

## Legal comment

# Overview of European legislation on informed consent for neonatal research

Euricon, a European Union funded study,<sup>1</sup> had the objective of examining the issue of obtaining informed consent for neonatal research across Europe. As part of that project, legal representatives from these countries (see acknowledgements) were invited to a colloquium to report, discuss, and analyse European legal frameworks governing informed consent for neonatal research. The first author (PDV) presented a general overview of European law, which is the basis for this report. Furthermore, specific supplemental information from different countries was given by legal representatives from these countries, and is summarised in table 1.

Legally and ethically, informed consent of the subject is a requirement for biomedical research. However, there are differing interpretations in European Law of this requirement for neonatal research. Increasingly, to answer many neonatal research questions, there is a need for multinational recruitment to randomised controlled trials and studies, and thus a need for investigators to be aware of the differing, relevant, national legislation.

The aim of this paper is to discuss areas of consistency and inconsistency in the law or practice governing informed consent for neonatal research in ten European countries (Denmark, Finland, France, Germany, Greece, Ireland, Norway, Spain, Sweden, and the United Kingdom). In particular, the following areas are examined: whether there is specific law governing informed consent for research and, if so, what it is; the ethical review system, whether there are specific requirements for consent, whether benefit for the individual child is a specific requirement, and whether research of no direct benefit (so called non-therapeutic research) is legally permitted in minors—for example, the taking of extra blood samples purely for research purposes.

### The law governing neonatal research across Europe

A variety of laws and a plethora of ethical and professional guidelines govern the conduct of research within individual countries and across Europe.

The Declaration of Helsinki,<sup>2</sup> first adopted by the World Medical Assembly in 1964 and last amended in 1996, acts as a universal ethical guide. Throughout Europe, research ethics committees require that research trials and studies comply with this Declaration. Further guidance is proffered in the 1989 United Nations Convention on the Rights of the Child.

The principles of the Declaration of Helsinki have been incorporated into the International Conference on Harmonisation *Guidelines for good clinical practice* (ICH GCP).<sup>3</sup> United States and Japan, as well as the European regulatory authorities, have adopted the latter, to which all regulatory trials must comply in order to be granted authorisation to market a medicinal product.

A further measure to introduce harmonisation across Europe for the conduct of research is the Council of Europe's 1997 Convention for the Protection of Human

Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine.<sup>4</sup>

Article 16 of the Convention sets out general conditions to research on human beings:

- (a) there is no alternative of comparable effectiveness to research on humans;
- (b) the risks are not disproportionate to the potential benefits of the research;
- (c) the research project has been approved by the competent body after independent examination of its scientific merit, including assessment of the importance of the aim of the research, and multidisciplinary review of its ethical acceptability;
- (d) the persons undergoing research have been informed of their rights and the safeguards prescribed by law for their protection;
- (e) the necessary consent has been given expressly, specifically and is documented. Such consent may be freely withdrawn at any time.

The Convention further sets out restrictions for research on persons not able to consent, such as neonates. This research may only be undertaken when:

- (a) the above mentioned general conditions on research are fulfilled;
- (b) the results of the research have the potential to produce real and direct benefit to their health;
- (c) research of comparable effectiveness cannot be carried out on individuals capable of giving consent;
- (d) the necessary authorisation has been given specifically and in writing.

Exceptionally, research that does not have the potential to produce results of direct benefit to the health of the child is authorised in Article 17 of the Convention if additional conditions are satisfied:

- (a) the research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age, category or afflicted with the same disease or disorder or having the same condition;
- (b) the research entails only minimal risk and minimal burden for the individual concerned.

A new European Union Directive is being amended currently which includes both the ICH GCP guidelines and the above Convention. It is designed to regulate clinical trials further, but probably will be limited to those used to develop medicinal products within the pharmaceutical industry and thus will harmonise regulation of this type of trial across Europe.

Non-pharmaceutical research is subject to less standardisation. For these, investigators should comply with the Declaration of Helsinki if not also the above Convention for the Protection of Human Rights. However, different cultural and religious contexts, professional practices and historical antecedents have resulted in variations in practice and law throughout Europe.<sup>5</sup> Differences and

Table 1 Summary of legal requirements in Europe for research in neonates

Country	Legislation on research	Ethical review system	Consent	Benefit of the child requirement	Research of no direct benefit in minors permitted
Denmark	Act 503 of 24 June 1992 as amended by Act 499 of 12 June 1996	Regional RECs review all biomedical research projects on liveborn human subjects	With proxy consent risk evaluation is stringent. (Report 1335 of April 1997 by commission of Minister of Research and Minister of Health). Consent from both parents required where custody is shared. If one parent withholds consent, research cannot proceed Written proxy consent by guardian or legal representative following information (Medical Research Act 8(3) and 6(2)). Both parents to consent unless health care procedure is "routine" or welfare of child demands immediate decision (Child Custody and Right of Access Act 1983). Research Act permits research without consent in situations of "urgency" and expectation of "immediate benefit to the patient's health". Written proxy consent by those legally responsible (usually both parents). Research can be commenced without consent in cases of emergency; then consent from "members of the family" should be sought Proxy consent for minors from both parents (if share custody). Presumed consent permitted in cases of clinical emergency	Yes	Yes, when only minimal risk involved
Finland	Finnish Medical Research Act 1999	Medical Research Act regulates RECs. Each of the 20 hospital districts to have at least one REC. Duties and composition regulated		Research should directly benefit child's health or be of special benefit to other children or those with the same state of health and not possible to use other research subjects.	Yes, provided only minimal risk of harm or distress, benefit to similar groups, and if unable to use other research subjects.
France	1988 specific legislation on research	Regional RECs	Written proxy consent by those legally responsible (usually both parents). Research can be commenced without consent in cases of emergency; then consent from "members of the family" should be sought Proxy consent for minors from both parents (if share custody). Presumed consent permitted in cases of clinical emergency	Research must aim to provide a direct benefit to the health of the minor. However, placebo-controlled trials permitted (guidebook of Department of Health) Yes. Child must be expected to derive therapeutic, diagnostic or prophylactic advantage. There is some question of whether placebo controlled clinical trials are legal for neonates	Yes, provided there is only minimal risk expected and research will benefit other children with the same disease, handicap and age or there is no alternative solution No
Germany	Law governing clinical trials of drugs and medicinal products provides rules for involvement of minors	Submission of research protocols to RECs required by law for clinical trials of drugs and medicinal products. Declaration of Helsinki and professional rules for physicians require submission to RECs for other research projects Scientific committees instead of RECs. RECs only function in a few hospitals. In clinical drug trials, control by the National Drugs Organisation.			
Greece	Specific legislation on clinical drug trials		Proxy consent required (by legal representative)	Not specifically mentioned for research but stated in general legislation	Yes, for diagnosis or prevention of diseases applicable to the child
Ireland	All pharmacological research controlled by the Clinical Trials and Drugs Acts 1987–1990, as amended by the Irish Medicines Board Act 1995. Non-pharmacological research regulated by common law principles, the constitution and professional canons.	Competence of RECs for clinical trials must be approved by the Irish Medicines Board. Clinical trials need permission (including approval of investigators' indemnity arrangements) from the Irish Medicines Board (prior to REC approval). The statutory requirements only relate to clinical trials involving pharmacologically active preparations. Medical Practitioners bound by "A Guide to Ethical Conduct and Behaviour and to Fitness to Practise of the Medical Council" Five regional RECs cover the country. No review by one of these committees on all research involving humans. No local hospital or other committee acknowledged in the system. Small country and research community said to be surveyable.	Proxy consent by person independent of investigator. A six day period must elapse after patient or patient's legal representative has been given information about a trial before the start of the trial. This provision can be amended with the permission of the Irish Medicines Board. "Therapeutic privilege" has no role in obtaining consent to participation in research. Consent to participation in research is required even in a clinical emergency.	Yes	Not clear. Lawyers have divided views. It may be permitted if interventions are minor with negligible risk and if increase in scientific knowledge gained which may benefit other children
Norway	Specific legislation on clinical drug trials (4 Dec 1992, no 132). Legal obligations governed by general principles of law, specifically individual autonomy, Penal Code offers protection against bodily harm and mental coercion. Courts apply provisions of the Declaration of Helsinki		Proxy consent for minors (aged less than 18 years)	Yes, in Act on Children and Parents and Act on Legal Guardianship	Not clear. Lawyers have divided views. It may be permitted if interventions are minor with negligible risk and if increase in scientific knowledge gained which may benefit other children

Table 1 Continued

Country	Legislation on research	Ethical review system	Consent	Benefit of the child requirement	Research of no direct benefit in minors permitted
Sweden	No specific legislation. Patients right to self determination governed by Act on Professional Activities in Health and Medical Services (1998:531) and Health and Medical Services Act (1982:763). Medical Products Act (1992:859) regulates pharmaceutical clinical trials	No statutory regulation for RECs; however, ten regional RECs connected to six faculties of medicine covers biomedical research on humans. However, there is no explicit legal demand for REC approval for non-pharmaceutical regulatory research. REC status is only advisory. Coordination of the independent RECs is provided by the Medical Research Council's National Board for Research Ethics. No appeal can be made to the latter for an individual case. For clinical trials on drugs, the permission of the Medical Products Agency is required by law	Oral consent is allowed. Parents and Children Code regulates rights and duties of custodians of minors. Both custody holders to consent unless health care procedure is minor or best interest of the child demands immediate decision. Sometimes unclear whether or not consent of one parent sufficient. In extraordinary situations, patients unable to give consent may be included if trial is linked to treatment of patient's illness, has REC approval and may benefit the patient	Yes, following Sweden's ratification of the UN Convention on the Rights of the Child (1989); Article 3.1 states that the best interest of the child must be a primary consideration in all decisions concerning children.	Yes, provided no more than minimal risk involved
Spain	Specific laws of 1990 and 1993 regulate clinical trials on drugs and these stipulate requirements for minors	Ethics committees for clinical research in all hospitals where research is carried out	Proxy consent by legal representatives (Royal Decree, art.12.1 stipulates requirements of proxy informed consent). Before research starts, the proxy consent by the legal representative is communicated to the Public Attorney (Royal Decree, art.12.5). Consent may be dispensed with in an emergency when research concerns the specific interest of the health of the child and if there is REC approval. Retrospective consent of the legal representative is then requested as soon as possible (Royal Decree, art.12.6). Consent of person legally responsible for the child required. Consent in writing not legally required.	Yes, within general legislation	Yes, provided there is adoption of measures to guarantee that risk will be minimal and relevant knowledge about the illness will be obtained
United Kingdom	No specific legislation and no specific case law. Legal rights and duties based on common law principles governing medical treatment and general principles in the Children Act 1989.	No statutory basis for ethical review but approval of (local RECs and medical RECs) required for research which is publicly funded or conducted on NHS premises.	Consent of person legally responsible for the child required. Consent in writing not legally required.	Yes. Welfare and best interests of child must be protected.	Probably not permitted.

REC, research ethics committee.

similarities in five areas governing informed consent for neonatal research across ten European countries are summarised in table 1. A wider discussion of the differing legislation and its implications for neonatal research will be presented elsewhere.<sup>6</sup>

#### LEGISLATION ON RESEARCH

Six of the ten countries examined (Germany, Greece, Ireland, Norway, Spain, and Sweden) have specific legislation governing pharmaceutical trials. The laws of Denmark, Finland, and France cover other types of research as well, and the United Kingdom has no legislation specific to research but relies on general principles of law, for example, governing protection against bodily harm.

#### ETHICAL REVIEW SYSTEM

Research involving humans is reviewed independently by multidisciplinary research ethics committees in all countries except Greece, where this is carried out more usually by scientific committees (which are not multidisciplinary). Here, as in Norway and the United Kingdom, review is not a statutory requirement, as it is for all research in Denmark, Finland, and France. In Germany, Ireland, Spain, Sweden, and Greece, research ethics committee review is a legal requirement for clinical trials involving medicinal products; for the last country, control is by the National Drugs Organisation.

#### CONSENT

Proxy consent by legal guardians is the norm for neonatal research. Five countries accept this from one adult, but in Denmark, if parents share custody, consent from both adults is necessary, otherwise the research cannot be conducted. In Finland and Germany, only in exceptional circumstances when emergency treatment is required, can consent from one parent be accepted. In France and Sweden, consent from both parents is the norm.

Most countries permit enrolment into research without consent where this is not feasible, as part of emergency care. This is not allowed in Denmark, nor Ireland where legislation on consent for research is stringent.

In Ireland, a further legal stipulation requires that, after informed consent to a clinical trial, a six day period should elapse before the trial can be started. This provision can be amended, if dictated by the trial protocol, by application to and with the approval of the Irish Medicines Board.

#### REQUIREMENT FOR BENEFIT OF THE CHILD

All ten countries require a potential of direct benefit for a child to be entered into a trial or research study, either through general or specific research legislation. Thus proxy consent is not without some legal limitation.

Clinical trials specifically provide legal uncertainty because, owing to their necessary condition of therapeutic equipoise, it follows that at the time of recruitment it is unknown whether a treatment arm will confer benefit, no benefit, or perhaps even harm to the patient.

#### RESEARCH OF NO DIRECT BENEFIT PERMITTED

Linked to the requirement for direct benefit to the child is the issue of whether a country's law will permit research of no direct benefit to children (so called non-therapeutic research).

Most of the ten countries will permit research of no direct benefit in minors, with the stipulation that it must involve no more than minimal risk (an uncertain and subjective criterion).

Finland, France, Greece, Norway, and Spain follow the Convention for the Protection of Human Rights and permit a wider community and scientific viewpoint,

allowing research of no direct benefit if the child's inclusion may result in increased knowledge about the illness to the benefit of other children (but again provided that no more than minimal risk is involved).

Research of no direct benefit in children is not permitted in Germany and Ireland.

## Discussion

Increasingly, European countries collaborate in research projects. This is due to scientific ties and cooperation between various European research centres and also to the need for multinational research which is increasingly required in order to recruit sufficient patients to attain results with statistical significance.

Although European countries share a common cultural heritage and many similarities in their legal regulations of various subjects, they also have many differences in their legal systems, their laws, their codes of practice, and even practice itself. In research, this is reflected in the Declaration of Helsinki which is generally accepted in Europe, while specific types of research, such as that involving minors or emergency research, are not regulated in the same way in different countries. Even in countries where regulation seems to be similar, there may be differences in the interpretation, based in some cases on court decisions or official guidance, and in others in the cultural background of those involved in research. Doctors who conduct research are not always aware of the legal framework and it is the research ethics committees that have to examine the legality along with the ethical acceptability of the research project, and their practice differs in turn.

The European Union and the Council of Europe are working in the direction of harmonisation of the existing legislation and professional rules on research in humans. The 1997 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the application of biology and medicine has already been signed by 28 countries and ratified by six, proceeding to become their internal law, and it is expected that more countries will do so in the near future. Also the protocol on research which will be an adjunct to the Convention is almost ready and this will give guidance to researchers all over Europe.

## CONCLUSION

Parents and babies must be given adequate legal and ethical protection with regard to research. At the same time, investigators need to be allowed to try to answer important research questions without excessive restriction, because the answers are likely to help improve neonatal care.<sup>7 8</sup>

Multinational research is increasingly required so that sufficient patients are recruited to attain the statistical power to answer relevant research questions within a meaningful time frame. The legislative application of ethical principles varies across Europe. This environment of legal variety in the matter of proxy consent for neonatal research results in differing practical implications for the conduct of pan-European research.

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- Mason SA. Obtaining informed consent for neonatal randomised controlled trials: an "elaborate ritual"? *Archives of Disease in Childhood* 1997;76:F143-5.
- World Medical Assembly. The Declarations of Helsinki. Ferney-Voltaire, France: The Association, 1964; amended in 1975, 1983, 1989 and 1996.
- International Conference on Harmonisation. *Guidelines for Good Clinical Practice (ICH GCP)*. London: The Association of the British Pharmaceutical Industry, 1997.
- Council of Europe. Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. European Treaty Series, No 164. Oviedo: Council of Europe, 1997.
- McHaffie HE, Cuttini M, Broz-Voit G, et al. Withholding/withdrawing treatment from neonates: legislation and official guidelines across Europe. *J Med Ethics* 1999;25:440-6.
- Megone C, Mason SA, eds. *Informed consent in European neonatal research*. Aldershot: Ashgate Publishing Ltd, 2000 (in press).
- Royal College of Paediatrics and Child Health. *Safeguarding informed parental involvement in clinical research involving newborn babies and infants. A position statement*. London: Royal College of Paediatrics and Child Health, 1999.
- Bonati M, Choonara I, Hoppu K, Pons G, Seybert H. Closing the gap in drug therapy. *Lancet* 1999;353:1625.