1. **What is the study’s purpose?**

The purpose of this study is to examine the regulatory framework for clinical trials with neonates (a baby aged 0-28 days) in Ireland, in order to make recommendations for reform. Neonatal clinical trials represent a growing area in Ireland. The number of neonatal trials is likely to continue to rise, due to the development of specialist research units, most notably the Irish Centre for Fetal and Neonatal Translational Research (INFANT) in University College Cork Hospital, which is seen as an international leader in perinatal healthcare.

The specific objectives of the study were to:

- a. analyse the current challenges in the regulatory framework for clinical trials with neonates in Ireland;
- b. assess the contribution that an approach based on international children’s rights law could make in this area;
- c. identify reform measures that are needed in the regulation of clinical trials with neonates in Ireland.

2. **How was the study undertaken?**

The thesis utilises a combination of doctrinal, socio-legal and comparative methodologies. As follows:

**Doctrinal methodology**

Doctrinal methodology refers to the analysis of legal materials, such as statutes, cases and critical commentary. This methodology was used to give an overview of the regulatory framework for clinical trials with neonates in Ireland. The main legal and ethical instruments are critically analysed and compared, in order to highlight common principles, areas of divergence and potential gaps in the current framework. Doctrinal analysis is also used to review and analyse the UN Convention on the Rights of the Child 1989, as well as General Comments by the Committee on the Rights of the Child, in order to assess the contribution that this branch of law can make in this area. Academic commentary is utilised to explore varying approaches and contrasting views on central issues in the thesis.

**Socio-legal methodology**

Socio-legal methodology is focused on how the law operates in society. The thesis uses such a methodology in order to ensure that the recommendations for reform are based on an analysis of how they will affect the lives of all those involved in clinical trials with neonates, such as researchers, research ethics committee (REC) members and proxy decision makers. The thesis draws on empirical studies relating to REC members in Ireland and parents whose children were involved in clinical trials. In addition, visits were undertaken to RECs and neonatal intensive care units (NICUs) in Ireland and the US. During these visits, informal interviews were undertaken with REC members, healthcare professionals, researchers and administrative staff in...
order to gain a comprehensive overview of the issues that are in need of reform in the area and also in order to ensure that the recommendations of the thesis are practically relevant.

**Comparative methodology**

The thesis also utilises comparative methodology. Aspects of the Irish regulatory system are compared at different points with systems in the US and various European countries. This is done in order to increase understanding of the central issues in the area and to identify possible solutions for reform. The approaches of European countries and the US are evaluated against the independent benchmarks of international children’s rights, and suitable recommendations for regulatory reform in Ireland are made based on this analysis.

**3. What are the key findings?**

**3.1 The regulatory framework for clinical trials with neonates in Ireland is insufficient.**

» There is a lack of legal regulation in this area. Clinical trials with investigational medicinal products (IMPs) are regulated by a statutory instrument (European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, S.I. No. 190 of 2004) and an EU Regulation (Council Regulation 536/2014 on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC (2014 Regulation)). However, all other types of clinical trials are not regulated by legal instruments.

» The law for clinical trials with IMPs lacks guidance on how researchers and RECs should carry out risk/benefit assessments.

» There is a lack of clarity regarding the legal permissibility of clinical trials with IMPs that do not offer the research participant the prospect of direct benefit (non-therapeutic clinical trials).

» Only RECs that govern clinical trials with IMPs are regulated by law in Ireland. All other RECs do not operate within a legal framework. For the latter type of REC, there is therefore a lack of guidance regarding their composition, structure and functioning.

» The law and policy surrounding proxy consent by parents and guardians for neonatal clinical trials lacks guidance in some key areas, in particular in relation to whose consent is required, whether the consent of both parents is required, and also in relation to minor parents.³

**3.2 The potential of international children’s rights law to enhance the regulation of clinical trials with neonates has, to date, remained unexplored.**


» Notwithstanding the fact that the CRC recognises the importance of evidence-based medical care for the realisation of children’s right to the highest attainable standard of health, the importance of clinical research has not been highlighted by the Committee on the Rights of the Child.

» The realisation of the rights of neonates as a group remains underdeveloped in international children’s rights law and guidance.

» There has been limited exploration in academic commentary of the issue of neonatal rights or children’s rights in the context of clinical research.

**4. What are the conclusions?**

**4.1 The Irish framework for clinical trials with neonates should be reformed in a number of respects. As follows:**

» The lack of regulation regarding clinical trials that fall outside the area of IMPs must be addressed. Clinical trials that do not include IMPs can also involve measures which may pose risks to participants and therefore must also be regulated by law.

» Legal clarity is required for all clinical trials with neonates regarding risk/benefit assessments and the level of risk that should be permitted in non-therapeutic clinical trials.

» Legal clarity regarding the composition, structure and responsibilities of all RECs in Ireland must be provided.

» Clear guidance and training are required for REC members in Ireland regarding neonatal clinical trials.

» Legal clarity regarding who must provide consent for neonatal clinical trials should be provided.

» Guidance and training for researchers and REC members should be developed regarding the manner in which consent should be obtained from proxy decision makers.

³ Parents who are under the age of 18.
4.2 An approach based on international children’s rights law can greatly contribute to the reform of the regulatory framework for clinical trials with neonates in the following ways:

- A children’s rights approach is a particularly practical way of reforming the regulatory framework for neonates in clinical trials. It provides a set of overarching norms which can be used to develop more specific recommendations in areas inadequately addressed by research law and ethics. The following benchmarks were developed in order to assess the law in the area, and make recommendations for reform:
  - The neonate is an independent rights-holder;
  - The requirement for a protective framework (Article 19 CRC);
  - The requirement for rights-based decision-making (Article 3 CRC and General Comment No. 14);
  - Right to representation (Article 12 CRC);
  - Right to parental/guardian protection.

- A children’s rights approach ensures the centrality of neonates in the analysis and reform of the area. It aims to ensure that the rights of neonates shape the development of law, policy and practice in the area.

- An approach based on international children’s rights law is particularly useful in identifying areas in need of reform. It focuses on the particular characteristics of neonates and draws attention to the need for additional measures or adjusted practices for this group.

- The practical relevance of a children’s rights approach is also linked to the fact that international children’s rights law is binding on UN Member States which have ratified the CRC.

- A children’s rights approach also draws attention to wider governmental and social obligations. It focuses on states’ obligations to develop a broad supportive infrastructure, including the conduct of national review of law and policy, the development of national policies, as well as the introduction of monitoring, children’s rights training and awareness-raising.

- A children’s rights approach is of particular relevance to neonates. Such an approach aims to ensure the realisation of neonates’ rights, notwithstanding the fact that they cannot contribute their views. In such a way, the regulatory framework for neonates in clinical trials can be improved, despite their inability to participate in the process of regulatory reform.

5. What are the recommendations?

1. Recommendations regarding law and policy reform

   Legal reform:
   1.1 A new Act should be developed to address all matters in health research with humans (Health Research Act).

   Risk and benefit:
   1.2 With regard to risk/benefit assessment for clinical trials with neonates, the adapted component analysis and its accompanying graph (see pp. 101-108) should be provided to researchers, RECs and bodies such as the Health Products Regulatory Authority (HPRA) and the European Medicines Agency (EMA). This approach involves the assessment of each individual intervention in trials to ascertain whether the risks outweigh the benefits, as well as an assessment of the impact of the intervention on the rights of the children in the trial.

   1.3 The proposed Health Research Act and the 2014 Regulation governing clinical trials with IMPs must be clear that non-therapeutic clinical trials with neonates are permissible so long as they involve no more than “minimal risk” and “minimal burden”.

   1.4 The following definition of minimal risk, drawing on the Council of Europe’s Additional Protocol to the Convention on Human Rights and Biomedicine, Concerning Biomedical Research 2005, should be adopted: “minimal risk refers to, at the most, a very slight and temporary negative impact on the health of the person concerned”.

   1.5 Minimal burden should refer to: “discomfort, which at the most, is temporary and very slight for the person concerned” (Additional Protocol 2005).

   1.6 The provision of examples of minimal risk in the Explanatory Report to the Additional Protocol 2005 is important in promoting consistency in this area.

   1.7 The Committee for Medicinal Products for Human Use (CHMP), a branch of the EMA, should draw up additional guidance for minimal risk in Phase I trials with IMPs with neonates.

   1.8 Training should be provided on the application of the adjusted component analysis.
The particularly vulnerable neonates:

1.9 For neonates who are non-viable or of uncertain viability, non-therapeutic interventions should be permitted only when the research cannot be carried out with other less vulnerable groups and when there is essentially “no risk” involved.

1.10 In emergency research, the approach of the 2014 Regulation is appropriate, as it requires such research to offer the prospect of direct benefit. However, the Regulation should address the level of risk allowable in situations where there is no standard treatment, and this should be compared with the “risk to the patients’ condition if left untreated”.

Complaints procedures and redress:

1.11 There should be an accessible complaints mechanism for parents or persons who were injured in a neonatal trial. This could be organised by an office within the Health Information and Quality Authority (HIQA).

1.12 There should be a no-fault compensation scheme for neonates who are injured in clinical trials, i.e., compensation should be automatically provided to neonates who sustain injury. Compensation should be paid for injury of an “enduring and disabling character”. It should not be provided for minor/curable effects or known side effects. However, a definition and examples should be given regarding “minor complaints”. Provision should also be made for compensation for “curable complaints”, the cure for which costs a significant amount of money.

Child advocates:

1.13 Child advocates should be utilised in neonatal clinical trials and should act as a representative for neonates’ rights. They should be present at meetings between proxies and researchers. After research information has been given to proxies, advocates should test their understanding and answer questions that arise. In the ethical approval of research, advocates should assess the trial regarding its implications for children’s rights, and should require REC members to justify their decisions from this perspective.

1.14 Advocates should have a qualification in a healthcare-related field, as well as training in communication, obtaining informed consent and children’s rights law and policy. They should also complete any training relevant to researchers and REC members.

1.15 Advocates should be appointed and paid by the Health Service Executive or HIQA and be assigned to a number of hospitals in a certain county or province in Ireland.

Review and monitoring of implementation:

1.16 As required by the CRC, a rigorous review of legislative and administrative measures regarding clinical research with neonates should be carried out in Ireland.

1.17 A comprehensive national strategy regarding children’s involvement in clinical trials should be developed and should be supported by data collection and consultation with stakeholders in this area.

1.18 National human rights institutions should be involved in monitoring the compliance of research institutions with children’s rights standards in the area, and this could involve on-site visits and reports.

1.19 Cross-sectoral coordination across government, between different levels of government, and between government and society, is required.

1.20 Ireland will need to allocate resources for the implementation of these recommendations.

Composition of a research ethics committee (REC) for clinical trials with neonates:

2.1 Research ethics committees (RECs) for clinical trials with neonates should have the following composition:

» Up to 21 members

» One-third laypersons (appointed by the government) and two-thirds healthcare professionals;

» Majority of the healthcare professionals should be neonatologists;

» One member with expertise in the developmental, ethical and psychological aspects of childhood;

» One child advocate;

» One lawyer;

» One statistician, if required, for trials with complex risk/benefit ratios.
Training and accreditation of RECs:

2.2 HIQA should provide training courses for all RECs in Ireland.

2.3 A mentor should be appointed and induction packs should be given to new REC members.

2.4 Conferences for REC members should take place to discuss issues in the area.

2.5 Researchers and RECs should receive training in international children’s rights law. This could be provided by national human rights institutions, such as the Ombudsman for Children’s Office (OCO). However, this would require the OCO to receive education in the legal and ethical requirements and issues in this field.

2.6 Monitoring and accreditation of RECs should be undertaken by HIQA and should include on-site visits and dummy reviews. In order to be accredited, a REC should be obliged to demonstrate that its standards comply with legal and ethical requirements, and this accreditation process should be renewed every three years.

2.7 For RECs which evaluate paediatric research, the accreditation programme should focus on legal and ethical requirements for paediatric research. This would require HIQA to have expertise in this area.

2.8 The development of standards for accreditation of RECs should include the views of parents and children affected by research.

2.9 RECs which review paediatric research could consult parents and children who may have been affected by the condition that is being studied.

Consent in emergency trials:

3.4 Prospective consent should be used for emergency trials, where possible.

3.5 When consent can only be obtained after the trial (deferred consent), a data safety monitoring board and community consultation should be utilised.

Improving the consent process:

3.6 Consent forms should be short and concise, should use large fonts and should highlight important information.

3.7 The language used should take into account persons of low literacy levels, and use terms that are understandable to laypersons.

3.8 The use of graphics should also be used to explain complex topics.

3.9 Multimedia could be used, particularly for those who cannot read, or for those who have sight or hearing impairments.

3.10 A set of guidelines should be drawn up by HIQA for researchers and REC members regarding the layout and design of consent forms and ways in which to effectively use graphics and pictures.

3.11 Training on such guidelines should be carried out.

3.12 Laypersons on RECs should report on the readability of the forms in REC meetings.

3.13 An approach based on continuous consent should be adopted. Discussions about the research should be conducted with proxies at repeat visits, in order to ensure that they are fully informed and are aware of their right to withdraw.

3.14 Those who obtain consent must be able to adapt the provision of information to the needs of proxies and must be trained in assessing parental understanding through the use of open-ended questions.

3.15 The consent process must also be appropriately adapted for proxies who have visual and hearing impairments.

3.16 For those whose first language is not English, consent information must be translated into the proxies’ first language. This could involve the use of an independent interpreter or the use of different language options on multimedia devices.

3.17 The person who obtains informed consent should not be the neonates’ treating physician, as this may lead to therapeutic misconception on the part of proxies or feelings of obligation.

3. Recommendations regarding proxy informed consent

Who consents?

3.1 The consent of both parents for neonatal trials should always be sought where reasonably practicable.

3.2 Consent from minor parents should also be obtained. There should be ample time for minors to discuss the research with their own parents if they wish.

3.3 In the case of a disagreement between proxies, a trial should not be enforced against the wishes of one parent.
6. What are the benefits of the study?

A major benefit of the study is that it explores an area of Irish law, policy and practice which is underdeveloped. The area of clinical trials with neonates in Ireland has not been the subject of in-depth inquiry or regulatory efforts. In addition, there is a lack of academic analysis on the subject.

This thesis clearly sets out the inadequacies of law, policy and practice in this important area affecting children’s lives.

A central benefit of the study is that it provides a set of concise and detailed recommendations for the reform of law, policy and practice regarding clinical trial with neonates in Ireland. These relate to the areas of risk and benefit in clinical trials, research ethics committees and proxy informed consent. These recommendations are based on an analysis of the legal material and academic commentary in the area, as well comparative research.

A further benefit of the study is that it provides the Irish government with guidance as to how to ensure that the regulatory framework in this area complies with the State’s obligations under international law. The recommendations of the thesis are based on an analysis of central principles of the UN CRC with which Ireland must comply.

A final benefit of the thesis is that it brings together the disciplines of research law, research ethics and international children’s rights in order to analyse the issue of clinical trials with neonates. In this way, it provides a framework regarding regulatory reform for other UN countries that have ratified the CRC. It also gives general guidance as to how a children’s rights approach could be utilised to explore further issues that affect children’s rights in the medical setting.