What do research ethics committees say about applications to conduct research involving children?

Emma Angell, Research Associate, Social Sciences Research Group, Department of Health Sciences, University of Leicester, Leicester LE1 7RH, tel: +44 (0)116 229 7256, fax: +44 (0)116 229 7250, email: elj1@le.ac.uk [CORRESPONDING AUTHOR]

Hazel Biggs, Professor of Medical Law, School of Law, University of Southampton, Highfield, Southampton, SO17 1BJ, H.biggs@soton.ac.uk

Florian Gahleitner, Children’s Department, Leicester Royal Infirmary, Infirmary Square, Leicester, LE1 5WW, florian.gahleitner@doctors.net.uk

Mary Dixon-Woods, Professor of Medical Sociology, Social Sciences Research Group, Department of Health Sciences, University of Leicester, Leicester LE1 7RH, md11@le.ac.uk

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ABSTRACT

Objective
To identify issues raised by Research Ethics Committees (RECs) in letters about applications to conduct research involving children.

Methods
Analysis of 80 provisional and unfavourable opinion decision letters written by RECs in response to applications to conduct research involving child participants.

Results
RECs were most likely to be concerned about issues relating to consent, recruitment, care and protection of participants, scientific design, and confidentiality. RECs focused on children’s status as ‘vulnerable’. They sought to ensure that children would be protected, that appropriate written language would be used to communicate with children and that an appropriate person would give consent for children to participate.

Implications
Researchers should be attentive to issues of potential vulnerability when preparing applications. REC letters may be improved by giving clear and explicit reasons for their opinions.

Abstract word count: 131
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The potential for children to be involved in research is changing rapidly, not least because of growing dissatisfaction with the quality of the evidence-base for children’s medicines, disquiet at continued prescribing of unlicensed, “off label”, or unsuitable formulations, and changes in the regulatory and policy environment for drug development and testing of paediatric therapies. However, distinctive ethical issues arise in conducting health-related research involving children.

Ethical review of studies involving children must be conducted by a Research Ethics Committee (REC). When it first reviews an application, an NHS REC can issue one of three “opinions”: favourable, provisional, or unfavourable (Box 1). When reviewing applications, RECs are charged, among other things, with assessing the arrangements for consent to research. These vary depending on whether the study is a Clinical Trial of an Investigational Medicinal Product (CTIMP), and thus is governed by the Medicines for Human Use (Clinical Trials) Regulations 2004. The Regulations provide that parents or those with legal responsibility for children under 16 must give consent for a “minor” taking part in a trial, and that such consent represents the child’s “presumed will”. National Research Ethics Service (NRES) guidance on research involving children specifies that for trials, “children should [...] be asked for their assent, if appropriate”. However, assent is not a legally valid concept for purposes of the Regulations, and its use therefore has an ethical rather than a legal basis. For non-CTIMPs, UK law is untested. NRES guidance advocates the principle of Gillick competence, though this was developed in the context of treatment rather than research. This allows children who are felt to be competent to consent for themselves (usually if they are aged 10 years or older).

Little is known about the issues that concern RECs when reviewing applications to conduct research involving children. We aimed to analyse decision letters written by RECs in response to their reviews of applications for paediatric studies.
METHODS

We analysed 80 randomly sampled letters (see Box 2) issued by NHS RECs in the UK to applicants following the first meeting at which an application was considered. Ethnographic content analysis was applied based on a previously developed framework that was modified in response to the new data in this project. Data were assigned to analytic categories using explicit category specifications, facilitated by QSR N6 software. Statistical analysis was not appropriate given the small numbers in our sample, but it was possible to offer simple counts of findings in particular categories.

Our project was deemed by NRES not to require research ethics committee review as it was considered to be service evaluation. Letters were fully anonymised before analysis.

RESULTS

There were 2261 applications for ethical approval to conduct research involving children in our sampling frame that met our inclusion criteria. The 80 randomly-sampled letters were about applications to conduct a variety of study types (Table 1), with most receiving a final favourable opinion (Table 2).

Ethical issues raised

Of the 80 letters, 59 identified ethical troubles specifically related to child participants. These 59 letters are the focus of the following analysis. Many (48, or 81% of the 59 letters) were concerned with the potential vulnerability of child participants, and raised issues including: use of child-friendly language; responsibility for consent; and the need for special protection of children.
Child-friendly language

Issues specific to written language for children were raised in 68% (40/59) of the letters. In 16 letters there were concerns about ‘young’ children, 17 raised concerns about ‘older’ children and 24 raised concerns about children of any age. Three letters recommended that researchers consult external guidelines when amending their information sheets.

*The Committee felt that the Information sheet for Young Persons was generally too complicated for an 8-year old child and would like it revised using simpler language.*

*(Pid0025, non-CTIMP, provisional opinion then favourable)*

Responsibility for consent

Discussion about who should give consent was included in 24% (14/59) of the letters. Of these, four letters suggested that a child’s wishes should override those of a parent or carer, and explicitly stated that children should not be enrolled into studies if they did not wish to take part, regardless of parental wishes. Eight letters stated that children should sign their own consent form. There was some evidence of concern about what would happen if only one parent gave consent.

*Children should be encouraged to sign a consent form and a suitable document should be produced.* *(Pid0077, non-CTIMP, unfavourable opinion)*

Four letters made reference to children’s assent being obtained.

*[There] should be a consent form for parents and older children who are consenting in their own right, and for minor children below the age of consent (in addition to the parental consent form), an assent form.* *(Pid1316, CTIMP, provisional opinion then favourable)*

Protecting children

Specific concerns about children needing protection were raised in 31% (18/59) of the letters. As well as ‘child protection’ issues (in seven letters), four letters prescribed that children should be excluded from studies, five suggested that children should be protected from the burden of
participation, three specified that an adult should be present during study procedures, and six queried what would happen if distress was caused.

*The study will be a good student project, but the design is more complicated than it needs to be, particularly as the children may become distressed at being asked some of the questions.*

(Pid1703, non-CTIMP, provisional opinion then favourable)

**DISCUSSION**

When RECs raised issues specifically concerning children, as they did in nearly three-quarters (59/80) of letters we analysed, they tended to focus on children’s status as ‘vulnerable’. They sought to ensure that written language that was to be used to communicate with the child participants was appropriate, and expressed concerns about consenting procedures, and emphasised the need for children to be protected in research. These findings suggest that applicants to conduct research involving children should be attentive to these issues: RECs will be looking for evidence that applicants are aware of the ethical issues raised by research with children, including evidence that they have given explicit attention to how children’s particular vulnerabilities will be sensitively handled and that they have thought carefully about how to communicate with children.

Our study design does not allow us to analyse the materials submitted to RECs. It is thus difficult to comment on how far the absence of comments on particular issues reflects RECs’ perception that all was well with the application, or how far it might reflect a lack of attention by RECs to these issues.

Our data suggest that there are a number of areas where REC advice may be in addition to or different from what is required by law. The concept of assent has not been tested in law. The need for, and effect of, children’s signatures to indicate consent, or the suggestion the child’s wishes should take precedence over those of the parents, also has no authority in law. Similarly, CTIMP Regulations require only the consent of one person with parental responsibility. Thus, while RECs...
may express concern about obtaining consent from only one parent, the law would find it unproblematic. Of course, ethical practice may well impose requirements above and beyond those demanded by law, but it might be helpful if RECs clearly indicated whether their advice is in addition to legal requirements, especially when RECs are drawing on their own authority to make ethical decisions.⁹ RECs should, as far as possible, make the reasoning behind their advice clear and explicit, and refer to any published guidance on which they are drawing in coming to their conclusions.
Box 1: Decisions a REC can make on first review of an application

A ‘favourable’ opinion means that an application is approved without further revisions; these constitute ~17% of decisions made by RECs at first consideration of an application.

‘Provisional’ opinions constitute ~66% of decisions at first review, and require applicants to make a response addressing issues raised in the letter before a final opinion can be issued. The final opinion may be either favourable or unfavourable.

An ‘unfavourable’ opinion (~8% of all submissions) at first review amounts to a rejection.
**Box 2: Description of letters**

*Data source:* NRES Research Ethics Database

*Timeframe:* 1st March 2004 (when the database began) to 22 December 2006 (when the data were provided)

*Sample size:* 80 letters (chosen for pragmatic reasons)

*Inclusion criteria:* Letters relating to applications where the applicants had indicated (via a tick box on the application form) that their project involved the recruitment of children under the age of 16; letters that communicated a provisional opinion or an unfavourable opinion at first review.

*Exclusion criteria:* Letters communicating favourable opinions (as they contain no requests for changes, and offering little opportunity for analysis); letters where the final outcome of the application was unknown; letters in response to requests for protocol amendments and site-specific assessments.
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Competing interests
None.

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What is already known about this topic?

1. There is now considerable momentum for increased research with children but there is some variability in the guidance available on ethical issues in involving children in research, and this guidance sometimes differs from legal requirements.

2. Every project involving children to be undertaken in the NHS must first be reviewed by a research ethics committee, but little is known about the child-specific issues that RECs raise in their reviews.

What this study adds

1. RECs tended to focus their concerns on the children’s status as ‘vulnerable’.

2. Applicants might increase their chances of achieving a favourable opinion by being explicit about how they will handle these vulnerabilities and RECs’ letters should give clear and explicit reasons for their opinions.

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References


### Tables

**Table 1: Types of applications involving children**

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Number (%) of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trial of an investigational medicinal product (CTIMP)</td>
<td>8 (10%)</td>
</tr>
<tr>
<td>Non-CTIMP</td>
<td>72 (90%)</td>
</tr>
<tr>
<td>Educational</td>
<td>33 (41%)</td>
</tr>
<tr>
<td>Commercial</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Publicly funded</td>
<td>31 (39%)</td>
</tr>
<tr>
<td>Establishing a database</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Taking new tissue</td>
<td>12 (15%)</td>
</tr>
<tr>
<td>Accessing stored tissue</td>
<td>3 (4%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong>*</td>
<td><strong>80 (100%)</strong></td>
</tr>
</tbody>
</table>

* The sum of study types does not equal 80 as some applications were specified as more than one type, e.g. a commercially-sponsored CTIMP.
**Table 2: Application decisions**

<table>
<thead>
<tr>
<th>Decision</th>
<th>Number (%) of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provisional opinion then favourable</td>
<td>72 (90%)</td>
</tr>
<tr>
<td>Provisional opinion then unfavourable</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Unfavourable opinion at first review</td>
<td>6 (8%)</td>
</tr>
</tbody>
</table>