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PART B

Setting the scene
Chapter 3

THE ETHICS OF MEDICAL RESEARCH:
INFORMED CONSENT AND
THE THERAPEUTIC MISCONCEPTION

Parts of this chapter have been published in Dutch:
ABSTRACT

Pediatric oncology has a strong research culture. Most pediatric oncologists are involved in clinical care as well as research. Consequently, various concepts analyzed in research ethics are also relevant when studying the pediatric oncology practice. This chapter offers a theoretical introduction to the ethical concepts studied empirically in chapter 4.

Medical-ethical approval of research involving human beings is based on two pillars:
(1) ‘assessment’ by an institutional review board (IRB) or by a Central Committee of the scientific merit of the research and the risks and burdens for the research subject, and
(2) ‘informed consent’ by the research subject or his legal representatives.

Discussions on the ethical acceptability of research generally focus on the 1st pillar, assessment by an IRB or Central Committee. Much less frequently there is concern about the 2nd pillar, obtaining informed consent from the research subject. In this chapter we analyze some ethical concepts which play a role when asking informed consent. We describe the criteria for valid informed consent: knowledge, competence and voluntariness.

We especially focus on the concept of ‘therapeutic misconception’: the misconception that participating in research is the same as receiving individualized treatment from a physician. We assess this concept in the light of the fundamental difference between the research relationship (between investigator and subject) and the treatment relationship (between physician and patient). We argue that understanding the concept of ‘therapeutic misconception’ is essential to explaining why it is often difficult to obtain valid informed consent from patients or parents for medical research.
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INTRODUCTION

Pediatric oncology has a strong research culture. Most pediatric oncologists are involved in clinical care as well as research. Consequently, various concepts analyzed in research ethics are also relevant when studying the pediatric oncology practice. This chapter offers a theoretical introduction to the ethical concepts studied empirically in chapter 4. We describe the criteria for valid informed consent: knowledge, competence and voluntariness. We pay extra attention to the concept of therapeutic misconception, i.e. the tendency to mistake the scientific aim of the trial for the therapeutic aim of a treatment.

RESEARCH ETHICS IN THE MEDIA

On the 23rd of January 2008, the medical center of the University of Utrecht (UMC Utrecht) announced that during a randomized study on the effects of probiotics on patients with acute pancreatitis an unusually high mortality rate occurred among the group of patients who received treatment with probiotics (UMC Utrecht 2008). In total, twenty-four patients (16%) from the study group died, as compared to only nine patients (6%) from the control group (Besselink et al 2008a; 2008b). There were various responses to the press release. Some people wondered whether there had been a stratification problem in the inclusion phase. Others raised doubts about how the research was performed. Still others expressed worries about the way in which the participants were informed about the trial. The media openly asked the question whether this outcome could have been prevented and whether the research had been performed in the proper way. The government health care inspectorate announced an investigation into the execution of the research. At the talk show Pauw en Witteman a patient who had participated in the trial stated that he had not been sufficiently informed during the informed consent procedure (show of January the 24th 2008; http://pauwenwitteman.vara.nl). In his perception, he had not been told about the possible risks involved in participating in the trial. He claimed that the doctors had told him that the medication was ‘as safe as one of those probiotic drinks from the supermarket’. Moreover, he ‘might as well have been buying a house’ when he signed the informed consent form, indicating that he did not know what he was signing for.

The responses to the news from the UMC Utrecht reflected the two pillars on which the ethical acceptability of medical research involving human subjects is based, namely:

1. the assessment of the scientific soundness of the trial and the risks and burdens for
Figure 3: The two pillars of ethical acceptability of research. In the Netherlands, there is supervision by a local review board (IRB) or by the Dutch Central Committee for Research involving Human Subjects (CCMO). ‘Informed consent’ is achieved through the relationship between the physician-researcher and the patient and/or his legal representatives. Pitfalls during the informed consent procedure are indicated underneath the three criteria for informed consent.
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The subjects by an institutional review board (IRB) or by a Central Committee, and (2) the obtainment of informed consent from the subject or from his or her legal representative (see figure 3). In the Netherlands, these 2 pillars have been laid down in the Medical Research with Human Subjects Act (WMO, Wet Medisch-wetenschappelijk Onderzoek met Mensen).

This chapter will examine some of the ethical concepts involved in the pillar of informed consent. As mentioned above, the focus will be on the concept of ‘therapeutic misconception’. This concept is crucial to understanding why it is so difficult to obtain valid consent for medical research from subjects.

INFORMED CONSENT AS PILLAR OF ETHICAL ACCEPTABILITY OF RESEARCH

In discussions on the ethical acceptability of research, the focus is generally on the first pillar: supervision by a review board. The second pillar, the obtainment of informed consent for research approved by an IRB, rarely gets questioned. But this second pillar requires discussion as well. For example: do subjects actually understand what the research entails? Are they able to weigh the risks and burdens themselves? Is it at all possible to obtain valid consent in emergency situations?

According to the researchers from the UMC Utrecht, their research was conducted in compliance with the prevailing regulations and with the law. They point at the methodological soundness of the research and at the approval obtained from the local review board of every participating hospital. This means they mainly base their claim on the first pillar. They are supported by peer reviewers of the scientific article on the research results (Van Santen 2008). But what about the second pillar? Was informed consent obtained in a valid way as well?

CRITERIA FOR INFORMED CONSENT

The principle of informed consent does justice to the ethical ideal of respecting a patient’s autonomy, and his right to self-determination. A valid informed consent meets 3 criteria (see figure 3): knowledge, competence, and voluntariness.

Knowledge requires that the subject is supplied with sufficient information to be able to make a deliberate choice. Knowledge transfer, however, may be problematic. For instance, research shows that a large number of patients find the written information they
receive hard to read and to understand (Paasche-Orlow et al 2003; Grossman et al 1994; Tarnowski et al 1990). Even after explanation by the physician, many of the patients who agree to take part in a trial still have misconceptions about the research procedures (Greenley 2006; Wendler 2004). In many cases, they do not have sufficient insight in necessary elements of informed consent, such as risks, burdens, possibility of alternative treatments, duration of the trial, the right to withdraw, and the voluntariness of participation.

*Competence* means that the subject is able to understand the information he receives and that he realizes the consequences of his choice to either participate in the trial or decline participation. When the decision whether or not to participate in research occurs at the onset of treatment for a severe illness, patients may be under extreme psychological and emotional pressure. One may question their competence under such circumstances. The subjects in the UMC Utrecht trial all came in with an acute pancreatitis which was predicted to take a serious course - not an ideal situation to be in when one needs to weigh information and make a deliberate choice. In hindsight, patients may start to doubt their apparent competence at the time, as did the patient in the talk show *Pauw en Witteman*.

*Voluntariness* means that the subject is able to give his or her consent without being coerced or influenced. However, it is easy to influence a patient. By the way in which the information is given or by not mentioning some of the information, physicians even unconsciously manipulate the choice of the patients or their representatives. The emotional circumstances surrounding a serious disease foster reliance on the doctor who brings up the treatment and the trial (Ong et al 1995). In pediatric trials, parents indicate that they find it difficult to oppose the physician’s proposal because they are afraid this will have an adverse effect on their child’s treatment (Heneghan et al 2004). Moreover, they may be under the pressure of having to decide on participation in the trial within a few hours or days.

**THERAPEUTIC MISCONCEPTION**

One aspect of the informed consent procedure which merits separate attention is the so-called ‘therapeutic misconception’: the tendency to mistake the scientific aim of the trial for the therapeutic aim of a treatment. This therapeutic misconception was first described in 1982 as the misunderstanding that taking part in a trial is the same as receiving individualized treatment (Appelbaum et al 1982; Appelbaum et al 1987). Subjects may have difficulty to recognize that the aim of a trial is to obtain scientific information.
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(even if this will contribute to enabling better care in the future); they may not understand that potential benefits for the subjects themselves are formally a mere by-product of gaining such information, and that research participation may involve the sacrifice of some degree of personal care.

Research shows that 40-80% of study participants express inaccurate beliefs regarding the degree of individualization of their treatment, or regarding the likelihood of benefit, given the methods of the study (Appelbaum et al 2004). Current medical practice, in which research and treatment may be closely interrelated, leaves much room for such misunderstandings. For instance, participants in a randomized trial may think that they can decide for themselves which arm they will be assigned to, or that a physician will decide on the basis of what seems best for them. It may not always be clear that the assignment will actually be random.

Physicians, too, may suffer from the therapeutic misconception. They may, for example, experience tension between their role as a clinician and as a researcher. Two studies show that oncologists, even those with plenty of research experience, mostly adopt the perspective of clinician instead of that of researcher when they discuss participation in a trial (Joffe et al 2002; Taylor 1992). They often sincerely think that clinical trials provide a perfect harmony between the aims of patient care on the one hand and scientific advancement on the other. The best possible treatment then seems to be offered in the strict set-up of a research protocol (Joffe et al 2002).

TREATMENT RELATIONSHIP AND RESEARCH RELATIONSHIP

A fundamental point of departure in medical ethics, however, is the important distinction between the treatment relationship which exists between clinician and patient, and the research relationship which exists between researcher and subject (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). In the treatment relationship, the individual well-being of the patient prevails. The ethical principles of beneficence and non-maleficence are important here. Incidentally obtained new information is secondary to the overriding goal of the medical activity, i.e. treating the patient. The treatment is often conducted without explicit consent from the patient. This is called implicit or presumed consent and is exemplified in a patient’s stretching of an arm for a vena puncture. Concerning children, pediatricians routinely carry out medically indicated procedures on children without obtaining consent or assent. Indeed, many procedures are even performed over the child’s vigorous objections. This is acceptable because it is the interest of the child which is the sole motivation prompting the intervention (Lee et al 2006).
In a research relationship, by contrast, the aim of the researcher is to obtain new knowledge and thus enable the improvement of future treatments. Potential therapeutic advantages are secondary to the prevailing aim of obtaining information. Therefore, every act of research requires explicit consent.

It is sometimes claimed that in randomized trials the basic requirement of therapeutic benefit is met because of the so-called ‘clinical equipoise’; the researcher sincerely does not know which of the trial arms will turn out to be the best for the group of patients as a whole at completion of the trial. However, the fundamental difference between a treatment and a research relationship is that the experienced clinician selects and conducts the treatment – in accordance with individual, patient-specific considerations – while the researcher refrains from patient-specific considerations and opts for randomized assignment in order to obtain general results for the group of patients as a whole, with no importance given to individual traits or preferences. And even though the benefits and risks of participating in a trial may seem to be at least as favorable as those of undergoing a standard treatment, a characteristic of randomized trials remains precisely that researchers may never positively know in advance what the actual benefits and risks will turn out to be – as the UMC Utrecht study clearly shows. If one, in spite of this, communicates the absolute equality of the arms of a trial to potential subjects, this will increase the chance that they will fall prey to the therapeutic misconception (Miller and Brody 2003).

DISCUSSION

Obtaining valid consent is not an easy task. The informed consent procedure should start with a clarification of the situation: subjects who think they will receive individualized treatment, while in reality they will be treated according to the research protocol, cannot give their valid consent. Subjects have the right to a fair opportunity to make a deliberate decision on whether or not to participate in a trial. Therefore, clinicians and researchers should clearly explain the difference between the standard treatment and the treatment administered in the trial (Appelbaum 2002). This may take a fair amount of time, especially in a setting where research and treatment are closely interrelated. When the research pertains to an acute disorder and when the intervention involves taking a nutritional supplement, as was the case in the UMC Utrecht study, it seems natural to rely on the argument of clinical equipoise. However, approval by an IRB and the reasonable expectation of clinical equipoise may never replace the consent procedure.
Well-formulated written information may help researchers in explaining which elements of a treatment protocol are in fact part of research and therefore optional (Ungar et al 2006). In a study in pediatric oncology, parents themselves were asked for advice on how to improve the informed consent procedure (Eder et al 2007). They stated that the information should be based on the individual situation of the subjects and not on legal requirements – the latter often leading to long and complicated patient information forms. Parents also wanted a clearer distinction, in time and/or in spokesperson, between consultations regarding the treatment on the one hand and the trial on the other. Finally, they desired more time to decide. It is precisely this last point which is hard to realize if the trial has to start immediately after the diagnosis and the patients are critically ill, as in the probiotics study.

A first step towards solving this problem might be to always have a close relative of the patient present, who listens in on the informed consent procedure. Moreover, the informed consent procedure should be seen more as a process than as one decisive moment. During the course of a trial, there should be multiple moments in which patient_participants are again informed of what the trial entails, what the risks are, and what the difference is with regular treatment. This will prevent them from afterwards feeling that they have not been sufficiently informed.

Notably, most researchers indicate hardly having received any training in conducting consent consultations or in the requirements that such consultations should meet. And IRBs are confined to assessing the written information, and do not monitor the actual informed consent procedure with patients.

CONCLUSION

The above proves that the informed consent procedure is full of pitfalls, and that it is difficult to obtain consent that is actually valid, especially when it comes to trials involving acute disorders. It therefore seems necessary to provide physicians involved in such trials with additional training in this area. The focus should then be at perceiving the informed consent procedure as a process in which the subject gains more insight throughout the study into what the trial actually entails.