Making Doable Problems within Controversial Science

U.S. and Swedish Scientists’ Experience of Gene Transfer Research

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To my beloved family
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CHAPTER 1
Introduction

‘I think one point that you might want to look into more in your study is “What is it about gene therapy that has made it such a contentious area?” Some of those things involve certainly the actions of the field itself and the investigators in the field who promise too much and talk too much and develop protocols that are not very rigorous and clear, but also the poisonous effect of having expectations so high that you could never fulfill them.’

With these words, Stuart, a U.S. gene transfer scientist, emphasized a very common theme in my interviews regarding gene transfer research – that it is a contentious field of research to work in. Innovative and groundbreaking technologies like gene transfer are often the subjects of ethical discussion (Spink and Geddes 2004). Even though somatic gene transfer has been, in the years of professional discussion, framed as an extension of conventional medical treatments (Juengst and Granqvist 2007) it has met a great deal of adversity and controversy during its development compared to other areas of research (Kimmelman 2008). What is it that makes gene transfer research such a contentious area? More importantly, what consequences, if any, does this have on gene transfer scientists and their work?

This study is about the gene transfer practice, and how gene transfer scientists make their research doable in a technically advanced and highly controversial field of research. It is primarily based on interviews with gene transfer scientists in Sweden and the U.S.A. The central focus of this study is on how gene transfer scientists describe, reason about, and handle their work practice. It focuses on the research process from bench to bedside – from basic science to clinical application on human subjects. Particularly, what do they regard as problems and how do they handle these problems in order to make gene transfer research doable? Consequently, I analyze how gene transfer scientists maneuver in this controversial field of research and especially how they reason about their maneuvering.

I entered this study knowing that gene transfer research is not only regarded as controversial. It is also intensively and extensively debated due to its character, which raises various ethical, social, and legal issues. What I did not know was what these factors implied for the gene transfer practice and how they affected gene transfer scientists in their work.
Gene transfer is different from any other kind of biomedical research. It is science that has never been done. This means working on an ad hoc basis. Consequently, it is a technology that carries uncertainty and risks as well as involves difficulties in anticipating the long-term consequences of an eventual implementation. Furthermore, conducting gene transfer research means facing problems in the scientific practice, but also in the outside world. In many ways, gene transfer is as much about gene transfer scientists and their work as it is about innovative and groundbreaking procedures and technologies.

The Technology of Gene Transfer

Gene therapy (hereafter referred to as gene transfer) is a technology in which genetic sequences or genetically modified organisms are used in order to treat or prevent diseases in humans. Gene transfer has the potential to revolutionize medicine, gene transfer scientist Andrew Mountain (2000:119) claims, as it treats the underlying defect or cause of the disease rather than merely the symptoms. In gene transfer the function of a defective gene can either be corrected or replaced. Gene transfer can also change the disposition of somatic cells and instruct them to adopt new therapeutic properties.

There are two different types of gene transfer interventions that can be performed on humans. The first type is somatic gene transfer in which the somatic cells of a human (any cell in an organism that is not a reproductive cell) are genetically modified. This means that the genetic modification should not have any effect on the germ-line – that is, the lineage of cells resulting in germ-line cells – and thus not on future generations. However, somatic gene transfer has the undesirable side effect of being able to unintentionally affect the germ-line. There has been one case where the germ-line cells have inadvertently been affected in somatic gene transfer. In a clinical gene transfer trial to treat hemophilia, traces of the new genetic material were found in the semen of some of the patients, but not in the sperm cells themselves (Marshall 2001a, Marshall 2001b). This has raised the question of what level of unintentional insertion is tolerable (Coutelle and Rodeck 2002).

The second type is germ-line gene transfer, in which it is the germ-line cells – that is gametes such as egg and sperm cells as well as precursor cells from which gametes are derived – that are genetically modified. Germline gene transfer involves the making of a genetic change that can be transmitted down the generations. This means that the genetic modification is transferred to future generations, and can hence affect descendants.

At present, the use of somatic gene transfer is only acceptable in the treatment of severe fatal diseases and genetic disorders in which there are no other medical

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1 Who at the time also held a senior management position at Cobra Therapeutics, the first gene transfer company in the U.K.
options available, or where all other medical options have been tried without success. Germ-line gene transfer, on the other hand, is forbidden, either through laws or national and federal recommendations.

**Why is Gene Transfer Research Controversial and Morally Debated?**

Gene transfer presents the therapeutic possibility to treat severe fatal diseases as well as genetic disorders for which there are no other medical options. Jayne Spink, geneticist and head of Genetic Science, Safety and Regulation at the U.K. Department of Health and physician Duncan Geddes (2004) argue that this therapeutic possibility is beyond comparison. Due to gene transfer’s ability to manipulate genetic characteristics, it contests some of the most basic dividing lines in our society. More specifically, it contests what is considered as nature and culture, safe and risky, moral and immoral.

In the international bioethical literature the fact that scientists can manipulate the genome and make alterations in human characteristics is described as presenting different social implications which raise concerns. I have found four main arguments in the international bioethical literature for why gene transfer research is regarded as controversial and hence is intensively and extensively morally debated. They are: (1) the modification is intentional, (2) genetic modifications could lead to genetic enhancement, (3) there are associations to eugenics, and (4) there may be unknown and unforeseen risks to human research participants as well as to future generations.

What raises concerns is first the fact that gene transfer can be used to intentionally modify somatic as well as germ-line cells for other purposes than therapeutic ones. Concerns are raised especially regarding intentional modifications of the germ-line, as these modifications will be transferred to descendants and thus to future generations.

Second, genetic modifications could open the door to genetic enhancement in which gene transfer can be used in order to improve performance, extend life, or modify other valued human traits. In some views this may put people who do not fit into an alleged genetic norm in need of therapy or correction as they may be regarded as abnormal. Consequently, this may change the attitude toward the individual, which could also aggravate prejudice against people with disabilities and make society unwilling to accept their difference. This raises a third concern, that of a resurgence of the eugenics movement, which was present during the Nazi regime and

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2 The controversy surrounding gene transfer is to some extent similar to that around genetically modified (GM) food, especially regarding issues concerning risks and potential hazards. However, GM food does not contest the boundaries between nature and culture, moral and immoral, or raise different social concerns, as gene transfer does. Consequently, I will not discuss the GM food controversy.
at the Cold Spring Harbor Laboratory in the U.S.A. as well as at the Institute for Race Biology in Uppsala in Sweden. This ‘new eugenics’ will be more difficult to refute as it is based on more rigorous science compared to the one during, for example, the Nazi regime.

Genetic modifications are thus still associated with eugenics, especially if they concern genetic enhancement. From a historical perspective, visions of gene transfer originate from ideas presented during pre-World War II. At that time, the vision of gene transfer was primarily promoted as a kind of biological engineering in which mankind could be modified. The modification of mankind was regarded as a way to combat the degeneration of the human race (Pauly 1987). This vision of gene transfer can be tied to the history of eugenics, with its program of segregation followed by the compulsory sterilization of individuals considered to be born with substandard and inferior genes (Buchanan et al. 2000). In this vision, gene transfer was to be used in an attempt to counter what was believed to be genetically-based behavioral and social problems, and not to prevent or cure diseases. In other words, gene transfer is a field of research that touches upon basic questions of human existence and human dignity.

Finally, concerns have been raised about social implications in which an implementation of gene transfer may result. Gene transfer also presents technical difficulties and scientific uncertainties, as well as unknown and unforeseen risks to the human research participants enrolled in clinical gene transfer trials. There are concerns about the lack of knowledge regarding how a gene transfer treatment affects not only the individual undergoing treatment, but also future generations. This uncertainty is not so much focused on the nature or purpose of gene transfer as on its possible impact on settled expectations of safety and order. As sociologist Bruno Latour (1998:208) puts it, the understanding of scientific development has moved from a culture of science to a culture of research characterized by uncertainty, controversy, involvement, and values. This means that in order to be able to successfully conduct gene transfer research and move it into clinical reality, scientists must deal with how different uncertainties and risks should be handled as well as evaluated. They must also pay attention to how gene transfer as a novel knowledge should be deployed and employed, and how possible negative side effects should be controlled and delimited. How gene transfer scientists do this will be explored in this study. So, what are the technical difficulties and the scientific uncertainties as well as the unknown and unforeseen risks of gene transfer? This will be outlined in the following section.

Technical Difficulties, Scientific Uncertainties, Unknown and Unforeseen Risks

Gene transfer means, as stated above, that the work is mainly conducted ad hoc, due to its novel character. The research is hence very uncertain. Consequently, there are many different problems that need to be addressed in the scientific practice if
the technology of gene transfer is to be developed, tested, and eventually clinically implemented.

Gene transfer is accompanied by many technical difficulties. It is difficult to develop systems and design vectors, that is, the ‘vehicles’ to which the gene is coupled and which will transport the gene into the cell. In order to be suitable for gene transfer purposes, vectors should be capable of delivering genetic material to the correct cells if they are to attain site-specific integration, stable integration, and long-lasting gene expression, resulting in a high degree of efficiency. This is currently difficult to attain. It is also difficult to create vectors without toxic side effects.

In gene transfer, viruses like retroviruses, lentiviruses and adenoviruses\(^3\) are the most commonly used vectors. These viral vectors can, however, impose two different risks. One is the risk of insertional mutagenesis, in which the gene transfer vector integrates at the wrong site in the genome. This causes changes in the cellular genome, which somehow perturbs the DNA. This could lead to development of leukemia. The risk of insertional mutagenesis is only present in the use of retroviruses and lentiviruses. The other risk is immune response, in which a previous exposure to the adenovirus has resulted in a preexisting immunity towards the virus. This preexisting exposure cases problems with the delivery of the adenoviral vector as it could trigger a strong response from the immune system of the individual undergoing gene transfer treatment. Because of the problems with designing viral vectors and the safety problems that they involve, scientists have begun to design non-viral vector systems, that is, synthetic vectors that are not based on viral systems. Instead they are based on DNA.

The high degree of scientific uncertainty in gene transfer research was revealed in 1999 when 18-year-old Jesse Gelsinger became the first person to die as a direct result of participating in a clinical gene transfer trial. The reason was the use of an adenovirus gene transfer vector to which he unknowingly had a preexisting immunity. Gelsinger participated in a Phase I\(^4\) study for a rare disorder called partial ornithine transcarbamylase (OTC), an X-linked defect of the urea cycle. The defect affects the nitrogen metabolism leading to a spectrum of neurological symptoms including mental retardation and seizures in severe infantile cases and manageable, non-neurologic problems in its milder form (Shreenivas 2000). He suffered from a rather mild form of the disease which was manageable by a combination of drugs

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\(^3\)Retroviruses are RNA viruses that possess a reverse transcriptase which enable them to synthesize a cDNA copy of their genome. Retroviruses can only infect dividing cells. A lentivirus is a modified retrovirus that can infect non-dividing cells. An example of a lentivirus is the HIV virus. Adenoviruses are DNA viruses which are only used for the infection of postmitotic cells. Adenoviruses and especially adeno-associated viruses are common cold viruses. Consequently, almost 90% of the human population has previously been exposed to adeno-associated virus serotype 2 and hence has a preexisting immunity towards this virus.

\(^4\)Phase I studies are initial studies done in order to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increased doses, and to gain early evidence of effectiveness. The main goal with a Phase I study is to determine the safety of the drug.
and diet (Walters 2000). After being injected with the gene transfer vector, developed in order to treat this disease, Gelsinger developed a high fever which caused an acute respiratory distress syndrome. Within four days, many of his organs were failing as they could not be supplied with a sufficient amount of oxygen. Due to this, he died (Hollon 2000). It turned out that Gelsinger, because of his preexisting immunity to the vector used, had a severe immune response. This had not happened to any of the 17 human research participants that preceded Gelsinger in the cohort (Raper et al. 2003).

During the same period as the Jesse Gelsinger case, the first successful attempt to use gene transfer was shown in the treatment of several children with X-linked severe combined immune deficiency (X-SCID), also known as ‘bubble babies’ (Cavazzanna-Calvo et al. 2000). A group of European scientists in Paris, London, and Milan treated 17 out of 18 children with the rare immune disorder X-SCID or adenosine deaminase deficiency (ADA-SCID). In the treatment bone marrow stem cells were removed from the children, genetically altered in the laboratory, and then transferred back. The goal of this procedure was that the genetically altered bone marrow stem cells would multiply into normal immune cells, thus reconstituting their immune system (Cavazzanna-Calvo et al. 2004). In 2002, the field struck a serious setback when two children in the French trial developed T-cell leukemia as a result of the therapeutic intervention. After an investigation it was concluded that the cause of the development of leukemia was that the viral vector used had during the intervention integrated itself near an oncogene, a cancer-promoting gene called LMO2, thus producing an insertional mutagenesis. This led to an overexpression of LMO2, which is believed to be the cause of the development of leukemia (Berns 2004, Hacein-Bey-Albina et al. 2003). The appearance of insertional mutagenesis in the French X-SCID trial raised several safety concerns and as a result similar clinical trials were put on hold. A review of the technology later indicated that the unexpectedly high occurrence of leukemia is likely to be unique to patients with X-SCID due to propensities of the disease (Kohn et al. 2003).

In 2004, one of the children who had developed leukemia died and thus became the second human research participant to die in a clinical gene transfer trial. The following year a third case of leukemia occurred in the French trial, which once again halted several clinical trials (Couzin and Kaiser 2005). Since then, two more children have developed leukemia in the French and the British trials. Altogether, five patients with X-SCID from the two trials have within two to six years after the procedure developed the leukemia-like disease clonal T-cell proliferation caused by insertional mutagenesis. In one patient the outcome was terminal while the leukemia in the other four patients was reversed by chemotherapy (Fisher and Cavazzanna-Calvo 2008, Aiuti and Roncarolo 2009).

In the summer of 2007, another serious setback occurred to the gene transfer field when 36-year-old Johlee Mohr became the third human research participant to
die from participating in a clinical gene transfer trial. Mohr suffered from rheumatoid arthritis and was recruited, by her rheumatologist, into a Phase I/II\(^5\) arthritis study (Kasier 2007) in which a novel arthritis treatment was to be tested for its safety (Weiss 2007). When Mohr was injected for the second time with the gene transfer vector developed to treat the disease, she acquired a severe febrile illness and died three weeks later after massive organ failure (Kaiser 2007, Wilson 2008). It was claimed by the company in charge of the study that only Mohr had suffered serious side effects. The other volunteers in the study had only suffered short-lived side effects (Weiss 2007).

**Gene Transfer – A Contested Technology and Field of Research**

Gene transfer has the potential to improve the human condition. Despite this and for the reasons that I have outlined above it is a contested technology. It is a field of research in which history echoes loudly. It is closely associated to eugenics and raises many public concerns. Media attention has especially been drawn to the possibility of using gene transfer to improve mankind or to design new life forms to create ‘brave new worlds’. Public attention has also been drawn to the concept of biomedicalization, in which social problems previously outside of the medical jurisdiction have been transformed into medical problems (Clarke et al. 2003). However, it is not only the use of gene transfer that is contested and evokes concern. The materials and technologies used in gene transfer are also contested. In gene transfer the materials used are living organisms, mainly viruses, that are manipulated in different ways. Occasionally, the manipulated materials do not work or behave as presumed when transferred into human research participants. This means that gene transfer has a high degree of task uncertainty and thus also unknown risks and consequences for human research participants. It is research that is intrinsically uncertain and exceptional. Gene transfer is not what Latour (1987) calls a *black box*, a standardized technology.

Gene transfer, like genetically modified food, genetic testing, nuclear power, and other biomedical technologies such as fetal surgery and stem cells, are contested technologies trapped in historical controversies. They are also technologies that have evoked much public interest. In the public media, these technologies have been covered as both having enormous potential benefits for humans and also raising possible ethical, social, and legal concerns. According to Spink and Geddes (2004), gene transfer is commonly regarded internationally as an experimental treatment subject to the same legislation as conventional drugs. The controversial and contested character of gene transfer is, however, perceived differently in different parts of the world. Consequently, gene transfer research is regulated, monitored,

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\(^5\) Phase II studies are controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study. Further, the goal is to determine the common short-term side effects and risks.
and evaluated quite differently depending on country. In this study I will analyze two different regulatory frameworks. This means that I will analyze the policies that regulate gene transfer research and the regulatory structure in which applications for clinical gene transfer trials are evaluated. I am interested in whether working within different regulatory frameworks results in different consequences for scientists and for regulators. Specifically what, if any, problems does the regulatory framework place on their work? As will be shown in this study, this means that the situation in which clinical trials are conducted varies around the world.

**Aims of this Study and Delimitations**

The purpose of this study is to investigate how research is made doable in a controversial field of research. My general research question is: How do gene transfer scientists reason about how they make their work doable? In other words, how do gene transfer scientists gather the necessary elements and articulate different activities in order to do their work? What do gene transfer scientists regard as problems and important uncertainties?

More specifically, I deal with the following questions:

- How do they handle problems like getting funding, dealing with scientific uncertainties with living materials and technological difficulties, responding to various regulatory frameworks and public concerns, and accusations of working in the shadow of eugenics?
- What effects do different ways of regulating and monitoring clinical gene transfer research have on gene transfer practices?

Part of this study also takes up different points of view on ethics. More specifically, it deals with how gene transfer scientists feel morally about their work. The specific research question that addresses this issue is:

- What are the ethical complications that gene transfer scientists experience in their work, and how do they handle these complications?

This study also deals with how gene transfer scientists handle public concerns and relate to the outside world. My question here is:

- What arguments are used by gene transfer scientists to ensure that their work with gene transfer will get a legitimate public image?

I am interested in how the situation in which this practice is situated shapes the practice and the gene transfer scientists who work in it and especially in how these
actors describe and handle this influence. Hence I have conducted interviews with
gene transfer scientists.

The study is primarily based on interview data from ten scientists from two
countries, but I have also used documents such as published research reports, regu-
latory documents, and scientific articles as well as other secondary sources. Because
of my purpose it was not sufficient to use either questionnaires or observations in
the laboratories. To be able to conduct participatory observations would require
access to laboratories and other sites of importance. In a controversial field of re-
search like gene transfer this could be difficult to achieve. I also wanted to interview
actors from different disciplines in two countries and hence study actors from con-
trasting situations. Consequently, participatory observations were not an option due
to time limits.

The interviews have been conducted in two different countries, Sweden and the
U.S.A. As discussed below, not only does the extent of gene transfer research differs
between the chosen countries, but the regulatory framework also differs. Because of
the regulatory framework's importance I also conducted interviews with members
of regulatory agencies and advisory boards in Sweden and the U.S.A., with a focus
on what they described as problems or challenges when implementing the guid-
lines.

The Chosen Countries

By choosing two countries with completely different attitudes and approaches to-
wards gene transfer research, I aim to capture a greater diversity of the dynamics
and complexity within this field of research.

I chose to conduct my interviews in Sweden and the U.S.A. because they offer
very contrasting situations. This choice was primarily based on two elements: the
extent of gene transfer research in the country and the regulatory framework with its
regulation and regulatory structure.

The U.S.A. leads the world in gene transfer research and accounts for two-
thirds of all the conducted clinical gene transfer trials, or more exactly 63.9% in
2011 (Edelstein 2011). Gene transfer scientists form a widespread scientific com-
munity established all over the U.S.A. Consequently, this country has several re-
search centers and institutes at the cutting edge of gene transfer research, including
vector development, preclinical studies in animal models, and clinical trials on hu-
man subjects. According to ClinicalTrials.gov⁶, which is a database provided by the
National Institutes of Health (NIH), there were, as of July 2011, 1690 clinical gene
transfer trials performed in the U.S.A. Of these, 789 clinical trials were open studies
while the other 901 were closed studies, meaning that they were terminated, com-

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⁶ When I performed the search in this database I used the search term ‘gene therapy’ and the loca-
tion as either the U.S.A. or Sweden.
pleted, or active but not recruiting human subjects. Of these trials, 521 were Phase I, 642 were Phase II, 130 were Phase III\(^7\), and finally 62 trials were in Phase IV\(^8\) (ClinicalTrials.gov 2011).

Sweden, on the other hand, has a small scientific community of gene transfer research with few research centers and gene transfer scientists. In fact, there are only five gene transfer centers or universities that work in the field of gene transfer research, including vector development, preclinical studies in animal models, or clinical trials on human subjects. Regarding conducted clinical gene transfer trials worldwide, Sweden accounts for only 0.5% in 2011 (Edelstein 2011). A search in the ClinicalTrials.gov database showed that there were, as of July 2011, 36 clinical gene transfer trials performed in Sweden. Seventeen of these studies were open studies while 19 studies were closed studies. Six of these trials were Phase I, 15 were Phase II, 13 were Phase III, and finally two were Phase IV (ClinicalTrials.gov 2011).

It is not only the extent of conducted gene transfer research that differs between the two countries. The regulatory framework, that is, the policies that regulate gene transfer research and the regulatory structure\(^9\) in which applications for clinical gene transfer trials are evaluated, also differs. These differences will shortly be presented here (for an extended description of the two regulatory frameworks and their differences, see Chapter 5). While the U.S.A. regards gene transfer as presenting significantly different ethical challenges to those in other medical contexts and therefore requires more oversight, Sweden regulates gene transfer no differently than other experimental innovative therapies. Consequently, applications for clinical gene transfer trials only undergo review at the regional ethical review board level in Sweden. In the U.S.A., say gene transfer scientists Kenneth Cornetta and Franklin Smith (2002) and regulatory scientist William Lee (2006), clinical gene transfer trials are one of the most regulatory scrutinized and extensively regulated research areas. As a result, applications for clinical gene transfer trials typically undergo review by at least four different bodies on local and national levels. From the aims of this study, these differences are interesting to take into account.

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\(^7\) Phase III studies are controlled clinical studies conducted to confirm the effectiveness of the drug or treatment, to monitor side effects, and to compare it to commonly used treatments. Furthermore, the goal is to collect information that will allow the drug or the treatment to be used safely.

\(^8\) Phase IV studies are done after a drug has been shown to work and it has been granted a license. They are post-marketing studies to delineate additional information including the drug’s risks, benefits, and optimal use.

\(^9\) By regulatory structure I mean regulatory agencies such as the Swedish regional ethical review boards, the Swedish Medical Products Agency, the U.S. Food and Drug Administration, the U.S. IRBs and IBCs, and advisory boards such as the Swedish Gene Technology Advisory Board and the American Recombinant DNA Advisory Committee.
Relevance and Contribution of this Study in Relation to Previous Studies

As noted earlier, this study is not about the ethics or the regulation of gene transfer. Nor is it about lay understanding of gene transfer. Rather it is about scientific work and how this work is made doable in a technically advanced and highly controversial field of research. More specifically, it is about how scientists perceive the situation in which gene transfer research is situated, and how it affects research and the actors who work with it. I am interested in how gene transfer scientists describe, reason about, and handle the situation in which gene transfer research is situated. This is the first area of relevance for this study as it approaches gene transfer research from a different perspective, the scientists’ views, compared to the earlier studies of gene transfer research which are to be described below. I will show that gene transfer research is about so much more than ethics, social concerns, legal issues, and regulations. It is about people and their work and how gene transfer scientists make do with whatever is at hand. In this context it is important to analyze the specific situation in which gene transfer research is situated.

The second area of relevance for this study is the interdisciplinary field of Science and Technology Studies (STS). This field studies how technology is shaped by society, politics, and culture as well as how technology, in turn, shapes society, politics, and culture. This means that science and technology are regarded as social activities – active processes situated in and shaped by cultural contexts. STS researchers explore, for example, the ways in which scientists try to construct durable structures and networks in their attempt to construct scientific knowledge. This is essential in the process of formulating and/or reformulating a research question or a project that is ‘doable’; this is also a central focus for my study (Sismondo 2010, Clarke and Fujimura 1992, Fujimura 1987, 1988, 1997, Latour 1987, 1999).

However there are few, if any, previous studies of gene transfer research with an STS perspective. I will therefore give only a short overview of the field of social science studies of gene transfer, before moving to two other areas of relevance within STS: studies of scientific, medical and ethical controversies, and studies of scientists’ work and of how scientific knowledge is produced.

Studies of Gene Transfer


Several empirical studies have also been conducted about gene transfer and clinical gene transfer trials. These studies have explored lay understanding of gene transfer (Horst 2007, Scully et al. 2004, Stockdale 1999, Blair et al. 1998), why
people enroll in early phase clinical gene transfer trials (Kim et al. 2006), and the ethics of gene transfer research (Henderson et al. 2006, Kimmelman and Palmour 2005). These studies primarily discuss research ethics in, especially, medical experiments on human subjects.

My study differs from previous empirical studies of gene transfer regarding focus. The focus in previous studies has been on the understanding and experience of gene transfer and its research from a lay, patient, or medical practitioner’s perspective. In my study the focus is instead on gene transfer scientists, that is, actors who have not been particularly visible in earlier studies of gene transfer research, and their views on gene transfer. Previous studies, however, provide this study with an interesting contrast. Are the ethical complications described by gene transfer scientists the same ethical issues or dilemmas as described by lay people, patients, medical practitioners, or bioethical experts?

Studies of Scientific, Medical and Ethical Controversies

Innovative and groundbreaking technologies often spark controversies. These controversies can be between different scientists, between scientists and the public, or between various lay persons. Gene transfer is in particular a controversy between scientists and the public. It is an open controversy, which means that it has yet to end. It is especially ethical, social, and legal issues that raise public concerns over the implications of gene transfer. Specifically, concerns are raised by the fear of adverse consequence, the threat to individual rights, the potential of misusing scientific findings, and the breaching of social and/or moral values. In order to understand the situation in which gene transfer is situated, and under what conditions gene transfer scientists try to make their work doable, I must take into consideration its surrounding controversies.

Several studies in STS investigate controversies surrounding innovative and groundbreaking technologies, especially between scientists and the public. These are of particular interest for this study as they provide me with an understanding of how controversies work in practice. They have also revealed the ethical dilemmas involved in making a decision where conflicting values are at stake.

How scientists in a controversial field of research describe their work is the interest of anthropologist Hugh Gusterson. In Nuclear Rites (1996), he investigates a nuclear weapons laboratory in the U.S.A. by conducting interviews with people who work there. The question that interests Gusterson is what it is that makes people become weapon scientists. More specifically, what do members of a nuclear weapons laboratory regard as important in their work, and what are their own views on what they do and why? Gusterson’s interests further lies in how nuclear weapons scientists feel about their work morally, how they create meaning and relate to the outside world.

Another study with a focus on controversial scientific work practices within biomedicine is sociologist Monica Casper’s The Making of the Unborn Patient (1998).
She studies the emergence of a new medical specialty called fetal surgery, using multisite ethnography in three countries. Casper investigates the complex hybrid, as well as interdisciplinary, nature of fetal surgery and how this medical specialty has moved from the laboratory to the operating room and hence to clinical trials on fetuses. She concentrates on the different social and ethical dilemmas involved in experimental studies on human subjects. She also analyzes the interactions between scientists, in the form of the fetal surgery team, and the Institutional Review Board whose duty is to protect human subjects. Casper also turns her attention to how the human subjects approval process has shaped and delimited the implementation of fetal surgery in clinical practice.

The two studies above are closely connected to mine both in data and interest, as they focus on how scientists located in controversial areas describe their work. More importantly, they have made me realize that people who work with controversial technologies do not necessarily see their work as morally wrong or problematic. Instead, these people may see themselves as contributing to ‘the good’. Consequently, the meaning context is important.

Other studies of scientific, medical and ethical controversies of relevance, although not focusing on how scientists describe their work, include theory of science researchers Fredrik Bragesjö and Margareta Hallberg’s study of the MMR controversy in I Forskningens närhet [Close to research, my translation] (2009). The authors investigate the aftermath of the publication of a study conducted by a British research group led by Andrew Wakefield in the Lancet in 1998. In this article claims were made of a possible link between the MMR vaccine, the vaccine for measles, mumps, and rubella, and juvenile autism. This led to a decline in vaccinations. The recombinant DNA controversy is of interest to philosopher Sheldon Krimsky. In Regulating Recombinant DNA Research and Its Applications (1992), he investigates how the risks, potential hazards, and consequences of genetic research created an intense debate regarding scientific autonomy, in which the public came to play an important active part. In these two studies the controversy is embedded in historical, political, scientific, and moral standpoints, in which the public is a key actor. This is also the case in gene transfer. Furthermore, their analysis of the public impact on a scientific practice regarding issues like funding, autonomy, and regulation is of relevance to understanding how gene transfer scientists reason in the interviews.

Controversies surrounding genetic modification have primarily been studied in relation to genetically modified food. For example sociologist Mikael Klintman (2002) focuses on the labeling controversy of genetically modified food products in The Genetically Modified (GM) Food Labelling Controversy: Ideological and Epistemic Crossover. He examines the conflicting arguments among policy-makers, social coalitions, and corporations primarily in the U.S.A., but with some European comparisons. In her doctoral thesis From Persona to Person: The Unfolding of an (Un)Scientific Controversy, theory of science researcher Lena Eriksson (2004) investigates the controversy regarding genetically modified food, especially the Pusztai affair. These studies also
bear relevance to my study, as they deal with genetic modification, although these take place in plants, fruits, and vegetables.

**Studies of Scientific Work and how Scientific Knowledge is Produced**

Many studies in STS investigate how scientific work is conducted and how scientific knowledge is produced. The majority of these studies are referred to as laboratory studies, often ethnographic small-scale studies of a single laboratory, which investigate how scientific knowledge is constructed and stabilized in order to become established facts.

One of the most influential early laboratory studies is sociologists Steve Woolgar and Bruno Latour’s *Laboratory Life* (1986 [1979]). In this study a detailed investigation of the daily activities and actions – the routine work at a laboratory – is conducted. By observing the daily practice of different laboratory members, Woolgar and Latour show how scientific work is conducted and scientific facts are constructed through processes of transformation. They also show how laboratory staff create legitimacy and acceptance for their results, thus revealing the complex relation between activities and elements conducted within the laboratory and the activities conducted outside the laboratory.

Another study by Latour is *Science in Action* (1987), which also investigates how scientific facts are constructed and established by scientists. Latour examines science and technology in action – through its practice – and discusses how controversies and dissent make scientists use different strategies in the making of science. He describes how scientists enroll allies and try to keep these allies in line in order to establish the facts, which they do by working with other scientists and translating their interests so that they coincide with theirs. These strategies or processes constantly occur in order to make research work.

How scientists assemble and articulate different tools in order to do their work is also the interest of sociologists Adele E. Clarke and Joan H. Fujimura’s introductory chapter in their edited book *The Right Tools for The Job* (1992). They argue that scientific work is situated in particular situations. In order to understand how science is being done, one needs to understand the specific situation in which the scientific work is conducted. Scientific activities are performed at specific places, at specific times, with specific actors, and within specific practices. Consequently, the specific situation in which the work is done affects the work as well as the outcome of the work. In a scientific practice the ‘tools’, ‘jobs’, and the ‘”rightness” of the tools for the jobs’ are, according to Clarke and Fujimura (1992:5) ‘co-constructed’ by all the different elements present in the situation through articulation. Clarke and Fujimura turn their attention to the processes of co-construction and how doable problems are constructed, how ad hoc arrangements in the research process are made, how different elements are stabilized and standardized, and how science as a craft work is made.

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My study differs from these studies methodologically as I have conducted interviews with gene transfer scientists, and not participatory observations of their work. Because the laboratory studies that I have come across regarding scientific work are based on participatory observations, they provide another picture of how scientific work is done in practice than an interview study of scientific work can provide. This means that the focus also differs. My focus is not on gene transfer scientists’ concrete work in the laboratory. It is on how they describe and reason about their work both inside and outside the scientific practice. On the other hand, the approaches in scientific work and the production of scientific knowledge outlined above have provided me with knowledge and understanding about the conditions under which scientific work is conducted and scientific knowledge is produced. They have especially provided me with knowledge about the strategies that scientists use in different contexts like scientific, regulatory, and public, in order to make their work doable. In other words, they have been an important inspiration for parts of my analysis. I have also used several theoretical concepts from these studies, especially Clarke and Fujimura’s (1992) and Fujimura’s (1987, 1988, 1997) concept of doable problems or doability, as it also is called. This concept highlights the work that is needed to make a problem doable. Specifically, it highlights the invisible and often difficult work of gathering various elements such as people, skills, technologies, and materials together in the right arrangement, at the right time as well as place, to achieve a specific goal. Two other important theoretical concepts that I have used are Latour’s (1987, 1999) concepts of enrollment and translation which highlight how different actors are enrolled into a project and how alignment between interests and activities between these actors and levels of work can be achieved.

Disposition

In this chapter I have described the technology of gene transfer and why it is regarded as a controversial and morally debated field of research. I have also outlined the aims, research questions, and delimitations of this study as well as why I chose the countries of Sweden and the U.S.A. for conducting the interviews. Finally, I have pointed out some previous studies that relate to mine in different ways, in order to situate my study.

In Chapter 2, ‘Theoretical Tools’, I describe the theoretical tools and concepts that I have used for analyzing the material.

In Chapter 3, ‘Materials and Methods’, I describe the methodologies used for collecting the material of this study. I also present the selection of interviewees, how the study was conducted, and the process of analyzing the material.

In Chapters 4 to 7 I answer the questions: What are the conditions under which gene transfer scientists make problems doable? How is doability manifest in the actual work processes of gene transfer scientists? I show that gene transfer is presented by gene transfer scientists as a dynamic, diverse, and contested field of re-
search. In the first empirical chapter of these four, Chapter 4, ‘Making Doable Problems: At the Beginning and at the Bench’, I analyze how the gene transfer scientists whom I interviewed describe their work and actions to make gene transfer research practically doable. Here we are mainly at the beginning of the research process but also at the bench. I focus on the practical problems of getting funding, the expertise problems when gathering the necessary elements, as well as aligning their activities with each other. I also focus on the problems of finding the ‘right’ material and of handling technical problems with the material used for gene transfer as described by the interviewees.

In Chapter 5, ‘Resolving Tensions: Handling the Regulatory Setting’, I analyze what the specific regulatory setting means for the gene transfer scientists and the members of regulatory agencies and advisory boards whom I interviewed, and the consequences it has on their work. I show that different problems arise in Sweden and the U.S.A. and argue that what I call the loosely-regulated conduct of clinical gene transfer trials in Sweden versus the highly-regulated and -monitored conduct in the U.S.A. result in different ways of working.

In Chapter 6, ‘Meeting “Ethics”: Handling Ethical Complications in Clinical Practice’, we are at the bedside, that is, the clinical practice. I investigate how gene transfer scientists deal with the different ethical complications that they face in the clinical practice of gene transfer. I argue that gene transfer scientists, in order to make the ethical complications encountered in their clinical practice doable, need to demonstrate their commitments to ‘ethics’ as a way to legitimize their choices and actions, and more importantly, to establish an ethical acceptability of their work.

In Chapter 7, ‘Gaining Public Acceptance’, I discuss how gene transfer scientists experience public concerns regarding gene transfer, both as a technology and a field of research, and how they respond to these concerns, thus relating to the outside world. I show how gene transfer scientists distinguish and promote their work in order to reduce its controversial character and combat misunderstandings. I argue that the scientists by establishing a new frame of reference, present gene transfer as an ordinary kind of therapy in an attempt to gain public acceptance.

In the last chapter, Chapter 8, ‘Summary and Conclusions’, I present and discuss the conclusions and implications of this study. I turn to some of the major issues and questions raised in the introduction and proceed to weave together and discuss the different contributions of the study.
CHAPTER 2
Theoretical Tools

The previous chapter, Introduction, indicated the need to investigate how work is made doable in the controversial and morally debated field of gene transfer research. This chapter will describe and discuss those theoretical concepts from the Science and Technology Studies (STS) perspective that have helped me investigate how work is made doable. This perspective makes it possible to consider the production of scientific knowledge as an activity in which scientific facts are created in a social process. Theoretical concepts in STS such as ‘doable problems’, ‘articulation work’, and ‘boundary-work’ have shaped my questions and perspectives. They have further generated a greater understanding for my data as well as influenced my interpretation of it. In the following sections I describe concepts and theories, from the previous studies described in Chapter 1 but also from other studies, that have guided me in the analysis.

Making Research Work

Gene transfer research is unique. It is performed in complex circumstances, and actualizes multiple and varying elements from different materials, skills, established practices, and social ties to the public controversies surrounding it. Consequently, gene transfer research is situated in and shaped by different scientific, political, regulatory, social, and cultural contexts.

Controversy

As described above, I am interested in how work is made doable in gene transfer research. Conducting gene transfer research means that the scientists involved are presented with various problems. Not only is the research new, groundbreaking and uncertain in its outcomes, but its regulation and oversight vary. Furthermore, gene transfer research is surrounded by controversy. Given this situation, gene transfer research needs to be situated within a controversy perspective. It has to be placed in a broader scientific, historical, and social context in order to create an understanding for what the controversy is about – and more importantly, why there is a controversy, and between whom.

A controversy perspective is, according to theory of science researchers Margareta Hallberg and Fredrik Bragesjö (2003), a descriptive and explanatory perspective in which the researcher maintains a neutral perspective, so that he or she does not become a part of the controversy being studied. They write that controversies can be divided into three phases, each with its own focus. The first phase is between
scientists, the second between scientists and the public, and the third among actors located outside the scientific world, who interpret and use scientific knowledge in a rather freestanding way. The first phase of controversy, that is, between scientists, does exist in gene transfer research, for example in regard to which living material is best to use for gene transfer in terms of safety and efficiency. However, I have not paid attention to this kind of controversy. Instead, I have focused on the second phase of controversy, that between scientists and the public, which also involves other social actors such as regulators and politicians.

A controversy perspective is useful as a tool to map the current work situation for gene transfer scientists. It enables me to see the consequences that the controversies surrounding gene transfer, as both a technology and a field of research, have had on gene transfer scientists’ work. I use the perspective to understand why gene transfer scientists talk about their work the way they do, particularly why they constantly seem to want to define and defend their work, and why they consequently mobilize against what they consider to be misunderstandings.

**Situatedness and Doability**

A highly relevant concept to combine with a controversy perspective is what sociologists Adele E. Clarke and Joan H. Fujimura (1992:4) call situatedness, that is, how the specific practice where the work is done affects the work. They argue that scientific activities are conducted in particular locations and times, with specific actors, and within specific practices. All these factors make the outcome uncertain. In order to understand gene transfer research I therefore need to take into account important elements in the situation, such as the workplace, the scientists and their career issues, and the other workers who do the practical work. It is also necessary to discuss research materials, instruments, technologies, techniques, and skills, as well as work organization, sponsorship, regulatory authorities, audiences, and consumers of the work. In this study, these elements are accounted for, as they enter into the reasoning of the gene transfer scientists and regulators whom I interviewed.

Throughout this study my general research question is: How do gene transfer scientists reason about how they make their work doable? In the first empirical chapter, Chapter 4, I analyze how gene transfer scientists handle various problems in order to make their research work practically doable. Specifically, I analyze how they get funding, pull together various elements needed for research, as well as articulate different activities, and handle scientific uncertainties when working with living materials. Fujimura (1987, 1988, 1997) and Clarke and Fujimura (1992) call this process one of constructing doable problems. The concept of creating doable problems, or establishing doability, is used throughout this study. The concept relates to sociologist Anselm Strauss’ concept of articulation work (1988:164) and refers to ‘the specifics of putting together tasks, task sequences, task clusters’ in order to achieve work flow. Articulation work is further described by Clarke and Fujimura (1992:9) as ‘the invisible and unacknowledged but often arduous work of pulling various
elements together in the “right” sequences and at the “right” times and places in order to achieve particular goals’. Successful articulation work results in alignment across several levels of work and the coordination of various, often discontinuous, elements. In other words, different lines of work and subprojects must be aligned with the main project through articulation work in order to achieve what Strauss calls (1988:164) ‘work flow’.

Fujimura investigates how doable problems are constructed in basic cancer research. ‘Doability’, she writes, ‘is better conceptualized as the alignment of several levels of work organization’ (1987:258; italics in original). There are three levels of work organization, according to Fujimura. They are the experiment, the laboratory, and the social world. The experiment is located in the laboratory and consists of different laboratory tasks. The laboratory is instead a collection of various experiments and other assignments. Finally, the social world is the larger context in which experiments and laboratories are situated. In order to make a problem ‘doable’ these levels of work organization must be aligned with each other. The articulation work involved in achieving the goal of a given project includes planning, collecting, coordinating, and integrating various tasks and assignments within, but primarily between, the three levels of work organization. In other words, articulation work deals specifically with organization and reorganization of work. In order to make a project successful scientists thus have to gather several essential factors, like capital, infrastructure with laboratory space, production facilities, staff, technologies, and research materials, as well as people with different skills. They also have to find audiences that are interested in their findings and find them worthwhile. In this process different elements in the research situation are actively manipulated and articulated in order to achieve a doable problem. The problem can also be reconstructed over time as different circumstances occur. This means that articulation work is necessary if a technology is to become integrated effectively into the situated activities of its use. It is the scientists’ efforts to combine all these things, and more importantly, to create doable problems of them, that make research work (Fujimura 1987, 1988, 1997).

For my analysis of gene transfer research, paying attention to doability means paying attention to the situation in which gene transfer is situated. The concepts of doability and articulation work are useful to understand the work needed to begin a research process within gene transfer research, and to move it along the different

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10 Fujimura’s (1987) definition of social world emanates from Clarke’s (1991:131) definition in which social worlds are defined as ‘groups with shared commitments to certain activities, sharing resources of many kinds to achieve their goals, and building shared ideologies about how to go about their business’. However, when investigating how doable problems are constructed in basic cancer research, Fujimura uses a specific definition of social world in which it is the larger context in which experiments and laboratories are situated. In her case the experiments on oncogenes are situated in the scientific worlds of molecular biology and cancer research. I see social worlds in the same way as Clarke does but when analyzing how scientists make their work doable I specifically look at the social world of gene transfer research and how it interacts on specific matters with other social worlds such as those of regulators, investors, the media, and the public.
steps of basic science, preclinical studies, and clinical trials. This means that my use of doability and articulation work is more modest than Fujimura's. I look for how the gene transfer scientists whom I interviewed reason about how they try to make their work doable. I have not been in the laboratories, as Fujimura (1987, 1988, 1997) was, and actually seen how work is made doable. Despite this, I argue that by using the concepts of doability and articulation work, I can show how gene transfer scientists meet the problems of getting funding and pulling together and coordinating various elements like people, skills, materials, and technologies. This also involves how they handle technical difficulties at the bench, that is, in basic and preclinical research, in their pursuit of finding the ‘right’ material that works properly; this is something which can be decisive for scientific commitments, and also for financial commitments. By analyzing the interviewees’ descriptions of their articulation work I can understand which elements, both human and non-human, are needed in order to make gene transfer doable, and consequently how they are aligned in order to create doable research. In other words, making research doable in gene transfer is to a large extent about uniting and aligning various social worlds, inside and outside the laboratory and clinic. By looking at articulation work I can also understand how the social world of gene transfer research interacts on specific matters with other social worlds such as those of regulators, investors, the media, and the public, and how scientists try to align these various actors’ interests and activities with their own, in order to achieve doability. I therefore find it useful to employ the concepts of doability, articulation work, and alignment with varying emphasis throughout the four empirical chapters.

**Boundary-Work**

Making gene transfer doable also involves the process of moving gene transfer from bench to bedside, that is, from experimental studies in the laboratory to clinical trials on human subjects. This means among other things that gene transfer scientists must make their work doable within the regulatory framework, that is, within existing policies and regulations. Specifically, they must get their applications for clinical gene transfer trials accepted by different regulatory agencies and advisory boards. In Chapter 5, I analyze how the different regulatory settings in the two chosen countries affect how clinical gene transfer research is done, or more specifically, what effects different ways of regulating and monitoring clinical gene transfer research have on gene transfer practices.

The concept of *boundary-work* is useful here, in order to understand the tensions between gene transfer scientists and regulators. It captures the dynamic and contradictory character of discourse and practices in these two differently situated perspectives. This term originates from sociologist Thomas F. Gieryn (1983, 1999) and is used by him to analyze demarcation strategies used by scientists to distinguish their scientific practice from, for example, non-science in the form of religion or technology.
I discuss two forms of boundary-work used by both scientists and regulators. The first of them is used to affirm the existence of boundaries between scientists and regulators. Here the boundary-work is about acknowledging and accepting the different authorities, jurisdictions, and responsibilities of the two different social worlds of scientists and regulators. The second form is instead used to transgress the boundaries. In this case the boundary-work is about trying to influence each other’s social world by transgressing the boundaries, and occasionally even crossing them. By using the concept of boundary-work I can understand how scientists handle the regulatory demands implemented by the social world of regulators and how regulators try to accommodate the demands of the scientists.

**Ethical Boundary-Work**

Making gene transfer doable for the scientists also means meeting ‘ethics’. By ‘ethics’ I mean the ethical principles and guidelines, as well as the regulatory framework that provide legal and ethical models for the clinical gene transfer practices in the two chosen countries. In Chapter 6, I examine the ethical complications that gene transfer scientists experience in their work, and how they handle these complications. I look particularly at how ‘ethics’ is discussed by the gene transfer scientists whom I interviewed and how they viewed their obligation to ‘ethics’, but also how their ethical considerations have become a way to legitimize their choices and actions.

Ethical principles\(^{11}\), guidelines, and the regulatory framework jointly provide a map of a legal and ethical landscape to guide gene transfer scientists in their clinical work. However, the problem with this kind of map, as communication scientists John Seely Brown and Paul Duguid (1991:41-42) write, is that it ‘inevitably smoothes over the myriad decisions made with regard to changing conditions’. This means that a map does not take into consideration the fact that conditions may change. Nor does it take into consideration the fact that the actual practice of going from one place to another is complex. In clinical gene transfer research, I argue, gene transfer scientists are not helped by the models that the regulatory frameworks or the ethical principles and guidelines provide. Instead they need help to meet the difficult situations that they face in the everyday clinical practice of gene transfer, and the often ad hoc decisions that they have to make. According to Brown and Duguid (1991:42) the more complex a journey gets, the more evident it becomes that improvised actions need to be taken in order to accomplish the journey. An actual practice, they write, ‘inevitably involves tricky interpolations between abstract accounts and situated demands’. In other words, a map of a legal and ethical land-

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\(^{11}\) The ethical principles that I refer to is the four basic principles of biomedical ethics. They are: respect for autonomy, beneficence, non-maleficence, and justice. For an extensive discussion of these principles see Beauchamp and Childress (2009) book *Principles of Biomedical Ethics*. 
scape is often, to various degrees, detached from the actual practices of navigating through it.

In relation to the detachment between ethical principles, guidelines and regulatory framework and the actual clinical practices of gene transfer scientists, the concept of ethical boundary-work is useful. This concept was introduced by medical sociologist Steven P. Wainwright et al. (2006), emanates from Gieryn’s (1983, 1999) concept of boundary-work, and investigates how scientists draw ethical boundaries regarding their scientific work. It attends to ‘what is deemed socially acceptable, good, or right, and to what principles and other normative frameworks suggest ought to be considered’ (Wainwright et al. 2006:734; italics in original). The authors investigate what embryonic stem cell scientists in two laboratories in the U.K. viewed as ethical problems in their work. These scientists placed themselves in an ‘ethical space’, with boundaries to the formal ethical and legal framework that allows and defines what is considered as ethical science. This enabled them to make moral judgments, to assert an ethical position, and also to prepare for ethical argumentation. They drew ethical boundaries around their work as a way to present the substantive ethics of their practice, and themselves as deliberative, serious and ‘right seeking’ scientists. These actions were made in order to define and defend their work in a controversial and morally debated field of research. Wainwright et al. conclude that by examining how ethics are interpreted in a specific practice, insights can be gained regarding how scientists will conduct themselves in a complicated moral, political, and epistemic field.

By using this concept I can understand how the interviewees frame and handle ethical complications in different situations that they face in the everyday clinical practice. I can also understand what the substantive ethics of the clinical gene transfer practice is about, and how the scientists draw boundaries to the legal framework, but primarily how they make and remake the boundaries between what is regarded as ethically acceptable and unacceptable, boundaries that often have to correspond to bioethical experts’ as well as society’s and the general public’s concerns about the ethical and social implications of gene transfer research. This is done to justify their choices and actions, and to establish an ethical acceptability of their work.

**Frame of Reference**

As described above, an integral part of making research work doable is to gain acceptance for the work. In Chapter 7, I analyze how gene transfer scientists handle public concerns and how they relate to the outside world. The scientists whom I interviewed defined the ‘outside world’ as involving actors from various other social worlds such as regulators, the public and the media located outside the social world of gene transfer research, who could affect scientists’ work and their ability to conduct research. I am especially interested in what kind of arguments gene transfer scientists use in order to present their work with gene transfer as legitimate and ethically acceptable, thereby gaining public acceptance.
In order to understand how gene transfer scientists try to reduce the controversial character of gene transfer I use the concept of *frame of reference*. Sociologist Erving Goffman (quoted in Flichy 2007:80) regards any social event as organized by a frame, ‘that is seen as rendering what would otherwise be a meaningless aspect of the scene into something that is meaningful’. The use of frames, mass communication scientists Dietram Scheufele and David Tewksbury (2007) write, makes it easier to introduce complex issues to the public because frames influence how the individual perceives meanings attributed to the issue.

A frame of reference consists of terms that are organized around particular metaphors and figures of speech. This means that frames are used to transform something diffuse, unfamiliar, and sometimes also frightening into something comprehensible, by putting it into a familiar context. The concept is useful to understand how gene transfer scientists try to combat misunderstandings about gene transfer, as a technology and a field of research, and try to convince different audiences of the legitimacy of gene transfer research.

**A Practice Embedded in Controversy**

To summarize, this study focuses on how research is made doable in the controversial field of gene transfer from the scientists’ point of view. I focus primarily on how gene transfer scientists reason about making their work doable from the beginning of a research process to clinical trials with human subjects. What do gene transfer scientists regard as problems, and more importantly, how do they handle these problems? And how do gene transfer scientists feel morally about their work? How do they meet public concerns and gain public acceptance for their work? In this chapter I have outlined the theoretical tools used to understand these practices.

I use a controversy perspective as a point of departure for my analysis. This means that I try to maintain a distance to the actual controversies in gene transfer research. I do not question the different facts, standpoints, and opinions in the controversies. Instead I try to describe and highlight gene transfer scientists’ understandings, descriptions, and actions as they work in a contested field of research.

The overall research question is how work is made doable in gene transfer research, given the situation in which it is situated. I investigate the work of getting a research process started and how it then moves along to finally end in clinical implementation. Inspired by studies of scientific, medical, and ethical controversies as well as studies of scientific work and how scientific knowledge is produced, I focus on how gene transfer scientists reason about making research doable by articulation work and alignment of different tasks and assignments, as well as levels or work organization, to handle various problems and uncertainties in their work. I analyze how a research process is started, what is needed, how the process is moved along, and what actions that gene transfer scientists take in order to achieve their goals. By using boundary-work I investigate how gene transfer scientists affirm, transgress, defend, and cross boundaries, both scientific and regulatory, between themselves
Chapter 2

and regulators. I also analyze, by looking at ethical boundary-work, how gene transfer scientists make, remake, and maintain both legal and ethical boundaries around their work, primarily corresponding to other actors’ views of gene transfer research, to justify their actions, but especially in order to gain acceptance. I also analyze how gene transfer, as a technology and a field of research, is framed and labeled in a new frame of reference by gene transfer scientists to meet public concerns, but also to present a legitimate public image of their work.

As will become apparent in the empirical chapters, I have also used other theoretical concepts such as enrollment of allies, translation, and the deficit model, but not as extensively as the ones outlined and discussed in this chapter. These will be introduced and discussed in the chapters in which they are used.
CHAPTER 3
Materials and Methods

In this study, I look at how scientists make their research doable in the controversial field of gene transfer. In designing this study I aimed at interviewing gene transfer scientists in two different countries, Sweden and the U.S.A. My primary interest, at the time, was to explore biotechnology and ethics, especially the ethical, legal, and social issues related to the development and application of gene transfer. Based on this criterion, I selected interviewees and then began to analyze the data. It was during the analysis that I realized that I had to reorient the focus of my research questions as well as of my analysis, as the gene transfer scientists whom I interviewed were not particularly interested in talking about the ethical, legal, and social issues of gene transfer. Instead they talked about how difficult it was to make gene transfer research doable, given its controversial character and the moral debates that it raises. Consequently, I began to investigate the research process from bench to bedside, that is, from basic science to clinical trials on human subjects. More specifically, I began to investigate how the gene transfer scientists themselves described their work, what they regarded as problems, and how they handled these problems in order to make gene transfer research doable. Something that was also interesting to examine was if the countries’ different ways of regulating and monitoring clinical gene transfer research had any effect, and if so, in what way, on the gene transfer practice and especially on gene transfer scientists. The regulatory framework is of significant importance in gene transfer research. More importantly, it differs considerably between Sweden and the U.S.A. Because of this I also wanted to interview members of regulatory agencies and advisory boards, and look at what they described as problems or challenges when implementing the policies.

In this chapter I describe and discuss my research process. Accordingly, I explain how I selected the interviewees, what ethical considerations were made, and how I conducted the interviews. Finally, I delineate how I analyzed the data.

The Interviewees

The interviewees in this study were scientists in the field of gene transfer research and members of regulatory agencies and advisory boards in Sweden and the U.S.A. As my main interest is how problems are made doable in a controversial field of research like gene transfer, it is necessary to interview the people who work in this practice, that is, gene transfer scientists. I chose to interview scientists at the frontier of gene transfer research. This meant that they had prominent positions in the gene transfer field. This choice was based on the assumption that they would have the
most experience of conducting gene transfer research. I further believed that they, with their extensive experience in this field of research, had been exposed to the surrounding ethical and social issues relating to the application of gene transfer. I chose to interview members of regulatory agencies and advisory boards, as they are important actors involved in the process of gene transfer application. They are the ones who implement the policies and ensure that they are followed by gene transfer scientists in their research.

Interviewees were strategically selected so that leading groups in gene transfer research as well as the most influential regulatory agencies and advisory boards were to be covered in both Sweden and the U.S.A. I wanted to interview scientists and members of regulatory agencies and advisory boards in both academic and commercial settings, thereby obtaining a greater diversity in experiences and accounts. Seventeen men and seven women were invited\(^\text{12}\). Two men and two women declined the invitation to participate. In the end I conducted twenty interviews: ten with gene transfer scientists (five in each country), and ten with members of regulatory agencies and advisory boards (also five in each country). The group of gene transfer scientists ranged from scientists working with vector development and studies in animal models to scientists working with clinical gene transfer trials in human subjects. In the other group, some of the interviewees were the obvious candidates as they held important positions in regulation of clinical gene transfer research at a regulatory agency or an advisory board\(^\text{13}\). The others were selected in an attempt to achieve a diversity regarding their scientific and professional background. The interviewees were all senior professionals.

As described above, when this study was designed, my primary interest was to investigate the ethical, legal, and social issues related to the development and application of gene transfer. Based on this criterion, I began to search for interviewees. At first I conducted a document analysis of the ongoing international bioethical discussion. In this analysis I found several names of U.S. gene transfer scientists and people working at different U.S. regulatory agencies and advisory boards who frequently published articles concerning gene transfer and its applications. It was, however, difficult to find any Swedish gene transfer scientists in this discussion. As gene transfer research is a small scientific community in Sweden I instead mapped the five gene transfer centers or universities that worked in the field of gene transfer in order to identify the leading scientists. I also performed an informal interview with a

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\(^\text{12}\) The reason for the unequal gender distribution was that it was difficult to find and get in contact with female senior gene transfer scientists in Sweden. This was also the case in the U.S.A. The women in this study are therefore all members of regulatory agencies and advisory boards.

\(^\text{13}\) These obvious candidates were, however, difficult to interview in Sweden. Members of regional ethical review boards as well as members of the central ethical review board whom I approached all declined to participate in this study. Their stated explanation for their refusal was that they had not been in contact with applications regarding clinical trials in gene transfer and therefore lacked experience in this matter.
senior professor in a scientific field closely related to gene transfer. In this interview I asked the interviewee to describe the most prominent research groups in gene transfer research, especially in Sweden. He named a couple of leading gene transfer scientists in Sweden, and also in the U.S.A. Some gene transfer scientists were reached through referrals from the colleagues I had interviewed. One of the U.S. scientists was contacted especially because another interviewee emphasized that this scientist was conducting ethically complicated gene transfer research. The names presented in the different interviews were then matched against published articles so that prominent scientists within this field could be identified.

Eight of the ten scientists interviewed held both MDs and PhDs. This means that they were not only clinicians but also clinical researchers in scientific fields like internal medicine, pediatrics, oncology, immunology, and hematology. The other two scientists, who were Swedish, held PhDs in molecular genetics and molecular biology, respectively, and focused their work mainly on basic and preclinical gene transfer research. These scientists all held leading positions at departments, institutions, companies, gene transfer programs, or centers. More specifically, they were directors of gene transfer programs, directors of gene therapy centers, coordinators at gene therapy programs, or project leaders in gene transfer research. One of the scientists worked in a commercial setting, as he worked at a gene transfer vector company. Several of the other interviewees had also, to different extents, previously worked in commercial settings. Some had been founding members in the creation of different gene transfer vector companies. Five of the scientists worked with basic and preclinical gene transfer research, whereas the other five worked with clinical gene transfer research. Several of these interviewees also held other positions, such as members of different committees and advisory boards.

The ten interviewed members of regulatory agencies and advisory boards worked at various agencies and departments, and on various committees. Their individual tasks ranged from being regulatory and advisory to being monitoring or controlling. Some of them also did research. I expected these interviewees to be familiar with gene transfer research through their concrete work at regulatory agencies or advisory boards. As it turned out, not all interviewees were as familiar with gene transfer research as I had expected. This was the case when I interviewed members of advisory boards in Sweden. It was difficult, in practice, to get members of regional ethical review boards (who are the obvious interview candidates, as they are the ones who monitor and evaluate clinical gene transfer applications) to participate in this study. Consequently, the Swedish regulatory interviewees are only from

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14 This interviewee worked at the same university as most of the Swedish scientists whom I later interviewed.

15 Examples of these ethics committees are, on a university level, the Institutional Review Board and the Institutional Biosafety Committee, or committees on a federal level like the Recombinant DNA Advisory Committee, the Office of Technological Assessment, and the Congressional biomedical ethics committee.
advisory boards which may not discuss gene transfer research to the same extent as regional ethical review boards do.

As I noted earlier, gene transfer research is a small scientific community in Sweden. This fact has affected how I selected which Swedish gene transfer scientists to interview. As I wanted to interview preclinical scientists as well as scientists involved in clinical trials, most of my interviewees were from two of the five gene transfer centers or universities that work in the field of gene transfer research. They are the ones who had the greatest preclinical and clinical experience of gene transfer research. As a result, these leading scientists all knew each other due to various collaborations and/or through participation in gene transfer conferences. Although the scientific gene transfer community in the U.S.A. is more widespread and diverse, all the leading U.S. scientists whom I interviewed knew each other. They had all, to different extents, collaborated with each other on different scientific issues. They were also all members of the American Society of Cell and Gene Therapy (ASCGT). Among the Swedish gene transfer scientists almost all of the interviewees were members of the Swedish Society for Gene Therapy (SSGT) and three of the scientists also, at the time of the interview, held important positions in the European Society of Cell and Gene Therapy (ESCGT).

**Invitation and Initial Contact with the Participants**

The initial contacts I made with the interviewees and the processes of invitation to participate in this study differed. In Sweden I made the initial contacts with all the interviewees and invited them to participate in the study. In the U.S.A. I instead used a ‘gate opener’. There was a practical reason behind this decision: I needed to conduct my interviews during a limited period of time. I also wanted to interview people at key positions within scientific research and different regulatory agencies and advisory boards, people who probably would be difficult for me to meet if I contacted them myself. In the invitation to my U.S. interviewees I therefore used Eric T. Juengst as a gate opener. He is Professor in Bioethics and, at the time of my interviews in late 2005 to spring 2006, Director for the Center for Genetic Research Ethics and Law within the Department of Bioethics at Case Western Reserve University School of Medicine in Cleveland, U.S.A. Having him standing behind my research project, with his name as well as his scientific and regulatory prestige, made it possible for me to interview people in key positions in different regulatory agencies and advisory boards, as well as U.S. scientists at the cutting edge of gene transfer research. It has probably made some of the interviewees more interested in participating in my study. However, I do not believe that this affected how the inter-

16 In retrospect I should perhaps have used a gate opener in Sweden as well. This could have affected some of the members of regional ethical review boards and the members of the central ethical review board whom I approached and made them more interested in participating in my study.
viewees chose to answer my questions or discuss their experiences of working in/with gene transfer research.

The first contact with the interviewees was made through e-mail. With the invitation to participate I included a description of the project in which I explained that the aim of the study, as well as the aim of the interview, was to focus on the interviewees’ own experiences and opinions of gene transfer research, and the ethical and social problems in the application of gene transfer. I also explained that the interviewees were selected through a strategic sampling, in order to cover leading groups in gene transfer research as well as the most influential regulatory agencies and advisory boards in Sweden and the U.S.A. Finally, I clarified that the interviewees were selected because they worked with gene transfer research and its applications in different ways.

With the invitation I also included a description of how the collected data would be used. Here it was explained that the data would not be used for any other purpose than research. During the interview a mini disc recorder would be used, provided that permission was given by the interviewee. The recorded and printed material would be stored in a locked cupboard. It was also clarified that information used from the interviews would be used in an anonymous form and that the interviewees had a right, and would be given the opportunity, to review and approve all quotations or excerpts from their interviews before publication.

**Ethical Considerations**

This study follows current ethical norms for research according to the Swedish Research Council’s ethical principles for research in the humanities and social sciences (Vetenskapsrådet 2002). It has, however, not been approved by a regional ethical review board. When designing this study the question arose of whether or not this study needed an approval from a regional ethical review board. At first I discussed this matter closely with the participating researchers. I also discussed it with a former member of a regional ethical review board. The outcome of the discussions was that an ethical approval was not needed as I was going to interview people in their roles as professionals, and also as my interest was in their professional role and not in them as private persons. In addition, the general understanding was that the interviews did not involve any questions that were considered personally sensitive for the interviewees. It is important to note that the central focus of this study is on the interviewees’ experiences and opinions, what they chose to talk about in the discussion with me, and not on the interviewees as persons. Nor were patients involved in any way.

As stated above, this study follows the Swedish Research Council’s ethical principles for research in the humanities and social sciences. These ethical principles involve several rules regarding information, consent, confidentiality, and how research data may be used (Vetenskapsrådet 2002). All persons included in this study have been given, as described above, information about how the collected data
would be used, who would have access to it, how it would be stored, and that they had the right to review and approve any quotations before publishing. They all gave their informed consent to participate. This consent was obtained at the beginning of the interview when I informed the interviewee of his or her right to end the interview at any time or to choose not to answer any particular question. Before this study was sent to be printed all the interviewees have been given the opportunity to review and approve quotations and excerpts from their interview. An electronic copy of their individual quotations was sent to the interviewees. They then had two weeks to respond with disagreements regarding the quotes or the analysis of the quotes. A few interviewees wanted to make changes or additions in their quotes, as well as clarifications that they wanted to add to the text. I have implemented these changes to the text as they have not affected the original content of it.

In order to guarantee confidentiality I have, in presenting my analysis of the data, chosen not to indicate the positions of the interviewees. In addition, all names are fictitious. In order to make it easy to distinguish between gene transfer scientists and members of regulatory agencies and advisory boards, all the fictitious names of the scientists begin with the letter S. Consequently, all the regulators’ fictitious names begin with the letter R. In order to distinguish the Swedish interviewees from the U.S. interviewees I have chosen Swedish-sounding names and American-sounding names, respectively. In some cases where the interviewees discussed specific places I have chosen to name the places XX to further protect the anonymity of those involved. In presenting my analysis I often use excerpts from the interviews. These excerpts are chosen because I consider them suitable to illustrate the gene transfer practice as it is accounted for by the interviewees. They also exemplify and explain certain views, actions, and experiences that the interviewees expressed. In the text each excerpt is followed by a page number. This is the page number in the transcript of the interview from which the excerpt was taken. Some interviewees are quoted more often than others. This is because these interviewees were more talkative and eloquent than the others. Similar experiences and apprehensions were, however, also present in the less-quoted interviews. I have furthermore, in the selection process of the quotes, been careful to ascertain that the quotes are not taken out of context as this could lead to misunderstandings.

Qualitative In-Depth Interviewing – Its Meaning and Inherent Problems

In order to study how research is made doable in the controversial field of gene transfer as described by gene transfer scientists, it was not sufficient to use questionnaires or participatory observation. It was impossible for me to determine in advance what the interviewees would want to talk about. More importantly, I wanted the interviewees to be able to expand on issues that they considered important or relevant to discuss with regard to their professional experience. Qualitative in-depth interviewing served this purpose. It also made it possible for me to ask
follow-up questions if the interviewees discussed something interesting or were unclear. There was also another reason for the choice of qualitative in-depth interviewing. As gene transfer research is a controversial and morally debated field of research it would probably be difficult to gain access to laboratories and other sites of importance. Access is of necessity if one wants to conduct participatory observations. Because of this, participatory observations were not an option in this case. Choosing qualitative in-depth interviewing as a methodological tool also had another benefit. It made it possible for me to interview actors from different disciplines and countries and hence study actors from contrasting situations. This would not have been possible if I had chosen to conduct participatory observations, as this methodology only would have allowed me to study a significantly smaller sample of actors, due to time limits.

An interview is a communicative event in which something is jointly created by the interviewer and the interviewee (Gubrium and Holstein 2001, Kvale 1997). More precisely, a qualitative research interview is a professional conversation, with a specific structure and purpose in which knowledge is constructed. The goal of interviews is to obtain ‘descriptions of the life world of the interviewee in order to interpret the meaning of the described phenomena’ (Kvale and Brinkmann 2009:3). In other words, interviewing is about understanding how people perceive and make sense of different phenomena in the world.

A qualitative interview is not an everyday conversation. It is a conversation in which the participants are unequal, as it is the interviewer that controls the interview. This raises issues of power. The power asymmetry between the interviewer and the interviewee may affect the interviewee’s answers. The interviewee may unintentionally angle answers during the interview so that they fit with what he or she believes the interviewer expects. In other words, it is impossible to extract the ‘true’ opinion or experience of an interviewee.

There is thus a power asymmetry during the interview, depending on who interviews whom, where, and about what. When I conducted the first interview I thought that I had the advantage in this power relation since I was the one who asked the questions and hence controlled the interview. After a couple of interviews I realized that it was instead the interviewees who exerted power in these interviews. First, they were all senior professionals and mainly men, and I was a female PhD candidate. Second, the interviews took place in their offices. In other words, they were in control of the interview situation. Moreover, if they did not want to answer one of my questions, they talked about other things instead. As an example, one of

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17 This was for example the case for Hugh Gusterson (1996) when he wanted to get access to a nuclear weapons laboratory in the U.S.A. in order to investigate how the members of this laboratory created meaning and related to their outside world as well as how they felt morally about their work. As the nuclear weapons industry is indeed a controversial field of research, conducting participatory observation was not an option. Instead he conducted interviews in the homes of the interviewees or in one of the laboratory cafeterias.
the gene transfer scientists whom I interviewed had been one of the leading investigators in a clinical gene transfer trial in which one of the enrolled human research participants died. When I asked him what he thought was the ethical questions of gene transfer, he answered that there were only generic ethical issues, that is, common ethical issues that were present in any clinical research. I wanted to ask him a follow-up question regarding the ethics of the specific clinical trial in which the human research participant died, because I knew that the procedures conducted during this trial had been extensively debated and described as unethical in the international bioethical literature. However, I did not dare to ask this question as I feared that he would end the interview immediately if I did so. This interviewee also exerted another kind of power which affected the symmetry during the interview. He had a colleague with him during the interview. This was something that none of the other interviewees had. This colleague occasionally intervened in the interview to make clarifications about what the interviewee just had said. This happened especially when we discussed the ethical questions of gene transfer research.18

There are also problems regarding how data from qualitative interviews should be validated. Sociologist Robert W. Witkin (1994:268; italics in original) explains that ‘to invite someone to answer questions about what they do and how they do it is an invitation to them to theorize about their actions’. In this context it becomes important to clarify that the interviewees’ statements are not just collected by me as an interviewer. They are co-authored by me and the interviewed person in the sense that it is my questions that lead up to the aspects of a topic that the interviewee will address. It is the active listening of the interviewer and the follow-up of the interviewee answers, educational psychologist Steinar Kvale and psychologist Svend Brinkmann (2009:3) claim, that co-determine the course of the conversation. This means that I, as an interviewer, and my interviewees to a certain extent created the outcomes together.

The Interviews

I conducted the interviews in Sweden between February and June 2005 and the interviews in the U.S.A. between November 2005 and April 2006. All interviews were performed in the interviewees’ offices at their department or agency and lasted from 45 minutes to two hours.

As described above, the primary interest of this study was to explore the ethical, legal, and social issues related to the development and application of gene transfer. This resulted in the following research questions: What ethical, legal, and social issues in gene transfer research, whether somatic or germ-line, did the interviewees find relevant, interesting, and important to discuss? And how did they handle the ethical issues in practice? What were the medical and clinical issues, and how were

18 I have, however, not used any examples of this in this book.
they handled in practice? I was also interested in the ‘ethics discourse’ in the interaction between the field of gene transfer research and the regulatory agencies and advisory boards. It was against this background that I made a document analysis of the ongoing international bioethical discussion before I conducted the interviews. I needed to grasp what the ethical, legal, and social issues related to gene transfer research were about. The document analysis gave me a first impression of the controversies surrounding gene transfer research and hence influenced how I designed the interview guides.

In conducting the interviews I used two semi-structured interview guides which addressed specific topics (see Appendix A). The interview guides contained open-ended questions and covered political and commercial aspects, but concentrated mainly on ethical and social aspects related to the development and application of gene transfer.

The interview guide for gene transfer scientists contained specific questions regarding problems and challenges in their research, including technical problems, funding, commercialization, or policies that regulated their research. I asked these questions in order to try to understand what the scientists considered to be important circumstances that influenced their gene transfer practice.

The interview guide for members of regulatory agencies and advisory boards instead emphasized questions regarding regulatory aspects of preclinical and clinical trials, the review process of applications for clinical trials in gene transfer, and the policies put in place. It is important to note that this interview guide also contained questions similar to the ones in the interview guide for gene transfer scientists. Nevertheless, only the parts regarding policies, implementing policies, regulatory structure, and the different review processes of applications present in the interviews have found their way into this study. The reason for this is that I had to make delimitations, based on the specific aim and the research questions of the final study. Despite having to exclude much data from these interviews, they have been of significant importance, especially in Chapter 5. They have illustrated both similar and different views on the gene transfer practice, in relation to the illustrations given by the gene transfer scientists whom I interviewed.

I began all interviews in the same way. I opened the interview with a short description of the purpose of the study. I then informed the interviewee of his or her right to end the interview at any time. The scientists were asked to describe their scientific background and how they came in contact with gene transfer, especially what practical experience they had in this field. Members of regulatory agencies and advisory boards were also asked to describe their scientific backgrounds and the positions they held at their regulatory agency/advisory boards. They were then asked whether, and if so how, they had been in contact with gene transfer re-
After these introductory questions I began to ask the questions outlined in the relevant interview guide. Depending on what the interviewees chose to talk about, I added follow-up questions.

In the interviews, the majority of the questions were related to somatic gene transfer. This is because somatic gene transfer is carried on in basic, preclinical, or clinical gene transfer research. Germ-line gene transfer, on the other hand, is only hypothetical. Consequently, the interviewees’ descriptions, experiences, and opinions were more extensive and detailed when relating to somatic gene transfer. I also realized that several of the interviewees, especially the Swedish scientists, avoided questions regarding germ-line gene transfer by emphasizing that it was forbidden by law to perform germ-line gene transfer in Sweden. All of the scientists seemed to feel uncomfortable with questions regarding germ-line gene transfer. One of the interviewees from a regulatory agency became very insulted when I asked him what he thought about germ-line gene transfer. He promptly replied that this kind of research was something that they [at his university] were not involved in, and in addition, no research was moving in that direction either. I later realized that there must have been some misunderstanding regarding the question. Maybe the formulation of this question implicitly implied that, in order to be able to have any thoughts about germ-line gene transfer, one must have worked with it in practice. This event proved to me what I already knew, and what I suspected when I outlined this study – that germ-line gene transfer is indeed a controversial field of research.

All the interviews were recorded on mini discs and transcribed. The interviews were transcribed word for word but intonations or dialects are not indicated in the citations given in this text. Longer pauses and laughter or sighs are indicated as well as intrusions into the interviewee’s spoken sentences.

**Considerations during Translation**

I have gathered my interviews in both Swedish and U.S. settings. This means that two languages were used. In the Swedish setting all interviewees, with the exception of one with whom English was used, spoke Swedish. In the U.S. setting all the interviewees spoke English.

I transcribed all the Swedish interviews and a professional, native U.S. transcriber familiar with the medical and technological terms used in the interviews transcribed the U.S. ones. I have, however, listened to the U.S. interviews twice each to make sure that the transcripts were correct. If they were not, I made the necessary

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19 The purpose of this question was to investigate how much encounter they had had with gene transfer research. This turned out to be a very important question as it revealed that some of the members, especially in the advisory boards in Sweden, had a low level of knowledge regarding gene transfer.

20 The transcribed interviews resulted in slightly more than 400 pages.
changes. In the following empirical chapters Swedish excerpts are translated into and presented in English. In the translation process of the Swedish excerpts I replaced Swedish expressions with similar expressions in English. It should, however, be noted that language carries different social and cultural meanings which need to be acknowledged and taken into account. This was, for instance, the case when the notion of enhancement as improvement was discussed among the Swedish interviewees. It turned out that the Swedish word ‘förbättring’ translates as both ‘improvement’ and ‘enhancement’ in the English language. In other words, the same word can mean different things. Aware of these difficulties, I used transcripts in Swedish when conducting the analysis of the Swedish interviews. The translation of the excerpts into English came last. With the intention of losing as little as possible of the social and cultural meanings in Swedish when I translated the excerpts into English, I sometimes discussed the translation with a person who has English as a native language. Some of the quotes, in cases where it was needed, have been edited for readability.

Another important aspect that needs to be addressed is that when an interview is transcribed, it converts and translates from being an oral conversation into a written text. It becomes a transcription, a written copy, of a conversation (Kvale and Brinkmann 2009). This means that the interviewee’s tone of voice, intonations, and physical gestures, things that were observable during the interview, are lost. Because of this a transcription becomes a rather abstract and fixed written form. In my case, this has not been a problem as I have conducted all the interviews myself. I have seen the interviewee’s gestures and heard their tones of voice as well as intonations. I have also listened to the recorded interviews afterwards which allowed me to ‘re-live’ the interviews.

I also want to emphasize that I have not focused on the transcripts as a mere collection of statements. Instead I have entered into an imagined conversation, a dialogue, with the text, about the meaning of it. The conversation that started in the interview situation has been continued throughout my analysis of the transcribed interviews.

The Analysis

After the transcription of the interviews was done, I began to analyze the data. In this section I will describe my analytical process and the analytical strategies that I have used. Looking back at the analytical process, I want to point out that this process has been more complicated and tentative than the presented simplification of it here.

To begin with I first did a descriptive analysis of the interviews, in order to familiarize myself with the data. I basically went through what the interviewees discussed during their interviews. I looked for recurring topics in the interviews and tried to identify patterns both within and between the interviews. I then conducted a thematic analysis that was based on a grounded theory perspective. The choice to
use grounded theory as a method was made because I needed something that practically, as well as analytically, could help me to sort all my data. According to sociologist Kathy Charmaz (2006:2), grounded theory ‘consists of systematic, yet flexible guidelines for collecting and analyzing qualitative data to construct theories “grounded” in the data themselves’. This was exactly what I needed. Consequently, I used her guidelines as a basis for the analysis of the collected data.

In the first phase of the analysis of my data I conducted a line-by-line analysis in specific sections of the interviews in which I had identified different statements regarding gene transfer – its research as well as its applications. I gave each line of written data or sentence in these sections an initial code – a short name closely related to the data. These initial codes were either descriptive and described events, specific contexts, or perspectives, or they were clarifying, proving reasons and explanations. Some of the initial codes are terms or native concepts, like ‘good for the country’, ‘educate the people’ and ‘implied authority’ expressed by the interviewees. I developed other terms myself in my process of getting a better understanding, interpretation, or explanation of the data.

In the second phase, after the initial coding, I began to select, separate, and sort the codes as well as specific sections of the data so that I could begin to get some higher level of understanding of what it meant. In order to find variations in the data I compared data from different interviews like the interviewees’ views, accounts, actions, and experiences of gene transfer research. I also compared data from the individual interviewee at different points in time during the interview. Making these comparisons stimulated my thinking about what it really was that the interviewees talked about. It also helped me to search for patterns that I previously might have failed to notice. It was during this part of the analysis that I began to develop themes such as ‘handling conflicts of interest’, ‘obtaining a valid informed consent’, and ‘combating misunderstandings’, which will be discussed in Chapters 4, 6, and 7, respectively.

When I outlined this study I especially wanted to investigate what ethical, legal, and social issues in gene transfer research, whether somatic or germ-line, were considered as relevant, interesting, and important to discuss by the gene transfer scientists and members of regulatory agencies and advisory boards. As it turned out, the gene transfer scientists were not all that interested in taking about the ethical, legal, and social issues of gene transfer, unlike the members of regulatory agencies and advisory boards. Instead they discussed their work and how the policies, the oversight system, the media’s framing of gene transfer, and other circumstances affected and influenced the gene transfer practice in general and hence also their work. They talked about how to make research doable in a controversial and morally debated field of research. More specifically, they talked about the research process and how a complex technology like gene transfer required handling various problems and conducting different activities. It required getting funding, pulling together various actors and factors, handling problems in basic research during vector development, moving gene transfer from preclinical studies in the laboratory to clinical trials on
human subjects, getting applications for clinical gene transfer trials accepted by regulatory agencies, and dealing with different ethical complications in the clinical practice. In other words, they talked about gene transfer research from the bench to the bedside, and all the different activities that it involved. As these issues were present in all the scientists’ interviews I realized that I had to reorient the focus of my analysis and find theoretical concepts that would help me generate a greater understanding of what it was that my interviewees talked about, and particularly how I should interpret what they talked about. I found these theoretical concepts within Science and Technology Studies (STS). More specifically, I found them in studies of scientific, medical, and ethical controversies as well as studies of scientific work and how scientific knowledge is produced.

The last phase of the analysis, the application of different theoretical concepts from these STS studies, highlighted new aspects in my data. As described in the theory chapter, these theoretical concepts sharpened my interpretation, and hence also my analysis of the data. They became what Herbert Blumer calls sensitizing concepts, that is, analytical tools that helped me to analyze my data from new perspectives. According to Blumer these concepts ‘give the user a general sense of reference and guidance in approaching empirical instances […] they merely suggest directions along which to look’ (cited in Clarke and Star 2008:118). The use of these theoretical concepts has enabled me to better capture ‘the big picture’ or ‘the core problems’ of conducting research in a controversial field of research by turning my attention towards the situation in which the two gene transfer practices are embedded. These concepts further helped me to refocus my research questions, making me rethink, reevaluate, and reinterpret my data.

The analysis of my data has been a continuous process in which I have constantly moved between data and theoretical concepts. It has been a process of ‘double fitting’ – manufacturing the key and the keyhole simultaneously (Berner 2005:140). The theoretical concepts have made certain themes stand out in my analysis, like those involving doable problems, doability, articulation work, and handling and meeting various problems. The data, however, also shaped how I understood and applied concepts. As an example, it was the data, or what the gene transfer scientists said themselves, that led to metaphors such as ‘from bench to bedside’ and ‘equivalent to established medical treatments and standard procedures’. In the analysis, all the different phases of coding, sorting, comparing, and grouping data, using sensitizing concepts, and finding empirically grounded analytical concepts have been of crucial importance in the analytical process. In this trial-and-error-process of going back and forth between data and theoretical insights my themes have been refined. Similarly, writing analyses, discussing them with my supervisors and at seminars as well as with others, and rewriting them again have sparked new ideas, and

21 It is important to note that the interviewees did not choose to talk about how different laboratory tasks were done in detail, nor did I ask any questions about this kind of work.
analytical points, and has thus helped me carve out better arguments in the writing of the final analysis.

**Reflections**

Looking back at the research process and the way that I have conducted this study there are some methodological limitations that need to be addressed.

I have conducted qualitative in-depth interviews with gene transfer scientists in Sweden and the U.S.A. about their work. This has allowed me to get an understanding of how they describe and reason about their work, inside as well as outside their gene transfer research. It has not, however, enabled me to see how they do their work. This means that I only know how they talk and reason about it. I can therefore not discuss any differences between what they say they do, and what they actually do.

Interviewing gene transfer scientists moreover carried the risk that I would get biased and partial descriptions of how it was to work in a contested and controversial field of research. I ran the risk of getting ‘official’ versions of their experiences and opinions and the risk of them giving propaganda speeches in their defense, as well as self-justifications. My impression was that occasionally some of the interviewees, both scientists and regulators, gave me the ‘official’ version in which they recited PR rhetoric or phrases from various public policies and guidelines, rather than their personal opinions or experiences. This was especially the case when we discussed germ-line gene transfer, but also to some extent when we discussed regulatory frameworks. Yet this is understandable, if one takes into account the deeply controversial nature and context of gene transfer, and especially of germ-line gene transfer.

For a researcher, studying gene transfer research means ‘going native’ in a field surrounded by controversies. It is easy to get involved in the troublesome situation described by all the gene transfer scientists whom I interviewed. I have tried to handle this problem by interviewing both scientists and regulators. For example, the interviews with regulators provided me with another point of view – the regulatory viewpoint - that helped to put the scientists’ arguments into perspective. I also chose to take a controversy perspective in my analysis. This meant that it was important that I did not take any side in the controversies. My task was instead to keep a distance from what the interviewees talked about, maintain a neutral perspective,

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22 When my primary focus was on the ethical, legal, and social issues related to the development and application of gene transfer I also conducted eight preliminary interviews with bioethical experts (three in Sweden and five in the U.S.A.). The reason for interviewing bioethical experts was that I wanted to achieve a greater diversity of experiences of gene transfer research. These bioethical experts were selected as they were prominent actors within the ethical debates of gene transfer. They were all senior professionals.
and to provide a descriptive and exploratory perspective of the interviewees’ descriptions.

The gene transfer scientists’ defensive propaganda speeches during the interviews, their need to define their work, and their urge to defend, often by self-justification, their work and actions drew my attention to the specific situation of gene transfer research. My attention was drawn as well by the question of why they continued to work in the field of gene transfer, and not just scientific work per se. However, the fact that the interviewees used ‘propaganda’ is not a problem. The problem is that they used this representation during the interview with me, and that it is this specific picture of conducting gene transfer research that they want me to convey in this study. Again, I have tried to maintain a neutral perspective to their descriptions and only described what they have said, while at the same time trying to find explanations for why they talked this way. Consequently, I have not accepted their descriptions as the only truth of the matter.

This study was conducted in Sweden and the U.S.A. This means that it provides two pictures of gene transfer research, a Swedish one and a U.S. one. In the following empirical chapters the similarities or differences between these two pictures are not always distinct. This is especially evident in the interviews with scientists. My impression is that the gene transfer scientists whom I interviewed in the data appear as a homogeneous group with similar, if not identical, views and experiences of gene transfer as well as of working in this field of research. Although I have looked for disagreements in the data, I have not found any obvious ones. I have, however, found varieties in the data, and in the cases where a clear distinction could be made or where one theme was present in one picture but not the other, I have clearly stated this. This study does not aspire to say anything about gene transfer research in general, nor about how controversial research is conducted in general. It aspires only to say something about how the gene transfer scientists in Sweden and the U.S.A. whom I have interviewed described and reasoned about making their work doable.
Gene transfer is a complex process that requires both specific expertise and skills as well as groundbreaking and innovative technologies. It requires a significant amount of expensive implementation, from experimental studies in the laboratory to preclinical studies in animal models, to scale up and the manufacture of clinical-grade gene transfer reagents in order to conduct clinical trials in human subjects. Gene transfer is furthermore a research field that is highly controversial. Its safety and clinical efficacy is disputed by scientists as well as the public and there is an absence of imminent clinical success.

In this first empirical chapter and the following three chapters, I describe and discuss how scientists handle the research process in gene transfer research from bench to bedside. I show that scientific work involves many different components, such as specific actors and practices, research materials, technologies, techniques, and skills. It also involves organizations, investors, industrial sponsorships, regulatory authorities, and audiences such as the general public and the media. All of these components make the process uncertain and must hence be handled in some way by gene transfer scientists in order to make their work as well as their research doable.

This chapter deals with how the gene transfer scientists whom I interviewed constructed doable problems at the beginning of a research process. More specifically, how do they handle funding problems, and expertise problems when gathering the necessary elements such as specific skills, technologies, and materials, that are needed in order to conduct basic, preclinical, and clinical research? When the basic and preclinical research have begun, at the bench, how do gene transfer scientists find the ‘right’ material to use as vectors for the transport of the genetic material into the cell? And are there other technical problems that need to be handled?

**Making Research Work – A Question of Making Doable Problems**

Making gene transfer research work means that doable problems have to be constructed. Not only do scientific problems regarding the technology need to be doable. Instead, it is mainly the problems of getting funding and gathering the necessary elements that need to be constructed so that they become doable. In other words, they must be transformed from being problems into being ‘doable’ problems that can be solved and make the research work possible. In my analysis I have used sociologists Adele E. Clarke and Joan H. Fujimura’s (1992) and Fujimura’s (1987, 1988,
1997) concept of ‘doability’ and sociologist Anselm Strauss’ (1988) concepts of ‘articulation work’ and ‘alignment’ to investigate how the gene transfer scientists whom I interviewed constructed doable problems. As described in the theory chapter, for a problem to become doable, various work activities must be aligned with each other. Constructing doable problems is about alignment, that is, pulling together various elements needed for research in the right sequence, at the right time, and at the right place, by articulation work. This is done in order to achieve a particular goal. The goal must further be coordinated with other work activities or goals to achieve the primary goal of moving gene transfer from bench to bedside. This means that constructing doable problems is to a large extent about coordinating, and if necessary re-coordinating, various work activities with each other. This demands, I argue, an intricate collaborative work between different actors, locally within the scientist’s own university, and also nationally and internationally, and both within and between academia and more commercial settings. It is important to note that I only investigate how doable problems are constructed on two of Fujimura’s (1987) levels of work organization – the laboratory\(^{23}\) and the social world\(^{24}\) and not on the level of experiment\(^{25}\). This means that I look at the social world of gene transfer research as a whole and at how this larger context as well as various work activities in the laboratory in general are described by the interviewees. I also look at how the social world of gene transfer research interacts on specific matters with other social worlds such as those of investors and commercial sponsors. Despite the fact that the interviewees and I did not discuss how they conducted different laboratory tasks, they emphasized the importance of finding the ‘right’ material, thus revealing important strategies for how they constructed doable problems in the laboratory.

When I asked the gene transfer scientists in this study what they considered to be the largest obstacles in getting their research going they all emphasized two specific problems – unique funding problems and expertise problems.

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\(^{23}\) With the laboratory I refer to the unit were scientists conduct their research. Examples of these units are the scientists’ own research divisions, departments, centers, or institutions.

\(^{24}\) Fujimura’s (1987) definition of social world emanates from Clarke’s (1991:131) definition in which social worlds are defined as ‘groups with shared commitments to certain activities, sharing resources of many kinds to achieve their goals, and building shared ideologies about how to go about their business’. However, when investigating how doable problems are constructed in basic cancer research, Fujimura uses a specific definition of social world in which it is the larger context in which experiments and laboratories are situated. In her case the experiments on oncogenes are situated in the scientific worlds of molecular biology and cancer research. I see social worlds in the same way as Clarke does, but when analyzing how scientists make their work doable I specifically look at the social world of gene transfer research and how it interacts on specific matters with other social worlds such as those of regulators, investors, the media, and the public.

\(^{25}\) The reason for this is that I do not have material regarding the first level of work organization, that is the experiment. Interviewees did not choose to talk about how different laboratory tasks were done, nor did I ask any questions about this kind of work (for a further discussion see Chapter 3).
Unique Funding Problems

The general view among the interviewees was that gene transfer research was a difficult field to work in. And many of them, as Scott voiced it, were very ‘upset about the funding situation’ (p. 17). Gene transfer was described as an expensive technology to develop and implement. It was expensive to design and develop vectors, as well as suitable animal models for preclinical studies. It was even more costly to scale up the research and move to clinical trials with human subjects. This was due to the high expenses involved in producing clinical-grade gene transfer reagents, such as vectors, to use in clinical gene transfer trials.

In both Sweden and the U.S.A., gene transfer research is mainly sponsored by the national and federal government. However, even if gene transfer scientists receive national and federal research funding, carrying out gene transfer research is exceedingly expensive. It cannot be covered by academic funding alone. As a result, gene transfer scientists try to get funding from other actors, like commercial sponsors and investors, patient associations, or individual patients and their families.

Getting funding for gene transfer research was described by the interviewees as presenting a challenge. They defined the funding problems as being unique to gene transfer research, as compared to other medical research. There were four factors that contributed to the funding problems. First, there is not yet any gene transfer product or procedure approved by the U.S. Food and Drug Administration (FDA) or the Swedish Medical Products Agency (MPA). This means that the prospects of a rapid commercialization are low. Second, gene transfer is a novel and thus a rather uncertain technology, surrounded by hype and high expectations that are difficult to fulfill. As previous clinical gene transfer trials have shown, gene transfer is difficult to develop and implement successfully. Third, there are risks associated with the vector systems used, and fourth, previous adverse events in gene transfer research have damaged the reputation of the field and still continue to cast a shadow over it.

The Absence of Approved Gene Transfer Procedures or Products

There is today only one gene transfer product in the world that has obtained market approval. This product, Gendicine®, has been approved by the Chinese FDA for the treatment of head and neck squamous cell carcinoma, which is a nonmelanoma skin cancer with a high risk of metastasis. There are, however, notable products that have received orphan drug designation in Europe and the U.S.A. The fact that there was an absence of an FDA-approved gene transfer product or procedure in the U.S.A. was described by Spencer as making it more difficult to get funding for

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26 An orphan drug designation is given to a pharmaceutical agent that is developed specifically to treat a rare disease or condition, that is, an orphan disease. The designation provides several incentives such as that it is easier to gain market approval and financial incentives like extended exclusivity periods. The main goal with an orphan drug designation is to stimulate the development of medicines and treatments for orphan diseases.
gene transfer research. He explained that ‘if you label your company as a gene therapy company you will have great difficulty in raising money’ (p. 14). The difficulty, he explained, was that gene transfer could be viewed as a ‘commercial failure’. Despite large investments from the venture capital community, gene transfer had yet not presented any imminent clinical successes or a commercial product. This made it difficult to attract investors. It therefore became important to try to determine in which area gene transfer could be successful. He explained that

once you understand where you work well and you appreciate what disease sets that are applicable, from a funding perspective, then you need to show potential investors that they should invest in your company amongst the large number of choices that they have. (p. 13)

It seems that in order to make the XX company, where Spencer works, interesting as an investment opportunity, several criteria had to be met in terms of risks and potential benefits of the investment. There was, however, one criterion in particular that he talked about, and that was patentability. This was a prerequisite in order to attract potential investors. In any grant setting, Spencer explained, gene transfer is only attractive to invest in for a venture capital firm if the new information can be patented. If new information, like vectors, could not be patented then they could not be commercialized. No commercialization meant no profits. What Spencer discussed was the importance of scientists aligning the interests of investors with the interests of the XX gene transfer company. This sometimes meant that the interests of the company needed to be adjusted so that it met the investors’ demands.

A Novel Technology Surrounded by Hype and High Expectations

The second contributing factor described by the interviewees was that gene transfer was a novel technology and field of research. Despite high hopes for clinical efficacy and effectiveness it has become clear that it is difficult to achieve an effective and therapeutic effect in humans. Although several studies have shown beneficial features, like the somewhat stable transfer of genes as well as the improved gene expression of foreign genes, they have not shown a sufficient degree of efficiency; instead they have shown serious and sometimes fatal unexpected side effects. This has come as a harsh surprise to scientists, regulators, investors, and others, and consequently caused disappointments as well as concerns which have affected the possibility of funding. In this context two of the interviewees clearly stated that the difficulties in getting funding for gene transfer research were mainly due to previous actions by the researchers themselves. Much of the hype and many of the unrealistic high expectations of gene transfer were caused by, as Stuart explained it, ‘the field itself and the investigators in the field who promised too much’ (p. 13). Sixten concurred with this view and said ‘I think we can all agree that in order to enhance
Making Doable Problems

one’s possibilities to attract venture capital there have been people who have promised too much with regard to the gene transfer technology’ (p. 4). The exceedingly overstated possibilities and current state of gene transfer have had, Stuart explained, a ‘poisonous effect’ on the funding situation as well as on gene transfer research in general (p. 13).

Risks Associated with the Vector Systems Used

The third contributing factor described was related to the vector systems used. Some vector systems, such as viral ones, had been involved in the previous unexpected and unforeseen adverse effects that had occurred in the Jesse Gelsinger case and the X-linked severe combined immune deficiency (X-SCID) trials. Because of this, viral vector systems were generally regarded as involving greater risks. Despite the fact that these risks were only associated with viral vector systems, people tended to believe that these risks were also present in non-viral vector systems. In practice, this is not the case as non-viral vector systems are synthetic vectors based on DNA. They cannot integrate with mammalian cells and are thus safer in this aspect, compared to viral vectors. Spencer described the recent events concerning toxicities with viral vectors which, he argued, tended to ‘cloud the thinking about our [the company’s] non-viral systems in ways in which it shouldn’t’ (p. 13). Consequently, the risks associated with the viral vector systems used in gene transfer had a negative impact on investors. And for Spencer, who worked with non-viral vector systems, this was a major problem. Luckily, this kind of thinking, he explained, was not prominent within federal funding or the grant setting. It was therefore easier to get funding from NIH and foundations than from other investors.

Previous Events’ Influence on Gene Transfer Research

The fourth contributing factor consisted of previous events in gene transfer research. It was, in particular, protocols that in retrospect had turned out to be not so ‘very rigorous and very clear’, as Stuart put it (p. 13). The protocol that he referred to was the one used in the partial ornithine transcarbamylase (OTC) trial at the University of Pennsylvania in which one of the human research participants died. Investigations of the protocol revealed that the lead investigators in this clinical trial had misrepresented the clinical findings to the National Institutes of Health (NIH) and the FDA (Couzin and Kaiser 2005). Federal rules were violated in the conduct of the clinical trial. The lead investigators deviated from the approved study design, thus exposing human research participants to greater risks. They moreover did not report adverse events to the appropriate authorities. A subsequent investigation of other clinical gene transfer trials revealed that a widespread non-compliance with federal requirements for clinical research seemed to have taken place (Steinbrook 2002). Members of the NIH Recombinant DNA Advisory Committee (RAC), at the time, Theodore Friedmann et al. (2001), concluded that these events and the subsequent concerns regarding gene transfer research and its quality as well as safety for
patients had damaged the field. Consequently, concerns have been raised among potential investors that gene transfer scientists, due to financial conflicts of interest and to their ambitions to be the first (and famous) to succeed in gene transfer research, may choose not to comply with federal requirements and hence jeopardize the health and well-being of participants in clinical trials.

To summarize, the interviewees discussed four main factors that contributed to the difficulty of getting funding for gene transfer research. All these factors had, in different ways, a negative impact on investors. More specifically, they affected their willingness to invest in gene transfer as they revealed that gene transfer was still experimental and exploratory in character, that it involved various degrees of risk, that it was a field of research surrounded by hype and high expectations, and that previous events had raised concerns regarding the entire field. In theory, gene transfer holds great promise (Smith 2003) and its advantages are beyond question (Rubanyi 2001). In practice, however, gene transfer is a complex process. According to medical writer Jack McCain (2005:52) gene transfer in its current state is an ‘elegant concept crudely executed’.

There is an additional reason for why it is difficult to get funding for gene transfer research. Gene transfer has from its beginning had as its main target what is called orphan diseases — inherited monogenetic diseases such as X-SCID, hemophilia, and cystic fibrosis, which affect only small, limited parts of the population. Due to their low prevalence in the general population, investing in treatments for these diseases has often been regarded as unprofitable by the pharmaceutical industry. It is not cost-effective to make or to market new medications or treatments for orphan diseases (The National Organization for Rare Disorders 2003).

Strategies to Attract Funding

The interviewees described several strategies that they employed in order to handle the problem of getting funding. Common to these strategies was that they were employed in order to meet demands from national and federal governments, sponsors, and other investors. It should, however, be noted that strategies such as these are common in all medical research. Nevertheless, as discussed in previous sections, gene transfer research struggles with funding problems that are unique compared to those in other medical research.

I will now show how the interviewed gene transfer scientists, by aligning their research interests within the interests of investors, shifted the targeted diseases, had individual patients and their families fund specific gene transfer projects, and most importantly, collaborated with the biotechnology and pharmaceutical industry. A

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27 An orphan disease is a rare disease or condition that has a low prevalence. Commonly this means that it affects between 1/1500 to 1/2000 people according to U.S. and European criteria. Diseases that are common in developing countries but not in the developed world can therefore be regarded as orphan diseases. Examples of these diseases are tuberculosis and malaria.
fifth strategy, concerned handling conflicts of interest. These are strategies also used in other medical research. Through these strategies they carried out what may be called articulation work, that is work to align and coordinate the research interests between different levels of the social world and the laboratory, and thereby achieve doability.

**Shifting Targeted Diseases**

Diseases and conditions that affect a large part of the general population necessarily receive a larger amount of national and federal funding. Due to the problem of getting funding for orphan diseases, the field of gene transfer has shifted a large part of its research toward diseases like cancer and infectious diseases such as HIV. This has been done to attract national and federal funding as well as commercial sponsors like biotechnological companies and big pharmaceutical companies. Scott described this strategic action and explained that there has to be a corporate interest for this kind of research, otherwise it would be difficult to get funding. This was, as he remarked, the reason for why there has been a shift in gene transfer from single monogenic disorders, which only affect a few, to cancer, which affects a large amount of people. Gene therapy, he explained

was originally thought about to treat single monogenic disorders, like genetic diseases, most of which are extremely rare. There wasn’t a lot of corporate interest in this at the time, because these are not money-making diseases to try to develop therapies for, but then people soon realized that you could put genes in that would have other effects for other diseases, like cancer, which is now probably the number one disease for which gene therapy trials have been developed. I mean clearly in our western world that is a major disease entity for which the therapies are not optimal, so there is a lot of interest in that. (p. 4)

As stated above by Scott, the key to getting funding was to localize a major disease entity, like cancer, for which current therapies were not optimal. The reason for this strategy was that it is generally private companies that manufacture innovative new therapies or procedures. They want guarantees that they can make a profit on the research findings through patents and commercially viable products. In other words, they want to make sure that it is cost-effective to make and market a new therapy or procedure. Several of the interviewees explained that to align the corporate interests with those of the scientists was the only way to be able to do research. Thus, it seems that it is to a large extent the corporate interests that direct the research orientation. However, among the interviewed Swedish scientists the corporate interest and the scientists’ interests coincided with one another. Four of the Swedish scientists worked with various forms of cancer and the fifth worked on different forms of cardiovascular disease. The U.S. scientists, however, worked primarily on various
hereditary disorders such as hemophilia, cystic fibrosis, Batten disease, and Lesch-Nyhan disease, or other diseases such as diabetes.\textsuperscript{28}

**Having Individual Patients and their Families Fund Specific Gene Transfer Projects**

Many gene transfer scientists are nevertheless interested in finding treatments for orphan diseases. This was the case for some of the interviewees in this study. Knowing that these diseases were difficult to get funding for, one of the interviewees described the strategy that he had developed in order to make his research doable.

Shane participated in a clinical study on Batten disease, an inheritable disorder of the nervous system that begins in childhood and is fatal in the late teens or twenties. He explained that

\begin{quote}
from the time we start, that is from the gene, to the time of finishing the clinical study in 11 patients, which will be a total of about 5 years, the research will have cost about $10 million. (p. 13)
\end{quote}

This is a significant amount of money that Shane, among others in the project, had to figure out how to get. This, he went on to explain, was ‘part of the job’ (p. 13). The strategy employed by Shane and his co-workers in the project was to let the parents of the 11 patients pay for their children’s participation in the clinical trial. This meant that they possibly paid for the entire gene transfer project. This is what they allegedly did, according to other interviewees, but Shane did not tell me this himself. Whether or not this is a common strategy in the attempts to get funding, I do not know. Bioethical experts and members of regulatory agencies and advisory boards have raised concerns about this way of managing the difficulty of developing resources for gene transfer research. It remains clear, however, that occasionally individual patients, their relatives, and patient organizations contribute to, and hence to a varying extent, pay for gene transfer projects aimed at their particular disease or condition.

**Collaborating with the Biotechnology and Pharmaceutical Industry**

As previously described, the interviewed gene transfer scientists described how they had shifted targeted diseases in order to attract investors. However, getting com-

\textsuperscript{28} Although these diseases are mainly located outside of the corporate interest it could be easier to get funding for them in the U.S.A., as many of these diseases such as cystic fibrosis and hemophilia have strong patient organizations behind them, and that fact may affect the research orientation in gene transfer.
commercial sponsors such as the biotechnology and pharmaceutical industry to invest money in research was not enough. Nor was it sufficient with national or federal funding. The reason was that gene transfer is expensive both to develop and to implement in clinical practice. This meant that the biotechnology and pharmaceutical industry had to be enrolled as active collaborators in the development and clinical implementation of gene transfer.

In order to be able to move experimental studies of gene transfer from the laboratory into clinical trials, the interviewees described that joint collaborations were necessary between different research groups within academia as well as with commercial sponsors and investors. The Swedish interviewees emphasized especially the indispensability of joint collaborations. As an example, Sune explained that in gene transfer research the high expenses were the clinical trials when the produced material was to be tested in human subjects. ‘Today’, Sune explained, ‘it is mainly Phase I and II studies that are being performed as these studies demand very small amounts of material’ (p. 12). If it instead was a question of a Phase III or IV study, then it was described as more difficult for a single research group to perform the clinical trial.

Clinical trials like these, Sune went on to explain, often demand ‘that different research groups joined forces’ or that the single research group has a ‘commercial sponsor’. This was according to him the ‘only possibility in order to perform a clinical trial today’ (p. 12), due to the high expenses which could not be covered by academic funding alone. This view was further emphasized by Staffan, who explained that not only was there no special investment in gene transfer research in Sweden, but

> ...a big problem for those of us who conduct clinical research with so-called academic money and without industrial sponsorship is that it is terribly expensive, and when it comes to, for example, the documentation demanded by these viral vectors. [...] The really big problem is when you’re producing a clinical batch that costs over a million. With all the attendant costs you eventually end up with costs of up to four or five million, maybe more, to treat 12-15 patients. Then you can’t do it with academic money. (p. 10-11)

By cooperating with other actors in their experimental work, gene transfer scientists can draw resources from both the academic and the commercial world. Collaboration with private companies, with regard to sponsoring, is a way to reduce development costs. This was described as something that was essential in the pursuit of moving gene transfer research into a clinical practice.

Sixten explained to me that the directors of different institutes at universities in Sweden often emphasized that collaborations with commercial groups outside academia were a prerequisite in the development of a commercial gene transfer proce-
dure or product. The reason behind this standpoint, he continued, was that ‘as a researcher you normally can’t develop a finished method of treatment; for it to become a product you need a company to cooperate with in its development’ (p. 19). This is why the aspects of commercialization were regarded as requirements and of significant importance among the interviewees. One U.S. interviewee, Sean, described the importance of commercialization like this:

The only viable way in our society of testing and distributing therapies is through the commercial sector, because government and universities are not into developing and distributing drugs. Actually quite frankly, we [gene transfer scientists] have a responsibility, as I view it, if we’ve discovered something in the lab that may help people, to try to facilitate its commercialization. I guess for that reason, because I don’t want our discoveries to sit around and rot in the lab, I have realized that really the only way we’re going to get it out to help people is to figure out a way to convince companies to take it on and to commercialize it. (p. 11)

As Sean stated, in order to be able to commercialize a gene transfer product, or any other product for that matter, scientists working in academia must establish collaborations with commercial companies because the goal of academia is not primarily to fund the commercialization of its findings. This means that gene transfer scientists who work in academia must collaborate with private companies such as the biotechnology and pharmaceutical industry, whose sole purpose is commercialization, if they want to commercialize their findings. Again, the concept of alignment becomes important. It is important for gene transfer scientists to investigate where the corporate and commercial interests lie and then convince companies that they will make a profit based on their research findings through patents and commercially viable products. In other words, they must align their interests with one another, as well as create what sociologist Bruno Latour (1999:104) calls alliances or enrollment of allies. These allies, people who are interested in their findings, must be made to realize that investing in gene transfer is going to be beneficial, something that will improve their business.

In this context, Scott described an aspect that he believed should attract investors, both federal and commercial. He thought that making an investment in gene transfer should be seen as something that comes back to help the economy and the country. It was something that was ‘good for the country’. What he underlined was that when academic people did research and there was a clinical application, new biotechnological companies sprang up. Large pharmaceutical companies commercialized the clinical application, and as a consequence got intellectual property rights by licensing the finding from the university. All made a profit from the clinical application (p. 16).
Handling Conflicts of Interest

The four factors contributing to the funding problems of gene transfer research, as discussed above, also demanded specific strategies. In the following three chapters I will discuss the strategies employed to attain an FDA-approved gene transfer procedure or product. These strategies are to handle the novelty and uncertainty as well as the high expectations and disappointments regarding the current state of gene transfer, and the risks involved in gene transfer due to the vector systems. Here, I will only describe how the interviewees tried to reduce, and if possible minimize, the influence of previous events on their funding strategies.

Most interviewees, when describing how conflicts of interest had affected them in their work, referred to one specific event, the Jesse Gelsinger case. As described above, this case revealed non-compliance with federal requirements. Deviations were made from the approved study design, clinical findings were misrepresented to the NIH, and adverse events were not reported to appropriate authorities. It was also revealed that there were substantial financial interests in the research for the principal investigator as well as the host institution. This had not been disclosed to the human research participants.

One of the U.S. gene transfer scientists, Stuart, who at the time of the Gelsinger case was chairing a federal regulatory advisory committee, told me the story of how this case had cast a shadow over clinical gene transfer research.

In 1999, a boy named Jesse Gelsinger died in Philadelphia in a gene therapy study, and that was another shock, because it involved again not terribly good science and not terribly good clinical research, but also all sort of ethical problems, conflicts of interest, uncertain use of money, funding other studies from various sources, and nobody knew what was being used for what. So everyone again felt very insecure about the whole thing, and the field was attacked and rightly so. (p. 10-11)

In the quote above Stuart underlined how the Gelsinger case made people insecure and doubtful regarding how clinical gene transfer research was being conducted. As a response to these concerns a new more specific regulation, involving three different restrictions regarding financial conflicts of interest, was implemented in clinical gene transfer research. Scott referred to these restrictions.

First, there is a restriction regarding what kind of job a gene transfer scientist can have as a sideline if working in academia. In consequence, being a consultant for a company while having a position at a university was suddenly more complex than before. ‘We started a company based on some discoveries that we made here [at the university],’ Scott said, ‘but we patented it through the university and then the university negotiated a license with the company’ (p. 21). Since then the company had been bought by another company and Scott was no longer directly involved in any
kind of business dealings. He said, though, that he still does a lot of consulting for them.

…and there is a Conflicts of Interest Committee [at the university] that meets every six months or so. I forget the exact frequency. I have to write a report as to how I manage the conflict. (p. 21)

Open handling of the financial conflicts of interest is in other words very important – especially if one has a position at a university, as Scott has. It is essential, he continued to explain, that academic faculties are not an ‘extension of the company, so that the lab isn’t being used to promote the company’ (p. 21). Instead, one’s academic position should show that the laboratory is a training center, a learning center, in which students and trainees evolve, get their PhDs or post docs and in the end become faculty members. The university merely wants to make sure, Scott concluded, that the work conducted there is not being inhibited in any way, based on an agreement that a faculty member has with a company (p. 21).

Second, there is a restriction regarding how much involvement a gene transfer scientist can have in a clinical gene transfer trial, while also having financial interests in its outcome. According to changes made in the U.S. federal regulations concerning research funding from a public health service agency after the Jesse Gelsinger case, a gene transfer scientist can no longer have financial interests in a study’s outcome and simultaneously be involved in the clinical trial. Scott described the effect of these changes. ‘The university will not let you do the clinical trial’, he said, ‘if you have a financial interest in the outcome’ (p. 22). Let’s say, he said,

…you discover a new vector, a company licenses it. You get some consulting fees or you get some money from the company for that, and then the company develops it and wants you to participate in a clinical trial with them. I mean there are real conflict issues there. [...] So if it is your discovery, or if you are working with a company that pays you some consulting fees or you have some equity in, stock option or whatever, you cannot control it. You cannot be in control of the clinical trial. You can participate in some respects in the planning of the trial, but you can’t have direct patient treatment with that. (p. 22-23)

This restriction was also discussed by Sixten. ‘I think it sounds completely reasonable’, he said, ‘that you should not be involved in a study if you are in charge of the clinical trial while also having financial interests in the outcome’ (p. 13). However, he concurred with Scott in the sense that he considered it ‘not unreasonable’ to participate in some respect in the clinical trial on the basis of the knowledge one could contribute (p. 14).
The third restriction applies to all medical research, and is a principle established by scientific journals, in which authors must disclose conflicts of interest before an article can be accepted and published.

The interviewees described the aftermath of the Jesse Gelsinger case as a professional and moral challenge that had troubling effects on clinical gene transfer research, especially regarding funding. In order to remove the shadow that this event had cast, and still continues to do over gene transfer research and clinical trials in particular, they all emphasized the importance of acknowledging the conflicts of interest in the setting of clinical trials, making sure that the line to what is considered not appropriate was never crossed.

To summarize, the interviewees described mainly four strategies that they employed to handle the funding problems of gene transfer research. The main goal with three of these strategies was to align the gene transfer scientists’ interests with the interests of other actors, primarily financial investors and private companies. In order to achieve this, the gene transfer scientists sometimes had to readjust their own research interests in the direction of potential investors. In order to get funding for finding treatments for orphan diseases, the scientists instead had to align their interests with those of individual patients, their families, or patient organizations. Besides aligning various interests with one another it was important to create alliances with actors such as the biotechnology and pharmaceutical industry. By collaborating with these actors, the expensive costs of scale up and manufacturing of clinical-grade gene transfer reagents for clinical trials could be reduced. The main goal of the fourth strategy, publicly handling conflicts of interest, was to show that they were honest scientists doing unbiased research within current regulations, and were thus safe to invest in.

Based on the interviewees’ descriptions of how they tried to handle the problem of getting funding for gene transfer research, I believe that by creating the powerful alliances with the biotechnology and pharmaceutical industry, gene transfer scientists can reduce their development costs and increase their possibilities of moving gene transfer from experimental studies in the laboratory to implementation in a clinical setting. More importantly, being a part of an alliance not only eases the funding problems. It also eases the gathering of expertise, skills, technologies, materials, laboratory space, and production facilities needed to make research work.

**Expertise Problems**

Gene transfer was described by the interviewees as extremely complex as it was a very broad field of research that covered the entirety of medical science. Due to its complex character, gene transfer research demands collaborations and commitments in various degrees from human actors inhabiting various social worlds, each with its own activities and interests. It needs the collaboration of gene transfer scientists, chemists, biophysicists, biologists, molecular modelers, basic researchers, preclinical researchers, clinical researchers, regulatory agencies and policymakers,
prospective patients and patient organizations, medical doctors, and other health professionals.

Gene transfer research is however not merely about different human actors, it is also about what Latour (1987) calls nonhuman *actants* – that is, actors that are not human. The most important nonhuman actants for gene transfer scientists are: gene transfer technologies, materials such as vectors and animal models, other technologies, laboratories, and production facilities. Put together with various human actors, these nonhuman actants form the basic elements of gene transfer work.

There are also other nonhuman actants important to gene transfer research. These are: funding resources, which I discussed in the first section of this chapter, as well as policies and guidelines, which I will discuss in the following chapter. All these actors and actants are pulled together in different work activities, that is, lines of research and subprojects. In order to achieve doability in gene transfer research all these actors, actants, and work activities must be aligned. This is, however, often difficult to achieve as these elements not only belong to different social worlds but also to different lines of research and subprojects.

**Problems of Coordinating Research Elements**

‘To do gene therapy, clinical gene therapy, you have to have the basic science. You have to have the translational. You have to be able to make the virus, or whatever the vector is that you’re doing. You have to have a regulatory group; I spend a million dollars a year on the people that just do the regulatory things. You have to have a group that can produce the virus, or someplace where you can get the drug, and if you don’t have access to that, you can’t do the study. I spend another million dollars a year doing that.’

The need to coordinate – to organize and integrate diverse elements in accordance with each other in order to make a gene transfer project doable – was described by Shane, in the quote above, as being of crucial importance. What Shane in fact talked about was the necessity of articulation work and the need to align different levels of work organization as well as various lines of research with each other in order to achieve doability. This was a very common theme in my interviews.

Doability, as previously described, demands alignment which is achieved by articulation work. The goal of articulation work is to maintain the work flow between different levels of work organization. In practice, this means that the work done by different actors, as well as the tasks they carry out, must fit together in time and place.
Gene transfer research involves three different lines of research: basic research, preclinical studies, and clinical trials. A successful coordination of these lines of research increases doability as one line of research normally uses the results of another line of research as its starting point. For example, clinical scientists use the results from preclinical scientists, who in turn use the results from basic scientists. The results from clinical trials on human subjects are then used again by basic scientists in their attempt to produce better vectors for clinical applications. This requires what Latour (1987:117) calls translation, which, in this case, refers to the process of moving gene transfer from one place to another, and from one line of research to another. In this sense translation has according to Latour a geometric meaning. More specifically, here the translation is a process by which gene transfer moves from ‘the bench’ with basic science, where it begins, to the clinical level, or the patient’s ‘bedside’.

Through the interviewees’ descriptions I have realized that articulation work also involves another aspect of translation. When gene transfer is incorporated into a new context, for example when it is implemented in clinical trials on human subjects, it is disembedded from a previous context and re-embedded into a new one. In order to make the transfer between two contexts successful it is important that gene transfer is perceived as similar, if not the same, by the enrolled actors in different lines of research. In this sense translation has a linguistic meaning in which translation from one context to another is done, as in translating from one language to another, with awareness of the fact that every context contains different social and cultural meanings.

The Need to Create Stable Milieus

In a study about the emergence of reproductive science in the U.S.A. Clarke (1997:75) points out that the social world of reproductive science is an intersection that composes ‘relatively stable milieu’. This ‘relatively stable milieu’ consisted of scientists in biology, medicine, and agriculture. Each of these fields individually, Clarke argues, was ‘sufficiently established with its own special markets, audiences, sponsors, and consumers bound to them by tradition and interest’. It was this that made the intersection considered as a ‘relatively stable milieu’. In these milieus scientific information, skills, and technologies were shared. They also shared materials in terms of animal models. Research ideas were further shared through their collaborations, which often resulted in jointly scientific articles. It is important to note that the various actors involved in the intersection became allies rather than competitors.

Because gene transfer is science that has never been done it involves high degrees of scientific uncertainties as well as unknown consequences for both humans living now as well as our descendants. It also involves diverse fields of research as well as actors outside of academia. In other words, it is an untested field of research lacking special markets, specific audiences and consumers as well as particular spon-
sors and investors. This means that it does not compose the same ‘stable milieus’ to which Clarke refers in her study. Creating stable milieus for gene transfer research is hence of significant importance for the scientists involved. How did the gene transfer scientists whom I interviewed manage to create stable milieus for gene transfer research?

**Strategies to Achieve Successful Alignment**

The interviewees described two strategies that they employed in order to handle the problem of gathering the expertise that gene transfer research demanded, and to align these various actors as well as their work with one another.

I will now show how the gene transfer scientists whom I interviewed, by creating alliances as well as creating a GMP laboratory tried to achieve doability in their work.

**Creating Alliances**

In order to make the gene transfer enterprise successful, collaborations with other laboratories and entities have to be established. Such collaborations depend on but also create alliances that are often powerful. In the first section of this chapter, I discussed how the interviewees created what Latour (1999) refers to as *alliances* with the biotechnology and pharmaceutical industry by aligning their interests with the interests of potential investors, in order to handle the funding problems. In the interviewees’ descriptions of how they tried to make their research doable I found similar descriptions of alliances, and especially of how these allies were enrolled.

When enrolling allies to create alliances it is important to enroll people that are interested in a particular goal, who see the collaboration as something beneficial which also contributes to their research and business. Being a part of an alliance facilitates the gathering of expertise, skills, technologies, materials, and production facilities. An alliance furthermore makes it easier to align all the diverse work activities, especially if the alliance is within a specific organization, like within a university. It is by creating alliances that stable milieus can be established.

For example, in order to make the development of gene transfer vectors doable, allies, often colleagues in other scientific fields, had to be enrolled into the project. Not only were these scientists in possession of the necessary skills and expertise, but they also often had access to needed technologies, techniques, and materials. One of the interviewees, Sixten, described that in order to develop gene transfer vectors he (a biologist) worked with a chemist, a person with molecular modeling skills, a biophysicist, and the person in charge of the production facility (p. 3). Three of these four diverse scientists were located within the same university, whereas the fourth worked at another university in the same town. The enrolled allies most frequently described by the interviewees were thus scientists in their own re-
search groups, laboratories, or universities. In other words, they were within the same organization.

If an alliance could not be created within an organization, like at a specific university, allies had to be enrolled from outside the university. Alliances such as these were sometimes described by some of the interviewees as problematic, as they often resulted in national and/or international collaborations. Consequently, it became much more difficult to align the different lines of research and subprojects within as well as between the levels of work organization. Because of existing restrictions from the universities, due to concerns regarding conflicts of interest and lawsuits, collaboration outside the university and especially exchanges of materials were not that easy to implement. Stuart described this often troublesome collaboration to me. In his words:

I can’t send a sample of things to anybody I want to any longer, and I can’t receive materials from people without convincing the university officer that it is the right thing to do. It used to be that you called your friend in New York and you’d say, ‘Could you send me a plasmid?’ and three days later you’d have it. Here, and now with this sort of Material Transfer Agreement function of institutions, you maybe never get it because some decision is made that this is not an appropriate thing for the university to do. (p. 27)

As Stuart emphasized in this statement, it could become quite costly as well as time-consuming to be unable to develop the needed materials within the limits of the organization. More importantly, it could result in problems that were not doable.

Creating a GMP Laboratory

The Swedish scientists whom I interviewed described another strategy used to create cooperation and a stable milieu. They described how different actors, themselves included, at the XX Hospital at the XX Institute had joined forces and established a Good Manufacturing Practice (GMP) laboratory. A GMP laboratory is certified by the Medical Products Agency, which means that the clinical production of vectors is guaranteed quality and prosecuted according to current GMP regulations. These regulations are equivalent to the regulations in pharmaceutical production.

Because the XX Hospital had a GMP laboratory, it had what Svante called ‘a big advantage’ as ‘from basic to the clinic, all steps are available’ (p. 7). As it turned out, the GMP laboratory had become a powerful milieu for the actors involved. It made all the steps from basic research to clinical implementation possible. The GMP laboratory meant that all steps within the laboratory level of work organization were available within the organization. It was therefore easier to articulate the work between the different lines of research as well as the different subprojects. All the actors, actants, and work activities needed to make the project doable were

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present within this particular level of work organization. For example, they had the production facility that could produce the virus or the vector, and this facility met the national requirements for production. They also had the production facility to produce animal models used in preclinical studies, as well as preclinical scientists who could perform translational studies in animals. Finally, when it was time for a clinical trial with human subjects, different medical professionals from the organization were enrolled in the project so that the human research participants could be selected and enrolled.

In addition, establishing the GMP laboratory had resulted in extended collaborations between different actors within academia and with private companies on both national and international levels. Svante explained that

now from basic research there are many groups that are doing basic research and there are many groups now interesting in conducting clinical trials and then between there is the GMP facility. This is a big advantage. We have everything. (p. 7)

Sixten also talked about the importance of the GMP laboratory. He explained that this facility was an important part of their gene transfer activities as it was a step towards moving gene transfer into the context of traditional pharmaceuticals. ‘This facility’, Sixten clarified, ‘has been used to, among other things, treat patients at the XX Hospital but altogether this enterprise has been used to develop different products that have been used in order to treat 150 patients all over the world’ (p. 3). In other words, creating a GMP laboratory increased doability.

To summarize, the interviewees described the importance of creating alignment between different lines of research, subprojects, and between levels of work organization. They also described the need for stable milieus. In order to achieve this they described two strategies that they employed to handle the expertise problems in gene transfer research. The main goal of these strategies was to create stable milieus in which gene transfer research could flourish. In order to achieve these goals the gene transfer scientists created alliances, particularly within their own organizations. Another strategy was to create a GMP laboratory which became a powerful milieu of diverse actors and actants. This increased the possibility for collaborations within the organization, but more importantly, it became a way to establish new alliances with other actors through national and international collaborations. It also made it possible to cross the borders between the academic and the commercial settings.

Among the interviewed U.S. scientists this strategy was not mentioned. A possible explanation for this could be that the U.S.A., as I described in the introductory chapter, accounts for two-thirds of all the conducted clinical gene transfer trials worldwide. Consequently, the interviewed U.S. scientists may already have established these GMP laboratories in their organizations.
This could have a positive impact on the gene transfer scientists’ funding situation and thus increase the doability of their research.

Problems at ‘the Bench’

Although the interviewees and I did not discuss their work in the laboratory, they emphasized the importance of finding the ‘right’ material.

Finding the ‘right’ material means creating vectors that meet several criteria. First, the vector should be capable of integrating and delivering the genetic material to the correct cells and to a specific site in these cells. Second, the integration needs to maintain a long-lasting gene expression, thus resulting in a high degree of efficiency. Third, it should be without toxic side effects. As previous animal studies as well as clinical trials with human research participants have shown, meeting these criteria is difficult. The vector sometimes integrates randomly in the genome or triggers the immune system. Risks such as these are primarily present in viral vector systems. Consequently, it becomes important to figure out how the human immune system works and, more importantly, what it is that these vectors trigger in the immune system in order to become toxic.

Doing gene transfer research at the bench means working on an ad hoc basis. This is above all due to the novelty of the manipulated material which consists mainly of viruses. A virus is a living biological material that is relatively easy to control when it is only present in the vector. However, when the vector interacts with an animal or a human being the virus becomes unpredictable. Previous studies, such as the Jesse Gelsinger case and the X-linked severe combined immune deficiency (X-SCID) trials (see Chapter 1), have shown that vectors do not always behave as gene transfer scientists expect. This was also illustrated in a case described by Scott. He elaborated,

hemophilia is a really interesting example, because we have very good animal models. There are dogs that have the disease, and there are mice that have the disease. The disease is very similar to what humans have, and we were able to cure the dogs and there was no toxicity, no problems. Some of the dogs are about six years old and they are still treated. But when we did it in humans, the treatment was only temporary. It only lasted for a short period of time, and it was because humans had a different immune response, immunologic response, than any animal that we looked at. We looked at a lot of species. (p. 9)

What he emphasized in this statement was that there is a significant difference between preclinical studies and clinical trials. What may work well in different animal models may not work at all, or may work differently in humans due to the biological differences between humans and animals. This was a very common theme in my
interviews, that humans are unique in some way. And what gene transfer scientists learned over and over again, Shane explained to me, was that humans were not merely big mice or bigger monkeys (p. 11).

It was thus almost impossible to estimate a possible outcome when developing vectors, as there are too many factors that contribute to uncertainty. This means that working with biological materials, especially living ones like viruses which can integrate into the host cells’ chromosomes, raises constant problems. As previously described in the introductory chapter, viruses raise concerns regarding insertional mutagenesis and immune response, as well as safety in relation to other vector systems used in gene transfer such as synthetic ones. These concerns are raised by gene transfer scientists themselves as well as by other actors, such as regulators, investors, bioethical experts, and the general public.

To have the ‘right’ material that works properly is thus decisive for gene transfer scientists. Without a vector that works appropriately it is difficult to commit other actors to gene transfer research and to further gene transfer in new lines of research. The most essential part in gene transfer, the vector, has to work adequately and efficiently enough. Without a vector there is nothing to build the research on, which obviously makes it difficult to attract investors. A vector that works improperly cannot be commercialized, which means that no profits can be made.

In Fujimura’s (1987) study about how doable problems in cancer research are constructed she points to how scientists in order to meet concerns from regulators, investors, sponsors, other scientists, and the general public, make changes in their experimental laboratory work through what she refers to as a specific form of articulation work. The main goal with this strategy is, Fujimura (1987:275; italics in original) argues, to ‘make adjustments in work organization within levels in the context of what is needed to create alignment between levels’. This is what also happens in many cases in gene transfer research.

**Strategies to Solve the Problems with Viral Vector Systems**

As described above, in gene transfer research there have been some unexpected results in clinical trials in terms of insertional mutagenesis and immune response. This has revealed the still very novel and experimental state of gene transfer. It is a state that also involves risks, especially if viral vector systems are used.

The interviewed gene transfer scientists met the concerns raised by different actors regarding viral vectors, as well as the new demands regarding safety through various forms of what I call articulation work. More specifically, they readjusted their work and shifted the material, or made further developments in the one they were using.
Shifting to Synthetic Vector Systems

When the use of viral vectors in early Phase I clinical trials with human subjects was shown to be problematic, several laboratories shifted their research direction. So did some of the Swedish gene transfer scientists whom I interviewed. They described one central strategy employed to find the right material. This was to shift the material for manipulation from viruses to synthetic vector systems. These ‘new’ vectors did not pose the same problems of safety as the old ones. More specifically, they are considered to pose less risk to patients with regard to insertional mutagenesis and immune response.

As an example, Sixten described the new research direction of his laboratory. We have developed our own technologies for gene transfer, he explained, where we depart from pure DNA. We culture plasmids in bacteria, then we refine these plasmids. This leaves us with what one could call a circular DNA, which is also twinned similar to a rubber band. [...] Then we add different components to this circular DNA so that it acquires special characteristics which make it easier to bind to cells, be taken up into cells, and end up in the cell nucleus. (p. 2)

Synthetic vectors, like the ones that Sixten talked about in the quote above, are not based on viral systems. They are instead based on DNA. Synthetic vectors have similar beneficial features to those of viruses but lack their unwanted properties. This means that synthetic vectors are safe in terms of being less immunogenic (causing or producing immunity or an immune response). Moreover, synthetic vectors are easy to produce.

This change in research direction was also expressed by Sune, who explained that the use of viral vectors ‘will be reduced as these systems are complicated to manufacture’ (p. 4). What he referred to was that high-quality viral vectors were difficult to produce. Sixten provided an illustrative example of this problem. When producing manipulated viruses, irrespective of their use, he explained, ‘of 1000 viruses there may be only one that is good, the other 999 may be altered somehow’ (p. 2). Faulty alterations like these were not only unwanted, but more importantly made the vectors unusable.

Because of the problems with producing viral vectors as well as the safety concerns that they raised, Sune predicted that the use of non-viral vectors in gene transfer would become more frequent. The reason for this, he went on to explain, was that by ‘picking qualities from viruses’ and then coupling them with plasmids, safer vectors could be developed as ‘the plasmids normally don’t integrate with mammalian cells; they can move between bacteria but they can’t normally integrate with human cells’ (p. 4).
However, it should be noted that there are also problems with synthetic vector systems. Although they pose less risk and are easier to produce than viral vector systems, they have a low gene transfer efficiency and a more transient expression, which may require repeated treatments.

**Further Developments of Viral Vectors**

Despite the adverse side effects of viral vectors, many gene transfer scientists have chosen to continue to work with them. Some of the interviewed gene transfer scientists had done so. One of the Swedish interviewees, Staffan, described a common theme in my interviews. Hitherto, nothing had been better to use than ‘nature’s own instruments’ in order to build and construct the more or less intricate vectors (p. 7). What he referred to were viruses. They often have a high degree of efficiency as well as a high level of gene expression. This was because many of these viruses have the ability to infect both dividing and non-dividing cells. Consequently, they are the most frequently used vector systems in gene transfer.

Among the five U.S. interviewees, four worked with viral vector systems. Among these interviewees, as well as for one of the Swedish scientists, the general notion was that current viral vectors needed to be improved and modified. New viruses also needed to be evolved and discovered, viruses that could be effective to use for the transfer of genetic material. It was, however, not only viral vectors that were described by the interviewees as needing further development. More knowledge also had to be gained regarding what happened in animal models and human subjects when new genes were added. How did the human immune system react? Where in the genome did the vector integrate? These questions, among others, regarding the presence of immune response and insertional mutagenesis when transferring genes, made it important to learn more about how viral vector systems worked in the patients.

In discussing the problem of immune response it was described as important to gain knowledge about how the human immune system managed the different viral vector systems. This was because some of the components used in gene transfer are foreign to patients with a normal immune system. Some of the interviewees also emphasized their wishes for a test that could be used on a human research participant before a gene transfer procedure, to see whether or not he or she had a preexisting immunity towards the vector that would be used in the procedure.

The problem of insertional mutagenesis which could lead to leukemia development was often referred to as a technological issue which in the future eventually would be solved. Insertional mutagenesis was only relevant in some settings and in a minority of applications like in the treatment of X-SCID. ‘It may be a disease-specific phenomenon’, Scott explained, due to X-SCID’s pathophysiology. This meant that it might not be a side effect in the treatment of other diseases (p. 5).

Sylve concurred and claimed that there must be something in this disease that added to vector effect causing the leukemia development. ‘We should otherwise
have seen this in some of the thousands of patients who have been treated with viral gene transfer vectors, but we haven’t, he said (p. 6). In practice, there are no sufficient scientific explanations for why insertional mutagenesis has happened in X-SCID patients and not in the ones treated for their severe combined immune deficiency resulting from adenosine deaminase deficiency (ADA-SCID), although almost identical conditions have been used (Kimmelman 2008).

To summarize, finding the ‘right’ material is difficult. It is about making the manipulated material work, regardless of its source, while simultaneously meeting existing demands regarding safety. The interviewees described two main strategies in their pursuit of the ‘right’ material, which involved readjusting their work. They shifted the material from viral systems to synthetic non-viral systems or became engaged in further developments of viral vectors. Despite the fact that developing vectors means working on an ad hoc basis and constantly facing different contingencies, all interviewees agreed on one point. It was important to continue to develop vectors. This general view is illustrated by this quote from Shane. ‘It’s going to take a while to get it right but eventually we will get it right and then these therapies will work’ (p. 7).

Concluding Discussion

In this chapter I have shown how gene transfer scientists try to construct doable problems out of a complex and controversial situation at the beginning of a research process as well as at the bench.

The theoretical concepts of alignment, articulation work, enrollment of allies, and translation have aided an understanding of the interviewees’ accounts of how they solved problems of funding, research organization, and laboratory work. They have had to use various forms of articulation work (Strauss 1988) in order to align their interests with those of other actors and actants, if necessary translate them, enroll them in their work, and thereby create doable research.

Two basic kinds of alignment seemed necessary to achieve. The first was the need to align the scientists’ own interests with those of others central actors, such as national and federal governments, commercial investors like biotechnological and pharmaceutical companies, individual patients, their families, and patient organizations. The second was to align the interests of other scientific experts with their own, in order to coordinate and conduct research within and between three lines of research, that is, basic science, preclinical studies, and clinical trials.

The articulation work used for this purpose involved the enrollment of allies. Two main forms of enrollment seemed important. The first was that of other scientists within academia or industry, with specific expertise and skills and working with one specific part of gene transfer research, whether it was vector development, preclinical studies in animal models, or clinical trials in human subjects. They are essential as they form the basic elements of everyday gene transfer research and have similar, if not the same, interests as gene transfer scientists. The second type of ally to
enroll is the biotechnology and pharmaceutical industry. It was necessary to have them on one’s side in order to meet the high costs of scale up and manufacturing of clinical-grade gene transfer reagents required in the clinical implementation of gene transfer, as well as its further commercialization.

In order to enroll allies and create alignment of interests, the scientists interviewed described various form of translation work. Translation is the process by which something is physically moved from one place to another. It could also be how something is translated from interpretations in one context to interpretations in another context (Latour 1987). One form involved the move of gene transfer from one line of research to another. For example, a successful clinical implementation of gene transfer demands that research results from vector developments in basic research can be used and tested in animal models during preclinical trials. This means that the results from one line of research must be able to be physically moved and applied to another line of research. It also means that every line of research has to do its specific part of a larger project. This is of crucial importance as one line of research in gene transfer normally uses another line of research results as its starting point. If a vector does not work or there are no suitable animal models to conduct preclinical studies on, then there is no reason for enrolling health care personnel and prospective patients for clinical trials on human subjects. This necessitated creating a common perception of what gene transfer is among all actors involved in the different contexts, from gene transfer scientists to other scientists involved in parts of gene transfer research, commercial investors, medical doctors, and other health care personnel. The gene transfer scientists needed to translate these actors’ interests in order to channel their work in the right direction, and construct doable research.

Reciprocally, the gene transfer scientists described how they needed to translate their own interests in order to align them with those of others. They readjusted their research orientation as well as their meaning of their work in order to meet the interests of potential investors. For example, some of them shifted their research orientation from single monogenic disorders to cancer because these diseases were easier to attract investors to and hence to get funding for. They also adapted their laboratory work in order to comply with current safety concerns, especially regarding the vector systems used in research. These various forms of articulation work seemed necessary in order to attract investors and research collaboration and achieve a stable research milieu – and thereby attract the necessary further investment and collaboration.
Resolving Tensions: Handling the Regulatory Setting

In the previous chapter, I discussed the beginnings of a research process in gene transfer. Particularly, I discussed the difficulty for gene transfer scientists to get funding for gene transfer research due to its controversial character. Gene transfer is furthermore a complex technology which requires advanced expertise and competence. It demands the participation and coordination of a broad array of actors and actants, each with their own unique expertise. Consequently, I showed how gene transfer scientists engaged in different activities in order to handle the funding problems and to attract and enroll powerful allies. I also showed how gene transfer scientists tried to find the ‘right’ material to use as vectors for the transport of the genetic material into the cell, and how they handled different problems at the bench. The goal of these activities was to construct doable problems in gene transfer research. Making clinical gene transfer research doable is in a sense not only about handling the uncertainties of funding, coordinating various actors, actants and work activities, or solving technological problems. It is also about constructing doable problems within the limits of existing policies and regulations. This is of crucial importance if gene transfer is to be moved from the laboratory to clinical practice.

As previously described, gene transfer research presents many social implications regarding issues like deliberate genetic modifications of human beings and thus of human dignity. It also presents unknown and unforeseen risks for human research participants enrolled in clinical gene transfer trials. Moreover, there is insufficient knowledge regarding how genetic interventions affect the individual undergoing treatment, and also future generations, as well as health personnel, society at large, and the environment.

The situation concerning the conduct of clinical gene transfer research varies in the world. For example, the acceptability of risks and potential harm and threats is perceived differently in different countries. Consequently, the policies that regulate gene transfer research and the regulatory structures in which applications for clinical gene transfer trials are evaluated differ between countries. Nevertheless, it is common to all countries that gene transfer, according to geneticist Jayne Spink and physician Duncan Geddes (2004), is internationally regarded as an experimental treatment, and is thus subject to the same legislation as conventional drugs.

This chapter deals with how the different regulatory settings in the two chosen countries affect how gene transfer research is done. I analyze what the regulatory setting, that is, the actual regulatory situation, means to the gene transfer scientists and the members of regulatory agencies and advisory boards whom I interviewed,
and the consequences that it has on their work. The emphasis, as in the other chapters, is on how the interviewed gene transfer scientists perceive the regulatory setting. As the regulatory framework is of significant importance in gene transfer research, I also interviewed members of regulatory agencies and advisory boards to investigate what they described as problems or challenges when implementing the policies.

As I show, different problems arise depending on in which country the clinical gene transfer research is conducted. Particularly, I show how what I call the loosely-regulated conduct of clinical gene transfer trials in Sweden versus the highly-regulated and monitored conduct in the U.S.A. result in different ways of working. In order to understand the tensions between gene transfer scientists and regulators, as presented in my material, I use the concept of boundary-work in my analysis. This term was originally coined by sociologist Thomas F. Gieryn (1983, 1999) to examine demarcation strategies used by scientists to distinguish their scientific practice from, for example, non-science in the form of religion or technology. I use boundary-work to examine how gene transfer scientists handle regulatory demands and the boundaries between the two social worlds of scientists, on one hand, and regulators, on the other. This results, I argue, in two forms of boundary-work in the U.S. setting; one that affirms the existence of boundaries between the two different social worlds involved, and one that transgresses it. Due to the different regulatory setting in Sweden, compared to the U.S.A., boundary-work is not necessary for Swedish gene transfer scientists. I will now present and discuss the two regulatory settings in turn, beginning with the Swedish regulatory setting and continuing to the U.S. one. The main focus will be on the U.S. regulatory setting for the rest of the chapter.

The Swedish Regulatory Setting

In this section, I first outline the policies that regulate gene transfer research in Sweden and the regulatory structure in which applications for clinical gene transfer trials are evaluated. Second, I present and discuss how the Swedish gene transfer scientists whom I interviewed described the Swedish regulatory setting and how it affected their work. I also comment briefly on how the members of advisory boards regarded the Swedish regulatory setting.

The Swedish Regulatory Framework

In Sweden the conduct of clinical gene transfer trials is what I consider loosely-regulated. The Swedish guidelines from 2006 recommend that somatic gene transfer research should be regarded as an experimental innovative therapy. This means that clinical gene transfer research is considered to present similar, if not the same, ethical issues as those in other medical contexts. Consequently, it is regarded as being in no need of special regulation. Germ-line gene transfer, on the other hand, is forbidden according to law, and has been since 1991. At present, it is regulated by the Act
on genetic integrity (*Lag om genetisk integritet m.m.*, SFS 2006:351). Gene transfer, like any other research involving human research participants, is further regulated by the Act concerning the ethical review of research involving humans (*Lag om etik av forskning som avser människor*, SFS 2003:460). According to this Act, all clinical gene transfer trials, regardless of funding source, must be reviewed and approved by a regional ethical review board before they can begin.

Clinical gene transfer trials do not require centralized ethical review in Sweden. Instead, they are mainly regulated on a regional level, at *Regionala Etikprövningsnämnden*, (the regional ethical review board). In the application for ethical vetting, the principal investigator must submit information regarding the study design. It must include where the clinical trial will be carried out, examination procedures used (such as the kind of interventions), methods of measurements, differences from routine clinical measures (if any and in what way), data collection including record-keeping (registering and processing of data), selection of human research participants (the risks they may be exposed to and possible compensation for participation), as well as informed consent procedure and conflicts of interest (*Etikprövningsnämnden 2009*).

Gene transfer applications intended for clinical use or commercialization must furthermore be approved by *Läkemedelsverket*, (the Medical Products Agency, MPA). In the application to the MPA, the principal investigator must submit a copy of the report from the regional or central ethical review board, the informed consent document, information regarding the human research participants of the study, a list of ongoing clinical trials with the same substance, a compilation of information regarding the tested drug or substance, and the manufacturing permission (*Läkemedelsverket 2006:3*).

If an application for a clinical gene transfer trial is deemed to be in need of further inquiry, *Gentekniknämnden* (the Swedish Gene Technology Advisory Board) and *Naturvårdsverket* (the Swedish Environmental Protection Agency) are contacted. They are the national advisory bodies for all applications regarding genetically modified organisms. Scientific and technological advances in gene technologies and biomedicine, especially the ethical issues that these technologies may raise, are, if deemed as required, also inquired into by another national advisory body *Statens Medicinsk Etiska Råd* (the Swedish National Council of Medical Ethics).

Transparency and public openness in clinical gene transfer research is almost non-existent in Sweden. Although gene transfer protocols reviewed by a regional ethical review board, or occasionally by the central ethical review board, are public documents, they are often not easy to obtain. They are not posted on the web and they are difficult to obtain from the ethical review boards upon request. In order to obtain a gene transfer application one must know either the name of the study, the name of the principal investigator, or the registration number of the application. Even if one is able to obtain a gene transfer application, there is a great possibility
that most of the application is classified due to confidentiality of, for example, issues regarding patents \(^{30}\).

**The Situation According to the Swedish Interviewees**

This quote from Sixten illustrates the general opinion among the Swedish gene transfer scientists regarding the policies that regulate clinical gene transfer research. As the policies did not cause any problems in their work of moving gene transfer from the laboratory to clinical practice, they were regarded as reasonable. They were seen as adequate and valid.

Only one interviewee, Staffan, emphasized a problem with the Swedish policies. This problem, according to him, was that the European view on clinical gene transfer research, and thus also the Swedish view, was more strict and restrictive compared to the U.S. one. As an example, he described what happened after the adverse events in the clinical X-linked severe combined immune deficiency (X-SCID) trial in France (see Chapter 1, p. 18). In the U.S.A., he explained, this resulted only in a dead stop for a short time with regard to the use of retroviral gene transfer vectors. It did not take long before the Americans continued their clinical gene transfer trials in X-SCID patients, using the same vectors as the ones used in the French trial. In Europe, however, all clinical trials that involved retroviral vectors came to a halt (p. 8).

As I noted above, the Swedish gene transfer scientists are content with the current regulation and oversight of clinical gene transfer research. An explanation for this could be that applications regarding clinical gene transfer trials often have to be submitted to only one ethical review, on a regional level. In other words, the scientists do not have to go through the intensive regulatory oversight of clinical gene transfer research that I will show that their U.S. colleagues have to do. Also they do not need to provide any information in the application beside that which is required for clinical trials in general.

On the other hand, the members of the Swedish advisory boards whom I interviewed regarded the policies that regulate clinical gene transfer research in Sweden

\(^{30}\) This was my experience when I tried to obtain applications concerning gene transfer clinical trials. See also the Edelstein et al. (2007) article ‘Gene therapy clinical trials worldwide to 2007 – an update’, for an experience similar to mine.
as problematic\textsuperscript{31}. They described that their main concern was indeed that clinical gene transfer research was fairly unregulated. The research area had no specific regulation and almost no central review of applications for clinical trials. There was moreover no adequate system in place to monitor the applications. This was considered to be especially problematic as it allowed for a high degree of arbitrariness in the regional ethical review boards. The six regional ethical review boards\textsuperscript{32} in Sweden operate as independent authorities, which means that as it is left solely to them to make decisions regarding clinical gene transfer research, there will be no assurance of a national uniform standard. There is also no public openness or transparency in the review process. Accordingly, the members of the Swedish advisory boards explicitly emphasized that the existing regulation and regulatory structure needed to be improved. Some of the interviewees explained that Sweden needed to establish a special regulatory and advisory authority on the national level, which should provide a standardized review of all applications for clinical gene transfer research. This review should be publicly available.

To summarize, clinical gene transfer research has no special regulation in Sweden. It is a fairly unregulated field and applications only undergo review at regional ethical review boards. Neither the Swedish policies nor the oversight system seem to cause any problems for the Swedish gene transfer scientists, and they have not adopted any specific strategies in order to make their research doable in the light of regulations.

As it is today, the Swedish regulatory framework can be described as being conducted at arm’s length; regulators and scientists live and operate in different arenas. Gene transfer scientists and regulators\textsuperscript{33} seem to have little contact with each other. Similarly, the public is held at ‘arm’s length’, meaning that information released to the media is sparse, and therefore the public is unaware of what is happening in the field of gene transfer research. This lack of communication and concern may be explained by the fact that there are few clinical gene transfer trials going on in Sweden today. As indicated by the interviewed regulators, the need for regulation and public openness may change, if and when there is more research in the area.

\textsuperscript{31} The Swedish regulatory interviewees were all from advisory boards as I could not get members from regional ethical review boards to participate. This has caused limitations in the material as advisory boards may not discuss gene transfer research to the same extent as regional ethical review boards do. For example, as the interviewees did not talk about review processes, the Swedish picture that I present of relations between scientists and regulators as well as the regulators’ view is quite different compared to the U.S. one.

\textsuperscript{32} There are six different regional ethical review boards in Sweden. They are located in Gothenburg, Lund, Linköping, Stockholm, Uppsala, and Umeå.

\textsuperscript{33} It is important to note that of the five Swedish regulators whom I interviewed only one had his or her scientific background in molecular biology, endocrinology, cell biology, or virology like the U.S. regulatory interviewees. Instead two of the regulators were physicians, one was a psychiatrist, and one a lawyer. Several of them also had PhDs in a different area of expertise.
The U.S. Regulatory Setting

In this section, I describe and discuss the U.S. regulatory setting. First, I outline the U.S. policies and guidelines that regulate gene transfer research as well as the regulatory structure in which applications for clinical gene transfer trials are reviewed and evaluated. Second, I present and discuss the U.S. gene transfer scientists’ views. We shall see how they described the U.S. regulatory setting as a limiting factor—a problem that affected the doability of their work. We shall also see that the members of regulatory agencies and advisory boards, on the other hand, mainly emphasized that the different review processes presented several advantages and were important to adhere to, for many reasons.

The U.S. Regulatory Framework

According to gene transfer scientists Kenneth Cornetta and Franklin Smith (2002) and regulatory scientist William Lee (2006), clinical gene transfer comprises one of the most regulatory scrutinized and extensively regulated research areas in the U.S.A. This means that scientists who want to conduct clinical gene transfer trials must be prepared for an intensive regulatory oversight.

In the U.S.A., research involving recombinant DNA molecules, which includes gene transfer research, is considered to be in need of special regulation and is thus strictly regulated by National Institutes of Health (NIH) Guidelines, and especially by its Appendix M.34 In this regulation, particular demands have been added to clinical gene transfer trials that investigators need to comply with. The U.S.A. has no regulations (only recommendations) against germ-line gene transfer. At present there are, however, no research projects moving towards germ-line interventions and, more importantly, the Recombinant DNA Advisory Committee (RAC) which is located in the Office of Biotechnological Activities (OBA) at the NIH will not entertain any proposals involving modifications of the germ-line.35 Gene transfer research involving human participants is further controlled by the regulations for the protection of human subjects, that is, the U.S. Department of Health and Human Services (45 CFR 46 and 21 CFR 56) and the U.S. Food and Drug Administration (21 CFR 50, 54, 58, 312, 314, 812 and 814) (Cornetta 2003). The NIH Guidelines are only mandatory for investigators at institutions who receive NIH funds for research involving recombinant DNA. Nevertheless, they are adhered to voluntarily by many companies and institutions that are not subject to these requirements.

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34 The title of Appendix M is ‘Points to consider in the design and submission of protocols for the transfer of recombinant DNA molecules into one or more human research participants’ (also referred to as ‘Points to Consider’).

35 This information regarding the RAC’s position on proposals regarding applications for germ-line modifications is from one of the U.S. regulators whom I interviewed, who worked at the NIH and had a clear insight into the work of the RAC.
There is thus a tight regulatory structure and hence also oversight of clinical gene transfer trials in the U.S.A. This has been established due to several concerns raised among the lay public regarding the technology behind gene transfer as well as its research. In practice, an application for a clinical gene transfer trial typically undergoes review by at least four different regulatory bodies on both local and national levels. On the local level, the review takes place at the individual institutions, universities, or medical centers. On this level there are two separate committees. The task of the first committee, the Institutional Review Board (IRB), is to protect the rights and safeguard the welfare of human research participants. It is IRBs that approve protocols for clinical trials as well as informed consent forms (Cornetta and Smith 2002). All clinical trials are subject to review and approval by an IRB before they can begin. The second committee is the Institutional Biosafety Committee (IBC), whose origin is embedded in the requirements of the NIH Guidelines for research involving recombinant DNA molecules (NIH 2011). The IBC’s task is to review applications that are subject to the NIH Guidelines. In their reviews the IBCs investigate potential risk to public health as well as the environment. They also check that that compliance with guidelines regarding surveillance, data reporting, and adverse events reporting is obtained (NIH 2007). When a principal investigator proposes a clinical gene transfer trial, he or she must address several aspects of Appendix M. It is especially important to submit to the IBC\textsuperscript{36} information regarding the vectors to be used, the source of the DNA, and the nature of the inserted DNA sequence. They must also report on whether expression of a foreign gene is attempted (and, if this is the intention, which protein will be produced) and finally, containment conditions that will be put into action (Lee 2006:49).

It is not sufficient to just send a gene transfer protocol and Appendix M to the IBC. Applications for clinical gene transfer trials must also be reviewed on the national level. There are two regulatory bodies – the OBA at the NIH, and the U.S. Food and Drug Administration (FDA) and especially its Center for Biologics Evaluation and Research (CBER) – that review these applications. Before a final IBC approval can be made the gene transfer protocol must also be submitted to the OBA. This means that the national advisory committee, the RAC, must have had an opportunity to review the gene transfer protocol and to present issues raised or recommendations made (Cornetta and Smith 2002, Cornetta 2003, NIH 2007). More specifically, the RAC evaluates the quality of the science involved in gene transfer research by conducting a broader scientific and ethical review as well as raising the importance of transparency. Simultaneously, the FDA evaluates product characterization and clinical trial design, especially safety and efficacy from a regulatory pers-

\textsuperscript{36} It is noteworthy that the Swedish principal investigator does not need to submit this kind of information anywhere in the application to a Swedish regional ethical review board.
Human gene transfer products or procedures intended to be commercialized fall under its authority. When a molecule, or in this case a gene transfer vector, is to be tested in human research participants it is, according to the Federal Food, Drug and Cosmetic Act, regarded as a new drug and is thus subject to particular demands regarding the regulation of drugs. This means that an Investigational New Drug Application (IND) must be obtained from the FDA (FDA 2010). In the IND application, information about animal pharmacology and toxicology studies, manufacturing information, clinical protocols, and investigator information must be submitted. In order to get the IND application approved, an IRB approval is required (FDA 2010:1).

The RAC posts on the OBA website its reports in which the gene transfer protocols are reviewed, issues raised are presented, and recommendations are made. Furthermore, gene transfer protocols involving human subjects who are approved by an IBC are kept on file at the OBA. These protocols are available to the public upon request. The FDA and the OBA have also established the Genetic Modification and Clinical Research Information System (GeMCRIS) website, on which different information regarding clinical gene transfer protocols can be obtained.

The FDA and the OBA at the NIH also collaborate in other ways. Two of the regulators whom I interviewed, Reese and Rachel, described the important collaboration between the OBA and the FDA regarding applications for gene transfer research. Rachel at the OBA described that their complimentary oversight systems had resulted in a communication procedure being established between the OBA and the FDA. ‘Whenever they [the FDA] get an application’, she explained, ‘they send us a note saying “We have an IND for this area”, and we check our files to see if we have the protocol’ (p. 30). If no files on this application were found and the investigators were under NIH purview, they were contacted. We say, she said, ‘A little bird told us that you have filed an IND. Hello, you need to file here’ (p. 30). Reese at the FDA also described the benefits of collaborating like this. For us it has been very valuable, she remarked, because these trials [clinical gene transfer trials] will go to them [the RAC] for open discussion before the IND comes in and that ‘helps us to get a better feel for what are some of the issues out there outside of our review’ (p. 26).

The Situation According to the U.S. Gene Transfer Scientists

In analyzing how the U.S. gene transfer scientists whom I interviewed described the U.S. regulatory setting, I found that two problems were constantly emphasized. First, the gene transfer scientists saw themselves as being overly regulated. Second, they saw themselves as being intensively scrutinized. It was, however, not the FDA

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37 The FDA is the regulator of the clinical practice of gene transfer as well as of the clinical practice of other medical and biotechnological fields of research. Any procedures or products intended to be commercialized fall under their authority.
that the interviewees described as troublesome, as every scientist regardless of his or her field of research has to go through their review process if they want to conduct clinical trials. Instead it was the fact that they had to be publicly scrutinized by the RAC that made them feel unjustly ‘singled out’ and called in question. It also made them describe gene transfer as ‘under the microscope’ as there were hardly any other areas of biotechnology that had developed under this lens of public scrutiny.

The first major problem emphasized by the interviewees was that of being overly regulated. When I asked Sean how he felt about the policies that regulated his research he replied that gene transfer research was ‘highly regulated in more ways than you care to know about’ (p. 17) and then described how everything within gene transfer research was regulated, from animals, radiation, and environmental health, to intellectual property rights. There was, according to him, a reason for this high level of regulation. Historically, Sean explained, we ‘as a community of scientists, have done a bad job’, namely by not paying attention to existing regulations or choosing to neglect them (p. 17). Although Sean did not himself give an example of what this ‘bad job’ could be, many of the interviewees, both the U.S. and the Swedish ones, often referred to the Jesse Gelsinger case as an example of scientists choosing to neglect existing regulations. This event was described as having raised concerns regarding the ethics of gene transfer and thus continued to cast a shadow over gene transfer research and the scientists who work with it.

Another explanation given for the high level of regulation was that gene transfer involves the aspect of deliberate genetic modifications of living people as well as their descendants and this causes concerns about the use of gene transfer. ‘Genes are different’, Shane explained to me, ‘because society is not ready for it’ (p. 6). This could also be related to the scientists’ ‘bad job’. ‘It’s partly our own fault’, he continued to explain, as we have not educated the world, the politicians, and those who control and regulate the field (p. 20). What he referred to was that gene transfer scientists had not explained the purpose of gene transfer or when and for what it could be used, to other actors, especially to regulators. There were therefore a lot of misconceptions about gene transfer research, which had resulted in tight regulation.

As discussed above, there are several reasons given by the interviewees for why gene transfer research is regarded as being in need of extensive regulation. It is important to note that, when the interviewees talked about being highly regulated, they referred mainly to the fact that they had to comply with the NIH Guidelines. This means that they have to submit their gene transfer protocols to the OBA and give the advisory committee, the RAC, the opportunity to review them and make recommendations. If the RAC regards it as necessary, the protocol could be selected for in-depth review, which means that the principal investigator has to come in to present the protocol formally and address concerns raised by the RAC regarding it. So how did the interviewees feel about the policies that regulate their research? Again, the interviewees talked mainly about the NIH Guidelines, and there were varying conceptions among them about the effects of the policies. Their views
ranged from the guidelines slowing down the advancement of science to them causing no problems at all.

Shane explained that he considered the policies to be burdensome but not impossible to work with. However, he chose to separate himself from any kind of regulatory work. Instead, he had established a regulatory group of his own, a group of people whose main task was to solve different regulatory issues that could arise in his research. Their purpose was to write and file the proper applications so that he could concentrate on his research work. The work done by his regulatory group thus enabled him to be deeply involved in bench work instead of struggling with the policies and the different review processes as the other scientists did. Nevertheless, he wished personally that the NIH and the RAC did not exist because their review caused him, as a scientist, more work (p. 21) ‘I spend a million dollars a year’, he continued, ‘on the people who just do the regulatory things’ with the FDA and the OBA (p. 12). Hence the policies were both time-consuming and expensive.

This was also Scott’s general opinion. The policies were, according to him, ‘overly protective to the point of slowing the advancement of science’ (p. 31). Whereas Shane and Scott felt burdened by the regulations, Stuart explained that he had never felt personally inhibited or burdened by the policies. His personal opinion was that scientists had to agree to being regulated. Furthermore, all areas of society needed to be regulated. Gene transfer research was no exception. Stuart articulated this view especially clearly and stated that he had no problem with people, primarily regulators, watching ‘over their [the gene transfer scientists’] shoulders’ (p. 33). However, this opinion was contradicted later in the interview when he expressed that he was ‘not very happy with some of the decisions that were made’, and particularly the stem cell area struck him as being ‘a very unenlightened policy’ (p. 33). The reason for his opinion was that the existing U.S. policies regarding stem cell research in 2006, established by the Bush administration, made it difficult for Stuart to conduct some of his research.

Whereas all interviewed gene transfer scientists agreed that gene transfer research needed to be regulated, four of them described it as burdensome to be intensively scrutinized by the RAC. This was the second major problem emphasized by the interviewees. Although there were a few unique things about gene transfer, the differences from other medical technologies had become very small they argued. Because of this many of them expressed that the RAC needed to change its focus and interest. ‘I think’, Scott said to me, ‘that the RAC has to change its focus on some of these more routine gene transfer trials, but that is my opinion’ (p. 24). What he meant was that many of the currently conducted clinical gene transfer trials did not involve any specific or significant safety issues that were out of the ordinary. They were pretty much standard clinical trials. Instead, he wanted the RAC to get involved in more controversial issues about gene transfer. He meant issues that would come down the line, when gene transfer was implemented in new clinical practices, such as using gene transfer in the treatment of disorders that are more in the ‘gray zone’, like various issues about behavior.
Although the RAC only provides non-statutory advice as it has no legal authority it, its review process, and especially the implications of its recommendations, was described by the interviewees as problematic and, at times, even overly redundant. The following quote from Scott gives an example of how the recommendations made by the RAC influence the work of local regulatory agencies (IRBs and IBCs).

The RAC has no legal authority. They can’t tell you “You can’t do the trial, because we want you to do x, y or z”. They can give recommendations. I am on the Biosafety Committee. They get those recommendations. Obviously, I can’t comment on my own trials at the Biosafety meeting, but nobody wants to vote against what the RAC says, because if something goes wrong, the media is going to pick up “well XX [the university] went against a national body”. Even though it has no legal authority, it has a lot of implied authority. (p. 33)

In this quote, Scott particularly emphasized how discussions regarding clinical gene transfer applications were influenced by recommendations made by the RAC, and that they further affected the decisions made by the university’s IBC. When discussing the RAC and its impact on the IBC’s work he underlined that the RAC had something that he called ‘implied authority’. Implied authority, Scott explained, was that the RAC, although not being a regulatory body and thus lacking legal authority, in practice had a significant authority and an important impact on clinical gene transfer research. Although suggestions made by the RAC are merely recommendations and not requirements, it was somewhat implied that they were requirements, that is, issues that had to be addressed. They were federal recommendations and to go against these could have serious consequences.

Scott continued to discuss the impact of the RAC on local regulatory agencies. He explained that he wanted the IRBs and the IBCs to become more ‘independent in their evaluation of clinical trial applications and protocols’ and also to a higher degree ‘question the recommendations made by national and federal advisory boards’ (p. 34). What he argued was that the IRBs and the IBCs should begin to think on their own and not merely state that they have to follow the recommendations made by the RAC. ‘I think’, he said, ‘that because everybody wants to cover themselves, they are afraid to take a stand on what they really believe’ (p. 33).

38 When I interviewed Ryan, the chairman of a local IBC, he explained that for the IBC it was important that an regulatory agency such as the FDA or an advisory committee like the RAC looked at the clinical gene transfer application. Preferably, the application should have been reviewed or at least read before it came to the IBC and they considered it. This means that local regulatory agencies like the IRB and the IBC are not independent in their evaluation. Instead they are by their own choice highly dependent on the recommendations made by the RAC.
The ‘implied authority’ of the RAC on universities was something accentuated also by Stuart. He underlined that universities constantly fear and worry about going against federal recommendations, something which could have devastating consequences for a university’s ability to get federal funds. In his words:

At a federal level, policy affects how the university functions. To try to get some activities underway here within the university is very difficult sometimes, because the university always has to think, “Are we doing something that the federal government is going to be unhappy with?” And if the federal government gets unhappy with an institution, the money stops and that means the institution is dead. So you have to live in the real world. (p. 33)

There seems to be a general reluctance among scientists, universities, and their local regulatory agencies to go against federal recommendations made by the RAC. A related issue was that the RAC review process has a high degree of transparency and public openness. This played an important role for the interviewees. When given recommendations by the RAC the principal investigator must address the comments and the recommendations. In the event that they choose not to implement the recommendations made by the RAC, the principal investigator must explain why the recommendations will not be met. The explanation, as well as the recommendations, goes into public records. More specifically, it goes to the IRB, the IBC, and the FDA. I believe, in line with some of the regulators that I interviewed, that to have in a public record that an NIH advisory committee has pointed out a problem and that an investigator has not addressed this, is a big liability.

Gene transfer scientists therefore need to take into account the recommendations made by the RAC if they want to move their research from the laboratory to clinical practice. This was something that the gene transfer scientists in this study were well aware of. They needed the RAC’s endorsement for their research. There was nothing that they could do to change this. They just had to accept and adapt to the situation in which they were not going to do any clinical gene transfer research unless they got the RAC’s support for it. The following quote by Spencer sums up the common theme in the interviews regarding accepting and adapting to the regulatory situation.

It’s what you need to do. So, I don’t view it as a negative. Rather I embrace it as the way to get there. I just seem to understand it and embrace it. It’s the path to get there [to a clinical gene transfer trial]. (p. 22)

To summarize, clinical gene transfer research is in the U.S.A. extensively regulated and put under intensive regulatory oversight. This means that the U.S. gene transfer
scientists, by extension, are highly regulated and monitored. Being overly regulated was, however, something that gene transfer scientists had to accept if they wanted to conduct gene transfer research and move it from the laboratory to clinical practice. Nevertheless, this influences their ability to move their research from preclinical to clinical studies as it is both time-consuming and expensive to get approval from at least four different regulatory bodies on national and local levels. The recommendations made by the RAC were regarded as particularly problematic, especially if the principal investigator or any other actor involved in the application did not agree with them and hence chose not to consider them. This would have serious consequences. It could be difficult to get federal and private funding, as well as to attract and enroll powerful allies. Who would want to finance or collaborate with scientists who go against federal recommendations? In other words, the regulatory framework affects the doability of the scientists’ work, as described in the interviews.

**The Situation According to the U.S. Regulators**

As we have seen in previous sections, the two different regulatory frameworks are described by the interviewed gene transfer scientists as being unproblematic in the Swedish setting, while in the U.S. setting it is seen as a limiting factor strongly affecting the scientists’ work. Because the regulatory framework in the U.S.A., and especially the RAC, is described as burdensome and problematic by the interviewed U.S. gene transfer scientists, it caused tensions between them and the regulators. In order to understand these tensions, as well as getting both sides of the regulatory story, it is also important to briefly present the regulators’ views on this matter.

All the members of regulatory agencies and advisory boards whom I interviewed, with the exception of one, expressed that they were aware that gene transfer scientists in general regarded the policies that regulate clinical gene transfer research as burdensome, and especially the oversight systems with their different monitoring processes. They also believed that it was difficult for gene transfer scientists to accept the demands for transparency and public openness of clinical gene transfer research. One of the regulators, Rachel, stated that some people wished the RAC would not say anything because it was seen as just ‘one more pseudo-regulatory hurdle’ that they needed to ‘jump through’ (p. 15). Another regulator, Russell, also discussed the RAC and explained that while the RAC had no enforcement powers ‘the community of scientists have accepted that they are not going to do somatic gene transfer research unless they present it to the RAC and get the RAC’s endorsement for it’ (p. 19). Nevertheless, the policies and especially the two complementary systems of oversight were regarded by the regulators as being appropriate and also presenting several advantages for the scientists. The RAC and its transparent review process should, for instance, be seen as a way for the scientists to redeem themselves from events in the past. It was also a way to engender public trust and confidence in the field of gene transfer, as it allowed society to participate in the scientific and regulatory dialogue. It was regarded as important that the general public became actors involved in the dialogue and not merely, as Roslyn put it, ‘held at
arm’s length’ (p. 13), especially as the NIH depended on public money to fund gene transfer research. It was therefore significant to have public trust in gene transfer research. Furthermore, to discuss matters in public meetings would present a general sense that nothing in clinical gene transfer trials was swept under the rug. In other words, complying with the NIH Guidelines and adhering to being publicly open with one’s research was a way to legitimize the research and attain legitimacy for one’s work.

The main problem for the interviewed members of U.S. regulatory agencies and advisory boards was the tensions between them and gene transfer scientists caused by the U.S. regulatory setting. Particularly, they resented that they, as regulators, were regarded as restraining the advancement of gene transfer research due to the highly regulated and monitored context of U.S. clinical gene transfer research. This made, in their view, for an unnecessary reluctance from gene transfer scientists to interact with the RAC and occasionally also with the FDA.

Resolving the Tensions

As discussed in previous sections, being overly regulated and intensively scrutinized was described as influencing the U.S. gene transfer scientists’ ability to move research from preclinical to clinical studies, as obeying existing policies and the regulatory oversight was seen as both time-consuming and expensive. At times this was even regarded as slowing the progress of gene transfer research. This caused tensions between the gene transfer scientists and regulators. More specifically, these tensions were primarily between gene transfer scientists and the RAC.

I have previously analyzed how the ‘arm’s length’ distance between regulators and scientists in the Swedish case made gene transfer research doable for the scientists. This is not possible in the regulatory setting of the U.S. scientists. Instead, the concept of boundary-work is useful to understand how scientists as well as regulators achieve doability in their work, given the regulatory circumstance in which they are situated. I argue that two forms of boundary-work are essential parts of making gene transfer doable in the U.S. regulatory setting; one that affirms the existence of boundaries between the two different social worlds involved, and one that transgresses it. The purpose with these two forms of boundary-work is to acknowledge and accept the different authorities, jurisdictions, and responsibilities of the two different social worlds of scientists and regulators. It is also to try to influence each other’s social world by transgressing the boundaries, and occasionally even crossing them. I will now discuss these two forms of boundary-work in turn.

Scientists: Affirming the Regulatory Framework

The U.S. regulatory framework provides a legal and ethical map for the practice of gene transfer research. Provided that one followed this map a legitimacy of one’s research could be attained. Shane emphasized a very common theme in my U.S.
interviews regarding the policies that regulate clinical gene transfer research. ‘This [the policies]’, he said, ‘is what allows us to do our work from a society point of view, so therefore we do it’ (p. 21).

The policies were seen as allowing gene transfer scientists to do their work. It was often emphasized by the interviewees, as shown in the quote above, that the policies were established for a reason, which from a societal point of view made sense. What is interesting in this context is why the interviewees regarded it as important to comply with the policies. Shane told me his personal opinion regarding the policies and, more importantly, why he complied with them. In his words:

> Like many things in life, very often you do things because they are important. Because others believe they are important. Therefore that enables you... Therefore, I think we should be supportive of them. (p. 21)

What Shane emphasized in this quote was that the fact that others regarded the policies as important was a reason for why they, as scientists, should be supportive of them. Who were the ‘others’? Did he mean society, regulators, or ethicists? And why did he not consider the policies as important himself? Unfortunately, Shane never told me why he did not regard the policies as of significance to himself. Instead he explained that the NIH, the RAC, and the FDA, although demanding much effort, were there for a purpose. They were there to protect people. And through abiding by the policies, clinical gene transfer research could attain legitimacy.

The regulatory framework with its policies and, importantly, abiding by these policies was seen as essential to the interviewees, in that it enabled gene transfer scientists to ‘do their work’. This was work that was authoritatively and demonstrably legal and ethical. Being supportive of the policies is a necessity and thus the only way that research from preclinical to clinical research is made doable.

Here, the scientists did exactly what the interviewed regulators earlier in this chapter emphasized. Complying with the NIH Guidelines and adhering to being publicly open with one’s research was a way to legitimize the research and attain legitimacy for one’s work. It was also a way to engender public trust and confidence in the field of gene transfer. This means that concerns regarding the ethics of gene transfer research can be deflected because being extensively overseen by regulatory authorities ensures high ethical standards. This form of boundary-work is about accepting the boundaries between different jurisdictions and adapting the work accordingly. The interviewed scientists handled the detailed demands and intensive regulatory oversight through various forms of what I call articulation work. They enrolled various allies such as the public and investors by showing that they adapted their work in accordance with the existing regulatory framework.
Scientists: Influencing Regulations

Whereas several of the U.S. gene transfer scientists whom I interviewed found the detailed demands and intensive regulatory oversight burdensome, they also had to accept these constraints as a necessary prerequisite for conducting gene transfer research in a context where it is seen as controversial and having risky medical and social implications. They had to adapt to this situation in order to legitimize their work and to get funding for their research from various actors. Thus, the interviewees, at least in their rhetoric, seem to have accepted the regulatory situation for conducting clinical gene transfer research. However, they also described how they tried to influence the regulatory framework and the decisions in various ways. This was done by getting involved in the regulatory process and through maintaining good contacts with individual regulators. In practice, this meant transgressing the boundaries between the two different social worlds of scientists, on the one hand, and regulators on the other.

The interviewed U.S. gene transfer scientists described that it was important to participate in and collaborate with different institutional boards and national or federal advisory committees. Many of the gene transfer scientists described that they were members or advisers, and sometimes even chairpersons or presidents, on these committees and boards. Some of them were also, or had previously been, presidents of different professional associations. It seems that developing policy and oversight was something that several of the gene transfer scientists were involved in. In the following two examples I will show how the gene transfer scientists described that they involved themselves in regulatory work.

Scott was not only a member of the university’s Institutional Biosafety Committee, that is, the IBC. He had also on several occasions testified in front of the RAC as well as the FDA, the latter in public, on issues regarding gene transfer research. Furthermore, he was the President of the XX Society of XX. As the President of this Society he had shortly before our interview met the director of the RAC. “We went to voice some concerns of people within the Society”, Scott said, “about some of the regulatory stuff” (p. 35). According to his descriptions, Scott was not only involved in regulatory work on his own. He was also involved through the professional association of which he was the President. However, in the latter, getting involved in regulation was as much about being able to influence regulation and policies as it was to maintain good contacts with individual regulators. By doing so, he transgressed the boundaries between himself, as a scientist, and the regulators, as he had become a part of the regulation and decision-making himself.

39 This necessity was not as explicit among the Swedish gene transfer scientists whom I interviewed. One of the gene transfer scientists, Sylve, was the only one who described that he participated in regulatory committees and on a committee in a professional association. More specifically, he had been a chairperson of an ethical committee at the university where he worked. He was also, at the time of the interview, the chairperson of the committee for Regulations and Ethics at the XX Society of XX.
Like Scott, Stuart involved himself in various ways in regulatory work. He described that he had been a member of several university committees. His major regulatory contact had, however, been on a national, federal level. He had been a member of the RAC, of committees on AAAS, and of the Congressional Biomedical Ethics Advisory Committee. He was also at the time of the interview the incoming President of the XX Society of XX (p. 34-35). The main reason for involving himself with regulators and their work, he explained, was that he wanted to try to make policy and hence affect the regulatory decisions made regarding gene transfer research.

Another way for U.S. gene transfer scientists to involve themselves in policy making was to organize professional associations. Almost all of the interviewed gene transfer scientists, both the Swedish and the U.S., were members of one or more of the professional associations of gene transfer. These include the American Society of Gene and Cell Therapy, the Swedish Society of Gene Therapy, and the European Society of Gene and Cell Therapy. Through these professional associations and their annual meetings, which are attended by gene transfer scientists from around the world, efforts are made to gain allies for particular perspectives, theories, and research. Although the members in these gene transfer societies may have very different and even conflicting perspectives towards specific issues regarding gene transfer research, they cooperate in some actions taken towards these issues. Moreover, the opportunity to actually have an influence on regulations may be much greater for a professional association than for a single scientist. In other words, the scientists handled the regulatory demands put on them by using what I call articulation work. They enrolled regulators in their work by trying to translate both their own and the regulators’ interests regarding how clinical gene transfer research should be regulated and decisions made.

**Regulators: Helping and Influencing Scientists**

Although the emphasis in this chapter is on how the gene transfer scientists interviewed perceived the regulatory setting, and more importantly, how they tried to achieve doability given the regulatory circumstance it is nevertheless interesting to note the boundary-work done by regulators to resolve the tensions between scientists and regulators.

Whereas the scientists acknowledged the work of regulatory agencies, and adapted their work accordingly, also the regulators affirmed the need for independence and difference between what scientists demanded and what the regulations allowed. In an attempt to resolve the tensions and hence improve the communication and collaboration between gene transfer scientists and regulators, the members of U.S. regulatory agencies and advisory boards whom I interviewed tried, as did the gene transfer scientists, to transgress the boundaries between scientists and regulators, thus affecting each other’s work in various ways. While the scientists tried to influence the regulatory framework and the decisions made by involving themselves
in regulatory work, the regulators tried to assist scientists in framing their applications and research in ways that would be acceptable by the regulatory agencies and thus speed up the process. I do not know whether this collaboration is an actual form of boundary-work or just an effect of the interview situation. It could, for example, merely be that the interviewed regulators wanted to emphasize that they were not getting in the way of science. Instead they were there to help scientists and to facilitate their application processes.

Knowing that the policies, guidelines, and especially the two complimentary systems of oversight were burdensome to gene transfer scientists, Reese described the FDA as being extremely obliging towards their particular situation. For example, as gene transfer products are novel and constantly evolving, the same demands were not put on gene transfer as were put on other biotechnologies. This meant that the FDA had a more adaptive and progressive approach that helped the gene transfer scientists to develop better products.

Reese described how the FDA, in order to improve the communication and collaboration between regulators at the FDA and gene transfer scientists, tried to enroll scientists early in the application process. As an example, the FDA was particularly described as being there to encourage sponsors and investigators and, more importantly, to help scientists in their work. We are ‘becoming a friendlier regulatory agency’, Reese emphasized, (p. 29) and remarked that the FDA did not merely make decisions. Instead it became part of the research process due to the close collaborative work between different review teams and sponsors during the process of an investigational new drug application (IND).

In this way the IND process at the FDA was redefined as being a part of the research process, and the boundaries crossed between the regulators and the gene transfer scientists. The IND process became a cooperative work, a process of give and take, in which the regulators listened to the gene transfer scientists as the gene transfer scientists did to the regulators. They both learned from each other. Consequently, if regulators and gene transfer scientists communicated and collaborated with each other in this cooperative way, gene transfer scientists could get better support and help. The IND process would also be less time-consuming and expensive for gene transfer scientists as problems with the application could be detected, discussed, and solved much earlier. In other words, the regulators met the resistance from some scientists to interact with regulators through various forms of what I call articulation work. More specifically, they tried to enroll the scientists as allies in the application process and translate the scientists’ interests into considering the regulators’ work as being supportive and beneficial, and as something that would speed up the application process significantly.

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40 By sponsors the interviewees meant scientists and investigators, but also commercial sponsors like biotechnological and pharmaceutical companies as well as the advisers in different review teams.
As previously described, the FDA and its review process seem to cause no problems for the U.S. gene transfer scientists. The RAC, on the other hand, and its review process (but especially the implications of its recommendations) seem to be a major problem for the gene transfer scientists, causing tensions between them and the RAC. A possible explanation for this could be the different roles and authorities of the FDA and the RAC. As previously described, the FDA is the regulator of any procedure or product intended to be commercialized in the U.S.A. This means that all clinical practice of medical products or procedures, whether gene transfer or anything else, must be reviewed by the FDA. It is the same for all scientists regardless of their field of research. The regulatory scrutiny of the RAC on clinical gene transfer applications regarding their quality of science was, however, unique for gene transfer. I believe that it is this situation and its attendant feeling of being ‘singled out’ and ‘publicly scrutinized’ that makes it difficult for the interviewed U.S. gene transfer scientists to fully accept the regulatory framework of clinical gene transfer research.

Concluding Discussion

In this chapter, I have shown how what I call the loosely-regulated conduct in clinical gene transfer research in Sweden versus the highly-regulated and -monitored conduct in the U.S.A. resulted in different ways of working.

The Swedish gene transfer scientists whom I interviewed had no problems with the existing policies or the oversight system. Here, it was instead the members of advisory committees who wanted to implement a higher degree of regulation of clinical gene transfer research, which also needed to be publicly open. At present, the Swedish regulatory framework can be described as being conducted at arm’s length, that is gene transfer scientists and regulators do not normally interact with each other. If the Swedish regulatory setting instead became more like the U.S. one, which some members of the advisory boards proposed, then there could be a risk that similar tensions could appear, as there have in the U.S. setting, between regulators and gene transfer scientists.

In the U.S. regulatory setting the gene transfer scientists whom I interviewed were prepared for the intensive regulatory oversight. They had to accept that this was a part of conducting gene transfer research due to its controversial character as well as its social implications. They furthermore had to adapt to the existing situation in order to achieve legitimacy for their work, but also to get funding for their research. Nevertheless, the highly-regulated and -monitored conduct of clinical gene transfer trials also caused some tensions between scientists and regulators.

In this chapter we have seen examples in the U.S. regulatory setting of the problems that can arise when two social worlds with different goals, commitments, and ideologies regarding how to conduct their work, come together in an intersection, that is an area of mutual interest, in order to move gene transfer into clinical practice. For the work in this intersection to become doable the conflicting perspec-
tives of scientists and regulators as well as their various work activities need to be coordinated and, as much as possible, also mutually agreed on. The problem is that social worlds often have different agendas that they want to further and different responsibilities, and this is the case in clinical gene transfer research. Here the concept of boundary-work has helped to highlight practices from both sides that attempt to resolve the tensions between scientists and regulators.

In the U.S. interviewees’ descriptions I found two forms of boundary-work used by gene transfer scientists and regulators in the U.S.A. The first form of boundary-work affirmed the existence of boundaries between scientists and regulators. The scientists affirmed the regulatory framework and acknowledged the work of regulatory agencies and adapted their work accordingly. Abiding by the policies and the regulatory framework is a way for gene transfer scientists to deflect concerns regarding the ethics of gene transfer research and to obtain legitimacy for their work. The scientists’ accounts suggest that it is their compliance with the regulatory agencies and the advisory boards that will ensure a high ethical standard of gene transfer science. The regulators also affirmed the need for independence and difference between what scientists demanded and what the regulations allowed.

The second form of boundary-work transgressed the boundaries between scientists and regulators. The main goal with this boundary-work was to influence the opposite party. The scientists described how they by involving themselves and their professional associations in regulatory work tried to influence the regulatory framework and decisions made. They also tried to get closer to regulators to understand the regulators’ aspects of the gene transfer regulation as well as what they regarded as important issues to address in their applications. The regulators, primarily at the FDA, on the other hand, tried to help and influence the scientists by assisting them in framing their applications and research in ways that would be acceptable by the regulatory agencies and consequently, speed up the process. The regulators also redefined themselves as being a part of the research process. Here, we again see examples of how various forms of articulation work (Strauss 1988) are used to align different actors’ interests and activities with one another. We especially see what sociologist Bruno Latour (1987) calls ‘enrollment of allies’ and ‘translating interests’. The scientists enrolled various allies such as the public and investors by showing that they had adapted their work in accordance with the existing regulatory framework. They also enrolled regulators in their work by trying to translate both their own and the regulators’ interests regarding how clinical gene transfer research should be regulated and decisions made. The regulators, on the other hand, tried to enroll the scientists as allies in the application process and translate the scientists’ interests into considering the regulators’ work as being supportive and beneficial, and thus as something that would speed up the process. These two forms of articulation work - enrollment and translation - seem important for both kinds of actors. They enable them to align their interests and activities into a common frame, and work towards what they described as the common aim of conducting socially responsible clinical gene transfer research.
In the emergence of another controversial medical specialty, fetal surgery, medical sociologist Monica J. Casper (1998) observed a similar tension to that which I have found in this study between scientists and regulators. In her study the tension was between fetal surgeons, who wanted to move fetal surgery from experimental studies in the laboratory to the operating room and clinical trials on fetuses, and the hospital’s IRB, whose main task was to protect the rights and safeguard the welfare of human research participants enrolled in these clinical trials. She showed that fetal surgeons at this hospital viewed the IRB and its demands as an obstacle – a kind of ‘clinical trial’ – to what they saw as their work of saving dying fetuses by performing surgical procedures, and simultaneously advancing biomedical knowledge. The fetal surgeons were therefore unwilling to subject themselves to the ethical regulations secured by the IRB and were reluctant to incorporate suggestions made by the IRB into their protocols. Casper (1998:165) refers to this working relationship as resembling a kind of tango, a dance in which one partner leads and the other follows. It was a tangled and complicated process. The fetal surgeons decided to solve their problem with the IRB by transforming all fetal surgery procedures to something that would lie outside the authoritative scope of IRB. This meant that it was transformed into standard care or routine medicine and no longer defined as experimental research.

Although it is unlikely that U.S. gene transfer scientists can solve their problems with regulations and regulators in a similar way to the one that the fetal surgeons used\(^{41}\), there are other points of resemblance. The gene transfer scientists in the U.S.A. whom I interviewed, just like the fetal surgeons, regarded the demands from the OBA and the recommendations made by the RAC as obstacles. They were also reluctant to incorporate suggestions made by the RAC into their protocols. The U.S. gene transfer scientists, however, had to accept and adapt to the regulatory situation, which meant that suggestions made by the RAC have to be incorporated. Otherwise, doability in clinical gene transfer research cannot be attained. Another point of resemblance is the dance metaphor used by Casper (1998). Despite the boundary-work conducted by gene transfer scientists as well as regulators, the problem still remains for gene transfer scientists: they have to follow the regulators’ demands and choices of ‘dance’. Nevertheless, gene transfer scientists want to be able to influence the steps of the dance, the duration of it, and if possible, also which kind of ‘dance’ to dance.

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\(^{41}\) I personally believe that it is difficult, if not to say impossible, to redefine clinical gene transfer research as a standard medical procedure, before it has been thoroughly investigated and evaluated in clinical studies. Gene transfer is unique, as it does not merely affect the individual undergoing gene transfer treatment, but also can affect families, future generations, health personnel, and society, as well as the environment.
CHAPTER 6
Meeting ‘Ethics’:
Handling Ethical Complications in Clinical Practice

In the previous two chapters I have shown the first steps in the research process of moving gene transfer from bench to bedside. As we have seen, gene transfer research is not merely a question of doing experiments in the laboratory and getting the technology to work. It is also about convincing regulators, colleagues, politicians, and commercial investors in the biotechnological and pharmaceutical industries that gene transfer research is worth doing. More specifically, it is about creating stable milieus and enrolling powerful allies. It also involves being able to construct doable problems within current policies and regulations, and getting applications for clinical trials accepted by different regulatory agencies and advisory boards.

In this chapter we have moved from ‘the bench’ and reached ‘the bedside’. This means that we are in a clinical practice instead of, as previously, the laboratory or in between the two. As earlier described, gene transfer is controversial. It involves a high degree of scientific uncertainty, struggles with several technological problems, and hence also with unknown and unforeseen risks for humans. Clinical gene transfer trials on human subjects are thus experimental studies. With gene transfer, new ethical and social quandaries have appeared due to gene transfer’s scientific uncertainties and unknown risks for human research participants enrolled in clinical trials, but also for the entire society. These quandaries raise ethical complications such as what diseases are appropriate to select for gene transfer treatment, what risks can be considered as morally acceptable, and how a valid informed consent should be obtained, given that the human research participants in these trials are often at their most vulnerable due to serious illness. Gene transfer research further raises concerns that the distinction between health and illness will change, as science locates the gene/genes responsible for various diseases and conditions. It also raises concerns that social problems outside of the medical jurisdiction will be biomedicalized – transformed into medical problems – and that gene transfer procedures used to treat diseases and disorders can also be used to enhance non-medical characteristics.

This chapter deals with how ethical complications in the clinical practice are made into doable problems, as described by the gene transfer scientists whom I interviewed. More specifically, it deals with what they consider to be the ethical complications or the substantive ‘ethics’ of gene transfer research, how they handle these complications, and how they feel morally about their work.
The Need to Meet Ethical Complications

In a study about how nuclear weapons scientists in the U.S.A. describe their work, anthropologist Hugh Gusterson (1996) points out that working with nuclear weapons brings with it moral dilemmas that the scientists must either confront or ignore as they go on with their work. Weapons scientists at the Lawrence Livermore National Laboratory, rather than ignoring the moral dilemmas of their work, learned to resolve these dilemmas in two different ways. First, they learned to pay regard to specific fears, concerns, emotions, and particular questions regarding nuclear weapons while simultaneously learning to disregard others. Second, they also learned that an active learning of various discourses, feelings, and practices could be invaluable as it showed them how to respond to the ethical dilemmas in specific socially patterned ways. Becoming a weapons scientist thus involved the social processes of producing and reshaping the identity as well as the conception of the weapons scientist’s experience and interpretation of the world of this specific laboratory. Reproducing scientists like this, Gusterson (1996:43) explains, not only shapes the scientists’ ‘beliefs and their vocabularies, it also molds their fears, their joys, and their excitements, turning them to the service of nuclear deterrence’.

I consider Gusterson’s approach to be interesting as a starting point for my analysis of how gene transfer scientists handle ethical complications in gene transfer research. Although Gusterson shows in his study how nuclear weapons scientists feel morally about their work and why it is regarded as ethical to work on nuclear weapons, he says nothing about how the scientists solve moral dilemmas practically in their work because, as he explains, the informal norm at the laboratory is that ‘the ethics of weapons work is more a matter for private reflection than public debate’ (Gusterson 1996:220).

Inspired by Gusterson’s approach, I present how the interviewed gene transfer scientists talked about how they handle ethical complications in their clinical practice. In the concluding discussion I will then connect my analysis to two theoretical concepts: map/itinerary and ethical boundary-work. These will help me understand how gene transfer scientists maneuver in this controversial field of research and especially how they reason about their maneuvering.

During the interviews I asked the interviewees questions like ‘What are considered to be the greatest risks concerning gene transfer?’ and ‘What are the ethical questions of gene transfer?’ It was mainly when addressing these questions that the interviewees began to talk about the ethical complications in their clinical work. Nevertheless, some interviewees began to discuss these issues much earlier in the interview when we talked about the past, present, and future of gene transfer.

In analyzing what the interviewed gene transfer scientists described as ethical complications in their clinical work, two different complications were constantly emphasized: how to select appropriate diseases and how to obtain a valid informed consent. There was also a third ethical complication discussed, about making a distinction between treatment and enhancement purposes. This ethical complication
was, however, not something that the interviewees talked about spontaneously. Instead, I introduced this ethical complication into the conversation by asking if they considered there to be ‘an ethical difference between eventually using gene transfer to treat diseases and using it to enhance non-medical (normal) characteristics’. It is important to note that many of the interviewees referred to the first two ethical complications, but not the latter, as ‘generic’, meaning that they were always present in clinical research. In fact, the ethical questions of gene transfer were explicitly emphasized as no different from the ones in any other experimental treatment.

Selecting Diseases – Balancing Risks versus Benefits

As discussed in the introductory chapter, the use of gene transfer is, according to existing guidelines, only acceptable in the treatment of severe fatal diseases and genetic disorders, in which there are no other medical options available, or where all other medical options have been tried without success. There is also another condition that needs to be met by gene transfer scientists before they can begin an early clinical gene transfer trial. According to bioethicist LeRoy Walters and legal scholar Julie Gage Palmer (1997), before an early clinical gene transfer trial can begin, the benefits of the trial, that is the knowledge gained from the trial and its use to future gene transfer research, must be considered to outweigh the risks to the people enrolled in the clinical trial. Consequently, evaluating the risks versus the benefits was of significant importance.

This raised the first ethical complication discussed by the interviewed gene transfer scientists. They emphasized that the disease itself, in which gene transfer is initially to be implemented, must be severe and without suitable alternative treatments. In other words, there had to be an unmet medical need. It was also important that there was a high likelihood of success. It was merely ‘as simple as that’, Sean explained to me (p. 8). However, in order to meet the requirements for clinical gene transfer trials, the potential risks as well as the potential benefits to human research participants had to be predicted and determined. This was regarded by the interviewees as difficult due to the highly experimental character of gene transfer and the fact that the manipulated material did not always behave as predicted. Instead, it was the specific case of the patient that became the determining factor in evaluating risks versus benefits. It was this determining factor that set the limits for which risks could be accepted and thus taken. As long as the risk was low and the benefit was high it was regarded as appropriate to conduct clinical trials in humans. However, it could also be acceptable to take higher risks in order to treat a severe disease. This is the primary situation in which gene transfer currently is used.

42 It should be recognized, however, that this is a common problem in many medical therapeutic treatments that often have serious side effects. The negative side effects have to be weighed against the potential benefits.
In selecting diseases and balancing the risks versus benefits in clinical gene transfer trials, two diseases were often discussed: the inherited monogenic disorder X-linked severe combined immune deficiency (X-SCID) and cancer.

**Gene Transfer and X-SCID Treatment**

There were several reasons for why this disease was appropriate to treat with gene transfer. First and foremost it was a severe lethal disease. ‘You have to realize’, Scott said, ‘that this is a lethal disease, it is a horrible disease’ (p. 5). X-SCID is a severe primary immune deficiency, only affecting males, which results in a lack of critical immune defense. This means that children born with X-SCID often die within their first two years due to the onset of serious infections such as meningitis, pneumonia, or bloodstream infections.

Due to the disease’s severe character, it was regarded as appropriate to try an experimental treatment like gene transfer, despite its risks. Indeed, the treatment of X-SCID by gene transfer came with a risk – the risk of developing leukemia. Since 2002 five cases of leukemia development have occurred in the French and the British clinical gene transfer trials. In one of these five cases the boy later died due to the leukemia. There is further evidence that it was the gene transfer that contributed to the leukemia development. ‘No one performed this study so that the children would get leukemia’, Sune underlined, ‘they did it in order to be able to cure these boys of their serious immunodeficiency’ (p. 11). Despite the risk of leukemia development, Shane emphasized, gene transfer was worth doing. In the long run, he explained, children affected with a disease like X-SCID, would get infections and they would die (p. 6).

However, there were not only risks involved in the gene transfer treatment of X-SCID. When discussing the potential risks of gene transfer, another important aspect was raised by the interviewees – other treatments also came with risks. For example, there were risks with bone marrow transplants, the usual treatment for X-SCID. If this treatment was chosen there was still a risk of the patient dying. This was due to the patients’ immune deficiencies, which made them susceptible to severe infections. Consequently, the mortality of the procedure was approximately 50%. The choice, Staffan explained,

is between a complete cure but with a certain risk for leukemia development alternatively 50% risk of dying after a bone marrow transplant, or being cured but often having rather severe side effects after the transplantation. (p. 8)

Despite the risks in the gene transfer treatment the ability to have a normal life, outside the secluded bubble that these children previously had lived in, was something that Stuart emphasized as important. He explained that the children who had not
developed leukemia were now, years after the treatment, living perfectly normal lives.

Now they are outside playing with their friends and rolling around in the dirt and having normal lives. [...] Six years might not be enough to convince people that the children are cured, but they have been treated. The point that I emphasize is that this is certainly the proof that the gene transferring approach in gene therapy does provide treatment, and that I think is an epochal event in medicine. (p. 11-12)

Thus the interviewed gene transfer scientists often contrasted the risks present in gene transfer against the risks of other medical treatments (this will be further discussed in Chapter 7).

**Gene Transfer and Cancer Treatment**

As described above, gene transfer is considered applicable when nothing better is available or when the treatment possibilities are very limited. This argument favors the enrollment of cancer patients who often are severely ill in the final stages of the disease.

It was primarily the Swedish interviewees who described why cancer was an appropriate disease to treat with gene transfer. There were several reasons for this evaluation. First, as both Sune and Sixten explained it, cancer is a common disease, which provides a large number of potential patients. Genetic diseases, on the other hand, Sune continued, ‘are often rare which results in a small amount of patients’ (p. 4). Second, cancer provided a greater applicability of the produced vectors or products developed for gene transfer treatments. Sixten explained that

one can imagine that a certain product that is developed, or a research vector... a tool that you develop can be used on patients with several different cancer diagnoses. If you have a hereditary disease and develop something for it, well then it only works on that particular disease and no other disease. (p. 5)

What Sixten emphasized in the quote above is that vectors or products developed for cancer treatments can more easily be used on patients with different diagnoses of cancer because they are less limited to one or several particular genetic loci or genes. Hereditary diseases, on the other hand, are often caused by one or several particular genetic loci or genes being impaired. Developing a gene transfer vector in order to treat an inherited monogenic disorder, like X-SCID, therefore means that the vector only works on that particular genetic locus or gene. Consequently, there
is more profit to be made from producing vectors for cancer treatments due to their greater applicability.

Third, and as discussed in Chapter 4, it is easier to get funding for a major disease entity, like cancer, for which current therapies are not optimal. There is corporate and commercial interest in funding a therapy in addition to the medical need. This favors the enrollment of cancer patients in clinical gene transfer trials. Moreover, as described above, the applicability of gene transfer vectors or procedures for the treatment of cancer is significant. This means that the pharmaceutical or biotechnological companies involved are almost guaranteed a profit from the research findings through patents and commercially viable products. Whereas this argument was not explicitly expressed by the interviewees when discussing which disease to select for gene transfer treatment; they discussed it as a strategy to attract investors and increase funding opportunities for their research (see Chapter 4).

These three reasons, as expressed by the Swedish gene transfer scientists, are primarily practical. However, one of the scientists, Staffan, also explained that cancer was appropriate to focus on from a risk perspective. ‘If you have a patient who is therapy-resistant to conventional cancer treatments, then it is very easy from an ethical point of view to try another experimental therapy’ (p. 3). Greater side effects as a consequence of the gene transfer treatment could be accepted in a patient where gene transfer was considered a last option, something to try when all other treatments had failed. ‘One maybe tends to accept greater side effects on such a patient’, Staffan said, ‘than on a healthier one who may have alternative treatment options’ (p. 3). It became apparent that the evaluation of risks was again closely related to the level of illness of the disease. As earlier described, gene transfer scientists evaluate risk based on what the alternatives are. In the above case it was regarded as morally acceptable to take a higher risk, as gene transfer was the last alternative. In other words, it was better to take a risk than to do nothing. Staffan, as a clinician, could indeed accept an increased risk of side effects under these circumstances. This was also emphasized by several of the other interviewees, both Swedish and U.S., and as Staffan emphasized, it was the accepted position in the discussion regarding enrollment criteria in clinical gene transfer trials. ‘There is apparently the same reasoning in the rest of the world’, he concluded, ‘and it is no coincidence that more than 70% of all Phase I-II gene transfer trials are on cancer’ (p. 6).

Although both the Swedish and the U.S. interviewees considered severe diseases and hence severely ill patients to be appropriate candidates for clinical gene transfer trials from a moral standpoint, they also raised problems. Some of the interviewed U.S. gene transfer scientists talked about the clinical consequences of enrolling severely ill patients in clinical gene transfer trials. It was their level of illness that made them unsuitable when it came to evaluating and establishing the efficacy of the treatment. This argument was illustrated by Scott, who explained that in the early trials of gene transfer for cancer, gene transfer was only allowed when all other options had failed. By that time, however, the patients had often passed ‘the point of no return’, meaning that there was nothing that could cure the patient at this
point. ‘The disease was too far advanced’, Scott explained (p. 13). From a clinical perspective, it was therefore extremely difficult to try to prove efficacy in this population. Even if it is justifiable to enroll these patients, their level of illness has an impact on the evaluation of clinical gene transfer trials and will therefore cause bias on the research outcomes and results. As a consequence, scientists wanted to treat patients earlier. ‘You really have to start to treat people at an earlier stage of the disease’, Scott clarified (p. 13). One of the Swedish interviewees, Staffan, described why he, in one of his applications for a clinical gene transfer trial on urinary bladder cancer, wanted to enroll participants who were not in the final stage of the disease. He explained that

> it gets interesting to see how the ethics committee will react when we don’t do it [the gene transfer treatment] immediately before a cystectomy, that is right before you remove the entire urinary bladder – instead we want to do it at an earlier stage so that you can actually see, have time to see, an effect on the tumor before you then possibly remove the bladder. (p. 10)

I do not know whether Staffan was able to do the clinical trial on human subjects less affected by urinary bladder cancer. However, it is clear that focusing on severe diseases and disorders in their final stages makes it difficult to evaluate research findings and outcomes as well as to get good scientific results.

To summarize, although gene transfer involves unknown and unforeseen risks it was, by almost all of the interviewees, considered to be an appropriate treatment to offer to a patient if there was no other better alternative treatment available, or if the choice was between treating a severely ill patient despite the risks or doing nothing. Taking risks was always regarded as a better alternative than doing nothing. For Shane and Staffan, the issue of risk was thus between treating a severely ill patient despite the risks of using gene transfer, or doing nothing and letting the disease run its course, something which meant that the patient inevitably would die. Whether a medical treatment is regarded as clinical best practice or experimental is of significant importance from a medical treatment perspective. A treatment that is clinical best practice, such as bone marrow transplant, means that it is evidence-based. It has been thoroughly investigated clinically. An experimental treatment, on the other hand, is as the name implies experimental and has not been extensively evaluated clinically. For Sixten and Stuart, however, the issue of risk was instead about the risks involved in gene transfer compared to an alternative treatment such as bone marrow transplants. In other words, they contrasted the risks of an experimental treatment with a clinical best practice treatment, underlining that the risks were similar, if not the same, in the two treatments. These different interpretations of the risk/benefit calculations served as ethical boundaries between the risks of gene transfer compared to other risks. It is also a way for the scientists to assert an ethical
position, that is, that their primary commitment is toward the patients and that it is the best interest of the patient that needs to be considered above all. It is also the individual patient and his or her situation that sets the limits for which risks can be acceptable to take.

There was, however, one noteworthy exception to this general opinion, made by Svante. ‘In my opinion’, he explained, ‘you should always try to help the patients’ (p. 9). But if one could not help, he regarded it as important that the natural condition of the patient was not to be disturbed or made worse (p. 11). What he meant was that, if it could not be established that an experimental medical treatment or therapy, or any other medical treatment or therapy for that matter, was beneficial for the patient, then it was better to refrain from the procedure so that the patient’s present state was not affected or worsened. In this sense, it was better to do nothing rather than take unnecessary risks. In the end, evaluating risks was always a balance between possible benefits and potential risks. However, it was not only the gene transfer scientists that needed to do these risk/benefit calculations. The human research participants enrolled in a clinical gene transfer trial also needed to address this issue with the help of the informed consent process.

**Obtaining a Valid Informed Consent**

The second ethical complication described by the interviewed gene transfer scientists was related to the problem of obtaining valid informed consent.

When recruiting human research participants to clinical gene transfer trials, the risk or loss to participants must be minimized as well as the risk for therapeutic misconception, that is, the risk that participants will misunderstand the goal of the clinical trial. At the same time, a good study population must be involved in order to provide good scientific results. Enrolling severely ill patients in early clinical gene transfer trials means minimizing what the participants could lose (as severely ill patients in any case risk dying). Using severely ill patients, however, has two disadvantages. One is the higher presence of therapeutic misconception. The other is that it is more difficult to get good scientific results. It is easier to avoid therapeutic misconceptions with relatively healthy participants. The scientific results will furthermore be less biased because the disease is often moderate and not so far advanced. It is also possible to evaluate the scientific results extensively for a longer period of time, as gene transfer in these participants is not a last option before, for example, surgery. There is nevertheless one important problem, which is that the healthier the participants are, the more they stand to lose if something goes wrong.

Among the interviewed Swedish gene transfer scientists the discussion regarding informed consent was almost non-existent. It was only discussed when they explained why they chose to focus their research on severe diseases, like cancer. For example, cancer involves many adult patients, which facilitates the informed consent process. The ethical part is easier, Sixten explained, as ‘they are adult patients who can make their own decisions’ (p. 5). This made the informed consent process much
easier as involving minors, or someone who is declared incapacitated, demands that either a parent or a representative signs the informed consent form. For the U.S. interviewees, on the other hand, the informed consent process was considered to be of essential importance in clinical gene transfer research.

There are three possible reasons for why the U.S. gene transfer scientists discussed the ethical complication of obtaining a valid informed consent to an extent so much greater than their Swedish colleagues did. First, there have only been a couple of clinical gene transfer trials conducted in Sweden to date, whereas two-thirds of all clinical gene transfer trials worldwide have taken place in the U.S.A. As a result, U.S. gene transfer scientists are more accustomed to the ethical and practical problems in the informed consent process; it is a common feature in their work. Second, there are different legal systems in Sweden and the U.S.A. with an important difference in the informed consent process. In Sweden, it is recommended by the regional ethical review boards, as well as by the central ethical review board, that the informed consent form should be short and only in exceptional cases exceed three to four pages (Etikprövningsnämnden 2010). In the U.S.A., the consent form should be written in a language that is comprehensible to the human research participant or the representative (45 CFR 46). Nowhere is it stated how long the consent forms should be but, as Scott described to me, they are often 15 to 20 pages long and should be written at an eighth grade reading level (p. 23). The most important legal difference is, however, that U.S. gene transfer scientists run a much higher risk of actually having to pay for their mistakes in the process of informing patients. They may be sued by human research participants and thus may have to pay large indemnities. The risk of something similar happening in Sweden is unlikely.

The question that the U.S. gene transfer scientists raised when discussing the ethical issue of informed consent was if it was indeed possible to obtain a valid informed consent, given the situation in which clinical gene transfer trials are conducted. This is the topic for the following section in which we shall see examples of how the interviewees described that they handled this ethical complication in practice.

Handling the Dynamic between Patients’ Hope and the Purpose of Clinical Trials

“You could be as honest as you possibly can, and yet from the other point of view [the view from the human research participant and his/her family], it doesn’t matter.’

This quote from Shane illustrates the general view among the interviewed U.S. gene transfer scientists regarding the ethical complication of obtaining a valid informed consent. Obtaining a valid informed consent, given the circumstances of a clinical
gene transfer trial, presented a complex dilemma for gene transfer scientists. Not only were there unknown risks to human research participants, there was also no way of knowing beforehand whether the treatment would work or not. On top of this was the risk of therapeutic misconception. How should the dynamic between patients’ hopes and the purpose of clinical gene transfer trials, often early Phase I trials, be handled?

In the bioethical literature, the assurance of an informed and voluntary consent from human research participants enrolled in clinical trials is considered one of the cornerstones of research ethics. However, the fact that gene transfer is used on severely ill patients, where it often is the last option, causes difficulties with informed consent. The main difficulty is, according to medical sociologist Gail E. Henderson et al. (2006), that severely ill human research participants tend to have unrealistic expectations of the medical benefit of participating in a clinical trial. They misunderstand the meaning of research, an event called therapeutic misconception. This situation occurs when human research participants fail to recognize that ‘the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial’ (Henderson et al. 2007:1736).

There are two possible explanations, Henderson et al. (2006) write, for why therapeutic misconception occur during the informed consent process. First, early phase I clinical trials do not present any direct medical benefits to participants. This is perhaps not always clearly communicated to participants. One of the interviewees, Scott, also emphasized this problem and explained that the often difficult and circumstantial language used in the informed consent form may have an influence on the patients’ understanding of the purpose of the clinical trial. “They [the informed consent forms] are supposed to be written at an eighth grade level, but they get very complex”, he concluded (p. 23).

Second, participants may not understand the difference between medical treatment and clinical research (Henderson et al. 2006). According to the U.S. interviewees, the patients’ failure to recognize this difference was because the human research participants enrolled in clinical gene transfer trials primarily were afflicted with disabling lethal diseases, and often reached for the last ray of hope. Consequently, the vulnerable and emotional state of the patients and their families had a significant impact on how they understood the information presented regarding their participation in a clinical gene transfer trial. All of the interviewees underlined that they believed that it was impossible to completely eliminate therapeutic misconception, regardless of how good and valid the information that the human research participants received was. It was especially the difficulty for patients to separate expected hopes of benefit from the reality of gene transfer and its limitations that was emphasized as troublesome and impossible to overcome.

Sean described that with any cutting-edge technology, untested but novel, there was a hope that it could address serious medical problems that other approaches
had failed to do. He continued by describing his experience from one of the Phase I gene transfer trials in which he gave information regarding the purpose of the trial to patients enrolled.

A Phase I study, which is the first evaluation of a therapy in the clinic, is the study’s design to determine whether the therapy is safe, not effective. It is not designed that way. It is impossible. It is very difficult to do and one needs to convince the patients, the research subjects, that when they participate in that Phase I study that “This is designed simply as a way of assessing safety.” And you can tell them that. You can say, “Repeat after me,” and you leave the room, and if someone asks them why they are doing it, they’re going to say, “Because it may help me.” Why? Because they have a lethal, disabling disease for which there are no other potential options, and that drives right to the heart of the consent. (p. 12-13)

For gene transfer scientists the purpose and goal of a Phase I trial is to assess safety. This means that phase I trials are conducted in order to determine the metabolism and pharmacologic actions of a specific drug, to see if possible side effects are associated with increased doses, and to gain early evidence of effectiveness. But for patients it is something else. It is a last ray of hope, something that might work when there are no other options or choices left, besides giving up and letting the disease run its course. Under these circumstances it is difficult, if not to say impossible, to obtain a valid informed consent.

Scott also emphasized the difficulty that the emotional state of the patient presented for getting a valid informed consent. He explained that patients with severe fatal diseases do not listen, or do not automatically take into account that they are participating in the trial to help medical research. Instead, they still hope that clinical trials are curative. Scott raised the question if a valid informed consent could be obtained under these circumstances. ‘Do they [human research participants] always really comprehend what they are doing?’ he wondered (p. 23). This raised ethical issues, not merely in gene transfer, but in all clinical trials.

Shane also questioned the possibility of obtaining a valid informed consent. He further wondered if therapeutic misconception indeed was an ethical dilemma. He explained that

when you’re talking about genetic diseases and you have a therapy that you have no idea whether it works or not. You put in your consent forms, “We have no evidence that this works. It may kill the person getting it,” or your child or whatever. You think that you’re being open and honest about that, but then look at it from the other point of view, if somebody who has a fatal disease, late-stage cancer or Alzheimer’s disease or terrible heart disease or some terrible genetic disease or a child is going to die. They
look and say: “Wait a minute. What are my alternatives here?” So that becomes less important. Of course, in the ethical world, that’s referred to as therapeutic misconception, but it depends very much on who is thinking about it. (p. 18)

With this statement one could say, as did Shane, that it is easy for an ethicist who is not present in the actual clinical situation and maybe never has been, to raise concerns about therapeutic misconception as an ethical issue. Shane, on the other hand, who had experienced this situation several times, considered therapeutic misconception to be a practical problem. He explained that given the situation in which a mixture of the patient being severely ill, his or her emotional state given the fact that the clinical gene transfer trials might be the last hope, and his or her hope for the treatment to work, despite the fact that the trial only is to assess safety, made it impossible to obtain a valid informed consent. From a patient perspective, it is quite understandable that it is difficult to grasp the information regarding the purpose and goal of the trial, the precise procedures to be followed, as well as the risks and benefits involved due to the limited information from previous preclinical trials, Shane concluded.

It seems that therapeutic misconception is regarded as less important among the U.S. gene transfer scientists in this study as it was described by them as inevitable, given the circumstances in which clinical gene transfer trials are conducted. The enrollment of severely ill patients for whom gene transfer is the last hope somewhat contradicts the possibility of obtaining an informed consent. The interviewees were well aware of this situation and instead tried to find the best possible informed consent that could be obtained, given the circumstances, although this might not be considered valid according to ethical principles and guidelines.

Some of the interviewees explicitly stated that it was immoral of them, as scientists and clinicians, to strip the patients and their families of their hope. For example, Sean and Scott, explained that it was important to make sure that participants in early phase I clinical gene transfer trials received all the information that they needed to make their decision. Nevertheless, Sean said to me ‘at the end of the day it is their decision. I feel that it is not appropriate for me to pass judgment on why they decide to participate’ (p.13). The fact that participants in clinical gene transfer trials are able to make well-founded decisions, and that this capacity should not be neglected, was something that Scott emphasized also. ‘I think that people should be able to make up their own minds to some degree on some of these things’, he said (p. 13).

This is a strategy that enables the interviewed gene transfer scientists to rise above the issue of obtaining a valid informed consent. That is to say, it shifts the ethical focus from gene transfer scientists obtaining a valid informed consent to the

43 The ethical principles that I refer to are the four basic principles of biomedical ethics. They are: respect for autonomy, beneficence, non-maleficence, and justice. For an extensive discussion of these principles see Beauchamp and Childress (2009) book Principles of Biomedical Ethics.
one of them respecting the decisions made by the enrolled human research participants themselves.

To summarize, handling the dynamic between patients’ hope and the purpose of clinical gene transfer trials and thereby obtaining valid informed consent was described by the interviewees as difficult. There were two main reasons for this. First, human research participants enrolled in clinical gene transfer trials were primarily afflicted with fatal diseases. Due to their severe illness they were in a vulnerable and emotional state. These two aspects affected how they understood the information regarding the purpose and goal of the clinical gene transfer trial. Second, the language used in informed consent forms was often circumstantial and difficult. In order to make the informed consent process doable, given these circumstances, the interviewees described how they tried to obtain the best possible informed consent, despite the fact that it probably was not valid according to ethical principles and guidelines. More importantly, they shifted the ethical responsibility in the informed consent process away from themselves, and from their duty to obtain a valid consent, to the participants. Thus, being ethical meant respecting the participants’ decisions, and not always ethical principles and guidelines to the letter.

**Making a Distinction between Treatment and Enhancement Purposes**

As mentioned above, a third ethical complication was presented in the interviews, although only when raised as a question by me.

In both popular media and academic publications it has been considered an ethical dilemma that biotechnologies developed for treatment of diseases and disorders can also be used for enhancement applications. Such applications include extending human life, improving functioning in sports and athletics, or improving intelligence (Ter Meulen et al. 2007). This is an ethical complication in gene transfer research, too.

In public debates about gene transfer, there has been a concern that the technology can be used to enhance non-medical traits and characteristics to improve mankind or design new life forms and thus create ‘brave new worlds’. The danger of biomedicalization has also been discussed – that social problems would be transformed into medical problems and their definitions and solutions thus be located solely within a medical jurisdiction. As gene transfer becomes more common in clinical practice, what is regarded as an acceptable use of gene transfer might move towards less severe diseases, and possibly ‘gray zone’ cases, like intelligence, height, or socio-behavioral disorders. This means that the ethical and social implications of using gene transfer to go beyond therapy for disease are often seen as negative, dubious, and ethically unacceptable. Due to these concerns it is, according to the gene transfer debates, important to discuss and, if possible, try to make a distinction between what is regarded as treatment and enhancement in clinical gene transfer practice.
The gene transfer scientists whom I interviewed did not talk about this ethical complication before I asked them the question ‘Some people say that there is an ethical difference between eventually using gene transfer to treat diseases and using it to enhance non-medical (normal) characteristics. What is your opinion?’ In analyzing the interviews it became clear to me that making a distinction between treatment and enhancement was not always that easy for the interviewees, as illustrated in the interview with one of the Swedish gene transfer scientists, Svante, in the following quote.

I think for somatic gene therapy our aim is always to cure. We want to cure the disease, the patients. Of course, gene therapy can be used in combination with other treatments and this is a kind of enhancement, but that doesn’t mean enhancement of the good things to get qualities like higher IQ. (p. 10)

As described by Svante, in practice it often became difficult to distinguish between what was a case of treatment, enhancement, or improvement. This was a common theme in my interviews. The interviewees often described how they based their decisions on the distinction between medical and non-medical traits and characteristics. Despite the use of these distinctions, it was indeed sometimes rather difficult to decide what constituted a treatment versus an improvement or enhancement, given the diverse cases in which gene transfer could be applied.

The interviewed gene transfer scientists referred to many cases as clear-cut, where the sole purpose of using gene transfer was to address serious medical problems. The Swedish gene transfer scientists also discussed cases of improvement. This was not something that was explicitly discussed by the U.S. interviewees. Instead they discussed ‘gray zone’ cases, something that their Swedish colleagues did not. There are three possible explanations for this difference. First, as earlier pointed out, there have only been a couple of clinical gene transfer trials conducted in Sweden to date. Second, the Swedish word ‘förbättring’ translates as both ‘improvement’ and ‘enhancement’ in the English language, something which may have caused confusion during the interviews. Third, to date more than 1690 clinical gene transfer trials have been conducted in the U.S.A. Maybe the U.S. gene transfer scientists are so accustomed to cases of improvement that they consider them to be ‘standard’ cases and instead focus on ‘gray zone’ cases, new borderline cases, that may come down the line in the clinical application of gene transfer and thus raise new ethical concerns.

**Cases of Improvement**

Several of the Swedish interviewees described cases where it was not that easy to distinguish whether the gene transfer was actually only a treatment. Instead it was regarded as an improvement in the sense that even if the patient could not be com-
pletely cured, the symptoms or conditions of the disease might be alleviated. As a result, the patient’s life could be prolonged as well as achieve a better quality. Among these interviewees, improvement was always discussed with regard to somatic gene transfer and in a therapeutic setting. Staffan, for example, considered cancer to be an excellent case where improvements could be made through vaccination and immunotherapy\textsuperscript{44}. We cannot expect a complete cure, he explained, but we have sufficient data to show that immunity-stimulating genes modify the immune defense in a favorable way so that tumor cells can be eliminated (p. 9). The benefits of immunotherapy as a form of improvement was also emphasized by Sylve. When it comes to cancer, he said,

we cannot be sure that it will be curing. In cancer patients it may be like cytostatic. On certain patients it will reinforce the effect of the immune system. It can possibly make the disease somewhat manageable, or cure it. Many people will still have the disease but may survive longer, and have a better life. (p.14)

‘Gray Zone’ Cases

The U.S. gene transfer scientists whom I interviewed instead primarily discussed what they referred to as ‘gray zone’ cases. Some of these cases became ‘gray’ because it was often very difficult to make a distinction between treatment and enhancement. What is regarded as treatment in one case could be regarded as enhancement in another. Other cases became ‘gray’ because they involved using gene transfer to treat psychological or socio-behavioral disorders. This raised concerns regarding biomedicalization.

There was, however, one exception among the U.S. interviewees when it came to what was considered to be acceptable use of gene transfer. Spencer explained that the therapeutic needs set aside all enhancement purposes for the moment. I would say, he said,

just to pick an example of hair growth that could potentially be addressed with gene therapy in theory. At some point it may be a practical solution, if it’s safe and effective. So whether that’s considered as cosmetics or whatever you’re addressing a medical condition with a series of real medical-related concerns, I think that’s an individual basis. […] But, no, I think right now the focus is on existing unmet medical needs and extending life and improving the quality of life for people with diseases. (p. 20)

\textsuperscript{44} In immunotherapy the immune system is boosted by the use of gene transfer so that it can target and destroy cancer cells. This approach is used to create recombinant cancer vaccines.
With the exception of Spencer, all the U.S. interviewees regarded gene transfer as acceptable to use in two particular 'gray zone' cases, were the purpose was to treat or enhance a physical disease or condition. These were baldness and loss of muscle function due to aging.

The first case – baldness – was described by Sean and Shane. They had each developed a strategy to grow hair in mice. The question was nevertheless, Shane said, ‘Should we try to do this on humans?’ (p. 17). In practice, he and his colleagues had not yet tested the technology on human research participants. The reason was that to grow hair to treat baldness could be seen as a kind of enhancement therapy. Still, Shane explained that he had a personal interest in this treatment as he was beginning to become bald himself but, as he continued, using gene transfer for this purpose was enhancement (p. 17). Sean also raised the question of whether gene transfer was an appropriate therapy or treatment for men who had male pattern baldness. ‘Some would say no’, he said (p. 14).

What about if it instead was a woman undergoing chemotherapy for metastatic breast cancer who would lose all her hair because of the cancer treatment?, Sean asked. Would it be appropriate in this case? ‘Possibly’, he said (p. 14). ‘She might not want to take chemotherapy’ otherwise, Shane concluded, ‘and there are articles written about this, because she is going to lose her hair’ (p. 17).

These statements by Shane and Scan show that what is regarded as enhancement in one case could be regarded as treatment in another. The problem regarding making a distinction between treatment and enhancement also includes the constantly contested line between health and illness. In order to be able to make some kind of distinction in this situation, Shane and Scan both underlined that it was the individual patient and his or her needs that should be the primary focus when deciding whether or not gene transfer was morally appropriate to use.

The second case – loss of muscle function due to aging – was described by Stuart. The first question was, however, if loss of muscle function due to aging was a disease? Second, was it something that should be interfered with? ‘Our society has answered this question already’, Stuart concluded, as we currently interfere with it in many pharmacological ways (p. 22). Despite the fact that pharmaceuticals were used to treat the loss of muscle function due to aging, the use of gene transfer for the same purpose was quite different, at least from a regulatory perspective, according to Stuart. The RAC and the U.S. regulatory agencies are not willing to review these kinds of studies at the moment, Stuart continued, as they do not accept enhancement protocols. Nevertheless, he explained that

there are ways that one can imagine to improve muscle function and prevent muscle degeneration. If someone developed a good, safe technique for introducing into a large block of muscle, for instance, a growth factor such as IGF or could turn off the myostatin gene. I'm not sure that I could make a terribly good argument against that. I
could in fact find personal interest in those kinds of potential enhancement procedures. (p. 22-23)

In this quote, Stuart referred to a technique that would make it possible to turn off the myostatin gene, a technology that already exists. In 2004 several articles were published about a German boy who had a mutation that blocked the activation of muscle stem cells by turning off the myostatin gene. This resulted in an increased muscle growth. As this mutation results in increased muscle growth, it can be used to treat muscle-wasting diseases, such as Duchenne muscular dystrophy or loss of muscle function due to aging. The problem, however, with this gene transfer treatment is that its specific technology can also be used for enhancement purposes, like gene doping in sports. In consequence, there is a fear that gene transfer could be the next trend in sports, as Science writer Gretchen Vogel (2004) argues, and that many athletes might be interested in injecting a myostatin-blocking gene to enhance muscle growth. More importantly, injecting genes like this is a kind of gene doping that is almost undetectable.

To perform non-medical enhancement for athletic purposes was described by Stuart, and several other interviewees, as morally wrong and unacceptable. But medical enhancement with a therapeutic purpose, more in terms of improvement, was described as morally acceptable. In fact two of the U.S. gene transfer scientists expressed personal interests in the medical enhancements of treating baldness or to stop decreased muscle functioning due to aging. However, while Shane was hesitant to use this technology due to its status as an enhancement therapy, Stuart explained that if gene transfer became technically safe and accurate he had no personal qualms about using it in order to interfere with aging at a somatic level. ‘I am not so sure that I have a very good argument’ for declining the use of gene transfer in this case, he concluded (p. 22). When discussing these ‘gray zone’ cases in which gene transfer could be used, it was common that the interviewees felt it awkward to pass judgment. Instead they wanted ‘society’ to decide whether gene transfer was morally acceptable to use in these ‘gray zone’ cases, or not.

In the previous illustrative cases described by the interviewees, gene transfer was always used for the treatment or the enhancement of physical diseases or conditions. But what happens if gene transfer is to be used for other diseases and medical conditions, like psychological and socio-behavioral disorders? Scott elaborated on the ‘gray zone’ that he considered gene transfer to present in these cases. As an example, he told me his beliefs regarding a future in which genetic testing was common and where there were genetic tests available for IQ and height. Let’s say, he said,

based on some genetic test that you do, you know that somebody is going to have a low IQ. I mean really low IQ, mentally retarded even. What if you could put a gene in, to make them at least have normal IQ. What would you do? If somebody is going to
be below the fifth percentile in height or something, and you could give them something to enhance their growth? (p. 26)

People who are under the fifth percentile with regard to height are currently given growth hormones. In this quote, the question is raised whether or not it would be deemed appropriate to also use gene transfer to treat a person’s short stature or an IQ below normal. Scott further remarked that people who are within normal growth curves also take growth hormones for enhancement purposes. ‘Where do you stop?’, he asked me (p. 26). It is interesting to see how the concept of ‘normality’ is raised as problematic within the ethical distinction between treatment and enhancement.

That gene transfer for enhancement purposes could have social implications was something that Scott underlined as important to discuss. The issue that he raised was that in the future socio-behavioral disorders and other personal and social propensities could eventually be treated by gene transfer and thereby be biomedicalized. I think that they are going to have genetic tests for people who have propensities, he said, and

say you have a socio-behavioral disorder like high rate of crime or rape. If you could do gene therapy to treat those people, is it appropriate or not? That gets into these really, really gray zones. There are all sorts of issues, like obsessive-compulsive diseases. If you could do gene therapy to fix that, is it wrong, or is it appropriate? […] What about homosexuality? I mean if they find the genetic basis for that, would you do gene therapy? Let’s say you could do a genetic test for homosexuality and you found out that your expected child had that gene or parents insisted that they wanted gene therapy so their child would not grow up to be gay. You know that is going to cause lots and lots of debate. These are going to be huge ethical issues, in my mind. (p. 26-27)

Scott’s statement shows that there are concerns raised regarding the use of information from genetic tests as well as how this information may change the distinction between what is considered as health and illness, and also what is regarded as normal. Whether he is aware of it or not, Scott used a slippery slope argument in his discussion: If we allow the use of genetic information from genetic tests to determine propensities for what is considered socio-behavioral disorders, we are taking a first step in a problematic direction and ultimately, this will result in an acceptance of this kind of genetic investigation for all kinds of conditions. Seen from the perspective of the slippery slope argument, concerns are raised that disorders and conditions that at present have no genetic explanation could, due to new knowledge regarding genetic information, be regarded as originating from genetic defects and therefore be considered as in need of medical treatment.
To summarize, the interviewees described that it was quite difficult to make a distinction between treatment and enhancement because there was no obvious dividing line between the two. Acceptable gene transfer treatments were instead divided by the interviewees into two different categories. On one side were cases of unproblematic medical treatments like the treatment of X-SCID, and cases of improvement such as vaccination and immunotherapy. On the other side were unacceptable cases in which gene transfer would be used to treat or enhance conditions such as psychological or socio-behavioral disorders like those concerning intelligence, obsessive-compulsive disorders, or homosexuality, or for gene doping in sports. In between were the ‘gray zone’ cases in which gene transfer was used to treat or enhance a physical disease or condition such as baldness or loss of muscle function due to aging; these cases were mainly regarded as morally acceptable.

However, the use of gene transfer for ‘gray zone’ cases or cases that were regarded as unacceptable by interviewees raised an important question. Who should decide where the line should be made regarding the application of gene transfer? In these cases, where the use of gene transfer became morally questionable, the interviewees shifted the ethical focus from themselves to ‘society’. They did not want to pass judgments regarding what was ethically acceptable to do, given that gene transfer was technically safe and accurate. They merely indicated some ethical issues that needed to be addressed, and that it was society that needed to address these issues and decide the moral acceptability of when and how to use gene transfer.

Concluding Discussion

In this chapter I have shown what the interviewed gene transfer scientists regarded as the two major ethical complications in their work. These were how to select appropriate diseases and how to obtain a valid informed consent. A third ethical complication was introduced by me, and contained the problem of how to distinguish between treatment and enhancement purposes of gene transfer.

Just like the nuclear weapons scientists that Gusterson (1996) interviewed confronted and learned to resolve the moral dilemmas in their work, the gene transfer scientists whom I interviewed have reacted towards the ethical complications of conducting clinical gene transfer research. Rather than ignoring these problems they try to align their research with existing ethical principles, guidelines, and regulatory frameworks.

However, and as I have shown in this chapter, the gene transfer scientists interviewed sometimes regarded the ethical principles and guidelines as difficult to apply to clinical practice. Consequently, they transformed the ethical problems to practical problems and situation-specific problems. As an example, the interviewees evaluated the risks and benefits in relation to various diseases or to a specific case. In doing so, they could handle the ethical choices in a practical way. Another example is the informed consent process, which raises many problems due to the severe illness of participants enrolled and their emotional state in which gene transfer is the last
hope. There is also a lack of scientific information regarding the possible risks and benefits in the clinical trial due to its experimental character. Here the interviewees handled the problems by making sure that the participants received the information that they needed to make their decision, and then the scientists respected the decisions made by the participants themselves. In other words, the gene transfer scientists tried to obtain the best possible informed consent, given the circumstances (although this might not be considered perfectly valid according to ethical principles and guidelines), while simultaneously shifting the ethical responsibility from themselves to the participants.

To make a distinction between treatment and enhancement was quite difficult, according to the interviewees. Cases of medical treatment, improvement, and enhancement, such as treatment of X-SCID, immunotherapy, and gene doping in sports, was according to the interviewees unproblematic. ‘Gray zone’ cases in which gene transfer was used to treat or enhance a physical disease or condition, such as baldness or loss of muscle function due to aging, were also mainly unproblematic. But when it came to ‘gray zone’ cases in which gene transfer was to be used to treat or enhance psychological or socio-behavioral conditions such as intelligence, obsessive-compulsive disorders, or homosexuality, it became problematic. In these cases, the interviewees did not want to pass judgments themselves regarding what was ethically acceptable to do. Instead they indicated that society should decide the moral acceptability of when and how to use gene transfer. Again, the ethical responsibility was shifted from science to society.

Ethical principles, guidelines, and the regulatory framework jointly provide a map of a legal and ethical landscape to guide gene transfer scientists in their clinical work. As we have seen in the examples above, ‘the map’ that guides the clinical gene transfer practice is deemed difficult to apply and follow. Instead gene transfer scientists find alternative ‘itineraries’ when they maneuver in this complex ethical and legal landscape. As communication scientists John Seely Brown and Paul Duguid (1991:41-42) put it, this kind of map raises problems as it ‘inevitably smoothes over the myriad decisions made with regard to changing conditions’. This means that a map is often, to various degrees, detached from the actual practice as it does not take into account that conditions could change or that the actual practice is complex. The more complex a journey gets, the more evident it becomes that improvised actions need to be taken in order to accomplish the journey. Faced with the three ethical complications discussed above in their work, the gene transfer scientists whom I interviewed tried out new itineraries and rearranged boundaries, in a search for acceptable alternatives.

The ethical complications in clinical gene transfer research and complexity of gene transfer scientists work can further be highlighted by the concept of ethical boundary-work. This term emanates from Gieryn’s (1983, 1999) concept of boundary-work and was introduced by medical sociologist Steven P. Wainwright et al. (2006). It investigates how scientists draw ethical boundaries regarding their scientific work. Gene transfer scientists handle the ‘ethics’ of gene transfer research by em-
ploying ethical boundary-work. The main goal with this strategy is to draw ethical boundaries regarding what they consider as ethically acceptable to do in their work, to legitimize their choices and actions, but also to establish an ethical acceptability of their work. As an example, when the interviewed gene transfer scientists discussed how they selected appropriate diseases for clinical trials, evaluated risks and benefits, obtained informed consent, or problematized ‘gray zone’ cases, they always shifted the ethical responsibility from themselves to the individual participant, his or her unique situation, or society. The ethical boundary of what is regarded as ethically acceptable or not instead became other actors’ problems; that is, the boundary of their jurisdictions shifted. Gene transfer scientists themselves should not decide or pass judgment. They should only respect the decisions made by either participants or society.

All in all, these accounts signal that the interviewed gene transfer scientists wanted to present themselves as deliberate, serious, and right seeking scientists who reflected morally about the complications that they face in their work.
CHAPTER 7
Gaining Public Acceptance

So far I have discussed how the interviewed gene transfer scientists make their work doable, primarily inside the social world of gene transfer research. But how do they handle public concerns and fears about gene transfer and their work? That is, how do they relate to the outside world?

One of the main concerns of the gene transfer scientists whom I interviewed was that there were a lot of misconceptions about gene transfer. More specifically, society misunderstood the purpose of gene transfer, as well as when, and for what, it could be used. A general misunderstanding was that somatic gene transfer was often confused with germ-line gene transfer. But ‘as gene therapists’, Scott explained, ‘we’re not promoting germ-line gene therapy’ (p. 7). Instead their main goal was to cure diseases in living patients using somatic gene transfer. Svante emphasized this and underlined that ‘we want to cure the disease, the patients, so all other issues are not our main focus’ (p. 11). It was not only that society got confused about the concept of gene transfer. Public fears were also created because gene transfer involved genes. ‘It is just because it is genes’, Shane said, ‘and genes are different because society is not ready for it’ (p. 6).

The problem was not only that the general public did not understand gene transfer. Misconceptions about the technology and its use occurred everywhere, according to the gene transfer scientists interviewed. The media often got it wrong, as did regulators and politicians. These misunderstandings and the fears they often resulted in could have significant consequences for gene transfer scientists’ work and their ability to conduct research. They could affect, as previously discussed, the ability to get funding from the national and federal government in Sweden and the U.S.A., but also from commercial sponsors and investors as well as from patient organizations. They could also affect the ability to conduct clinical gene transfer trials, as misconceptions and misunderstandings could influence how different authorities, regulatory agencies, and advisory boards regulated, monitored, and reviewed applications for clinical trials with human research participants.

This chapter deals with how the gene transfer scientists whom I interviewed experienced public concerns regarding gene transfer, as both a technology and a field of research, and how they responded to these concerns. More specifically, what arguments were used by gene transfer scientists in order to present their work with gene transfer as legitimate and ethically acceptable, and thereby gain public acceptance?

In this chapter I first examine what I see as the gene transfer scientists’ use of a deficit model (Wynne 1991, Irwin and Wynne 1996) in order to explain why the
public was worried. Then I turn to how they try to handle what they regard as misconceptions regarding gene transfer and its research through educating society, that is, by making scientific information regarding gene transfer more accessible to the public. Finally, I outline the arguments that gene transfer scientists claim they use to help society understand gene transfer and the research that it entails in a proper way. As I show, gene transfer scientists transform the common notion of gene transfer as controversial research into something that could be regarded as a conventional medical procedure. This transformation was made by constructing a frame of reference that put the research in an acceptable and accessible light. What is noteworthy is that during the interviews I never asked any questions regarding public concerns or problems experienced in relation to the public. Still, the gene transfer scientists talked about these issues. This shows that responding in an appropriate way to public concerns is of crucial importance for them in their attempt to construct doable research.

**Worries are due to Misunderstandings and Lack of Scientific Information**

Gene transfer has been, and still is, presented in the media as well as in the bioethical literature as a field of research that raises various ethical, legal, and social issues. The media and bioethical experts use four main arguments to stress why gene transfer is considered controversial. They are: (1) the modification is intentional, (2) genetic modifications could lead to genetic enhancement, (3) there are associations to eugenics, and (4) there may be unknown and unforeseen risks to human research participants as well as to future generations (see Chapter 1). These possible problems make society worry about gene transfer.

On the other hand, and according to political scientist Herbert Gottweis (2002), many gene transfer scientists themselves believe that the public’s concerns and fears about gene transfer are based on misunderstandings and lack of scientific information. However, social scientists Patrick Sturgis and Nick Allum (2004) argue, assuming that it is a lack of understanding or knowledge that accounts for the concerns and (misplaced) fears among the public as well as the media is a simplification that the scientific community often makes in order to explain the public’s attitudes towards science. This view is called ‘the deficit model’ (Wynne 1991, Irwin and Wynne 1996), in which science is seen as ‘sufficient’ while the public is judged as ‘deficient’ (Gross 1994). The model indicates that the reason why the public doubts and fears novel innovations is because it does not understand the circumstances under which innovations are developed, nor their scientific foundations. Instead,

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45 It should be noted that the public (mis)understanding of science is a theme also present in other fields of biotechnology such as stem cell research or genetic technologies (see Wainwright et al. 2006, Lassen and Jamison 2006).
people resort to ‘mystical beliefs and irrational fears of the unknown’ (Sturgis and Allum 2004:57).

The public (mis)understanding of gene transfer was a common theme in almost all of my interviews. Somehow the public got the purpose and goal of gene transfer wrong, as well as how it should be deployed and employed. The interviewees believed that these misunderstandings were due to the public misunderstanding the existing status of gene transfer and what was practically possible to do with it. Another explanation given was that there was a lack of scientific information from the scientists’ side. In other words, there was a communication gap between gene transfer scientists and society, which needed to be overcome. The scientists’ responsibility was therefore above all to educate, that is, to give meaningful and correct information regarding gene transfer to society. By ‘society’, the interviewees primarily meant the public and the media, but also authorities, regulators, and politicians, that is, people who were non-scientists and not working in the field of gene transfer research. Education was hence seen as the solution to the problem. It seems that gene transfer scientists regard themselves as experts and gene transfer as an entity that is too complicated and specialized to be understood by the public. Better information and more exposure would thus act as countermeasures to collective responses based on ‘misconceptions’ of gene transfer, that is, an incorrect understanding of the facts.

However, educating the public was not only a question of educating ‘people’; it was also about educating the media. This was problematic, as the media was regarded among the interviewees as being focused on sensations. This meant that the media presented all the sensational things about gene transfer, especially the adverse events that had happened and the risks of gene transfer, while simultaneously portraying gene transfer scientists as playing God. This was believed to cloud the public opinion of gene transfer. In other words, it was important to educate the media also, especially as the interviewees wanted the media to help them with the task of educating society.

In order to educate society the interviewees described two different strategies that they employed. The first strategy was to combat misunderstandings and to do it in three different arenas: in relation to the general public, the authorities, and the media. Here the scientists’ task was to make information about gene transfer more accessible to the non-scientists. The second strategy was to present gene transfer in a more positive and understandable way by constructing a frame of reference that would put the research in an acceptable and accessible light. The scientists’ task in this case was to try to present a legitimate public image of the technology as well as of their work, in order to try to gain public acceptance. I will now discuss these strategies in turn.
Combating Misunderstandings

There are, according to the gene transfer scientists interviewed, several misunderstandings regarding gene transfer and the research that it entails. Some of these misunderstandings are ascribable to gene transfer scientists themselves and their previous actions. Other misunderstandings are ascribable to the media and their portrayal of gene transfer.

According to sociologist Dorothy Nelkin (1996), journalists often portray speculative findings, especially if they are in the field of genetics, as ‘the medical story of the century’ because they will be able to ‘unlock the secrets of life’ and ‘allow prediction and control of disease’. However, scientists are also portrayed in the media as going mad ‘tampering with genes’ and ‘playing God’, thus playing on public concerns raised by new biotechnological advances (Nelkin 1996:1600-1602). Consequently, scientists are concerned about how journalists portray them in the media. Scientists feel, Nelkin argues, that their credibility is often questioned and that the media has the possibility to influence medical research policies as well as research funding and thus research priorities. This could jeopardize and affect the autonomy of science. Communication scientist Susanna Hornig Priest and sociologist Toby Ten Eyck (2003) argue, like Nelkin, that how media frame and legitimize biotechnology, and in this case gene transfer, certainly affects public debate as well as public opinion. This is because the public in general often does not have access to other sources of expert information.

Among the interviewed gene transfer scientists the general opinion was that it was of significant importance to give meaningful and correct information about gene transfer to other actors, especially the general public, authorities, and the media. It was also important that the information was neither too complicated nor made claims that were untrue. As an example, Sylve emphasized that it was important that gene transfer scientists did not oversell gene transfer by stating ‘now we shall cure all diseases with gene transfer and it’s going to be great’ (p. 12). Much of the hype and many of the unrealistic high expectations of gene transfer were caused by, as Stuart and Sixten explained it, the field itself and its investors, who had promised too much in order to attract venture capital, and thus oversold the current efficacy of gene transfer.

It was important that gene transfer scientists, in their dialogue with others, were precise in the description regarding the practical reality of gene transfer and its technical limitations. ‘As gene transfer scientists’, Sixten explained, ‘we should try to reach out to the public and explain what is possible and what is not so that the public doesn’t have these expectations that do not meet the prerequisites’ (p. 14).

It was not only regarded as important to reach out to the public and educate them. Equally important was it to keep the authorities as well as the rest of society posted about the progress of gene transfer research, and more importantly, to report adverse events, if they happened, in preclinical and clinical trials. As an example, Sylve told the story of something that had happened to him when he held a lecture
at a Swedish national advisory board regarding the successes and setbacks in gene transfer. In his words:

When I held my lecture and described among other things these cases [the X-SCID patients] from France, I had 10 or 15 minutes for my presentation and I had a chart where I had written among other things the two cases of the leukemia-like disease. There was a person there who apparently had stepped out for a while, or whatever he did. The auditorium was full of people and he returned when I continued talking about the successes and challenges, mainly the successes when he was there it would seem. A few days after that conference, he sent an email to the entire group saying that ‘Sylve was completely unethical when he talked about the cases in Paris because he hadn't mentioned that two of the patients had gotten leukemia’. (p. 12)

This story illustrates how easily gene transfer scientists consider their work to be misunderstood. Sylve emphasized that ‘one cannot frequently enough, if given the opportunity, repeat as clearly as possible what you regard as correct information’. In retrospect, he continued, maybe he did not dwell upon the adverse events in gene transfer enough during the presentation. He concluded the story by saying that it was important not to ‘wriggle out’ if anything unexpected or adverse happened. It was just a matter of ‘getting it up on the table as quickly as possible’, and showing that there was nothing to hide (p. 13).

Being easily misunderstood when working with gene transfer was however not the only problem, Sylve explained. There was also the difficulty of removing the image established by the media of gene transfer scientists as mad scientists. Despite giving proper and thorough information whenever possible I still get the question, he said, referring to an interview with the Swedish Broadcasting Corporation: ‘Don’t you consider yourself to be playing God when you do gene transfer or work with genes?’ (p. 13). This portrayal was something that he considered to have been spread by the media.

Educating society and combating misunderstandings, while at the same time attempting to remove the current portrayal of gene transfer scientists, was a task that required organization. Not only was the commitment of gene transfer scientists required; it also required knowledgeable mediators such as scientific spokespersons and journalists. The need for powerful mediators was emphasized by Scott when he explained the important role of the American Society of Gene and Cell Therapy (ASGCT). ‘As a society I think’, he said, ‘it is our duty to try to educate the public about what gene therapy is’ (p. 36). He further explained that

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46 It is interesting to note that Sylve told me this story when I asked him, ‘What do you think are the ethical and social questions of gene therapy?’
what we have done is we’ve raised, this year we’ve raised money. We raised almost $200,000 and we are hiring a firm to help us organize ourselves so we can educate the appropriate people. (p. 36-37)

During the interview I did not reflect on what he meant by ‘appropriate people’. Consequently, I never asked any follow-up questions about this. During the analysis I began to wonder, however, who ‘the appropriate people’ were. Did he mean that it was important to educate specific spokespersons from the scientific community or was it people in their different professional associations? Maybe it was journalists and the media that he referred to? Perhaps it was by educating journalists, and making them better informed mediators of gene transfer, that society could become more educated about gene transfer and its research? This could be the way to go in order to remove the current portrayal of gene transfer scientists and to get the focus more on the technology and its possibilities. It was apparent that he, as well as the other interviewees, believed that combating misunderstandings of gene transfer would lead to greater acceptance.

According to Nelkin (1996:1600), the relationship between scientists and journalists is ‘uneasy’ as they ‘depend on each other in the communication of science’ and more importantly in ‘the shaping of the public meaning of science and medicine’. It is noteworthy that the gene transfer scientists whom I interviewed only described the importance of journalists and the media in relation to society’s misconceptions about gene transfer and its research. They did not describe them as of importance when communicating positive findings and progress in gene transfer research.

To summarize, the interviewees described how they tried to combat misunderstandings regarding gene transfer and their work by making the scientific information about gene transfer more accessible to actors such as the public, the media, and the authorities. In order to achieve this, the gene transfer scientists needed to improve how, about what, and how often they mediated scientific information. This also demanded different mediators. However, a greater understanding of gene transfer could not be attained just by combating misunderstandings in the media and elsewhere. Even more important was to make gene transfer understandable by using a frame of reference that put the research in an acceptable and accessible light.

**Making Gene Transfer Understandable**

As described above, the gene transfer scientists report many misunderstandings regarding gene transfer and consequently also many fears and concerns about it. Handling these concerns and fears is not only about combating misunderstandings. It is also about attaining ethical acceptability for gene transfer. The gene transfer scientists whom I interviewed tried to attain this support for gene transfer by construct-
ing and using a familiar frame of reference that was intended to make gene transfer less complex and more understandable to the public.

Sociologist Erving Goffman (quoted in Flichy 2007:80) regards any social event as organized by a frame, ‘that is seen as rendering what would otherwise be a meaningless aspects of the scene into something that is meaningful’. The use of frames, mass communication scientists Dietram Scheufele and David Tewksbury (2007) write, makes it easier to introduce complex issues to the public because frames influence how the individual perceive meanings attributed to the issue.

A frame of reference consists of terms that are organized around particular metaphors and figures of speech. In this case, frames were used by the interviewed gene transfer scientists to transform something diffuse, unfamiliar, and sometimes also frightening into something comprehensible, by putting it into a familiar context. In other words, the gene transfer scientists’ accounts were put together in a certain way in order to portray their actions and beliefs as socially appropriate.

Three arguments were consistently used to frame gene transfer as legitimate and gain acceptance: (1) it was favorably contrasted with other risks, (2) it was made equivalent to established medical treatments and standard procedures, and (3) it was seen as a complement to existing medical technologies. These arguments will be discussed in the following sections. Noteworthy is that they portray gene transfer in positive and beneficial ways. One of the primary motives underlying the use of such frames is, what Nelkin (1995) calls, ‘selling science’. This means claiming that the more knowledge people have about science, the more favorable their attitude towards it will be.

**Contrasting with Other Risks**

Gene transfer was regarded among the interviewees as getting a significant amount of media attention. The problem was not the attention per se. Instead it was that the media, in their coverage of gene transfer and its research, only focused on the adverse events and the risks of gene transfer. It thus became important for the interviewees to compare and contrast the risks of gene transfer to the risks of other medical treatments. In order to do this they described three different cases: Jesse Gelsinger, Vioxx, and the clinical implementation of neurosurgery and bone marrow transplants.

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47 Two other arguments also frame gene transfer as legitimate and have been discussed in Chapters 4 and 6. First, gene transfer is framed as ‘for the good of the country’, referring to macroeconomic effects of gene transfer research such as strengthening the national economy and setting up new companies. It also gives beneficial economic consequences for biotech companies, big pharmaceutical, and other individual companies, such as profitability and developments in the stock market. Second, the ethical complications present in gene transfer research are framed as ‘generic’, meaning that they always exist in clinical research, whether it is gene transfer or something else.
Several of the interviewees explained, as did Scott, that there was especially one specific event – the death of Jesse Gelsinger – that had attracted the media’s attention. In his words:

Now Jesse Gelsinger I think is unique, but I would say that there have been small molecule drugs that have killed people, that have been extremely toxic, and those don’t end up on the front page of the paper. But if a gene therapy vector kills somebody, even if it is a valid trial and it is a disease for which there are no other treatment options, that’s going to end up on the front page of the paper, and I think this is a double standard. (p. 33-34)

According to Scott it seems that there is a difference between how the media covers adverse events in gene transfer research, as compared to coverage of other medical treatments. The Jesse Gelsinger case was indeed troublesome, as it not only resulted in the death of a research participant but also involved non-compliance with federal regulations and requirements for clinical research. The lead investigators of the clinical trial did not disclose all potential risks to the human research participants in the informed consent process, nor the substantial financial interests in the research from both the principal investigator and the host institution. They further showed a lack of medical caution when the transfer of the gene took place (Friedmann 2000, Walters 2000, Rasko et al. 2006).

Circumstances like these were, however, according to the interviewees, not exclusive to gene transfer research. They were present in other fields of research as well. It was the fact that gene transfer research received more extensive negative headlines in the media than other experimental innovative treatments that made Scott refer to it as a ‘double standard’.

One of the Swedish interviewees, Sixten, contrasted the risks of gene transfer, as presented in the media, with the recent case of Vioxx in the U.S.A. Vioxx is a COX-2 inhibitor, that is, a nonsteroidal anti-inflammatory drug used in the treatment of pain and inflammation due to arthritis among other conditions. In 2004 a study conducted by the U.S. Food and Drug Administration (FDA) showed that Vioxx could have contributed to 27,785 heart attacks and sudden cardiac deaths between 1999 and 2003. It was established that high doses of Vioxx increased three-fold the risks of heart attacks and sudden cardiac deaths (Consumeraffairs.com 2004). “The few deaths due to gene transfer”, Sixten explained, ‘have received much more media attention than the more than 10,000 estimated deaths in people that used COX-2 inhibitors’ (p. 20). In other words, there are significantly more people affected by taking Vioxx compared to those undergoing gene transfer treatment.

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48 This case happened in 2004-2005, but it was recent at the time of the interview.
Imagine, he continued, if all the people who died due to Vioxx separately got the same media attention and headlines as the few who died due to gene transfer. By emphasizing the difference in media coverage in these two cases, he underlined that there was a ‘lack of proportions’ which he believed was interesting to note (p. 20).

There is, however, a possible explanation for why gene transfer attracts such negative headlines in the media. Sixten explained to me that nowadays there are higher expectations of new fields of research then there were fifty years ago. Today research has to show results or lead to something. There is also a kind of ‘zero tolerance’ regarding risks. However, Sixten explained, there are always risks involved in the implementation of new medical technologies or therapies, and there always have been. This was, according to him, something that modern society seems to have forgotten. ‘You have to think along the lines that there is always a price’, he said, ‘and if you don’t develop new treatments then the price is that nothing happens’ (p. 8). Remember, for example, he said, when neurosurgery and bone marrow transplants were first introduced into clinical practice.

When we started operating on people’s brains, all the patients died. When we started performing bone marrow transplantations, all the patients died too – and it was because we essentially didn’t know enough about this. We can expect that same thing from gene therapy. There will be deaths. It is inevitable. (p. 7)

The nature of experimental research is that the outcome is unknown. Consequently, Sixten regarded the striving for zero tolerance regarding risks as unfortunate because this meant that many medical advances could not be made, or at least they would be much delayed, thereby significantly influencing the health of patients (p. 20).

That adverse events and deaths occurred was something that Shane and the other gene transfer scientists underlined as unfortunate. Nevertheless it was present in the global concept of drug development. ‘In our hospital and in every hospital’, he said, ‘deaths occur all the time from drugs’ (p. 6). In gene transfer, he remarked, there have been three deaths, one at the University of Pennsylvania and two in the X-linked severe combined immune deficiency (X-SCID) trial, and that ‘compared to any other drug is probably just par for the course’ (p. 6). What he meant was that it was terrible that deaths occurred in gene transfer, but it happened, just like it inevitably happened in other medical treatments and therapies.

Contrasting the risks of gene transfer to the risks in other medical treatments was framing it in a way that showed that gene transfer actually entailed fewer risks. Another important framing was to argue that gene transfer indeed was equivalent to established medical treatments and standard procedures.


**Equivalent to Established Medical Treatments and Standard Procedures**

In the interviews I asked, ‘How is gene transfer different from other medical technologies?’ Interestingly, almost all interviewees answered that it was not different. Gene transfer was instead described as equivalent to established medical treatments or standard procedures. By establishing the frame of reference of gene transfer as an established medical treatment like a drug, or a standard procedure like organ transplantation, it was connected to familiar contexts. The gene transfer scientists in their descriptions referred to three familiar medical contexts: drugs, delivery methods, and organ transplantations.

First, gene transfer was described by the interviewees as ‘being like any kind of drug development’, as Scott did (p. 7). The only difference was the use of genes instead of chemical constituents as in drugs. ‘I try to convey’, Scott explained to me when discussing how the word gene, due to lack of understanding, seemed to install fear in people, ‘that DNA is just another drug’ (p. 7). Gene transfer was also regarded as equivalent to another kind of drug – cytostatics, that is, anti-cancer drugs. This concept was emphasized by Sylve. While placing gene transfer on an equal footing with cytostatics, he also emphasized that he considered it to be preferable to use gene transfer, if possible, instead of cytostatics, as gene transfer entailed less risk of side effects.

Gene transfer was, second, described as ‘just a drug delivery system’ – a delivery method for administering drugs, as Shane did (p. 5). The difference was, Sune explained, that it was genes or other kinds of genetic material that were delivered rather than ordinary drugs (p. 3). It was this that made gene transfer different in the public’s eye. Shane elaborated further on this. In his words:

> Gene transfer is different because of social aspects of genes, and people are concerned about that, and that is probably our fault. I mean scientists and clinicians who are interested in gene transfer, we probably haven’t been very good at articulating it to the public. But I think that people historically are worried about modifying the genome. I think that there is a fear of using genes, but really it is just a drug delivery system and, of course, genes have been delivered to people. (p. 5)

Gene transfer was, third, described by Shane, and other interviewees, as similar to organ transplantations. Gene transfer is about treating a defective function in a gene by replacing it. More specifically, it is about moving genes, but genes can be transferred in different shapes. It does not have to be solely genes as in gene transfer. It can also be genes in the form of entire organs, as in organ transplantation. If a person has a defective organ, Sean said, we would replace the defective function of that organ with a new one, like a kidney or a liver (p. 4-5). Shane concurred with Sean’s view of gene transfer and argued, ‘If you think about liver transplants and heart transplants, that’s gene therapy’ (p. 5).
Another kind of organ transplantation that was likened to gene transfer was bone marrow transplants with a sibling donor. This was ‘one kind of gene transfer that has been extremely successful during the past thirty years’, Staffan clarified, as ‘new cells and therefore also new genes have been transferred to the patient resulting in hematopoiesis based on a new genome’ (p. 2). To describe gene transfer as equivalent to organ transplantation – an established medical procedure – was thus to put it into an established frame of reference, referring to a therapy that was already in clinical use.

The interviewees did not only try to present gene transfer as being on an equal footing with other medical treatments and standard procedures. Due to the previous overselling of gene transfer they wished to frame it in a more modest way, thus presenting gene transfer as a complement to existing medical technologies.

A Complement to Existing Medical Technologies

When I asked the interviewees how gene transfer was different from other medical technologies, some of them seemed to regard it as important, when answering this question, to simultaneously underline that gene transfer was a complement to existing medical technologies. It was often emphasized among the interviewees that gene transfer would not make traditional drug treatments, that is, symptomatic treatments, irrelevant. On the contrary, symptomatic treatments were regarded as the major way to treat diseases in a foreseeable future. Gene transfer was merely an alternative that could be considered, if no other medical treatments had worked or if there were no other medical options available. In other words, it gave people affected with genetic or fatal diseases one more alternative.

The possibility of using gene transfer in combination with other symptomatic treatments was described by Staffan and Svante as a promising approach in the pursuit of curing cancer. ‘Gene transfer in combination with immunotherapy’, Staffan said, ‘is an approach for curing cancer that I really believe in’ (p. 6).

In regard to why gene transfer was important, some of the interviewees described that it was reasonable to try different approaches, as did Scott and Sixten. This was because it was impossible to establish which therapy would in the long run be the best one for a particular disease. I believe, Sixten said, that gene transfer will be the standard treatment for some diseases, and for others it will be used as a complement (p. 9).

There is an explanation for why the interviewees may regard it as important to discuss gene transfer and its possibilities in this more modest way. Gene transfer has since its beginning been marketed as a new and possibly more effective technology for treating or preventing inheritable genetic disorders and fatal diseases, like cancer, where conventional treatments often have failed. It has been, and still is, described as a technology that could treat the underlying cause of the disease instead of just its symptoms. It is the possibility that genes, by modification of their gene expression, could be replaced and made to function properly that makes the therapeutic possi-
abilities of gene transfer incomparable and new. However, in the last decades it has become evident that gene transfer still struggles with different technical problems and that it is difficult to establish clinical efficacy. It has not yet been able to fulfill the promise of ‘revolutionizing medicine’ – a statement that thus has oversold the current therapeutic abilities of gene transfer. Consequently, gene transfer scientists, instead of promoting gene transfer as something that would revolutionize medicine, nowadays present the technology and its possibilities in more modest ways. This is done in order to work around the previous overselling of gene transfer and thus attain ethical acceptability for this research.

To summarize, the interviewees described how they tried to make gene transfer understandable to different actors by using a specific frame of reference that made gene transfer equivalent to an established medical treatment like a drug, or to a standard procedure like organ transplantation. It was also framed as a complement to existing medical technologies instead of something that would revolutionize medicine. The main goal of this frame of reference was to connect gene transfer to familiar contexts and thereby make it less complex, more understandable and ethically acceptable. Within this frame of reference gene transfer was also framed as entailing fewer risks compared to some other accepted medical treatments.

It is interesting to note that the gene transfer scientists also used another frame of reference during their conversations with me. When talking about the past, present, and future of gene transfer – questions often regarded by the interviewees as explicitly connected to the development of gene transfer and hence also to their practical work in the laboratory – they used technical terms. They talked to me as if I was one of them, that is, another gene transfer scientist. But when we discussed issues like risks and whether gene transfer was different from other medical technologies as well as the policies that regulate gene transfer research, something changed. They began to talk about gene transfer differently. Almost all interviewees then framed gene transfer as being equivalent to established medical treatments and standard procedures. Consequently, different aspects regarding risks or ethical issues (like those discussed in Chapter 6) were all made within this frame of reference. As soon as ethical, legal, and social issues were on the agenda most of the interviewed gene transfer scientists immediately changed their frame of reference and transformed these issues from being ethical, legal, and social problems into being practical problems. These practical problems of course needed to be solved. However, in many discussions (as described in Chapter 6) the gene transfer scientists tended to shift the ethical responsibility for solving these practical problems away from themselves to other actors such as society, bioethical experts, or regulators.

Although a common opinion among the interviewees was that gene transfer is a complement to existing medical technologies, there were some noteworthy excep-

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49 A possible explanation for why they often regarded me as one of them could be because I introduced myself as a biochemist currently conducting sociological research.
tions. A few of the interviewees, even though they had already explained that gene transfer was equivalent to established medical treatments and standard procedures as well as a complement to existing medical treatments, also regarded gene transfer as something completely unique. Stuart described that in the beginning of medical history the treatment of diseases was symptomatic but now, with gene transfer, the underlying defect or cause of the disease could be treated as the nature of the genetic material could be changed. It was this, he said, that made gene transfer unique as well as such ‘an important event in the history of medicine’ (p. 14).

Gene transfer’s uniqueness was something that Spencer also emphasized, and he was the only one of the interviewees who only emphasized its uniqueness. The gene used in gene transfer, he stated, was a ‘new chemical entity’ (p. 7).

That genes were new entities, however, not chemical but medical, was also underlined by Shane. He explained to me that we, as humans, have approximately 25,000 genes. If it could be established how these genes could be used, then this meant that each of our bodies contained 25,000 potential drugs or treatments (p. 5). Despite the very limited applicability of gene transfer at the moment, all the interviewees considered the future of gene transfer to hold great promise. More importantly, they strongly believed that gene transfer at some point in their lifetimes would become standard care for some diseases.

Concluding Discussion

In this chapter I have discussed how the gene transfer scientists whom I interviewed experienced public concerns regarding gene transfer. I have also discussed how they responded to these concerns in their conversations with me. When talking about why the public was concerned about gene transfer, the important concept put forth by the gene transfer scientists was that society lacked a proper understanding of gene transfer. Therefore, the public needed education, which was to be provided by the gene transfer scientists themselves, as well as by different mediators, for instance the media. A greater understanding of gene transfer could first be attained by combating misunderstandings. This required that scientific information about gene transfer became more accessible to the public. Getting information out to the public in turn demanded that gene transfer scientists improved their communication skills as well as their PR relations by enrolling, for example, the media as a mediator.

Second, it required the transformation of, and the framing of gene transfer from being a controversial and contested field of research into something that was regarded as a standard medical procedure within biomedical science. In other words, it needed to be seen as less dangerous, more understandable and less complex by the public as well as by other actors. This transformation was made by establishing a new frame of reference, consisting of three main elements.

First, the risks of gene transfer were framed as similar to those existing in clinical research, whether it was gene transfer or something else. In contrast to the risks in other medical treatments, however, the risks of gene transfer were often pre-
sented as significantly lower. The purpose of this frame was to establish understandable relationships in which the controversies and problems of gene transfer became governable. Second, gene transfer was framed as equivalent to established medical treatments and standard procedures. This frame was used in order to connect gene transfer to something that was regarded as familiar by the general public, and thus change the common concept of gene transfer from being a controversial research area into something that was regarded as a standard medical procedure. Third, gene transfer was framed as medical progress that included new possibilities to treat desperately ill patients or prevent the onset of severe incurable diseases, where conventional treatments often have failed. It was so far only a complement to existing medical technologies but it also had the promise of being something completely unique – a significant scientific progress – referred to as ‘an important event in the history of medicine’.

In this chapter I have shown examples of how important the interviewed gene transfer scientists regard it to be to have an outward image of being trustworthy and honest scientists conducting ethically acceptable research. As described in the previous Chapters 4 to 6, conducting gene transfer research is difficult, as it involves many different components and raises many unique problems regarding funding, expertise, material, regulation, oversight, and ethical concerns. Many of these problems are affected by the public’s fears about and understanding of gene transfer. For example, getting funding for gene transfer can be more difficult if there is a public outcry against this kind of research. Another consequence could be a significantly stricter regulation and oversight of gene transfer research, as the public often has the ability to influence politicians and hence also authorities. In order for the gene transfer scientists to be able to construct doable problems it is therefore important for them that the public has a positive understanding of gene transfer and that the public considers its use to be ethically acceptable. This is a prerequisite for constructing doable problems as gene transfer research is strongly affected by funding, politics, and the public discussion and opinion about gene transfer.

As we have seen examples of in these four empirical chapters, the gene transfer scientists interviewed are well aware of the controversy that surrounds gene transfer and the ethical, legal, and social issues that it raises. According to them, it is a lack of public understanding or knowledge that creates the public concerns and fears for gene transfer. In other words, the public is ‘deficient’. Using the deficit model, as the interviewees did, is a way to transform the problem into a governable entity – a practical problem where the solution is to educate the public. This education is believed by the interviewees to result in a greater public acceptance of gene transfer.

The frame of reference that the interviewees used to gain public acceptance for gene transfer and their work was also something that I believe they use in order to legitimize gene transfer research for themselves, as well as to motivate why it is reasonable to work on it as they do. By using this frame of reference, gene transfer scientists acknowledge the problems entailed in the technology and the research,
while simultaneously being open about them. This is a prerequisite for having a trustworthy image.
CHAPTER 8
Summary and Conclusions

This thesis has analyzed how scientists reason about how to make their work doable within the controversial and morally debated field of gene transfer research. Gene transfer is a technology in which genetic sequences or genetically modified organisms are used to treat or prevent diseases in humans. The technology presents the therapeutic possibility to treat severe fatal diseases as well as genetic disorders for which there are no other medical options, or where all other medical options have been tried without success. Due to gene transfer’s ability to manipulate genetic characteristics, it is regarded as controversial to use because (1) the modification is intentional, (2) genetic modifications could lead to genetic enhancement, (3) there are associations to eugenics, and (4) there may be unknown and unforeseen risks to human research participants as well as to future generations.

The focus of the study is on how gene transfer scientists handle various problems from bench to bedside – from basic science to clinical application on human subjects – and in relation to regulation and public understanding of their research. This is something that has been studied relatively little, if at all, from the scientists’ perspective. This study is therefore meant as a complement to previous studies of gene transfer which have focused on the ethics, legal issues, and social concerns of this research. It uses concepts from the Science and Technology Studies (STS) field, concerning scientific, medical and ethical controversies as well as how scientific work is made possible, in order to show how gene transfer scientists gather the necessary elements for their research, articulate different activities, and handle external challenges in order to get their work done.

In order to capture the involved scientists’ views, the study is based on qualitative in-depth interviews with ten gene transfer scientists in Sweden and the U.S.A. I have also interviewed key individuals from different regulatory agencies and advisory boards in the two countries. Qualitative in-depth interviews provide a useful methodological tool to study how scientists and regulators reason about their work. Doing interviews in two countries with very different attitudes and regulatory approaches towards gene transfer research, as well as different extents of research activities within this area, also made it possible to investigate how the specific setting in each country affected the scientists’ work.

The main perspective used in this study involves the notion of ‘doability’, that is, in sociologist Joan H. Fujimura’s terms ‘the alignment of several levels of work organization’ (Fujimura 1987:258; italics in original). I also employ the related notion of ‘articulation work’ (Strauss 1988, Fujimura 1987, Clarke and Fujimura 1992), which in-
includes planning, collecting, coordinating, and integrating various tasks and assignments within, but primarily between, different levels of work in order to achieve the goal of a given project. Sociologist Bruno Latour’s (1987, 1999) concepts of enrollment of allies and translation are also helpful to show how gene transfer scientists create stable research milieus and how they physically move gene transfer from one line of research to another, how they translate gene transfer to create a common perception of it, and how they translate their interests and views on gene transfer to fit others. Two overarching concepts are used in this study. The first concept is sociologists Adele E. Clarke and Fujimura’s (1992:4) concept of ‘situatedness’, that is, how the specific practice where the work is done affects the work. The other is ‘social worlds’, that is, as Clark (1991:131) puts it, ‘groups with shared commitments to certain activities, sharing resources of many kinds to achieve their goals, and building shared ideologies about how to go about their business’. This means that the social world of gene transfer research contains mainly actors such as gene transfer scientists and their academic and commercial colleagues, as well as actants like materials, experiments, and laboratories. On specific matters, the social world of gene transfer research interacts with other social worlds such as those of regulators, investors, the media, and the public.

These studies have primarily used ethnographic fieldwork in laboratories to investigate how scientists construct doable problems in practice. This study has taken a different route, as it is not based on an ethnography within a laboratory but on interviews. However, the concepts help provide a detailed picture of how various problems are handled within gene transfer research from the perspective of those involved.

**Making Gene Transfer Research Work**

Gene transfer is a complex scientific process that brings together many different components, such as scientific experts and practices, research materials, technologies, techniques, and skills. It also involves organizations, investors, industrial sponsorships, regulatory authorities, and audiences such as the general public and the media. In addition, it is a largely untried and potentially risky technology with an unclear success rate and a controversial and publicly questioned practice. All of these elements make research in this area into an uncertain process which must be handled in some way by gene transfer scientists in order to make their work doable and reach results. In the thesis I discuss this in relation to four central areas which involve different challenges and problems for scientists within gene transfer research.

**Making Doable Problems**

The first empirical chapter, Chapter 4, investigates what gene transfer scientists regarded as problems at the beginning of a research process as well as at the bench,
and how they constructed doable problems out of an uncertain and contested situation. In other words, how did they make their work practically doable?

The gene transfer scientists stated that they faced unique funding problems for gene transfer research, as well as problems in getting the right kind of qualified scientific expertise. These were the largest obstacles in getting their research going. At the bench, their main problem was to find the ‘right’ material and to make it work properly, that is, integrating at the right site while simultaneously maintaining a long-lasting gene expression, without risks of insertional mutagenesis or immune response.

The chapter shows that it seemed necessary to achieve two basic kinds of alignment in order to achieve doable problems in gene transfer research. On the one hand, it was essential to align the scientists’ own interests with those of other central actors in order to gain funding. On the other hand, it was important to align the interests of other scientific experts with their own, in order to gather the necessary skills, materials, and technologies and to coordinate them with one another, thus being able to conduct research from basic science to clinical trials. In other words, the scientists had to use a form of articulation work that involved the enrollment of allies (Latour 1999). Allies to enroll included scientists within academia or industry who had the expertise and skills for specific parts of gene transfer research. They are essential as they form the basic elements of everyday gene transfer research. Other necessary allies were biotechnology and pharmaceutical companies. These could provide the necessary funds to meet the high costs of scale up and manufacturing of reagents required in the clinical implementation of gene transfer as well as in its further commercialization. In order to get funding for gene transfer research, especially for orphan diseases, individual patients, their families, and patient organizations also became important allies to enroll.

The interviewed gene transfer scientists detailed what I see as three forms of translation work in order to enroll these allies and create an alignment of interests and activities between different actors and levels of work. The first form involved the physical transfer of gene transfer work from one line of research to another, that is, from the laboratory setting to the clinic. The second, and related, form was to translate different views of what gene transfer meant into a common perception among all actors involved in the various stages and settings of gene transfer research. The third form of translation work concerned the activities of the gene transfer scientists themselves. They had to transform their own research interests in order to align them with those of other necessary actors. This meant that they, in certain cases, had to readjust their research orientation as well as their meaning of their work in order to meet the interests of potential investors. They also had to adapt their laboratory work to comply with safety concerns regarding especially the vector systems used in gene transfer research and translate the risks of viral vector systems from being ethical issues to being scientific and technological limitations that were, in principle at least, surmountable.
Handling the Regulatory Setting

Making gene transfer research doable is also about constructing doable problems within the limits of existing policies and regulations. Chapter 5 investigates the consequences on the meaning and actual conduct of research work of the different regulatory settings in Sweden and the U.S.A., for both the gene transfer scientists and the members of regulatory agencies and advisory boards.

I show in this chapter that what I call the loosely-regulated conduct in clinical gene transfer research in Sweden versus the highly-regulated and monitored conduct in the U.S.A. resulted in different ways of working. In Sweden, the gene transfer scientists had no problems with the existing policies or the oversight system that did not single out gene transfer but considered it to be like any other kind of medical research. The existing Swedish regulatory framework can thus be described as being conducted at arm’s length, and gene transfer scientists and regulators do not normally interact with each other. However, members of advisory boards interviewed wanted to implement a higher degree of regulation of clinical gene transfer research and also wanted it to be more open to public scrutiny. The opposite situation prevailed in the U.S.A. Here, the highly-regulated and monitored conduct of clinical gene transfer trials caused tensions between scientists and regulators, which both parties tried to handle in various ways in order to make gene transfer research doable. Whereas several of the interviewed scientists found the detailed demands and intensive regulatory oversight burdensome, they also had to accept these constraints as a necessary prerequisite for conducting gene transfer research in a context where it is seen as controversial and having risky medical and social implications. They have to adapt to this situation in order to achieve legitimacy for their work, but also to get funding for their research from patient organizations and pharmaceutical companies.

The analysis uses the concept of boundary-work, coined by sociologist Thomas F. Gieryn (1983, 1999) to examine, on the one hand, how the U.S. gene transfer scientists handled the regulatory demands implemented by the social world of regulators and, on the other hand, how the regulators tried to accommodate the demands of the scientists. I found that two kinds of boundary-work were involved; one affirmed the existence of the boundaries between the two different social worlds involved, and one transgressed it. On the one hand, thus, scientists acknowledged that the work of regulatory agencies to intervene in and control their work was necessary and adapted their work accordingly. The regulators also affirmed the need for independence and difference between what scientists demanded and what the regulations allowed. On the other hand, scientists tried in various ways to influence the regulatory framework and the decisions, and regulators also crossed the boundaries by trying to assist scientists in framing their applications and research in ways that would be acceptable by the regulatory agencies and thus speed up the process. Another way of phrasing this is to use medical sociologist Monica J. Casper’s (1998) dance metaphor: I found that scientists, despite having to follow the
regulators’ demands and choices of ‘dance’, wanted to be able to influence the steps of the dance, the duration of it, and if possible, also which kind of ‘dance’ to dance.

**Handling Ethical Complications**

Gene transfer raises many ethical issues. It involves a high degree of scientific uncertainty, struggles with several technological problems, and hence also with unknown and unforeseen risks for humans. Clinical gene transfer trials on human subjects are thus experimental studies. Chapter 6 investigates what gene transfer scientists considered to be the main ethical and moral complications of their research and how they handled these complications. In other words, what was the substantive ‘ethics’ of gene transfer research and how did the scientists handle this ‘ethics’ in their everyday work?

The two major ethical complications discussed by the gene transfer scientists concerned the issues of how to select appropriate diseases for clinical gene transfer trials and of how to obtain a valid informed consent from the participants to be involved. These complications were, however, not considered specific to gene transfer but regarded as ‘generic’, meaning that they were seen as always present in clinical research. A third ethical complication, one which is more specific to gene transfer, has been extensively discussed in the public debate as well as in the ethics literature; it concerns the problem of how to distinguish between treatment and enhancement purposes of gene transfer. This complication was not, however, spontaneously raised by the interviewed scientists but was only discussed after I had introduced the issue.

I used anthropologist Hugh Gusterson’s (1996) analysis of how nuclear weapons scientists confront the moral dilemmas of their work and learn to resolve these dilemmas as they go on with their research as a starting point for my analysis of how the gene transfer scientists handle these ethical complications in clinical gene transfer research. This means that I was interested in understanding how moral dilemmas and ethical complications were solved in practice, in the particular situations that the gene transfer scientists had to confront. Whereas Gusterson’s study describes how nuclear weapons scientists feel morally about their work and why they regarded it as ethical to work on nuclear weapons, my study goes one step further by also analyzing how the gene transfer scientists tried to solve ethical complications concretely in their everyday work.

The chapter shows that, rather than ignoring the ethical complications, gene transfer scientists tried to align their research with existing ethical principles, guidelines, and regulatory frameworks. More specifically, they transformed the more abstract ethical guidelines into practical and situation-specific issues and thus made them doable and possible to handle. Hence, the gene transfer scientists evaluated the risks and benefits of using gene transfer in clinical practice situationally and depending on the specific disease and specific patient concerned. This meant that they handled the ethical choices in a practical way. They also tried to obtain the best
possible informed consent from the patients, given the particular circumstances of their disease situation and in relation to the problems of using an experimental therapy with unknown effects on the patients’ trajectory. This meant that they could not always achieve a perfectly valid consent according to general ethical principles and guidelines, but had to negotiate what information each patient needed in order to make an informed decision in their specific circumstances. Finally, gene transfer scientists also tried to navigate within the shifting boundaries of acceptable and unacceptable uses of gene transfer, that is, between treatment and enhancement. Certain forms of therapy were regarded as ethically unproblematic, such as clear cases of treatment and improvement and even some cases of enhancement such as treating baldness or loss of muscle function due to aging. But when it came to such ‘gray zone’ cases where gene transfer was to be used to treat, or enhance, psychological or socio-behavioral conditions such as intelligence, obsessive-compulsive disorders, or homosexuality, it became difficult and problematic, and not ethically acceptable.

To understand how the scientists maneuvered in this controversial field of research and how they drew ethical boundaries regarding their work, the notion of a discrepancy between what a map shows and the actual landscape that one has to navigate within and the itineraries thus taken has been useful (Brown and Duguid 1991). I have shown that gene transfer scientists tried out new itineraries in a search for acceptable alternatives when faced with ethical complications in their work. Another useful concept has been that of ethical boundary-work (Wainwright et al. 2006) to show how the scientists drew ethical boundaries regarding what they considered as ethically acceptable to do in their work, thereby establishing an ethical legitimacy of their choices and actions. In crucial cases they also shifted the ethical responsibility away from themselves to others – either to the individual participant, his or her unique situation, or to society. Thus they tried to make the problem doable by re-drawing the boundaries of their responsibility; what was ethically acceptable or not thereby became other actors’ problems.

Gaining Public Acceptance by Combating Misunderstandings

Making gene transfer research doable does not just mean constructing doable problems within the social world of gene transfer. It also means relating to the outside world, that is, to actors from various other settings located outside the social world of gene transfer research, who could affect scientists’ work and their ability to conduct research. Chapter 7 investigates how the gene transfer scientists experienced and responded to public concerns and fears regarding gene transfer, both as a technology and a field of research. In other words, how did they make the problems of public (mis)understanding of their work doable and possible to handle?

A controversy perspective has been useful to understand why gene transfer scientists constantly seem to want to defend their work and mobilize against what they consider to be public and media misunderstandings. The scientists accounted for these misunderstandings in terms of a deficit model of understanding, which
states that the public lacks proper information about gene transfer. In doing so, they transformed the problem into a governable entity – a practical problem where the solution was to educate the public. Consequently, if the public got more and correct information, misunderstandings would disappear and the public would accept gene transfer to a greater extent.

This change required that scientific information about this research became more accessible to the public, and did that in two ways. The first involved gene transfer scientists’ improving their communication skills as well as their PR relations by enrolling mediators like the media. Second, gene scientists needed to transform the prevailing negative image of gene transfer and frame it into something more accessible by, and acceptable to, the outside world. Thus, it required the reframing of gene transfer from being a controversial and contested field of research into something that was regarded as a standard medical procedure within biomedical science. Using sociologist Erving Goffman’s concept of frames (as discussed by Flichy 2007) I analyze the frame of reference that the gene transfer scientists put forward in order to combat misunderstandings and give what they considered to be a correct picture of gene transfer’s risks and benefits. Whereas sociologist Patrice Flichy (2007) studied how scientists used a frame to create a common understanding for their phenomena under study in order to facilitate the organization of work for the scientists involved, my analysis thus uses it to see how the scientists frame their research in relation to the world outside their own social practice.

The presented frame consisted of three main elements. First, the risks and ethical problems of gene transfer were constructed as similar to those existing in all clinical research, whether it was gene transfer or something else. Second, gene transfer was framed as equivalent to established medical treatments and standard procedures, such as the use of drugs or transplants. Third, gene transfer was framed as a complement to other medical treatments that included new possibilities to treat desperately ill patients or prevent the onset of severe incurable diseases, where conventional treatments had failed. In addition, the gene transfer scientists also framed their research as ‘for the good of the country’, referring to macroeconomic effects of gene transfer research; it would lead to new companies, increase the profits of existing biotech and pharmaceutical companies, and thus strengthen the national economy. Framing gene transfer in these different positive and beneficial ways can be seen as an example of what sociologist Dorothy Nelkin (1995) calls ‘selling science’, that is, with the intention that the more knowledge people get about science, the more favorable their attitude towards it will be.

I have shown that gene transfer scientists regarded it as important to have an outward image of being trustworthy and honest scientists conducting ethically acceptable research. They presented themselves as deliberate, serious, and right seeking scientists who reflected morally about the complications that they face in their work. In trying to counter what they saw as a lamentable deficit of information among media and the public, they framed their research in a somewhat contradictory way – as, on the one hand, rather similar to established medical practices, and on
the other hand, as something with novel and potentially large contributions to both patients and the economy.

**Conducting Controversial Research**

The major aim of this study has been to understand how gene transfer scientists maneuver in a controversial and contested field of research. The focus has been on how they themselves describe, reason about, and handle their work practices, with an emphasis on situatedness and doability (Clarke and Fujimura 1992, Fujimura 1987, 1988, 1997). I was interested in what the main problems were, according to the scientists, and how they made them doable. I will now briefly summarize what my study has to say about these issues.

Making research doable in gene transfer may appear to be something restricted to the handling of different tasks in the laboratory or at the clinic. It is this, but it is also, as I have shown, to a large extent about uniting and aligning various social worlds, inside and outside the laboratory and clinic. Gene transfer research was described by the interviewees as raising unique new problems regarding funding, expertise, regulation, and oversight, as well as ethical issues and public concerns and fears. All these problems had to be handled in order to make gene transfer research doable.

The gene transfer scientists described how they negotiated doable problems through the use of various forms of articulation work (Strauss 1988). They needed to align their interests with those of other important actors and actants, and did so through enrolling them in their work and by trying to translate both others’ and their own interests and activities into a common frame of what gene transfer entailed. That is, the gene transfer scientists had to align their interests with those of funders and other scientists, and they also had to adapt their work in line with current demands regarding vector systems to be used in gene transfer. Importantly, they also had to align their interest according to existing ethical principles, guidelines, and regulatory frameworks. Various allies were enrolled in order to create stable research milieus and powerful alliances, but also to influence regulatory demands and the public image of gene transfer. In order for gene transfer to attract positive attention, the gene transfer scientists framed gene transfer as being something with novel and potentially large contributions to both patients and the economy.

However, faced with public concerns and fears regarding gene transfer and the ethical and social implications that the research entailed, the gene transfer scientists also reframed gene transfer from being novel (and thus also a controversial and contested field of research) into something rather similar to established medical practices. They argued that it involved the same generic ethical issues and aspects of risk as non-controversial medical treatments and standard procedures, and even fewer risks than these. In effect, it was downplayed as a revolutionary technology but was rather to be seen as a complement to existing medical technologies. The various ethical concerns raised in the public debate were also translated by the scientists into prac-
tical and standard medical problems – of what treatment to use for individual patients or conditions, and of how to obtain valid informed consent. Boundaries were drawn between their own ethical concerns, involving treatment and some non-controversial improvements with the help of gene transfer, on the one hand, and more problematic enhancements which were to be the domain of ‘society’ and not their own domain. Thus, reframing and boundary-work strategies were used to make doable the various ethical concerns raised by gene transfer.

The various ways that the interviewees framed gene transfer indicate the complexity of conducting research in controversial science. I have shown that there is a contradiction in the various strategies employed to make research doable. Consistent strategies, actions, or meaning making are not possible when interacting with and trying to ally actors within many different social worlds. Instead, and as I have shown in this study, making gene transfer doable is about maneuvering in a complex field of actors and interests, constructing and reconstructing doable problems, and simultaneously negotiating the meanings of what the technology is all about – its risks, problems, and possible benefits.

Contributions to Research

I see this study’s contribution to previous research, as outlined in the introductory chapter, as twofold. It adds to the social understanding of gene transfer research and it provides a broader picture of how scientists construct doable problems in order to get their work done.

The Ethics and Public Understanding of Gene Transfer

As indicated in the introductory chapter, previous studies of gene transfer have focused on the ethics of gene transfer, on regulatory and monitoring issues and on the understanding of gene transfer from a lay, patient, or medical practitioner’s perspective. In addition, previous studies have mostly investigated how bioethical experts and regulators have reasoned about the ethics of gene transfer.

What makes my account of gene transfer research different is that I have investigated this technology from the gene transfer scientists’ perspective; that is, I have focused on the actions of those who are most intimately involved in creating new knowledge and applications in this medical field. In doing so, I have shown that doing gene transfer research is not only about handling ethical problems; it is also about creating doable research in many other different domains.

It is nevertheless interesting to analyze whether the ethical and moral problems of gene transfer research described by the gene transfer scientists whom I interviewed were the same as those described by lay people, patients, medical practitioners, and bioethical experts in previous research. My impression is that their construction of relevant ethical and moral problems differs substantially. The interviewed gene transfer scientists translated the sometimes overwhelming ethical, legal,
and social issues of gene transfer into doable and situation-specific scientific problems, that is, practical and sometimes technical problems. They did this in order to get on with their work, but also to draw boundaries between what actually should be their ethical concerns and what was the domain of other social worlds – that of patients, regulators, or ‘society’. What some see as specific ethical problems of gene transfer were, in addition, reframed into standard medical issues – although with the additional and somewhat contradictory framing of gene transfer as something completely new and revolutionary.

Thus, bioethical experts’ views of gene transfer may appear to be detached from the actual practices and meaning constructions of gene transfer scientists. The ‘map’ and the actual everyday ‘itineraries’ of those involved differ. While it is important for bioethical experts and the public debate to understand and take into account the actual dilemmas and problems that gene transfer scientists face in their everyday work, scientists reciprocally have to adapt to the views of the outside world. Bioethical discussions are invaluable to outline ethical principles and guidelines and necessary checks and balances in relation to scientific work. This study shows that scientists try to align their understanding of ethical concerns with those raised in society; it also shows that these are often rather difficult to apply in the messy reality of research and clinical work.

**Constructing Doable Problems in a Larger Context**

The second contribution of my study relates to previous social science studies of scientific work. Studies by sociologists including Woolgar and Latour (1986 [1979]), Lynch (1985), Latour (1987), Fujimura (1987, 1988, 1997), Clarke (1997), Knorr-Cetina (1999) and Kruse (2006) have mainly used ethnographic fieldwork in the laboratories to investigate how scientists in practice construct data, analysis, and interpretations. One important focus has been on how scientific problems are made doable in the laboratory. As stated in the beginning of this book, this study has taken a different route. By using interviews and looking at research within a larger perspective and not only as experiments and work in a laboratory, I have captured the necessary contexts of funding, regulation, research collaboration, and public debate. In other words, making research doable is not just about handling various challenges in the laboratory. It is also about negotiating with various external and internal actors, enrolling them and, if necessary, translating their and one’s own interests in order to create doable research. Concepts from laboratory studies have, however, been useful to understand gene transfer scientists’ actions in relation to other social worlds in the making of doable research, from bench to bedside.

Another important difference is that I have added regulators’ views and the relationships between regulators and scientists into the discussion of how to make research doable. The comparative perspective used has revealed the tensions between gene transfer scientists and regulators in the U.S.A. caused by the U.S. regulatory framework. If a similarly highly regulated situation were to be introduced in
Sweden, as suggested by the Swedish regulators interviewed, such tensions might also appear here. The study has highlighted the complicated 'dance' between regulators and scientists that prevails in the U.S. context, in which it is the regulators that choose and lead the dance, while scientists try to influence the steps of the dance, the duration of it, and if possible, also the choice of dance.

I do not claim that the results of this study are generalizable to gene transfer research as a whole or to how controversial research is conducted in general. But, given the choice of central and important persons as interviewees and the use of in-depth qualitative interviews, the study gives, I claim, important insights into how this field of research is understood by the scientists involved. By taking their opinions and actions seriously and trying to understand the context of their choices and activities, a controversial scientific research area is seen from a new – and necessary – perspective.

**Reflections and Further Research**

Making research doable in gene transfer is a complex process taking place on more and different levels than simply in the social world of scientists and the practice of the laboratory or the clinic. It is a practice embedded in controversy where various social worlds, actors, and contexts influence and thus affect the research. As I have shown in this study, gene transfer scientists (re)organize, (re)form, (re)adjust, and adapt to external concerns and demands placed on them, without necessarily agreeing to these demands. These are the only ways available for them to make their work doable in a controversial field of research. The meanings that they created around gene transfer, and about their work in particular, are, I show, intertwined with the controversies that surround it.

Information about gene transfer is not limited to the scientific information provided by scientists and scientific journalists. Many debates and contentions about gene transfer can be understood in the light of media images of gene transfer, its applications, and gene transfer scientists themselves. These media images present one important frame of reference for the public debate and one that problematizes the risks of the possible further development of gene transfer research. There is a longstanding popular interest in utopian and dystopian visions of new biotechnologies, colored by the suggestive accounts of classic novels such as *Brave New World* and films such as *Gattaca*, *The Island*, and *Jurassic Park*. These accounts do not discuss the existing work and possibilities of gene transfer, but bring the future possibilities and risks of gene transfer to a head. They have created room for speculations, fantasies, and horror scenarios. It is in the light of this frame of reference that gene transfer scientists try to gain public acceptance for gene transfer and their work.

Studying how scientists within the controversial and technically advanced scientific field of gene transfer make their research doable brings into focus the social, practical, scientific, regulatory, and medial contexts in which these scientists are situated, and especially how the interviewed scientists handle and make sense of what
they do and why they do it. In the beginning of this study I wanted to explore how gene transfer scientists, that is, those who are most intimately involved in creating new knowledge and applications in this medical field, regarded the ethical, legal, and social issues related to the development and application of gene transfer. But as I rather soon realized, there were other issues beside these that were equally important in gene transfer but also significant in order to understand ethics in practice. For a researcher, studying gene transfer research means ‘going native’ in a field surrounded by controversies. It is easy to get involved in and to accept the troublesome situation involving all the gene transfer scientists whom I interviewed. I have tried to steer clear of this by also interviewing regulators, and thus getting another point of view – the regulatory viewpoint, while simultaneously paying attention to how gene transfer research is discussed in ethical debates. I have also conducted preliminary interviews with bioethical experts in Sweden and the U.S.A. What I have become aware of during this journey is that it is quite easy to sympathize with the interviewed scientists and their struggles, while at the same time recognizing various regulatory and ethical demands and their importance. I have realized that conducting controversial research is not always as black-and-white as it is made out to be in the ethical debates or the media. Instead it is what this study shows, an intricate maneuvering in a controversial field of research including many and difficult ‘gray zones’.

In this study I have only investigated how gene transfer scientists describe, reason about, and handle their work practice. It could therefore be interesting to study gene transfer from other angles, too. One possible area for future research is that of how patient organizations, such as the Cystic Fibrosis Foundation or the National Hemophilia Foundation, affect gene transfer research, with regards to funding, what diseases or conditions to focus on, as well as with regards to which human research participants to enroll in clinical trials. Another interesting study might be to investigate how members of regulatory agencies and advisory boards on local, regional, and national levels discuss, reason about, and handle applications for clinical gene transfer trials. What makes them select some applications for in-depth review, and not others? On what grounds are applications rejected? How do they evaluate the balance between risks and benefits in a clinical gene transfer trial? The latter two areas would be interesting to pursue in order to create a broader understanding of what gene transfer research is being done and what is not being done. They would also shed light on the differences between European and U.S. patient organizations and their involvement in research, as well as between the Swedish regulatory framework of gene transfer and the U.S. one. These studies could give additional insights into how the challenges of gene transfer have been handled worldwide in such different ways.
Books and Articles


References


References


Official Texts


SFS 2006: 351 Lag om genetisk integritet [Swedish White Paper on Genetic Integrity], Socialdepartementet.


References

Appendices
Appendix A: Interview Guides

Interviewees were asked questions such as those below (although the exact phrasing of the questions varied). Depending on what the interviewees chose to tell, I also followed up their reflections with other questions.

Interview Guide for Scientists

Questions on Interviewees’ Experiences

Would you describe your background and how you came in contact with gene therapy?

• What experience do you have in the field of gene therapy?

What is your present research assignment?

Where do you get your research funding from?

Who are your collaborators?

Gene Therapy in General

Can you describe the history of gene therapy’s development?

How is gene therapy applied today?

How is gene therapy different from other medical technologies?

What are considered to be the greatest risks concerning gene therapy?

What do you think the future development will be?

Practical Issues

Some people say that the future of gene therapy is germ-line. What do you think?

Do you disagree?

Are there techniques, other than gene therapy, that are considered more promising?

What kind of diseases and conditions do you think one should focus on with regard to gene therapy?

• Difference between somatic and germ-line gene therapy?

Do you think that we should focus more on basic research instead of applied? If so, why?

Funding

What do you consider to be the largest obstacles in your research?

• Technical problems?
Do you have any concerns about funding for your research?
Where do you get your research funding from?
Have you ever received funding from a private company?
Are there any restrictions from the funding agency about what you can do with your research?
  - Publication?
  - Patents?
  - Confidentiality?
  - Data sharing?
  - Who owns your research results?
Do you remember signing any contract that discussed these restrictions?
In what way do your research results have a commercial interest?
Do you feel any pressure to patent your results or commercialize them?

**Ethical Issues**

What do you think are the ethical questions in gene therapy?
  - Are there others you can think of?
  - Of these, which do you consider most important?
  - Are any of these specific to germ-line gene therapy?

Some people say that there is an ethical difference between eventually using gene therapy to treat diseases and using it to enhance non-medical (normal) characteristics.
  - What is your opinion?
  - Do you think there is a difference in whether enhancement is obtained through somatic gene therapy or through germ-line gene therapy?

Do you have any concerns about how your research will be used?
Do you have any concerns about how others will use the techniques you developed?
Do you feel any personal responsibility?
Is there anything that you do to make sure that your research is not misused?
  - Data?
  - Technique?

How do you feel about the policies that regulate your research?
  - On a university level (IRB & IBC)?
  - On a federal level (NIH & FDA)?

Do you think that the policies will change? And if so how? How would you like to see them changed?

What kind of contact have you had with regulatory bodies? Could you describe that contact?
• On a university level?
• On a federal level?

Research Groups
Which are the strongest gene therapy research groups in the U.S. (or Sweden), in your opinion?
• Internationally?

Are there any aspects you consider important to discuss that we have not discussed during the interview?

Interview Guide for Regulatory Agencies and Advisory Boards

Questions on Interviewees’ Experiences
Would you describe your background?
In what way did you come in contact with questions regarding gene therapy?
What is your position at this regulatory agency/advisory board?
Who are your collaborators?

Gene Therapy in General
How would you describe the history of gene therapy’s development?
• From a regulation/ethical perspective?
• From a research perspective?
How is gene therapy applied today?
• For what kinds of applications are people coming to you?
What do you think the future development will be? What are the challenges concerning gene therapy?
• Technical?
• Regulatory?
What regulating aspects do you consider most important concerning gene therapy?
• Potential risks?
• Potential benefits?

Practical Issues
What are considered to be the greatest risks concerning gene therapy?
Some people say that the future of gene therapy is germ-line. What do you think?
Do you disagree?
Are there techniques, other than gene therapy, that are considered more promising?
What kind of diseases and conditions do you think one should focus on with regard to gene therapy?

- Difference between somatic and germ-line gene therapy?

**Ethical Issues**

What do you think are the ethical questions of gene therapy?

- Are there others you can think of?
- Of these, which do you consider most important?
- Are any of these specific to germ-line gene therapy?

Some people say that there is an ethical difference between eventually using gene therapy to treat diseases and using it to enhance non-medical (normal) characteristics.

- What is your opinion?
- Do you think there is a difference in whether enhancement is obtained through somatic gene therapy or through germ-line gene therapy?

**Clinical Trials**

What kinds of concerns have been raised with regard to applications for clinical trials?

What regulatory aspects are important in the discussion of preclinical and clinical trials?

Who participates in the discussion of preclinical and clinical trials at your agency/in your committee?

Are there different regulatory concerns depending upon where the researchers’ funding comes from?

- NIH?
- Private companies?
- Should there be different policies?

Are the present policies adequate for addressing the complications of privately funded research?

Which policies regulate the implementation of gene therapy?

- Are there any conflicts or frictions between the U.S. policies and the European Union policies?

What policies do you think the U.S. will pursue in the future concerning gene therapy?

Which authorities and participants are involved in the U.S. regulation of gene therapy?
Research Groups

Which are the strongest gene therapy research groups in the U.S. (or Sweden), in your opinion?

- Internationally?

Are there any aspects you consider important to discuss that we have not discussed during the interview?
# Appendix B: Fictitious Names of the Interviewees

## Fictitious Names of the U.S. Interviewees

<table>
<thead>
<tr>
<th>Scientist</th>
<th>Name</th>
<th>Date of the Interview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interviewee 1:</td>
<td>Sean</td>
<td>December 1, 2005</td>
</tr>
<tr>
<td>Interviewee 2:</td>
<td>Shane</td>
<td>December 12, 2005</td>
</tr>
<tr>
<td>Interviewee 3:</td>
<td>Scott</td>
<td>March 10, 2006</td>
</tr>
<tr>
<td>Interviewee 4:</td>
<td>Stuart</td>
<td>March 17, 2006</td>
</tr>
<tr>
<td>Interviewee 5:</td>
<td>Spencer</td>
<td>April 7, 2006</td>
</tr>
</tbody>
</table>

## Members of Regulatory Agencies and Advisory Boards

| Interviewee 6: | Ryan | November 29, 2005 |
| Interviewee 7: | Russell | December 6, 2005 |
| Interviewee 8: | Roslyn | December 15, 2005 |
| Interviewee 9: | Reese | February 7, 2006 |
| Interviewee 10: | Rachel | February 7, 2006 |

## Fictitious Names of the Swedish Interviewees

### Scientists

| Interviewee 11: | Sixten | February 23, 2005 |
| Interviewee 12: | Sylve | March 8, 2005 |
| Interviewee 13: | Svante | March 8, 2005 |
| Interviewee 14: | Staffan | April 8, 2005 |
| Interviewee 15: | Sune | April 18, 2005 |

### Members of Regulatory Agencies and Advisory Boards

| Interviewee 16: | Rikard | February 23, 2005 |
| Interviewee 17: | Rasmus | March 2, 2005 |
| Interviewee 18: | Rut | March 4, 2005 |
| Interviewee 19: | Ragnhild | March 10, 2005 |
| Interviewee 20: | Ruben | June 16, 2005 |
Appendix C: Abbreviations

ADA Adenosine Deaminase Deficiency
ASCGT American Society of Cell and Gene Therapy
CBER Center for Biologics Evaluation and Research
CFR Code of Federal Regulation
DNA Deoxyribonucleic acid
ESCGT European Society of Cell and Gene Therapy
FDA U.S. Food and Drug Administration
GM Genetically Modified
GMP Good Manufacturing Practice
IBC Institutional Biosafety Committee
IND Investigational New Drug
IRB Institutional Review Board
MPA Medical Products Agency
NIH National Institutes of Health
OBA Office of Biotechnological Activities
OTC Partial Ornithine Transcarbamylase
RAC Recombinant DNA Advisory Committee
RNA Ribonucleic acid
SCID Severe Combined Immune Deficiency
SSGT Swedish Society for Gene Therapy
STS Science and Technology Studies
X-SCID X-linked Severe Combined Immune Deficiency