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Introduction. The European Clinical trial Directive 2001/20/EC was intended to be a European-wide harmonization of the provisions concerning clinical pharmacological trials, with the focus on the facilitation of multinational clinical research [1]. Since its publication in 2001, several articles have drawn attention to the serious threat to the development of critical care and emergency research within the European Union (EU) posed by the Directive 2001/20/EC which requires prior informed written consent before subjects can be recruited to clinical trials of medicinal products [2-16].

The Directive makes no direct exceptions for critical care and emergency situations, thus threatening to prevent all trials that involve patients with acute catastrophic illness which entails the loss of decision-making capacity and very short therapeutic time windows. These include conditions such as severe shock, circulatory arrest, acute myocardial infarction, severe infectious diseases, severe stroke and other acute neurological conditions, as well as patients suffering from moderate and severe traumatic brain injury.

Implementation by all EU countries was required by May 2004. The wording of the Directive permitted some flexibility so that variations were expected that might impact on emergency research. Lemaire et al [4] described the variations in national legislative responses to the Directive within Europe; they called on legislators to permit waivers of informed consent for critical care and emergency medicine research, to clarify terms and definitions, and to remove the artificial distinction between interventional and observational research. In the Netherlands, the requirements of the Directive have been transposed into the revision of the Medical Research in Human Subjects Act (WMO) and the Medicines Act (WoG) [17]. The amended WMO has changed the rules governing drug studies in the Netherlands. There is little, if any, change to non-drug-related research.

The Dutch Parliament accepted the plans for the amendment of the WMO on November 22 2005 and the revised Act became effective in the Netherlands on 1 March 2006.

The Directive was conceived in part to ensure that participants enrolled in research projects are given adequate information about the nature of the trials and their associated risks. Legislation to protect the interests of patients was necessary and timely. Most of the articles in the Directive were welcomed by the research community; they offered guidance and will help to maintain confidence in the probity of medical research. Unfortunately however, neither those responsible for the Directive, nor many who drafted enabling legislation within the Member States, considered the particular problems relating to research in emergency and critical care situations, where consent cannot be obtained from subjects and where the need for emergency treatment does not allow time for contact with relatives or other legal representatives. Moreover, in 1996 in the United States the FDA announced a waiver of informed consent for certain types of critical care and emergency medicine research after earlier, stricter provisions had brought to a halt important progress in some critical clinical situations.

This shortcoming and the variable response within European Member States to the requirements of the Directive, prompted the convening of an expert meeting in Vienna, Austria on 30 May 2005 (‘Vienna Initiative to save European Research’ (VISEAR)). This initiative was supported by the Department for Ethics in Medical Research of the Vienna Medical University, in cooperation with the European Forum for Good Clinical Practice (EFGCP), the European Clinical Research Infrastructures Network (ECRIN), and the Vienna School of Clinical Research. One of the six working groups aimed at clinical trials including patients who are not able to consent; the concept of individual direct benefit from research and informed consent in case of the temporarily incapacitated patient’ (Members of this working group; Prof dr C.Wiederermann [Medical University of Innsbruck, Austria & Hospital of Bolzano, Italy], Dr K. Liddell [Faculty of Law, University of Cambridge, United Kingdom], dr E.J.O. Kompanje [Department of Intensive Care and Department of Neurosurgery, Erasmus MC University Medical Center Rotterdam, The Netherlands], Prof dr B. Vehovac [Medical school University of Zagreb, Croatia], dr F.J.P. Lemaire [Service de Réanimation, Hôpital Henri Mondor, Créteil, France], Prof D.K. Menon [Division of Anaesthesia, University of Cambridge, United Kingdom], Prof J. Bion [Department of Intensive Care, University of Birmingham, United Kingdom], Prof D. Chamberlain [Resuscitation Council, University of Cardiff, Wales, United Kingdom]) and dr E. Nimmesgern [Directorate Health, European Commission, Brussels, Belgium].

The final VISEAR report was presented in December 2005 [18] and was published in the Wiener Klinische Wochenschrift in April 2006 [19]. Reports with recommendations from the sixth working group (‘clinical trials including patients who are not able to consent; the concept of individual direct benefit from research and informed consent in case of the temporarily incapacitated patient’) appeared this year in Resuscitation and the Wiener Klinische Wochenschrift [20,21]. This article summarizes the recommendations made by this working group, which could be of...
interest for Dutch critical care and emergency medicine researchers conducting trials in the European Community.

**Items discussed**
The items discussed by the working group are:
1. The implementation of the EU Directive 2001/20/EC insofar as it related to research involving adult patients unable to give consent
2. Legal, ethical and practical difficulties experienced as a result of implementation of the directive
3. Possible solutions to the problems experienced

As those problems in the Directive concerning intensive care and emergency research are especially relevant to Article 5 (Clinical trials on incapacitated adults not able to give informed legal consent), these were the main focus of the VISEAR working group.

**Article 5 of the Directive**
Article 5 of the Directive starts with the statement that: ‘in the case of other persons incapable of giving informed 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 not refused informed consent before onset of their incapacity shall be allowed only if...’ Nine further conditions follow, four of which warrant further comment concerning critical care and emergency research:
1. Article 5 (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’.

In circumstances of critical care or emergency medicine, the strict requirement to obtain prior consent from a legal representative in order to enrol incapacitated patients in clinical trials can make such research either extremely difficult or impossible to perform, especially if the intervention has to be made as a matter of urgency. The relevant clinical conditions include stroke, acute and severe coronary disease, severe and moderate head injury, severe shock, infectious diseases complicated by organ failure, and circulatory arrest. The effects of Article 5a, and its implementation in many EU Member States, seriously limits research in these groups of patients in a manner that the working group believes was unintended and is certainly undesirable.

The commonly used term ‘legal representative’ is not defined in the Directive, and it was explicitly stated that it was to be determined by national law. Thus Member States understandably have differing interpretations [4]. In Austria and Germany the surrogate decision-maker must be appointed by a judge. In Norway, the impact of the Biobank Act of 2003 is such that research involving tissue sampling (e.g. blood analysis) requires the consent of the subjects themselves [15]. Most other Member States are however less restrictive, recognizing a close or appointed relative as a legitimate representative. But even this is problematic as it erroneously assumes that there is sufficient time to obtain proper informed consent from a representative before the research can start. This is not the case in many of critical and life-threatening conditions. In one study, 87% of the European neuro-trauma centres sampled, reported that consent procedures significantly delayed the initiation of study treatment in patients with traumatic brain injury [8]. The varying interpretation of ‘legal representative’ creates difficulties for international trials where protocols and practice are expected to be uniform.

The working group emphasized the need for further work to harmonize international terminology and recommended solutions adopted in other countries. Some of the EU Member States have deferred or waived the requirement to obtain the consent of a legal representative where treatment must be started within a short time: a limit of eight hours has been suggested. This has some support in the literature. Ågård et al. found that 84% of patients with myocardial infarction were willing to allow the physician to make the decision on including them in the trial in the event of their being too ill to be asked about participation [12]. More recently, a study about consent for stroke research found that 92% of a small sample of patients thought the physician should be able to decide whether the patient is enrolled in a study if there is insufficient time to seek consent from a family member or surrogate [23]. Similarly 76% of European neuro-trauma centres (n=79) questioned the ethics of raising the issue of trial inclusion with relatives of a patient with severe traumatic brain injury so soon after admission [8]. A study in the United States by the National Acute Brain Injury Study: Hypothermia (NABIS-H) straddled a change in the law. This led to the finding that waiving the requirement for consent reduces the time to treatment by approximately 45 minutes and safely enrols a substantially larger number of patients (24). This was highly significant for the study, which had a treatment window of less than six hours. An alternative approach adopted by some Member States is to defer the need for consent for an agreed interval either until the subject regains capacity or until a legal representative is available and able to cooperate. This is advantageous in that it responds to the problems of the consent process without eliminating the involvement of family members.

Revocation of consent presents other potential difficulties. The practical implications are unclear and have caused confusion. Accepting that many treatments must be started as soon as possible if any benefit is to be obtained, and that this may inevitably precede any opportunity to consult, the question is whether or not participation can be continued. Nobody doubts a legal representative’s power to halt the administration of a medicinal product or to order that no additional data be collected. But what should be done with data collected up to that point? Bias could arise from revocation of consent by survivors whereas non-survivors would not of course be able to do so. On the other hand, survivors who are aware that they have recovered from serious illness as a result of treatment would be unlikely to withdraw consent for data to be used, whereas a relative functioning as the legal representative may well do so if treatment is unsuccessful. Bias can be averted only if data collected up to the point of withdrawal from the trial can be included in final analyses.

2. Article 5 (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’.

In most cases the first condition in relation to validation presents no problem. Although some forms of treatment will be appropriate only for incapacitated individuals and will therefore never be used in other clinical trials, data will always be available from animal studies or other sources. The second condition, however, that research must relate directly to a life-threatening or debilitating condition could be interpreted in an unfavourable way that the legislators may not have intended. Patients who are critically ill require a great deal of therapeutic support, including mechanical ventilation, sedation and artificial feeding. Research may indeed be required to improve adjunctive patient care. Valid and necessary studies must be permitted in order
to improve clinical care in situations where the incapacity arises from the treatment and not from the condition.

3. Article 5 (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”.

Ethics committees are often the only arbiters of the acceptability of a research project. An ill-advised adverse decision leads to much delay or, all too frequently, to inappropriate and necessary research being abandoned. The resources available to ethics committees and their degree of expertise vary appreciably within the EU and also within individual Member States. Multi-centre and international research projects may have to be submitted to several committees and different decisions are sometimes made on the same protocol. To a degree such problems reflect the lack of necessary expertise; this is understandable within a committee but many do not have systems for routinely making use of expert advice. Multi-centre committees may also require local committees to endorse their decisions, thus adding an additional layer of bureaucracy and increasing delays. Every effort should be made to simplify the process consistent with ensuring fair and appropriate decisions that safeguard the interests both of individuals and the wider population. A prerequisite for patient protection is careful and independent safety monitoring to limit risks. Current practice is that safety monitoring committees, although independent, are convened and sponsored by the pharmaceutical companies who initiate the trials, consequently leading to a potential conflict of interest. For emergency and intensive care trials, especially those conducted under waiver of consent or deferred consent, we would prefer the institution of an independent safety committee, under the auspices of regulatory authorities.

4. Article 5 (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”.

There are two serious problems with this Article. The first is that the requirement that the medicinal product should be expected ‘to produce a benefit to the patient outweighing the risks or no risk at all’ is incompatible with the well-established ethical principle of equipoise. The second is that Article 51 (and the Directive as a whole) does not take into account observational research, where there can be no direct benefit to the individual patient, but there may be substantial benefit to future patients though improved understanding of diseases processes and established treatments.

Equipoise is a necessary prior condition for conducting any prospective randomized trial comparing a promising but unproven therapy against an alternative treatment or placebo. This is the only mechanism for determining the risk-benefit ratio of a new treatment, and is therefore, a favourable ratio, logically cannot be a condition for performing a clinical trial. If benefit can be expected for patients in critical or emergency situations, how can a placebo group be an ethical component? Enrolling patients in a trial in which some sub-group may pro-duce a benefit is not ‘may produce a benefit’. The requirement to ascertain a favourable risk/benefit ratio should, however, be carried out in relation to the non-therapeutic components of the trial. The wording of the Directive cannot be changed but the legal implementation within Member States can still be modified to achieve the intended purpose of the Directive. It is in the interests of those who will require critical or emergency care in the future that intensivists should be prepared to do so. The situation as it now appears does not makes the European Union a particularly attractive place to do multi-national critical care research, with a negative effect on ongoing research.

Recommendations made by the working group

The working group made 18 recommendations concerning ‘clinical trials including patients who are not able to consent; the concept of individual direct benefit from research and informed consent in case of the temporarily incapacitated patient’ (18):

1. Article 5(a) should be amended as necessary (by extension, deferral or waiver) to permit and harmonize critical care and emergency research involving incapacitated persons where treatment must be commenced as a matter of urgency.

2. Member States should implement systems for legal representation that are compatible with critical illness research. Countries which ordinarily rely on court-appointed representatives should check the system is making timely appointments.

3. Countries which usually rely on family members to act as legal representatives should permit decisions to be made by other persons (unconnected with the research) when family members are too overwhelmed, or stressed to decide, or should defer or waive the consent requirement.

4. Further legal research should be undertaken to ascertain the definitions of ‘legal representative’ that apply in Member States. This could be used as a resource to ensure the lawfulness of international trials, for the basis of public debate and discussion papers, and to analyze the extent to which current definitions cause problems for research about emergency and critical illness.

5. The EC and Member States should clarify the extent of a legal representative’s power to revoke the individual’s participation in a clinical trial with reference to the future analysis for research purposes of data or tissue already collected.

6. Ethics committees should ensure that they interpret the phrase ‘research directly related to a life-threatening or debilitating clinical condition’ in the case of critical care of emergency medicine appropriately, and not too narrowly. The interpretation should permit research in conditions accompanied by incapacity, research in settings where incapacity is the consequence of essential therapy, research that addresses the common complications of incapaci-
tating conditions, and research to improve methods of supportive therapy.
7. The EC and Member States should increase the resources available for Ethics Committees to secure members or advisors with specialist knowledge relevant to clinical trials with incapacitated patients.
8. The EC and Member States should develop centralized bodies, guidelines and records of precedent decisions for ethics committees to increase the efficiency, consistency and predictability of their decisions.
9. The EC and Member States should recognize that in circumstances of clinical equipoise there will be substantial uncertainty whether administering a medicinal product will benefit a patient. The requirement that the trial be expected to produce benefits outweighing risks (or no risk at all) must be interpreted in this light.
10. The EC and Member States should publish guidance about ‘component analysis’ to clarify that when assessing whether a trial will produce a benefit to the patient outweighing the risks (or no risk at all), the judgment should be made with reference to the benefits and risks associated with the research component of the trial (rather than components of the trial that reflect accepted medical therapies or treatments in equipoise).
11. In conjunction with component analysis, the EC and Member States should review or clarify the requirement that the trial produce “a benefit to the patient outweighing the risks or produce no risk at all”. This should allow a protocol to include non-therapeutic components (e.g. scans, chart checks, blood tests) of no benefit to the individual, provided they represent no more than minimal risk, are minimized and proportionate to the knowledge gained.
12. When national legislation implementing the Directive covers more than clinical drug trials, Member States should ensure it permits research with no therapeutic benefit for the individual provided it poses them no more than minimal risk (for example observational studies, research using human tissue samples).
13. Researchers should document instances where non-therapeutic research has been unwisely prohibited by inappropriate implementation or extension of the Directive.
14. The EC and Member States should support ethical and legal research to develop guidelines for difficult risk comparisons.
15. Member States should monitor the impact of their laws on research involving incapacitated patients, particularly Member States which have applied the conditions of the Clinical Trials Directive to medical research other than clinical drug trials.
16. The EC and Member States should publish guidance to assist researchers and ethics committees with the interpretation of the Directive and implementing legislation.

References
18. Report of the 1st Meeting of the “Vienna Initiative to Save European Academic Research (VISEAR)” organised by the Medical University of Vienna Department of Medical Research, in collaboration with the European Forum for Good Clinical Practice (IFGCP), the European Clinical Research Infrastructures Network (ECRIN), and the Vienna School of Clinical Research (VSCR), December 2005.