

## Research with Minors in Greece and the EU Directive on Clinical Trials

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### Abstract

This article describes the legal rules for research with minors in Greece in relation to the EU Directive on clinical trials and the Greek Code of Medical Ethics.

### Keywords

Minors; clinical trials; EU Directive on clinical trials; Greek Code of Medical Ethics

The Directive 2001/20/EC on the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use<sup>1</sup> has been effective for about seven years in Europe. It deals with crucial questions about the conduct of clinical trials in Europe, aiming, as every Directive, at the harmonization of laws in this specific area. The field of medical research law and ethics has had its infamous instants of medical research with humans in the past; when the medical research subjects are minors, and therefore, legally incapable to grant consent, the rules to follow become all the more important. Simultaneously, there can be no medical research for a pediatric drug using adults as research subjects.<sup>2</sup>

Greece is bound by the Oviedo Convention on Human Rights and Biomedicine.<sup>3</sup> The Convention includes general provisions which refer to the conduct of clinical trials (Art. 15-17). Greece is also bound by the Nuremberg Code and the Declaration of Helsinki of the World Medical Association.

The Greek lawmaker implemented the Directive via a Ministerial Decision of 1973. This was a sort of a shortcut, bypassing the usual tool the Greek lawmaker uses to implement the European Directives, which is to propose and enact a statute by the Greek Parliament. Obviously, the enactment of a Ministerial Decision

<sup>1</sup> European Parliament (2001) Directive 2001/20/EC of the European Parliament and Council of April 4 2001. Official J L 121: 33-34.

<sup>2</sup> On the need for clinical trials to develop better or new drugs (for example, immunizations) for minors see the preamble of the Directive, under 3.

<sup>3</sup> See ed. J.K.M. Gevers, E.H. Hondius & J.H. Hubben, *Health Law, Human Rights and the Biomedicine Convention, Essays in Honor of Henriette Roscam Abbing*, 2005.

entails a procedure far less time-consuming, publicity-generating and debate-provoking than the enactment of a statute, as a statute has to be discussed in detail in Parliament, by both government and opposition. In sort of an 'exchange' perhaps, for the deviation of the usual procedure for the implementation of important Directives, the Directive was repeated almost verbatim in the Ministerial Decision that implemented it.<sup>4</sup> This, again, is a practice not exactly usual for Greece, where many article of various European Directives have been transformed when implemented by a statute (a phenomenon, of course, very well known in other European legal orders).

### 1. Minority and Clinical Trials

Minority in the administration of medicine and in medical law has always been an extra 'problem' because a minor generally lacks the capacity to consent to a (beneficial/necessary) medical procedure. The Directive avoided offering a definition of minority in Art. 2, titled 'definitions', therefore this matter was left to the discretion and internal laws of the member states. The Ministerial Decision also avoided offering a definition, which however, could prove very useful to medical researchers dealing with minors. This omission cannot be justified in the case of the Ministerial Decision as it surely is, for the Directive. Moreover, there is no statute in Greek law laying down a clear rule of when a person is a minor, when the context is medical law and consent to a medical procedure-or medical research. The Code of Medical Ethics, a rather new statute of 2005 (which replaced the older Code, a royal decree of 1955, after fifty years), again omitted to define minority in numbers.

Minority in Greece has been, in a way, the 'cause' of judicial decisions widely reported, but only when physicians were accused of illegally transfusing blood to minors without the consent of their parents, who were Jehovah's Witnesses.<sup>5</sup> Evidently, these texts cannot lend any help towards resolving the question of who is a minor for medical acts (and medical research). The proposed application by analogy of the relevant articles of the Greek Civil Code (Art. 127CC and others) dealing with minority and capacity to consent ('δικοιοπρακτική ικανότητα') to a legal act ('δικοιοπραξία') suffers from the inherent vulnerability that consent (for example) to a real estate transfer and consent to a medical act present quite different legal problems to be resolved. There is no prevailing view as to whether consent (to a medical act) is a legal act, in the sense of all legal acts recognized in Greek law, and necessitating capacity, the lack of which defeats their validity. Anyway, the fundamental principles of these general articles on capacity are that

<sup>4</sup> As the Directive was implemented with the Ministerial Decision almost as a translation to Greek (in the case of minors, it is a translation) I do not lay down here this Ministerial Decision in detail.

<sup>5</sup> See extensively Androulakis N, *The Jehovah's Witness Father*, *PoinChron K* (1970), 241.

a minor under ten, is liable to draw legal benefits (e.g. repay a loan), may legally consent to capacity to consent

These fundamental principles are in force when it comes to research. In this context, a physician's acts, a physician must have at least one parent or guardian, less austere as to the consent of the minor. In only one case where a medical act is performed, the minor may only offer consent to be transplanted (transplant met (transplant met parents is necessary). The consent of the minor must also be given by L. 2737/1999, a law that states that a minor over twelve years of age or parents or guardian

Under the Greek Civil Code (L. 3418/2005), a minor is not allowed to exercise parental responsibility for his legal care ('έναντι της ηλικίας του μινωρ είναι ληφθέντος της ανωριμότητας (in terms of maturity) and the risks of this matter

This article, 127CC, only to a minor's consent to medical research. Incompetent (suicidal) acts of a minor under ten to legitimize his participation may lead to a directive trial must be possible (Art. 24.3.c). Conditions must be

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a minor under ten years old is totally incompetent, a minor under fourteen, but over ten, is limitedly competent to consent to legal acts from which she only draws legal benefits but cannot incur any liabilities (such as the obligation to repay a loan), over fifteen her position is even better in terms of competence (she may legally contract to work), and over 18, there is no doubt whatsoever as to capacity to consent.

These fundamental rules in the first part of the Greek Civil Code do offer guidance when it comes to the question of consent to a medical act and to medical research. In this sense, and taking into account the entirely special nature of medical acts, a physician may use as a guide that, under ten, consent of the parents or at least one parent or guardian is always necessary, the situation becoming less and less austere as the minor approaches the legal age of majority, 18 years old. The only case where a Greek statute explicitly deals with the consent of a minor to a medical act is L. 2737/1999, a special statute on organ donation. A living donor may only offer an organ for transplantation if he is over 18; if bone marrow needs to be transplanted from a person under that age, and some other conditions are met (transplant to a sibling only, necessary to save his life), the consent of both parents is necessary. If the parents are not alive or have lost the right to custody, the consent of the minor's legal guardian is necessary. If the minor is over twelve, he must also give consent. So here, we can also apply by analogy Art. 10 L. 2737/1999, and support that also in the case of consenting to medical research, a minor over twelve must also, always give consent (additionally, apart from the parents or guardians).

Under the Greek Code of Medical Ethics, which has been enacted as a statute (L. 3418/2005), Art. 12b.aa., if a patient is minor, then persons who are entitled to exercise parental custody over the person ('ύσκηση γονικής μέριμνας') or enjoy his legal care ('επιμέλεια') may consent in his place. However, the opinion of the minor is taken into account, when a physician judges that the minor has the maturity (in terms of his age, state of mind and his emotional state) to understand the status of his health, the nature of the medical act and its consequences or risks of this medical act.

This article, 12b.aa of the Greek Code of Medical Ethics, refers in its essence only to a minor's consent to therapeutic and necessary medical acts and not to medical research. Article 24.3, however, completes the picture about consent by incompetents (such as minors) to medical research. Under this provision, consent of a minor under Art. 12b.aa (as analyzed in this paragraph) is equally necessary to legitimize his participation to medical research. Clinical trials with incompetents as participants (minors are included in this class) must lead to results that may lead to a direct benefit of the person's health (Art. 24.3.b). No other clinical trial must be possible, of an equal effectiveness with persons able to consent (Art. 24.3.c). Consent must be granted under Art. 12. Additionally, the following conditions must be met: a. the clinical trial is conducted freely and fundamental

intellectual and moral values are respected, as well as human dignity and value. 2. the person is informed about the existence and magnitude of risks, the right to protect his person 3. the voluntary nature of his participation to the trial without any financial reward and 4. the possibility to revoke his consent to the trial at any time. These provisions refer mainly to adult participants, but they are certainly applicable by analogy to the extent that it is reasonably feasible, in the case of minor participants. Another condition to be met is that the risks to be undertaken because of the trial must be very small in relation to the expected benefits. Lastly, the National Ethics Committee must have granted a positive opinion about the clinical trial.

It follows that the Greek Code of Medical Ethics, a parliamentary statute, an Act enacted two years after the implementation of the Directive 2001/20/EC on clinical trials, includes provisions about clinical trials in general and specifically, about a minor's consent to a clinical trial. These provisions are in effect simultaneously with the provisions of the Ministerial Decision, which implemented the Directive and obviously, they are not identical. The Ministerial Decision, a verbatim translation of the Directive in relation to the special provisions on clinical trials to minors, contains a series of conditions (Art. 4) of clinical trials, which do not coincide with the Code of Medical Ethics' relevant articles analyzed in the previous paragraph. For example, the condition of a clinical trial with minors under Art. 4z of the Ministerial Decision, that the clinical trials must be designed so as to minimize pain, discomfort, fear and other foreseeable risks depending upon the disease and its stage (and that the levels of risk etc must be monitored) is not included in the Greek Code of Medical Ethics.

It is not easy to explain exactly why this 'overlap' and admittedly, confusion, has occurred. In terms of legal interpretation, the Ministerial Decision is a legal source of lesser effect than a parliamentary statute; in case of conflict, the statute controls the legal outcome. However, as in the case here no possible conflicts are apparent, a legal clinical trial with minor participants in Greece today should follow the rules of both the Code of Medical Ethics and the Ministerial Decision on clinical trials.

What is clear, however, is that the Greek lawmaker failed to articulate, when implementing the Directive and also when enacting the Code of Medical Ethics, a rule on the age of minority for the purpose of consenting to medical research. This cannot be seen as a successful outcome, especially for physicians who need legal certainty when engaging in such research, especially with minors. Lastly, the Ministerial Decision does incorporate the Directive's provision that the minor (any minor, of any age, taking part in a clinical trial) must be informed about the trial, the risks and expected benefits by certain personnel, experience in dealing with minors (Art. 4b). Additionally, the parent's consent must reflect the presumed will of the minor and may be revoked at any time, without detriment to the minor, a provision of the Directive (4a) again verbatim incorporated in the

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Ministerial Decision. The same is true of Art. 4c of the Directive, declaring the right of the minor (again, any minor capable of forming an opinion and assess information offered about the clinical trial) to refuse his participation or to be withdrawn of the clinical trial: his explicit wish must be respected.

Lastly, it should be mentioned that under L. 2519/1997, special organs in Greek hospitals are competent to protect the rights of hospitalized patients, with wide discretion. The rights of minors participating in clinical trials in hospitals can, therefore, be safeguarded by these organs.

## 2. The Formation of the National Ethics Committee for Clinical Trials

The Ministerial Decision implementing the Directive included detailed rules for the formation of a (new) National Ethics Committee for Clinical Trials. The Greek lawmaker could allocate these responsibilities to the existing National Bioethics Committee, which could undertake this task amongst the others; however, a special body was deemed necessary. Under Art. 6 of the Ministerial Decision, an independent consulting body is instituted, seated at the National Organization for Drugs. Nine members (six health scientists, one lawyer, one theologian and one scientist specialized in bioethics) comprise the Committee.

The National Ethics Committee for Clinical Trials is responsible to receive applications for all clinical trials under the Directive and, hence, all clinical trials involving minors. The Committee is obliged to check, before granting a positive opinion about the conduct of a clinical trial involving minors, the correctness and inclusiveness of the written information offered to the prospective participants to a clinical trial and the process to be applied to secure informed consent to the trial, from the legal representatives (parents/guardians) and/or the minors (MD Art. 6.3.z-the provision refers generally to persons incapable to offer consent by themselves, and therefore it includes mentally impaired persons e.tc.). Greek law, therefore, has provided for a mandatory check of the legality of consent of minors to a clinical trial by an independent body.

## 3. Conclusion

The Greek National Bioethics Committee has dealt with the important matter of clinical trials in Greece and has issued an Opinion. This opinion is general and does not refer exclusively to clinical trials with minor participants. It is however, useful as guidance in the context of these clinical trials as well. The Opinion stresses the importance of the implementation of the Directive 2001/20/EC, noting that it is a positive step that the National Ethics Committee for clinical trials is able to veto a clinical trial in Greece, if problems are detected. In its opinion there is no reference to trials with minor participants.

In the text of another relevant 2005 Opinion of the Greek National Bioethics Committee, on the Ethics Committees for Biomedical Research, it is acknowledged that in Greece, the systematic submission of research protocols for ethical control is lacking (p. 1). This is again acknowledged as a deviation from the internationally set standards and as lessening the validity of the research occurring in Greece.

The European Directive 2001/20/EC on clinical trials, fully implemented in Greece since 2003, contains provisions which extensively protect minors from any possible exploitation or disadvantage in the course of a clinical trial to which they participate. In Greece, additional protection is offered by the provisions of the Code of Medical Ethics of 2005. It seems that there is no lack of legal rules in the interest of minors. The omission of a legally set age of minority in this context is a disadvantage.

In the end, it is the application of rules that matter and not only their theoretical existence. Data on clinical trials with minor subjects in Greece are not widely reported. The submission of research protocols for ethical control by the competent committees is not systematic, as the National Bioethics Committee has noted. There is no reason whatsoever to doubt the integrity of Greek medical doctors and researchers. No incident defeating a presumption of this integrity has been widely reported. However, it seems that the road towards full transparency of procedures and practical compliance with international, European and national law is still long. The lawmakers have fulfilled their obligations. It is up to the enforcers but better, the medical researchers themselves, to ascertain the legality, transparency and morality of these absolutely commendable endeavors.