Presidenza del Consiglio dei Ministri

COMITATO NAZIONALE
PER LA BIOETICA

CLINICAL TRIALS IN ADULT OR MINOR PATIENTS WHO ARE UNABLE TO GIVE INFORMED CONSENT IN EMERGENCY SITUATIONS

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INDEX

Presentation

The document deals with the ethical problems of randomised clinical trials on ill or injured patients, adults or minors, who are unable to give their timely informed consent. These are specific situations for which treatment exists but which is not very effective and not able to improve the prognosis. To take away the possibility of clinical trials from these subjects would mean on the one hand to reduce the hope that they might benefit from it and that their illness might be treated, and on the other to stop the therapies available from being improved for patients in the future too.

In the light of the analysis of the international and Italian regulations, the NBC considers a number of solutions emerging in this practice (reference to the members of the family and carers, opinion of the ethical committee, appeal to the state of necessity), showing their limitations.

In stressing the absolute need to safeguard the subject's rights, safety and wellbeing, the Committee justifies the licitness of clinical trials in emergency situations, should the patient be unable to give his/her valid informed consent and in the absence of a legal representative, in specific conditions: the approval of a protocol – based on strong experimental evidence – by a national ethics committee set up *ad hoc*, independent, made up of doctors and nurses working in the specific sector, jurists, forensic scientists, patient rights representatives and bioethicists; the ascertainment of any possible desire to the contrary previously expressed by the patient; the request for consent deferred by the patient or his/her legal representative; the publication of the results of the trials to avoid unnecessary duplications.

The document was elaborated by a workgroup coordinated by profs. Lorenzo d'Avack, Silvio Garattini, Rodolfo Proietti, who also drafted the text. Profs. Adriano Bompiani and Laura Palazzani gave their written contributions. The text was discussed in the working group in which profs. Amato, Morresi, Nicolussi took part.

The text also availed of the contribution of experts who discussed the subject during the hearing: Dr. Carlo Petrini, responsible for the Unità di Bioetica of the Italian National Institute of Health (24 June 2011) and Dr. Carlo Tomino, Director of the Research and clinical trials Office of the Agenzia Italiana del Farmaco (AIFA) (27 January 2012). The pressing need for the document came from a request by Prof. Antonio G. Spagnolo, Director of the Bioethics Institute of the Università Cattolica del S. Cuore (with letter of 26 April 2011), who – in outlining the emergence of the issue in the practice of ethical committees – contributed to the formulation of the text.

In the plenary session of 28 September 2012 the document was unanimously approved by those present: profs. Salvatore Amato, Luisella Battaglia, Adriano Bompiani, Stefano Canestrari, Cinzia Caporale, Antonio Da Re, Francesco D'Agostino, Lorenzo d'Avack, Riccardo Di Segni, Carlo Flamigni, Romano Forleo, Silvio Garattini, Laura Guidoni, Laura Palazzani, Rodolfo Proietti, Monica Toraldo di Francia, Giancarlo Umani Ronchi, Maria Grazia Zuffa.

Profs. Bruno Dallapiccola, Maria Luisa Di Pietro, Marianna Gensabella, Assunta Morresi, Demetrio Neri were not present at the vote on the document but their approval was given at a later date.

The President
Prof. Francesco Paolo Casavola

1. Premise

The randomised clinical trial (RCT: *randomised clinical trial*) is today the most reliable methodology by which to establish the efficacy of therapeutic interventions constituted by drugs, medical devices, surgery, etc.

Any participation at all in an RCT requires the consent of the patient who must be suitably informed: (a) of the uncertainty of the expected benefits and the possible toxic effects; (b) the fact that the trial is the only scientifically and ethically correct way to treat patients in situations of clinical uncertainty and to resolve this very uncertainty.

There is nonetheless a category of patients or injured, adults or minors, who are not able to give their timely informed consent for various reasons and this raises a serious problem when the efficacy and safety of the therapy is highly conditioned by the rapidity of the intervention itself. Scientific data shows the increased risk of death in the case of delay associated with the need to get the patient's consent. For example, patients with acute traumatic brain injuries, heart attacks, bad ischemic attacks or cardiac arrest. All these situations require prompt action. It is also true that existing treatment can be carried out on these patients, but in many cases this can prove inadequate and not able to improve the prognosis; it is also just as true that if new treatment is proposed, which is potentially more effective and of greater benefit to the patient, these therapeutic protocols need a randomised clinical trial that demonstrates their real efficacy.

As said above, the problem arises above all when the effect of the drug or the procedure is 'time dependent'. In this sense, numerous other examples could be given of situations in which prompt action must be taken:

- tranexamic acid in the control of *post-traumatic haemorrhage* (CRASH-2 trial). Maximum effect for start of therapy within 1 hour. Administration time limit: within 3 hours of the trauma. The delay of 1 hour in the start of treatment reduces the benefit by 63% to 49%;
- induced hypothermia during cardio respiratory intensive-care. Start of therapy within few minutes of beginning of *cardiac arrest*;
- pharmacological therapies (hypertonic solutions; drugs that reduce cerebral metabolism) or surgical therapies (decompressive craniectomy) in patients with *acute traumatic brain injury* or *massive cerebral haemorrhage* with high risk of evolution into 'cerebral death' or 'vegetative state'. Start of therapy in shortest time possible (minutes/hours). Corticosteroids in *traumatic brain injury* (CRASH Trial) (within 6 hours);
- thrombolytic therapy in *strokes* (within 3 hours);
- pharmacological therapy in *myocardial heart attack* (best results with fibronolytic treatment within 1 hour);
- corticosteroid therapy *bone marrow trauma* (within 6 hours).

Less urgent and therefore more easily having the possibility of obtaining informed consent by a legal representative are the cases in which the intervention time is not so immediate, like for example:

- mechanical ventilation in patients with acute lung injuries or *Acute Respiratory Distress Syndrome* (within 36 hours);
- corticosteroid therapy in patients with *Persistent Acute Respiratory Distress Syndrome* (within 48 hours).

To deprive these subjects of the possibility of clinical experimentation would mean on the one hand to reduce the hope that they might benefit from it and that their illness might be treated and on the other to stop the available therapies from being improved for patients in the future too. It is thus a question of finding the ethically justified conditions for which trials, even temporarily, may be set up or pursued without harming the rights of the patient.

2. The legislative limitations today

In Italy the problem arises from the impossibility – in practice – to carry out clinical trials in patients that are unable to give informed consent, so much so that it amounts to legal incapacity or actual incapacity, in emergency situations when the 'therapeutic window' is minutes/hours.

Ministerial Decree 15/7/1997 Arts. 4.8.1. ff. (*Implementation of the European Union guidelines for good clinical practice for the execution and clinical trials of medicines*) foresaw that a subject incapable of giving his/her informed consent could be involved in a trial only if such consent had been expressed by his/ her legal representative, together with the fact that, if it were a non-therapeutic trial (with absence of any direct clinical benefit for the subject), further conditions should be foreseen among which the fact that the foreseeable risks and the negative impact on the wellbeing of the subject were mild.

Nonetheless, as already foreseen in the *Declaration of Helsinki* (1984, present version 2008), even these guidelines granted a significant exception to the need for the legal representative's informed consent. In fact Art. 29 foresaw 'emergency situations' and situations in which it was not possible to obtain the person's prior consent, nor was a legal representative present. In such circumstances it was considered possible to enrol the person in the presence of three concurrent requisites: 1) the patient's enrolment must take place according to the measures described in the protocol and the protocol must set out the specific reasons explicitly justifying the involvement of research subjects who find themselves in conditions such as to render them incapable of giving informed consent; 2) such protocol must have received the documented favourable opinion of the Ethics Committee; 3) the subject, or his/her legal representative must be informed as soon as possible and his/her consent must be asked for.

The same normative content was then adopted by Art. 3.7.8. of M.D. 18.3.1998 (*Reference guidelines for the establishment and functioning of Ethics Committees*).

These provisions have now been replaced by the regulations introduced by Leg. Decree No. 2011/2003, which enforces Directive 2001/20/EC. These regulations are far more restrictive considering that in the case of trials in incapable subjects, no exception with regard to the need for the legal representative's informed consent is foreseen. It follows that it will be possible to disregard the informed consent of the legal representative only in the

hypothesis of evident treatment in a 'state of necessity' according to the general exempting contained in Art. 54 of the penal code.

In Italy the legal representative or care support administrator are appointed by the judge. This procedure takes time, while most of the clinical studies aimed at emergency situations assess the effects of the therapies given in the immediacy of the critical situation.

It must be remembered that the *Oviedo Convention* (1997) – ratified by Italy, even though the ratification instrument has not been lodged – foresees a guarantee system to safeguard the incapable similar to the one established by Directive 2001/20/EC. The general principle (Art. 6) is stressed that the trial is licit on an incapable adult only on condition that there is the authorisation from an 'authority or person or body provided by for law'. In emergency situations, without informed consent, it grants the possibility to proceed immediately to any medical intervention indispensable for the benefit of the health of the person concerned (Art. 8).

This possibility is nonetheless limited to non-experimental interventions, but which already have a proven direct benefit on the patient. The Convention also refers to 'the patient's previously expressed wishes' (Art. 9): this reference can be interpreted as the patient's openness to leave prior declarations with respect to his/her willingness to possible clinical trials in specific conditions of successive incapacity.

Eight years later the *Additional Protocol to the Convention on human rights and biomedicine involving biomedical research on human beings* (2005) explicitly deals with clinical trials in emergency situations (Art. 19: research on persons in emergency clinical situations), inviting the various national legislations to define the additional conditions for safeguard. The Protocol sets out a number of specific conditions: the ascertainment that the research cannot be carried out on patients not in a state to give consent who are not in a condition of urgency; the protocol shall be approved specifically by a competent body; any relevant previously expressed objections of the person known to the researcher shall be respected; if the expected results of the research do not have the potential to produce 'direct benefits' for the patient, the research must have the aim of contributing to the improvement of scientific knowledge and entail minimal risk to the patient. Any consent or authorisation to continued participation shall be requested as soon as reasonably possible.

At present the *Proposal for a Regulation of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC* (2012) is being debated at Community level and deals with the question of Art. 32 (clinical trials in emergency situations), introducing innovative elements with respect to the directive. The proposal for Regulation takes up once again and reformulates a number of conditions already present in the Protocol: the absence of previously expressed objections by the patient to trials known to the researchers; the direct connection between research and the pathology of the patient on whom the trial is carried out; the presence in the trial of a foreseeable risk and minimal burden; the need to obtain – where possible – the consent of the patient or his/her legal representative.

3. Solutions for informed consent in incapable patients in emergency situations

Faced with these limits, one solution can be to wait for the results of rationalised clinical trials conducted in other countries. This is a solution that raises concern of a scientific nature, insofar as it would involve a delay in the application of new treatment compromising its efficacy, and of a moral nature insofar as use would ultimately be made passively of results of trials carried out by others, without actively contributing to the advancement of knowledge. Not only, but an intelligent use of the results obtained by others nevertheless implies a presence in the field of research.

The problem thus arises of finding a solution that bears in mind the need to safeguard and harmonise important constitutional rights such as the fostering of scientific research (Arts. 9 and 33) and the protection of health (Art. 32). In Italian hospitals a number of ethics committees have formulated operational proposals that have already come into effect, but which maintain a strictly ethical value as they are not in conformity with the juridical norms in force. For example, it is accepted that in the case of children, consent can be expressed by the parents, while for demented adults or adults in a state of coma, the opinion of the legal representative must be sought[1].

Other solutions with regard to the identification of figures that may carry out the function of legal representation in the case of clinical trials on incapable subjects can be found in other legislations in and outside Europe.

1) A first practice is the one referring to members of the family or, should there be none, to the caregivers of the patient who are willing to be informed and to collaborate for the purposes of carrying out the trial. They are asked to undersign a form of 'recognition' of the clinical situation and of non-opposition to the clinical trial.
Should these not be available, the enrolment of the patient takes place according to the provisions in the protocol and approved by the competent ethics committee.
In cases of temporary incapacity, at the moment of regaining his/her decision-making ability, the subject shall be asked for his/her informed consent for the continuation of the trial and the use of the data already collected. It is furthermore foreseen in these cases that should the incapacity not be temporary the consent must be obtained by the appointed legal representative according to the modalities established by the law.

2) Another type of practice on the other hand takes advantage of the full responsibility of the ethics committee authorising the clinical trial, as the sole decision-making body, barring a request at a later date for the consent to be

[1] From the data available at the AIFA (Clinical Trials in Italy. 10th National Report 2011, pp. 191-198) it can be concluded that starting from 2006 over 3000 clinical research protocols were carried out on drugs of which 218 concern studies on subjects who were not able to express informed consent. Over 65% regards trials promoted by profit bodies and the rest by non-profit organisations. About 85%of the clinical trials have as objective the ascertainment of efficacy and safety. 114 trials are considered phase 3 trials; 22.7% concern trials in the neurological field.

obtained from the patient for the use of the data gathered from the trail carried out when he or she was incapable of giving consent. In this way the family's consent is foregone from the very start and the ethics committee takes upon itself the title of authority or body foreseen by the national legislation.

3) A final option can be referred to the 'state of necessity', claimed by the doctor or the medical team and recognised by the ethics committee, extending a circumstance to the case in point of clinical trials that is usually used for a consolidated medical intervention able to give a real possibility of saving oneself or others from the danger of serious harm to the person.

This option is included in the need to distinguish within the context of 'research', the type preordained for a huge case record, studied in the smallest detail, expressed in protocols approved by ad hoc ethics committees, from the type of research classified as therapeutic 'trial' (or sometimes mere 'attempt') and which is translated in the use of an intervention or product that seems suitable for use in the case being examined and therefore 'justified' use in the doctor's own responsibility.

4. The NBC's position

a) The NBC considers it necessary to stress the absolute need to safeguard the subject's rights, safety and wellbeing. It retains that in emergency situations, should the patient be unable to expressly give his/her informed consent, then the consent to undergo a clinical trial be usually given by a legal representative or should this be lacking by other subjects, established by the law, able to carry out such function in a sufficiently timely manner, according to the criteria already adopted in other circumstances involving the health of the subjects[2].

Nevertheless, should they not be present and should their involvement not be possible in time to respond to the need for intervention (circumstances to be documented), the NBC considers it necessary to entrust the doctor or the medical team with the decision to resort to medical treatment which is still in an experimental phase, scrupulously keeping to the conditions, measures and techniques set down in the protocol previously approved by the ad hoc national Ethics Committee (EC) and made up of doctors and nurses working in the specific sector, jurists, forensic scientists, patient rights representatives and bioethicists. The EC must be independent from research bodies.

It must be ascertained – as far as possible - that the patient taking part in the trial has not expressed the desire to not be the subject of experimentation. This is difficult to establish in an emergency, but in some possible situations like for example in the case of a heart attack patient whose doctor already knows his/her wishes or in the case of declarations made before treatment, considered valid for the purposes of consent or dissent to therapeutic/experimental treatment.

Lastly, the criteria of 'differed consent' must be applied in the case in which the therapy must continue, given either by the patient, who has regained the capacity to express informed consent, or by his/her legal representative in the case of continued incapacity.

[2] For example Law 91/1999, Art. 23 (removal of organs); Art. 408 c.c. (care support administrator, appointed to give informed consent to treatment).

b) With regard to the Protocol the NBC makes the following recommendations:

The EC must apply the usual rules applying to clinical trials. The experimental project must have controls with '*gold standard*' features: it must be a superiority trial with respect to the best that is already available with an evaluation of efficacy carried out randomly on important therapeutic parameters (mortality, morbidity) and a sample adequate for the tested hypothesis. The trials must be randomised so as to guarantee equal treatment.

The protocols must be made available to the medical community for opportune knowledge and debate. And independently of a positive or negative result, the trials must be published by way of information and to avoid unnecessary duplications. The EC must be periodically informed of the progress of the trial.

The EC should in any case establish a set of additional rules as listed below:

- The new therapy must be directed at conditions characterised by high mortality and disability (acute brain injuries, cardiac arrest, heart attack, ischemic attacks, etc.) and at high risk, with the need for immediate emergency intervention, given that the 'therapeutic window' is very short.

- The new proposed therapy must be backed up by important elements establishing a strong likelihood of success. The elements must be based on biological plausibility, pre-clinical studies including animal experimentation models, trials aimed at demonstrating the safety of the proposed therapy to guarantee an adequate risks-benefits ratio. Research must have been carried out on the definition of the dosage to be given and the pharmacokinetic and pharmacodynamic profile as well as, wherever opportune, tolerability trials carried out on healthy individuals (phases 1 and 2). In particular, if possible, the proof must already have been obtained in a healthy volunteer that the new treatment has the foreseen pharmacodynamic effect.

The risks associated with clinical trials must be reasonable in relation to the clinical condition and, in the case of a drug already used for other types of therapy, take the risks-benefits ratio into consideration too.

Conclusions

The NBC:

a) stresses the absolute need to safeguard the rights, safety and wellbeing of the patient;

b) considers it urgent, on the part of the legislator, to enact a modification of Art. 5 del Leg. Decree No. 211/2003 allowing clinical trials on incapable adults (legal or actual incapacity) to expressly give their informed consent to clinical trials in emergency situations;

c) considers it necessary, on the part of the Health Ministry, to proceed with the drafting of a regulation making it possible to realise rationalised clinical trials in emergency conditions, when it is necessary to validate prompt new experimental treatment in patients not able to give informed consent;

d) considers that in the case of incapable adults or minors the consent to clinical trials can be given by the legal representative or in their absence by other subjects identified by the legislator, according to criteria already adopted in other circumstances involving the health of the subjects;

e) considers that it is necessary, whenever possible, to bear in mind the patient's previously expressed wishes in a formal and controllable way (in an electronic health file for example), in favour of or contrary to any possible trial and furthermore retains that the criterion of 'deferred consent' given by the patient is necessary should he/she regain the capacity to express informed consent, or by the legal representative should the incapacity persist;

f) in the case in which it is nevertheless possible to obtain the above mentioned subjects' consent in time or to verify prior wishes, the NBC considers it necessary to entrust the doctor or the medical team with the decision to include patients in clinical trials of new treatment, scrupulously keeping to the conditions, measures and techniques described in the protocol approved by the Ethics Committee set up *ad hoc*;

g) considers that the ad hoc Ethics Committee must be independent of the research bodies and made up of doctors and nurses expert in the sector, jurists, forensic scientists, patient rights representatives and bioethicists;

h) considers that the protocols must be made available to the medical community for opportune knowledge and debate and that, independently of whether the results are positive or negative, the trial results must be published by way of information and to avoid unnecessary duplications.

Appendix: International and community documents

***Declaration of Helsinki* (1984/2008)**

Art. 29: Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

***Convention for the protection of human rights and the dignity of the human being with regard to the application of biology and medicine*, 1997 (Steering Committee on Bioethics, Council of Europe, STE N° 164)**

Art. 5: General rule

An intervention in the health field may only be carried out after the person concerned has given free and informed consent to it.
This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks.The person concerned may freely withdraw consent at any time.

Art. 6: Protection of persons not able to consent

1. Subject to Articles 17 and 20 below, an intervention may only be carried out on a person who does not have the capacity to consent, for his or her direct benefit.
2. Where, according to law, a minor does not have the capacity to consent to an intervention, the intervention may only be carried out with the authorisation of his or her representative or an authority or a person or body provided for by law.
The opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to his or her age and degree of maturity.
3. Where, according to law, an adult does not have the capacity to consent to an intervention because of a mental disability, a disease or for similar reasons, the intervention may only be carried out with the authorisation of his or her representative or an authority or a person or body provided for by law. The individual concerned shall as far as possible take part in the authorisation procedure.
4. The representative, the authority, the person or the body mentioned in paragraphs 2 and 3 above shall be given, under the same conditions, the information referred to in Article 5.

5. The authorisation referred to in paragraphs 2 and 3 above may be withdrawn at any time in the best interests of the person concerned.

Art. 8: Emergency situations

When because of an emergency situation the appropriate consent cannot be obtained, any medically necessary intervention may be carried out immediately for the benefit of the health of the individual concerned.

Art. 9: Previously expressed wishes

The previously expressed wishes relating to a medical intervention by a patient who is not, at the time of the intervention, in a state to express his or her wishes shall be taken into account.

Art. 16: Protection of persons undergoing research

Research on a person may only be undertaken if all the following conditions are met:

i. there is no alternative of comparable effectiveness to research on humans;

ii. the risks which may be incurred by that person are not disproportionate to the potential benefits of the research;

iii. 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;

iv. the persons undergoing research have been informed of their rights and the safeguards prescribed by law for their protection;

v. the necessary consent as provided for under Article 5 has been given expressly, specifically and is documented. Such consent may be freely withdrawn at any time.

Art.17: Protection of persons not able to consent to research

1. Research on a person without the capacity to consent as stipulated in Article 5 may be undertaken only if all the following conditions are met:

i. the conditions laid down in Article 16, sub-paragraphs i to iv, are fulfilled;

ii. the results of the research have the potential to produce real and direct benefit to his or her health;

iii. research of comparable effectiveness cannot be carried out on individuals capable of giving consent;

iv. the necessary authorisation provided for under Article 6 has been given specifically and in writing; and

v. the person concerned does not object.

2. Exceptionally and under the protective conditions prescribed by law, where the research has not the potential to produce results of direct benefit to the health of the person concerned, such research may be authorised subject to the conditions laid down in paragraph 1, sub-paragraphs i, iii, iv and v above, and to the following additional conditions:

i. 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;

ii. the research entails only minimal risk and minimal burden for the individual concerned.

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

Art. 5: Clinical trials on incapacitated adults not able to give informed legal consent

In the case of other persons incapable of giving informed legal consent, all relevant requirements listed for persons capable of giving such consent shall apply. In addition to these requirements, inclusion in clinical trials of incapacitated adults who have not given or refused informed consent before the onset of their incapacity shall be allowed only if:

(a) the informed consent of the legal representative has been obtained; consent must represent the subject's presumed will and may be revoked at any time, without detriment to the subject;

(b) the person not able to give informed legal consent has received information according to his/her capacity of understanding regarding the trial, the risks and the benefits;

(c) the explicit wish of a subject who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except compensation;

(e) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods and relates directly to a life-threatening or debilitating clinical condition from which the incapacitated adult concerned suffers;

(f) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress shall be specially defined and constantly monitored;

(g) the Ethics Committee, with expertise in the relevant disease and the patient population concerned or after taking advice in clinical, ethical and psychosocial questions in the field of the relevant disease and patient population concerned, has endorsed the protocol;

(h) the interests of the patient always prevail over those of science and society;

(i) there are grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risk at all.

***Additional protocol to the Convention on Human Rights and Biomedicine, relative to biomedical research* (STCE, N°195), 2005**

Art. 19 (Ch. VI: Particular situations): research on persons in emergency clinical situations:

1. The law shall determine whether, and under which protective additional conditions, research in emergency situations may take place when:

i. a person is not in a state to give consent, and

ii. because of the urgency of the situation, it is impossible to obtain in a sufficiently timely manner, authorisation from his or her representative or an authority or a person or body which would in the absence of an emergency situation be called upon to give authorisation.

2. The law shall include the following specific conditions:

i. research of comparable effectiveness cannot be carried out on persons in non-emergency situations;

ii. the research project may only be undertaken if it has been approved specifically for emergency situations by the competent body;

iii. any relevant previously expressed objections of the person known to the researcher shall be respected;

iv. where the research has not the potential to produce results of direct benefit to the health of the person concerned, it 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 category or afflicted with the same disease or disorder or having the same condition, and entails only minimal risk and minimal burden.

3. Persons participating in the emergency research project or, if applicable, their representatives shall be provided with all the relevant information concerning their participation in the research project as soon as possible. Consent or authorisation for continued participation shall be requested as soon as reasonably possible.

Proposal for a Regulation of the European Parliament and of the Council on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC, 2012

Art. 32: Clinical trials in emergency situations

1. By way of derogation from points (c) and (d) of Article 28(1), from points (a) and (b) of Article 30 (1) and from points (a) and (b) of Article 31(1), informed consent may be obtained after the start of the clinical trial to continue the clinical trial and information on the clinical trial may be given after the start of the clinical trial provided that all of the following conditions are fulfilled:

(a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden acute medical condition, it is impossible to obtain prior informed consent from the subject and it is impossible to supply prior information to the subject;

(b) no legal representative is available;

(c) the subject has not previously expressed objections known to the investigator;

(d) the research relates directly to a medical condition which causes the impossibility to obtain prior informed consent and to supply prior information;

(e) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject.

2. The informed consent referred to in paragraph 1 shall be obtained, and information on the clinical trial shall be given, in accordance with the following requirements:

(a) regarding incapacitated subjects and minors, the informed consent referred to in paragraph 1 shall be obtained as soon as possible from the legal representative and the information referred to in paragraph 1 shall be given as soon as possible to the subject;

(b) regarding other subjects, the informed consent referred to in paragraph 1 shall be obtained as soon as possible from the legal representative or the subject, whichever is sooner and the information referred to in paragraph 1 shall be given as soon as possible to the legal representative or the subject, whichever is sooner.

For the purposes of point (b), where informed consent has been obtained from the legal representative, informed consent to continue the trial shall be obtained from the subject as soon as it is capable of giving informed consent.

Further documentation

Superior Health Council, Section V, Sitting of 10 July 2008

The Council expressed its opinion to follow Great Britain's legislation of December 2006, an amendment foreseeing exceptions to the regulations on informed consent. The departure from the rules is granted in a series of cases: when, in specific conditions, the treatment must be given urgently; if the nature of the trial requires urgent, non-deferrable action; if consent with the legal representative's authorisation is absolutely impossible; and lastly if the procedure is approved by the Ethics Committee.