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CLINICAL COMMENTARY

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The European Union Directive and the protection of incapacitated subjects in research: an ethical analysis

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Abstract *Objective:* We perform an ethical analysis of European Union Directive 2001/20/EC on the simplification and harmonization of guidelines regarding good clinical practice in the conduct of clinical trials involving drugs. *Background:* The Directive provides guidance on protecting incapacitated subjects who participate in drug clinical trials. Such guidance promotes society's obligations of beneficence because the participation of incapacitated subjects in research is crucial in advancing the understanding and treatment of serious diseases. The Directive requires proxy consent for incapacitated subjects which adheres to the principle of respect for persons. The Directive also recommends additional safeguards to further protect subjects against exploitation and harm. These include respect for the assent and dissent of incapacitated subjects and the "necessity" and "subject-condition" requirements. *Results:* While these essential protection mechanisms are commendable, the Directive fails to endorse other safeguards that have been recommended by other research ethics guidelines, especially for riskier research. The Directive's silence regarding research in the emergency setting frustrates the principle of beneficence because the lack of guidance might prove to be a barrier for the conduct of such potentially beneficial research. *Conclusions:* We conclude that the European Directive fails in many respects to promote several important ethical principles in research involving incapacitated subjects.

Keywords Research ethics · Intensive care · Proxy consent · Vulnerable populations · Informed consent · Emergency research

Introduction

European Union Directive 2001/20/EC seeks to simplify and harmonize good clinical practice guidelines for the conduct of clinical trials involving drugs [1, 2]. The Directive was adopted on 4 April 2001, and Member States were required to pass national laws incorporating the general principles contained in the Directive by May 2004. Several articles in the Directive provide guidance regarding the protection of clinical trial subjects (Article 3). For adult persons who are incapable of giving informed consent to clinical trials the Directive states that such vulnerable persons "should be given special protection." Accordingly, additional guidance is given for the participation of these vulnerable persons in clinical trials (Article 5).

The Directive's concept of "special protection" for vulnerable subjects is congruent with other research ethics guidelines asserting that ethically acceptable research may proceed with such subjects if additional safeguards, including appropriate proxy consent, are in place to minimize the risk of harm and exploitation [2, 3, 4, 5, 6, 7]. Our aim, however, is to analyze the actual *content* of the Directive's guidance on research involving incapacitated

subjects and determine the extent to which it adheres to the following ethical principles in the research context: respect for persons, beneficence, nonmaleficence, and justice. In providing our analysis we realize that the Directive must achieve a balance between ethical concepts that should be universally applied and the flexibility that addresses the needs of Member States with varying local conditions informed by different religions, cultural attitudes, legal rules, and judiciary traditions. However, as implied in the Directive (Article 3, paragraph 1), any national provisions at odds with the Directive should be more protective.

Research involving incapacitated persons

Principle of beneficence

Society has obligations of beneficence in promoting research that can improve the health of its citizens [8]. Medical advances in the understanding and treatment of medical conditions such as cardiopulmonary and psychiatric illnesses depend on research involving persons who are incapacitated. As such, the Directive's attempt to harmonize practices regarding the protection of incapacitated subjects represents an important step in fulfilling these obligations of beneficence, especially since many Member States lack national laws that specifically address research involving such vulnerable persons.

Proxy consent for incapacitated subjects

Principle of respect for persons

Respect for persons entails that persons should be treated as autonomous agents and persons with diminished autonomy require special protection against exploitation of their inability to provide consent [8]. For persons who are incapacitated, such protection entails obtaining "appropriate" proxy consent for their participation in clinical trials. The phrase "appropriate" refers to acceptable individuals who are legally authorized to make decisions for incapacitated subjects and the decision making standards on which such decision are based.

Identification of individuals who should provide consent

The Directive states that, "inclusion in clinical trials of incapacitated adults... shall be allowed only if... the informed consent of the legal representative has been obtained...." Hence persons providing consent for incapacitated subjects must be legally authorized to provide such consent. The Directive clarifies that, "The notion of legal representative refers back to existing national law and consequently may include natural or legal persons, an authority and/or a body provided for by national law." Accordingly, the Directive recognizes that proxy consent might involve either a person previously appointed through a legal process (i.e., a legal person) or a family member or close friend (i.e., a natural person). By using the phrase "natural" person, the Directive recognizes that the laws of Member States could grant legal authority to family members or friends to provide informed consent for incapacitated persons. Without such automatic legal authorization given to family members or friends many previously healthy persons who become temporarily incapacitated might not be able to participate in many types of research studies (e.g., critical care research) because such persons will not have had previously appointed legal representatives and appointment of legal representatives usually involves a long process.

The Directive does not specify the identity of natural persons who may provide consent for incapacitated subjects. Frequently such persons are identified on the basis of a hierarchy of relationships widely thought to reflect closeness, such as the spouse and then an adult child. The Directive's intentional ambiguity on the identity of proxy decision makers allows different Member States to adopt differing hierarchies of persons informed by their different local conditions.

Such ambiguity, however, have led Member States to consider varying approaches to proxy consent that are either more or less restrictive than the provisions of the Directive. For example, the United Kingdom developed draft guidance recognizing that family members or persons with the closest personal relationship may act as the "personal legal representative" and provide proxy consent [9]. When no person who has a "sufficiently close personal relationship with the potential subject is available," a physician responsible for the care of the patient but not involved in the clinical trial may act as the subject's "professional legal representative" and provide proxy consent. This concept of a professional legal representative, however, is morally flawed because such professional individuals might not know subjects well enough to make a decision that reflects their desires regarding research participation.

Other Member States are contemplating vastly different regulations. The Netherlands intends to rely on an existing law that specifies the following priority of individuals to provide consent for incapacitated persons in the research context: legal representative, a spouse, life companion, or an individual specified in writing by the subject to act on his or her behalf [10, 11]. This list, however, would exclude a significant number of persons from participating in research, for example, unmarried adults without a companion, divorced or widowed adults with parents, and adult children. In France a proposed law authorizes a family member or a *personne de confiance* to provide consent to research participation for incapacitated

persons [12]. The notion of *personne de confiance* refers to a 2002 law that allows hospitalized adults to nominate in writing someone who could make decisions on their behalf in case of their incapacity. This person could be a relative, a person with a close relationship to the patient, or even the physician in charge [13].

Italy recently passed a law stipulating that patients not able to provide consent are required to have a legal representative to provide consent for their participation in clinical trials. However, the notion of legal representative is referred back to the Italian Privacy Act, which states that a legal representative must be nominated according to the general principles of the civil law [14]. Such a procedure might be time consuming, thus preventing the timely participation of many incapacitated persons in research. The Austrian draft for the new Drug Act [15] does not allow family members to be automatically authorized to provide research consent for incapacitated persons. Hence patients who become temporarily incapacitated will not be eligible to participate in research because they will not have previously appointed legal representatives, and research interventions normally must occur before there is time to nominate a legal representative.

Decision making standards

The Directive states that "consent must represent the subject's presumed will." This statement is consistent with the "substituted judgment" standard, which theoretically carries the most moral weight, because decisions made under this standard are based upon a good faith judgment of what subjects would have chosen if capable of making a decision themselves. However, studies in both the clinical and research settings suggest that such a standard is frequently unrealistic, because proxies often do not know patients' previous preferences [16, 17]. Rather than attaching exclusive importance to the substituted judgment standard, proxies should also be instructed to consider what would be in the "best interests" of the patient. Finally, studies have shown high levels of anxiety and psychological distress in family members of critically ill patients, which might impair their ability to give adequate informed consent for research participation for incapacitated patients [18, 19]. Further research is needed to determine the extent of this concern for proxy consent.

Additional safeguards beyond proxy consent

Principle of nonmaleficence

The principle of nonmaleficence warrants the specification of other safeguards to minimize the risk of harm and the potential exploitation of incapacitated subjects' inability to provide consent. The term nonmaleficence is preferable to the term beneficence because it emphasizes that risks rather than benefits to research subjects should serve as a central organizing principle in the conduct of research, thus avoiding a therapeutic orientation to clinical trials [20].

Assessment of risk

To provide adequate protection to incapacitated subjects research ethics guidelines have recommended various frameworks in which additional sets of safeguards are linked to a hierarchy of permissible risk levels of the research. The Directive, however, eschews a hierarchical organizing scheme for risk levels and instead requires that the research study as a whole to be placed in a single risk category. Specifically, the Directive states that persons incapable of giving their consent should be enrolled in clinical trials only if "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." Such an emphasis on a singular risk category fails to acknowledge that drug trials might consist of therapeutic as well as nontherapeutic procedures, i.e., those with and without the prospect of direct benefit. A nontherapeutic procedure might be simple and innocuous, for instance, additional blood samples for pharmacokinetic information, chart review, and completion of a survey. Other types of nontherapeutic procedures might, however, be invasive and present additional risks to subjects, for example, additional blood samples for genetic information, organ biopsy, bronchoscopically obtained bronchoalveolar samples, and wash-out of medicines that patients have been receiving.

The practice of assigning risk levels to the two distinct components of a research study (i.e., therapeutic and nontherapeutic procedures) rather than to the research study as a whole [21, 22] entails that multiple judgments regarding justifications of different types of procedures might need to be made before granting approval to a research study. Risks posed by procedures with potential direct benefits should be weighed only against those potential benefits, just as in clinical practice. If clinical equipoise exists, it follows that the net balance of risks and expected benefits in either trial arm (and the alternatives available in clinical practice) are equivalent. Hence subjects are not disadvantaged by participating in the study or by randomization to either trial arms, and therefore the risks associated with therapeutic procedures are justifiable and hence permissible. In contrast, risks associated with nontherapeutic procedures need to be categorized by increasing levels of risk because they are not offset by the prospect of any compensating benefits. The concept of minimal risk is central to this risk categorization.

Concept of minimal risk

Commentators have recommended a concept of minimal risk indexed to the risks of everyday life and routine medical care encountered in the daily lives of normal, healthy adults, i.e., by the population as a whole [2, 21]. This concept would make reference to an absolute standard of risks that are common and familiar to most persons, such as those encountered while driving to work or crossing a street or during the performance of routine physical or psychological examinations or tests. This position regarding minimal risk conveys a defensible normative judgment that the types of minimal risks considered socially acceptable might also be acceptable in research [21].

If this argument regarding acceptable risk is tenable, the justification for proceeding with research containing nontherapeutic procedures that carry no more than minimal risk is embodied within the concept of minimal risk itself. In contrast, research containing nontherapeutic procedures presenting greater than minimal risk needs to be justified by the importance of the knowledge to be gained from the research study, a so-called risk-knowledge calculus. Use of a component analysis to assess risk for the different components of a protocol protects research subjects better than a whole protocol approach, because with the latter approach, the risks of nontherapeutic procedures might claim to be justified by the procedures that do offer the prospect of direct benefits to subjects.

Specification of essential safeguards

Once risk levels are delineated and justified, essential safeguards to protect vulnerable subjects can be specified. For the one research risk category stipulated in the Directive several essential safeguards for incapacitated subjects are recommended for all such research. First, it requires investigators to obtain, in addition to a proxy's consent, the assent (i.e., the affirmative agreement), of those subjects who are able understand some aspects of the study. Specifically, the Directive requires that "the person not able to give informed legal consent has received information according to his/her capacity of understanding regarding the trial, the risks and the benefits." An assent requirement recognizes that in some instances the decision making capacity of some subjects might not be completely diminished, and hence the potential subject might still be able to understand some aspects of a study. Such an assent requirement has been recognized by several research guidelines [3, 5, 6] and ensures that adults with mild to moderate decisional impairments have an appropriate level of involvement in the decision for their study participation.

The Directive also requires that a subject's dissent to initial or ongoing participation be honored. It states that "the explicit wish of a subject who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator...." The Canadian Tri-Council guidelines would allow research regardless of dissent if it offers the potential for direct benefit, whereas other research guidelines would prohibit the conduct of such research [2, 4, 5, 6].

Congruent with other guidelines [2, 3, 4, 5, 6, 7], the Directive also endorses the "necessity" requirement for all clinical trials. It states that enrollment of incapacitated subjects should be allowed only if "such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods...." Although this statement is somewhat ambiguous, it can be interpreted as capturing the idea that the participation of incapacitated subjects should occur only when (a) the scientific question can only be answered with their participation (i.e., the condition being studied causes incapacity in all persons, such as severe head trauma and severe psychiatric disorders), or (b) the research cannot be conducted in competent subjects with the same disorder (e.g., the numbers of competent subjects are such that the research is prohibitive due to time or cost constraints). To enroll incapacitated subjects when it is not scientifically necessary raises the concern that such subjects are being approached merely because they cannot provide consent and are less able to protect themselves. An injustice occurs when the burdens of research are imposed unduly on those who are selected merely because of their easy availability [8]. The principle of justice requires just distribution of benefits and burdens and that there are good reasons to justify departures from equal distributions. When enrollment of vulnerable subjects is needed to address the scientific hypothesis, exploitation of their impairment is not present because they are being enrolled to obtain important information, not because they are unable to consent.

Finally, consistent with other research ethics guidelines [2, 5, 6, 7], the Directive endorses the requirement that research involving vulnerable subjects is permissible only when such research "relates directly to a life-threatening or debilitating clinical condition from which the incapacitated adult concerned suffers...." This subject-condition safeguard entails that the research must involve a condition from which the subject suffers.

While the Directive's endorsement of the assent, dissent, necessity, and subject-condition safeguards are commendable, it fails to mention other safeguards that other guidelines have recommended for all research studies. These include the requirement that investigators outline a specific plan to assess the capacity of all potential subjects when groups that might involve incapacitated per-

sons are targeted for research, for example, patients receiving mechanical ventilation or individuals with mild to moderate schizophrenia [2, 5, 6]. The failure to assess capacity can be problematic because incorrect judgments that incapacitated persons are capable of exercising autonomy might involve such persons in research that is not sufficiently understandable to them. Finally, research ethics guidelines have also recommended for subjects who regain decisional capacity during the clinical trial and were entered into the trial through proxy consent that their informed consent be obtained as a condition of continuing participation [3, 6, 7].

Additional safeguards for research involving nontherapeutic procedures

Additional safeguards beyond those previously mentioned are not necessary for research involving non-therapeutic procedures associated with no more than minimal risk. Various approaches have been used for research presenting greater than minimal risk. For example, the Council of Europe guidelines [4] prohibit research that poses greater than minimal risk, whereas other research guidelines agree that incapacitated subjects can be adequately protected without placing a restriction on the risk level of research containing nontherapeutic procedures [2, 3, 5, 6, 7].

The Directive's use of a singular risk category expressed in terms of risk and benefits to subjects makes it unclear as to whether the Directive intended to limit the conduct of research containing nontherapeutic procedures that pose greater than minimal risk. If the Directive intended to allow such research, no guidance is given regarding whether and what additional safeguards are needed to protect incapacitated subjects. As such, there are shortcomings in the Directive regarding specifying further obligations of nonmaleficence. Examples of additional safeguards for greater than minimal risk research include the presence of an independent person to perform capacity assessments [2] and the requirement of independent consent monitors who could witness the informed consent process and provide independent assurance that proxies deciding for incapacitated adults understand sufficiently the "goals and risks of the research" [5, 6, 23, 24]. Alternatively, one could adopt for such research a risk ceiling that is intermediate between minimal risk and greater than minimal risk [7].

Research performed in the emergency situation

At times important research needs to be carried out involving the investigation of novel therapies in the emergency situation, such as cardiac arrest, stroke, severe arrhythmias, and life-threatening traumatic injury. In such situations, due to the narrow time window that might exist for administering the intervention, there might not be sufficient time to obtain consent from a legal representative [25]. Recently the United States government specified several protection mechanisms under which research involving incapacitated subjects in the emergency situation can be allowed with an exception from the requirement for informed consent of a legally authorized representative [26]. Although the Directive states that consent for research involving incapacitated subjects "has to be granted by the patient's legal representative," it is unclear whether the Directive intended to preclude emergency research, or whether it merely failed to address such research [27]. Such ambiguity has raised concerns among many intensivists because a literal interpretation of the Directive could prevent potentially beneficial research in the emergency setting and hence, expose many patients to the hazards of unvalidated clinical practice [28, 29, 30, 31].

Several Member States, however, have outlined vastly different conditions under which emergency research involving incapacitated subjects may proceed with a waiver of the informed consent of their legal representatives. For example, the United Kingdom has drafted regulations that would allow the participation of incapacitated persons in emergency research with the consent from a professional legal representative (who could even be a paramedic) in the absence of a personal legal representative [9]. In France draft legislation currently states that an ethics committee can determine when research in the emergency setting involving incapacitated persons may proceed without the consent from family members [12]. Similarly, the Dutch and Belgian proposed regulations include provisions for emergency research involving incapacitated persons without the consent of their legal representatives. In Austria an emergency waiver of consent can be obtained for incapacitated persons under the current law if certain criteria are met, including approval from an ethics committee. However, it is unclear whether such trials will be possible under the new law [32]. Member States that decide to forgo such research might still benefit, nonetheless, from the results of such research performed in other countries. The resulting unequal distribution of burdens and benefits of such research raises an issue of justice.

Concluding remarks

The European Union Directive has provided several commendable directives regarding research involving incapacitated persons, thus ensuring that such potentially beneficial research can proceed. The Directive, however, fails in many respects to promote several important ethical principles in such research. Ambiguity regarding the identity of proxies might lead different Member States to endorse requirements for proxy consent that are less restrictive than intended. There is also incomplete guidance

regarding essential safeguards for all types of research involving vulnerable subjects and ambiguity regarding additional safeguards for riskier research involving non-therapeutic procedures. Ambiguity and incomplete guidance regarding proxy consent and essential safeguards relies too heavily on the diverse views of individual research ethics committees that might lead to inadequate and inconsistent safeguards [33]. Such a situation might make such research ethically problematic. In the United States, where the federal regulations regarding the participation of incapacitated adults in research offer only general guidance [34], there have been lawsuits [35], governmental sanctions [36], and most recently investigations by the Office of Human Research Protections in certain critical care trials [37]. Finally, lack of clarity regarding research in the emergency setting might prove to be a barrier for the conduct of such research in some countries. Although Member States could adopt laws that are more protective than the guidance given in the Directive, a future analysis of these laws might very well indicate the need for the European Union to adopt amendments to ensure adequate protection of vulnerable subjects.

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