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

de Jong, Jean Philippe

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Chapter one: Introduction

This thesis studies how independent ethical oversight on medical research with human subjects functions in practice. In the introductory chapter, I explain why there is a need to study ethical oversight and what my approach is for doing so. In most countries, a system for ethical oversight on medical research, with Research Ethics Committees as its cornerstone, has been in place for many years. Such a system aims to ensure that the ethical quality of research is in order and that subjects are protected. The ethical quality of a study depends on whether the study 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. I define ethical oversight as the activities of independent organizations that work on the ethical quality of medical research.

Although Research Ethics Committees are generally considered to play an important role in the system of ethical oversight, they have also been criticized. There has been frustration about the efficiency of committees and some feel that they unnecessarily impede the progress of science. At the same time, there have also been doubts about whether Research Ethics Committees provide adequate protection for research subjects. In reality however, little is known about the functioning of Research Ethics Committees or the broader practice of ethical oversight: the oversight system is a ‘black box’. The central aim of this thesis is to open this black box and to help understand how ethical oversight, especially by Research Ethics Committees, works in
practice. A secondary aim of this thesis is to help improve the functioning of ethical oversight.

To achieve these aims, this thesis addresses the following five research 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?

To enter the black box of ethical oversight and answer these questions, I have looked for the contrasts – oppositions that emphasize differences – within the practice of ethical oversight, in order to describe different ‘ways of doing good’. In each of the following five chapters I take up one of the research questions and analyze the contrasts within them. In the concluding chapter, chapter seven, I take my analysis of ethical oversight one step further and synthesize the contrasts I uncovered in the preceding chapters into a more general understanding of ethical oversight.

Chapter two: Ethical review from the inside

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 improve the ethical quality of research proposals.

Chapter three: Compliance or quality improvement?

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 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.

Chapter four: Publication rate of clinical studies

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. Prediction of a failure to publish could thus 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 actually included research subjects remain unpublished. Furthermore, by comparing studies that have 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), was 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.

Chapter five: Tumour tissue – who is in control?

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.
Chapter six: Justice in clinical research methods

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 argue that three elements of the current ‘gold-standard’ of research methods – the randomized controlled trial (RCT) can potentially lead to an unfair distribution: (1) RCTs tend to standardize study groups, and results in standardized study groups can be difficult to extrapolate to disadvantaged groups outside a study; (2) RCTs standardize the delivery of health care within studies, and disadvantaged patient groups outside a study may have more difficulties adapting to these standardized interventions; and (3) the focus of RCTs on standardized interventions directs medical research away from more complex interventions such as lifestyle interventions, which are needed especially by disadvantaged patients. I conclude that, although standardization can help to generate valid knowledge, in particular cases it can also 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 have a strong tendency 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.

Chapter seven: Discussion

In the concluding chapter, 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. First, ‘(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 second, ‘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. 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. Although (dis)approving is closer to what people expect from Research Ethics Committees and is the dominant approach to ethical oversight, improving is a valuable alternative for supporting scientific progress and guarding the interests of research subjects.