‘No Time to be Lost!’
Ethics and Consent Procedures in Severe Traumatic Brain Injury in the European Union

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Main topics of Research Ethics

The Ethics of medical research focus mainly on:

1. (Informed) consent (Respect for persons);
2. Risk/benefit (Beneficence and Nonmaleficence);
3. Access to clinical trials and selection (Justice)
Nuremberg Code (1947)

10 standards to which physicians must conform

The first: “The voluntary consent of the human subject is absolutely essential”
Emergency Research, Definition

- *Research on patients suffering from critical illnesses and injuries.*
- Most medical conditions studied rendered the patient unconscious or unstable (e.g. cardiac arrest, profound shock, stroke, traumatic brain injury).
- Treatments under study had to be administered in a time frame that made obtaining consent of the patient or relatives problematic.
Specific ethical issues pertaining to clinical trials in emergency research

- 1. The emergency nature of research
- 2. The incapacity of subjects to consent
- 3. Short therapeutic time windows
- 4. Different risk/benefit ratio (adverse side effects may be acceptable)
Two important challenges of emergency research ethics

- (Written) Proxy consent in case of incapacity of subjects to consent
- Narrow Time Windows for treatment
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
EU Directive 2001/20/EC

- The Directive concerns a European-wide harmonisation of the provisions concerning clinical pharmacological trials, aiming at facilitation of multinational clinical research.

- Published May 1, 2001 (Official Journal of the European Communities)

- The Directive was to have been incorporated and made effective in the Member States national laws by May 1, 2004
In the case of other persons incapable of giving their consent, such as persons with dementia, psychiatric patients, etc., inclusion in clinical trials in such cases should be on an even more restrictive basis. Medicinal products for trial may be administered to all such individuals only when there are grounds for assuming that the direct benefit to the patient outweighs the risks. Moreover, in such cases the written consent of the patient’s legal representative, given in cooperation with the treating doctor, is necessary before participation in any such clinical trial.

(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;
Article 5a of the Directive assumes that it is possible and ethically valid to consult a ‘legal representative’ in every situation.
Scientific ‘outcry’ from the field of ICU and EM
“The EU Directive, although well-meaning in intent, has not taken into account the particular needs of research in the critically ill patient and in emergency circumstances. This is causing significant difficulty in incorporating Directive into national statutes”
The VISEAR (Vienna Initiative to Save European Academic Research) brings together leading stakeholders from academic research groups and interested parties from industry and regulatory authorities to focus on the issues of concern regarding the organisation and funding of academic clinical research in order to improve the development and use of medicines in Europe.

- First meeting May 30, 2005 in Vienna, 6 workshops
Clinical trials including patients who are not able to consent; the concept of individual direct benefit from research; informed consent – the temporarily incapacitated patient
Report of the 1st Meeting of the
”Vienna Initiative to Save European Academic Research (VISEAR)”

organised by the
Medical University of Vienna
Department Ethics in Medical Research

in collaboration with the
European Forum for Good Clinical Practice (EFGCP)
Vienna School of Clinical Research (VSCR)
European Clinical Research Infrastructures Network (ECRIN)

Scientific Secretariat
Ethics Committee of the Medical University of Vienna

The European Clinical Trials Directive revisited: The VISEAR recommendations

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Received 6 December 2005; accepted 10 December 2005
Position Paper

Recommendations in relation to the EU Clinical Trials Directive and Medical Research Involving Incapacitated Adults

A working group report of the Vienna Initiative to Save European Academic Research (VISEAR)

supported by the Department for Ethics in Medical Research of the Vienna Medical University in cooperation with the European Forum for Good Clinical Practice (EFGBP), the European Clinical Research Infrastructures Network (ECRIN) and the Vienna School of Clinical Research (VSCR)

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(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;
‘Legal representative’

- ‘Legal representative’ is not defined in the Directive
- It should be determined by national law

- Austria/Germany: appointed by a judge
- Norway (Biobank Act 2003): only consent of the individual themselves
- UK: independent physician
- Other states: close relative
Consequences of pluralism in defining the legal representative

- The highly variable definitions in the different member states may have a negative impact on international trials.

- Researchers in countries with narrow interpretation of legal representative report difficulties carrying out important types of research (e.g. emergency research; dementia research).
VISEAR recommendations concerning legal representatives

- Member States should implement systems for legal representation that are compatible with critical illness research.

-Countries that rely on relatives to act as legal representatives should permit decisions to be made by other persons when family members are too stressed to decide, or should waive or defer the consent requirement.
Availability of relatives after injury

- Most severe TBIs occur outside the domestic situation, making that family members are rarely available during the first hours after traumatic injury

- Average arrival time: 78 minutes

- (Wright at al. *Necessary time to achieve next of kin proxy consent for acutely injured patients.* Acad Emerg Med 2001; 8: 419-420)
Do patients want to be represented by a relative?

*Roupie et al.* Intensive Care Medicine 2000; 26: 52-56

- France, n=1089
  - 29.6% would not want a surrogate
  - 40.6% indicated that they would their spouse/partner to be their surrogate
  - 29% want to be represented by the physician in charge
Do patients want to be represented by a relative?

*Blixen & Agich. J Med Ethics 2005; 31: 608-611*

- Stroke patients, USA
  - 83% expressed willingness to participate in the trial
  - 92% said they would want the physician to ‘go ahead and enrol them in the trial’
Time windows *versus* Consent requirements

- “In EM and ICUM is a conflict between the desire for early initiation of treatment with the time required for consent procedures”
Solution

- One of the solutions for these problems is adopting:
  
  1. Deferred consent
  2. Waiver of consent
  3. Consent by an independent physician
In accordance with the Directive?

- YES and NO!

- Regulatory bodies in Brussel did not object when the French, Belgian and Dutch provisions – which all entail a waiver of consent in emergency situations – were first presented.

- For many Member States it is also relevant that a waiver accords with the Additional Protocol to the Convention on Human Rights and Medicine (Oviedo 4 IV 1997).

- The UK government has recently proposed to amend its laws to implement a system of deferred consent (valid for 24 hours).

- An independent physician can be a legal representative.
In accordance with ethics?

- The patient is in a life threatening situation (principle of beneficence)
- Available therapies are unproven or unsatisfactory (principle of justice, beneficence, non-maleficene)
- Risk and benefits are considered reasonable in relation to the patient’s condition and to what is known about other available therapies (principle of justice, beneficence, non-maleficene)
- Participation yields the prospect of possible direct and real benefit (principle of justice, beneficence, non-maleficene)
Which ethical principle is lacking?

- The principle of *respect for autonomy*

Because:
- The patients are mentally incapacitated (informed consent not possible)
- Proxies are not always available within hours (proxy consent not possible)
- Proxies are ‘overwhelmed’ and make decisions based on what they hope rather than on weighing the provided information
- It is doubtful whether proxies will indeed make similar decisions as patients
‘Scientific research is a moral duty

- **Nonmaleficence**: ‘Because medical research is necessary to relieve need, medical research becomes a moral obligation’
- **Fairness**: ‘We all benefit from the existence of the social practice of medical research’
Effect of waiver of consent: NABIS:H study

- National Acute Brain Injury Study: Hypothermia

- 9 months were conducted with only prospective informed (proxy) consent (year 1)
- Subsequent 32 months with ability to use waiver of consent (year 2 and 3)
- In Year 1, 65 patients enrolled (proxy consent, randomized $4.4 \pm 1.1$ h)
- In Year 2, 139 patients enrolled (waiver, randomized $3.7 \pm 1.1$ h)
- In Year 3, 115 patients enrolled
Effect of waiver of consent: NABIS:H study
Cliffton et al., J Neurotrauma 2002; 19: 1121-1126

- With **proxy consent** reaching target temperature of 33°C: mean 11.7 ± 2.6 h after TBI

- With **Waiver of Consent** reaching target temperature of 33°C: mean 7.9 ± 2.7 h after TBI
113 patients randomized with waiver of consent

- Only 11 arrived within the time window of 6 hours
- Only 1 family requested that the patient be withdrawn from the study
EBIC Questionnaire on consent procedures in TBI

- 148 EBIC associated neuro-trauma centers in 19 European countries
- Response rate 53% (n=79)

- 48% believed that relatives were not able to make a balanced decision
- 72% believed that consent procedures are a significant factor causing decrease in enrollment rate
- 83% stated that consent procedures delay initiation of study treatment
- 64% considered TBI an emergency situation with exception for consent
Within which time period should proxy consent be obtained?
Dexanabinol Phase III trial on efficacy and safety

- January 2001 – March 2004
- Multicentre placebo controlled Phase III trial (Europe, Israel, Australia, USA) to evaluate efficacy and safety of a single dose of Dexanabinol in severe Traumatic Brain Injury
- Dexanabinol is a synthetic cannabinoid analogue devoid with strong neuroprotective potential
- Aim: recruit 860 patients with severe TBI
Efficacy and safety of dexamabnil in severe traumatic brain injury: results of a phase III randomised, placebo-controlled, clinical trial

Andrew R. Moss, Gordon Murray, Herbert Henney III, Noorjan Kassem, Vincent Logsdail, Mikkael Margolis, Jean-Paul Mabie, and Nino Stocchetti

Summary

Background Traumatic brain injury is a major cause of death and disability. We sought to assess the safety and efficacy of dexamabnil, a synthetic cannabinoid analogue devoid of psychotropic activity, in severe traumatic brain injury.

Methods 861 patients with severe traumatic brain injury admitted to 86 specialist centres from 15 countries were included in a multi-centre, placebo-controlled, phase III trial. Patients were randomised to receive a single intravenous 150 mg dose of dexamabnil or placebo within 6 h of injury. The primary outcome was the extended Glasgow outcome scale assessed at 6 months, with the point of dichotomisation into unfavourable versus favourable outcome differentiated by baseline prognostic risk. Prespecified subgroup analyses were defined by injury severity, recruitment rate, and time to dosing. Secondary analysis included control of intracranial pressure and quality of life. Analysis were prespecified in the protocol and the statistical analysis plan. This study is registered with ClinicalTrials.gov, number NCT00129857.

Findings 846 patients were included in the efficacy analysis. The extended Glasgow outcome scale at 6 months did not differ between groups: 215 (50%) patients in the dexamabnil group and 214 (51%) patients in the placebo group had an unfavourable outcome (odds ratio for a favourable response 1.04; 95% CI 0.79–1.36). Improvements in the control of intracranial pressure or quality of life were not recorded and subgroup analysis showed no indication of differential treatment effects. Dexamabnil was not associated with hepatic, renal, or cardiac toxic effects.

Interpretation Dexamabnil is safe, but is not efficacious in the treatment of traumatic brain injury.
Therapeutic time window of Dexanabinol

- Animal model: up to three hours: protective against breakdown of the BBB and reduced formation of edema
- Between 4-6 hours, no significant reduction of cerebral edema, neurological symptoms improved
- Patho-physiologic endpoint: three hours?
Consent procedures in the Dexanabinol trial

- **Informed consent** (from the patient) not possible
- **Proxy consent** (from relatives) accepted in all participating countries
- **Deferred consent** allowed in Austria, Australia, Finland, France and Germany
- **Consent by an independent physician** allowed in Israel, Spain and United Kingdom
631 patients included

Selection criterion: study drug was administered after written proxy consent

501 patients (79.4%) directly admitted to the neuro-trauma centre

130 (20.6%) secondary referrals

4 time windows: 1. Between injury and admission NTC
2. Between admission and CT scan
3. Between CT scan and proxy consent
4. Between consent and SDA
### Time windows in the Dexanabinol Trial

**Kompanje, Slieker & Maas** (in press)

<table>
<thead>
<tr>
<th>Country (N)</th>
<th>Hours between injury and admission NTC</th>
<th>Hours between Admission NTC and CT scan</th>
<th>Hours between CT scan and obtained consent</th>
<th>Hours between obtained consent and SDA</th>
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* Countries with small populations (United Kingdom, Denmark, Austria, Poland and Turkey) were combined.
Time windows in the Dexanabinol Trial
Kompanje, Slieker & Maas (in press)
Time between injury and SDA, Dexanabinol

Kompanje, Slieker & Maas (in press)
Conclusions Time windows

Kompanje, Slieker & Maas (in press)

- Between injury and admission NTC: 1.16 – 2.35 hour
- In all patients time between admission and CT scan within 1 hour
- Time between CT scan and written proxy consent 1.71 – 2.74 hour
- After consent almost all patients receive SD within 1 hour
- In 60% time between injury and SDA was longer than 5 hours
- In 85.3% longer than 4 hours
Conclusions

- Physicians have the professional and ethical duty to provide patients with a form of treatment that they believe to be the most appropriate (In TBI this could be inclusion in a RCT in a particular time window)
- Risks and benefits should be carefully scrutinised
- Deferred consent and Waiver of consent are ethically defendable
- Legal representative should be defined narrowly
- An independent physician can serve as a legal representative
- The EU Directive article 5a hinder ICU and EM research in the member states