Chapter 9
Cervical Cancer and the Development of HPV Vaccines in Guanacaste, Costa Rica

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9.1 Introduction

Cervical cancer is the second most frequent cancer in women worldwide, and the second most frequent cause of cancer death for women between the ages of 14–45 years. Eighty-three percent of cervical cancer cases occur in residents of developing countries, and it is the primary cause of cancer deaths in women of Central America (WHO/ICO 2009). Unfortunately, cytology-based prevention programs (such as Pap smears) have been less effective in developing countries than in countries with adequate health systems (Robles and Roses Periago 2004), leading to continued efforts to develop better methods to prevent and treat the disease.

Between 1985 and 1987, the United States National Cancer Institute (NCI) sponsored a multi-center study to identify risk factors for cancer of the uterine cervix. The study group was composed of women living in the United States, Costa Rica, Mexico, Panama, and Colombia. The study resulted in one of the major health discoveries in the past two decades: that cervical cancer resulted from infection with the Human Papilloma Virus (HPV) (Herrero et al. 1997). The presence of the virus triggers a series of events that over the years can result in cancer.

Once the relationship between HPV infection and cancer had been recognized, hope arose that a vaccine to prevent infection and any resulting cancers could be developed. But not all women infected with HPV developed cancer, and it remained necessary to look for other contributors to the development of the disease. One such study, also sponsored by the NCI, took place in Guanacaste, Costa Rica, between 1993 and 2001. It is now known that the majority of HPV infections (more than 90 %)

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are self-limiting, but certain HPV serotypes (15 of the 40, which have been identified) may result in cancer of the cervix, vulva, vagina, anus, penis, or oropharynx if the infection persists (WHO/ICO 2009). Only two of these serotypes, 16 and 18, are responsible for 70 % of cervical cancers.

With this information, the NCI developed technology to prepare vaccines against HPV serotypes 16 and 18, and in 2004 and 2005 sponsored a Phase III trial with a vaccine produced by GlaxoSmithKline (GSK). This clinical trial took place in Costa Rica and recruited thousands of women, some of whom continued their participation in secondary studies on the effectiveness and safety of the vaccine.

Cervical cancer studies in Costa Rica are scientifically and probably economically important. An analysis of their implementation process reveals some of the administrative challenges and a series of conflicts of interest and ethical concerns faced by the sponsors of long term studies. This information has been obtained by groups of scientists, politicians, and journalists who have great knowledge of their country and also of the ethical principles that should guide research involving humans. They used different means and agencies – including the Legislative Assembly of Costa Rica and the Comptroller General of the Republic – to denounce irregularities and obtain information, which is usually kept secret.

Box 9.1 describes all the studies on HPV and cervical cancer conducted in Guanacaste. Box 9.2 describes the institutions and Costa Rican companies that had important roles in the study process, as well as their formal or informal interrelationships during the studies.

Box 9.1: HPV and Cervical Cancer Studies Conducted in Guanacaste

1985–1987. **Multi-center case-controlled study (United States, Costa Rica, Colombia, Mexico, and Panama) to determine the risk factors for cancer of the uterine cervix.** Sponsored by the United States National Cancer Institute (NCI). Conclusion: infection by certain types of human papilloma virus resulted in a series of events leading to cervical cancer.

1993–2001. **Study of the natural history of infection by the human papilloma virus in Guanacaste (Costa Rica).** Sponsored by NCI (N01CP-21081; N01CP-31061; N01CP 40542; N01CP 50535; N01CP 81023; NCT00342173). The goal of the study was to investigate why a small proportion of women infected with HPV developed cancer, but the majority did not; a secondary objective was to develop better techniques to detect cervical lesions. A future study would test a vaccine against HPV. One fifth of adult women (18 years or older) in Guanacaste were invited to participate in the study, plus all residents who developed invasive cervical cancer detected between June 1993 and November 1994 (n = 28) were included. The final sample was 10,049. A subsample of approximately 3,000 women was examined every 12 or six months to monitor the course of the disease. At the conclusion of the study, all women had a follow-up appointment.

2001–2003. Five studies took place utilizing various women in the cohort.

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Box 9.1: (continued)

2004. **A randomized, double-blind, population study of the efficacy and safety of a vaccine against HPV 16 and 18 developed by the NIH of the United States and produced by GSK** (NCI-04-C-N191, NCI-590299/009, GSK-590299/009, NCT00128661). This study took place in Guanacaste, Puntarenas, and Upala. From a total of 24,467 women, 7,466 were included in the study. Criteria were healthy women, from 18 to 25 years of age, not pregnant or breastfeeding, at least three months postpartum, and willing to use contraception from one month before the first vaccine dose until two months after the third. The follow-up period was for four years.

2009. Continued follow-up of healthy young women in Costa Rica, vaccinated or not vaccinated against HPV. Women vaccinated during the clinical trial received an additional six year follow-up, and 3,000 women were recruited to serve as an unvaccinated control group during the follow-up study period.

Box 9.2: Who Is Who in the Guanacaste Project

Costa Rican Social Security Agency (CCSS). A public agency responsible for the provision of health services to the population of Costa Rica. There is a regulation for the conduct of clinical trials (versions 1998, 2001, 2003, 2004, and 2005). Rules in 1998 and 2001 require contracts to be signed between the study sponsor and the Director of the center where the study will take place; in the 2003 and 2004 versions the contract is between CENDEISSS and the sponsor; changing again in 2005 to the sponsor and the Chief Medical Officer of CCSS (León González and Vargas Navarro 2006:258). All versions indicate that they should buy an insurance policy for each of the participants. The CCSS had a Committee for Ethics in Science (CEC), which became the Institutional Committee for Ethics in Science (CECI) in 2003.

Center for Strategic Development and Information on Health and Social Security (CENDEISSS). This Center is part of the CCSS and includes a Bioethics Unit, which, among other functions, has the responsibility to protect, regulate, advise, monitor, and manage studies with human subjects that take place in the health centers of the CCSS. It serves also as the technical office of COIBI-CCSS (Institutional Committee for Bioethics in Research)

Ministry of Health (MS). In 1998, when Dr. Rogelio Pardo was the Minister of Health, the Executive Decree 27349-8 for the conduct of clinical trials was issued. This Decree was in violation of CCSS regulations, and was challenged by the Legal Department and the Bioethics Unit of the CCSS. It was

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Box 9.2: (continued)

subsequently condemned by the Legislature for procedural irregularities and for having been prepared by people with conflicts of interest. In 1999, the Ombudsman's Office recommended the rejection or modification of the Decree, but it was not repealed until 2003 by Decree MS 31078-S (León González and Vargas Navarro 2006:243). In 2010, the Decree of 2003 (MS 31078-S) was itself repealed.

Costa Rican Institute of Research and Education on Nutrition and Health (INCIENSA). A State Institute attached to the Office of the Minister of Health, with responsibility for research in public health among other duties. The INCIENSA Ethics Committee approved the clinical trial conducted by PEG on May 28, 2004. This decision was later questioned by CONIS.

National Council on Health Research (CONIS). Founded by Decree MS 31078-S, it is an advisory and consultative Council to the Minister of Health on research involving human subjects. CONIS accredits ethics committees and research-conducting institutions, and registers and approves all research projects involving human subjects which take place in the country. It is financed by quotas on approved projects (5.5 %) (León González and Vargas Navarro 2006:244).

Epidemiology Project of Guanacaste (PEG). A private company with its own researchers which has been responsible for conducting studies related to the human papilloma virus and cervical cancer in Costa Rica. In August 2010, it had about 120 employees.

Costa Rican Foundation for Teaching in Health Sciences (FUCODOCSA). A private foundation attached to CENDEISSS, it was responsible for the financial management of clinical trials, and charged 15 % of the total budget.

INCIENSA Foundation (FUNIN). A private foundation established by the staff of the Costa Rica Institute for Research and Teaching Nutrition and Health (INCIENSA – Instituto Costarricense de Investigación y Enseñanza en Nutrición y Salud), an Institute of the Ministry of Health to administer PEG project funds, and can also channel funds from other health research projects. Its office is located in PEG. FUNIN works through the INCIENSA Ethics Committee for project approval. INCIENSA and FUNIN are closely related; for example, the Executive Director of INCIENSA was also Secretary of the Board of Directors of FUNIN, and the coordinator of INCIENSA's Ethics Committee was a member of the Board of Directors of FUNIN until April 24, 2004.

The University of Costa Rica. The University of Costa Rica is a public university, which has conducted laboratory tests for PEG since 1999, enabling it to purchase equipment valued at US $269,000.00.

9.2 Description of Guanacaste

Guanacaste is one of the seven provinces of Costa Rica. It is situated in the far northwest region of the country, with an area of 12,241 km^2 (7,606 sq. miles – almost one quarter of the country), and had 280,488 inhabitants in the year 2010 (about 6 % of the national population). Nicoya and Liberia are the two largest cities, with the remaining population dispersed in rural areas. The principal sources of income are cattle ranching and agriculture (with sugar cane and cotton being the major crops), with tourism developing during the past 10 years, especially along the 1,022 km (635 miles) of coastline. This change has reduced the poverty index in the province from 52 % in 1991 to 26 % in 2008.

As mentioned in the previous chapter, the Costa Rican Social Security Institute (CCSS) is the primary health services provider in Costa Rica, with almost universal coverage. It offers a broad package of good quality interventions and medicines, all of them free at point of service. The Ministry of Health is responsible for stewardship and public health activities, including community health and health promotion, especially in rural areas.

Guanacaste has always had one of the highest cervical cancer rates in Costa Rica, and in Latin America, averaging 33 cases per 100,000, age-standardized rate to the world population between 1982 and 1992, which is four to five times greater than the United States average (Herrero et al. 1997). This explains the interest of both the Costa Rican government and scientists, in studying this health problem in this population. Guanacaste, even with its low population density, has good health infrastructure: two regional hospitals, 11 health centers of medium complexity, and almost 100 health posts. All health posts have a health promoter who makes frequent health promotion visits to homes located in the service area, and all the facilities have electricity, a consulting office, and a waiting room. Herrero et al. (1997) reported that these centers were used only sporadically, and were ideal for epidemiological studies.

9.3 Epidemiological Studies on the Natural History of Cervical Cancer

A cohort study was begun in 1993 to (1) determine the role of HPV and other factors in the development and evolution of cervical cancer in residents of Guanacaste province; and (2) to study different laboratory techniques for the diagnosis of cervical lesions. Following the first survey and data analysis, follow-up studies of some of the women in the cohort were added, and a study of the effectiveness of a vaccine against HPV was announced.

The studies (N01CP-21081; N01CP-31061; N01CP 40542; N01CP 50535; N01CP 81023; NCT00342173) were conducted by a private company, the Epidemiology Project of Guanacaste (PEG) which in August 2010 had 120 employees, and were sponsored by the National Cancer Institute of the United States (NCI). The NCI

contracted the financial administration of the project to the Costa Rican Foundation for Teaching in the Health Sciences (FUCODOCSA), a private company, and also had collaboration agreements with the Ministry of Health (MS) for the use of the health infrastructure and with the Pan American Health Organization (PAHO) to facilitate tax-exempt importation of equipment and supplies (Herrero et al. 1997). Utilization of the CCSS infrastructure resulted from an agreement signed by the Executive President of CCSS and FUCODOCSA, which was never officially recognized by the Board of Directors of CCSS, and which expired in 1997. The reason why the agreement was never recognized by the CCSS is not known, but it is possible that it was due to a conflict of interest as the President of FUCODOCSA was, at the same time, director of the Center for Strategic Development and Information on Health and Social Security (CENDEISSS), a department of the CCSS.[1]

The central office of PEG was in San José, the capital of Costa Rica, and a field office was opened in each of the regional hospitals of Guanacaste (in Liberia and Nicoya). All vehicles and offices used during the studies carried the CCSS logo, and the study also utilized the CCSS radio (Herrero et al. 1997).

Between February and March, 1993, 95 health promoters from the Ministry of Health were trained to identify women over 17 years of age residing in a randomly selected geographic area where they expected to recruit 10,000 women. All the eligible women were invited to participate by means of a personalized letter, which included an appointment at the nearest clinic. If the appointment was not kept, home visits were made – sometimes by the health promoters of the Ministry of Health – to answer questions and offer transportation to the clinics. The study also included 28 residents of Guanacaste who, between June, 1993 and November, 1994, were being treated for cervical cancer at other hospitals. By December 1994, 10,049 women had been recruited (93.6 % of all eligible women) (Herrero et al. 1997).

During the first visit, women answered a questionnaire and gave a 15 ml. blood sample. Sexually active women received a pelvic examination, a cervigram,[2] and a test of the cells of the uterine cervix. Depending on the results, some women were referred for colposcopy in one of the two regional hospitals, together with randomly selected 2 % of the study participants. On referral, they answered a more extensive questionnaire, had additional blood and cervical cell tests, and biopsies when indicated. All the biological samples and the cervigrams were subsequently evaluated in various laboratories in the United States, and women diagnosed with serious lesions or with cancer received treatment through the CCSS.

Women who did not need cancer treatment were included in the cohort study, divided into groups by risk for developing cancer. Women at the greatest risk for developing cancer had follow-up appointments every six months (n = 492). Women with lower risk factors received annual follow-ups (n = 2,574), and the remainder (n = 6,034) had a passive follow-up, every five to seven years, with instructions to keep appointments for routine examinations at the CCSS. Each follow-up visit

[1] According to information presented in the Asamblea Legislativa de la República de Costa Rica (2005) he was also the principal investigator for PEG.

[2] Photographic images of the cervix

included a repetition of tests performed at the first visit, and a questionnaire on behavioral changes. All women with possibly serious lesions were referred for colposcopy and medical treatment, and were withdrawn from the study. After seven years, all the women remaining in the study were re-evaluated, but 14.9 % of women in the passive follow-up group could not be located (Bratti et al. 2004).

This is the largest cohort study worldwide for HPV and cervical cancer, and had good quality control. The richness of information gained from this study has resulted in many scientific publications and has maintained interest in studying this population. Between 2001 and 2003, other studies took place with many women from the cohort, to (1) determine HPV genetic factors associated with grade three intra-epithelial neoplasms and cervical cancer; (2) provide follow-up to women with high grade cytological lesions or cervical cancer; (3) observe differences in fluctuations in immunological markers during the menstrual cycles between women using or not using contraceptives; (4) study the indicators of HPV infection in women between the ages of 45 and 70 years; and (5) analyze the immunological indicators of the natural history of infection with cancer-causing HPV (Proyecto Guanacaste n.d.).

This knowledge has been of crucial importance in the development of vaccines to prevent cervical cancer. It has also, however, given rise to major controversy in the country.

9.4 Questions Related to the PEG Company, the Dismissal of FUCODOCSA, and the Change to FUNIN

Although the year the project began is officially considered to be 1993, 1991 dated documents requesting CCSS guidance on appropriate techniques for the transportation of biological specimens indicate that some project activities had already commenced.[3] For its part, the CCSS Ethics Committee never approved the project, although one publication (Herrero et al. 2000) stated that the project had been approved in Costa Rica by an institutional ethics committee. Other publications (Herrero et al. 1997; Bratti et al. 2004) do not include statements of approval by an ethics committee.[4]

PEG projects were not alone in being questioned. At the end of the 1990s there were many complaints about irregularities in the conduct of clinical trials in sessions of the Legislative Assembly. On October 11, 1999, the Board of Directors of the CCSS admitted irregularities, and asked for an investigation by the Internal Audit department. Eight months later, the audit report agreed with the complaints made to the Legislative Assembly and the Board of Directors.

[3] Personal communication, José Miguel Esquivel Chinchilla.

[4] Legislation in effect at that time in Costa Rica, Executive Order of December, 1975, required that a participant must consent to participate in research and that an Institutional Scientific Committee must be established to evaluate the ethical and scientific aspects of the study.

Referring to PEG, the Internal Audit of the CCSS (Auditoria Interna de la CCSS 2000) and other studies raised the following issues:

- Utilization of infrastructure, vehicles, equipment, supplies, and personnel from the public health services network without the knowledge of the CCSS, without compensating the public sector and leading study participants to identify the project as a governmental initiative, a factor that could have influenced their decision to participate
- Non-compliance with the CCSS regulations. The unofficial agreement between the Executive Director of CCSS and FUCODOCSA for the PEG project expired in 1997, yet the project continued. The CCSS never approved the implementation of the project, which was not evaluated by its Ethics Committee. CCSS was not able to review the informed consent form
- Contracts for the study to take place in CCSS facilities were established through intermediaries, in this case FUCODOCSA, which benefitted economically, although many personnel were CCSS employees and received a salary from CCSS for serving this population. FUCODOCSA received 15 % of the contracts they administered, which amounted to 1 million dollars during the first five years of the PEG project (Asamblea Legislativa de la República de Costa Rica Legislative Assembly 2001:60[5])
- Contracts and agreements including the use of public resources by private companies were in violation of Article 11 of the Political Constitution and Article 11 of the General Law of Public Administration. This was confirmed during a meeting in 1997 (León González and Vargas Navarro 2006:108)
- Possible violation of Law 6577, which prohibits the use of CCSS facilities and equipment for private medical practice such as the use of hospitals and clinics for clinical trials (León González and Vargas Navarro 2006:109)
- Accusations that the Medical Directors of CCSS and CENDEISSS did not comply with the policies of the CCSS Board, and had acted outside the law

In addition, the CCSS audit (Auditoría Interna de la CCSS 2000) confirmed that the existing regulations in Costa Rica were not sufficient to protect study participants because, according to existing laws, the sponsors and clinical researchers were not punishable. As mentioned in Chap. 8, new bills have been proposed, but up to this date (November 2013) none has been approved. This may explain the behavior of those involved in carrying out clinical trials, including those responsible for their oversight (León González and Vargas Navarro 2006:273; Castro Fernández 2002).

The majority report of the Legislative Assembly (Asamblea Legislativa de la República de Costa Rica 2001) arrived at similar conclusions[6] and using various

[5] This Majority Report was prepared by two members of the Partido de Liberación Nacional and one of Partido de Integración Nacional

[6] Criticized that most of the clinical study was designed by external investigators and implemented through private companies acting outside the rules of the CCSS and international standards (Asamblea Legislativa de la República de Costa Rica 2001:58–59)

reports of the CCSS Internal Audit (AO-360-95; AHC-300-R-98; AHC-125-R-2000) exposed conflicts of interest and administrative actions which left study participants unprotected. These reports involved high executives at CCSS, including the Board of Directors (see Box 9.3). The reports indicated that the greatest contribution to the weakness of the system was complicity between the Executive President and the Medical Director of CCSS, CENDEISSS, and the physicians who have dual employment, that is, they work for CCSS while at the same time own companies that facilitate the implementation of clinical trials in the country. For example, the Medical Directors of CCSS and of CENDEISSS participated in writing the Ministry of Health Decree of 1998, which contradicted the standards of CCSS, authorized clinical trials that did not comply with CCSS standards, and eliminated the systems of control and follow-up of clinical trials. At the same time, the Medical Director dissolved the CCSS Bioethics Committee, which had functioned adequately, and replaced it with another consisting of participant recruiters, the assistant director of CENDEISSS (who was the Principal Investigator in clinical trials carried out in the CCSS hospital San Juan de Dios), clinical trial researchers, and the manager of FUCODOCSA. The majority report recommended an investigation on experimentation with human subjects and the immediate re-instatement of the CCSS Ethics Committee.

Box 9.3: Conflicts of Interest

The relationship of FUCODOCSA – CCSS

On March 26, 1992, the President of CCSS signed an agreement with the owner of a company for clinical research, (ICIC.SA) to conduct studies involving human subjects in the CCSS facilities for 10 years. During negotiations, CCSS was represented by the Director of CENDEISSS, who was also President of FUCODOCSA and supervisor of the owner of ICIC, who was also working at CCSS. The agreement was signed without being reviewed by the Legal Office of CCSS, and was approved by the CCSS Board of Directors eight days later. This agreement was never monitored nor controlled by the CCSS (Legislative Assembly. Majority's report 2001:60; Bloque Patriótico Parlamentario 2004).

In January, 1993, the President of CCSS signed a five-year agreement with FUCODOCSA to carry out the PEG program. The principal participants were the same as in the 1992 agreement, and the President of FUCODOCSA continued as Director of CENDEISSS. This agreement expired in January, 1997, and was not renewed.

The relationship of CCSS – CENDEISSS

There was a conflict of interest between the Medical Directors of CCSS and CENDEISSS. In 1998, the Medical Director of CCSS nominated the Director and Assistant Director of CENDEISSS, who, without legal support, decided

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Box 9.3: (continued)

not to apply the standards of CCSS. The Assistant Director of CENDEISSS conducted clinical trials at the CCSS hospital San Juan de Dios (Legislative Assembly. Majority's report 2001).

The relationship between the Ministry of Health – INCIENSA, and FUNIN
The project was presented to the public as if FUNIN would strengthen the programs of INCIENSA, even though INCIENSA's mandate does not include the implementation of pharmaceutical research. FUNIN's employees were working for INCIENSA. INCIENSA did not receive financial compensation.

The relationship between CEC-INCIENSA-FUNIN
In May, 2004, the Coordinator of the Ethics Committee of INCIENSA, approved the research protocol for the study carried out by the PEG company in Guanacaste. Before accepting the Coordinator position, she had been employed by FUNIN.

Other conflicts of interest
In January, 2004, Dr. Olga Arguedas joined PEG, but left in August, 2004 to become the Director of CENDEISSS (without competition). Dr. Olga Arguedas was a member of the Ethics Committee of the Children's Hospital, where the Minister of Health during the two most recent governments (2006–2010, and 2010–2011) –did much of her research (Mora Ramírez 2006a). (see also Chap. 8)

Private companies conducting clinical trials often hired former or current CCSS employees.

These conflicts of interest, in addition to enriching the private sector at the expense of the public, left the study participants unprotected, and increased the difficulty of obtaining information. Not even the Internal Audit Department of the CCSS could gain access to the informed consent procedures of many projects (León González and Vargas Navarro 2006), and the PEG company systematically refused to provide information to the Internal Audit Department and the Board of Directors of the CCSS (Asamblea Legislativa de la República de Costa Rica 2001:61).

The Comptroller General of the Republic also conducted fiscal studies and repeatedly called to the attention of the CCSS executives their neglect in resolving the problems shown in the 2000 CCSS audit and their slowness in implementing the recommendations called for in the CCSS audit, in other reports written by the Legislative Assembly, by the CCSS Board of Directors, and by the Comptroller's office (Masís Figueroa 2003).

The CCSS audit (Auditoría Interna de la CCSS 2001) recommended that the contract with FUCODOCSA to test the efficacy of the HPV 16/18 vaccine not be renewed until: (1) all the problems identified in various audits and reports were

corrected; (2) mechanisms were established to protect study participants; (3) CCSS executives with conflicts of interest were not permitted to have input into the project, and (4) it was determined if an agreement for vaccine studies could be made directly with the NCI, USA.

In January, 2004, the Principal Investigator of the PEG company wanted a contract between FUCODOCSA and the medical administration of CCSS to conduct colposcopy studies on CCSS patients in PEG clinics, stating that CCSS did not have sufficient equipment available. The auditing department analyzed the contract and recommended that it not be signed, among other reasons, because (Asamblea Legislativa de la República de Costa Rica 2005:15–18[7]):

> . . . once more, an attempt is made to involve the institution in research with human subjects without clearly establishing and properly defining responsibilities in the relationship, which eventually could have legal implications because it would support an activity sponsored by a private company

As a result, FUCODOCSA resigned from its association with PEG.

The Minister of Health, Dr. María Rocío Sáenz, tried to rescue the project and proposed to the NCI that the INCIENSA Foundation (FUNIN)[8] be contracted (Asamblea Legislativa de la República de Costa Rica 2005:26–27) arguing that:

> . . . [FUNIN is] linked to the health sector because it operates in support of the Costa Rican Institute of Research and Education on Nutrition and Health (INCIENSA), an organization attached to the Ministry of Health, and could take over the financial administration of the project

She added that the Ethics Committee of INCIENSA had approved the protocol, was committed to the project, and had signed a letter of intent with NCI. On April 30, 2004, the recently created FUNIN assumed all the rights and obligations associated with the clinical trial of the safety and effectiveness of the GSK vaccine HPV 16/18 (see Box 9.3.)

9.5 The Second Part of the Project: Safety and Efficacy of the HPV 16/18 Vaccine

The Phase III clinical trial to test the safety and efficacy of the HPV 16/18 vaccine was a double blind, randomized study to be conducted over eight years (NCI-04-C-N191, NCI-590299/009, GSK-590299/009, NCT00128661). It was funded by the NCI, which contracted with FUNIN to act as intermediary. PEG, which now had its own facilities, continued to be responsible for carrying out the study, and, although

[7] This Unamimous Report was prepared by members of the following political parties: Partido de Liberación Nacional, Bloque Patriótico, Partido Unidad Social Cristiana, Partido Patria Primero and Partido Movimiento Libertario

[8] Communication DM-1759-04, Dr. Sharon Miller, contracts officer for NCI research contracts. Cited in Asamblea Legislativa de la República de Costa Rica (2005)

there was resistance from CCSS, patients found in need of medical treatment were referred to CCSS clinics. GSK provided the experimental vaccine. From 24,467 healthy women between 18 and 25 years of age, a total sample of 7,466 was selected to participate in the study. Of this number, 3,727 received the HPV vaccine, and 3,739 received the vaccine for Hepatitis A. Study participants had to agree to use any method of contraception (including withdrawal or abstinence) beginning one month before receiving the vaccine until two months after the third dose; they could not be breast-feeding, and they had to be at least three months post-partum. Study details and procedures the women would undergo were included in a table at the end of the informed consent.

The project was valued at almost US $20 million, and FUNIN probably received about US $3 million for its administration. Implementation of this study had the ethical-administrative problems discussed below (see Box 9.4).

Box 9.4: Organization and Ethical Problems of the Clinical Trial of the HPV 16/18 Vaccine (NCI-04-C-N191, NCI-590299/009, GSK-590299/009, NCT00128661)

Study responsibility: Epidemiological Project of Guanacaste (PEG)

Contract between NCI – FUNIN (INCIENSA Foundation). Signed April 30, 2004.

Approved by the ethical committees of INCIENSA, the University of Costa Rica, and CONIS.

Use of the same public resources used during the study of the natural history of cervical cancer (including physical infrastructure, vehicle, radio system and personnel). PEG clinics were also used.

The Ministry of Health promised to obtain the assistance and approval of CCSS, but never did.

Administrative and ethical problems

In 2005, a Legislative Commission censured the Minister of Health at that time, Dr. María del Rocío Sáenz, for ethical, legal, and administrative problems with projects that she directed (Mora Ramírez 2006b).

CONIS reprimanded the INCIENSA ethics committee for approving a project which did not meet existing standards.

Recruitment of study subjects began before receiving the approval from CONIS and the ethics committee of the University of Costa Rica.

CCSS wanted to separate from PEG, but was not able to. Its name was included in the informed consent material.

The contract between the NCI and FUNIN stated that explicit support and approval had to be obtained from the Ministry of Health and from the CCSS, as well as from all the ethics committees, for the expected eight years of the duration of the study. CCSS never reviewed nor authorized the project.

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Box 9.4: (continued)

The sponsor did not cover the cost of adverse reactions. The consent form stated that women in any way involved with the study could receive treatment from the Ministry of Health or CCSS if they had any adverse effects.

CCSS infrastructure was used, with the excuse that physicians were involved in the "Mixed Medicine" program.

Employees of a private project had access to CCSS patient files, but no note was made in the clinical history of the CSSS stating that the woman was taking part in a research study.

More than one million biological specimens were sent outside the country without any formal agreement.

According to the NCI – GSK contract, all the intellectual property rights were retained by NCI and GSK, and they were governed by US law.

It was not determined how the study results would benefit Costa Rica and its citizens.

Some participating women did not understand the informed consent material.

9.5.1 Relation with CCSS

The relationship between PEG – FUNIN – CCSS was controversial. CCSS did not want to be part of the trial conducted by PEG, yet the CCSS name continued to appear on project documents. This was questioned by the institutional ethics committee (CECI) and the CCSS auditor, neither of whom had reviewed nor approved the project (Asamblea Legislativa de la República de Costa Rica 2005:18–19).

In December, 2004, in a meeting between three representatives from PEG, the President of the CECI, the Director of CENDEISSS, and the Executive President of CCSS, it was decided not to remove the name of CCSS from the informed consent, and to maintain the message that if the women in the study had any medical problem they should seek treatment through the CCSS. A note was added clarifying that the CCSS was not part of the research team for the clinical trial. This indicates that the CCSS executives ignored the concerns expressed by the CCSS compliance offices (Asamblea Legislativa de la República de Costa Rica 2005:19).

In January and February 2005, the Comptroller General of the Republic and the Executive President of CCSS, reversing the December, 2004 position, said that the CCSS name should not appear anywhere, because CCSS had not agreed to be a part of the clinical trial, and that to continue to include the name or services of the CCSS in the official documents of a private project could result in a legal summons (Asamblea Legislativa de la República de Costa Rica 2005:20). The final version of the informed consent included a phrase stating that the CCSS was not part of the research team, which could give the impression that it was involved in other activities. The PEG non-compliance with the requirements of the Comptroller and CCSS has not had any consequences.

The CCSS position was a problem both for the Ministry of Health and for FUNIN. A year earlier, on December 12, 2003, while negotiations on how to

administer the project were ongoing, the Minister of Health signed a letter of intent with NCI confirming that the work of PEG was of interest to the Ministry of Health and of importance to the people of Costa Rica, and agreeing to facilitate the authorization of CCSS to implement the clinical trial of the vaccine and give access to health records (Asamblea Legislativa de la República de Costa Rica 2005:2). FUNIN, upon accepting the contract with the NCI, agreed to obtain the support and explicit approval of the CCSS and the Ministry of Health for the duration of the project[9] (Asamblea Legislativa de la República de Costa Rica 2005:21).

FUNIN, without obtaining institutional support, decided to enroll seven PEG physicians in the "mixed medicine" program[10] so that they could refer patients to the clinics and welfare services of CCSS, even though this program was not set up to include clinical trial participants. Standards for research conducted in CCSS facilities stated that all economic aspects related to clinical research had to be in a contract which included, among other items, 100 % reimbursement of incurred costs (Asamblea Legislativa de la República de Costa Rica 2005:21–22). By using the "mixed medicine" program, FUNIN: (1) improperly used the CCSS "mixed medicine" program because the PEG clinics had been set up to conduct research, not ambulatory care; (2) gave a false understanding that the CCSS was a part of the research project; (3) transferred project costs to the CCSS, which did not receive any financial compensation for the referred patients; (4) violated CCSS standards, and (5) facilitated private sector access to the clinical records of the CCSS,[11] with the additional violation that the participation of the woman in the research project was not recorded in her clinical record. Eventually, this last situation caused administrative action against FUNIN employees (Asamblea Legislativa de la República de Costa Rica 2005:28).

9.5.2 Problems with Approval by the Ethics Committee

Despite all these controversies and conflicts of interest, this research project was approved by three ethics committees – those of INCIENSA (May 30, 2004), the University of Costa Rica (December 1, 2004), and CONIS (November, 2004). Of the three, only CONIS questioned the approval of the clinical trial for not complying with existing standards. In September, 2004, CONIS wrote an official letter to a member of the INCIENSA ethics committee questioning the approval of the clinical trial, which, in CONIS opinion, had been granted with insufficient and

[9] Contract N01-CP-11005, signed on April 27, 2001, by Dr. León de Mezerville Cantillo and Dr. Sharon Miller (NCI), and amended on April 30, 2004, when FUCODOCSA resigned from its association with PEG, and FUNIN became responsible.

[10] The CCSS mixed medicine program (*programa de medicina mixta*) allows physicians in private practice, who enroll in the program, to refer CCSS beneficiaries, seen in their private practice, to CCSS facilities for medications and health services, including diagnostic tests and hospitalization.

[11] This violated Articles 12 and 16 of the General Law of Internal Control, No. 8292 (Asamblea Legislativa de la República de Costa Rica 2005:9).

incomplete information (a lack of insurance policies and copies of contracts, and problems with informed consent). Not receiving an adequate response, CONIS cautioned the ethics committee and the Director of INCIENSA that they should respond to their concerns. Finally, in November 2004, almost five months after the study had begun, and after 1,599 doses of the experimental vaccine had been given, CONIS stated that they had received the insurance policies and approved the project. CONIS approved the project knowing the conflicts of interest between the INCIENSA ethics committee and FUNIN. CONIS knew that the coordinator of the ethics committee had been a member of the Board of Directors of FUNIN until April 21, 2004. Surprisingly, CONIS announced that a letter of resignation from the Board of Directors of FUNIN was sufficient to indicate that there was no conflict of interest (Informe de Conis 2005).[12]

9.5.3 Donation of Materials for Research in Other Countries and Benefits for Costa Rica

The informed consent said that the specimens would be stored in a space sponsored by the United States National Institutes of Health, without specifying how they would be used and in violation of existing regulations. The contract with the NCI[13] stated that the collection of biological specimens had to comply with local standards, and Costa Rica requires the signature of transfer agreements protecting the intellectual property rights of the participants or the national institutions (Asamblea Legislativa de la República de Costa Rica 2005:37). These agreements were not established by the PEG Company, although a very large quantity – more than one million- biological specimens were exported. In contrast, clauses related to intellectual property and patents are highly detailed in the contract between NCI and GSK.

The informed consent did not mention how the results of the study would benefit participating women or the population of Costa Rica, and it was not until the middle of 2005 that this topic received attention.[14] Additionally, such was the interest that the study should take place in Costa Rica that, due to the intervention by CONIS, the PEG Company was exonerated from payment of 0.5 % of the project's total budget to the Ministry of Health (Vargas Carmona 2005).

[12] The delays in the signature of the contract between FUNIN and the University of the Costa Rica explain the delay in project approval by the University's IRB.

[13] N01-CP-11005 cited in (Asamblea Legislativa de la República de Costa Rica 2005)

[14] In contradiction to the principles behind Executive Decree No. 31078-S (Asamblea Legislativa de la República de Costa Rica 2005:39).

9.5.4 *Problems with Informed Consent and the Recruitment Process*

A report from the Board of Directors of the College of Physicians (Páez Montalbán 2005) questioned the imprecision of the informed consent process, demonstrated the presence of contradictions in the text (which could confuse participants and in some cases put them in danger), and warned that the presentation of the information and the various omissions of content could have altered the participants' response. For example, while one part of the document stated that the women had to use contraceptives, another section minimized the importance of pregnancy stating that there was no evidence that the vaccine endangered the pregnant woman or her fetus; the text implied that the vaccine would prevent HPV infection without mentioning that there was a high probability that they already had or had had the virus, and also that the project was of public interest when the greatest beneficiaries were institutions and private companies. Nowhere was it said that one of the study objectives was to monitor the occurrence of adverse events, including the appearance or exacerbation of auto-immune diseases, nor did it mention that the researchers wanted to study the effectiveness of the vaccine in women infected with HPV, and in pregnant women.

Without underestimating the importance of the above mentioned concerns, there were other problems with recruitment and the process of obtaining informed consent. The newspaper *Pregonera* (Town Crier) of Costa Rica published a special report (Vargas Carmona 2005) that included interviews with six women who were "invited" to receive the vaccine, providing insight into the recruitment process and the women's understanding of this clinical trial. In the following paragraphs we reproduce some excerpts of those interviews (our translation).

9.5.4.1 Marianela Alvarado Solano. "It is an Experiment."

Mariana Alvarado Solano lives in the "El Guabo" neighborhood. She is 24 years of age, and before going to work she had to leave her nine year old daughter in school and her three year old toddler in the care of her mother.

> We asked her "what was the first contact you had with the project?" She replied "a young man came with an invitation, and said that I was lucky to be in this project, that I would be like a guinea pig participating in it."
> Interviewer: Why like a guinea pig?
> Marianela: "Because it is a study, it is something experimental"
> Interviewer: This is what they said about the project?
> Mariamela: "Yes, and they gave a pamphlet which explained quite a bit, they told me that it was a blind study and that no-one would know the type of vaccine I would receive."
> This young mother had been vaccinated twice and stated: "I went mostly because my mother told me it was good because they were helping people and giving people physical exams"

9.5.4.2 Johanna Gutiérrez Gutiérrez. "Nobody Told Me Anything."

Johanna Gutiérrez Gutiérrez, is a young 23 years old woman who worked with her mother in a food stall. In addition to her work, she studied Family and Social Education. Johanna said that she did not want to be vaccinated, but a friendly young man came to her house and gave information about the project as well as an appointment. We asked her "*why did you not want the vaccine?*" In her own words:

> because from the beginning nobody explained anything, the pamphlet had some information, but the truth is that I did not feel it was safe, that is, there was too much I didn't know, and this is why I was afraid and when I talked to my friends that had already been vaccinated they said that they did not know what was in the first vaccine

Johanna had doubts, and said that she was not going to be among those vaccinated, questioning the focus of the project:

> just think that they want you to feel so special that they say 'we will pick you up and take you back' and the truth is that no one has seen this before and we want to know - What is the real interest of these people?

9.5.4.3 Alejandra Morales Álvarez. "Something Strange Happened to Me."

Behind the display case in the shop where she worked, we talked to Alejandra Morales Álvarez, the youngest of those interviewed. She had been told:

> that it [the study] was a test that was going to be done on women, emphasizing that it was a virus transferred through. . .well, when you were with a man

She told us that in the clinic she saw films and they asked her questions such as "how many men have you had relations with?", and then they gave her the vaccine. She said that after the vaccine she felt very ill and did not go to work –

> my arm was very red, I felt nauseated, but they (the people in the clinic) told me that this happened; in a few days I pressed my breasts and had a milky discharge, which is still there. I went to the doctor who examined me and I asked her why I had this after the injection and she said that it was too many hormones, but I still have it

Alejandra has had breast complications for 2 months, and assured *Pregonera* that she would not go to the clinic because in her opinion they did not know how to adequately help her.

9.5.4.4 Yanel Contreras Cavaría. "It is too Much."

Yanel is a 22 year old woman who lives in the Santa Cecilia neighborhood. A good part of her time is spent working as a receptionist in a beauty salon. She is on the list

of eligible women, but refused to participate. This resident of Guanacaste does not trust the regulations and the insistence of the project staff that she participates:

> they told me that they would fetch me if I could not go, that I would only have to call. They gave me an appointment, and if I couldn't keep it, they would change it, I could go to the clinic when and as often as I wanted; I live 300 meters (just over 300 yards) from the clinic, and that they would send a big car to pick me up, this is too much

Yanel has not been vaccinated, and took that decision because of the project conditions such as avoiding a pregnancy, as well as hesitation about the safety of the series of examinations to which she would be exposed.

On the other hand, she had several questions. One is that she knows that the CCSS does not participate in PEG; but

> they (the project people) say that CCSS agrees with the project, and they gave me the example of the many doctors who are working with them

9.5.4.5 Querely Araya Morales. "I Decided to Be Vaccinated"

Querely Araya Morales is included in the list of women who have been vaccinated. Born in Santa Cruz, Costa Rica, she is the single mother of a three year old daughter. At 22 years of age, she is employed by a local store. She has received two dosages of the vaccine, and, as with the other women, we asked her about the information she was given prior to agreeing to take part in the PEG study:

> the young woman explained to me that the vaccine had no problems; that more than one thousand women in Liberia had been vaccinated, and that there were two types of vaccine, for "papilloma" and the other, I think, for hepatitis, but they could not tell us which we would receive because it is decided by chance." Following this explanation, I decided to be vaccinated because" it sounded good to me, the young woman said that it was to prevent cancer from HPV and this seemed a good idea

Asked about the effects after receiving the vaccine, she said

> my body was itching and two days after being vaccinated I had a menstrual period which lasted almost 10 days, and my periods are still irregular

At the end of our conversation, Querely stated that she had decided to continue with the remaining vaccinations because for her "everything was fine."

9.5.4.6 Jenny Rodríguez Gómez. "Women Must Be Warned."

At 24 years of age, with two children to care for and her job, Jenny Rodríguez Gómez is dedicated to "warning" the women of Guanacaste through various articles in the *El Sabanero* newspaper. This young woman did not participate in the study because, she said, she really studied the project.

> I read all that they gave me and I had doubts; I talked to some local physicians and they told me that receiving the vaccine or not was my personal decision, but it wasn't recommended because of bad reactions

Having made the decision not to be vaccinated, she wanted to share her point of view with other women by publishing several articles, which, in her words, "have become the foundation of the Congressman's reports." She added:

> "it seems to me that they are offering too many things; that made me suspicious, and I wanted to alert other women. . .because here we are known for being very meek people." Jenny emphasized the importance of being well informed, and "invited women to study this project, not to sign the consent without reading it, to ask for a copy, and that if they had a friend who knew the law, that they talked to that person"

This clinical trial has greatly contributed to the advancement of knowledge on the epidemiology and prevention of cervical cancer, and has also allowed many scientists – including Costa Ricans – to publish articles in prestigious scientific journals. In the words of the President of the University of Costa Rica:

> The University has been enriched by this scientific investigation, becoming an institution in the forefront of this topic worldwide

The studies in Guanacaste continue (see Box 9.1), and it is very probable that they will contribute to scientific knowledge. It is not known if, in the process, ethical-administrative irregularities will also continue, and if the advances in knowledge will benefit the women who participated in the study and the Costa Rican population in general. At present the vaccine is very expensive for national economies such as that of Costa Rica, which prevents the public health sector from offering it to all adolescents.

9.6 Conclusions

Costa Rica has a long tradition of clinical research, and complaints about irregularities in research involving humans date from the mid-1970s. These irregularities have been attributed, at least partly, to the absence of an appropriate legislative framework, but the complicities documented in this article question if a new law will resolve the problem. Public agencies and the judicial system are responsible for ensuring compliance with existing laws and regulations but, as this case study illustrates, individual agendas of powerful researchers and conflicts of interest among senior executives of public institutions (CCSS and the Ministry of Health) can derail all efforts, including those of the Legislative Assembly, to remedy the situation.

The problems described in this chapter are not due to ignorance or lack of information. In this case study, the PEG company, the researchers, the intermediaries (FUCODOCSA, FUNIN), the public institutions (CCSS, Ministry of Health, INCIENSA), the legislators, and the agencies responsible for respecting the rights of research participants (CONIS, CENDEISSS, CEC-INCIENSA) were aware of the irregularities that affected the PEG projects. For example, the same person that as Minister of Health promoted in 2003 and 2004 the activation of the clinical trial

through FUNIN a year earlier (August, 2002) had stated (Asamblea Legislativa de la República de Costa Rica 2005:8):

> Research benefits are not helping the public institutions where the research takes place, the institutions do not benefit either economically or from the results of the studies, although the studies take place in the facilities of these institutions. . . There is no clear separation of duties between those who authorize the studies and those who take part in the research. . . At present, clinical studies are rapidly moving to the private sector. . .

The stories of the women of Guanacaste show that they were of humble origin, were not informed sufficiently about the study, and some had felt coerced by recruiters. We do not know how this influenced the quality of information obtained in the study, for example: were all perceived adverse events shared with the PEG physicians, or, as in the case of Alejandra, did women leave the study without further explanation? Or, as with Querely, they failed to report the effects of the vaccine because they were not thought to be very important? How many of these women experienced other complications that could not be linked to the vaccine, because they received treatment from CCSS without informing the PEG company physicians and without the CCSS physician knowing that the woman was a participant in the study?

Study sponsors are often aware of these problems and conveniently choose to ignore them. For example, the contract with NCI failed to address intellectual property rights issues, did not specify the benefits for the Costa Rican population and did not require the insurance policies for research participants. NCI knew the problems between FUCODOCSA and the CCSS, but had no problem transferring the contract to another private body, FUNIN, without modifying the terms of the contract, as they would have had to do in high-income countries. Moreover, if the NCI and GSK had monitored the implementation of this clinical trial, they would not have been able to overlook the concerns about the project voiced by the CCSS Auditor, the Comptroller General of the Republic, and the Legislative Assembly. The possibility that the NCI and GSK preferred to ignore those problems, many of which had simple solutions, and obtain the data at any cost, marks them as accomplices.

Also of note is that Costa Rica has not required sponsors to pay custom duties for the importation of supplies and equipment, or for the use of facilities, supplies, equipment, and personnel. No one knows the amount of the debt, but if it is not collected and this issue is not addressed in future contracts, Costa Rica will continue to subsidize foreign sponsors and the pharmaceutical industry in exchange for very few benefits. As in this case study, the Costa Rican population pays for some research expenses that are not reimbursed to the CCSS, and the main benefactors from clinical research are the Costa Rican researchers, academics, and intermediary agencies – in this case, FUCODOCSA and FUNIN-, and the pharmaceutical companies.

The problems described in this chapter can only be resolved by the express commitment of study sponsors, who have in their power not only the ability to establish standards of good clinical practice, but also compliance with ethical principles and national and international standards governing research involving humans. Regulatory agencies in high-income countries must also question the quality of information obtained in countries which do not uphold these principles.

At the same time, consumer advocacy groups and organized community representatives should establish and maintain pathways to channel information and complaints related to the conduct of clinical trials.

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