Article 5 of the UN Convention on the Rights of the Child: parental guidance and the evolving capacities of the child

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5 The proxy dilemma

Informed consent in paediatric clinical research – a case study of Thailand

Abstract

Informed consent is an essential requirement for the ethical conduct of research. It is also necessary requirement for the lawful conduct of research. In clinical research, voluntary and informed consent provides the legal basis to enrol human subjects. In paediatric clinical research, where children do not generally enjoy a presumption of competence, a legal representative must authorise a child's enrolment. Determining who should act on behalf of the child is a matter of law, rather than ethical principle. But, if national laws are lacking or do not address socio-cultural realities, legal uncertainty arises, which can have implications for children's enrolment in clinical research. Using Thailand as its case study, this chapter contemplates how international legal frameworks, such as the UN Convention on the Rights of the Child, could be leveraged to address legal uncertainty in informed consent to enable more children to access and participate in paediatric clinical research.

Introduction

In 1964, the World Medical Association adopted a set of guidelines for human subject research, in what would become the foundational framework for the ethical oversight of medical research. The Declaration of Helsinki[1] superseded the Nuremberg Code in scope and content.[2] It introduced a concept of proxy informed consent,[3] breaking from the absolute requirement of voluntary and

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1 World Medical Association, *Declaration of Helsinki* (1964), adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964.

2 J. Katz, 'The Consent Principle of Nuremberg: Its Significance Then and Now' in G. Annas and M. Grodin (eds) *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation* (New York: Oxford University Press, 1992) 227-239.

3 Declaration of Helsinki, 1964 (n 1). Part II, principle 1 and Part III, principle 3a.

informed consent[4] in human subject research, and paving the way for ethical medical research in all categories of persons, including children.

At the crux of informed consent in children is the role played by the proxy – the legally competent person who holds an ethical duty to safeguard the interests of the child participant and a responsibility to authorise their lawful enrolment in clinical research.

Yet the role of proxy is not explicated under international and regional ethical guidelines. The Declaration of Helsinki does not elaborate on the proxy decision-making role nor does it provide a framework to determine who should act as proxy. Over the course of its eight revisions, the Declaration has employed diverse terminology and ascribed different levels of decision-making authority to the proxy. In earlier versions, it called on a 'responsible relative'[5] to give permission replacing 'that of the [child] subject',[6] while in later versions it permitted only the 'legally authorized representative'[7] to provide informed consent, with an understanding that a child's dissent should be respected,[8] and where possible her assent obtained.[9]

Comparing current international and regional guidelines, there remain notable differences in the terminology used and levels of decision-making authority ascribed to the proxy (see Table 1). Determining who should act as proxy is only vaguely discussed, with wide deference given to the 'applicable laws' in the jurisdiction of the clinical study.

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4 Nuremberg Code, *United States of America v Karl Brandt et al.*, 21 November 1946-20 August 1947, judgement reprinted in G. Annas and M. Grodin (eds) *The Nazi Doctors and the Nuremberg Code* (New York: Oxford University Press, 1992) 61-144.

5 World Medical Association, *Declaration of Helsinki* (1975), revised by the 29th World Medical Assembly, Tokyo, Japan, October 1975 (Principle 11); World Medical Association, *Declaration of Helsinki* (1983) revised by the 35th World Medical Assembly, Venice, Italy, October 1983 (Principle 11); World Medical Association, *Declaration of Helsinki* (1989), revised by the 41st World Medical Assembly, Hong Kong, September 1989 (Principle 11); World Medical Association, *Declaration of Helsinki* (1996), revised by the 48th General Assembly, Somerset West, Republic of South Africa, October 1996 (Principle 11).

6 See Declaration of Helsinki, 1974 (Principle 11); Declaration of Helsinki, 1983 (Principle 11); Declaration of Helsinki, 1989 (Principle 11); Declaration of Helsinki (1996) (Principle 11).

7 World Medical Association, *Declaration of Helsinki* (2000), revised by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000 (Principle 24); World Medical Association, *Declaration of Helsinki* (2004), revised by the 55th WMA General Assembly, Tokyo, Japan, October 2004 (Principle 15); World Medical Association, *Declaration of Helsinki* (2008), revised by the 59th WMA General Assembly, Seoul, Korea, October 2008 (Principle 27); World Medical Association, *Declaration of Helsinki* (2013), revised by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013 (Principle 28).

8 Declaration of Helsinki, 2008 (Principle 28); Declaration of Helsinki, 2013 (Principle 29).

9 Declaration of Helsinki, 2000 (Principle 25); Declaration of Helsinki, 2004 (Principle 16); Declaration of Helsinki, 2008 (Principle 28); Declaration of Helsinki, 2013 (Principle 29).

Table 1: The role of 'proxy' in paediatric informed consent in international and regional guidelines

Instrument	*Terminology for 'proxy'*	*Authority of 'proxy'*	*Definition for 'proxy'*
Declaration of Helsinki, 2013[10] World Medical Association Principles 28 and 29	**Legally authorized representative** (LAR)	Provide **informed consent** and where possible, the child's dissent must be respected and assent from the child obtained.	No definition provided
CIOMS, 2016[11] Council of International Organisations of Medicine Guideline 17	**Parent** or **legally authorized representative (LAR)**	Provides **permission** and where possible the agreement (assent) of the child should be obtained	**Parent**, **legal guardian** or **legally authorised representative**, consistent with applicable laws and regulations
Good Clinical Practice: Consolidated Guidance E6(R2) (1995, 2006, 2016)[12] International Council of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Section 1: Glossary, para 1.37	**Legally acceptable representative (LAR)**	Provides **informed consent** and where appropriate, child provides written assent	An individual or juridical or other body authorised under applicable law to consent on behalf of a prospective subject, to the subject's participation in the clinical trial

10 Declaration of Helsinki, 2013 (Principles 28 and 29).

11 Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), *International Ethical Guidelines for Health-related Research Involving Humans* (2016), (Geneva: CIOMS, 2016). ('CIOMS 2016') (Guideline 17: Research involving Children and Adolescents).

12 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 'Integrated Addendum to ICH E6(R1): Guidelines for Good Clinical Practice E6(R2)', Current Step 4 Version, 9 November 2016. (ICH-GCP E6(R2)). Accessed at: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf (27 October 2021) (Section 1: Glossary, para 1.37).

Instrument	*Terminology for 'proxy'*	*Authority of 'proxy'*	*Definition for 'proxy'*
ICH Harmonised Guideline: Clinical Investigation of Medicinal Products in the Pediatric Population E11(R1)[13] International Council of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Section 2: Guidance, para 2.6.3.	Parent(s) or **Legal Guardian**	Provides **fully informed consent** in accordance with regional laws or regulations. Where appropriate, child provides assent (consistent with local legal requirements)	No definition provided.
WHO Guidelines on Good Clinical Practice[14] World Health Organization Principle 7	**Legally authorised representative (LAR)**	Provides **permission** in accordance with applicable law	No definition provided.
EU Regulations on clinical trials on medicinal products for human use No 536/2014[15] European Parliament **Article 2, Para 20**	**Legally designated representative (LDR)**	Provides **informed consent**	A natural or legal person, authority or body which, according to the law of the Member State concerned, is empowered to give informed consent on behalf of a subject who is an incapacitated subject or a minor.
Convention on Human Rights and Biomedicine (1997)[16] Council of Europe Article 6	**Representative or an authority or a person or body**	Provides **authorization** with opinion of minor taken into consideration	Representative or an authority or a person or body provided for by law

13 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 'Guidelines for Clinical Investigation of Medicinal Products in the Pediatric Population E11(R1)', 1 August 2017 (ICH-GCP E11(R1)). Accessed at: https://database.ich.org/sites/default/files/E11_R1_Addendum.pdf (27 October 2021) (Section 2: Guidance, para 2.6.3).

14 World Health Organization, *Handbook for Good Clinical Research Practice (GCP) Guidance for Implementation* (Geneva: World Health Organization, 2002)(Principle 7).

15 European Parliament, Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, *European Parliament and of the Council*, 16 April 2014. Accessed at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf (27 October 2021) (Article 29; Article 2, para 20).

16 Council of Europe, Convention on Human Rights and Biomedicine (ETS No. 164) (Oviedo Convention), adopted 4 April 1997, entered into force on 1 December 2009. Accessed at: https://www.coe.int/en/web/bioethics/oviedo-convention (27 October 2021) (Article 6).

Instrument	*Terminology for 'proxy'*	*Authority of 'proxy'*	*Definition for 'proxy'*
Additional Protocol on Biomedical Research (2005)[17] Council of Europe	**Legal Representative** or **an authority** or **body provided for by law**	Provides **authorization** with opinion of minor taken into consideration	A legal representative or an authority or a person or body provided for by law

This legal ambiguity can have practical implications for children's enrolment in paediatric research,[18] particularly in lower- and middle-income countries[19] where national laws may be lacking;[20] regulatory oversight remains weak; and socio-cultural realities of family and parenting do not reflect international guidelines.[21] As Cheah and Parker explain, '[r]egulations for research in children in developing countries are often rigid, confusing or non-existent.'[22] Moreover, research ethics committees 'rarely offer clear guidelines for research in children', and those that 'adopt international guidelines, with the noble intention of protecting children', often do so with 'little reflection on their relevance to the local setting, resulting in practical problems for the conduct of the research.'[23] In these settings, the legal uncertainty, coupled with vague international guidelines become barriers, preventing children from accessing research rather than protecting them through research.[24] Bwakura-Dangarem-

17 Council of Europe, Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research (ETS No. 195), adopted 25 January 2005, entered into force on 1 September 2007. Accessed at: https://rm.coe.int/168008371a#:~:text=Parties%20to%20this%20Protocol%20shall,in%20the%20field%20of%20biomedicine. (27 October 2021).

18 M. Colom, and P. Rohloff, 'Cultural considerations for informed consent in paediatric research in low/middle-incomes countries: a scoping review' (2018) 2 *BMJ Paediatrics Open* 1-14.

19 This chapter adopts a definition of 'lower- and middle-income countries' used by the World Bank. Accessed at: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519 (27 October 2021)

20 M. Kalabuanga, R. Ravinetto, V. Maketa, H.M. Mavoko, B. Fungula, R.I. Da Luz, J. Van Geertruyden, and P. Lutumba, 'The Challenges of Research Informed Consent in Socio-Economically Vulnerable Populations: A Viewpoint from the Democratic Republic of Congo' (2016) 16(2) *Developing World Bioethics* 64-69.

21 Council for International Organizations of Medical Sciences, *Clinical research in resource-limited settings: A consensus by a CIOMS Working Group* (Geneva: CIOMS, 2021). Appendix 1, Special Populations, 84-85.

22 P.Y. Cheah and M. Parker, 'Consent and assent in paediatric research in low-income settings' (2014) 15(22) *BMC Medical Ethics* 1-10, 6.

23 Ibid, 6.

24 P.D. Joseph, J.C. Craig, A. Tong, and P. Caldwell, 'Researchers', Regulators', and Sponsors' Views on Pediatric Clinical Trials: A Multinational Study' (2016) 138(4) *Pediatrics* 1-13. DOI:10.1542/peds.2016-1171; N. Vischer, C. Pfeiffer, A. Joller, I. Klingmann, A. Ka, S.K. Kpormegbe, and C. Burri, 'The Good Clinical Practice guideline and its interpretation –

bizi et al., recount similar experiences in Zimbabwe, where there are no specific laws on paediatric clinical research: 'a substantial number of potential research participants were orphans … whose relatives wanted them to be involved in the study but could not because of the requirement … for consent from a parent or legal guardian.'[25]

Focusing on Thailand, where there is currently no law on human subject research and no specific regulations on informed consent in children, this chapter examines two areas of legal uncertainty, which commonly arise in the enrolment of children in clinical research: (1) who should act as the 'legally acceptable representative' for the child; and (2) how informed consent should be obtained in children without a legally recognised representative – children of minor parents,[26] children of parents without legal status, and children living without parental care. It suggests that international legal instruments, such as the UN Convention on the Rights of the Child (CRC), could be leveraged to navigate legal uncertainty in informed consent, providing a framework that not only considers socio-cultural environment, but also the child's right to guidance in the informed consent process in paediatric clinical research.

1 Background – The legal and regulatory framework for informed consent in paediatric clinical research in Thailand

In Thailand, as in many lower- and middle-income countries (LMICs),[27] there is no specific law on human subject research and no regulations directly addressing informed consent in paediatric clinical research. Instead, legal codes, statutes and regulatory notifications are pieced together to create an ethico-legal framework for the informed consent process in paediatric clinical research. However, because it falls on individual ethics committees to lead this process on a case-by-case basis, there is considerable uncertainty and inconsistency in how legal requirements are interpreted and applied across the informed consent process in paediatric clinical research in Thailand.

Advisory guidelines have been developed to support ethics committees in their oversight of clinical research. The Forum for Ethics Review Committees in Thailand (FERCIT) – a coordinating body for ethics committees established

perceptions of clinical trial teams in sub-Saharan Africa' (2016) 21(8) *Tropical Medicine and International Health* 1040-1048, 1043. DOI:10.111/tmi.12734

25 M. Bwakura-Dangarembizi, R. Musesengwa, K.J. Nathoo, P. Takaldza, T. Mhute, and T. Vhembo, 'Ethical and legal constraints to children's participation in research in Zimbabwe: experiences from the multicenter pediatric HIV ARROW trial' (2012) 13(17) *BMC Medical Ethics* 1-5, 3.

26 The term 'minor parents' is used to refer to parents who are not 'sui juris' or 'legally competent', see *Thailand Civil and Commercial Code 2468 B.E.,* Book I: General Principles, Title II: Persons, Chapter I: Natural Persons, Part II: Capacity, sections 19, 20.

27 CIOMS 2021 (n 21).

in 2000[28] – developed *Ethical Guidelines for Research* in 2007. The National Research Council of Thailand (NRCT), the main institutional body overseeing all research in Thailand, issued *National Policy and Guidelines for Human Subject Research* in 2015 aimed at addressing the legislative gap on human subject research.[29] While both of these guidelines are useful in the ethical oversight of clinical research generally, neither of them provides specific guidance on the legal requirements for informed consent in paediatric clinical research. In 2012, the Forum for Ethics Review Committees began a process to develop specific guidelines for paediatric research, issuing *Ethical Guidance for Research involving Children* in 2015. The 2015 FERCIT guidelines go further in their guidance on informed consent than any previous guidelines.[30] However, in the absence of a direct law on human subject research, there remain conflicting approaches on how Thai law should be interpreted and applied in the paediatric clinical research setting, which has resulted in uncertainty over the legal requirements for informed consent in children in Thailand.

2 Discerning who is a Legally Acceptable Representative – 'LAR'

As a starting point, both the *National Health Act B.E. 2550 (2007)* and the *Mental Health Act B.E. 2551 (2008)* require written informed consent for medical treatment. This legal requirement is extended to medical research, requiring a prospective research participant to provide voluntary and informed written consent as a condition for their lawful enrolment in clinical research. The *Mental Health Act B.E. 2551 (2008)* further adds, 'where the patient is less than eighteen years of age … [a] protector, curator, guardian or a person who takes care of that person, as the case may be, shall give consent … on his behalf'.[31] The *Mental Health Act B.E. 2551 (2008)*, however, does not provide a legal definition for the persons designated as 'protector, curator, guardian' nor does it reference a statute or legal code as its basis to define who may act as the proxy.

Apart from the *Mental Health Act B.E. 2551 (2008)* there is no other legal code or statute that directly addresses the legal requirements of informed consent in clinical research for adults or children in Thailand. The Food and Drug Administration (FDA), embedded within the Ministry of Public Health, has regulatory oversight of clinical trials involving the use of drugs in Thai-

28 Forum for Ethical Review Committees in Thailand, 'Background' (unofficial translation). Accessed at: http://www.fercit.org/about.php (27 October 2021)

29 National Research Council of Thailand, *National Policy and Guidelines for Human Research 2015* (Bangkok: National Library of Thailand, 2015) 1-112, vii.

30 Forum for Ethics Review Committees in Thailand, *Ethical Guidelines for Pediatric Research* (Bangkok: FERCIT, 2015). Accessed at: http://www.fercit.org/index.php (27 October 2021)

31 *Thailand Mental Health Act B.E. 2551 (2008)*, Section 20 and 21.

land. The FDA has not issued specific regulations for paediatric clinical research.[32] However, in its *2013 Clinical Trial Notification*, it specified that all clinical trials must comply with the good clinical practice guidelines issued by the International Conference of Harmonisation (ICH-GCP).[33] To this end, the FDA has designated ethics review committees to monitor and ensure compliance with the ICH-GCP guidelines as a condition for regulatory approval for a clinical study.

The ICH-GCP have issued at least two sets of good clinical practice guidelines relevant to informed consent in paediatric clinical trials. Under the ICH-GCP(E6), the general guidelines on good clinical practice in clinical trials, a legally acceptable representative must provide written consent on behalf of a child (a legally incompetent research participant) to authorise that child's enrolment in a clinical study. Deference is given to the 'applicable laws' in the jurisdiction of the clinical trial to define the scope and meaning of 'LAR'.[34] Under the ICH-GCP(E11), the guidelines for the use of medicinal products in children, a legal guardian must provide 'fully informed consent … in accordance with laws or regulations.'[35] Notwithstanding the discrepancy in terminology, the ICH-GCP(E6) and ICH-GCP(E11) guidelines impose similar requirements for the role of proxy: (1) the individual must be authorised under the law to act as the legal representative for the child; (2) the individual must be legally competent and capable of providing informed consent on behalf of the child.

Under Thai law, however, there are conflicting legal frameworks to discern who is responsible for the child, and who is legally authorised to represent the child. Using a series of case studies, we consider the practical implications of this legal ambiguity on children's enrolment and participation in paediatric clinical research in Thailand.

2.1 Who is a parent for the purposes of informed consent in children

There are conflicting legal definitions for 'parent' under Thai law, which can directly affect a father's ability to act as a legal representative for his child in paediatric clinical research. Under Thai family law, the biological mother

32 There are no specific guidelines for reviewing drugs for children and infants in Thailand, and currently no regulations on the oversight of clinical trials in children (unofficial translation). Original version accessed: https://he01.tci-thaijo.org/index.php/TJPP/article/view/169678/122040 (27 October 2021)

33 Thai Ministry of Public Health, FDA Regulations for the import of drugs for the purposes of clinical research, current as of January 2021. Original version accessed at: https://www.fda.moph.go.th/sites/drug/Shared%20Documents/Law05-Bureau-Drug-announced/A20210205-i.pdf (27 October 2021)

34 ICH-GCP E6(R2) (n 12) Section 1: Glossary, para 1.37.

35 ICH-GCP E11 (n 13) Section 2.6.3.

is the presumptive legitimate parent of the child.[36] A father does not enjoy presumptive parental status based on parentage, but rather on the basis of marriage. In other words, if the mother is married to the father at the time of the child's birth or the child is born within 310 days after the termination of the legal marriage, the father is presumed as the legal parent of the child.[37] If the father subsequently marries the mother after the child's birth, he becomes the legal parent of the child on the basis of that marriage.[38] If, however, the mother and father are unmarried at the time of the child's birth and do not subsequently marry, the father must make a formal application to register his status as the legal parent of the child.[39] Whether a father has cared for, or lived with his child since birth, will not be determinative of his legal status as a parent under Thai law. Even when a father's biological link to the child is not contested, in the absence of marriage a father will need to register his legal status as the child's parent. Moreover, if the mother contests the application, a formal hearing will ensue to determine where the father has a biological link or other legal claim to parent the child.

In contrast, section 4 of the *Child Protection Act B.E. 2546 (2003)* recognises both the 'father and mother of a child, regardless of whether they are married or not.'[40] The *Child Protection Act B.E. 2546 (2003)* also recognises parental status on the basis of an ongoing caregiving relationship, acknowledging a range of informal carers not biologically linked to the child, yet acting as the primary caregiver for her.

For its part, the FERCIT *Ethical Guidelines on Paediatric Research* suggests a definition for 'parent' that aligns with the *Child Protection Act B.E. 2546 (2003)* recognising both the father and mother as the child's legal representatives, irrespective of their marital status or formal registration. In the absence of a specific law or regulations on paediatric clinical research, however, there is no legal basis to favour the FERCIT guidelines or the *Child Protection Act B.E. 2546 (2003)* over the provisions under Thai family law.

Given the uncertainty of a father's legal status as 'parent', it is not uncommon for research sponsors, particularly foreign commercial sponsors, to require informed consent from a mother (irrespective of a father's eligibility to consent), to ensure the legality of informed consent. This can result in a

36 *Thailand Civil and Commercial Code 2468 B.E.*, Book V: Family, Title II: Parent and Child, Chapter I: Parentage, Section 1546.

37 *Thailand Civil and Commercial Code 2468 B.E.,* Book V: Family, Title II: Parent and Child, Chapter I: Parentage, Section 1536.

38 *Thailand Civil and Commercial Code 2468 B.E.*, Book V: Family, Title II: Parent and Child, Chapter I: Parentage, Section 1547.

39 *Thailand Civil and Commercial Code 2468 B.E.,* Book V: Family, Title II: Parent and Child, Chapter I: Parentage, Section 1548.

40 *Thailand Child Protection Act B.E. 2546 (2003)* (Unofficial Translation). Accessed at: http://web.krisdika.go.th/data/outsitedata/outsite21/file/CHILD_PROTECTION_ACT_B.E._2546.pdf.

child's exclusion from research, even if the father is the biological parent and primary carer for the child. Consider the following scenario.

Scenario #1: The legal status of fathers

> The biological mother provides written informed consent (in the presence of the father) for her son to be enrolled in a clinical trial. The boy is enrolled and the study commences. Mid-way through the trial, changes in the protocol require a re-consent process for the child However, only the child's father is available to provide re-consent. When the trial staff ask for legal documentation, they discover the father is not married to the child's mother. Unsure if the father is the legal parent of the child, the trial staff attempt to contact the mother, but are unable to locate her. The trial staff then tell the father that he cannot consent for the child unless he is legally registered as the child's parent. The trial staff remove the child from the study.

2.2 Who is a guardian for the purposes of informed consent in children

There are conflicting legal definitions and frameworks for determining who is a legal guardian for the purposes of informed consent. Under Thai family law, a legally competent adult may be appointed as legal guardian[41] through the will of the last surviving parent,[42] or by application to the Court from a relative or the Public Prosecutor.[43] A legal guardian is generally appointed when a child is without parental care either because both parents have died or one or both parents have been deprived of parental rights and responsibilities – partially or fully – through a legal order.[44] The guardian becomes the legal representative for the child until he or she becomes '*sui juris*'[45] (either by age or legal marriage).[46] The role of a guardian is thus envisaged to replace a parent, extinguishing their rights and responsibilities, including their authority to act as the legal representative for the child.

In contrast, the *Child Protection Act B.E. 2546 (2003)* offers a broad definition for 'guardian', which includes adoptive parents, step parents, employers, and

41 *Thailand Civil and Commercial Code 2468 B.E.,* Book V: Family, Title II: Parent and Child, Chapter III: Guardianship, Section 1587.

42 *Thailand Civil and Commercial Code 2468 B.E.,* Book V: Family, Title II: Parent and Child, Chapter III: Guardianship, Section 1585-1586.

43 *Thailand Civil and Commercial Code 2468 B.E.,* Book V: Family, Title II: Parent and Child, Chapter III: Guardianship, Section 1586.

44 *Thailand Civil and Commercial Code 2468 B.E.,* Book V: Family, Title II: Parent and Child, Chapter II: Rights and Duties of Parent and Child, Section 1582.

45 The term 'sui juris' is used to denote 'legal competence', see *Thailand Civil and Commercial Code 2468 B.E.,* Book I: General Principles, Title II: Persons, Chapter I: Natural Persons, Part II: Capacity, sections 19, 20.

46 *Thailand Civil and Commercial Code 2468 B.E.,* Book V: Family, Title II: Parent and Child, Chapter III: Guardianship, Section 1585.

any other persons providing care or shelter to the child.[47] The *Child Protection Act B.E. 2546 (2003)* does not enumerate a formal legal process to establish guardianship over a child; and a person acting as 'guardian' for a child under the *Child Protection Act B.E. 2546 (2003)* does not appear to extinguish the rights and responsibilities of the child's legitimate parent.

The FERCIT *Ethical Guidelines on Paediatric Research* propose a definition for 'guardian' that encompasses both formally appointed legal guardians under Thai family law, and persons designated as guardians under the *Child Protection Act B.E. 2546 (2003).* However, in bringing together formally appointed legal guardians, and guardians informally caring for a child, the FERCIT guidelines introduces more confusion than clarity over who is authorised to represent the child for the purposes of informed consent.

To confuse matters further, it is common for children to grow up in intergenerational or skip-generation households in Thailand. Consider the following scenario.

Scenario #2: Intergenerational households – grandparents caring for the child

> In northeast Thailand, a grandparent brings his sick grandchild to a community health clinic. When the child tests positive for a parasite, clinical trial staff explain to the grandfather that the child is eligible to participate in a clinical trial. The grandfather is keen to enrol his granddaughter. But, when he is asked to produce legal documentation, the trial staff discover he is not formally recognised as the legal guardian of the child. The grandfather explains that he takes care of his grandchild while his son and daughter-in-law work to support the family. The researchers tell the grandfather that given the nature of the study (and the risks), written informed consent must be obtained from at least one parent, preferably the mother. The researchers try to contact the child's mother by phone. She provides verbal consent, but is unable to travel to the study site to provide written consent. The child is not enrolled in the study.

In Thailand, as in much of Southeast Asia, it is not uncommon for children to grow up in the care of grandparents.[48] Childcare and elderly care are intertwined in a broader system of intergenerational reciprocal family care.[49] Adult children assume social and financial responsibility for their ageing parents,[50] and in exchange grandparents contribute to the care and upbringing

47 Section 4, *Thailand Child Protection Act B.E. 2546 (2003)* (Unofficial Translation). Accessed at:http://web.krisdika.go.th/data/outsitedata/outsite21/file/CHILD_PROTECTION_ACT_B.E._2546.pdf.

48 J. Knodel and M.D. Nguyen, 'Grandparents and grandchildren: care and support in Myanmar, Thailand and Vietnam' (2015) 35 *Ageing & Society* 1960-1988, 1963; J. Knodel and W. Pothisiri, 'Intergenerational Living Arrangements in Myanmar and Thailand: A Comparative Analysis' (2015) 30(1) *J Cross Cult Gerontol* 1-20, 17.

49 Ibid.

50 Ibid.

of grandchildren.[51] As part of this arrangement, parents often leave children in the care of grandparents, while pursuing work outside the home for the financial benefit of the entire family.[52] According to Knodel et al., the majority of elderly Thais receive some form of material or financial assistance from their adult children, and at least half contribute to some form of childcare.[53] Because intergenerational family care is a widely accepted socio-cultural norm in Thailand, grandparents seldom seek formal recognition for their role as primary caregivers for their grandchildren. Moreover, in the vast majority of cases, parents are still actively involved in the care and upbringing of their children, albeit remotely, whilst working for the benefit of the whole family. If grandparents were to formalize their status as legal guardians, it could potentially extinguish the rights and responsibility of parents, while not capture the intergenerational dimension of childcare. But, in the absence of a legally recognised caregiving relationship, the status of grandparents remains unclear for the purposes of informed consent in paediatric clinical research. The FERCIT ethical guidelines appear to acknowledge this quandary: 'in Thailand, it is not common to go to court to seek an order for guardianship, so it is a problem with whom to get consent.'[54]

Kalabuanga et al., observed similar challenges in the Democratic Republic of Congo, noting that a requirement for a legally authorised representative 'fails to take into due account informal social mechanisms' which often rely on relatives and community to care for a child in *lieu* of biological parents.[55] So, 'when a child is brought to a clinic and is eligible for a trial, a question arises whether the caregiver is legally entitled to consent'.[56] Vischer et al., in their study on perceptions of the Good Clinical Practice Guidelines (ICH-GCP) in sub-Saharan Africa observed that it was common for relatives to care for a child in place of biological parents, making it difficult for trial staff to include such children.[57] Strode et al., have highlighted an ethico-legal tension in South Africa, whereby the *National Health Act* (section 71) recognises only parents

51 J. Knodel and N. Chayovan, 'Intergenerational Relationships and Family Care and Support for Thai Elderly' (2009) 33 *Ageing International* 15-27.

52 J. Knodel, B. Teerawichitchainan, V. Prachuabmoh and W. Pothisiri, *The Situation of Thailand's Older Population: An Update based on the 2014 Survey of Older Persons in Thailand*, (HelpAge International: November 2015). Available at: https://www.helpage.org/where-we-work/east-asia/thailand/ (27 October 2021) Knodel and Nguyen 2015 (n 48) 17.

53 J. Knodel and B. Teerawichitchainan, 'Grandparenting in developing South East Asia: comparative perspectives from Myanmar, Thailand and Vietnam' in V. Timonen (ed), *Grandparenting Practices around the World* (Bristol: Policy Press Scholarship, 2018) 65-88; see also B. Ingersoll-Dayton, S. Punpuing, K. Tangchonlatip and L. Yakas, 'Pathways to grandparents' provision of care in skipped-generation households in Thailand' (2018) 33 *Ageing and Society* 1429-1452; Knodel and Nguyen 2015 (n 48) 10.

54 FERCIT Ethical Guidelines for Pediatric Research 2015 (n 31#0) Section 2.3.

55 Kalabuanga et al., 2016 (n 20) 66.

56 Ibid, 66.

57 Vischer et al., 2016 (n 24) 1043.

and legal guardians as legal representatives for the purposes of consent, while national ethical guidelines allow parental substitutes if certain conditions are met.[58]

This gap between formal legal requirements and socio-culturally realities can lead to an ethically perplexing outcome, whereby a primary carer holds no legal authority in the informed consent process, while the legal representative holds little or no role in the everyday care of the child.

3 DISCERNING THE LEGAL REQUIREMENTS FOR CHILDREN WITHOUT A LEGAL REPRESENTATIVE

There are certain categories of children whose particular circumstances pose unique legal challenges to the informed consent process. For instance, children of minor parents, children of parents without legal status, and children without parental care do not readily have legally recognised representatives to act on their behalf. The lack of ethical guidance to navigate the legal requirements of informed consent in these children has tended to result in their presumptive exclusion from paediatric clinical research.

3.1 Children of minor parents

International and regional ethical guidelines do not address the informed consent process in children of minor parents. Domestic laws also tend to obscure the distinction between who is the legitimate parent for a child and who is the legal representative of a child. This has implications for the child of a minor parent, whose legitimate parent may not be legally competent to act as a legal representative. In this regard, determining who should provide informed consent for a child of minor parents can become an ethico-legal quandary, both in deciding who is best placed to hold the ethical duty to safeguard the interests and welfare of the child, and who holds legal authority to act on behalf of the child for the purposes of informed consent.

Under Thai family law, a child is a 'minor', and subject to the authority of a legal representative until he or she becomes *sui juris* (legally independent).[59] A child becomes *sui juris* when he or she turns 20 years of age, or enters into a legal marriage prior to the age of 20 years.[60] The age of

58 A.E. Strode, P.P. Singh, C.M. Slack, and D.R. Wassenaar, 'Research ethics committees in a tight spot: Approving consent strategies for child research that are *prima facie* illegal but are ethical in terms of national guidelines' (2018) 108(1) *SAMJ* 828-832, 829.

59 *Thailand Civil and Commercial Code 2468 B.E.,* Book V: Family, Title II: Parent and Child, Chapter II: Rights and Duties of Parent and Child, Section 1566.

60 *Thailand Civil and Commercial Code 2468 B.E.,* Book I: General Principles, Title II: Persons, Chapter I: Natural Persons, Part II: Capacity, sections 19, 20.

marriage is 17 years (or the completion of the eighteenth year). However, it is legally possible for a child as young as 13 years old to enter into a legal marriage with Court approval.[61]

This raises the question of who is the legal representative for a child of an unmarried minor. According to Thai family law, a child born of a woman who is not married is the legitimate child of that woman.[62] However, a legitimate parent can only be the legal representative for a child if the parent is also *sui juris*. In other words, an unmarried minor could not be the legal representative of her child, even if she is the legitimate parent of the child. That marital status should be the sole basis to determine the suitability of a minor parent to provide informed consent for a child raises obvious concerns as to the ethical validity of informed consent, but it also raises concerns for the protection and fair treatment of children of minor parents in clinical research. For instance, a child of a married 14 year-old mother could be enrolled in a clinical trial on the basis that her mother is presumptively competent as a result of her marriage, whereas a child of an unmarried 19-year old mother would not be eligible to enrol in a trial, even if her mother demonstrated sufficient maturity, understanding and capacity to consent on behalf of her child. Consider the following scenario.

Scenario #3: Children of minor parents

> A toddler (3 years old) arrives at a village health clinic with his 17 year-old unmarried mother and grandmother. The young mother is soothing her son who has a high fever and is crying. The clinic trial staff tell the mother that her son is eligible to participate in a clinical trial on febrile illness, which will help diagnose and treat the cause of his fever. The mother, who is studying to be a nurse, listens intently and is keen to enrol her son in the study. The grandmother, however, is suspicious of the clinical trial staff and does not want her grandson enrolled. The trial staff are unsure whether to accept the consent of the mother who appears to be the primary carer for her son and better informed on her son's care needs, or to respect the refusal of the grandmother, given the mother's young age. In the end, the child is not enrolled in the study.

De Pretto-Lazarova et al., conducted a systematic review of informed consent in children of minor parents, citing an apparent lack of an 'ethically acceptable

61 *Thailand Criminal Code B.E. 2499 (1956)*, Book II: Specific Offences, Title IX: Offences Relating to Sexuality, Section 277.

62 *Thailand Civil and Commercial Code 2468 B.E.,* Book V: Family, Title II: Parent and Child, Chapter I: Parentage, Sections 1546; *Thailand Civil and Commercial Code 2468 B.E.,* Book V: Family, Title II: Parent and Child, Chapter II: Rights and Duties of Parent and Child, Sections 1564, 1566.

approach to the IC [informed consent] process' in paediatric research.[63] It may be possible to resolve the ethico-legal gap in some instances through a modification of informed consent requirements, particularly in research that envisages a risk that is negligible or well below the *de minimis* range. However, in the absence of any ethical guidance on this point, it is likely that children of minor parents will be presumptively excluded from clinical research, not out of an ethical concern but due to the absence of a legal framework to recognise the role of minor parents the informed consent process.

3.2 Children of parents without legal status

There appears to be no ethical guidance on how to navigate informed consent in children of parents without legal status. In some cases, a child may be an illegal migrant, or undocumented refugee, living with parents who do not have legal status or standing in the jurisdiction of the clinical research study. In other instances, a child may be part of an ethnic minority or religious group that is persecuted or discriminated and, as such, denied legal standing in the jurisdiction of the clinical research study. In both situations, the parent is not legally recognised to act on behalf of the child in the informed consent process. In the absence of specific laws or ethical guidance on this point, there remains a degree of legal precarity as to whether the parent will be allowed to give informed consent, which can affect the fair treatment of children of parents without legal status. Consider the following two scenarios.

Scenario #4A: Children of refugee parents

> A child, born in a Thai refugee camp, is eligible to enrol in a malaria study. The malaria clinical trial is run out of a health centre that has been providing health care services to undocumented migrants and refugees living in the area for over forty years. The research clinic has built strong ties with local government authorities, which has allowed them to establish an ethically and socio-culturally appropriate process for recruiting and enrolling children of parents without legal status. The mother is keen to for her son to join the study and the child is enrolled.

Scenario#4B: Children of persecuted or discriminated ethnic minorities

> A child, born in an ethnic hilltribe in North eastern Thailand, is eligible to enrol in a vaccine trial. The clinical trial is being conducted by a foreign commercial sponsor through a Thai university-hospital. The mother is keen for her son to join the study. However, when the trial staff ask for legal documentation, they learn

63 A. De Pretto-Lazarova, D.O. Brancati-Badarau, and C. Burri, 'Informed consent approaches for clinical trial participation of infants with minor parents in sub-Saharan Africa: A systemic review' (2020) 15(8) *PLOS One* 1-23. DOI: 10.1371/journal.pone.0237088.

> the mother does not have legal status in Thailand. The child is not enrolled in the study.

A child of parents without legal status is likely to be viewed in the same way as a child living in the informal care of grandparents or relatives. It would fall on the ethics committee to determine when and under what conditions the legal requirements of informed consent could be modified to recognise carers not legally authorised to provide informed consent. Such a decision would likely turn on the nature of the research study – the benefit-risk ratio, the age of the child participants, and the research sponsor's willingness to deviate from international guidelines. It is important to underscore that a child's exclusion would not necessarily be out of ethical concern, but due to a lack of legal guidance on how to navigate the informed consent process in children without legal representatives. Moreover, any modification to the informed consent process, while enabling a child's enrolment, would not address the broader question of whether children, as a class of persons, are entitled to the guidance and support of a proxy in the informed consent process to enable their participation in clinical research, particularly where the research holds a prospective medical benefit for the child.

3.3 Children living without parental care

Beyond the question of who should act as proxy for a child, is the broader question of when a child should be ethically and legally entitled to provide informed consent in clinical research. For the most part, ethical guidelines have deferred to domestic law to determine when and under what conditions a child will be legally permitted to provide informed consent in medical research. However, in the absence of specific laws on human subject research, there may be differing age-barriers for adulthood, which can introduce confusion around when a child will be deemed legally capable of providing informed consent in research. As Colom and Rohloff observe, 'regulations vary significantly from country to country regarding when adolescents can provide legal consent' and 'even when legal frameworks allow adolescents to seek contraception services without parental permission', they may still require a legal representative to consent on their behalf to medical research.[64] Consider the following scenario.

Scenario #5: Children living without parental care

> An 18 year-old boy is living on the streets in Bangkok. An NGO worker notices the boy is unwell and takes him to a public university-hospital. The boy is diagnosed with cancer, and is placed on a waiting list for treatment. The oncologist

64 Colom and Rohloff 2018 (n 18) 12.

> tells the boy that he may be eligible for treatment through a clinical drug trial. However, because he is under 20 years of age, written consent is required from both parents or a legal guardian. The boy tells the oncologist that he was kicked out of his home when he was 13 year-old and has been living on his own since. After consulting with the ethics committee and the research sponsors, the oncologist regretfully tells the boy he cannot enrol him in the trial.

Under Thai law, there are conflicting definitions for a child, and differing age barriers for adulthood. Under the *Child Protection Act B.E. 2546 (2003)* a child is defined as a person under the age of 18 years but does not include persons legally married before the age of 18 years. Under the *Civil and Commercial Code B.E. 2468 (1925)*, a child 'ceases to be a minor and becomes *sui juris*[65] *when they reach the age of 20 years, or become legally married prior to 20 years of age. Under the Mental Health Act B.E. 2551 (2008)*, a patient who is 18 years or older and legally competent can provide written informed consent to medical treatment. However, children are not recognised as legally competent until they become 'sui juris', leaving open the question of whether a child who is 18 years old but unmarried is legally competent for the purposes of providing informed consent in medical research.

In the absence of specific legislation establishing a minimum age for informed consent in medical research or a clear framework to assess children's capacity to provide informed consent in medical research, there is no clarity on when and under what conditions a child will be able to provide informed consent in a research study. This uncertainty has direct implications for children living without parental care, who may be presumptively excluded from a study – not out of ethical concern, but due to an absence of a legally authorised representative and a legal mechanism to assess their capacity to consent. While it may be possible to obtain a waiver in the informed consent process to enable a child's participation in clinical research, particularly where the anticipated risk in a study is negligible, again, this does not resolve the broader question of whether all children – including those living without parental care – have a right to support in the informed consent process whether through a proxy or on their own, to enable their access to and participation in clinical research.

There have been calls for more pragmatic ethical guidelines for clinical research in children, which better account for the limited regulatory infrastructure and diverse socio-cultural realities in lower- and middle-income coun-

65 See Thailand Civil and Commercial Code 2468 B.E., Book I: General Principles, Title II: Persons, Chapter I: Natural Persons, Part II: Capacity, sections 19, 20.

tries.[66] However, the legal complexities surrounding informed consent in children are not unique to LMICs. As Lepola et al., reveal in their comparative study of 27 European countries,[67] there are considerable differences in national legal requirements on informed consent and assent, which have often resulted in considerable time and resources being spent on reconciling these differences in multicentre clinical trials.[68] Lepola et al., have developed an 'Informed Consent and Assent Guide' as a tool to not only enhance ethical standards of informed consent practice, but also engender common practices for informed consent across multinational clinical paediatric trials. Whether such a tool could be development and implemented in LMICs remains questionable. This is in part because many of the legal uncertainties arising in informed consent in paediatric clinical research emanate from the absence of relevant laws, rather than differences between existing applicable law. In this regard, we contemplate whether international legal frameworks, such as the UN Convention on the Right of the Child, could offer guidance on informed consent in paediatric clinical research where domestic laws are conflicting and ethical guidance is lacking.

4 Navigating legal uncertainty in informed consent in children

The UN Convention on the Rights of the Child (CRC)[69] is an international human rights treaty, adopted by the United Nations General Assembly in 1989.[70] It is said to be the most comprehensive,[71] and most ratified of all

66 P.D. Joseph, P.H.Y. Caldwell, A. Tong, C.S. Hanson, and J.C. Craig, 'Stakeholders View of Clinical Trials in Low- and Middle-Income Countries: A Systemic Review' (2016) 137(2) *Pediatrics* 1-19. e20152800.

67 P. Lepola, A. Needham, J. Mendum, P. Sallabank, D. Neubauer, and S. de Wildt, 'Informed consent for paediatric trials in Europe' (2016) 101 *Arch Dis Child* 1017-1025. DOI: 10.1136/archdischild-2015-310001.

68 P. Lepola, M. Kindred, V. Gianuzzi, H. Glosli, M. Dehliner-Kremer, H. Dalrymple, D. Neubauer, G.B. Boylan, J. Conway, J. Dewhurst, and D. Hoffman, 'Informed consent and assent guide for paediatric clinical trials in Europe' (2021) 0 *Arch Dis Child* 1-9. DOI:10.1136/archdischild-2021-322798.

69 United Nations Convention on the Rights of the Child, adopted 20 November 1989, entered into force 2 September 1990, 1577 U.N.T.S. 3 ('CRC').

70 UN General Assembly, 'Convention on the Rights of the Child,' UNGA Resolution 44/25, adopted without a vote, 61st plenary meeting, 20 November 1989.

71 J. Tobin, 'Introduction: The Foundation for Children's Rights' in J. Tobin and P. Alston (eds) *The UN Convention on the Rights of the Child: A Commentary* (Oxford: Oxford University Press, 2019) 1-20, 1.

human rights conventions, with 196 States parties agreeing to be bound by its legal provisions.[72]

At the crux of the CRC framework is its conception of the child as an independent rights-holder, whose voice and agency, even if not determinative, must be respected and listened to by adults exercising influence in her everyday life. It re-orients the informed consent process from an entitlement held by the proxy over the child, to a right vested in the child, placing an obligation on those adults around the child – the proxy, researchers and ethics review committees – to provide support and guidance that enables children's access and participation in informed consent in the research setting.

4.1 Recognising the common responsibilities of both parents in the informed consent process

A unique feature of the CRC is its respect and support for both parents in the care and upbringing of a child.[73] Indeed, when the CRC was adopted, it offered more support and assistance to parents than any previous instrument under international law.[74] Article 2(1) requires States to respect and ensure children's rights without any discrimination, which includes preventing discrimination against a child on the basis of his or her parents. Article 18(1) imposes a legal obligation on States to 'use their best efforts' to 'ensure recognition of the principle that both parents have common responsibilities for the upbringing and development of the child.' Article 5 enshrines a right for all children to receive appropriate guidance and direction from both parents that is consistent with their evolving capacities in the exercise of rights. Taken together, articles 2(1), 18(1), and 5 provide a framework to recognise the legal authority of both parents – fathers and mothers – in the informed consent process.

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72 As of June 2021, 196 State parties had ratified or acceded to the UN Convention on the Rights of the Child. See United Nations Treaty Collection, Status of Treaties. Accessed at: https://treaties.un.org/Pages/ViewDetails.aspx?src=TREATY&mtdsg_no=IV-11&chapter=4&clang=_en (27 October 2021).

73 J. Doek, 'The Human Rights of Children: An Introduction' in U. Kilkelly and T. Liefaard (eds) *International Human Rights of Children* (Springer Nature Singapore, 2018) 1-15, 12-13; J. Tobin and S. Varadan, 'Article 5: The Right to Parental Direction and Guidance Consistent with a Child's Evolving Capacities' in John Tobin and Philip Alston (eds) *The UN Convention on the Rights of the Child: a Commentary* (Oxford University Press, 2019) 159-185.

74 See Articles 3(2), 5, 9, 10, 16, 18(1), 18(2), 20, 21(a), 22(2), 23(2), 23(3), 24(2), 27(3), 27(4) and 29(1)(c), 37(c), 40(2)(b)(ii), 40(2)(b)(iii), CRC.

4.2 Recognising informal carers in the informed consent process

The CRC underscores the importance of 'family' and 'family environment' for children's realization and enjoyment of rights. The preamble of the CRC recognises 'family' as the 'fundamental group of society'[75] and the 'natural environment'[76] for the child's growth and well-being. Article 5 recognises the role of not just parents, but wider family and community 'where applicable' and 'provided for by local custom.'[77] The explicit reference to 'extended family and community' within article 5 reflects an understanding that family structures and parenting arrangements may not always be formalized under the law, and are often dictated by socio-cultural norms.[78]

Applied to the paediatric clinical research setting, article 5 and the CRC may offer a basis to justify a wider reading of 'legally acceptable representative' that takes into account extended family care arrangements where it is provided for by local custom. In this regard, if there is no direct legislation on paediatric clinical research, or conflicting legal frameworks, the CRC could offer guidance, recognising a child's right to receive support and direction from not just parents but extended family and community, where such caregiving arrangements are accepted within the community. Such an approach would not only enable practical solutions but also support community-led practices in the ethical conduct of research.

4.3 Recognising the child's right to guidance and direction in the informed consent process

The CRC recognises that all children, even very young children, are rights-holder entitled to guidance and direction that supports and respects their developing capacities in the exercise of rights.[79] The UN Committee on the Rights of the Child has said the concept of 'evolving capacities' should act as an enabling principle, requiring adults to provide guidance and direction that not only compensates for the child's lack of knowledge, experience and understanding but also supports the child's capacities to the maximum extent possible.[80] The CRC thus moves beyond the binary framework for legal com-

75 Preamble para 4, CRC.

76 Preamble para 5, CRC; A. Lopatka, 'An Introduction to the United Nations Convention on the Rights of the Child' (1996) 6 *Transnat'l L. & Contemp. Probs.* 251, 255.

77 Article 5, CRC.

78 Tobin and Varadan 2019 (n 73) 169-170.

79 S. Varadan, 'The Role of Parents in the Proxy Informed Consent Process in Medical Research involving Children' (2020) 28(3) *International Journal of Children's Rights* 521-546.

80 A. Daly, 'Assessing Children's Capacity: Reconceptualising our Understanding through the UN Convention on the Rights of the Child' (2020) 28(3) *International Journal of Children's Rights* 471-499; S. Varadan. 'The Principle of Evolving Capacities under the UN Convention

petency, acknowledging that a child's capacities – physical, cognitive, moral, social, emotional and spiritual – will likely be acquired in a dynamic and fluid process, influenced by genetic, cultural, social and environmental factors.[81] In the context of clinical research in Thailand, this would mean that children without legally authorised representatives would not be presumptively excluded from research, but rather assessed for their actual capacity to give informed consent, and then where necessary, provided with appropriate guidance to enable their participation in the informed consent process. In the case of children of minor parents, it would require a process that respects both the minor parent's 'capacity rights' to provide informed consent on behalf of her child, and the child's right to guidance that secures her protection and participation in the informed consent process in the paediatric clinical research setting.

It is important to clarify, that we are not proposing that the CRC be used as a direct substitute for national laws and regulations on paediatric clinical research. As with all international instruments, the CRC will generally not translate into national law, unless a State party takes direct measures to incorporate and implement its legal obligations into domestic law, policy and jurisprudence.[82] As Kilkelly and others observe, how a State chooses to implement the CRC, and the measures it takes in this regard, will have a bearing on the culture of compliance and support for children's rights.[83] As such, the degree to which the CRC will be able to function as a framework to negotiate the legal complexities surrounding informed consent in paediatric research will depend in some part on what measures the State has taken – legal and non-legal – to incorporate and implement the CRC.[84] That said, with every country in the world (except the United States of America) having agreed to be legally bound by the provisions of the CRC, it offers the prospect of a viable and common framework to navigate the legal uncertainties in informed consent in a manner that accords respect and protection to children's rights in the paediatric clinical research setting.

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on the Rights of the Child' (2019) 27(2) *International Journal of Children's Rights* 306-338; G. Lansdown, *The Evolving Capacities of the Child* (Florence: UNICEF Innocenti, 2005).

81 Tobin and Varadan 2019 (n 73) 173.

82 U. Kilkelly, 'The UN convention on the rights of the child: incremental and transformative approaches to legal implementation' (2019) 23(2) *The International Journal of Human Rights* 323-337. DOI: 10.1080/13642987.2018.1558974K; K. McCall-Smith, 'To incorporate the CRC or not – is this really the question?' (2019) 23(3) *The International Journal of Human Rights* 425-441. DOI:10.1080/13642987.2018.1558990.

83 U. Kilkelly, L. Lundy and Bronagh Byrne, 'The Convention on the Rights of the Child: A Thematic Analysis of the Incorporation Journey' in U. Kilkelly, L. Lundy and B. Byrne (eds) *Incorporating the UN Convention on the Rights of the Child into National Law* (Intersentia, 2021) 333-351; Kilkelly 2019 (n 82) 332-333.

84 McCall-Smith 2019 (n 82).

Conclusion

Conducting clinical research in children is ethically and legally complex.[85] Part of that complexity emanates out of the legal ambiguities surrounding the role of the proxy in the informed consent process. This uncertainty is compounded by the diversity of family structures and parenting arrangements, which in most parts of the world involves informal carers within the extended family and wider community. The aim of this chapter has been to unravel some of the legal complexity, by demonstrating the degree of uncertainty that can arise when there are no direct laws or regulations relating to informed consent in paediatric clinical research. It contemplated how international legal frameworks, such as the UN Convention on the Rights of the Child, could be applied to negotiate these legal uncertainties in a manner that recognises the child's right to access and participate in informed consent in paediatric clinical research. By placing the child at the centre of the decision-making process, the CRC provides a framework that accommodates a diversity of socio-cultural environments, while also recognising the child's right to guidance and direction that enables her access to and participation in the informed consent process.

However, more research is needed to better understand the implications of legal uncertainty in informed consent and its impact on children's recruitment and enrolment in paediatric clinical research. A more comprehensive comparative legal study is needed on informed consent laws for children in lower- and middle-income countries, as well as a survey of best practices which have been developed to resolve legal gaps in informed consent practices. Finally, further research is needed to explore how international legal frameworks, such as the CRC, could be practically applied in the everyday research setting, assessing the challenges and benefits of using human rights frameworks alongside ethical guidelines.

85 CIOMS 2021 (n 21) 84-85.