European network of paediatric research at the European Medicines Agency

Tuesday 30 August 2016

Consultation on the revision of "Ethical Considerations for Clinical Trials on Medicinal products Conducted with Minors": a response from Enpr-EMA and partners

Introduction

The EU Clinical Trials Regulation 2014 (CTRs) offers a great opportunity to improve research involving children. The supporting document "Ethical Considerations for Clinical Trials on Medicinal products conducted with Minors" is crucial to its implementation and achieving the Regulations' aims to facilitate research and promote the health of our children and young people (minors).

This document represents the response from Enpr-EMA, its working groups (including representatives of networks, National Competent Authorities and pharmaceutical industry), and partners. It was led and drawn up by Hugh Davies (European Forum for Good Clinical Practice), Pirkko Lepola (Finnish Investigators Network for Pediatric Medicines, chair Enpr-EMA working group on Ethics) and Martine Dehlinger-Kremer (chair paediatric working group of EUCROF and member of EFGCP Children Working Party); then circulated to Enpr-EMA members and partners for their comments.

It is in two parts:

Part 1: General comments on guidance layout and content

Part 2: Specific comment on the text in the guidance with recommendations at the end of each

Executive summary

1. This document must be written for all audiences, researchers, regulators, research ethic committees, but more importantly families and children.
2. To improve readability, use of modern technology would allow the text to be layered providing easier reading and increasing detail.
3. This guidance should

- be built around text from the regulations in each section
- offer advice on the interpretation of the regulations.
- seek and include evidence and practical examples wherever possible (we have tried to add some) .

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- call for more research

4. This guidance could profitably be built around "Principles underpinning ethical conduct of CTIMPS involving minors".

- Children have vulnerabilities both as research participants and as recipients of unresearched care so fair balance must be struck between the two.
- Minors (children, young people and their families) should be involved in research from inception, in its design and the material to be used.
- Research involving minors must be preceded by careful risk assessment (benefits and harms) and then management.
- The arrangements for consent, assent and recognising dissent require specific consideration in clinical trials involving minors.
- Extrapolation of adult data is possible but this must be done with due care.
- Those conducting research involving minors should have appropriate expertise.
- Those reviewing research involving minors should have appropriate expertise.
- Openness and transparency are important parts of ethical research.

Part 1: General comment on content and layout

General comment

We feel this document is very complicated and lengthy with repetition on some issues. All these will cause difficulties for readers of different audiences (**this must include families and participants**). We are sorry to be making such criticism and are keen to help and would be happy to be contacted for further collaboration.

Use of modern technology would allow the text to be layered providing increasing detail. It could start with a simple A4 size table (for those with limited time) of principles underpinning ethical conduct of CTIMPS (Clinical Trials with Investigational Medicinal Products") involving minors with hyperlinks in this table to more detailed text. The table would be a "summary" laying out questions researchers should ask of themselves and reviewers might use in review, along with considerations that arise. The text could contain links to more information. Alternatively it could be developed as a web page similar to http://www.reviewingresearch.com/clinical-trials-involving-minors-children-and-young-people/.

When looking at specific groups the question was raised whether "orphans" should be considered as a separate group -

"in some non-EU countries there are limitations on involvement orphans in clinical trials; the addressing this population in the EU regulations would also be a good incentive for non-EU regulators to change their approaches to stay harmonized with the EU legislation."

Comment was also received on "emancipated" minors and whether these warrant specific reference.

Further and specific comments on text

1. **A definition for DISSENT** is missing from the glossary. We would like to add this definition to the glossary as it is used in many subsequent parts of the guidance

Dissent means the expression of the minor's will not to participate,

2. **Permissible suggested sample sizes.** We believe a sample collection table should be inserted. We do recognise that evidence for this is limited but believe some guidance is necessary

Age group	**Weight (kg)**	**Normal daily fluid requirement (ml)**	**Circulating total blood volume (ml) – TBV (approx. 80-90 ml / kg, 100ml/kg neonates)**	**Maximum allowable sample volume – 3% (ml) over 4 weeks**	**Maximum allowable sample volume – 1% (ml) at single time**
Preterm neonate	0,5 -> 1,5	50-150	50 -150	1,5 -4,5	0,5 – 1,5
Full-term neonates	2,5 -> 5,0	250-500	250 - 500	7,5 – 15,0	2,5 – 5,0
Infant Less than 2yrs.	5,0 -> 12,0	500-1100	480 - 960	14,4 – 28,8	4,8 - 9,6
Pre-Schoolers 2-5 yrs.	12,0 -> 20,0	1100-1500	960 - 1600	28,8 – 48,0	9,6 -16,0

Age group	Weight (kg)	Normal daily fluid requirement (ml)	Circulating total blood volume (ml) – TBV (approx. 80-90 ml / kg, 100ml/kg neonates)	Maximum allowable sample volume – 3% (ml) over 4 weeks	Maximum allowable sample volume – 1% (ml) at single time
Schoolers 6-9 yrs	20,0 -> 30,0	1500-1700	1600 - 2400	48,0 – 72,0	16,0 – 24,0
Adolescents 10-18 yrs	30,0 -> 70,0	1700-2500	2400 - 5600	48,0 – 168,0	24,0 – 56,0

3. **The age range for adolescents** has been changed from 12-18 (17) to 10-18. An explanation might be useful.

4. **Line 31-33: Clarification of consent** After l.345, a paragraph, as follows, might be inserted: "In this document, the term "informed consent" should be understood as covering the following situations:
   Proxy consent on behalf of the young child, who is incapable of participating meaningfully in the decision-making process. In such circumstances, the parent(s)' permission alone is adequate to allow the child to be included in the trial.
   Consent by the parent(s) that the child may be approached to participate in the trial.
   Confirmatory consent that the child, having been approached and expressed a willingness to participate, may then entered into the trial."

5. **Lines 199-201: The "staggered approach"** has previously been recommended and is a common request from Ethics Committees. Reference should be provided in relation to the evidence that this has not safeguarded younger children. Also, this provides potential global paediatric challenges if FDA continue to request the staggered approach

6. **Lines 227-228**: The lack of distinction between commercial and non-commercial studies is to be welcomed.

7. **Lines 320-322: Assessing capacity**. How does an investigator satisfy an auditor or a Court that such an assessment has been carried in the absence of a globally-agreed assessment of maturity? Should a recommendation that researcher performs assessment based on training and experience which guides decision on the most appropriate ICF to be used be inserted? The assessment should be documented in the study file accordingly.

8. **Lines 463-468 Reaching age of maturity.** For the avoidance of doubt, the Guidance should state that the permission of the parents lapses upon attainment of capacity by the former minor.

9. **Lines 508-516:** This paragraph does not cover children with rare diseases where no standard of care is available.

10. **Lines 642-656:** The authority showing children aged 3-4 can express altruism is needed here, as this section brings Europe into direct conflict with the USA, where the AAP has long maintained that children below 7 years lack this ability.Reference is requested

11. **Lines 685-687**: Whilst accepting the variations of maturity which exists in adolescents, this part of the guideline does not assist sponsors to ensure consistent trial execution.

12. **Lines 770-771:** What evidence needs to be assembled to assure this review has been taken? Are we considering a non-medical parent/patient readability test to be performed?

13. **Lines 1083-108**: Does the EC have responsibility for rejecting protocols which do not limit the number of attempts to obtain a blood sample? If so, that should be stated here.
14. **Lines 346 – 380:** The two terms, Agreement and Dissent are mixed up in the same Glossary item. Their definitions should be provided in separate items.

Part 2: Specific comments on the text*

*We found the guidance rather difficult to follow in places; therefore, have shaped our response around key principles we have identified that underpin this research and the specific groups referred to in the text:

Principles underpinning ethical conduct of CTIMPS involving minors

1. Children have vulnerabilities both as research participants and as recipients of unresearched care so fair balance must be struck between the two.
2. Minors (children, young people and their families) should be involved in research from inception, in its design and the material to be used.
3. Research involving minors must be preceded by careful risk assessment (benefits and harms) and then management.
4. The arrangements for consent, assent and recognising dissent require specific consideration in clinical trials involving minors.
5. Extrapolation of adult data is possible but this must be done with due care.
6. Those conducting research involving minors should have appropriate expertise.
7. Those reviewing research involving minors should have appropriate expertise.
8. Openness and transparency are important parts of ethical research.

AND

Research involving particular groups

1. Neonatal research
2. Research involving healthy minors
3. Research recruiting female adolescents
4. Emergency research

Principle I: Children have dual vulnerabilities (as research participants and as recipients of unresearched care) and a fair balance must be struck

Comments and recommendations

This balance is crucial and central to any consideration of research involving minors. Most research is now of minimal or less than minimal risk and we believe these guidelines exaggerate the risks of research as now regulated. We must also acknowledge that minors are perhaps more at risk of receiving non-evidence based care (particularly the younger groups and neonates).

i. **Children and young people have the right to expect evidence based care founded on well conducted research. The CTR and this guidance recognise this necessary balance but overall opinion was that it adopted an unjustified precautionary positon.**

ii. **Recognising differing opinions about this balance and the uncertainty, this guidance doesn't go far enough to suggest future action (what we ought to be doing). We propose that guidance should promote and encourage research to derive evidence on this balance between the relative risks of currently regulated research and unresearched care. Guidance must encourage those involved to research this issue to provide a clearer footing.**

iii. **In neonatal medicine a clear stance should be taken that unlicensed and/or off label treatments commonly used in neonatal and paediatric populations without an evidence base need to be prioritised for Clinical Research particularly where no licensed alternatives exist.**

Principle II: Minors (children, young people and their families) should be involved in research from inception, in its design and the material to be used.

Comments and recommendations

Involvement of young people and children from the very beginning of a research project builds trust, improves design encourages participation and retention. There is a need for a genuine partnership.

Young people must be involved in learning about and designing health research. The aim is to improve health care by improving the way the research groups conduct the trials. By using the correct patient groups and families for evaluating research materials and protocols can better guarantee that research that is relevant, reliable and fits the needs of young people.

We think that the best way of preventing vulnerability is through researchers working in partnership with children, young people and parents. One way of doing this is for researchers to involve children, young people and parents in the design of their research from the beginning. This kind of partnership can help make sure that children and young people are not placed in situations where they may feel vulnerable.

All sponsors and researchers involving minors should have opportunity to consult "Young Persons Advisory Groups", or similar groups. This should include research design, the most relevant IC and assent practices, and the best information format suitable for the particular age groups. If this is deemed unnecessary, reasoning should be presented.

This is a central message from the Nuffield Council of bioethics report -

http://www.nuffieldbioethics.org/project/children-research

Patients & young person´s involvement:

All sponsors and researchers doing research work and clinical trials involving children and adolescents should have opportunity to consult existing "Young Persons Advisory Groups", or similar groups including both healthy persons and patients. By using these groups for review of study design and documentation for patients and families, it is easier to find out opinions of the most relevant IC and Assent practices, and the best information format suitable for the particular age group of the planned research or clinical trial, prior the Ethics Committee procedures.

We think that the best way of preventing vulnerability is through researchers working in partnership with children, young people and parents. One way of doing this is for researchers to involve children, young people and parents in the design of their research from the beginning. This kind of partnership can help make sure that children and young people are not placed in situations where they may feel vulnerable.

We think that:

- *Researchers should involve children, young people and parents when developing their studies.*

  Groups like Young Persons' Advisory Groups (YPAGs) are a good way of doing this.

- *Commercial companies should help pay for the costs of running groups like YPAGs. For example companies could contribute to a central pot of money to help fund lots of groups."*

There are several existing Young Person´s Advisory Groups and resources already globally, but more new groups are evolving to many new countries in Europe. The existing YPAGs are:

- *GenerationR*, UK: http://generationr.org.uk/about/
- *ScotCRN*, Scotland: http://www.scotcrn.org/young-people/
- iCan, U.S /global: http://www.icanresearch.org/
- *iCan*/KIDS, Spain: http://www.icanresearch.org/barcelona/
- *iCan*/KIDS, France: http://ripps.eu/en/the-french-and-european-networks/kids-france/events-kids-france/
- *KidsCan*, Canada: http://www.cfri.ca/kidscan/home
- *iCan*/KIDS, Australia: http://www.schn.health.nsw.gov.au/

This information about YPAGs and the resources should be included to this new revised guideline.

I. We support the guidance's commitment to involve children, young people and their families in the identification of necessary research, research prioritisation, its design and conduct.

II. We believe the guidance doesn't go far enough. We support the conclusions of the Nuffield Council of Bioethics report.

III. Commercial companies should help pay for the costs of running groups like YPAGs. For example companies could contribute to a central pot of money to help fund lots of groups." Or public private partnership may be the best way to address the funding issue and avoid any conflict of interest. A funding model based on "fee for service" could perhaps be established to collect contributions from commercial sponsors.

IV. The involvement of parental groups in Neonatal trials needs to be included/listed.

V. Although PPI (Public and Patient Involvement) is widely thought to improve research practice there is a lack of evidence on the impact of PPI in research and guidance on measuring the effect through qualitative research methods should be included and encouraged.

Principle III: Research involving minors must be preceded by careful risk assessment (benefits and harms) and their management.

Comments and recommendations

I. Guidance must emphasize young people's and family's involvement in assessing acceptability of harms and benefits acceptability and put this in a separate section.

II. We are involved in judging fair balance. Guidance requires "The child's interest should always prevail over that of science and society" but it should make it clear that this shouldn't be interpreted as a veto on science and society which is in effect how we improve care for others.

III. We have difficulties with the arguments proposed in the guidance as to how research involving minors can be justified.
Research investigates uncertainty. If we know a treatment is effective, or in comparative research one treatment is better than the other, we shouldn't do the research. Hence in theory joining a research will not be of direct benefit to the minor. If this weren't so, recruitment would be unethical. This is supported by current evidence although some claim, case by case, an "inclusion benefit" – that just taking part in research is better than standard care. This is currently uncertain. At the moment the honest approach, to maintain public trust and avoid excessive and unjustified claims is to say research participation is neither in nor against a minor's interest. Hence, with no direct benefit to the participant, little research can be justified on the basis of 32 1(g)(i).
But research **does** help future patients (and those with chronic conditions) so most research involving minors will meet the conditions in 32 1(g)(ii). Hence the definition of minimal risk and burden are crucial and Annex 3 will be important.

IV. We believe the characteristics of fair research and how we can maximise benefits require some development in the guidance. Justification of any research rests on demonstrable purpose. To achieve this , fair research requires

- A well- defined research question.
- A question that hasn't been asked before or can justifiably be asked again.
- A study design which will, or can fairly be expected to give, meaningful and valid answers.
- Acceptability to children young people and their families.

This should be confirmed by independent peer review, systematic review and consultation with patient groups.

V. We propose that when considering harms, it is crucial to separate (i) risk of harm from the disease, (ii) risk of harm from the treatment and (ii) risk of harm from the research.
It is the latter that concerns us. The minor will carry the consequences of the disease, whether he or she takes part in the research. The risk of treatment may or may not be part of the research.

The risk of the research risk is that attached to any change in treatment or management required by the research protocol, which might be the testing of an experimental treatment or the **comparison** of standard treatment**.** It is this additional risk that should be addressed in design and review.

VI. Guidance should provide definitions (and references to) minimal risk. Anyone undertaking research must be familiar with this concept and have a justifiable definition. Possible definitions and references to this should be laid out in guidance.

VII. Management of risk also needs to be explored. Much is done to assess risks prior to a decision if research should be conducted but little is mentioned in relation to the management of risks identified so that absolute risk is minimised.

Minimal risk:

"The research bears minimal risk if it is to be expected that it would result at most, in a very temporary negative impact on the health of the person concerned. We believe this is the most acceptable definition in practice." Royal College of Physicians 2007.

Or everyday comparison: "the probability and magnitude of harm or discomfort not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests"

VIII. Guidance need to help the proportionate and realistic assessment of "minimal additional risk or burden" in the case of low intervention clinical trials involving children, given that they will likely study off-label drugs with an "evidence-based and supported by published scientific evidence on the safety and efficacy" use.

IX. Guidance needs to recognise that before a trial there will probably be a degree of uncertainty as to benefits and risks and guidance should help researchers present this to possible participants.

X. Guidance as currently written:

1019 The accumulation of research projects in the same population (over-studied population) is another potential harm in addition to raising methodological issues. For both reasons, concurrent clinical trials using investigational medicinal products in an individual should be discouraged.

If this research doesn't threaten safety or wellbeing of minors, and the interpretability of results of other concurrent studies, what is the justification for this?

XI. Figure (Box 1) 5. While a figure might help, this doesn't. It is difficult to understand and if the argument above (IV) is accepted, Classification 1 can make no sense.

Principle IV. The arrangements for consent, assent and recognising dissent require specific consideration in clinical trials involving minors.

Comments and recommendations

I. **We recognise that the CTR places great emphasis on this issue and feel that relevant extracts from CTR should be at the top of the section, broken down into sub topics to define legal requirements.** Within each, guidance should address "how to interpret what might be deemed best practice" and seek and provide examples of good practice

II. **Given the importance of involving families and minors in research, guidance on a European level should be provided on "how the information is to be tested" (see Principe II).**

III. **Guidance discussed "CONTINUING CONSENT" but we couldn't find reference to this in the CTR. Is this over-interpretation?**

IV. **Guidance should expand on providing concise information and how researchers can match the amount of information with their study burden.**

V. **We agree with the guidance on LIMITATIONS TO CONSENT that a 'staggered approach' (starting by the older and going sequentially to the younger age groups), has not been shown to protect younger study participants but leads to delays in data availability, and is therefore not recommended.**

VI. **Enpr-EMA website has a table providing information on consent requirements from different member states. This might be included.**

VII. **We recommend including a new table Child involvement in consent / agreement process;**

Age groups	Child´s opinion / dissent	Child´s Consent / Assent / Agreement	Legally designated representative / parents
Newborns and Infants (0-2 years)	Any signs of resistance or protest should be identified and lead to discussion with parents / legally designated representative.	Not possible. Not mature enough to express agreement due to very limited understanding of the planned procedures and the trial purpose.	Need for written informed consent on behalf of a child. Signatures according to the national laws and requirements. Consider reasonable long enough time for questions and answers.
Pre-schoolers (2-5 years)	Limited or some capacity of understanding of the planned procedures and the trial purpose. Possible resistance, protest or signs of discomfort must be noted and dissent respected. In case of	Information in appropriate format is needed to support assent / agreement; visual aid and verbal explanations should be used. Consider reasonable long enough time for	Need for informed consent in addition to the child's assent. Signatures according to the national laws and requirements.

	these expressions discussion with the child and the parents / legally designated representative is needed.	questions and answers. Expression of the minor's will must be noted.	
Schoolers (6-9 years)	Understanding some parts of the planned procedures and the trial purpose, and the benefits and risks. Previous experience increases the capacity of understanding. Objections should be respected. In case of different opinions between parents and a child, discussion is needed.	For this group own assent / agreement / consent forms can be used, preferably in writing, according to the capacity to read and write. Information is needed to support assent / agreement; visual aid and verbal explanations should be used. Expression of the minor's will must be noted carefully. Consider reasonable long enough time for questions and answers.	Need for informed consent in addition to child's assent. Signatures according to the national laws and requirements.
Adolescents (10-18 years)	More mature understanding of the planned procedures and the trial purpose. Objections should be respected. In case of different opinions between parents and a minor, discussion is needed. Any form of forcing or pressure should not be used.	May have legal right or requirement to sign own consent, or assent in written form. Information must be given according to the level of understanding and maturity. Visual aid and verbal explanations should be used to support information if needed. Confidentiality of sensitive issues must be noted according to the national laws.	Need of supplementary informed consent in addition to a child. After legal independent consent age, notification may be required. Signatures according to the national laws and requirements.

		Consider reasonable long enough time for questions and answers. Independent decision making process must be respected. Parent´s / legally designated representative´s involvement and transparency of trial information should be considered.	

VIII. We recommend guidance contains a list of templates publicly available

Existing public templates for consents and assents and visual aid for pediatric trials:

Country	Consent template(s)/ guidelines / information sources
Finland	FINPEDMED guidelines; legal and ethical regulation – templates for age groups 6-17 and parents. Regulatory requirements for clinical trials in Finland Picture Cards to support IC process
France	Comité de Protection des Personnes Sud-Méditerranée II : http://www.cpp-sudmed2.fr/Information-et-autorisation-des?lang=fr National Consultative Ethics Committee for Health and Life Sciences: http://www.ccne-ethique.fr/en
Germany	ICF Guidance https://www.laekb.de/files/146A97FF999/AMG_Patienteninfo_Kinder_7bis11.pdf
Netherlands	Central Committee on Research Involving Human Subjects (CCMO) -> Human Subject -> Informed Consent – information available only in Dutch. http://www.ccmo.nl/en/ -> http://www.ccmo.nl/en/minors
Scotland (UK)	NRES Guidance http://www.hra-decisiontools.org.uk/consent/principles-children.html and http://www.ukctg.nihr.ac.uk/default.aspx
UK	NRES Guidance; http://www.hra-decisiontools.org.uk/consent/principles-children.html and http://www.ukctg.nihr.ac.uk/default.aspx

Principle V Extrapolation of adult data is possible but this must be done with due care.
Comments and recommendations
It is argued that because of the special protection they deserve, minors should not be the subject of clinical trials when the research can be done in legally competent subjects (i.e. adults capable of informed consent). But this conflicts with the concept that minors are not small adults and that data on effectiveness and safety cannot reliably be derived from data in adults (major changes in pharmacokinetics and pharmacodynamics occur with increasing age, due to changes in body composition, drug metabolism and transport and renal function. Growth and maturation processes, as well as certain specific diseases are unique to children). The balance of guidance is toward this second position (that "Children are not little adults and hence we can't extrapolate from adult experience"). There is a lack of fair balance in the guidance, with the danger that appropriate adult experience is not used. Given the frequent availability of large amount of appropriate adult experience that could guide care for minors, there is a need for more sophisticated discussion on when we and how we might extrapolate from adult research. Examples are needed for when we can and cannot.

Principle VI. Those conducting research involving minors should have appropriate expertise.
Comment The Nuffield report included the basic principles of reflexive ethical practise as a heart of professional practise, everyone should gain when conducting clinical trials with children and their families; • Trustworthiness, facilitating trust: children and parents will only feel able to take part in research if they can trust both the researchers with whom they are interacting, and the way the research is organised. Any functioning system of governance must also be able to trust the researchers who are subject to that governance. • Openness: researchers need to share information clearly and honestly with children and parents – when inviting them to take part in research, during the research itself, and afterwards. They also need to be willing to collaborate with, and learn from, other sectors of the research community, and across countries and continents. • Courage: some research is difficult to do, and it may seem easier just not to do it. But if research is not carried out, then children will not have the best possible healthcare, and may even be given treatments that are harmful, because no one has done the research to find out. The proper involvement of children and young people in the research process, which involves at least some degree of transfer of power between adults and children, also involves. We support these and believe these principles should be included to the guideline. **Structure of this part of the document:** The expertise required from the research personnel is written into several chapters and the text is partly overlapping and some principles repeatedly stated We recommend more simplified, reader friendly format with following: 1. Combine all overlapping parts (chapters and paragraphs) including same content and delete extra overlapping parts (of whole document !)

2. Add Nuffield Report´s reflexive ethical practice principles to the guideline
3. Add training requirement
4. Add list/table of qualifications and requirements for research personnel and study site

We believe that, given the central importance on the calibre and probity of the researches recognised from the early days of modern research (Ethics and Clinical Research Henry K. Beecher, N Engl J Med 1966; 274:1354-1360), there is inadequate reference to this in the guidance. Expected or suggested qualifications, training, professional accountability, experience and facilities should be laid out.

If the study personnel do not have enough expertise or only limited number of personnel planned to conduct clinical trials with children, the personnel should have opportunity to gain more knowledge and take part to relevant training programs PRIOR to the trial conduction.

List/table of personnel qualifications and requirements for research personnel and study sites

- Official and documented training; health care /medicine /paediatrics /relevant sub-specialties
- Additional training for clinical trials (GCP-certification or equivalent), focused on paediatric trials and including Data Protection, Safety Reporting and Ethics Guidelines
- Expertise in clinical trials with special groups – according to the trial protocol; neonates/children /adolescents
- Experience in clinical work / nursing
- Experience in blood sample-, other sample collections / tests / x-ray / measurements; neonates / children / adolescents
- Competence to work with children / families
- Competence and training in child protection procedures policy and legislation
- Knowledge / training about national laws and regulations, and requirements for trial related issues;
- Organisational trial approvals and agreements (process & documentation)
- Patient Insurance
- Drug damage insurance
- Covered expenses for patients / families during the trial
- Specific expertise for the preparation of information material for informed consent/assent, such as professionals acting in the educational field and/or with proved experience in communication with children and young people.

Principle VII. Those reviewing research involving minors should have appropriate expertise.

Comments

We would support Nuffield Council of Bioethics who conclude that

When RECs make decisions about research involving children, at least one person on the committee should be an expert in this area of children's healthcare. Sometimes RECs might need to invite an

expert to advise them, just for this one decision.

There should be a list of experts from different areas of children's and young people's healthcare who are willing to be advisors. […]

In addition to methodological expertise available for scientific and ethical review it would be advisable to have expertise available on regulatory review to ensure compliance and avoid duplication.

We believe the guidance does not go far enough and should recommend that RECs reviewing this research should be flagged/accredited, have corporate expertise, be trained in this area of research and review at least one study involving minors at each meeting.

Ethics Committees themselves should be audited to ensure that neonatal and paediatric clinical trials have been approved by the appropriately qualified personnel.

Principle VIII. Openness and transparency are important parts of ethical research.
Comments and recommendations **We support this section of the guidance and would suggest it includes guidance on how to meet this requirement:-** *The Clinical Trials Regulation provides for public access to the data held in the EU database and, in principle, **a summary of the results understandable to laypersons** should be on the database within 6 months from the end of the trial.* *Protocols that restrict independent publication by investigators should not be accepted, and the timeline for publication should be reasonable and specified in the respective protocols.*

Research involving particular groups

Neonatal research
Comments and recommendations
We believe that newborn babies may be vulnerable in a research project (although this can be contended) but are far more vulnerable to unresearched care so we believe guidance should place greater emphasis on these risks of unresearched care and this deserves greater emphasis in the guidance. It should be emphasized that currently many treatments routinely used in neonatal care are unresearched and off patent. Furthermore, for many neonates "polypharmacy" is unavoidable, and the goal is therefore to achieve "appropriate polypharmacy", where the prescriptions have been optimised and where the medicines are prescribed according to best evidence.

Healthy children
Comments and recommendations
I. This section needs to be qualified and we would suggest that it is retitled "Trials with healthy minors where no therapeutic benefit is expected". II. We recognise this is a highly contentious area, where we haven't moved forward. We would propose a call for more research and consultation with minors and their families through Young Persons Advisory Groups.

Enrolling young women
Comments and recommendations
This is a huge topic and the guidance barely scratches the surface (we can understand why!). It is worthy of much more work which should be commissioned through EMA, Enpr-EMA, EFPIA, Academia and obviously young persons groups. Guidance on how to inform these minors and their parents/legal representatives about possible contraceptive measures could be extremely useful, e.g. if the explanation should be done in writing, in the same time (patient and parents), what information should be provided. This should be done in respect of the different cultures, habits, religions, etc.

Emergency research
Comments and recommendations
I. With the CTR there are now pan European legal and ethical frameworks to conduct this research. **II. Guidance should provide (section 6.6) relevant recommendations about waiving assent in emergencies as well as waiving parental consent.** **III. The CONNECT study explored parent and practitioner perceptions and experiences of deferred consent in children's clinical trials. A practical (adult) example on how to address this is the paramedic study.** http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/trials/critical/paramedic2/ **Researcher and reviewer should agree a set of conditions for emergency research and waiving either consent or assent framed by the questions below** **1. Is this research needed?** This is a requirement of all research but particularly important here. Roberts outlines the lack of evidence and the consequent harm to those requiring emergency treatment (2). Researchers should define the research question, why it needs answering and how the method will answer it. **2. Is there uncertainty about treatment?** We shouldn't act against a patient's best interests, particularly if consent is not in place. This requires clear evidence of negligible possible harm and if we are comparing treatments, there must be uncertainty as to which treatment is better. If not, we would be acting against the best interests of those allocated to the inferior treatment. The researcher should provide scientific review to reassure

the REC that independent professional opinion is that there is uncertainty or "equipoise" (3) and how the trial would be stopped if accruing evidence indicated one treatment was superior.

3. Is there a need to recruit subjects who lack capacity?

Using such groups needs justification and we need to reassure ourselves that the study is related to the "impairing condition" and could not be conducted equally well on those who could provide consent (4).

4. In the context of the research is consent or consultation feasible?

Review is helped if RECs understand the context of research (a video might help). Where will it be conducted? Who will be there (and who won't be)? In reality, what are the constraints on any attempt to seek valid informed consent? Similarly is it feasible to consult others?

5. Does treatment need to be given quickly?

For some interventions it is obvious that any delay will harm. For others a judgement must be made about the likely significance of any delay. Biological plausibility, animal work, case reports/series or non-randomised studies may all add evidence to inform this decision.

6. Might delay change the effect of treatment or the results?

Roberts et al (5) provide evidence of how delay may harm patients and undermine the validity of any conclusion drawn from a study. It's also important to ask whether stipulations on consent would cause delay so that the research wouldn't replicate practice, in which case research loses validity and generalizability and is worthless.

7. Will procedures accommodate variations in capacity?

Incapacity should NOT be assumed (6) and it is a legal and ethical principle that we should try to help people make decisions. For some studies it will be clear that no subject will have capacity but for others capacity of individual subjects will vary. Those seeking consent should have appropriate skills and training to assess capacity.

8. Would the legal representative/consultee be likely to have capacity?

In the distressing circumstances of a loved one having a life-threatening accident or illness the legal representatives/consultees/welfare guardian may be unable to think clearly enough to be considered to have capacity. Clinicians make this point but evidence is lacking (and needed).

9. Should an independent professional legal representative be consulted?

In emergency this may be difficult and questions are asked whether this is of value. They will not know the patient's wishes but could give an opinion on eligibility and if it is fair to recruit the patient.

10. What should the patient or legal representative be asked later?

As soon as possible consent should be sought from the subject or legal representative. There is broad agreement on this but ongoing debate as to what such consent should address.

11. How will trial results be disseminated?

This raises particular difficulties when patients die before consent is in place. Should relatives be told of this research participation? Opinions are divided and research is needed.

Davies H et al 2014 Guide to the design and review of emergency research when it is proposed that consent and consultation be waived Emerg MedJ

http://emj.bmj.com/content/early/2014/07/31/emermed-2014-203675

Roberts I, Shakur H, Sandercock P 2005. Trauma care research and the war on uncertainty BMJ. 2005 November 12; 331(7525): 1094–1096. doi: 10.1136/bmj.331.7525.1094

Royal College of Physicians 2007. Guidelines on the practice of ethics committees in medical research with human participants paras 5.18 5.39

Roberts I et al 2011. Effect of consent rituals on mortality in emergency care research. The Lancet, Volume 377, Issue 9771, Pages 1071 – 1072.

Woolfall K, Frith L, Gamble C, et al. How parents and practitioners experience research without prior consent (deferred consent) for emergency research involving children with life threatening conditions: a mixed method study. BMJ Open 2015;5:e008522.doi:10.1136/bmjopen-2015-008522

I. Korotchikova, G.B. Boylan, E.M. Dempsey, C.A. Ryan, "Presence of both parents during consent process in non-therapeutic neonatal research increases positive response". Acta Paediatrica, vol. 99 (10), pp. 1484-1488, Ocotber 2010.

Claire Snowdon, Diana Elbourne, Jo Garcia. ''It was a snap decision'': Parental and professional perspectives on the speed of decisions about participation in perinatal randomised controlled trials.Social Science & Medicine 62 (2006) 2279–2290.

Natalie Edelman and Duncan Barron. Evaluation of public involvement in research: time for a major re-think? J Health Serv Res Policy. July 2016 21: 209-211, first published on October 27, 2015 doi:10.1177/1355819615612510

Data protection
Comments and recommendations
One novelty of the CTR is the introduction of secondary use of the data collected within the trial, without establishing special provisions for children, as well as for the use of 'special' data (e.g. genetic data) which can raise special concerns. Therefore, the guidance represents the right way to provide recommendations on how to protect data confidentiality and rights of children, and specifically for topics uncovered by the CTR. For example, the guidance should recommend that both parents/legal representatives and children should receive information on which data will be collected, and how they will be handled and stored, and should specify that this is be done verbally and in writing.