover, Viswanath and Kirbat have described how the researchers actively tried to make participation attractive to the participants so that they would not drop out. They mentioned that most of the hospitals where the trials were conducted had separate rooms for the trials. According to these authors, at one of the hospitals the trial center was a very pleasant room with posters and photos and a place to sit around. The clinical trial provided an opportunity for the participants to come and spend time at the trial center chatting while being served cold drinks and snacks. The women received reimbursement for their travel expenses and time lost from employment (Kirbat 1998, 4-5).

Kirbat concluded:

(...) women participating in clinical trials often use it as a means for improving their existing situation. They are in their own way getting access to an extra income, improved health care, and a sense of identity and social space outside their homes (Kirbat 1998, 5).

In other words, according to Kirbat, the researchers made special efforts to make participation attractive and discourage participants from abandoning the trial. As Kirbat's analysis has indicated, women's performance of agency was not limited to the enrollment stage. This author regarded women's continued participation in the trial as their able and knowledgeable performance in a
specific situation. Accordingly, the ethics (and politics) of the clinical trial were not confined to the enrollment stage. Kirbat continued:

On the other hand, one can argue that these motivations provided by the research center in some ways take undue advantage of the situation of low income, uneducated women by providing them with opportunities they would otherwise not have (Kirbat 1998, 5).

Thus, this author has described a tension between women as actively seeking to become research subjects in a specific situation, and women as victims of those circumstances and power relations. Importantly, the provisions that the researchers made were effective only in the light of the daily-life situations of poor women. In contrast, the provision of a social space outside the home might not have been of significant to men, and access to good-quality health care was not an issue for richer people. The arrangements that the researchers made suited a specific category of clinical trial participants.

The difference that social contexts and relational factors made in recruiting and keeping women in the trials can be illuminated by comparison with the Swedish phase II trial. Researchers had fewer opportunities to make participation in this trial attractive to women in Sweden. Improving their access to good-quality health care was not relevant for these women. Just as in the Indian phase II trial, participants were reimbursed for travel expenses, time lost for employment, and other trial-related expenses. But as in any country, offering payments as an inducement to take part in the trial was considered unethical, since it would limit the candidate's ability to consent freely. Apart from the eventual anti-fertility effect during the efficacy stage of the trial and a thorough medical examination, there were no personal benefits for the participants (Information brochure WHO/HRP). The researchers encountered various problems in enrolling and keeping a sufficient number of trial participants.

4. Reporting of the results: making the trials successful

To enrol enough and suitable trial participants was a necessary but not a sufficient condition for successful clinical trials. The researchers hoped to find a long-lasting and high level of antibodies against hCG in the blood of the participants, and they hoped that the women would display no side-effects. To substantiate the safety and efficacy of the vaccines in a successful clinical trial would provide an ardently needed basis to encourage further development (WHO/HRP 1985, 55). The field of immunological contraceptives had enjoyed the status of "showing promise" for over fifteen years now (WHO/HRP 1978, WHO/HRP 1988, Shegal 1976, Talwar 1976, Talwar 1993,
Mitchison 1990b, Griffin 1991, Griffin and Jones 1991, Jones et al. 1988), and as I discussed in chapter 3, this had been vital for the continuity of the research. Yet the efficacy of an anti-fertility vaccine had never been established in humans. It was high time to show result for these efforts.

As I described in chapter 1, the 1974 Indian trial had prompted a bitter competition between the anti-hCG vaccine developed by the NII team and the one developed by the American-Australian team under the auspices of the WHO, and the split was aggravated when Indian researchers tested the vaccine in fertile women. The ongoing competition between the American, Australian and Swedish researchers under the auspices of the WHO on the one hand, and the Indian team at the NII on the other contributed to the pressure to produce favorable outcomes. From both sides, doubts were expressed about the extent to which the published results indeed reflected the trial findings. As Talwar said about the report on the efficacy of the CTP-hCG-vaccine by the Task Force scientists:

> It will not work and they know that it won't. On paper it looks good, but many people have tried that. But you see people don't publish the negative results. Furthermore, you don't want to displease WHO. Because, you know, you want to receive money or invitations and so on (Interview with Talwar 1;21-22).

And as Stevens said about the published results on the safety of the HSD-hCG vaccine tested by the team at the NII:

> Talwar's vaccine, using [two large antigens] creates some concerns. But you can only believe what they report, and they say that there is not any notable disruption of ovarian function (Interview with Stevens 1;46).

These researchers thus seem to suggest that part of the production of promising results took place in the reporting about the work. Also constructivist STS scholars such as Latour (1987), Oudshoorn (1994), and van der Ploeg (1998) have described how the reporting of scientific results is more than a formalized account of the accomplishments achieved in the laboratory or the clinic. Scientific writing can be considered as part of the work itself, partly constitutive of the results. Therefore, I will have a closer look at the reporting of the trial results in scientific articles, in particular at the ways in which the participants figured in these texts. In what ways were clinical trial participants represented in the reporting of safety and efficacy results? Which efficacy and safety problems could not be resolved by the means of textual representation, and how were these issues dealt with?
4.1 The construction of efficacy

The first step in showing that anti-fertility vaccines would be effective was to generate a sufficiently high and sustained level of antibody response to hCG in phase I trials. As I have described in the former chapter, the scientists had made various modifications to the vaccine in order to achieve this goal. But the phase I trials with anti-hCG vaccines continued to produce substantial variation in the duration of the immune responses among women (Talwar et al. 1976b, Nash et al. 1980, Jones et al. 1988, Talwar et al. 1990, Brach et al. 1992). The results were not reassuring. What did the researchers do when the trials did not produce the results they were looking for? In so far as the problem of variation in the duration of immune responses had remained unresolved by modifications to the vaccine, it was remedied in the textual representations of the results. Notably, the clinical trial participants were invoked in these representations, but they were unable to talk back.

In the trial reports from India the attainment of a sufficiently high and sustained immune response was attributed to the participants and not to the vaccine. The subjects could fail, but not the vaccine. According to the report of the trial with fertile women in India in the late 1970s:

The results of this study indicate that Pr-beta-hCG-TT vaccine was immunogenic in the majority of subjects except for one subject who was totally unresponsive and another 2 who developed very low titers (Shahani et al. 1982, 432).

In addition, the researchers rated the findings in these "unresponsive" women as insignificant in evaluating the efficacy of the vaccine:

The occurrence of 10 pregnancies in 8 subjects during the trial need not yet be taken as a failure of antibodies to block the implanting blastocyst. (...) the pregnancy occurrence could be attributed to failure of contraceptive supportive measures, ovulative cycles, and the high fertility of this group (Shahani et al. 1982, 433).

These researchers thus concluded that the technology had not failed. Instead, the women had failed by not using the mandatory supportive contraceptives and simply by being too fertile. Once the capacity to fail was assigned, a distinction was made between good and poor responders. In the 1974 phase I clinical trial report:

All subjects gave a positive response to this vaccine. (...) N.D. was the best responder and A.M., the poorest in the group (Talwar et al. 1976b, 239).16
And in a 1979 article Talwar wrote:

There is (...) one other variable which every immunological approach has to face, and this is the difference from individual to individual in immunological responsiveness to a given antigen. There are good, moderate and poor responders (Talwar 1979, 464).

This same distribution of competencies was adopted by the Population Council. In the trial of the Population Council in the Dominican Republic and Chile in 1990, various dosages of vaccine were given to the participants. In the trial report the subjects are classified in terms of low, intermediate or high response to the vaccination, and not by dosage. Subjects with a low level of antibodies were referred to as "poor responders" who "did not achieve titers sufficiently high" (Brache et al. 1992).

The distinction in the textual representation of the results between good responders and women who failed to produce a sufficient antibody response was not without consequences. In this line of reasoning, the finding of variation in the duration of effective immune responses was not considered prohibitive for the further development of anti-fertility vaccines. Instead, the method was redefined as unsuitable for poor responders. In an interview with medical anthropologist and women's health advocate Anita Hardon, Talwar said:

The main disadvantage, as I see it, is that you have to be a responder. Around 20% of the women were poor responders (Talwar, quoted in Hardon 1997).

Another textual representation technique to resolve the problem of individual variation was by giving mean levels of antibody concentrations and mean durations. The report of the phase I clinical trial with anti-hCG vaccine developed under the auspices of the WHO in Adelaide in 1986 presented the mean concentrations of anti-hCG antibodies attained by each dose group. The researchers at the Bombay hospital did the same, and also in the 1990 report of the comparative clinical trial in India the results are presented in a table with mean peak titers and also mean duration of antibody levels above a certain threshold (Shahani et al. 1982, Jones et al. 1988, Talwar et al. 1990). In each of these studies, mean values were calculated even when the data had been obtained using of different batches of vaccine. In the case of the comparative trial in India, even data generated by different formulations of anti-hCG vaccines were pooled. All reports concluded that although the individual variation in immune responses required further examination, the results were promising, so that further trials could be undertaken.

The second step to assess the efficacy of the anti-fertility vaccines involved phase II trials. In the phase I trials, researchers had been able to
handle the problem of individual variation in immune responses by means of specific modes of reporting the results. But in phase II trials in fertile women, these textual representation techniques were no longer sufficient. Weak or short immune responses would inevitably fail to protect individual trial participants against pregnancy. As a result, this problem placed special demands on the phase II trials.

In the phase II trials in both India and Sweden, a participant would be advised to have her IUD removed, or to stop using other barrier methods, as soon as the anti-hCG antibody level in her blood would rise above the level estimated to provide protection against pregnancy (Talwar et al. 1994, Protocol WHO/HRP 1992 version). The duration of a protective immune response could not be predicted for an individual trial participant, and therefore her antibody level had to be carefully monitored. The researchers had envisioned that easy-to-use test kits for home or clinic use would be an appropriate way to address this problem (see chapter 3). But such test kits were not yet available. Moreover, knowledge and expertise required for the use of these assay techniques was not widely available. As Griffin and Jones, from the WHO Task Force on Immunological Methods for Fertility Regulation, put it:

In view of the genetically controlled variations in individual immune responses, frequent blood sampling for antibody titres estimations and rapid provision of the titre information to the clinical trial investigator will be needed. Access to a reliable assay facility, in which rapid and accurate estimations of the hCG antibody levels can be made, is therefore essential for a satisfactory outcome of the study (Griffin and Jones 1991, 187).

The efficacy of the anti-hCG vaccine could not properly be estimated just anywhere, but required a suitably equipped. The prestigious Karolinska Institute in Stockholm, Sweden, was selected. The principal investigator of the phase II trial, Marc Bygdeman, confirmed:

The capacity to do such analyses was one of the prerequisites for doing the phase II study on the contraceptive efficacy of the treatment (Bygdeman 1996, 322).

In addition, information about whether the antibody level in her blood was still sufficiently high had to be made available to participants on a short notice. For the phase II Swedish trial it was foreseen that:

Failure of a subject to be present on the specified day will necessitate a home visit to ensure that all blood and urine samples are obtained (Protocol WHO/HRP version 1992).
The phase II trial with fertile women in India also had to take into account the need to inform women quickly if their antibody levels should fall. The Information Brochure for the Indian phase II trial mentioned that

All participants will have to give their contact addresses and/or phone numbers so that the health workers can contact them anytime during the trial. In case they wish to leave town, they must inform the centre well in advance so that adequate measures can be taken by the clinical investigators (Information Brochure NII).

And the Indian sociologists Kirbat explained that for the Indian phase II trial: (... there was a whole team geared towards following the women's level of antibody titres, and blood tests were carried out every two weeks. When a booster vaccine was required for a participant, she was contacted - sometimes by going to her house at night in the hospital van. This kind of a follow up would be impossible in typical public hospitals (Kirbat 1998, 7).

In other words, the phase II trials in Sweden and India had to be organized in such a way as to counteract the individual variation in immune responses, involving accessible trial participants, frequent blood sampling, well equipped laboratories, and highly motivated health personnel.

To inform the women in time was one of the main problems that the scientists preparing the Swedish phase II trial foresaw:

To obtain the maximum number of study cycles in each subject and to ensure that subjects are not exposed to the risk of pregnancy against their wishes, it will be necessary to obtain reliable estimate of anti-hCG antibody levels within as short a space of time as possible, and preferably within 72h. Providing this information within the time constraints imposed by the assay procedure may prove difficult (Protocol WHO/HRP 1992 version).

There were thus two reasons why the women had to be informed as soon as possible about their antibody levels. First, to safeguard the women from unwanted pregnancy. And second, this was crucial to maximize the number of cycles that would be relevant for the assessment of efficacy. "Study cycles" meant menstrual cycles in women with a sufficiently high immune response. Menstrual cycles in women with a low level of antibodies would not be study cycles. As Griffin and Jones wrote in a description of their approach to calculating the number of trial participants required for the Swedish phase II trial:

This approach assumes that the different cycles contributed by each woman are independent (...). Because of the independence assumption
it is immaterial whether these (approximately) 750 cycles be observed on 125 women having six cycles of contraceptive immunity, or 250 women each with only three month immunity (Griffin and Jones 1991, 188).

In her analysis of the testing of the Pill in the 1950s, Nelly Oudshoorn (1994, 128-131) has described how veteran researcher Gregory Pincus represented the trial participants as menstrual cycles in his scientific reports. The researchers had experienced persistent problems of recruitment and of drop-out of women in the conduct of the trials, but these were made invisible by the means of this technique of textual representation. As Oudshoorn pointed out, referring to the number of menstrual cycles created the effect of impressive grand totals and thriving trials. Since then, menstrual cycles have become an established method of reporting in contraceptive research. More than replacing women with their "immaterial" menstrual cycles would be needed for the testing of anti-fertility vaccines, with their drawback of causing differing responses. Not all menstrual cycles could be treated as equal. Analogous to the distinction between good and poor responders, the researchers distinguished good and poor cycles. Only the good ones were study cycles.

In the phase II trial in India, the only completed study to assess the efficacy of anti-hCG vaccines, a distinction was also made between the cycles of women with a high antibody response and of those with a low antibody response. According to the trial report, 148 women completed the schedule of three injections. Of these, 119 (80%) generated antibody levels that were above 50 ng/ml, the estimated threshold necessary to prevent pregnancy. In approximately 60% of these 119 women, the protective level was sustained for six months or more. One pregnancy occurred in a woman having an antibody titer of over 50 ng/ml in 1224 cycles. Twenty-six pregnancies occurred in the other 29 women who had titers below this level and were not given booster injections, or who had not used alternative contraception effectively (Talwar et al. 1994). The researchers refer to these results in a 1997 article:

Observations recorded over 1,224 cycles showed only one pregnancy occurring above 50 ng/ml. The efficacy imparted by the vaccine at this threshold titre was thus very high (Talwar et al. 1997, 155).

Without the distinction between cycles with immune response above or below the threshold, the efficacy of the anti-hCG vaccine in the phase II trial would have been a relatively disappointing 60 to 80%.
The promising efficacy results produced in the Indian phase II trial were significant and influential. The 1994 report of the phase II trial was hailed as a landmark by other researchers in the field of contraception:

‘Bravo to Talwar’, says gamete biologist John Herr of the University of Virginia, who is working to develop an anti-sperm contraceptive vaccine. ‘It’s the result that says "go".’(...) That ‘go’ signal is sorely needed, say contraceptive vaccine researchers, who argue that their field, which shows great promise, has long suffered from sparse funding (Aldous, 1994).

As the managing editor of the American Journal of Reproductive Immunology, Carolyn Coulam, wrote in an editorial:

This milestone is very important in justifying further research and development of hCG vaccines and providing hope of social and economic progress in the developing world (Coulam 1997, 151).

In sum, to make the efficacy trials with anti-fertility vaccines successful, the researchers needed a suitable location and organization: frequent access to the participants for blood sampling and additional injections, centers where information on antibody levels could be generated, and ways to keep the participants promptly and regularly informed. The assessment of the efficacy of the vaccine would have been far less satisfactory if the personnel in the Indian trial had not put a great effort into giving booster injections in time. This efficacy also depended on specific textual representations of the results, such as the classification of menstrual cycles either as study cycles, or as those in which antibody titers were below the threshold.

In the construction of efficacy, the clinical trial participants were assigned the passive role of contributors of study cycles. There was one exception. The clinical participants could not possibly control their antibody responses, but they might be able to regulate their exposure to pregnancy. In this way they would be actively involved in the efficacy assessment. In preparation of the phase II trial in Sweden, Griffin and Jones wrote:

In order to demonstrate the efficacy of the vaccine, it is necessary to observe a minimum number of cycles in which intercourse took place at a time when there would be a high chance of pregnancy in the absence of effective contraception. Without recording the timing of acts of intercourse, the impact of couples deliberately or subconsciously avoiding intercourse at mid-cycle could not be assessed (Griffin and Jones 1991, 188).

The request that trial participants keep coital diaries was an attempt to account for this effect.
4.2 The construction of safety

The construction of safety is of special concern. Betsy Hartmann (1992) has signaled that contraceptive safety is defined in relative terms. She cited from a contraceptive study by the U.S. National Research Council:

All active drugs cause adverse effects in some users. If safety were understood as the total absence of adverse effects, then no drug could be called "safe". Safety of a drug is conceived as a favorable ratio of benefits to risks for the population of users of the drug as a whole (Mastroianni, Donaldson and Kane 1990, 102).

As Hartmann has concluded, given this definition, the question of how contraceptive safety is assessed becomes particularly relevant.

As I explained in chapter 3, researchers in fertility regulation successfully retained the assessment of safety within their scientific domain. The safety of the vaccine in humans was measured on the basis of parameters in the blood of the participants, clinical examinations, and the participants’ reporting of side-effects (Talwar 1976, Nash et al. 1980, Jones et al. 1988, Talwar et al. 1990). The involvement of the clinical trial participants in the first two aspects consisted of presenting themselves to the clinic to undergo the investigations by the research physicians. But by giving notice of side-effects the participants could play a more active role, and I will therefore concentrate on this aspect of the safety assessment. In what ways were the clinical trial participants portrayed in the scientific reporting of side-effects?

By reporting side-effects or not, the participants could influence the safety assessment of anti-fertility vaccines. But appraising the significance of side-effects was beyond their competence and control. The clinical investigators were entitled to make these assessments. For example, to affect the safety assessment of anti-fertility vaccines, observed side-effects had to be attributed to the method and not to the participants. In the phase I trial of the Population Council a distinction was made between the problems described by the trial participants, and other medical conditions. The researchers wrote:

Complaints voiced by subjects during the interval from first vaccination to the present, and conditions detected by physical examination, are summarized in table 2 (Nash et al. 1980, 332).

The conditions expressed by the participants were portrayed as "complaints" (Nash et al. 1980, Talwar et al. 1990). The use of the term "complaints" in describing the side-effects reported in clinical trials is not restricted to anti-fertility vaccines. But the use of this term was entrenched in a context in which complaining women were granted dubious legitimacy. Kirbat (1998) reported about one woman who told her that:
After she kept complaining for a few weeks she was told by the social worker that it was in her nature to complain. (...) Later this women was asked to leave the trial (Kirbat 1998, 7).

The researchers were also entitled to interpret and report on the seriousness of the side-effects in their scientific papers. In an article about the Indian phase I trial, this led to the following counterintuitive characterization of the problems. The researchers wrote:

(...) Out of 88 subjects who were immunized with different formulations of the hCG vaccine, 63 did not have any complaints following first injection. The remaining 25 subjects (28%) had minor complaints such as erythema, pain at the site of injection, fever, oedema, generalised rash, transient joint pain, nausea, muscle pain and giddiness. (...) Thus, further work can be undertaken to study the efficacy of these vaccines in humans for preventing pregnancy (Talwar et al. 1990, 302-306).

In an analysis of acceptability studies of Norplant®, Anita Hardon found this same tendency to qualify the side-effects that women reported as "minor" and "transient", and to stress that their relation to the new method had not been proven. As many women's health advocates have observed, from the perspective of women these so-called "minor" complaints might interfere deeply with a women's daily life and well-being. The "non-life threatening" side-effects of Norplant®, such as menstrual disturbances, headache, and dizziness, were the main reason for women to discontinue the use of drug (Hardon 1992). Outside the realm of contraception research, in his study of the development and testing of non-steroidal anti-inflammatory drugs to treat rheumatoid arthritis, John Abraham (1995) found a similar pattern. Scientists developing these drugs for the pharmaceutical industry tended to minimize side-effects and to exaggerate efficacy, in systematic accord with their commercial interests. In anti-fertility vaccines development, such interests are less apparent than the researchers' concern with maintaining the promising status of their field of technology development. Again, this labeling of the side-effects was significant. The conclusions about the degree of side-effects facilitated the further development and testing of anti-fertility vaccines. In the protocol for the phase II trial, the Indian researchers observed that in the phase I trials:

No notable side-effects of immunization were observed (Protocol NII 1990).

The other research groups as well invariably concluded that they found "no significant adverse effects (...) on health" (Nash et al. 1980, 328) and "no
serious adverse reactions" (Brache et al. 1992, 8), or that "no serious or unacceptable side-effects were observed by the investigators nor reported by the trial volunteers" (Griffin 1988, 177).

So far it seems that the trial participants’ complaints about side-effects made little difference for the safety assessment and the further development of the vaccines. But there was another way in which the trial participants could express their grievances: they could leave the scene. One of the side-effects that was noted by the trial participants in the Australian phase I trial was muscle and joint pain following the injection. As Griffin wrote:

The only side-effects considered significant by the resident physician, were transient muscle and joint pains reported by a few subjects. These symptoms (...) were satisfactorily controlled with analgesics and did not cause any of the volunteers to withdraw from the trial (Griffin 1988, 182).

The researchers counted on the participants’ capacity for foot-voting. The fact that women did not abandon the trial was regarded as an indicator of the weight of the side-effects. The pain was eased with analgesics. No further research into the causes of the pain was undertaken at this stage.

Side-effects turned out to be a very important indicator in the interrupted phase II trial in Sweden. Recruitment for this trial was started in December 1993, and the first women were vaccinated in March 1994. In June 1994 the trial was stopped. According to the newsletter of the WHO/HRP, Progress:

After consultation with Task Force advisers, and with the clinical trial investigators and trial monitors, the phase II clinical trial of the prototype anti-hCG vaccine developed with support from the Programme’s Task Force on Vaccines for Fertility Regulation was suspended in June 1994 following the occurrence of unexpected but transient side-effects in the majority of the first seven women volunteers admitted to the trial (Progress 1994, 8).

The principal investigator of the Swedish trial, Marc Bygdeman, wrote a progress report to Task Force Manager David Griffin. The adverse events that were considered to be related to the vaccination included sterile abscesses in two women, pain at the injection site, muscle and joint pain, fever in two women, and menstrual disturbances in three women, including a too early onset of menstruation and an episode of prolonged menstruation (Bygdeman 1994). Apart from the reported severity of the pain, the side-effects found in the Swedish phase II trial were not uncommon as compared with those in the earlier trials with anti-hCG vaccines. The nature of the side-effects was not different from that described in the reports of the Indian phase I trial (Talwar
et al. 1990) and that of the trial under the auspices of the Population Council (Nash et al. 1980, Brache et al. 1992).22 As Stevens and Crystle wrote in their report about their 1973 trial with six women in the United States:

After the initial injection (...) some itching and swelling at the injection site occurred. This was significant in 3 women and 1 had a sterile abscess at the injection site (Stevens and Crystle 1973, 488).

Stevens and Crystle ascribed these reactions to the adjuvant substance, which then was changed (Stevens and Crystle 1973). In the phase I trial in Australia by the Task Force scientists, several women in the higher dose group also experienced muscle pain, which was reported to be "mild and transient", and pain-killers had been provided. Two participants reported redness and itching at the injection site (Jones et al. 1988, 1297, Griffin 1988). In this Australian trial several women also had menstrual disturbances: three participants reported intermenstrual spotting and one had very heavy periods.23 In a 1994 article the Task Force scientists Griffin, Jones, and Stevens mentioned these disturbances:

There was nothing unusual about these events in a group of 40 previously sterilised women and none of these events was considered to be related to the vaccine (Griffin, Jones, Stevens 1994, 110).

But in the Swedish phase II trial the clinical investigators reported that the side-effects were serious, and they characterized the reactions as vaccine-related. This was in contrast to the dominant tendency of characterizing the side-effects of new contraceptives for women as minor, transient, and of unknown relation to the product. Why were the side-effects evaluated differently in this trial, resulting in the interruption of the vaccine development?

The clinical investigators attempted to control the side-effects by various means. Task Force manager Griffin wrote a letter to inform the Scientific and Ethical Review Group of the WHO/HRP of the interruption:

All 7 subjects experienced unexpected side-effects, such as transient fever, injection site pain and in two instances, sterile abscesses. Although these side-effects were reduced to a tolerated level by reducing the dose and splitting the injections, they could not be eliminated completely. The trial was stopped, therefore, and the cause of these side-effects was investigated (Letter Griffin n.d.).

While the side-effects were reduced to tolerable levels according to the researchers, some of the trial participants made a different assessment. Two of the seven women discontinued their participation on their own account because of the pain created by the vaccine. The report by Bygdeman men-
tioned that the pain of one of these women, and in the two women with the abscesses, was so severe as to prevent them from working. One of the seven, the only one who had received a second injection, became pregnant (Bygdeman 1994). By leaving the trial, the participants decisively influenced the course of research on anti-fertility vaccines. When the trial was stopped, the Task Force members proceeded with research to identify the causes of the side-effects, and undertook additional laboratory and animal studies for further vaccine development.

Another reason why the assessment of the side-effects in the Swedish trial differed from that in earlier trials might have to do with the international campaign to Call for a Stop on this research that had been launched in November 1993, one month before the start of the trial. The Task Force Manager, clinical investigators and members of the Steering Committee who took part in the decision to interrupt the trial were well informed that their work was being watch-dogged. The campaigners had sent their petition, the Call for a Stop to the Research on Anti-Fertility "Vaccines", to the press and to the research centers and funding agencies involved. In March 1994, the coordinator of the campaign, Beatrijs Stemerding, also sent a letter to the ethics committees of the hospitals where the trial was carried out, in which she asked them to reconsider their decision to proceed with the trial (Letter by Stemerding 31 March 1994). At the meeting of the Steering Committee Clinical Trials Subcommittee on 29 June 1994 in Uppsala, Sweden, both "the exchange of correspondence" between the campaigners and the researchers, and "the current status of the trial" were discussed (SubSC minutes 1994).

5. Conclusions

In this chapter I have traced the ways in which trial participants have been involved in the clinical research stage of anti-fertility vaccines development. Trial participants represented users in two ways: in that the trial findings would be extrapolated to users, and as the first embodied agents to be injected with the product. I analyzed the texts of contraceptive developers in order to explore the ways in which clinical trial participants figured at the selection stage, in the actual conduct of the trials, and in reporting about the efficacy and the side-effects of anti-fertility vaccines. For the Indian phase II trial I had access to some additional sources, namely the reports of Viswanath and Kirbat (1997) and Kirbat (1998), and the film by Schaz and Schneider (1991).

As I mentioned in the introduction to this chapter, analyses of clinical trial methodology often includes discussions about the capacity of the trial participants to represent future users in a variety of real-life circumstances. In
the former chapter I described how the reproductive scientists successfully insisted upon assessing the safety and efficacy of the developing artefact detached from such circumstances. In the same vein, the issue of selecting trial participants who would represent future users of different races, ethnicities, classes, and the rest, was not raised in organizing the trials. Instead, the efforts of the researchers were directed towards finding and keeping enough women in the trials. As against the AIDS treatment trials narrated by Epstein (1995, 1997), and similar to many other trials, the researchers in Australia and Sweden encountered difficulties in enrolling a sufficient number of suitable subjects. Another difference from the AIDS trials was therefore that the arguments to minimize the restrictions for participation were not so much methodologically or morally inspired as they were practically informed. In particular, the inclusion and exclusion criteria contained prescriptions for who might participate in the trials. Practical considerations relating to the wish to maximize the number of eligible women and to the institutional settings in which the trials took place influenced ideas about who might use the vaccine. As a result, the representation of future users as women at any stage of their reproductive life was established.

Examination of the roles assigned to the clinical trial participants permitted me to gain a number of new insights. The clinical trial methodology contained a script and the appropriate acting out of their roles by the participants was central to the researchers’ success. Their prescribed role in the conduct of the trials was to visit the clinic repeatedly, to submit their bodies to medical examination and blood tests, and to report side-effects. At all stages of the trials, the researchers from the WHO/HRP Task Force and from the NII also cast the participants as early adopters, and as important contributors to technology development who shared with the researchers the goal of making a new contraceptive available to the women of the world. In the enrollment stage they emphasized this role in the information they issued to women. Some participants were specifically assigned this role in the conduct of the Indian phase II trial, and the trial participants’ endorsement of the method was again reiterated in the acknowledgement sections of the published reports. The researchers brought the active involvement and commitment of the trial participants to the fore in order to promote the acceptability of the method. From this it appears that not only the efficacy and safety of anti-fertility vaccines were on trial, but also the legitimacy of the research. Indeed, one of the main conclusions reached on the basis of the completed trials was that the research should continue.

To make the trial participants actually perform their roles as reliable allies necessitated additional work in carrying out the trials. In the enrollment and conduct of the trials, the participants were present as embodied agents. Their embodiment endowed them with the capacity to foot-vote. It also
endowed them with vulnerability to pain and ethical abuse. It was at this stage that international differences between women’s options for action came most clearly to the fore. Because of women’s different spectrum of options for action, it was easier to recruit and keep women in the trials in India than in Sweden. For poor women in India, the clinical trials could provide a welcome opportunity to obtain better access to superior health care, an extra income and a social space outside their homes. This illustrates how the politics and ethics of clinical trials are not confined to obtaining women’s informed consent to become a research subject. Women’s participation and continuation in the trial depended not only on their understanding of the information provided to them, but also on the contexts and the power relations in which they were engaged.

Much of the work that the scientists did to find and keep women in the trial was invisible in their scientific publications. As compared to oral contraceptives, anti-fertility vaccines were designed to avoid difficulties in the administration of the method, such as expecting women to take the Pill daily. But this technology faced different problems in the encounter with women, such as the pain of the injection and the unpredictable duration of efficacy in individual women. In the reports there was no mention of home visits to administer booster injections to participants, provision of analgesics for pain, or an attractive room where participants could sit around. Such efforts on the part of the researchers decisively contributed to making the trials successful, because they encouraged women to enter and remain in the trials, thus enabling researchers to collect sufficient "study cycles". The published reports included representation strategies definitely designed to support the conclusion that the development of anti-fertility vaccines should continue. The efficacy and safety measurements were reported as if detached from the embodied agents from whom they had been taken. In order to achieve an effective method, embodied agents were replaced by study cycles: menstrual cycles in which the immune response was deemed adequate. Since Pincus first introduced the representation of women as cycles in the 1950s, this has become an established procedure in the reproductive sciences. These cycles are treated as immaterial and contextless, and therefore easy to handle. As Oudshoorn (1994) has described, representing women as menstrual cycles in the early testing of the Pill had the effect of emphasising similarity among women, while obscuring diversity. In anti-fertility vaccine development, reporting in terms of cycles had precisely the same effect: it camouflaged the variations among individual women in the duration of an effective immune response. But this was not sufficient to make the vaccine effective. In the efficacy trial with anti-fertility vaccine carried out in India, the researchers therefore introduced a new distinction between good responders and poor ones. The chance that the method might fail was thus minimized. On this
basis, the trial results were announced as promising. In the words of Franklin (1995), "a belief in the technique in general, ‘it does work’" prevailed over the fact that in many practical respects it did not work.

Not all efficacy and safety problems could be resolved at the level of textual representations. The Swedish trial participants were unwilling to endure the side-effects that they experienced, and two of them left the trial. Next, because of the researchers’ concerns about the side-effects, the trial was stopped. Thus, even in the testing of a technology designed to leave little room for the enacting agency of women, in this case they decisively affected the course of technological development. Once they were assigned a role in legitimating anti-fertility research and development, the foot-voting of clinical trial participants sent the researchers back to the laboratory bench.
Notes by chapter 4

1. In his book *The progress of experiment: science and therapeutic reform in the United States 1900-1990*, Harry Marks (1998) traces the history of clinical trial methodology, including the ongoing debates about its methodological and epistemological shortcomings. Trudy Dehue (1997) analyses how the randomized groups design should be understood as a late nineteenth-century accomplishment in experimental psychology rather than as a methodological inheritance from the natural sciences. Armstrong (1977) showed how the advent of the clinical trial upset the balance between "clinical sense and clinical science". Taubes (1995) reports on the discussion about tensions between the methodological and ethical requirements of trials. Pocock, Hughes, and Lee (1987) analyzed 45 clinical trial reports published in the *British Medical Journal, The Lancet*, and the *New England Journal of Medicine* and identified numerous statistical problems that may lead to problems of interpretation. The dilemma of controlled representativeness versus unconstrained heterogeneity, refueled by the 1993 FDA Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, is discussed by Sherman, Temple and Merkatz (1995) and Meinert (1995). The critique of Evelleen Richards (1988) goes beyond the methodological and epistemological level. This author has made a comparative analysis of the unresolved controversy between Noble laureate Linus Pauling and orthodox oncologists about the potential value of vitamin C in cancer treatment. This author concludes that the assessment of medical therapies is inherently a social and political process. She concludes that methodological reforms cannot resolve disputes over contentious therapies or technologies. These must be treated as essentially political issues, where there are no impartial experts.

2. This research helped to create and maintain a niche for the continuation of contraceptive vaccine development. For example, the WHO researchers discussed the early testing in non-sterilized women in India in the protocol for their trial in Australia. While mentioning that the Indian trial had many unsatisfactory features, the protocol commented: "The results and implications of these human trials provided encouragement for (...) the principle of hCG vaccination" (Project description 1984 version).

3. Six of these 43 women were not included due to medical reasons.

4. Another way of enrolling more women proposed by the researchers in the Steering Committee was via collaboration with women's health organizations (SC minutes 1991, 43), but this was never taken up. A third way to gain
access to a larger number of women discussed by the WHO/HRP Task Force Steering Committee was to extend the number of centers (SubSC minutes 1994).

5. See also Saheli (1998) and interview with Talwar 22 June 1996.

6. See also Jones et al. (1988, 1298). Scientists from the Population Council wrote in the report of their phase I trials in Chile, Dominican Republic, and Finland: "Our deepest gratitude to the women who participated in this trial for their dedication, cooperation and commitment" (Brache et al. 1992).

7. See also Griffin (1992, 116).

8. Cultural anthropologists have observed that the meaning given to autonomy is not universal, and that many cultures are inspired by values that may be contrasted with individual autonomy, such as communalism or interdependency.

9. Interview with Schrater, 22 October 1996.

10. The Indian science journalist K.S. Jayaraman opens a news item in Nature Medicine with: "Researchers in India appear to have the edge in a keenly watched race to develop a vaccine that will provide protection against pregnancy" (Jayaraman 1995, 609).

11. Two women dropped out because of (pre)menstrual problems; in one case the husband died; and one woman became sensitive to one of the vaccine components (Jones 1986, Jones et al. 1988).

12. Five women dropped out for medical reasons unrelated to the trial (Talwar et al. 1990).

13. Especially in the Postgraduate Institute of Medical Education and Research in Chandigarh, trial participants received more time and attention from the doctors than other patients, and also in this hospital the drop-out rate was lower (Preeti Kirbat, personal communication 10 December 1998).


15. In the interview Talwar referred to an article published by a research group consisting of Austrian, German, French, and Dutch researchers, in which questions are raised about both the efficacy and the safety of the CTP-hCG vaccine developed under the auspices of the WHO (Dirnhofer et al. 1993, Dirnhofer, Wick and Berger 1994).
16. Capabilities were attributed to antibodies: "The antibodies are not only capable of reacting immunologically with the whole hCG molecule but are also competent for neutralizing the biological activity of hCG in radioligand receptor assay" (Talwar 1976, 242).

17. As Nash et al. wrote: "Only one subject (...) failed to show a response" (1980, 333).

18. The four women who dropped out due to reactions following injections, such as erythema, redness, and itching, are not included in these 28% of participants (Talwar 1990 et al., 305).

19. Also Mitchison commented on this trial in a review article saying that "No important adverse reactions have occurred" (1990a, 726). See also Talwar and Raghupathy (1989).

20. See also Griffin, Jones and Stevens (1994, 110).

21. Patient no. 1: sterile abscess at the site of injection (16 O4 94) was incised and drained (27 O4 94); Until then patient was unable to work due to severe pain; Recovered fully.
Patient no.2: attack of unconsciousness due to alcohol intoxication; Menorrhagia of unknown causes, possibly drug related; Positive skin test against vaccine; Dysmenorrhea, possibly drug related; Abdominal pain, not drug related.
Patient no. 3: discontinued on her own account after first vaccination because of the pain created by the vaccine; Severe myalgia which made her unable to work, vaccine related; Episode of prolonged menstruation more than 12 days, possibly vaccine related.
Patient no.4 (got pregnant): Vaccinated 2X, second vaccination made in split doses; After first vaccination slight fever and severe myalgia for about 48 h. after vaccination, vaccine related; After second vaccination intense pain and lump at the site of earlier vaccination. Fever. Myalgia in both legs, severe enough to prevent patient from working; Dysmenorrhea and too early onset of menstruation, vaccine related, bleeding possible vaccine related; Pain at injection site. (hereafter trial stopped)
Patient no.5 vaccinated once, then trial stopped; Soreness at injection site as well as myalgia and antralgia, vaccine related; Acute cystitis, not vaccine related.
Patient no.6: vaccinated once, got split injections; Discontinued on her own account due to severe pain at first vaccination; Anthralgia and myalgia; Fever.

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Patient no 7: Vaccinated once; Mild myalgia and fever, vaccine related.

22. The reports of the early phase I trial with six women in India (Talwar 1976) and of the completed phase II trial (Talwar et al. 1994) do not include a description of side-effects.

23. One woman from the control group, who had received an injection with adjuvant and vehicle only, had an early menopause (Jones et al. 1988).