Position Paper

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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 (EFGCP), the European Clinical Research Infrastructures Network (ECRIN) and the Vienna School of Clinical Research (VSCR)

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Executive summary

This report records the views of a working group of the *Vienna Initiative to Save European Academic Research* (VISEAR). VISEAR, an association of European researchers predominantly from the public sector, seeks to improve European regulation of medical research. It is organised and financially supported by the University of Vienna, the Vienna School of Clinical Research and the Office of the Ethics Committee.

The report discusses:

(1) the implementation of the EU Directive 2001/20/EC ('the Clinical Trials Directive') insofar as it related to research involving adult patients unable to consent;
(2) legal, ethical and practical difficulties experienced as a result of implementation of the Clinical Trials Directive; and
(3) possible solutions to the problems experienced.

The report is concerned with a broad variety of research involving incapacitated persons including research about mental illness, intellectual disability, age-related illness, critical care and emergency medicine (e.g. stroke, cardiac arrest, traumatic head injury). The Working Group makes the following recommendations:

Implementation

1. 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.
2. The European Commission ('EC') and Member States should publish guidance to assist researchers and ethics committees with the interpretation of the Directive and implementing legislation.

Risk Assessment

3. The EC and Member States should recognise that in circumstances of clinical equipoise (which is an 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.
4. 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).
5. 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'. It

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 minimised and proportionate to the knowledge gained.

6. 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).
7. Researchers should document instances when non-therapeutic research has been unwisely prohibited by inappropriate implementation or extension of the Directive.
8. The EC and Member States should support ethical and legal research to develop guidelines for difficult risk comparisons.

Ethics Committee Review

9. 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.
10. The EC and Member States should develop centralised bodies, guidelines and records of precedent decisions for ethics committees to increase the efficiency, consistency and predictability of their decisions.

Revocation of Consent

11. 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.

Permitted Investigations

12. 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.

Legal Representatives for Proxy Consent

13. 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 debates and discussion papers discussing whether to broaden current definitions; and to analyse the extent to which current definitions cause problems for research about emergency and critical illness.

Emergency and Critical Illness Research

14. Article 5(a) of the Directive should be construed purposively or amended if 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.
15. 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.

Report

Introduction

A parallel working group of VISEAR convened in Vienna to discuss clinical trials including patients who are not able to consent. Its objective was to debate:

(1) the implementation of the EU Directive 2001/20/EC ('the Clinical Trials Directive') insofar as it related to research involving adult[1] patients unable to consent;
(2) legal, ethical and practical difficulties experienced as a result of implementation of the Clinical Trials Directive; and
(3) possible solutions to the problems experienced.

The meeting was concerned with a broad variety of research involving incapacitated persons including research about mental illness, intellectual disability, age-related illness, critical care and emergency medicine (e.g. stroke, cardiac arrest, traumatic head injury).

The following people were present at the parallel session or contributed by correspondence:

Christian J. Wiedermann (Chair) (Austria/Italy)
Kathy Liddell (Rapporteur) (UK)
Erwin Kompanje (Netherlands)
Bozidar Vrhovac (Croatia)
François Lemaire (France)
David Menon (UK)
Julion Bion (UK)
Douglas Chamberlain (UK)
Christiane Druml (Austria)
Apologies were received from Heiner Raspe (Germany).

Fundamental ethical considerations

The working group framed its discussion in light of four significant points about the public interest:

(a) Science, scientists, research and researchers should strive to serve the public interest, not their own interests.
(b) Incapacitated patients involved in research exercises are highly vulnerable and in need of protection. It is in the public interest that regulatory standards and procedures safeguard their rights, freedoms and interests.
(c) It is in the public interest to challenge therapeutic methods through research, in order to create the necessary evidence base for improving current clinical

[1] The participation of children in clinical trials was beyond the remit of the working party.

practice, both by finding new treatments, and by discarding ineffective and dangerous therapies.

(d) Research produces generalised knowledge to improve prophylactic, diagnostic and therapeutic procedures, and the understanding of the aetiology and pathogenesis of diseases [1]. This should not be denied to the population of incapacitated patients. Where this progress cannot be achieved except by involving incapacitated persons in research, it is in the public interest *and in the interest of incapacitated* patients that such research should not be unduly impeded.

Summarising these points, it is in the public interest and researchers' interests to establish a regulatory framework that balances the need to control research involving incapacitated patients with the need to facilitate it where important research objectives cannot be achieved by other means (e.g. research with competent adults, tissue cultures, simulations, or animals).

Implementation of the Clinical Trials Directive in specific countries

Article 5 of the EU Directive 2001/20/EC (the 'Clinical Trials Directive') directs Member States to implement laws that prohibit clinical trials on incapacitated adults, except where certain conditions are met. Passed in 2001, it was due for implementation in 2004. The steps taken in this regard by Member States are described by Lemaire et al. [2]. Since the publication of that article, we understand that implementation has occurred in all Member States, but that considerable variance remains. For example, we understand that research with incapacitated patients is much more difficult in Germany, where the law insists that the research should directly benefit the individual. In the UK, debates continue in relation to emergency research, and across all nations there is still much debate about ethics committees' decisions on research with incapacitated persons. Some Member States have implemented Article 5 of the Directive in relation to clinical drug trials only (as was intended), retaining separate laws for research on medical devices, research using human tissue or health records, and pathophysiological research. In contrast, other Member States have extended the stringent conditions of the Directive beyond clinical drug trials, which exacerbates the problems noted below. Some Member States have tried to interpret the Directive strictly, whereas others have taken more liberties with the legal margin for national interpretation. A stark example is the approach of the UK to emergency research compared with that adopted in France. To date the European Commission ('EC') has had no complaint about national methods of implementation, which suggests that it considers all variations acceptable. Nonetheless the differences are perplexing for researchers, regulators, ethics committees, and informed patients.

It is beyond the scope of this report to undertake a close comparison of national laws. Instead it focuses on a set of concerns which are attributable either to the terms of the Directive, the manner in which it has been implemented in some countries, or the absence of guidance about the Directive and implementing legislation. It is not envisaged that the Directive could be easily re-negotiated. However, we urge Member States to carefully consider *how* they implement it in law and governance, and to alter this as necessary. We also urge the EC and Member States to publish notes, guidelines and discussion papers to assist researchers and ethics committees with the interpretation of the Directive.

Recommendation:

- 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.

Problems stemming from article 5 of the Clinical Trials Directive

The conditions for lawful research with incapacitated persons are listed below. The provisions of the Directive that require special attention when implemented by Member States are highlighted in bold, and discussed in greater detail below:

(1) *Informed consent of the 'legal representative' has been obtained. The consent must represent the subject's presumed will and may be revoked at any time, without detriment to the subject.*

(2) The incapacitated person has received information according to his/her capacity about the trial.

(3) The explicit wish of the incapacitated person about participation is observed where they are capable of forming an opinion.

(4) No incentives or financial inducements are given, except compensation

(5) The research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods.

(6) *The research relates directly to a life-threatening or debilitating clinical condition from which the incapacitated person suffers.*

(7) The clinical trial is designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage.

(8) The risk threshold and the degree of distress is defined and constantly monitored.

(9) *The research protocol has been endorsed by a research ethics committee, having taken advice about clinical, ethical and psychosocial issues relevant to the disease and the patient population concerned.*

(10) The interests of the patient always prevail over those of science and society.

(11) *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.*[2]

[2] Although the punctuation in the English version of the Directive does not put it beyond doubt, we read this condition to mean that a clinical trial is permissible if (a) it is expected to produce a benefit for the individual that outweighs the risks; or (b) it is expected to produce no risk at all (whether or not it is expected to produce a benefit).

The purpose of the conditions is clear. Research should involve incapacitated patients only where: (i) there is a good scientific case; (ii) there is no alternative means to ascertain the information; (iii) the risks (including physical and psychological) are small, proportionate, minimised, and monitored; (iv) the limits of the risks are approved as satisfactory by an independent person(s); and (v) the individual's autonomous choices are actively facilitated and respected so far as possible.

These are admirable goals. However:

- Point (11) which corresponds with Art 5(i) is problematic unless interpreted in the context of the requirement for clinical equipoise.
- Point (9) which corresponds with Art 5(g) is commendable in theory, but presents difficulties in practice due to the variable quality of ethics committees' deliberations.
- Point (1) which corresponds with Art 5(a) creates serious difficulties for research on emergency and critical care. It erroneously assumes that it is possible to consult 'legal representatives' in every situation.
- Point (1) also raises questions about bias in data collections when consent for research is withdrawn.
- Point (6) which corresponds with Art 5(e) is problematic if it is interpreted to prevent important research where incapacity is not caused by disease.

These problems are described in more detail in the remainder of the report.

Risk assessment

It is widely accepted that the purpose of research is to produce knowledge that can be generalized to improve the well-being of individuals within the community. This means the purpose of research is not necessarily to provide benefit to patients who are asked to participate, and the risks associated with research must be carefully scrutinised in order that society does not take undue advantage of them. On this, there is consensus between the Member States. The difficulty has been to establish a method for assessing when the risks of medical research are acceptable.

The Directive and other European instruments [3] have gone some way towards resolving and harmonising the issues. These state that individuals should be included in research only if the ratio between risk and potential benefit is positive [4]. The phrasing in the Directive is that there must be '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'. This has encouraged some Member States, such as France, to revoke laws that required the research to involve direct individual benefit. This is a very positive step, however the precise manner in which this phrase is to be applied is not obvious. In particular, it is not clear how it may be said that the ratio between risk and potential benefit is positive when there is an ethical requirement that research should proceed only in circumstances of clinical equipoise.

Clinical equipoise is a fundamental tenet of medical ethics, but the concept is not addressed in the Directive. It is based on the principle that doctors have a professional duty to provide patients with a form of treatment that they believe on best available evidence to be most appropriate (provided it is affordable). It is contrary to a doctor's duty of care to enrol patients in a trial that is known to involve inferior treatment. Accordingly, research that compares treatments should take place only where there is genuine uncertainty amongst the clinical community (and informed competent patients) about the validity of the non-standard treatment. A rough rule of thumb is that research that compares treatment A and B should take place only where the clinical community believes that the likelihood of treatment A being better than treatment B is 50%. (Strict numerical equality is not essential; substantial uncertainty is considered sufficient).

In situations of clinical equipoise (i.e. uncertainty about preferred treatment), the Directive's requirement that research not be expected to produce a risk higher than the anticipated benefit can seem problematic. The uncertainty that is an intrinsic part of clinical equipoise seems to preclude a clear weighing of risks and benefits. A good trial is expected to be conclusive, hence one arm of the trial is *expected* to have a worse outcome.[3] However, there is substantial uncertainty as to which of the two groups this will be. This is a crucial point left unclear in the Directive.

One approach is to analyse the risk/benefit ratio in light of the entire clinical trial protocol. This is problematic for two reasons. It fails to acknowledge that a protocol may contain therapeutic procedures, non-therapeutic procedures or both. Research safety monitoring committees and ethics committees should not be concerning themselves with the risks associated with therapeutic procedures. Second it does not resolve the tension between clinical equipoise and the requirement for a positive risk/benefit ratio.

Weijer and Miller present a solution to the problem [5]. They argue that rather than assess the risk ratio of the clinical trial *in toto*, the risks in a trial protocol should be analysed in two steps. First, demarcate the components of the trial that relate to accepted treatment administered with therapeutic intent (the treatment component) from other components delivered solely to test a scientific hypothesis (the non-treatment component). The second step is to analyse the risks presented by the two components. The style of analysis to be directed at the two components is not identical since the researcher's intent differs in each component [6].

In so far as treatment procedures are concerned, Weijer and Miller argue that a research ethics committee should satisfy itself that the protocol involves only accepted forms of medical treatment or treatment in clinical equipoise. Significantly, 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.[4] The next step

[3] Except in equivalence trials, where both arms are expected to have the same outcome.

[4] The clinician may be required by national law governing treatment of incompetent patients to ascertain a favourable risk/benefit ratio before taking action with therapeutic intent. For example, in England the risks must be assessed to determine if the treatment is in the patient's best interests. This is a decision to be made within the doctor-patient relationship, not by a research ethics committee.

is to address the risks inherent in the *non-treatment components of the trial* [5–7]. This part of the trial (the monitoring and other procedures required for the conduct of the trial) is administered without therapeutic intent, accordingly it is these risks which must be strictly scrutinised and controlled. Many commentators recommend a concept of minimal risk indexed to the risks of everyday life and routine medical care encountered by patients [4].

By adopting this style of risk analysis, the judgment about clinical equipoise is separated from the assessment whether there is a favourable risk/benefit ratio. The requirement for equipoise ensures the patient does not receive therapeutic interventions known to be inferior. The requirement to ascertain a favourable risk/benefit ratio is carried out in relation to the non-therapeutic components of the trial.[5] This protects patients by ensuring that risks attributable to the quest for knowledge are not balanced against therapeutic benefits which the patient might receive whether or not they were enrolled in the trial (risks created without therapeutic intent must be separately justified), and means ethics committees will not make decisions for which they have no legal or ethical competency (treatment choice). Thirdly, this approach means that the risk assessment can be carried out notwithstanding uncertainty about the trial's outcome because it relates to a different set of procedures – the component of the protocol which is assigned for non-therapeutic reasons – which in most circumstances can be assessed straightforwardly.

Unfortunately, the Directive fails to take a clear stand on these issues. The wording of Art 5(i) states that the risk analysis should focus on the 'administration of the medicinal product under investigation', which leaves it ambiguous whether component analysis or some other form of risk assessment should be adopted. We recommend that Member States endorse component analysis and publish guidance to this effect in order to avoid the problems described above. Provided this approach is adopted – that is, provided the assessments of treatment risk and clinical equipoise are separated from the assessment of the risk/benefits associated with non-treatment component – there is no generic problem with the requirement to analyse the risk/benefit ratio in the face of clinical equipoise.

We think this is permitted by the Directive, however an important corollary follows. If component analysis is adopted it will be necessary to interpret pragmatically and purposively (rather than literally) the Directive's requirement that there be grounds for expecting the intervention will produce a benefit outweighing the risk or no risk at all. This is because component analysis focuses the risk inquiry on the non-therapeutic components of the trial which are not intended to produce benefits (although some do) and will necessarily be associated with some risk. The risk may range from the trivial risks of blood sampling (almost an invariable regulatory requirement in any drug trial), to (for example) the radiation burden associated with serial X-ray CT scanning to monitor the efficacy of a novel drug for treating cerebral haemorrhage [8]. Indeed, several of these procedures may be required to enhance patient safety, by allowing early detection and treatment of side effects and complications. Given these considerations, it would seem impossible to allocate a description of 'no risk' to the non-therapeutic (i.e. monitoring and enabling) component of most clinical trials. We therefore recommend the approach used by Weijer [6] who argues that risk should be minimised, proportionate to the knowledge gained and, be no more than minimal. In our view this is legitimate notwithstanding the text of the Directive, since the phrase 'no risk' can be construed purposively to mean 'no significant risk'.

This problem is exacerbated if Member States apply the language of Art 5(i) to other types of research beyond the definition of clinical trials. The working group is not aware of the extent of the problem, but heard that sectors of civil society in the UK lobbied strongly for a law that would prohibit research using tissue and data from incapacitated persons unless it would directly benefit the individual or involve absolutely no risk. Such a standard would have precluded research based on the collection of blood, tissue or data, research based on surveillance, or pathophysiological research (e.g. injecting dye to observe oedema formation).

The parallel group also discussed the difficulty associated with some risk comparisons. For example in severe traumatic brain injury is death a more serious risk for a patient than staying alive in a persistent vegetative state or with minimal consciousness? Or in stroke research is one to regard having an aphasia as more harmful than a paralysed arm? While subjectivity and incommensurability of risk is not caused by the Directive, it is an issue that must nevertheless be tackled by Member States when implementing governance frameworks. In our view, component analysis helps ameliorate the difficulties.

As a hypothetical example the group considered a research project where stroke patients are given a new thrombolytic agent (Drug X). If the law required the researcher and the ethics committee to examine the risks and benefits of the research study as a whole, it would take account of the likely benefits and risks of randomising a patient to receive Drug X (compared with giving the patient a standard stroke therapy), and insist on a conclusion that there are grounds to expect that Drug X will produce more benefits. However when Drug X and the standard therapy are in clinical equipoise (which they should be before a clinical trial is undertaken), it is fictitious to draw this conclusion. Furthermore this approach erroneously examines the benefits of treatment and the risks flowing from the underlying disease and standard treatments. If component analysis is adopted instead, one would compare the potential benefits and risks that are attributable to the aspects of the research protocol that are administered without therapeutic intent. This is the proper province of research governance and fits well with the ethical requirement for clinical equipoise. In this example, Drug X is in clinical equipoise with other therapies and administered with therapeutic intent. The risks associated with this component – principally the risk of haemorrhage – are therefore to be governed by clinical standards. The risks attributable to the non-therapeutic component of the research protocol are the risks associated with randomization, chart review and additional blood tests. The monitor-

[5] The risks associated with therapy are not irrelevant. They are considered separately when assessing whether a state of clinical equipoise exists.

ing associated with a trial may be expected to provide some benefit (e.g. additional imaging which detects abnormalities, complications or disease progress more quickly). But in any event the risks are minimal, therefore the trial should pass the risk assessment.

Recommendations:

- The EC and Member States should recognise that in circumstances of clinical equipoise (which is an 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'. It 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 minimised 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.

Ethics committee review

Members of the working group also noted concerns about the capacity for Ethics Committees to make wise decisions where research involves incapacitated patients. Art 5(g) of the Directive stipulates that ethics committees should have members with relevant expertise, or take advice, in relation to clinical, ethical and psychosocial questions. However, it is still the case that individual committees often lack the necessary expertise to assess the clinical, ethical and psychosocial questions that arise about the disease and patient population. It is important that they have opportunities to access specialist advice.

This is particularly important given that ethics committees are often the sole public arbiter of the acceptability of a research project. Conservative decisions fail to support the public interest in research, and unduly cavalier decisions fail to support the public interest in protecting individuals' rights and interests.

Multicentre and multinational research projects experience another difficulty. When required to seek the approval of several ethics committees, researchers are sometimes given different decisions in relation *to the same research protocol*. For example one multicentre, multinational survey of patient and relative opinions of the ideal qualities of an intensive care doctor was approved by ethics committees in eight Member States but rejected twice by a UK multicentre research ethics committee (MREC) before being approved on appeal to a second MREC; however, this MREC then required the local study coordinators to obtain approval from their local research ethics committees (LRECS) in each of ten participating hospitals. Whatever view one takes about ethical relativism, this level of review is overly demanding and is not serving the public interests described above.

The establishment of central and regional ethics committees helps to minimise undue bureaucracy and build specialist expertise. When setting up such systems, Member States must consider the powers (if any) that will reside in local committees. As the example above demonstrates, problems can arise if local committees have broad powers of veto. Their remit should therefore be tightly circumscribed [9, 10].

Overall, we suggest that if the system of ethical review is to function respectably, fairly and efficiently, it needs substantial centralisation, more resources and better systems for consistent and predictable decisionmaking [11].

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 centralised bodies, guidelines and records of precedent decisions for ethics committees to increase the efficiency, consistency and predictability of their decisions.

Revocation of consent

Art 5(a) states that consent to enrol an incapacitated patient in a clinical trial may be revoked at any time. Members of the working group noted that this had led to confusion about the extent of the power to revoke the individual's participation. Clearly it means the legal representative has the power to order that the giving of the medicinal product or placebo cease prospectively. The legal representative may also order that no additional tissue or data be collected prospectively. The question is whether the legal representative has the power to order that the tissue and data collected up to that point be destroyed or not be used for research? For example could the legal representative order that data about the patient recorded in tables and databases be erased or blocked? Such a power could create practical difficulties for researchers. It was also suggested that data could

become seriously biased if survivors retracted consent, but non-survivors did not. Researchers attending the meeting argued that too many revocations might jeopardize the process of randomization [12], particularly if survivors retract consent and non-survivors do not. In view of this researchers argued that the privacy interests of research participants are not disproportionately interfered with when data collected *up to the point of withdrawal* is used after withdrawal. However, members of the working group thought the arguments for this position were less persuasive where the requirements for proxy-consent had been waived or deferred, the data was sensitive, it was possible to separate out data and the risk of bias was small. The working group also noted that, arguably, this issue was governed by the Data Protection Directive rather than the Clinical Trials Directive.

Recommendation:

– 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.

Permitted investigations

Art 5(e) states that research with incapacitated patients should relate 'directly to a life-threatening or debilitating clinical condition from which the incapacitated person suffers.' The underlying purpose is to prevent researchers involving incapacitated individuals where the study lacks sufficient significance or could be carried out equally effectively with competent patients. This is an important safeguard. An injustice occurs when the burdens of research are imposed unduly on incapacitated persons who cannot protect themselves. However, it is important that the text of the Directive is not taken to mean that the research must relate to a condition which is *caused* by mental incapacity. This is not what it means, and to our knowledge this problem has not been reflected in national legislation implementing the Directive. However, it was an issue in the UK during the passage of related legislation [13], and it is important that similar mistakes are not made by ethics committees. It presents problems in several scenarios.

Some debilitating clinical conditions (e.g. organ failure) may result in mental incapacity which is a consequence of non-neurological disease, or due to essential therapy. For example patients with serious infections often develop severe respiratory failure; a scenario that represents the most common category of admissions to general intensive care units. In such patients the severe systemic illness may, in itself, affect capacity. In addition, artificial ventilation delivered through a tube in the windpipe is usually very uncomfortable and patients are given strong painkillers and sedatives to make them more comfortable. Research involving sedated patients is important in order to investigate the causes of organ failure and appropriate therapeutic responses. The text of the Directive clearly supports it, but Member States may misinterpret it in their effort to protect incapacitated patients.

A second set of circumstances relates to non-neurological complications of incapacitating disease. Airway reflexes are compromised in patients with a depressed level of consciousness, resulting in an increase in the incidence of aspiration pneumonia. Research aimed at preventing such pneumonia is clearly in the interest of the incapacitated patient.

A third set of circumstances is more complicated. Suppose we are looking at a new sedative drug to be used in intensive care for patients on ventilators. The question to be investigated is whether the drug is superior or safer. It might be said that this research is impermissible because it is not *directly* related to the principal life-threatening or debilitating clinical condition from which the patient suffers – namely organ failure. In contrast, the working group felt that Member States should take the view that this research complies with the Directive because ventilatory failure is a debilitating clinical condition, and sedation is a necessary part of its management. In this setting the 'debilitating clinical condition' may not be the *cause* of incapacity, but the research nevertheless meets the prime purpose of Article 5.

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.

Legal representatives for proxy consent

Members of the working group noted that Member States have defined the people that can act as a 'legal representative' in very different ways. A comparison is provided by Lemaire et al. [2]. For example, in the UK, a doctor primarily responsible for the patient's medical treatment or a person nominated by the health service can act as the legal representative Two caveats apply: the doctor or hospital nominee must not be connected with the conduct of the trial, and cannot make the decision if a person with a closer relationship with the subject is available and willing. This is adopted by very few Member States. In the majority, medical professionals cannot act as a legal representative.

This variation is lawful and not discouraged by the Clinical Trials Directive. It explicitly states that the concept of 'legal representative' is determined by national law, giving the Member States considerable discretion. Subject to concerns expressed in the next section in relation to emergency and critical illness research, each of the approaches is justifiable in a pluralist society.

But while pluralism is justifiable, it presents two sets of problems. In the first place, the highly variable definitions may have a negative impact on international trials. Secondly, researchers in countries with a narrow interpretation of 'legal representatives' report difficulties carrying out important types of research. This is relevant not only to emergency research (discussed below) but also research on other diseases such as dementia and stroke.

The Working Group took the view that greater harmonisation would be difficult to achieve at this point in time as Member States tend to regard their own approach as the most appropriate, and will not readily negotiate a new definition of 'legal representative'. However, if the implications of the narrow definitions were made clearer to the public in the countries adopting narrow definitions, there might be more support for broader definitions.

Recommendation:

– 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 debates and discussion papers discussing whether to broaden current definitions; and to analyse the extent to which current definitions cause problems for research about emergency and critical illness.

Emergency and critical illness research

The requirement that consent be given by a legal representative before enrolling an incapacitated person in a clinical trial is creating serious problems for emergency and critical illness research. This research relates to some of the most devastating conditions (cardiac arrest, strokes, arrhythmias, shock states) and should be considered a public health priority. National laws should make such research possible; not suppress it.

Emergency research

A common problem for emergency research is that researchers cannot contact a 'legal representative' (as defined by the Directive and implemented by Member States) in time to get their permission to involve the patient in a study. Some treatments must be provided as soon as possible and within several hours. Family members cannot be found, ambulance officers are unwilling to take on the responsibility for making a decision, and doctors on hand are usually connected with the treatment (and thus would be deemed to be connected with the conduct of the trial) [14–16]. Research studying cardiac arrest is a key example. The best available data shows that every minute of delay in definitive treatment reduces the chance of success by over 20% compared with that in the previous minute [17].

One solution, as implemented in the UK in 2004, is to permit the health service provider to appoint a suitably qualified individual to act in the capacity of legal representative. This solution is not always adequate. The National Acute Brain Injury Study (Hypothermia) demonstrated that using witness-signed proxy consent resulted in low accrual and late achievement of target temperature [18]. In the cardiac arrest example it would be unlawful and unethical to delay treatment whilst waiting to locate a hospital nominee for permission to enter the patient in the clinical trial. Yet there are many serious questions about treatment post-arrest that can be answered only through such research.

Another solution is to *waive* the requirement to obtain the consent of a legal representative where treatment (and any associated research) must commence as a matter of urgency (say within 8 hours). A set of criteria to define the circumstances where waiver of consent should be possible was discussed. Reference was made to the criteria of the FDA (US), the Tri-Council policy statement and the Declaration of Helsinki all of which countenance the waiver of consent in an emergency setting [19]. Some Member States have implemented such rules notwithstanding the apparent limits of the Directive [2].

It was suggested, but no firm view was expressed, that a complete waiver of the consent requirement does not provide sufficient safeguards for the rights and interests of the individual. An alternative is to *defer* the requirement to obtain the consent of a legal representative until a legal representative becomes available or the subject regains capacity. As a further safeguard, the period of time for deferral could be capped. Proxy-consent would be required to continue the trial.

In all proposals, it is envisaged that the prior approval of an ethics committee would be required. In this case, it is particularly important that the expertise of ethics committees be improved so that decisions are neither unduly conservative or cavalier (see recommendation above). It was also suggested that it would be preferable for a regulatory body to assess the safety of the trial [19], for example a safety monitoring committee established by the European Agency for the Evaluation of Medicinal Products.

Some lawyers have questioned whether systems of waived or deferred consent comply with the Directive. In the UK, it was argued that the language of the drafting indicates that a legal representative (however defined) must assess the subjective circumstances of each patient prior to enrolment. However, regulatory bodies in Brussels did not object when the French, Belgian and Dutch provisions – which all entail a waiver of consent in emergency conditions – 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 Biomedicine [3]. The UK government has recently proposed to amend its laws to implement a system of deferred consent (valid for 24 hours). Public consultation is afoot.

Whatever the existing diversity, it would be advantageous for Member States to adopt a common solution.

Recommendation:

– Article 5(a) should be construed purposively or amended if 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.

Critical illness research

Problems have also been experienced in critical illness research. The Directive leaves the definition of 'legal representative' to Member States. A variety of definitions apply, not all of which are pragmatic in the context of critical illness research. In some countries, such as Austria and Germany, a legal representative must be court-appointed. Often the courts will appoint a close family member. In other countries close relatives can automatically

qualify as legal representatives. Both systems present problems. The delay and complexity of court approval often precludes critical illness research. Furthermore, even supposing a family member is eligible to act as a legal representative and can be located in time to make the decision, the pressure of the situation means that that many find it difficult or stressful to make balanced decisions and misjudge the preferences of their family members [19].

It was thus suggested that a system for waiving or deferring consent of the legal representative should be implemented for critical illness research. For instance, if it were possible to defer obtaining consent, family members could be located, appointed by the court (if necessary), given the opportunity to come to terms with the acuity of the situation. A decision about research could be made shortly after it had commenced. The period of deferral could be capped.

An alternative approach is to permit persons other than family members to act as legal representatives for decisions about clinical trials. The UK has taken such an approach. It implemented the Directive such that a medical professional (unconnected with the trial) can act as the legal representative if a personal legal representative (e.g. a family member) is not willing to consider the question of research. The advantage of this approach is that it provides an alternative means of approval without removing the prerogative of family members to make decisions.

Recommendation:

– 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.

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