

Defining the Threshold of Permissible Risk for Non-Therapeutic Clinical Trials with Children in Europe

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Abstract:

It is important that clinical research with children is encouraged so that they are not exposed to the dangers of extrapolation from adult treatments. Clinical trials with investigational medicinal products are an important part of improving medical care for children. EU law has recognised the need for research. Both the *2001 Clinical Trials Directive* and the *2014 Regulation* permit such research. However, it is also recognised that a balance must be struck between permitting tailored medical care for children as a group on the one hand, and protecting individual trial participants from harm on the other. A central issue in striking this balance relates to defining the threshold of risk which should be permitted in such research. This article provides a critical analysis of the current European law in relation to the definition of acceptable risk for non-therapeutic clinical trials with IMPs and makes recommendations for reform, drawing on law from the Council of Europe, as well as law from the US.

Key words:

minimal risk, clinical trials, investigational medicinal products, Clinical Trials Regulation 2014, Clinical Trials Directive 2001, Oviedo Convention 1997

1. Introduction

The ethical permissibility of the conduct of non-therapeutic research with children has long been the subject of debate. Non-therapeutic research aims to benefit future generations but does not offer participants the prospect of direct medical benefit.¹ Conducting such research with children is seen as ethically challenging, due to their perceived inability to give informed consent. It has been argued that since children are not expected to benefit from non-therapeutic research, involving them in such research could amount to using them as a means to an end, namely, that of medical progress.² It is also thought that parents and guardians cannot be justified in providing consent to such research, as it does not promote the child's welfare.³ However, it has also been recognised that it is imperative to carry out clinical research with

¹ Labelling trials as "therapeutic" or "non-therapeutic trials" is problematic. This is because some trials may include interventions which offer benefit and those which do not. For reasons of brevity and ease of reading, this article will use the term "non-therapeutic research or trials". This refers to *trials* which offer the participants no prospect of direct medical benefit. It must be noted that trials which overall offer a benefit to participants may nonetheless include non-therapeutic *interventions*, such as the collection of blood or a lumbar puncture (taking of cerebrospinal fluid). Such interventions should be subject to the same recommendations as for non-therapeutic trials set out in this article.

² See S.D. Edwards and M.J. McNamee, "Ethical Concerns regarding Guidelines for the Conduct of Research on Children", *Journal of Medical Ethics* 31(6) (2004) 353.

³ See P. Ramsey, *The Patient as Person* (New Haven: Yale University Press, 1970). For a contrasting view, see R.A. McCormick, "Proxy Consent in the Experimental Situation" *Perspectives in Biology and Medicine* 18 (1974) 2-20.

children. Children are not miniature adults and they require treatment which is tailored to them.⁴ Since certain conditions arise differently in children and because certain diseases only affect them, extrapolating from adult data can expose them to unknown risks.⁵ As a result, there has been growing consensus that excluding children from clinical research can disadvantage them as a group, and is unethical for this reason.⁶

EU law in this area has recognised the need for such research.⁷ Since 2001, clinical trials for IMPs with children have been governed by the *2001 Clinical Trials Directive*. This is currently being phased out since the introduction of the *2014 Clinical Trials Regulation*, which is expected to be fully in force by 2016.⁸ These instruments permit non-therapeutic research with children in the area of investigational medicinal products (IMPs).⁹ However, a central issue is the threshold of risk which should be permitted in such research. This paper examines the current European law in relation to the definition of the threshold of risk permitted for non-therapeutic clinical trials with IMPs.¹⁰ It provides a critique of the current definition as set out in the *2014 Regulation* and makes recommendations for an improved definition of the risk threshold in non-therapeutic clinical trials with IMPs for the European legal framework, drawing mainly on law from the Council of Europe, as well as law from the US.

2. The Current Position in EU Law Regarding Non-Therapeutic Research with Children

2.1 The Position under the 2001 Clinical Trials Directive

The *2001 Clinical Trial Directive* provides a rather unclear position on the legal requirements for non-therapeutic clinical trials with IMPs with children. It states that clinical trials with IMPs can only be carried out with minors if:

some direct benefit for the group of patients is obtained from the clinical trial.¹¹

⁴ G. Pons and J.N. van den Anker, “Innovative Methodologies for Drug Evaluation in Children” in: K. Rose and J.N. van den Anker (eds), *Guide to Paediatric Clinical Research* (Basel: Karger, 2007) p. 108.

⁵ Institute of Medicine, *Ethical Conduct of Clinical Research Involving Children* (Washington, D.C.: National Academies Press, 2004) p. 58.

⁶ See N. McIntosh, “Ethical Principles of Research with Children” *Current Paediatrics* 14(6) (2004) p. 490; M.D. Roth-Cline and R.N. Nelson, “Ethical and Practical Considerations in Conducting Neonatal Research” in: A.E. Mulberg *et al.* (eds), *Pediatric Drug Development: Concepts and Applications*, 2nd edn. (West Sussex: Wiley-Blackwell, 2013) p. 73; A. Kent *et al.*, “Paediatric Medicines: A View from Patient Organisations” in: Rose and van den Anker, *supra* note 4, and P.J. Sauer *et al.*, “Research in Children: A Report of the Ethics Group of CESP”, *European Journal of Pediatrics* 161(1) (2002) 1-5.

⁷ Council Regulation 1901/2006 on Medicinal Products for Paediatric Use and Amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, 2006 OJ (378) 1.

⁸ See paras. 78 and 79, Preamble, Council Regulation 536/2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC, 2014 OJ (L 58) 1 [*2014 Regulation*].

⁹ EU law deals with clinical trials with investigational medicinal products. Other areas of research are not covered. It is with this EU legal framework that this article engages. However, it is arguable that similar standards for non-therapeutic interventions in other areas of research such as surgical research should also be subject to the safeguards outlined in this article for clinical trials with IMPs.

¹⁰ Some of the arguments in this article have been referred to in the context of the Irish legal framework for clinical trials with children in “K. Wade, “Children in Clinical Trials in Ireland: Addressing the Gaps in the Legal Framework” in M. Donnelly and C. Murray, eds., *Ethical and Legal Debates in Irish Healthcare: Confronting Complexities* (Manchester: Manchester University Press, 2016).

¹¹ Article 4(e), Council Directive 2001/20 on the Approximation of the Law, Regulations and Administrative Provisions of the Member States relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use, OJ L 121/34 (2001) [*2001 Directive*].

The meaning of this phrase is unclear and is open to different interpretations, some of which might be seen as permitting non-therapeutic research with children, and others as disallowing such interventions. For example, the term “group of patients” could be interpreted as referring to children *in general* who are afflicted with a disease or condition.¹² This would mean that there is no requirement for direct benefit to individual children in a trial and that non-therapeutic research with children would be allowed. However, the above requirement can be interpreted as *disallowing* non-therapeutic research with children. This can be seen in the Irish and UK interpretation of this requirement. Irish law transposes the requirement of the *Clinical Trials Directive* by stating that “some direct benefit for the group of patients *involved in the clinical trial* is to be obtained from that trial”.¹³ Referring to UK law, Cave argues that this interpretation appears to disallow research which does not have the prospect of direct benefit, since non-therapeutic research does not seek to benefit the group in the trial, but rather future generations.¹⁴ This would indeed seem to be the case, unless the word “benefit” is interpreted as encompassing “indirect benefits”, such as extra monitoring.¹⁵

Therefore, the *2001 Directive* and *S.I. 190* are open to different interpretations, some of which appear to permit non-therapeutic research and some of which do not. Importantly, one of the central failings is that no risk threshold is provided in the *Directive* or in the Irish and UK implementing legislation. This means that if the *Directive* is interpreted as permitting non-therapeutic research, no legal requirement for acceptable risk is set out.¹⁶

2.2 The Legal Requirements in the 2014 Regulation for Non-therapeutic Clinical Trials with Children

The *2014 Regulation*, which will be fully in force in 2016, takes a more definitive position on the permissibility of non-therapeutic research with children. In order for a clinical trial with IMPs to be carried out with minors, Article 32(1)(g) states that there must be “scientific grounds for expecting that participation in the clinical trial will produce”.¹⁷

- (i) a direct benefit for the minor concerned outweighing the risks and burdens involved; or
- (ii) some benefit for the population represented by the minor concerned and such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor’s condition.

¹² See E. Cave, “Seen but not Heard: Children in Clinical Trials” *Medical Law Review* 18(1) (2010) 18.

¹³ Part 4, s. 12, European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, (S.I. No. 190 of 2004) [*S.I. 190*].

¹⁴ See Cave, *supra* note 12, 17, citing The Medicines for Human Use (Clinical Trials Regulations), (S.I. No. 1031 of 2004).

¹⁵ *Ibid.*, 20-22.

¹⁶ See R. Andorno, “Regulatory Discrepancies between the Council of Europe and the EU Regarding Biomedical Research” in: A. den Exter (ed.), *Human Rights and Biomedicine* (Antwerp: Maklu Press, 2010) 125, and S. Simonsen, *Acceptable Risk in Biomedical Research: European Perspectives* (Springer: Dordrecht, 2012) pp. 176-179.

¹⁷ Council Regulation 536/2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC, 2014 OJ (L 158)1 [*2014 Regulation*]. The addition of the term “scientific grounds for expecting that the trial will produce” is also more appropriate to the wording of the *2001 Directive*, which states that “some direct benefit *is* obtained from the trial”. The latter phrase seems to suggest that there must be certainty that there will be a benefit to participants. However, due to the nature of research in which the outcomes are uncertain, this cannot be satisfied in most cases. See Cave, *supra* note 12, 19.

Article 32(1)(g)(i) refers to research where there *is* a direct benefit to the minor in the trial. Such research is permitted so long as the benefit outweighs the risks and burdens. Article 32(1)(g)(ii) permits research where there is “some benefit for the *population represented by the minor concerned*”.¹⁸ This means that clinical trials with IMPs can be conducted with individual children, even if it offers them no direct benefit. The trial is permissible if there is a benefit to the population they represent, i.e., children in general or children in the same age category.

The Regulation introduces a definition of minimal risk. It states that non-therapeutic clinical trial with IMPs with children:

“will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor’s condition.”¹⁹

The definition includes the threshold “of minimal risk and minimal burden”. This is the position taken in other legal instruments, as discussed below. However, the requirement is subject to the additional phrase “in comparison with the standards treatment of the minor’s condition.”²⁰

The question which arises relates to how this threshold is to be defined and applied. There is no guidance as to how this should be interpreted in the Regulation. In addition, as Westra notes, the background documents to the Regulation do not elucidate the definition in any detail.²¹

2.3 Issues with the 2014 Regulation Definition of Minimal Risk

The use of the phrase “in comparison with standard treatment of the minor’s condition” fails to provide clarity regarding the threshold of permissible risk for non-therapeutic trials with children. Making a comparison with “standard treatment” in order to determine acceptable risk levels in trials where there may be a *benefit* for the child is understandable. If a new drug or treatment poses risks which are comparable to those in the standard treatment received by the child, this risk level may be appropriate. However, in setting a risk threshold for non-therapeutic clinical trials with children, this phrase is inappropriate. The use of such a threshold of risk may allow for unacceptably high risks in non-therapeutic trials. For example, a child with cancer may be undergoing risks in receiving invasive biopsies or chemotherapy as part of their standard treatment.²² However, it would be difficult to justify the imposition of such risks on a child in research which offers them no prospect of benefit. Therefore, it is submitted that the phrase “in comparison with the standard treatment of the minor’s condition” does not provide sufficient protection for children in non-therapeutic clinical trials and is inappropriate.

The *2014 Regulation* appears to be attempting to introduce an approach which is similar to an aspect of the US regulation in the area. In the US, non-therapeutic research is permitted if there is minimal risk and minimal burden, the definition of which is discussed below. However, if

¹⁸ Italics inserted.

¹⁹ Article 32(g) (ii), *2014 Regulation*.

²⁰ *Ibid.*

²¹ A. Westra, “Ambiguous Articles in new EU Regulation may lead to Exploitation of Vulnerable Research Subjects” *Journal of Medical Ethics* 42(3)(2016), 189, citing European Commission. Assessment of the functioning of the “Clinical Trials Directive” 2001/20/EC. Public consultation paper. Brussels: European Commission, 2009, European Commission. Revision of the “Clinical Trials Directive”. Concept paper submitted for public consultation. Brussels: European Commission, 2011, Council of the European Union. Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Brussels: Council of the European Union, 2013.

²² Westra, *supra* note 21, 190.

the child has a condition or disorder,²³ non-therapeutic research involving a “minor increase over minimal risk” is permitted. The research must be likely to yield generalisable knowledge about the child’s disorder or condition, and the procedure must present experiences to participants *that are reasonably commensurate with those they ordinarily experience*.²⁴ Thus, in the US, if children have a disorder or condition, the risk threshold is defined in this “relative” way.²⁵

There are problems with the introduction of such a threshold for acceptable risk for non-therapeutic clinical trials with children in Europe. First, this definition in the *2014 Regulation* appears to be relevant only to minors with disorders and conditions. It seems to make little sense for the healthy child, for example, to be involved in a trial where a blood draw is taken and no medical treatment is being received by him or her. Additionally, the definition would appear to be difficult to apply if there were no standard treatment for the condition the child has. The apparent merging in the *2014 Regulation* of the definition of “minimal risk and minimal burden” with the concept that, for sick children, a relative standard should apply, lacks clarity.²⁶ In the US, a definition of minimal risk and minimal burden is provided in one section of the Regulations, with the relative standard for sick children set out separately.

In any event, the “relative” threshold for children with a disease or condition is seen as ethically problematic. As stated above, it would appear to permit additional risk for those with disease and conditions. However, it must be recalled that the research at issue does not aim to offer a direct benefit to the child with the disease or condition. As Iltis contends, the distinction between healthy and sick children in the US regulations “rests on the assumption that some children, but not others may be used for benefit to third parties”.²⁷ Furthermore, Ross argues that the distinction violates the principle of justice, by increasing burdens on those who are already burdened.²⁸

Given these challenges, the question which arises is how minimal risk should be defined. In this regard, guidance can be found in the *Ethical Considerations for Clinical Trials on Medicinal Products with the Paediatric Population* 2008, which is an ethical guide for paediatric clinical trials from the European Commission, and from the law of the Council of Europe.

2.4 Guidance in the Ethical Considerations for Clinical Trials on Medicinal Products with the Paediatric Population 2008

²³ §46. 406, Title 45, Part 46.102(i) of the Code of Federal Regulations, revised January 15, 2009 [45 CFR 46]. This applies to all federally funded research. FDA regulations specifically govern drugs at Title 21, Code of Federal Regulations, Part 50.3(k), revised April 1, 2014 [21 CFR 50].

²⁴ *Ibid.*

²⁵ See Westra, *supra* note 21, 189.

²⁶ It can also be argued that the term “in comparison to” lacks clarity. It is not clear whether this means the risks between the research intervention and the standard treatment must be “commensurate”. It merely states the risk of the research intervention and the risk of the “standard treatment” must be *compared*, which arguably provides no guidance.

²⁷ A. Iltis, “Pediatric Research Posing a Minor Increase Over Minimal Risk and No Prospect of Direct Benefit: Challenging 45 CFR 46.406” *Accountability in Research* 14(1) (2007) 27.

²⁸ L.F. Ross, “Do Healthy Children Deserve Greater Protection in Medical Research” *Journal of Pediatrics* 142(2) (2003) 108-112.

The *Ethical Considerations for Clinical Trials on Medicinal Products with the Paediatric Population* 2008 replicates the US regulations in terms of defining “minimal risk and minimal burden”.²⁹ The US regulations define minimal risk as follows:

the probability and magnitude of harm or discomfort anticipated in the research are 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.³⁰

At the outset, it should be noted that there are two aspects to the above definition. An intervention poses minimal risk if the risks are not greater than (a) those ordinarily encountered in daily life *or* (b) those posed in routine physical or psychological tests.

It is submitted that the approach taken in the *Ethical Considerations* is problematic, since the US definition of “minimal risk” fails to provide clarity and consistency. First, one of the difficulties relates to the arbitrariness of comparing research risks to risks in daily life or routine examinations and tests. For example, while it might be considered acceptable for children to be exposed to the risks of playing sports due to the attendant benefits, this does not necessarily mean it is acceptable to expose children to comparable risks for the purposes of research, particularly if there is no benefit for them.³¹ Secondly, defining minimal risk by reference to “daily life” or “routine physical or psychological examinations or tests” is problematic, since these concepts differ significantly depending on the child in question. As Varma and Wendler note, the risks faced by children in countries experiencing war, for example, are considerably greater than those living in peaceful countries.³² Similarly, routine tests for sick children might include significantly higher risks than those for healthy children. In addition, tests which are considered routine for a pre-term neonate may be quite invasive for an older neonate.³³

As a result of these difficulties, the “objective standard” for both the “daily life” and “routine tests” aspects of the definition has been endorsed by leading US organisations, such as the *National Commission for the Protection of Human Subjects in Biomedical and Behavioural Research*³⁴ and the Institute of Medicine (IOM).³⁵ Under this approach, the risks children encounter in daily life or during the performance of routine examinations or tests are assessed

²⁹ European Commission/Ad Hoc Group of Implementing Guidelines for Directive 2001/20/EC Relating to Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use, *Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population*, 2008 [*Ethical Considerations* 2008] at para. 11.1.

³⁰ §46.102(i) 46 CFR 45. See also §50.3(k), 21 CFR 50.

³¹ D. Wendler *et al.*, “Quantifying the Federal Minimal Risk Standard: Implications for Pediatric Research without a Prospect of Direct Benefit” *Journal of the American Medical Association* 294(7) (2005) 826-832.

³² See S. Varma and D. Wendler, “Risk-Benefit in Pediatric Research” in E.J. Emanuel *et al.* (eds.), *The Oxford Textbook of Clinical Research Ethics* (Oxford: Oxford University Press, 2008) p. 529.

³³ M. Perlman, “Ethics of Research in Neonates” in: G. Koren (ed.) *Textbook of Ethics on Pediatric Research* (Florida: Krieger Publishing: 1993) p. 86.

³⁴ National Commission, *Report and Recommendations: Research Involving Children* (Washington, D.C.: Government Printing Office, 1977) xix. It defined minimal risk as “the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination of *healthy children*” [emphasis added].

³⁵ Institute of Medicine, *Ethical Conduct of Clinical Research Involving Children* (Washington, D.C.: National Academies Press, 2004) pp. 121-122. It suggests that minimal risk should be interpreted based on the level of “harms or discomfort that *average, healthy, normal children* may encounter in their daily life or experience in routine physical examinations or tests”. The Institute also cites the National Bioethics Advisory Commission, *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries, Volume I* (Bethesda, MD: NBAC, 2001) and National Human Research Protections Advisory Committee, *Children’s Workgroup Report* (Draft) 2001. Retrieved 19 November 2014, <http://www.hhs.gov/ohrp/archive/nhrpac/documents/nhrpac16.pdf>.

by indexing them to the level of risks “ordinarily encountered in daily life by *average, healthy children*”³⁶ or those encountered by a normal healthy child who attends a healthcare professional for a check-up (“well child visit”).³⁷

However, there are also challenges with this approach. Studies show that the level of risk posed to average, healthy in children in the US is in fact quite high. For example, a study by Wendler and Varma estimated the level of risks that average, healthy children in the US ordinarily encounter in daily life, by combining data from the *Centre for Disease Control and Prevention’s National Center for Injury Prevention and Control* and the *National Highway Traffic Safety Administration American Sports Data*.³⁸ Data revealed that the ordinary activities of daily life, such as participation in sports, travelling in a car and routine clinical examinations, pose a 1 in 250 risk of injury and a 4 in a million risk of death to average, healthy children in the US.³⁹ Varma and Wendler note that these findings would suggest that the “risks of daily life” definition has the potential to expose children to significantly greater risks than US research ethics committees (IRBs) currently allow.⁴⁰

In light of these difficulties, a number of commentators have developed alternative approaches to defining minimal risk.⁴¹ For example, Nelson and Ross propose that minimal risk should be defined as “no more than that which is appropriate [for a scrupulous parent] to intentionally expose a child for educational purposes in family life situations”.⁴² They argue that the scrupulous parent standard provides a better test, since it provides greater moral context by “indexing ‘socially acceptable’ risks to which parents ought to expose their children rather than to what parents ordinarily do”.⁴³ However, as Varma and Wendler state, this test “leaves open the question of the standard by which a hypothetical parent qualifies as ‘scrupulous’”.⁴⁴ As Kopelman argues, since it is seen as legally permissible and socially acceptable for parents to permit their children to be involved in dangerous activities, such as hang gliding, for example, the use of this standard could allow high research risks.⁴⁵ Indeed, defining risk by reference to “scrupulous” or “reasonable” parents would give significant discretion to RECs and would add a considerable amount of subjectivity and flexibility into the assessment process for clinical trials. This is due to the variance in views on what constitutes “scrupulous” parenting and the range of activities in which parents allow children to partake. Moreover, as was set out above

³⁶ Varma and Wendler, *supra* note 32, 529. See National Human Research Protections Advisory Committee (NHRPAC) *Report from NHRPAC: Clarifying Specific Portion of 45 CFR 46 Subpart D that Governs Children’s Research*, 2002. Retrieved on 20 November 2014, <http://ctep.cancer.gov/forms/nhrpac16.pdf>.

³⁷ Institute of Medicine, 2004, *supra* note 35, 124.

³⁸ Varma and Wendler, *supra* note 32, 530.

³⁹ *Ibid.*, 532.

⁴⁰ *Ibid.*

⁴¹ One of these approaches is the “systematic approach” as developed by Varma and Wendler. This involves a complex procedural approach which uses empirical data about the risks to which children are exposed in everyday life and/or in research. Since this relates to the US “daily risk” definition, which does not exist in EU law, and uses US data, this approach is not the subject of detailed analysis. See Varma and Wendler, *supra* note 32, 530. See also the “charitable participation” standard, which states that the risk permitted should be “within socially accepted limits. D. Wendler and L.H. Glantz, “A Standard for Assessing the Risks of Pediatric Research: Pro and Con” *The Journal of Pediatrics* 150(6) (2007) 579-582. For more recent theories, see A. Binik, “On the Minimal Risk Threshold in Research with Children” *American Journal of Bioethics* (2014) 14(9) 3-12, which defines minimal risk by reference to children who have the “substantive goods of childhood”.

⁴² R.M. Nelson and L.F. Ross, ‘In Defense of a Single Standard of Research Risk for Children’ *Journal of Pediatrics* 147(5) (2005) 565-566. See also NHRPAC, *supra* note 36, para. 3.

⁴³ Nelson and Ross, *supra* note 42, 565. See T.F. Ackerman, “Moral Duties of Parents and Non-Therapeutic Research Procedures Involving Children” (1980) 2 (2) *Bioethics Quarterly* 94-111.

⁴⁴ Varma and Wendler, *supra* note 32, 535.

⁴⁵ L.M. Kopelman, “Minimal Risk as an International Ethical Standard” *Journal of Medicine and Philosophy* 29(3) (2004) 362-3.

regarding the justification for non-therapeutic research with children, making decisions for them based solely on the preferences of parents is inappropriate, since it fails to give adequate attention to the implications of the decision for the independent interests of children.

Other commentators have argued that minimal risk is a “common sense idea” and that the focus should be on aiding RECs to make ethical decisions, as opposed to developing definitions.⁴⁶ However, the argument that minimal risk is a “common sense idea” is also problematic as it lacks clarity. Such an approach would certainly fail to satisfy state obligations to ensure rights-based decision-making which is transparent, objective and consistent. If there is no guidance, minimal risk would be subjectively determined by different people, thereby inevitably leading to a lack of consistency. As Resnik states, “[l]ack of clarity concerning the interpretation of minimal risk can have an adverse impact on the consistency, fairness and integrity of human research and can lead to the exploitation of vulnerable subjects”.⁴⁷ Clarity in this regard is essential in aiming to ensure that all children involved in clinical trials receive the same level of protection regardless of the place in which it is carried out and the research ethics committee (REC) which assesses the research. In addition, clear definitions of risk are important in ensuring objectivity and transparency for decision-making. For these reasons, the US definition of minimal risk and minimal burden as set out in the *Ethical Considerations 2008* should not be adopted.

2.5 The Definition of Minimal Risk in the Additional Protocol on Biomedical Research 2005

An alternative definition of “minimal risk and minimal burden” is provided in the Council of Europe’s *Additional Protocol on Biomedical Research 2005*.⁴⁸ It states that:

For the purposes of this Protocol it is deemed that the research bears a minimal risk if, having regard to the nature and scale of the intervention, it is to be expected that it will result, at the most, in a very slight and temporary negative impact on the health of the person concerned.⁴⁹

It defines burden in the same way, and states that research carries a minimal burden “...if it is to be expected that the discomfort will be, at the most, temporary and very slight for the person concerned”.⁵⁰ It is submitted that the definition of “minimal risk and minimal burden” in the *Additional Protocol* is preferable to that in the *2014 Regulation*.

The definition in the *Additional Protocol* avoids the difficulties of the US definition, because it does not compare the concept of minimal risk for non-therapeutic trials to risks encountered in other situations. For an intervention to be considered minimal risk under the *Additional Protocol*, certain conditions must be met. In examining the “nature and scale” of the intervention, the risk of a “negative impact on the health of the person” must be first, “very slight” and, second, “temporary”. Therefore, if the intervention fails one or both of these tests, it cannot be considered minimal risk. If it is thought that the trial poses a significant negative impact and/or an impact which might be long-lasting, the threshold of acceptable risk has been

⁴⁶ M. Spriggs, “When “Risk” and “Benefit” are Open to Interpretation – As is generally the Case” *American Journal of Bioethics* 7(3) (2007) 20.

⁴⁷ D.B. Resnik, “Eliminating the Daily Life Risk Standard from the Definition of Minimal Risk” *Journal of Medical Ethics* 31(1) (2005) 38.

⁴⁸ Article 17(2) ii, *Oviedo Convention 1997* and Article 15(2)ii, *Additional Protocol on Biomedical Research 2005*.

⁴⁹ Article 17(1), *Additional Protocol on Biomedical Research 2005*.

⁵⁰ Article 17(2), *Additional Protocol on Biomedical Research 2005*.

exceeded. The trial must *also* only pose a minimal “burden” to participants. As noted above, the *Additional Protocol* states that “burden” refers to any discomfort caused by the trial. Thus, any pain or restriction of movement, for example, should be temporary and “very slight”. This definition also follows the different aspects of risk which are seen as elements of a sound risk assessment, as it requires researchers and RECs to examine the nature of the risk and to assess its magnitude and severity, including the reversibility or otherwise of the harm.⁵¹

While this definition is free of some of the difficulties which are present in the US approach, it could be argued that it simply replaces the word “minimal” with the term “very slight”, which again requires elucidation. However, in this regard, the *Additional Protocol* provides that the definition of minimal risk and minimal burden should be complemented by the inclusion of examples, as discussed in the next section.

2.6 The Provision of Examples of Minimal Risk

Paragraph 100 of the *Explanatory Report to the Additional Protocol 2005* sets out some concrete examples of interventions which pose a “minimal risk and minimal burden”.⁵² Examples of such interventions include:

- obtaining bodily fluids without invasive intervention, e.g., taking saliva or urine samples or cheek swab,
- at the time when tissue samples are being taken, for example during a surgical operation, taking a small additional tissue sample,
- taking a blood sample from a peripheral vein or taking a sample of capillary blood,
- minor extensions to non-invasive diagnostic measures using technical equipment, such as sonographic examinations, taking an electrocardiogram following rest, one X-ray exposure, carrying out one computer tomographic exposure or one exposure using magnetic resonance imaging without a contrast medium.⁵³

It is submitted that the above definition of minimal risk from the *Additional Protocol 2005*, coupled with the list of examples, represents a suitable approach to defining the risk threshold for children in clinical trials. It is clear that the risk and burden which is permitted is very low, in the sense that there may only be a “very slight and temporary impact” on the health of children involved in such research. Allowing more than a low level of risk in non-therapeutic research can be seen as inappropriately using children as a means to an end for the benefit of the group. In addition, the provision of examples of minimal risk and minimal burden is a positive measure. As Simonsen notes, “...concrete examples contribute to the ascertainment of the standard of minimal risk and burden by establishing palpable and familiar benchmarks”.⁵⁴ Such examples can help to ensure that researchers and RECs have standardised guidance in assessing research risks, thereby promoting transparency, objectivity and consistency in decision-making.

⁵¹ D.J. Mazur, *Evaluating the Science and Ethics of Research on Humans: A Guide for IRB Members* (Baltimore, MD: The John Hopkins University Press, 2007) p. 62. The different aspects of risk are (a) the nature of the risk, (b) the magnitude of the risk, (c) the severity of the harm and whether it is reversible, partially reversible or irreversible and (d) the chance that the risk will materialise.

⁵² *Explanatory Report to the Additional Protocol on Biomedical Research 2005*. In the US, such an approach is also taken. See NHRPAC, *supra* note 38.

⁵³ See also Annex 4, *Ethical Considerations 2008*, *supra* note 29.

⁵⁴ Simonsen, *supra* note 16, 199.

The development of examples of minimal risk interventions should be done in an open way, through public consultation.⁵⁵ Glantz takes this approach, arguing that, for example, the pain, anxiety and risk of a lumbar puncture needs to be determined and announced in a public forum, because ultimately this question is about what is socially acceptable regarding research with children.⁵⁶ He maintains that this would be a better approach than leaving such decisions to disparate RECs.⁵⁷ This is a positive recommendation that should also be made in the European context for children in clinical trials. The development of a European “Research Risk Repository”, which would collect data on the outcomes of research interventions, would be appropriate in this context.⁵⁸ Such a database would mean that, if the research under review involved a certain procedure, the REC could refer to a list of procedures to find out its perceived risk level according to current medical literature or medical experts. It would also be regularly updated as new data are collected.⁵⁹ In this regard, under the *2014 Regulation*, the European Medicines Agency (EMA) must establish an EU Portal and Database for all clinical trials in Europe in order to facilitate applications for clinical trials and provide information to the public.⁶⁰ This database could also be utilised to collect data on the estimated risk of different trial interventions.

It was argued above that examples must be given to researchers and REC members regarding the assessment of minimal risk in non-therapeutic interventions. However, it must be stressed that examples of minimal risk should only be used as a “supplement to, rather than a substitute for” the informed judgement of these individuals.⁶¹ As the *Explanatory Report to the Oviedo Convention 1997* states, procedures given in the list of examples may not always entail minimal risk or burden, and assessment on an individual basis must always be carried out.⁶² For example, a clinical trial may involve a number of the interventions on the list, which, taken collectively, could entail greater than minimal risks and burdens. In addition, regard must be had to the particular characteristics of the group in the trial. For example, the risks of a blood draw for neonates, especially premature neonates, might be greater than for older children, due to their lower blood volumes.⁶³ The possible effects of pain in neonates must also be considered. Studies show that pain in the neonatal period can negatively affect post-natal growth and neurodevelopment.⁶⁴ Furthermore, certain experiences, such as loud noises, can produce more fear in neonates or infants as compared to older children.⁶⁵ This is due to the

⁵⁵ L.M. Kopelman, “Children as Research Subjects: A Dilemma” *Journal of Medicine and Philosophy* 25(6) (2000) 757. See also Slovik, who also argues that there should be more public participation in risk assessment and risk decision-making. This, he states, would make the process more democratic and increase public acceptance of decisions in the area. P. Slovik, “Trust, Emotion, Sex, Politics, and Science: Surveying the Risk-Assessment Battlefield” *Risk Analysis* 19 (1999) 689-701.

⁵⁶ L.H. Glantz, “Research with Children” *American Journal of Law and Medicine* 24(2-3) (1998) 243.

⁵⁷ *Ibid.*

⁵⁸ A. Rid and D. Wendler, “A Proposal and Prototype for a Research Risk Repository to Improve the Protection of Research Participants” (2011) 8(6) *Clinical Trials* 705-715.

⁵⁹ *Ibid.*, 707.

⁶⁰ See Articles 80 and 81, *Clinical Trials Regulation, 2014*.

⁶¹ P. Miller and C. Weijer, “Moral Solutions in Assessing Research Risk” *IRB: Ethics and Human Research* 22(5) (2000) 8.

⁶² Para. 100, *Explanatory Report to the Oviedo Convention 2005*.

⁶³ W.G. Bartholome, “Ethical Issues in Pediatric Research” in: H.Y. Vanderpool (ed.), *The Ethics of Research Involving Human Subjects* (Frederick, MD: University Publishing Group, 1996) p. 356.

⁶⁴ See. J. Vinall *et al.*, “Neonatal Pain in Relation to Postnatal Growth in Infants Born Very Preterm” *Pain* 153(7) (2012) 1374-1381; R. Grunau, “Neonatal Pain, Parenting Stress and Interaction, in relation to Cognitive and Motor Development at 8 and 18 Months in Preterm Infants” *Pain* 143(1-2) (2009) 138-146.

⁶⁵ E.H. Wender, “Assessment of Risk to Children” in: M.A. Grodin and L.H. Glantz (eds.), *Children as Research Subjects: Science, Ethics and Law* (Oxford: Oxford University Press, 1999) p. 184.

impact of noise on sensory structures and a lack of understanding of the source of the noise.⁶⁶ It can be argued that because of such issues, guidance on minimal risk, including “risk repositories” should include specific guidance for different groups of children.

2.7 The Incorporation of the Council of Europe Definition

In terms of implementing the above framework for the threshold of acceptable risk in non-therapeutic clinical trials with IMPs with children, it must be noted that the *2014 Regulation* cannot be amended.⁶⁷ In addition, the framework for minimal risk which is contained in the *Additional Protocol on Biomedical Research 2005* and endorsed above has not been ratified by a number of Member States, including Ireland and the UK. However, it is submitted that it is possible to apply the framework in the *Additional Protocol* in the EU. Since the *2014 Regulation* does not provide a clear definition of minimal risk and minimal burden as outlined above, it can be argued that there is no conflict between legal requirements of the *Regulation* and the *Additional Protocol*. This is because it is a principle of the jurisprudence of the *European Court of Human Rights* that Community law is presumed to be consistent with law of the Council of Europe.⁶⁸ Thus, it can be argued that there is no legal impediment to applying the Council of Europe definition of minimal risk and minimal burden to the *2014 Regulation*.

In order to translate such law into practice, a new version of the “*Ethical Considerations for Clinical Trials on Medicinal Products with the Paediatric Population 2008*” could be drawn up.⁶⁹ This could give guidance on the *2014 Regulation* and could include the above recommendations for the threshold of risk in non-therapeutic trials with children. This approach should be included in training programmes for researchers and RECs in member states. One area in which further guidance may be required, however, is in relation to Phase I trials with IMPs, as discussed in the following section.

2.8 Minimal Risk in Phase I Trials with IMPs

Phase I trials with IMPs with children raise complex issues in terms of risk. Usually, such trials with children have already been through some phases of research with adults. By the time the trial is carried out with children, it is thought that the research may have some therapeutic effect for them. At the same time, Phase I trials do not generally offer the prospect of a direct benefit, in the sense that dosages are increased gradually to test for toxicity, thus making it unlikely that individual children will benefit. Additionally, since the drug is being introduced for the first time in children, there is always a chance of unforeseen risks. Therefore, guidance needs to be developed for the definition of “minimal risk” in the context of Phase I drug trials with children. The issue of risks in Phase I IMP trials concerns complex scientific factors relating to pre-clinical and laboratory data and exceed the scope of this thesis. However, a number of points can be made. It is submitted that guidance in this area could refer to the level of information

⁶⁶ *Ibid.*

⁶⁷ A. Westra, *supra* note 21, 190.

⁶⁸ Simonsen, *supra* note 16, 178. Simonsen cites the case of *Bosphorus Hava Yollari ve Ticaret Anonim Şirketi v. Ireland* (App. 45036/98), 30 June 2005 at paras. 159-165. This is known as the “presumption of Convention compliance.”

⁶⁹ See A. Westra, *supra* note 21.

on risks which should be available from pre-clinical testing on animals or adults.⁷⁰ In addition, the risk might be seen as minimal if some or all of the following steps are taken:

- Children who may be susceptible to adverse events are identified by conducting screening evaluations and obtaining medical histories from their primary physician.⁷¹
- A low dose of the intervention is used first and the dose is raised slowly.⁷²
- Frequent monitoring for adverse events and follow up evaluations are used in order to detect early signs of adverse events.⁷³
- Emergency treatment is available and the research is terminated if required.⁷⁴
- The principal investigator is reachable at all times, since adverse events may be unexpected.⁷⁵
- There are be provisions for unblinding if this is needed to guide a participant's care.⁷⁶

Such guidance would be relevant to researchers and RECs, but mostly to bodies which undertake scientific assessments of IMPs. However, it is submitted that additional guidance should be drawn up by an expert organisation, such as the Committee for Medicinal Products for Human Use (CHMP), which is a specialist body of the EMA. Since Phase I drug trials can, in particular, pose risks to the lives and health of children, additional attention must be directed towards the protective framework for children in this regard.

3. Conclusion

It is important that clinical research with children is encouraged so that they are not exposed to the dangers of extrapolation from adult treatments. An important element of such research may include non-therapeutic clinical trials with IMPs. However, a balance must be struck between promoting evidence-based healthcare for children and protecting individual trial participants from unacceptably high risks and burdens. Defining the threshold which is permitted in non-therapeutic clinical trials with IMPs is a crucial aspect of protecting children in this respect. It is important to have a clear definition in order to ensure objective, transparent and consistent decision-making by those who design and approve clinical trials

In terms of developing an appropriate threshold in this regard, the approach of the *Additional Protocol 2005* was endorsed. It was argued that this definition is appropriate, since it seeks to limit the risks in non-therapeutic research to those which have a “very slight and temporary negative impact on the health of the person concerned”. The provision of examples of minimal risk and the development of a “risk repository” were recommended. However, the need for the subjective interpretation of minimal risk was stressed, in order to ensure that guidance for the determination of risk levels reflect the particular characteristics of children. Such an approach could contribute greatly to protecting children involved in non-therapeutic research and to developing an objective, transparent and consistent decision-making process.

⁷⁰ J.A. Menikoff and E.P. Richards, *What the Doctors Didn't Say: The Hidden Truth about Medical Research* (Oxford: Oxford University Press, 2006), p. 179.

⁷¹ B. Lo, *Ethical Issues in Clinical Research: A Practical Guide* (Philadelphia, PS: Lippincott Williams & Wilkins, 2010) p. 42.

⁷² *Ibid.*

⁷³ *Ibid.*

⁷⁴ *Ibid.*

⁷⁵ *Ibid.*

⁷⁶ *Ibid.*

