Final report on 'The evaluations of the Dutch Central Committee on Research involving Human Subjects (CCMO) regarding minimal risk and minimal burden in paediatric research without direct benefit'.

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ABSTRACT

Background. The involvement of children in research that will not directly benefit them, poses an ethical dilemma. Paediatricians must often diagnose or treat children in the absence of sufficient data, and if research without direct benefit is not allowed, some of these important scientific data will never be available. However, as children cannot give consent, possible harms or burdens during research without direct advantages for the participants have to be strictly limited. According to Dutch law, the absolute limit is 'minimal risk and minimal burden'.

Research questions. a) To what extent does the requirement of minimal risk and minimal burden compromise the possibility to obtain scientific data that are necessary for improving paediatric care? b) Can the requirement of minimal risk and minimal burden provide a reliable threshold?

Methods. Systematic analysis of the decisions of the Dutch Central Committee on Research involving Human Subjects (CCMO). All 165 proposals for paediatric research without direct benefit reviewed by the CCMO between 01/2000 and 07/2007, were included. All studies involving MRI and all drug studies (18 early phase drug studies and 9 other non-therapeutic drug studies) were analysed in depth.

Results. Thirty-eight (23%) of the 165 proposed studies were rejected (18) or only approved after the investigators modified the protocol (20), because the CCMO did not regard their risks and/or burdens as minimal. Eleven studies (7% of 165) were definitively rejected. Four of the 11 studies that were definitively rejected, were early phase drug studies. Four other early phase drug studies were approved despite burdens that were not regarded as minimal. Risks and burdens were, as far as this could be evaluated, assessed fairly consistently, but it was not always clear whether a study could be considered to provide 'the prospect of direct benefit', i.e., whether the risks and burdens *should* be minimal.

Discussion. a) Early phase drug studies do relatively often not comply with the requirement of minimal risk and burden, which may hinder drug development for children. However, not every rejection based upon this requirement compromises the possibility to obtain necessary scientific data. b) The requirement of minimal risk and burden can provide a reliable threshold, especially when risks and burdens are assessed separately and systematically, and not compared with an external standard. Some protocols are complex though and the dichotomy between studies with and studies without direct benefit (the basis of the current regulations) is therefore not as sharp as suggested.

Recommendations.

1. Component analysis should be used for identifying risks and burdens that have to be minimal.
2. Risk assessment should be carried out more systematically.
3. Higher levels of risk and/or burden should be considered acceptable under strict conditions.

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INTRODUCTION

Background

The involvement of children in research that will not directly benefit them, poses an ethical dilemma. Paediatricians must often diagnose or treat children in the absence of sufficient data, and if research without direct benefit is not allowed, some of these important scientific data will never be available. However, as children are vulnerable and cannot give consent, research without direct benefit for the individual participants should not cause them harm or pose an unreasonable burden on them. Hence the central dilemma is how to allow research to be done that benefits children as a group rather than the individual participants, without jeopardizing the integrity or safety of those individuals.

Several international and national documents and laws have attempted to solve this dilemma by prohibiting paediatric research without direct benefit unless the risk of harm is below a certain limit. According to the European Convention on Human Rights and Biomedicine as well as Dutch law, this limit invariably is 'minimal/negligible risk and minimal burden/inconvenience'.[1;2] According to US legislation and recent EU recommendations (for implementing the Clinical Trials Directive), on the other hand, the limit is 'minimal risk' and if benefit for the group to which the children belong is expected: 'a minor increase over minimal risk'.[3;4]

These two options differ in two aspects. Firstly, the first option explicitly requires separate assessments of the research risks and burdens. The concept of 'research burden' relates to the drawbacks that are inherent to the study and will occur in any case. The burden of an observational study, for instance, may consist of visits to a clinic, undressing for Tanner-staging, venipunctures and/or lying still in a Magnetic Resonance Imaging (MRI) scan. Secondly, the second option clearly accepts a higher level of risk in case of benefit for the group. This 'group' consists of children with the same disease (EU) or condition (US). Group-benefit often applies and this option consequently potentially (depending on the interpretation of 'a minor increase') enables committees to approve more studies.

Another issue at stake is that 'minimal risk', the pivotal concept in both options, has been the subject of considerable debate in the international bioethical literature. According to most definitions, minimal risk means that: 'the risk may not be higher than those ordinarily encountered in daily life, or during the performance of routine examinations or tests'.[3] Despite this explanation, the assessment of risk among American paediatric department chairmen, clinical research centre directors and review board chairpersons varies considerably, which has put the concept's adequacy into question.[5] One of the suggested reasons is that both the 'daily risk' and the 'routine examination' standard can be interpreted based on the risks faced by an average child, or based on the risks of the group of children that will be enrolled in the study.[6] It has also been argued that regardless of *whose* life should be used to identify and estimate these daily risks, the concept of daily risks is too vague to provide a reliable threshold.[7]

Objectives

The present study aims to provide empirical data on the merits of the first option ('minimal risk and minimal burden') by analysing the evaluations of the Dutch Central Committee on Research Involving Human Subjects (CCMO).[*] During the past eight years in the Netherlands a substantial part of the studies at stake was reviewed by this committee. This has created a unique situation for this type of research. Questions that will be addressed are:

a. To what extent does the requirement of minimal risk and minimal burden for paediatric research without direct benefit compromise the possibility to obtain the scientific data that are necessary for improving paediatric care?
b. Can the requirement of minimal risk and minimal burden provide a reliable threshold?

METHODS

The Dutch Central Committee on Research Involving Human Subjects (CCMO)

The CCMO was created in 1999, is based in The Hague, the Netherlands and has 14 members.[8] Among its members are experts in paediatrics, pharmacology, nursing science, law, the methodology of scientific research and ethics, as well as a member who reviews research specifically from the subject's point of view.[8] The committee's broad range of tasks includes accrediting Medical Research Ethics Committees and, in specific cases, reviewing research protocols.[9] An important category of protocols that are on a mandatory basis reviewed by the CCMO is the group of 'non-therapeutic intervention studies' with children: studies that deliberately alter the condition of the subjects (in order to evaluate the effects of that intervention) without being of direct benefit to them.[9]

Inclusion

I analysed all proposals for paediatric research without direct benefit reviewed by the CCMO between January 2000 and July 2007. This means that all non-therapeutic intervention studies and all observational studies (invasive observational studies were reviewed by the committee between 2002 and 2005 to monitor this type of study) were included.[9] Just as the committee, I considered drug trials to be non-therapeutic if they were early phase (phase I and occasionally phase II) or if they had pharmacokinetic and/or pharmacodynamic objectives outside a (pharmaceutical) drug development plan. Placebo-controlled phase III drug studies (reviewed by the committee up to August 2001, because the committee at that time regarded them as non-therapeutic) were considered therapeutic and hence only included when healthy controls participated, for whom it would be an observational study.

[*] Although the Dutch law officially requires 'negligible risk and minimal inconvenience' we will use for the purpose of this study the term 'minimal risk and minimal burden' for this is the more common terminology and has a similar meaning.

Data

While analysing the decisions I recorded the following characteristics of the research projects: initiator (NL: 'verrichter/opdrachtgever'); single- or multi-centre; intervention or only observational; number of (Dutch) participants needed; health status and age of participants to be involved; and procedure(s) to be performed. The decisions by the CCMO and the underlying arguments were obtained from the pre-advices, the minutes of the committee-meetings and the subsequent correspondence with researchers. For the purpose of this analysis, 'approved' was defined as permission to conduct the study as originally proposed and 'rejected' as non-permission. The protocols that had to be discussed more than once and hence were only 'approved after revision' formed the third category. Some, but not all of these studies, required modifications before they could be approved en were consequently considered 'approved after modifications'. In case of rejection, the reasons for this decision were obtained from the rejection letter. Studies that were submitted again (after rejection, for a second review) were considered 'resubmissions'. Studies that were not resubmitted or that were rejected again and that could consequently not be conducted were called 'definitively rejected'.

Analysis

I performed a descriptive analysis of the data. Firstly, I classified all protocols according to their objectives. Secondly, all reasons for required modifications or for rejection were categorised by their relation to the requirement of 'minimal risk and minimal burden' (WMO art. 4.1), the requirement that the study can not be conducted without the participation of persons of the same category as the subject (group relatedness) (WMO art. 4.1) and the more general criteria for ethical scientific research (WMO art. 3).[10] The last category includes criteria such as that the trial will lead to advancement of medical science (art. 3a) which could not be achieved without the participation of human subjects or by less radical means (art. 3b), with a sound methodology (art. 3d) and an appropriate publication policy.

All studies with decisions based upon their levels of risk and/or burden (either rejection or approval after modifications) were selected and categorised by the type of research and the type of risk or burden in order to provide an overview and examples. Those studies that were definitively rejected were listed. Subsequently, in order to gather information for answering question b (whether the requirement of minimal risk and minimal burden can provide a reliable threshold), I analysed the CCMO's decisions on two subgroups (studies involving MRI and non-therapeutic drug studies) and the preceding assessments of risks and burdens in depth.

RESULTS

Characteristics of the proposed studies

During the 7.5-year period analysed, the CCMO reviewed 165 proposals for paediatric research without direct benefit. The characteristics of the protocols can be found in table 1. Observational studies make up more than half of the total number (111). Some of them (23) would be used for developing or evaluating diagnostic tools or guidelines; others (19) for identifying predictors for developing disease, during long-term follow up. Fifty-one other observational studies were aimed to acquire more knowledge about specific diseases. There was a wide variety in the level of invasiveness of these studies, ranging from questionnaires, venipunctures and/or blood sampling from pre-existing intravenous (IV) cannulas, to more invasive or time-consuming procedures, such as psychologically invasive questionnaires, MRI, anorectal manometry, sugar absorption tests and airway hyperreactivity challenges, to even more invasive procedures, such as bone marrow punctures and biopsies (in children anesthetised for clinical reasons).

Fifty-four of the 165 proposed studies were intervention studies. Twenty-seven of these would not evaluate the effects of medicinal products but of nutrients, vaccines, devices or life-style modifications. The other 27 were non-therapeutic drug studies. Eighteen of these were early phase drug studies, examples of which can be found in tables 7, 9 and 10. The other 9 studies were aimed to acquire more knowledge about the age-related pharmacokinetics and dynamics of commonly (although often unlicensed or off label) prescribed drugs such as dexamethasone.

Table 2 presents the characteristics of the required participants. The majority of the studies would only involve children with the disease to be investigated. A considerable part (42%) though, would (also) involve healthy children. Some participants were healthy but with an increased risk for the disease or disorder to be investigated; e.g. after TB contact, or when having parents with allergy or a psychiatric disorder. Those children presenting themselves with complaints were always considered ‘children with disease’, also if these complaints were a risk factor for the disease to be investigated rather than symptoms of the disease itself. The category ‘other disease’ comprises studies with measurements in children anesthetised for other reasons.

Decisions: general

Of the 165 proposed studies, 108 (65%) did not immediately receive approval. They required revision (63) or were rejected (45). Thirty-three of the 63 protocols that were approved after revision only required completion, clarification and/or rephrasing of the information and informed consent forms. The other 30 required more essential modifications in order to fulfil all criteria for ethical research. These modifications were related to the lack of group relatedness (2), to failure to meet the general criteria for ethical research (15) and/or to risks and/or burdens that were not considered to be minimal (20) (table 3).

Most of the 45 rejected studies were rejected for more than one reason. All but 4 failed to fulfil one or more of the general criteria for ethical research; 15 studies were (also) not group related. Eighteen studies involved risks and/or burdens that were considered to exceed the minimal level. Of the 45 rejections, 10 were appealed, 15 were resubmitted once and 2 even twice. In total, this resulted in 13 more approvals, as is illustrated by figure 1.

The 38 studies with risks and/or burdens that were considered to exceed the minimal level

Table 4 presents the categories of risks and burdens that were considered to exceed the minimal level. One should note that 5 studies involved risks *and* burdens exceeding the minimal level. In a majority of the 38 cases, only the burdens were not considered to be minimal.

It is not completely clear when failure to fulfil the requirement of minimal risk and minimal burden led to rejection, and when approval of a modified protocol was considered an option. However, table 4 provides some indications. It shows that risks in 3 out of 4 cases led to rejection if they were not only considered to exceed the minimal level, but also more or less inherent to the study (such as adverse effects of the drug to be tested, or risks related to the techniques or procedures used). Studies that were time-consuming *and* involved several invasive procedures were also most likely to be rejected. As can also be concluded from table 5, the invasiveness of procedures in itself was rarely considered to provide sufficient reasons for rejection. Intervention studies relatively more often led to rejection than observational studies (table 6).

Seven of the 18 studies that were rejected were approved later on, after appeal, resubmission of a modified protocol, or modifications during the second review process (figure 2). Eleven (7% of 165) studies were definitively rejected. Table 7 shows the objectives, risks and burdens of these 11 studies. All but 3 (no. 3, 4 and 7) were also rejected for other reasons. Among the 11 studies, 4 (22%) of the 18 early phase drug studies could be found (no. 1-4). Regarding the observational studies, studies involving MRI in young children seemed problematic (no. 7 and 11). The in-depth analysis therefore has focussed on all studies involving MRI and all non-therapeutic drug studies.

In-depth analysis of two subgroups

General observations regarding the committee's assessment of risks and burdens

The CCMO always (also if other criteria could also not be fulfilled) evaluated whether the risks and burdens were minimal. With a few exceptions (for instance, very common adverse effects of a drug) it was always clear whether something should be considered a risk or a burden. Risks and burdens were listed in order to determine whether they could be considered minimal. Listings of risks were not very specific (e.g. 'risks related to this or that procedure'; 'risk for adverse effects') and not compared with those of routine examinations or daily life. Listings of burdens were more specific for they included all procedures and visits involved. Non-physical risks such as psychological, economic or social risks were not systematically checked but were identified several times. The committee based its decisions on internal debate and, incidentally, on consultation of external experts or site-visits.

Studies involving MRI

Out of the 165 proposed studies submitted to the CCMO, 17 (10%) involved MRI scanning. As can be concluded from table 8, the most common reason for this was to map the brains of children with specific diseases, often in comparison with healthy children.

Regarding the levels of risk of these studies, the committee decided that the scanning procedure itself does not involve clearly identifiable risks: claustrophobia and other possible forms of anxiety were not considered as risks but as burdens. The risk of administering contrast fluids was twice topic of debate, albeit without major consequences: the researchers had to make this risk more explicit in their proposal. The other 2 proposals for studies that involved administering contrast fluids were approved without debate, neither on the contrast fluid nor on the drugs that were also involved: dobutamine (MRI heart, for long-term follow up after cardiac surgery) and buscopan (MRI bowel, in order to compare MRI with conventional diagnostic techniques for IBD).

Another topic of debate regarding MRI-related risks was the risk of anaesthesia. From the beginning, the committee agreed that scans requiring anaesthesia could not be approved. This position has been held throughout the years and has played a role in one rejection and in one request for clarification (the scan appeared to be a prolonged diagnostic scan which means that the anaesthesia only had to be prolonged). The risk of light sedation, on the other hand, was considered to be minimal. The committee rejected the one proposal for scanning healthy sleeping children aged 1-5 (under, at most, light sedation) mainly because of the feasibility and burden of this study - would it be possible to scan these sleeping children? After a notice of appeal, despite arguments of committee members that the children would not understand the situation, in case of waking up during the scan and that approving this study would create a precedent, the study was to be approved under strict conditions (pilot study with local ethics committee member present and anxiety levels monitored). The researchers, however, refused to adopt these conditions.

After this debate, the committee has always felt that the burden of MRI scanning could not be considered minimal for children below 6. Some members were even in favour of a minimum age of 12 years old as inclusion criterion for non-therapeutic research involving MRI, arguing that only children over 12 years old are capable to cooperate and to comprehend what is going on. This position has in 2 cases resulted in approval with a modified age for inclusion. However, the acceptability of scanning children between 6 and 12 years old remained topic of debate. New proposals were submitted and followed by detailed discussions between the various committee members. Children in this age group, the committee argued, do not necessarily require anaesthesia in order to lie still for 30-60 minutes, but they would have a very difficult time. Moreover, such young children may be afraid for the narrow and noisy machine. Experts in the fields of radiology were consulted and a delegation of the committee has travelled to the main research group involved, for a site-visit. Eventually, the committee took up the position that children need to get used to the machine by means of a simulation scanner *and* have to be capable to distinguish this simulation scan from the real scan. Children below 8

were not considered capable of doing this and were consequently excluded. The committee members have formulated their conclusions in an evaluation framework to be used by themselves and by the local research ethics committees. This framework also includes the requirement that an independent monitor has to report on the wellness of the participants. So far, the evaluation framework has resulted in several more approvals of modified protocols.

Non-therapeutic drug studies

In first instance, 12 of the 27 non-therapeutic drug studies were considered to involve risks (7x) and/or burdens (9x) exceeding the minimal level. It is remarkable, that 11 of the 18 early phase drug studies (61%) were part of this group of 12.

Three studies were considered to involve more than minimal risk due to their design: 2 studies involved a risk of over- or underdosing of painkillers; the last study a euglycaemic clamp. In 4 cases, the adverse effects of the drugs to be tested were not regarded as minimal: once, for instance, because of the expected toxicity of a chemotherapeutic drug and once because adult studies had shown a considerable risk of vomiting. In many other cases the study drug had been administered to adults and/or (older) children previously and was only administered once or twice. Therefore, the risk of adverse effects was regarded as minimal. Statines, sildenafil, bosentan and lamotegrine are examples of drugs that were considered to involve minimal risk of adverse effects despite a study duration of 7 days or more.

Regarding the burdens of these 27 non-therapeutic drug studies, the number of invasive procedures and the time-consuming character were the CCMO's main concerns. Fifteen studies only involved a few venipunctures, or blood sampling from pre-existing IV cannulas in hospitalised children, which was not considered a problem. Three others involved a one-day-admission to hospital with an indwelling IV cannula for blood sampling, followed or preceded by 1-6 short visits including venipunctures. These burdens were also considered acceptable. Eight studies involved more days in hospital (occasionally overnight), more visits, and/or more invasive procedures. In the last study, admission to hospital was not required, but the participating children would have to undergo a muscle biopsy, several injections and MRI scanning. The burdens of all of these last 9 studies were considered to exceed the minimal level.

Eventually, only 4 of the 12 studies that were not considered to comply with the requirement of minimal risk and minimal burden were definitively rejected (table 7). Four others were approved after the investigators modified the protocol to reduce the burden or risk. The last 4 studies were approved despite the fact that even after attempts to decrease their burdens; these burdens could still not be regarded as minimal.

In 3 of these last 4 cases the committee eventually reasoned that the burdens could be considered minimal 'for the particular groups of patients' (table 9). The committee members did not agree on the question whether invasive procedures are indeed less burdensome for children that have experienced them before, but the expected results of these studies were considered very important and

the committee therefore wanted to avoid rejection. One of the 3 studies was, after long debate and a site-visit, approved as originally proposed (table 9, no. 1).[11] The risks and burdens of the second study were reduced before approval, but the burdens were, even after modification, still higher than what was generally considered minimal (no. 2). The third study was rejected for several reasons but approved after an appeal procedure (no. 3).

In the fourth case, the committee argued that upon consideration, the study could be regarded as a therapeutic trial (table 10, no. 1). It is worth noting that this is not an isolated case: the therapeutic/non-therapeutic issue has caused considerable debate between the CCMO and local committees, between the CCMO and investigators and between the committee members themselves. Table 10 provides some more examples of early phase drug studies that were difficult to classify as either therapeutic or non-therapeutic.

DISCUSSION

Regarding paediatric research without direct benefit for the participating subjects, ethics committees are charged with the difficult task to assess whether the risks and burdens are below a fixed threshold. In the Netherlands, this threshold is 'minimal risk and minimal burden'. I analysed the decisions of the Dutch Central Committee (CCMO) in order to evaluate (a) whether this requirement compromises the possibility to obtain the scientific data that are necessary for improving paediatric care (b) whether this requirement can provide a reliable threshold.

a. Obtaining the scientific data that are necessary for improving paediatric care

Thirty-eight (23%) of the 165 proposed studies were rejected (18) or only approved after the investigators modified the protocol (20), because the CCMO did not consider their risks and/or burdens minimal. Seven of the 18 studies that were initially rejected, were approved after appeal or resubmission of a modified protocol. Eleven studies (7% of 165) were definitively rejected.

The CCMO's interpretations of minimal risk and minimal burden do not seem conservative: several procedures that are regarded as minimal risk/burden by the CCMO, are according to the EU recommendations, 'a minor increase over minimal risk' (e.g., peripheral venous lines; MRI for children above age 8; airway hyperreactivity challenges; use of contrast fluids).[4] This means that it is not likely that the number of rejections based upon the requirement of minimal risk and minimal burden is unnecessarily high. Theoretically, it could even have been higher: some international investigators may have decided not to submit their study in the Netherlands (anticipating the consequences of the requirement of minimal risk and minimal burden, which has not in all European countries been incorporated in the national law).

It is important to note though, that 8 of the 11 rejected studies were also rejected for other reasons (e.g., no sound methodology), which means that they would have been rejected regardless of

the requirement of minimal risk and minimal burden. In other cases the prospect of direct benefit seemed to be present or seemed to be possible after modifying the design. In other words: not every rejection based upon the requirement of minimal risk and burden, compromises the possibility to obtain necessary scientific data.

However, I have also found examples of studies without direct benefit that could not comply with the requirement of minimal risk and minimal burden and that could truly generate important data that could not be obtained otherwise. These studies are not on the list of studies that were definitely rejected: they were considered so important that the committee felt it had to resort to 'flexible' interpretations of the concepts involved.

b. Minimal risk and minimal burden: a reliable threshold?

Minimal risk and minimal burden

The in-depth analysis of the decisions on all 27 non-therapeutic drug studies and all 17 studies involving MRI, showed that the committee managed to assess very consistently whether the requirement of minimal burden was met. Early phase drug studies involving more than one day hospital admittance, for instance, were never considered a minimal burden. The same applies to MRI scans for children below 8 years old. The fact that 4 early phase drug studies were eventually approved despite burdens that were not considered minimal, does not prove a lack of consistency: that has got more to do with *applying* the requirement than with *assessing* whether protocols comply with it. It looks as if the committee in these cases felt that applying the requirement consistently would not lead to an optimal balance between the ethical demand to prevent harm to participants and the ethical demand to improve care by conducting research.

Regarding the risks, consistency was more difficult to assess than regarding the burdens, because the committee often listed procedures (and/or medicinal products) rather than the harms they could possibly cause and the chance that this would happen. IV cannulas, light sedation and use of contrast fluids were always considered minimal risk though, whereas central venous lines and anaesthesia solely for research reasons were not.

This consistency is in contradiction with a study conducted in the United States.[5] Shah and colleagues presented a series of hypothetical research vignettes to 188 IRB chairpersons and asked them to categorise the risks involved (minimal, a minor increase over minimal, or more) if the research participant was a healthy 11-year-old. They reported that the chairpersons' assessments differ widely and concluded that the 'daily life' and 'routine examinations' standards must be replaced by better standards because the children involved in such studies otherwise may be insufficiently protected.

The present study shows that the concepts of 'minimal risk' and 'minimal burden' can, at least within one (very experienced) committee, provide a reliable threshold in case of actual research protocols and group discussions. In my view the separate assessment of risks and burdens is one of the main reasons contributing to this as this creates a transparent overview of all possible harms and discomforts. Another important factor may be that the committee did not attempt to compare research

risks or burdens with those of daily life or of routine examinations. The interpretations used by the committee rather resemble (slightly more permissive) versions of the ones provided by the European Convention on Human Rights and Biomedicine. The Additional Protocol to this Convention states that 'minimal risk' applies if a study 'will result, at the most, in a very slight and temporary negative impact on the health of the person concerned' and 'minimal burden' if 'it is to be expected that the discomfort will be, at the most, temporary and very slight for the person concerned.'[12] Such interpretations are based on the factual meaning of 'minimal' rather than on an external standard, which leaves less room for ambiguity: one the one hand they are related to the individual participant (in the sense that the negative impact and discomfort must be temporary and very slight for *that* person); on the other hand they are absolute (in the sense that the negative impact and discomfort may not be higher for a sick child, merely *because* he suffers a lot in daily life as well).

The prospect of direct benefit

Although risks and burdens were, as far as this could be evaluated, assessed fairly consistently, it was not always clear to the committee whether a study could be considered a study with 'the prospect of direct benefit', i.e., whether the risks and burdens of a study *should* be minimal.

Taking the complexity of some protocols for drug development into account, this is not surprising. The committee has adopted the principle, that early phase drug studies (phase I and sometimes phase II) are non-therapeutic (i.e., cannot provide direct benefit) and phase III drug studies are therapeutic (i.e., can provide direct benefit). However, some early phase drug studies can provide direct benefit despite their clearly non-therapeutic objectives, because no or insufficient other treatment options exist for the participants. The 'net' research risks and burdens (i.e., those research-related risks and burdens that are not compensated by direct benefits) are in such cases lower than it may seem. On the other hand, some phase III drug studies entail considerable 'net' research risks and burdens, because their possible benefits do not outweigh all risks and burdens caused by the placebo-components, medicine wash-outs and/or additional blood sampling, scans and visits.

The consequences of the fact that the dichotomy is not as sharp as suggested are serious: participants may be underprotected in case such complex studies are evaluated as studies with the prospect of direct benefit, and important research may be needlessly rejected in case they are evaluated as studies without the prospect of direct benefit.

RECOMMENDATIONS

Three observations deserve serious consideration:

1. The dichotomy between studies with and studies without 'the prospect of direct benefit' is not always accurate enough to identify those research-related risks and burdens that are not compensated by direct benefits and that should therefore be minimal. (p.14)
2. When assessing research risks and burdens, the committee often only lists procedures (and/or medicines), which does not always provide enough insight in the actual risks of a study. (p.13)
3. Some data that are necessary for improving paediatric care cannot be obtained (with direct benefit or) with minimal risk and minimal burden. (p.13)

In this section, I will recommend for each of these problems a possible solution.

1. Component analysis should be used for identifying risks/burdens that have to be minimal.[†]

The dichotomy between studies with and studies without 'the prospect of direct benefit' is not always accurate enough to identify those research-related risks and burdens that are not compensated by direct benefits and that should therefore be minimal. Component analysis (be it the 'component analysis approach' or the 'net risk test') seems a more promising method for doing so.[13-15] This method is based on the assumption that studies often contain a mixture of components with and components without direct benefit. Analysing these various components individually provides insight in the 'net' risks and burdens of a study.

2. Risk assessment should be carried out more systematically.

When assessing risks and burdens, the committee usually lists the procedures (and/or medicines) that are part of a study, without the harms they may cause and the chance that this will happen. Such lists provide a lot of insight in the research burdens, which has in the time period studied, resulted in very consistent assessments of these burdens.[‡] However, such lists do not always provide enough insight in the actual risks of a study. Risk assessment may gain from a more systematic approach. For each component of a proposed study, possible harms (physical, psychological, economic and/or social) may be identified based on clinical and theoretical data. The chance that they will happen can often be estimated. Another step that may provide more insight, also in de research burden, is to separate in the format for pre-advices the question whether risks and burdens can be further minimised from the question whether they are minimal in the absolute sense. The item called 'risks and burdens' could for instance be subdivided into two questions: 'can the objectives be accomplished with lower levels of risk and burden' and 'are the risks and burdens minimal'.

[†] Implementation of this recommendation would require modification of the Medical Research with Human Subjects Law.
[‡] It must be noted that the fact that the assessments were consistent, does not automatically mean that they were right/just - more empirical data on children's anxiety and distress related to various procedures are needed.

3. Higher levels of risk and/or burden should be considered acceptable under strict conditions.[§]
Some data that are necessary for improving paediatric care cannot be obtained with direct benefit or with minimal risk and minimal burden. So far, the committee coped with this problem by occasionally resorting to 'flexible' interpretations of the concepts involved. However, the CCMO is assigned to apply the Dutch law and although ethical considerations are of utmost importance, the decisions of the committee have to fit in with this legal framework. If this framework seems inadequate, the need for revising the law must be discussed.

Unfortunately, merely adopting the recent EU recommendations (for implementing the Clinical Trials Directive), will not provide the optimal solution.[4] Firstly, allowing 'a minor increase over minimal risk' in all non-therapeutic drug studies with 'benefit for the group' may unnecessarily compromise the protection of research subjects. I have shown that the objectives of many drug studies can be accomplished with minimal risk, when faced with this absolute requirement. In other cases, (major) changes in the study design may create direct benefit. More importantly, there may also be studies that cannot comply with the requirement but can also not produce 'benefits for the group' that are important enough to justify a higher level of risk. This means that a higher level of risk is only acceptable in exceptional cases.

Secondly, allowing a minor increase over minimal risk in drug research may not completely solve the problem. One of the 'important' studies I described, involved a muscle biopsy (table 9, no. 1). Biopsies are generally considered to pose *more* than a minor increase over minimal risk.[4] What to do in such cases? Furthermore, the CCMO often considered the research burden to exceed the minimal level implying that guidance should not only focus on risks. Last but not least: not all studies that were definitively rejected because of the requirement of minimal risk and minimal burden were drug studies. The fact that the CCMO also almost approved one of the rejected observational studies, despite its more than minimal burden (MRI scanning in children 1-5 years old), illustrates that the committee struggles with non-drug studies as well.

A more promising option seems to maintain the basic principle (minimal risk and minimal burden) but occasionally allow for exceptions. Further discussion is required to establish under which specific conditions higher levels of risk and burden are acceptable. On the basis of this project, I recommend two conditions: 1) that the data-to-be-obtained are truly necessary for improving paediatric care, and 2) that these data cannot be obtained with less 'net' risks and burdens. The first condition may be further specified in relation to the disease burden, the available treatment options, and in case of drug research, the expected risk/benefit ratio of the drug (based on adult studies and/or theoretical evidence). The second condition seems obvious for this actually is one of the well-known general criteria for ethical research. However, some more pressure on this general criterion would be very welcome considering the fact that (pharmaceutical) investigators in these days often have other interests as well.

[§] Implementation of this recommendation would require modification of the Medical Research with Human Subjects Law.

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Table 1. Characteristics of protocols.

	Number of protocols (%)
Initiated by	
Academia/hospital	128 (78%)
Pharmaceutical industry	28 (17%)
Semi-governmental organisations	4 (2%)
Other	5 (3%)
	165 (100%)
Centres	
Single-centre	111 (67%)
Multi-centre	30 (18%)
Multi-centre, international	24 (15%)
	165 (100%)
Type of research	
Intervention studies	
Non-therapeutic drug studies	
Early phase drug studies	18 (11%)
Other	9 (5%)
Other non-therapeutic intervention studies	
Nutrients	13 (8%)
Vaccine development	9 (5%)
Devices and/or other non-drug treatments	4 (2%)
Life-style modification	1 (1%)
Observational studies	
More knowledge about specific diseases	51 (31%)
Diagnostic tools or guidelines	23 (14%)
Predictors for developing disease (long-term follow up studies)	19 (12%)
Direct and/or long-term harmful effects of a disease and/or its therapy	15 (9%)
Healthy controls in therapeutic drug studies	3 (2%)
	165 (100%)

Table 2. Characteristics of participants to be involved.

	Number of protocols (%)
(Dutch) Participants needed	
<20	47 (28%)
20-50	36 (22%)
51-100	27 (16%)
100-200	21 (13%)
>200	34 (21%)
	165 (100%)
Health status participants	
Only with disease to be studied	95 (58%)
Only healthy children	33 (20%)
Both children with disease to be studied and healthy children	30 (18%)
Other disease, or healthy but with increased risk of certain disease or disorder	2 (1%)
Combination of these groups	5 (3%)
	165 (100%)
Age of participants	
Newborns born <28wks and/or 750gr	7 (4%)
Preterm newborns	15 (9%)
Term newborns	17 (10%)
1-23 months	45 (27%)
2-5 yrs	54 (33%)
6-8 yrs	79 (48%)
9-11 yrs	88 (53%)
12-15 yrs	96 (58%)
16-18 yrs	72 (44%)

Table 3. Reasons for decisions.[i]

	Approval after modifications. Total number: 30[ii]	**Rejection. Total number: 45**[ii]
Requirement of minimal risk and burden	20	18
Requirement of group relatedness	2	15
General criteria for ethical research	15	41

[i] First submissions. Total number of studies: 165. Fifty-seven were directly approved and 33 of the 108 that were not directly approved only required completion and/or clarification.

[ii] For most decisions, more than one reason was provided.

Table 4. Risks and burdens that were considered to exceed the minimal level.

	Protocols approved after modifications regarding this type of risk or burden. Total number: 20.[i]	Protocols rejected because of this type of risk or burden. Total number: 18.[ii]
Type of risk		
Adverse effects of a (new) drug	1	3
Risks related to the procedures or techniques used (e.g. anesthesia)	1	3
Anaemia (after frequent blood sampling for several weeks)	-	1
Over- or underdosing of painkillers	3	-
Therapeutic misconception	2	-
	7	**7**
Type of burden		
Time-consuming and many or very invasive procedures	3	6
Many or very invasive procedures	3	3
MRI	4	1
Airway hyperreactivity challenges	2	1
Many or psychologically invasive questionnaires/tests	2	1
Spending several days in research institute (no hospital)	-	2
Burden of getting diagnosed with an untreatable disease	-	1
	14	**15**

[I] One protocols involved both risks and burdens exceeding the minimal level.
[ii] Four protocols involved both risks and burdens exceeding the minimal level.

Table 5. Decisions on the observational studies acquiring more knowledge about specific diseases.

	Total number of studies: 51 [i]	Modification required because of risk	Rejected because of risk	Modification required because of burden	Rejected because of burden
X rays, blood sampling from pre-existing IV cannulas, questionnaires and/or 1-5 venipuncture(s)	32	-	-	-	1
Psychologically invasive tests	3	-	-	1	1
MRI	3	-	-	1	1
Anorectal manometry	2	-	-	-	-
Sugar absorption test	1	-	-	-	-
Hyperreactivity challenges (airway or food)	4	-	-	-	1
Bone marrow puncture (in children anesthetised for strabismus or inguinal hernia repair surgery)	1	1	-	-	-
Biopsy (skin, palate or bowel) (in children anesthetised for clinical reasons)	5	-	-	-	-

[i] This analysis was done in the group of 51 observational studies 'acquiring more knowledge about specific diseases' for most of these studies only involved several common procedures or one major procedure. The studies were categorised according to these procedures.

Table 6. Decisions based upon risk and/or burden, per type of study.

	Number of protocols	Approval after modifications	Rejection	Definitive rejection
Intervention studies				
Non-therapeutic drug studies				
Early phase drug studies	18	4	5	4 (22%)
Other	9	0	1	0 (0 %)
Other non-therapeutic intervention studies				
Nutrients	13	1	2	1 (8%)
Vaccine development	9	1	0	0 (0%)
Devices and/or other non-drug treatments	4	0	1	0 (0%)
Life-style modification	1	0	0	0 (0%)
Total	54	6 (11%)	9 (17%)	5 (9%)
Observational studies				
More knowledge about specific diseases	51	4	4	4 (8%)
Diagnostic tools or guidelines	19	5	1	1 (5%)
Predictors for developing disease (long-term follow up studies)	15	2	2	1 (7%)
Direct and/or long-term harmful effects of a disease and/or its therapy	23	2	1	0 (0%)
Healthy controls in therapeutic drug studies	3	1	1	0 (0%)
Total	111	14 (13%)	9 (8%)	6 (5%)
Total	**165**	**20 (12%)**	**18 (11%)**	**11 (7%)**

Table 7. The 11 studies that were definitively rejected because of their risks and/or burdens.

	Objectives	Subjects	Main risks	Burdens	Reason for def. rejection
1	Defining PK, PD and efficacy (6 weeks) of rectal compared with oral treatment	Infants with reflux disease	Over- or underdosing	48 hours hospital admission for oesophageal pH monitoring and an IV cannula for sampling	Burdens and general criteria
2	Defining single dose PK and PD of a new cholesterol lowering drug combination	Children aged 10-17 with familial hyper-cholesterolemia	Adverse effects	5 visits and venipunctures (VP's); 2 one-day-admissions with IV cannula for sampling	Burdens; not group related; general criteria
3	Defining PK and safety of a new antiretroviral drug	Children aged 6-18 with HIV	Adverse effects	10 visits and VP's; 2 one-day-admissions with IV cannulas for sampling	Risks and burdens
4	Defining maximum tolerated dose, safety, PK and efficacy of a new cytostatic agent	Oncology patients aged 1-21 with very poor prognosis	Adverse effects (and anaemia)	10 visits and VP's; 3 one-day-admissions with IV cannulas for sampling; MRI	Risks and burdens
5	Defining the influence of various nutrients on the gastro-intestinal system	Healthy children aged 3-5	Gastro-intes-tinal adverse effects	4x one day in a research institute; 4x 0.25L soda; 4x fasting before/after	Burdens and not group related
6	Acquiring more insight in neonatal hypoglycaemia	Newborns with suspected hypoglycaemia	Related to VP's	5 VP's on first day of life	Burdens and general criteria
7	Mapping normal brains for comparison with scans of children with a disease	Healthy children aged 1-5	None	MRI (in sleeping children - no anaesthesia)	Burdens
8	Determining prevalence and variability in presentation of a rare eye disease	Patients and all their family members	Insurance issues (after diagnosis)	VP; fundoscopy; getting diagnosed with an untreatable disease	Burdens; not group related; general criteria
9	Acquiring insight in the mechanism that protects children's airways	Children aged 6-18 years with long disease	Airway hyper-reactivity	Skin prick test; airway hyperreactivity challenges and long function tests	Burdens and general criteria
10	Evaluating whether the position of pH catheters can be determined by manometry	Severely disabled children aged 2-18	Related to insertion of oesophageal catheter	Prolonged oesophageal pH monitoring; extra (manometry) catheter	Burdens and general criteria
11	Evaluating the relation between cerebral morphology and development of the child	Children aged 1-4 with cerebral palsy	Related to anaesthesia	3x 3 hour-visit to hospital; development tests; MRI (under anaesthesia)	Risks and general criteria

Table 8. Reasons for MRI scanning.

Reasons for MRI scanning	No
Screening and/or evaluating effect of treatment for muscle disease or malignancy.	2
Comparing MRI with conventional diagnostic techniques, for diagnosis of bowel disease, malignancy or hydrocephalus.	3
Identifying predictors for developing psychosis, during long-term follow up studies.	2
Mapping brains of children (and/or of healthy controls) with velocardiofacial syndrome, cerebral palsy, learning disorders following meningitis, or psychiatric disorders.	7
Evaluating long-term effects of cardiac surgery.	3

Table 9. The 3 early phase drug studies with burdens that were considered minimal 'for these patients'.

	Objectives	Subjects	Main risks	Burdens	Decision
1	Defining safety and local effect (proof of concept) of a potential gene correction therapy	Children aged 8-16 with a severe and progressive muscle disease	Adverse effects of the drug and risks related to the biopsy	Visits; 4 VP's; MRI; drug injections; muscle biopsy	Directly approved
2	Defining tolerance, PK and activity of a new maintenance antibiotic	Children aged 12-18 with a common but severe chronic multisystem disease	Adverse effects	120 hours in hospital; IV cannulas for sampling; 6 VP's	Tolerance tested in adults first, less VP's and time in hospital (but still more than what was otherwise considered minimal)
3	Defining PK of 2 single oral doses of a cholinesterase inhibitor	Children aged 9-16 with a common chromosomal disorder that may involve dementia	Adverse effects	3 visits; 2 one-day-admissions with IV cannulas for sampling	Approved after appeal

Table 10. Examples of studies that are difficult to categorise as either therapeutic or non-therapeutic.

	Objectives	Subjects	Main risks	Burdens	Decision
	Studies evaluating a new route of drug administration, with safety or PK as main outcome parameter.				
1	Evaluating safety, PK and PD of an alternative route of growth hormone administration, compared with injections	Children aged 6-18 in need of growth hormone replacement therapy	Over- or underdosing; adverse effects related to the specific route of administration	2 weeks of new route *and* injections (double placebo); 2x2 and 2x1 nights in hospital; 2 VP's; IV cannulas for sampling (51x); long function tests	Approved (therapeutic study)
2	Defining PK, safety and efficacy of a controlled release painkiller, compared with immediate release	Intensive care patients aged 6-16	Over- or underdosing	Multiple blood samples from IV cannula (finger sticks or VP's if cannula is not available)	Approved ('therapeutic study, on an individual level')
3	Defining PK, PD and efficacy (6 weeks) of rectal treatment, compared with oral	Infants with reflux disease	Over- or underdosing	48 hours hospital admission for oesophageal pH monitoring and an IV cannula for sampling	Rejected (non-therapeutic study; burdens and general criteria)
	Other early phase drug studies with possible benefit for the participants.				
4	Evaluating feasibility, safety, tolerability, engraftment kinetics and effects of co-transplantation of two types of stem cells	Children scheduled for stem cell transplantation	Graft versus host and other immuno-logical reactions	VP's; additional bone marrow samples	Approved (therapeutic study)
5	Defining PK and safety (12 weeks) of a new drug for children with a specific pulmonary vascular disease	Children with the disease aged 2-12	Adverse effects	6 visits; 1 one-day-admission with IV cannula for sampling; 1 VP	Approved ('might be therapeutic study')
6	Defining maximum tolerated dose, safety, PK and efficacy of a new cytostatic agent	Oncology patients aged 1-21 with very poor prognosis	Adverse effects (and aneamia)	10 visits and VP's; 3 one-day-admissions with IV cannulas for sampling; MRI	Rejected (non-therapeutic study; risks and burdens)

Figure 1. Decisions on the 165 protocols.

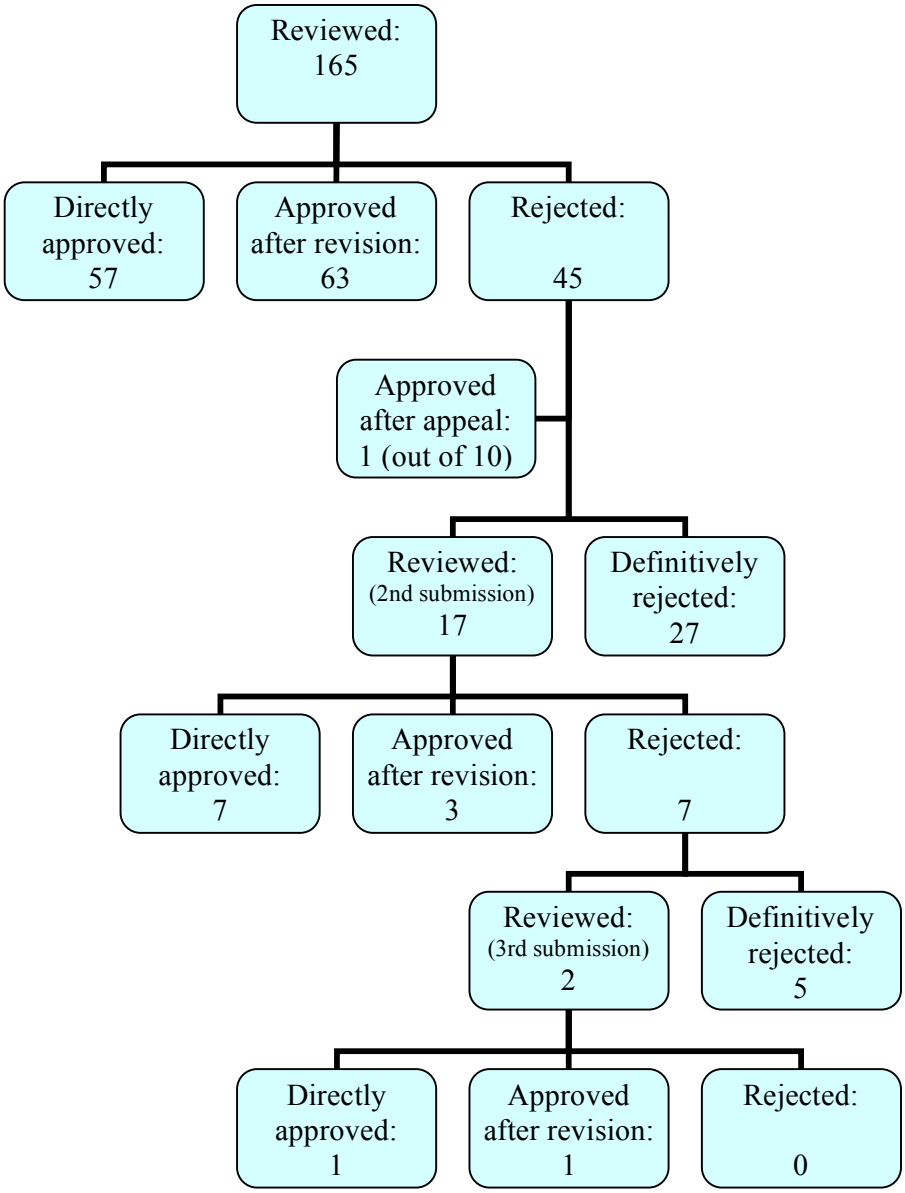

Figure 2. Decisions on the 18 studies that were rejected because of their risks and/or burdens.