The moral limits of medical research with children

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CHAPTER 10

SUMMARY

Some medical research studies may improve medical care for children as a group but cannot directly benefit the individual children involved. Review boards are not allowed to approve such so-called non-therapeutic studies with children, unless these studies involve 'minimal' risks and burdens. This restriction was established for a good reason: it ensures that individual children will not be exposed to (relatively) high levels of risk and burden solely for research purposes. However, as a consequence of this approach, some of the studies that are necessary for improving medical care for children as a group cannot be conducted. Therefore, this thesis examines the following question: 'How to facilitate more of those studies that may improve medical care for children as a group, while still adequately protecting individual research subjects against research risks and burdens?'

Chapter 1 gives a general introduction to the thesis. First, we explain the two sides of the dilemma: 1) Why medical research studies with children, including non-therapeutic studies, are necessary to improve medical care for children as a group; and 2) Why research subjects need to be protected, in particular if these research subjects are children. Subsequently, we describe how the Dutch Medical Research with Human Subjects Act (WMO) and other relevant ethical codes and regulations have addressed this dilemma, and how this has resulted in the current need for more research with children.

Chapter 2 reports on an analysis of the approval/rejection decisions made by the Dutch Central Committee on Research with Human Subjects (CCMO). This chapter shows that in particular early phase drug studies relatively often do not comply with the requirement of minimal risk and burden. The chapter also reveals that such studies are not always rejected: the CCMO occasionally finds ways to approve important studies that formally should be rejected. We argue that this is not an advisable solution: it may be that exceptions to the requirement of minimal risk and burden occasionally can be justified; yet, such exceptions should be made in a transparent and reviewable way.

Our analysis of the approval/rejection decisions made by the CCMO showed us that the requirement of minimal risk and burden in fact poses two more issues. The first is that it is not always clear whether a study should be regarded as a non-therapeutic study, and thus *should* fulfill the requirement of minimal risk and burden. The second is that without clear definitions of 'minimal risk' and 'minimal burden', the requirement of minimal risk and burden may not provide a reliable level of protection. Before addressing the main problem (i.e., that some data that are necessary for improving medical care for children as a group cannot be obtained with minimal risks and burdens for the individual subjects) in *Chapters 7 and 8*, we first in *Chapters 3-6* address these two issues.

Chapter 3 addresses the issue that it is not always clear whether a study should be regarded as a non-therapeutic study. This chapter shows that this issue is related to the fact that many studies are not entirely therapeutic or entirely non-therapeutic. Some so-called non-therapeutic drug studies may offer a reasonable

treatment option to the research subjects because there are no alternative treatment options available. And many so-called therapeutic studies incorporate non-therapeutic procedures such as extra blood draws, extra scans or extra hospital visits. In addition, some therapeutic procedures involve some 'net' research risks and burdens (i.e., risks and burdens that are faced solely for research purposes and that thus in principle should be minimal) because an alternative treatment option with a more favorable risk-benefit profile is already available. Thus, if one aims to accurately identify all risks and burdens that have to be minimal, one should distinguish between therapeutic and non-therapeutic *procedures* rather than between therapeutic and non-therapeutic *studies*, and one should consider the therapeutic procedures in relation to the alternative treatment options to the subjects. On the basis of an example study we show how two of such procedure-level approaches, the component analysis approach and the net risks test, can be of much use, particularly in combination.

Chapter 4 addresses the issue that without clear definitions of 'minimal risk' and of 'minimal burden', the requirement of minimal risk and burden may not provide a reliable threshold. First, we examine the problems related to the definitions provided by the US Federal Regulations, and conclude that following the US is not advisable. Subsequently, we develop new definitions. The definition of minimal risk is that 'empirical data and/or expert opinions suggest that in the persons concerned, the likelihoods that the procedure(s) will cause small, moderate, and/or serious harm are < 1/100, < 1/10,000, and < 1/1,000,000, respectively'. The definition of minimal burden, which in this chapter we name 'minimal risk of discomfort', is that 'empirical data, expert opinions and/or the procedural characteristics suggest that at most a quarter of the persons concerned will experience considerable discomfort'.

Chapter 5 reports on an empirical study assessing perceived discomfort levels in 670 healthy children aged 0-2 years undergoing vaccinations, venipunctures and nasopharyngeal swab taking. The proportion of children with moderate or high levels of discomfort was 12% for vaccination, 28% for nasopharyngeal swabbing and 49% for venipunctures. Within the reported age group of 0-2 years, increasing age was related with higher discomfort levels. These results may serve as a reference for the design and ethical review of future vaccine studies in children.

Chapter 6 reports on an empirical study assessing discomfort related to unsedated MRI. Self report scores, observation scores, heart rate standard deviation scores and incremental salivary cortisol levels were obtained from 54 children aged 5-12 years old with non-acute conditions undergoing diagnostic MRI. Of the 54 children, 19% scored relatively high values on the self report score and on one or two of the other measures, and another 28% scored relatively high on the self report score alone. No experimental evidence was found for the CCMO's assumption that those children at risk for higher levels of discomfort can be identified by their age.

Chapters 7 and 8 then address the issue that some data that are necessary for improving medical care for children as a group cannot be obtained with minimal risks and burdens for the individual subjects. *Chapter 7* considers the relevant European codes and regulations. It is shown that the Dutch problem cannot be solved by adapting the WMO to 'Europe', because in Europe there currently is no consensus. In a supplementary document to the Clinical Trials Directive, the EU recommends allowing 'a minor increase over minimal risk' as the upper limit of acceptable risk in non-therapeutic research with children. In the Clinical Trials Directive itself, however, no such upper limit is provided. Moreover, the European Convention on Human Rights and Biomedicine, which may soon be ratified by the Netherlands, resembles the WMO by allowing, at most, minimal risk and minimal burden.

Chapter 8 analyzes whether it would be advisable to follow the US Federal Regulations, which allow in two circumstances for exceptions to the requirement of minimal risk and burden. To do so, we first explore the ethical grounds for accepting only 'minimal' risks and burdens. From there we deduce that exceptions to the requirement of minimal risk and burden can be regarded as acceptable in case the study is exceptionally valuable and the potential subjects are able to give their assent to participate. We conclude that rather than following the US Federal Regulations completely, the Dutch and European regulatory frameworks should be revised to legitimize such exceptions in a transparent way. Thus, we recommend allowing exceptions to the requirement of minimal risk and burden in case of exceptionally valuable studies involving children who can give their assent to participate in the study.

In *Chapter 9* the findings of this thesis are summarized in relation to the three issues that we found to be related to the current restriction on non-therapeutic research with children. In relation to these three issues, we also formulate recommendations, discuss alternative solutions and provide suggestions for future research. The recommendations are the following: 1) To more accurately identify those research risks and burdens that have to be minimal, by distinguishing between therapeutic and non-therapeutic *procedures* instead of between therapeutic and non-therapeutic *studies,* and by considering the therapeutic procedures in relation to the alternative treatment options for the subjects; 2) To implement our proposed definitions of 'minimal risk' and 'minimal burden', and to make the decision of whether a procedure fulfils these requirements in each case as evidence-based as possible; and 3) To allow exceptions to the requirement of minimal risk and burden in case of exceptionally valuable studies involving children who can give their assent to participate in the study. Subsequently, we explore the implications of these recommendations. We conclude that it can be expected that by following our recommendations, review boards would be able to approve more studies, and the individual research subjects would be more adequately protected than they currently are.