Ethics in action: Approving and improving medical research with human subjects

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INTRODUCTION

The black box of ethical oversight on medical research and finding a way in

1.1 Ethical oversight on medical research with human subjects

This thesis studies how ethical oversight on medical research with human subjects functions in practice. Fueled by public outrage about experiments by the NAZI’s, the Tuskegee Syphilis Study, Henry Beecher’s revelation of unethical research practices at leading hospitals in the United States, and other such scandals, the need for independent oversight on the ethical quality of research with humans has long been highlighted in leading ethical guidance documents, e.g. the Declaration of Helsinki and the Belmont Report (18th WMA General Assembly 1964, Beecher 1966, Jones 1993, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). The ethical quality of medical research depends on whether it is in line with relevant moral principles: the social value of research, the scientific validity, a fair subject selection, a favorable ratio of risks and burdens to subjects and benefits for society, independent ethical review, informed consent of subjects, and respect for enrolled subjects (Emanuel et al. 2000). I define ethical oversight as the activities of independent organizations that work on the ethical quality of medical research.

In The Netherlands, as in most other countries, Research Ethics Committees (in Dutch called ‘Medisch Ethische Toetsingscommissies’; in the U.S. ‘Institutional Review Boards’) have become the cornerstone of ethical oversight on research. These committees review research proposals for medical research to help protect the rights and welfare of human subjects. Research Ethics Committees should function independently and often have a legal basis (in The Netherlands the Medical Research
Involving Human Subjects Act). In practice, most committees are linked to a research institution. Other organizations also contribute to overseeing the ethical quality of medical research. In The Netherlands, ethical oversight is also performed by the Central Committee on Research involving Human Subjects, the Health Care Inspectorate, public funding bodies, pharmaceutical companies, offices at research institutions and research leaders. Still, Research Ethics Committees are the most visible and authoritative bodies overseeing the ethical quality of research. Moreover, they are the only bodies that independently review all proposals for medical research that could affect the rights and welfare of human subjects.

According to Dutch law, the task of a Research Ethics Committee is, amongst others, to evaluate and judge proposals for medical research, based on considerations about the contribution of the study to scientific progress in relation to the interests of research subjects, including the burdens and risks of participating in the study (article 3, Wet Medisch-wetenschappelijk Onderzoek met Mensen 1998). Researchers can only start conducting a study after a committee has given formal approval. Furthermore, according to the Declaration of Helsinki, Research Ethics Committees also have the right to oversee (‘monitor’) ongoing studies.

Although Research Ethics Committees are generally considered to play an important role in overseeing the ethical quality of research (18th WMA General Assembly 1964), they have also been criticized (Ashcroft and Pfeffer 2001). There has been frustration in the research community, among regulatory authorities, and in the pharmaceutical industry about the efficiency of committees, and some feel that they unnecessarily impede the progress of science (Fost and Levine 2007, Koski 2003, Saunders 2002, Savulescu 2002, Shalala 2000, Steinbrook 2002). At the same time, there have also been doubts about whether Research Ethics Committees provide adequate protection for research subjects (Fost and Levine 2007, Koski 2003, Saunders 2002, Savulescu 2002, Shalala 2000, Steinbrook 2002).
1.2. The black box of ethical oversight

An important factor fueling the discussions about Research Ethics Committees is that little is publicly known about their functioning. Although Research Ethics Committees are to play an important role in safeguarding the interest of subjects in research and thus have a social function, committees take up this responsibility predominantly behind closed doors (Ashcroft and Pfeffer 2001). Many aspects of how Research Ethics Committees should work are prescribed by legislation on European (e.g. the Directive on Good Clinical Practice) and national levels, ethical guidance documents (e.g. the Declaration of Helsinki), and rules and regulations issued by Research Ethics Committees themselves (e.g. regulations governing committee activities, procedures for submitting research proposals, lists of documents to be submitted for review, procedures for lodging appeals and objections). These documents state that committees are to convene and discuss research proposals, specify what criteria committees should use to review proposals, describe procedural aspects of decision making (e.g. voting), and require that the committee notifies researchers of decisions in writing (Centrale Commissie voor Medisch-wetenschappelijk Onderzoek 2003, Code of Federal Regulations 2009, Wet Medisch-wetenschappelijk Onderzoek met Mensen 1998).

But how Research Ethics Committees actually work in practice is not public knowledge. Although authoritative handbooks on the management and function of Research Ethics Committees provide detailed information on the organization of committees and the process of review, they do not elucidate what actually happens during committee meetings, how criteria are applied, how discussions progress, and how decisions are reached (Amdur and Bankert 2002). Furthermore, committee meetings are closed to the public and both minutes of meetings, and letters sent to researchers, remain confidential (Centrale Commissie voor Medisch-wetenschappelijk Onderzoek 2003, Dixon-Woods et al. 2007).

Although I acknowledge that there might be good reasons for keeping meetings (partly) confidential (e.g. information in research proposals can be commercially sensitive and this warrants some sort of protection) and thus make meetings not directly accessible to the public, scientific knowledge of the practice of ethical oversight is also limited (Abbott and Grady 2011, Sheehan 2008). A 2011 systematic review of studies
that evaluated aspects of the functioning of U.S. Institutional Review Boards (IRB) collected forty-three empirical studies, which focused on IRB volume, characteristics of IRB members, costs associated with review, the extent to which federal regulations were implemented, variation in review of multicenter research, and the results of IRB deliberations (Abbott and Grady 2011). Information in these studies mainly came from surveys, interviews, institutional databases, and IRB records and letters. However, within these forty-three empirical studies, investigations of the actual practice of doing research oversight were virtually absent and researchers rarely visited the sites where review takes place, i.e. committee meetings. During the last two decades, the only study that visited IRB sites was a 1998 report by the Department of Health and Human Services (Department of Health and Human Services 1998). This study found that IRBs review too quickly, with little expertise and training, that conflicts threaten their independence, and that minimal continuing review occurs. Outside the U.S., the same picture emerges: empirical studies have been studying ethical oversight ‘from the outside’, leaving the actual practice of doing oversight a black box (De Jong et al. 2011). It thus remains essential to study in practice how Research Ethics Committees accomplish their objectives (Abbott and Grady 2011).

So, because limited public and scientific knowledge is available about how ethical oversight works in practice, we are, just as my neighbor Jan mentioned in the prologue, left wondering how the system of ethical oversight on medical research works. How does this system serve the public good and protect the interest of the – in The Netherlands alone – tens of thousands of persons who participate in research each year? This thesis takes up that question.

The central aim of this thesis is to help understand how ethical oversight, especially by Research Ethics Committees, works. A secondary aim of this thesis is to help improve the functioning of ethical oversight. This thesis therefore takes up the following questions: How do Research Ethics Committees evaluate proposals for medical research during their meetings? Do Research Ethics Committees and research institutions oversee whether the actual conduct of research is ethical, and if so, how? Do approved studies actually lead to scientific knowledge and how can Research Ethics Committees oversee that they do? How to handle cases where patients’ medical interests conflict with the interest of scientific progress? And how can oversight bodies
make sure that the benefits of research are distributed fairly among the population, thus serving the public good? Taken together, answering these questions will help provide insight in how ethical oversight on medical research works in practice.

1.3 Looking for a way into the black box

How to study ethical oversight on medical research? Traditionally, the study of moral questions has been carried out by the philosophical discipline of ethics, considering moral issues in health care and research as something to which moral theories could be 'applied'. However, this 'applied ethics' model has been criticized for failing to appreciate the circumstances and contexts that generate and structure issues, and the sometimes idiosyncratic reality of work in health care (Hoffmaster 1992, Ten Have and Lelie 1998). Furthermore, I believe that morality emerges from the practice of daily life rather than from transcendent theories (Dennett 2003, Ridley 1996), so to understand morality, it has to be studied in practice. What is more, studying morality within a practice allows one to 'articulate' – give words to – ideals and their related practices that remained implicit; opening up these ideals and practices for reflection (Pols 2008). In health care these ideas have led to an 'empirical turn' in ethics, encouraging ethicists to study phenomena in practice instead of from theory (Willems and Pols 2010). This turn has had its effect on the body of medical ethics literature: in the 1980ies 8% of studies had an empirical approach, rising to 16% at the beginning of this millennium (Sugarman et al. 2010). This thesis' quest to understand how ethical oversight on medical research works in practice follows this empirical turn.

So, how should we enter the 'black box' of ethical oversight? And when we enter, where should we look in order to understand what is going on inside? For studying the practice of ethical oversight, I was inspired by the methods used in the field of Science and Technology Studies (STS), in particular the ones described by one of the founders of the field, Bruno Latour, in ‘Science in Action’ (Latour 1987). In this book Latour demonstrates how social context and technological content are essential to a proper understanding of scientific facts and their production. He emphasizes that the production of scientific facts can only be understood by studying science as a practice
and examines science in action: the activities in research laboratories, the role of scientific literature, the institutional context of science in the modern world, and the means by which inventions and discoveries become accepted. To paraphrase this in terms of ethical oversight: ethical oversight can only be understood by studying it as a practice, by examining oversight in action: the activities of Research Ethics Committees, the role of ethical texts, the institutional context of ethical oversight, and the means by which research becomes ethically acceptable.

Latour’s emphasis on practice suited the aim of this thesis and encouraged me to follow his first rule of method: “We study science in action and not ready made science or technology; to do so, we either arrive before the facts and machines are black boxed or we follow the controversies that reopen them.” Latour used controversies as a way to get inside the practice of science. He looked for contrasting positions that turn into tensions between scientists, leading to open debate, visible to outsiders. I have taken up this lead and have looked for the contrasts – oppositions that emphasize differences – within the practice of ethical oversight, in order to describe different ‘ways of doing good’. The hypothesis that there were contrasts present in ethical oversight was also inspired by the idea of ‘pluralism’ in ethics: the idea that there are several, conflicting values which may be equally correct, i.e. that there is no objective way to order them in terms of importance (Berlin 1969, Walzer 1983). I have deviated from Latour’s approach since I did not focus on explicit controversies about ethical issues in research, but, keeping in line with the ideas of empirical ethics, have sought to articulate the more implicit contrasts. An additional motivation for focusing on implicit contrast was that public controversies regarding the ethics of research are few and far between. Although public controversies (e.g. the ones mentioned in the first paragraph) have had a major influence on how ethical oversight has been arranged (Emanuel and Grady 2007), the resulting institutionalized form of ethical oversight is performed behind closed doors, making controversies invisible. Moreover, differences of opinion are actively avoided in the current oversight system. For example, multicenter studies are to be reviewed in full by only one committee, aiming to avoid conflicts in review. Also, within committees, members strive for unity in decision making (De Jong, 2011, Directive 2001/20/EC ).
Thus, in order to understand how ethical oversight on medical research works, in each of the next five chapters I study different aspects of ethical oversight in practice and analyze the contrasts within them. In some chapters this will be done quite explicitly, and contrasts will be presented as a main result, whereas in other chapters this will be done in a more subtle way.

In the concluding chapter of this thesis I take my analysis of ethical oversight one step further by again following the lead from empirical ethics. Instead of applying moral theory to practice, as ethical studies have classically done, empirical ethics works the other way around: from moral practice to theory. This move is similar to how normativity is approached in Science and Technology Studies. In that field, the study of normativity is considered neither a matter of description arrived at by scientific study, nor of prescription by philosophy (including ethics), but as a matter of ‘re-scription’: developing new words, stories and theories for what is good (Harbers 2005, Mol et al. 2010, Willems and Pols 2010). In the concluding chapter I take up this lead and synthesize the contrasts I uncovered in the preceding chapters into a more general understanding of ethical oversight.

1.4 Data and Methods

This thesis contains five studies of ethical oversight, each conducted with different methods and based on different data. All five studies have been written as independent journal articles and contain a detailed description of the data and methods used. Therefore, I here describe the data and methods of this thesis on a general level. I also provide some additional background information on the research setting and my reasons for using particular data and methods.

The data for this thesis were collected through work on two projects. Firstly, in the period 2005-2012, I worked on a PhD project on oversight by Dutch Research Ethics Committees, sponsored by the Academic Medical Center in Amsterdam. Dutch data were complemented by a visiting scholarship at New York University in 2008, in order to study oversight in the United States. The Van Walree Fund sponsored this part of the study. Secondly, in 2006-2007, I worked on a project sponsored by the
Netherlands Cancer Institute to develop a guideline for the storage and use of patients’ residual (tumor) tissue. I was responsible for the ethical considerations underlying the guideline. Besides the issue of how to handle cases where patients’ medical interests conflict with the interests of scientific research, the guideline addressed various other issues concerning storage and use of human tissue. The guideline is attached as a supplement to this thesis.

The majority of the data that were collected in The Netherlands were retrieved from an undisclosed large academic medical center (to which I sometimes refer as the West Holland Medical Center), its corresponding Research Ethics Committee, and from the Netherlands Cancer Institute. Data collected in the United States were mainly retrieved from eleven research institutions in the northeast. Data used in this thesis consisted of: scientific literature, documentation (research protocols and submission forms for ethical review; committee websites and annual reports; internal regulations and procedures of committees; committee archives of minutes and correspondence; databases of research proposals; regulations and guidance documents), and ethnographic materials (stakeholder discussion sessions; observations of committee meetings; questionnaires to researchers; interviews with committee members, institutional officials, and scholars).

In order to analyze the data, my methods covered a broad spectrum, ranging from quantitative methods (e.g. a multivariate Cox regression analysis in chapter four) to qualitative methods (e.g. ethnographic techniques in chapter two). I chose to engage with a variety of data and methods because such a ‘multi-method’ approach can help to get a rich understanding of phenomena (Sulmacy and Sugarman 2010). Moreover, it allows for ‘triangulation’ (comparing the outcomes of different methods) to achieve more robust knowledge (Borkan et al. 2007).

1.5 Outline of this thesis

In this introductory chapter I have set the scene of this thesis: the limited knowledge about ethical oversight on medical research with human subjects. I have also described the aim of this thesis – understanding and improving how ethical oversight works in
practice – and my general approach. In the next five chapters I will take up five research questions to study ethical oversight. Together, these questions will help to achieve a better understanding of ethical oversight.

In chapter two I delve into one of the most important, but at the same time least transparent elements of the system of ethical oversight: the deliberations that take place during Research Ethics Committee meetings. I ask how Research Ethics Committees evaluate the proposals for medical research in practice, during their meetings. Finding an answer to this question could help improve how Research Ethics Committees protect the interests of both subjects and science. By sitting in on committee meetings and analyzing the discussions I discovered that committees are involved in two repertoires of evaluation: a repertoire that focuses on rules and judgments, and a repertoire that focuses on knowledge production and advice. I suggest that although the former repertoire is closer to what many expect from Research Ethics Committees, using the two repertoires in conjunction is worth the while, because it helps researchers to improve the ethical quality of research proposals.

In chapter three I move beyond the review of research proposals, and study what ethical oversight on the actual conduct of research amounts to in practice. I ask how Research Ethics Committees and research institutions monitor the conduct of research and why they have arranged it this way. Getting insight in monitoring practices is important because monitoring of ongoing research has been proposed as an additional way of improving the protection of the rights and welfare of research subjects. I studied Research Ethics Committees and research institutions in the U.S. because independent monitoring programs have been in place there for several years, unlike The Netherlands. My analysis showed that monitoring programs varied considerably, but gravitated towards two general types: compliance monitoring, which focuses on documentation, and can amount to disciplining researchers and requiring mandatory corrective actions; and quality improvement monitoring, which focuses more on actual research conduct, and can result in feedback to both researchers and the research institution on how to improve the research process. I argue that quality improvement monitoring is the better choice because it helps foster trust between researchers and Research Ethics Committees, leading to a better protection of the interests of research subjects.
In chapter four I further narrow down the question of how ethical oversight can influence the conduct of research. I investigate to what extent research studies lead to scientific progress, i.e. publications, and how Research Ethics Committees could ensure that they do. I ask to what extent study results are published, and whether a committee could predict failure to publish already during ethical review. Failure to publish is a grave way of treading research subjects’ interests, since failure to publish makes research subjects’ efforts go in vain and can bias the scientific literature. Being able to predict failure to publish could give Research Ethics Committees an important tool with which to better do justice to research subjects. I found that almost half of the studies that had actually included research subjects remain unpublished. Furthermore, by comparing studies that had been published to those that were not, I found that studies that had a problematic review process and studies that aimed to benefit patients directly (as opposed to fundamental research) were associated with publication failure. Research Ethics Committees could use this information to monitor whether studies lead to publication, and for discussing their worries with researchers during the review process in order to prevent non-publication.

In chapter five I study oversight on the use and storage of human tissue and describe the development of a guideline for the management of patients’ residual (tumor) tissue. Residual tissue is often stored for research purposes, but can also sometimes serve clinical ends at a later moment. This can lead to a conflict of interests between patients’ and research interests. This came to the fore when a woman, previously treated for breast cancer, requested her physician to have a new genetic test performed on her residual tumor tissue which had been stored for research. As guidance was lacking for how to handle this case and how to weigh the interests of a patient against those of research, developing a guideline seemed appropriate. The analysis conducted in this study showed that such a guideline should take four ethical principles into account: the responsibility of health care providers to provide good clinical care; the rights of patients regarding their bodily material, removed or not; the relative rights of family members regarding this material; and the overriding interest of patients’ medical interests over the interests of scientific research in cases where they conflict. The practical implications for the management of human tissue were also explored, including the practicalities of storing sufficient tissue for future clinical usage.
In chapter six I examine how considerations of justice can be relevant to ethical oversight and what implications this holds for research. I explore the idea that the choice for a specific research methodology can affect whether the benefits of research results are distributed fairly. Using the case of hypertension management as an example, I show how the current 'gold-standard' of research methods – the randomized controlled trial – aims at a standardization of patients, a standardization of care and a standardization of interventions. I argue that this philosophy of 'standardization' can mean that less relevant medical knowledge will become available for disadvantaged patient groups. I further argue that less standardization in RCTs could be beneficial, and that research methods that do not tend to standardize, such as qualitative methods, are needed to generate relevant knowledge for disadvantaged groups. These are considerations that could be taken into account in ethical oversight.

In the concluding chapter, chapter seven, I work towards a deeper understanding of ethical oversight, based on a synthesis of the contrasts uncovered in the studies in this thesis. I argue that there are two philosophies for doing good in ethical oversight: (1) '(dis)approving' which aims to ensure that research is ethical and works towards (dis)approval, is carried out within relationships based on authority, and focuses on documentation; and (2) 'improving' which aims to improve the ethical quality of research by giving advice, is carried out within relationships based on equality, and focuses on practice. After reflecting on the research methods used in this thesis I discuss the strengths and weaknesses of both approaches. Although (dis)approving currently is the dominant approach in ethical oversight, I argue that improving is a good alternative. Subsequently, I discuss how the two approaches to oversight interact, and how they can best be combined. In conclusion, I articulate the main lessons that can be drawn from this thesis. Ethical oversight can benefit from focusing more on actual research practices and less on paperwork, from avoiding relationships based on authority (if possible) and trying to work on an equal footing with researchers instead, and from improving the ethical quality of research instead of only (dis)approving research.
References

18th WMA General Assembly (1964) World Medical Association Declaration of Helsinki; Ethical Principles for Medical Research Involving Human Subjects.


Savulescu, J. (2002) Two deaths and two lessons: is it time to review the structure and function of research ethics committees?, *Journal of Medical Ethics, 28,* 1, 1-2.


