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COMMENTARY

The European Clinical Trials Directive revisited: The VISEAR recommendations

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An editorial in Resuscitation in June 2002[1] drew attention to the threat to the development of evidence-based resuscitation within the European Union (EU) posed by the Directive 2001/20/EC ('The Clinical Trials Directive') which requires prior informed written consent before subjects can be recruited to clinical trials of medicinal products. It made no direct exception for emergency situations, and therefore threatened to prevent all trials involving victims of catastrophic illness causing loss of mental capacity—such as cardiac arrest, stroke, or 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. The editorial urged that representation be made at national level to take advantage of this flexibility and thus safeguard the continuing development of evidence-based resuscitation medicine. As expected, interpretation has not been uniform. Lemaire et al.[2] have described the variations in national legislative responses to the Directive within Europe; they called on legislators to permit waivers of informed

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consent for emergency research, to clarify terms and definitions, and to remove the artificial distinction between interventional and observational research.

Given this unsatisfactory and variable response within Europe to the requirements of the Directive, a working group convened in Vienna on 30 May 2005 ('Vienna Initiative to save European Research' (VISEAR)) and presented a report 3 months later.[3] The 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, the European Clinical Research Infrastructures Network, and the Vienna School of Clinical Research. The draft document was circulated to other interested individuals who had been unable to attend the meeting but helped to formulate the final report.

The EU Directive was conceived in part to ensure that participants enrolled in research projects are given adequate information about the nature of the trials and the associated risks. Abuses have indeed occurred in the past, and for this reason 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 offer sound guidance and will help to maintain confidence in the probity of medical science. Unfortunately, however, neither those responsible for the Directive, nor many who drafted enabling legislation within Member States, considered the special problems relating to research in emergency situations, where consent cannot be obtained from patients and where the patients' need for emergency treatment does not allow time for consultation with relatives or other legal representatives. This situation had previously been addressed in the Declaration of Helsinki and its later revision[4] that placed an increased onus on Ethics Committees when they considered such trials. Moreover, in the United States the FDA had published in 1996 a waiver of informed consent for certain types of emergency research after earlier strict provisions had brought to a halt important progress in some critical clinical situations.[5] That the issue could have been overlooked by European legislators is therefore surprising.

Several of the problems in the EU Directive related to Article 5 (*Clinical trials on incapacitated adults not able to give informed legal consent*), and this was therefore a main focus of the VISEAR group. Some of the provisions impact particularly unhelpfully on those wishing to improve emergency care. They will be considered in turn, with discussion of the difficulties they pose and the recommendations that might be considered at national level for limiting the unintended hindrance to legitimate research. Amendment of the Directive itself is not a practical solution, but within its framework some countries have found a way forward that has preserved its undoubted benefits but mitigated the 'threat to evidence based resuscitation' that was foreseen in the earlier editorial. Colleagues elsewhere might note that liberal interpretations of the Directive that encapsulate all its fundamental objectives have drawn no adverse comment from Brussels.

Article 5 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. Several are unexceptionable but four warrant further comment.

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 emergency or critical care, the requirement to obtain prior informed consent from a legal representative in order to enroll 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 tend to be the most important public health priorities; they include stroke, coronary heart attacks, severe and moderate head injury, severe shock and cardiac arrest. The effects of Article 5, and its implementation in many Member States, seriously limit ethical research in a manner that we believe was unintended and is certainly undesirable.

The term 'legal representative' is not defined in the Directive, and indeed was explicitly stated to be determined by national law. Thus Member States understandably have disparate interpretations.[2] In Austria and Germany the surrogate decision-maker must be appointed by a judge. In Norway, the impact of the Biobank Act 2003 is such that research involving tissue sampling (e.g. blood gas analysis) requires the consent of the individual themselves.[6] Most other Member States are less restrictive, recognizing a close relative as a legitimate representative. However, even this is problematic as it

assumes that there is sufficient time to obtain consent from a relative before the research must start. This is not the case in many critical conditions such as those mentioned above. Cardiac arrest is a particularly good example; a recent study showed that for every minute of delay to definitive treatment, survival was decreased by 23% compared with that in the previous minute.[7] In another study, 83% of European trauma centres sampled reported that consent procedures significantly delayed the initiation of study treatment.[8] Even in less pressing emergencies, the narrow definition of legal representative adopted in many countries has posed major problems for researchers. In the United Kingdom, a broader definition was adopted. The doctor primarily responsible for the patient's care may be nominated provided they are not connected with the conduct of the trial and there is no person with a closer relationship able and willing to act. But this is an unusual and not entirely satisfactory solution. Moreover, the varying interpretation of 'legal representative' creates difficulties for international trials where protocols and practice are expected to be uniform.

The Working Group thus emphasized the need for further work to harmonise international terminology and recommended solutions adopted in other countries. Some Member States have waived the requirement to obtain the consent of a legal representative where treatment must be started within a short time: a limit of 8 h has been suggested. This has some support in the literature. Agard et al. found that 84% of patients with myocardial infarction were willing for the physician to decide the question of trial inclusion in the event of their being too ill to be asked about participation.[9] More recently, a study about consent for stroke research found that 92% of patients think the physician should decide whether the patient is enrolled in a study if there is insufficient time to seek consent from a family member or surrogate.[10] Similarly 76% of European trauma centres ($n = 79$) questioned the ethics of raising the issue of trial inclusion with relatives of a patient with severe traumatic brain injury soon after admission.[8] The National Acute Brain Injury Study: Hypothermia (NABIS-H) in the United States 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 min and safely enrolls a substantially larger number of patients.[11] This was highly significant for the study, which had a treatment window of less than 6 h. 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 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 of 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 likely death as a result of treatment would be unlikely to withdraw consent for data to be used, whereas a relative as legal representative may well do so when treatment is unsuccessful. Bias can be averted only if data collected up to the point of withdrawal from the trial be included in final analyses.

Recommendations:

- Article 5(a) should be amended as necessary (by extension, waiver or deferral) to permit and harmonise emergency research involving incapacitated persons where treatment must be commenced as a matter of urgency.
- 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. 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 stressed to decide, or should waive or defer the consent requirement.
- 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.
- 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.

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.*

The first condition in relation to validation presents no problem. Although some treatments 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. Those who are critically ill require a great deal of support, including — for example — ventilation, sedation, and feeding. Research may indeed be required to improve patient care in these adjunctive ways. An example[12] can be taken from recent studies that revealed important hazards to patients ventilated after a cardiac arrest at a rate commonly used in prehospital clinical practice; cardiac output and survival improved with slower rates. This was research that some could interpret narrowly as not related *directly* to the clinical condition from which the patients suffered: the cardiac arrest and its antecedent causes. Valid and necessary studies must be permissible in order to improve clinical care in situations where the incapacity arises from the treatment and not from the condition.

Recommendation:

- Ethics committees should ensure that they interpret the phrase '*research ... directly related to a life-threatening or debilitating clinical condition*' appropriately, and not too narrowly. The interpretation should permit research in non-neurological conditions accompanied by incapacity, research in settings where incapacity is the consequence of essential therapy, research that addresses the common complications of incapacitating conditions, and research to improve methods of supportive therapy.

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-advized adverse decision leads to much delay or, all too frequently, to appropriate and necessary research being abandoned. The resources available to ethics committees and their degree of expertise varies appreciably within the EU and also within Member States. Multicentre and multinational research projects may have to be submitted to several committees; different decisions have then sometimes been made on the same protocol. To a degree such problems reflect a lack of necessary expertise; this is understandable within a committee but many do not have systems for routinely making use of expert advice. Multicentre committees may also require local committees to endorse their decisions, thus adding an additional layer of bureaucracy and increasing delays. At a local level, powers should be circumscribed[13] and be concerned with guidance rather than possible veto. 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.

Recommendations:

- 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.
- 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.

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 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 the Article (and the Directive as a whole) does not consider 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 disease 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; therefore, a favourable ratio logically cannot be a condition for performing a clinical trial. Indeed, 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 participants will be known from the *outset* to be receiving inferior treatment would be contrary to a duty of care, particularly where full consent cannot be obtained because of mental incapacity. On the other hand, a randomized trial can be expected to show a worse outcome in one arm compared with the other by the time it has been successfully concluded.

If the stipulation for risk extends also to the necessary investigations, then other problems arise. For example, who could guarantee that a CT scan or even simple intravenous cannulation would involve no risk? And in a placebo arm, likely to be 50% of the trial population, how could there be benefit that would outweigh even these miniscule risks?

The primary purpose of research is to produce knowledge that can be generalized to members of the community who are in a similar clinical state to that of those enrolled. In doing so, any risks must be weighed carefully so that participants are not put at unnecessary or disproportionate risk; there should also be at least a *possibility* of benefit where active treatments are administered. But the wording of Article 5(i) is strong, possibly unintentionally where it states 'grounds to expect that [it] will produce a benefit' and not 'may produce a benefit'.

Some sections of society in one Member State (the UK) have sought misguidedly to apply the language of Article 5(i) beyond the definition of clinical trials, lobbying for a law that would prohibit research using tissue and data from incapacitated persons unless it would benefit directly the individual or involve absolutely no risk. Interpreted strictly, this could preclude research based on the collection of blood or tissue, or even accepted surveillance techniques.

The Working Group considered the possibility of 'component analysis' as one solution to the problem.[14] In such a model, the risks in a trial protocol would be analyzed in two steps. First, the components of the trial that relate to accepted treatment administered with therapeutic intent (the treatment component) are demarcated from other components delivered solely to test a scientific hypothesis (the non-treatment component). Only then are the risks presented by the two components analyzed separately. If the protocol involves only accepted forms of medical treatment or treatment in clinical equipoise, the risk/benefit ratio associated with the treatment procedures should not be scrutinized by a research ethics committee; the legitimacy of these risks are assessed according to clinical standards. If equipoise exists, then the patient will not receive therapeutic interventions known to be inferior. 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 concept is discussed more fully elsewhere.[15]

Recommendations:

- The EC and Member States should recognise that in circumstances of clinical equipoise (which is a fundamental ethical requirement for enrolling patients in clinical trials) 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 light of this.
- 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).
- 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.
- 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 or health records, and pathophysiological research).

- Researchers should document instances where non-therapeutic research has been unwisely prohibited by inappropriate implementation or extension of the Directive.
- The EC and Member States should support ethical and legal research to develop guidelines for difficult risk comparisons.

In addition to the recommendations in relation to Article 5 of the Directive, the Working Group made two general recommendations:

- 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.
- The EC and Member States should publish guidance to assist researchers and ethics committees with the interpretation of the Directive and implementing legislation.

The serious threat to evidence-based resuscitation that was foreseen in the editorial of 2002[1] has become a reality. The wording of the Directive cannot be changed but the legal implementation within Member States can be modified, within bounds, to achieve the intended purpose of the Directive. Such action is already being taken within the United Kingdom where a consultation exercise has taken place in relation to the 2004 implementation of the Directive[16]: a modification is expected. Clinicians may feel they have a duty to mobilise public and political opinion within their own countries. It is in the interests of those who will require critical or emergency care in the future that they should be prepared to do so.

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