

Informed consent in experimentation involving mentally impaired persons: ethical issues

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Summary. The problem of experimentation involving subjects whose mental condition prevents them from understanding information and providing proper informed consent has been addressed in various codes, declarations, conventions, treaties and regulations adopted by national, international and supranational institutions and authorities. This article summarizes the basic ethical criteria these documents provide and stresses the historical development from the nearly total exclusion of incapacitated subjects, established in the mid-twentieth century, to their contemporary inclusion in clinical trials on certain ethical conditions. The problem of proxy consent by legal representatives for participation in clinical trials is addressed particularly in reference to current Italian regulations. Exceptions to human experimentation requirements in emergency situations are also briefly discussed.

Key words: bioethics, clinical trials, informed consent, legislation, mental disability.

Riassunto (*Il consenso informato nella sperimentazione con persone affette da demenza: problemi di etica*). Numerosi codici, dichiarazioni, convenzioni, trattati, normative adottati dalle istituzioni ed autorità nazionali, internazionali e sopranazionali affrontano il problema della sperimentazione con persone le cui condizioni mentali impediscono la comprensione delle informazioni e l'espressione del consenso. L'articolo riassume i principali criteri di etica stabiliti in tali documenti ed evidenzia la loro evoluzione, da una pressoché completa esclusione dei soggetti cosiddetti "incapaci" intorno alla metà del Novecento fino ai criteri attuali, che consentono la partecipazione di tali soggetti in sperimentazioni purché siano rispettati alcuni requisiti di etica. Il tema delle deroghe in condizioni di emergenza è accennato limitatamente all'ambito della sperimentazione clinica.

Parole chiave: bioetica, sperimentazione clinica, consenso informato, legislazione, disabilità mentale.

INTRODUCTION

The key issue addressed here is the tension between two conflicting obligations: the duty to protect vulnerable subjects incapable of informed consent and the duty not to deny them potential trial benefits. The ethical assumptions to be considered when seeking an acceptable balance between these two contrasting needs are explored. This would be futile without reference to fundamental human rights and some of the precepts identified throughout the history of human thought. Although the term "bioethics" was coined in 1970 [1, 2], it would be reductive to suggest that the science of bioethics was actually born then. Its roots go back through the centuries of human cultural development; it is an inestimable treasure that we cannot and must not ignore.

This article does not intend to discuss advance directives or decisions made while a person still has the capacity to refuse treatments in the terminal stages of illness. Furthermore, no references are made to other situations, such as paediatric research, where the in-

ability to express consent has other causes (*i.e.* incomplete development) and, aside from special cases and conditions, the decision is normally made by someone acting *in loco parentis* (while only a minority of "incompetent" adults is legally represented).

INFORMED CONSENT

Throughout the ages, physicians have believed that they should make treatment decisions for their patients. This conviction is clear in the Hippocratic Oath: "I swear by Apollo and Aesculepius [that] I will follow that system of regimen which according to my ability and judgement I consider for the benefit of my patients" [3]. In 1847, the American Medical Association promulgated its first Code of Ethics. It admonishes patients that their "obedience (...) to the prescription of [their] physicians should be prompt and implicit. [They] should never permit [their] own crude opinions [...] to influence [their] attention to [their physicians]" [4]. The need to respect physician authority was supported by

three claims: 1) physicians have exclusive knowledge, incomprehensible to patients, acquired through arduous training and practical experience; 2) patients are incapable of making decisions on their own behalf due to the anxieties of illness; and 3) physician commitment to altruism is a sufficient safeguard against any abuses of their professional authority.

The idea that a physician should seek the patient's consent prior to any medical intervention developed gradually during the twentieth century. Though there are earlier traces of it, such as the British court decision *Slater v. Backer and Stapleton* in 1767 affirming the duty to inform patients about medical interventions on their own body though not giving them decision-making power, the notion of "informed consent" is recent. It entered into US law with a brief paragraph in a 1957 State Court decision (*Salgo v. Leland Stanford Jr. Univ.*, 1957), and was then developed in a lengthier 1960 opinion (*Natanson v. Kline*, 1960) [5]. The first recognition of informed consent in Italy came with the 1992 "Massimo Decision". In the case, Florentine surgeon Carlo Massimo fully excised a patient's rectum during a surgical operation without having provided information or asked for consent and without sufficient urgency to justify it [6]. There are certain differences, however, between the history of informed consent in the context of routine treatment and in the context of experimentation. We wish to explore the latter.

Informed consent is currently considered a cornerstone of bioethics. There are three basic components of informed consent: prerequisites, information and enrolment. The prerequisites are competence (*i.e.* understanding and decision-making capacity) and voluntariness. Health care professionals have a duty to give clear and truthful information to patients. Enrolment should be free and voluntary: a subject must have the opportunity to withdraw consent without prejudice unless it is irrevocable (such as in surgery). Consent is thus said to be simultaneously related (*i.e.* part of the therapeutic physician-patient "alliance"), informed (*i.e.* expressed after the subject has been informed of all the elements necessary for understanding the situation) and detailed (*i.e.* specific, referring to a real and definite situation) [7].

Faden *et al.* identify two meanings of informed consent. The first (which they call "Sense1") is "an autonomous action by a subject or patient that authorizes a professional either to involve the subject in research or to initiate a medical plan for the patient (or both)". "Sense2" informed consent is "legally or institutionally effective [...] authorization from a patient or subject [...] obtained through procedures that satisfy the rules and requirements defining a specific institutional practice in health care or in research" [8].

COMPETENCE: WHAT IT IS AND HOW TO ASSESS IT

For many years there has been significant and ongoing debate regarding competence assessment. Decision-making capacities entail at least four components:

understanding relevant information regarding treatment or research methods as well as risks and benefits, appreciating treatment methods and their consequences, reasoning about the different treatment options and communicating a choice [9]. Several instruments to assess these four components are available [10]. For example, Thomas Grisso and Paul S. Appelbaum have suggested some practical criteria for capacity assessment and have expounded their views in both handy guides [11] and review articles [12]. An analysis of these instruments goes beyond the scope of this article; however, it is relevant to note that while the literature about capacity assessment has been growing, relatively little attention has been paid to defining competence.

"Competence" is a term widely adopted in American legal writing and corresponds to the term "mental capacity" in British legal writing. Competence can be considered a normative ethical quality, a cognitive-psychological trait and a legal characteristic. It can take on five main forms: agency competence, task competence, decisional competence, societal competence and legal competence.

Agency competence is the necessary and sufficient condition for the development or actuation of any other competence. Agency competence entails the ability to generate freely chosen purposes and value the necessary means to those purposes in a categorical fashion. Agency competence has an ontological value analogous to the notion of "personhood". It includes the capabilities necessary for human action at all: consciousness, perception, ratiocination and volition. Task competence describes the ability of an individual with respect to a given task: A is competent at task B to degree C. Decisional competence is the ability of an individual to make a decision. Task and decisional competence can each be possessed by degrees. Societal competence refers to the display of a sufficient range of task and decisional competence for an individual to interact independently within the society or the community. Legal competence (or legal capacity) is the most contingent type: in its essential form, it is the exercise of a legally recognized power.

Competence to give informed consent is a form of decisional competence. A diagnosis of mental illness or of dementia does not necessarily imply incompetence; moreover, incompetence is correlated with an altered mental state, but is not identified as one. Sufficient competence depends on the subject's situation (though it was previously considered a characteristic of the individual regardless of the situation), may change even in the very immediate future and depends on the consequences of the decisions to be made (for example, consent to a high-risk treatment requires greater competence than consent to a low-risk treatment with considerable benefits) [11].

WHY RESEARCH?

In general terms, experimentation describes a procedure or investigation designed to test a hypothesis where it is not possible to know the exact outcome.

A more precise definition is not easy, but there have been various important contributions.

At the beginning of the nineteenth century, Thomas Percival claimed that medical experimentation takes place where existing medical practice proves unsuccessful and under circumstances not previously foreseen [13]. Almost 150 years later, McCance endorsed a definition of medical experimentation as a procedure that involves a subject, lacks a primary therapeutic benefit, is unable to assist the diagnosis process and whose results cannot be known in advance [14]. In roughly the same time period, the Declaration of Helsinki by the World Medical Association stipulated the types of medical research without stating what medical research actually is [15].

More recently, European Directive 2001/20/EC defined a clinical trial as “any investigation on human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy” [16].

The different terms adopted indicate different meanings: “experimentation” often refers to how a line of enquiry is addressed and “research” to the nature of the outcome it generates.

REFERENCE DOCUMENTS ADDRESSING THE ETHICS OF INFORMED CONSENT AND HUMAN RESEARCH

The major national, international and supranational institutions have published an extensive range of documents over the past century discussing clinical trials, the protection of enrolled subjects and informed consent. They are here divided into five main categories and listed in chronological order within each category.

I) Declarations, conventions, treaties and similar documents:

- The Nuremberg Code (1946) [17];
- The Declaration of Helsinki (1964-2008) [15];
- The Belmont Report (1979) [18];
- Recommendation n. R(90) 3 of the Committee of Ministers to Member States concerning medical research on human beings (1990) [19];
- Guidelines for good clinical practice (GCP) for trials on pharmaceutical products (1995) [20];
- Guidelines for good clinical practice (1996) [21], incorporated into Italian law by the Ministerial Decree on 15 July 1997 [22];
- Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: Convention on human rights and biomedicine (1996) [23], ratified in Italy by Law no.145 of 28 March 2001 [24]. Although this law has been passed by Parliament, it

has not yet been filed by the Italian government with the General Secretariat of the Council of Europe, and is therefore not in force. The Convention is nonetheless an important reference and is widely accepted in the field of bioethics;

- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (2001) [16], incorporated into Italian law by Legislative Decree n. 211 on 24 June 2003 [25];
- International ethical guidelines for biomedical Research involving human subjects (2002) [26];
- Additional protocol on the Convention of human rights and biomedicine concerning biomedical research (2005) [27];
- European Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (2005) [28], incorporated into Italian law by Legislative Decree n. 200 on 6 November 2007 [29];
- Universal Declaration on bioethics and human rights (2005) [30];
- Report of the International Bioethics Committee (IBC) on consent (2008) [31].

II) Ethical codes:

- The Code of medical ethics issued by the Italian Federation of Medical Doctors, Surgeons and Dentists (2006) [32].

III) Guidelines regarding the participation of subjects unable to express consent (in addition to the above documents):

- The ethical conduct of research on the mentally incapacitated (Medical Research Council, UK, 1991) [33];
- Guidelines for assessing the decision-making capacities of potential research subjects with cognitive impairment (American Psychiatric Association, 1998) [9];
- Position statement. Informed consent for research on human subjects with dementia (American Geriatrics Society, 1998) [34];
- Guidelines for researchers and for research ethics committees on psychiatric research involving human participants (Royal College of Psychiatrists, 2000) [35];
- Ethical issues in dementia research with special emphasis on “informed consent” (Alzheimer’s Association, 2007) [36].

IV) National legislation (examples):

- Legislative Decree n. 211 on 24 June 2003 (Italy). Transposition of Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use [25];

- Mental Capacity Act, England and Wales (Her Majesty's Stationery Office - Office of Public Sector Information, 2005) [37].

V) *Opinions of national bioethics committees and commissions:*

- Informazione e consenso all'atto medico [Information and consent for medical actions] (Comitato Nazionale per la Bioetica, Italy 1992) [38];

- Avis sur l'éthique de la recherche dans les sciences du comportement humain [Opinion on the ethics of research in human behavioural sciences], Rapport (Comité Consultatif National d'Éthique pour les Sciences de la Vie et de la Santé, France 1993) [39];

- Research involving persons with mental disorders that may affect decision-making capacity (National Bioethics Advisory Commission, USA 1998) [40];

- Avis n. 14 du 10 décembre 2001 relatif aux "Règles éthiques face aux personnes atteintes de démence" [Opinion n. 14, December 2001, regarding "Ethical regulations and persons affected with dementia"] (Comité Consultatif de Bioéthique de Belgique, Belgium 1998) [41].

HISTORICAL DEVELOPMENT

As already noted, the issue of informed consent is only addressed here with reference to clinical trials; however, it clearly cannot be examined without exploring its historical background. One authoritative historical example of the link between informed consent in trials and consent in general is in the Italian constitution. Article 32 states that "the Republic safeguards health as a fundamental right of the individual and as a collective interest, and guarantees free medical care to the indigent. No one may be obliged to undergo any health treatment except under the provisions of the law. The law may not under any circumstances violate the limits imposed by respect for the human person" [42]. In the first draft of this text, on which the final version approved in 1948 was modelled, the present article 32 bore the number 26 and stated: "The Republic safeguards health, promotes hygiene and guarantees care to the indigent. No health treatment can be made compulsory except by law. All healthcare practices that are injurious to human dignity are forbidden". Although they are not mentioned explicitly, there is a clear reference to the clinical trials and human rights violations perpetrated in the years immediately preceding the drafting of the constitution.

If we look at the documents chronologically, a process of development becomes apparent. The Nuremberg Code banned subjects unable to consent from participating in clinical trials and forbade the possibility of "surrogate" consent from representatives. Article 1 states this clearly: "The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise

free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision" [17]. In response to the human rights violations during the years leading up to it, the Code thereby excluded the possibility of conducting trials with mental incapacitated subjects. Additional criteria were later introduced that would permit the enrolment of such subjects on the condition that appropriate protection measures be enacted.

The exclusion of other categories of "vulnerable" subjects (*e.g.* children, the elderly and – for different reasons – women of child-bearing age) from clinical trial participation certainly affords them protection from the associated risks, but at the same time it precludes these subjects from potential benefits. Their exclusion means that the data gathered concerning the tested drugs and devices refer only to other populations. The case of paediatric treatment information makes this clear: all data derived from trials (efficacy, metabolism, safety, etc.) referred only to adult populations until recently. Thanks to significant efforts on multiple levels (*e.g.* EU Regulation 1901/2006), there are now policies allowing clinical trials – with the necessary safeguards – on children [43].

The Belmont Report was a major step in addressing the participation of incapacitated and other vulnerable subjects in clinical trials. It states that "an injustice occurs when some benefit to which a person is entitled is denied without good reason" [18]. Unfortunately, two problems have since arisen at the point of application. Article 28 of the updated Declaration of Helsinki, approved in Seoul in October 2008, alludes to both with this statement: "When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected" [15]. The two problems are (1) establishing the subject's ability to consent and (2) identifying valid yet effective forms of legal representation.

It is difficult but not impossible to identify operational means of handling these issues. For the first problem, neuropsychological tests based on sufficiently standardised behaviour patterns and involving qualitative parameters could be applied. The second problem is more complex. An attorney could be appointed by the competent authority with full legal power to act during a limited timeframe and only for clearly defined types of decisions. This would be much less invasive than the traditional measures of disqualification and interdiction, which effectively usurp the subject's management of his or her own rights unless they are of a "very personal" nature.

As already noted, the focus of this paper is less on the operational means and more on the underlying

principles and conditions that make trials involving subjects with dementia legitimate. Those looking to examine the operational means should consult other publications, including a paper published by the National Health Institute regarding the Italian situation in particular [44]. Suffice it to say that both problems are regrettably underestimated. Valid consent procedures for potential participants are often hastily followed or entirely omitted [45]. Consequently, relatives, caregivers, close friends, or others who are rightly involved but not legally qualified end up taking the responsibility for decisions [46].

The list of documents in the preceding section (“Reference documents”) is too lengthy to address each one, so we will look more closely only at two, which should be the most useful ones because of their broad scope: the Mental Capacity Act [37] passed in 2005 and in force since October 2007, and the UNESCO International Bioethics Committee’s report [31].

The Mental Capacity Act [37] of England and Wales provides a clear legal framework for the medical treatment of mentally incapacitated subjects over the age of 16. It replaces the earlier common law provisions and regulates the various decision-making options on their behalf, covering decisions as simple and frequent as eating and dressing and as important as health care and asset management. While it has been criticised on several topics, such as life-sustaining treatment for terminal patients [47, 48], none of them is relevant here. The Mental Capacity Act does provide a useful list of widely shared principles on the issue of clinical trials involving persons with mental incapacities. They are the following:

- a person is presumed to have capacity unless proved otherwise;
- a person is not to be treated as incapable unless all practicable steps to help have been taken to no avail;
- a person is not to be treated as incapable simply because he makes an unwise decision;
- any act done or decision made for or on behalf of a person who lacks capacity must be done or made in his best interests;
- before acting on a person’s behalf, it is necessary to consider whether the purpose can be as effectively achieved in a manner less restrictive of the person’s rights;
- anyone acting on behalf of an incapacitated person must ask what that person would wish if he had capacity;
- the opinions of relatives and other persons who know the subject well should be sought;
- the least intrusive alternative must be chosen.

The default assumption that a person has capacity unless proved otherwise is clearly emphasised. It is unacceptable to assume incapacity and require proof of capacity. Furthermore, decisions that appear unwise from the subjective onlooker’s perspective are not a sufficient reason to consider a person’s decisional capacity impaired; in other words, subjective criteria alone are inadequate.

The Report of the International Bioethics Committee on Consent published by UNESCO [31] takes a similar position. It more closely examines the principles expounded in articles 6 and 7 of the UNESCO Universal Declaration on Bioethics and Human Rights (19 October 2005) [30], looking at a broad range of situations and conditions from infancy to old age. Some of the proposals were highly disputed here as well, particularly those regarding end-of-life questions. The majority of its recommendations were widely accepted, however, and reflect the ideas in the Mental Capacity Act. The following two points are especially important:

- “The general safeguard of the freedom of patients in these situations is that no judgment of capacity to consent should be called for unless there is evidence to undermine the normal assumption that people are able to decide for themselves. In other words, proof of incapacity is required not proof of capacity. Foolish decisions can be voluntarily made by the most autonomous people and the freedom to do so should not be restricted by imposing over-stringent standards of capacity” (par. 80).
- “It would be unethical to take these patients any less seriously than fully competent patients. In approaching decisions concerning them we have much more to go on than we do in the case of neonates. These are people who have lived a full life, whose preferences, values and wishes are probably remembered by some, if not many, who knew them when well. Their offices should be sought when reflecting on what to do for the patient. They should not be asked to provide proxy consents but rather to help build a picture of the life of the patient in which to find the decision to be made. Insofar as it is possible to do this, then it might be said that a substituted judgment about what the patient would consent to is being built” (par. 91).

A SUMMARY OF THE CRITERIA

Emmanuel *et al.* summarized the main requirements for ethical conduct in clinical research with seven criteria [49]:

- value: health or knowledge advancement must derive from the research;
- scientific validity: the research must be methodologically rigorous;
- fair subject selection: scientific objectives and the potential for and distribution of risks and benefits, rather than vulnerability or privilege, should determine the communities selected as study sites and the inclusion criteria for individual subjects;
- favourable risk-benefit ratio: risks must be minimised and potential benefits enhanced in the context of standard clinical practice and research protocol, and the potential benefits to individuals and knowledge gained for society must outweigh the risks;
- independent review: unaffiliated individuals must

review the research and approve, amend, or terminate it;

- informed consent: individuals should be informed about the research and provide their voluntary consent;
- respect for enrolled subjects: subjects should have their privacy protected, their well-being monitored and the opportunity to withdraw guaranteed.

In addition to these, some other criteria are fundamental [15, 19]:

- respect for regulations;
- direct benefit for the subject (except in specific circumstances);
- direct association between the trial and the pathology affecting the subject (except in specific circumstances).

One of the more controversial issues in medical research is the contribute to the wellbeing of society in general. The need of direct benefit for research participants is a fundamental criterion unanimously recognised. The Declaration of Helsinki states: "In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests" (art. 6) [15]. In spite of this principle, the possibility of performing research without the prospect of a direct benefit is not refused a priori: it is admissible under well-defined conditions and circumstances. In particular, the importance of the project's objective, understood as both scientific and social importance, should outweigh the risks and burdens to research subjects. Furthermore, the population in which the research is carried out should benefit from the results of the research.

Additional criteria are necessary for the protection of incapacitated adults. Legislative Decree no. 211 of 24 June 2003 [25] incorporates into Italian law the already mentioned regulations contained in EU Directive 2001/20/EC relating to the implementation of good clinical practice in conducting clinical trials on medicinal products for clinical use [16]. Under the heading "Clinical trials on incapacitated adults not able to give informed legal consent", article 5 summarizes criteria with broad acceptance:

1. "In addition to the requirements specified in section 3 (*Protection of clinical trial subjects*), inclusion in clinical trials of incapacitated adults who have not given or not refused informed consent before the onset of their incapacity shall be allowed only if:
 - 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;
 - b) the person has received information according to his/her capacity of understanding regarding the trial, the risks and the benefits;
 - c) the explicit wish of a subject who is capable of forming an opinion and assessing this in-

formation 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;

- d) no incentives or financial inducements are given except compensation that, if the trial sponsor is a public body, may only be granted within the limits of the budget allocated to it;
 - 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;
 - f) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress shall be specially defined and constantly monitored;
 - 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;
 - h) the interests of the patient always prevail over those of science and society;
 - 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.
2. In cases of temporary incapacity, informed consent to continue the trial must be sought when the patient recovers his/her decision-making capacity."

THE ISSUE OF LEGAL REPRESENTATION

Normative context

According to Directive 2001/20/EC, "persons who are incapable of giving legal consent to clinical trials should be given special protection. It is incumbent on the Member States to lay down rules to this effect" ("whereas n. 3"). Moreover, "the notion of legal representative refers back to existing national law and consequently may include a natural or legal person, and/or a body provided for by national law" [16]. As mentioned earlier, the Directive was incorporated into Italian law with Legislative Decree n. 211/2003 [25].

The question of legal representation is therefore essential to clinical trials involving persons who are incapable of expressing consent. In Italy, Title XII in Book I of the Civil Code constitutes an important reference point. It discusses protective measures such as interdiction and disqualification in the case of persons with a total or partial lack of autonomy [50].

Article 414 of the Civil Code states that legal adults and emancipated minors in a condition of habitual mental infirmity, sufficient to render them incapable

of pursuing their own best interests, are to be interdicted; in other words, a guardian *ad litem* must be appointed. Following the interdiction procedure, the guardian is to take the place of the interdicted person in fulfilling all routine and non-routine acts of administration. The interdicted person is thereby completely deprived of the possibility to act.

Disqualification can instead be applied in the following situations: a condition of incapacity insufficiently severe for interdiction, the exposure of oneself or one's family members to a severe economic burden due to extravagant wastefulness or the habitual use of alcoholic drinks or drugs, and blindness or deaf-muteness from birth in subjects lacking an adequate education (that do not fall under the necessity for interdiction in more serious situations). The primary consequence of disqualification is that the disqualified subject must be assisted by a guardian in non-routine acts of administration.

Interdiction and disqualification are nonetheless often excessive and disproportionate measures. For this reason, Law n. 6 on 9 January 2004 established the possibility of administration support [51]. It is a new protective measure that can be modelled on the basis of specific and contingent situations and needs. Administration support has been adopted by many European nations. In some countries, such as Austria, it has become the only protective measure in the wake of the elimination of interdiction and disqualification. Other countries, such as France, Luxembourg and Holland, mirror the Italian situation: administration support accompanies the traditional judicial measures of interdiction and disqualification [52, 53]. In Italy, Title XII in Book I of the Civil Code was modified by article 3 of the 9 January 2004 law [51]. In fact, the section title "On infirmity, interdiction and disqualification" was replaced by the title "On protective measures for persons partially or fully lacking autonomy" [50].

Article 1 of Law n. 6/2004 clearly defines the purpose of a supporting administrator: "to protect persons who are fully or partially lacking autonomy, with the least possible infringement on their capacity to act, in the execution of daily functions through temporary or permanent supportive intervention". Administration support therefore differs from interdiction and disqualification in that the judge's pronouncement requiring the protective measure must explicitly and precisely state the types of actions with which the beneficiary is to be aided by the supporting administrator. Hence the subject's capacity to act remains intact for all actions not explicitly indicated for support. Law n. 6/2004 emphasizes care for the beneficiary not only in terms of his estate but particularly in terms of *cura personae*, or care of the person, in clear reference to the person's health. The supporting administrator is also granted the power to express informed consent for diagnostic or therapeutic procedures [51]. In fact, paragraph 4 of article 405 in the Civil Code names care of the person as one of the urgent measures to be taken in the best

interest of the infirm person and article 408 states that the choice of the administrator should be made "with exclusive regard to the care and best interests of the person who is the beneficiary" [50].

In the current normative context, the supporting administrator appears to be the most suitable individual to carry out the function of a legal guardian *ad litem* for incapacitated persons participating in clinical trials. This is in conformity with Directive 2001/20/EC [16] and Legislative Decree n. 211/2003 [25], which enacts the Directive in Italy, requiring the legal guardian's informed consent as a necessary condition for the participation of incapacitated subjects in an experiment.

In this regard, it is also important to recall that according to paragraph 3 of article 408 of the Civil Code, "public or private service workers with the beneficiary in their charge or under their care cannot carry out the function of supporting administrator". Nevertheless, according to article 406, "those who are responsible for health care and social services and are directly involved in providing care and assisting the person are required to petition the judge [for the nomination of a supporting administrator] when aware of reasons that would make it appropriate to initiate the administration support procedure" [50].

Though administration support therefore seems to be the most suitable means of legal representation for incapacitated persons participating in experimentation procedures in theoretical terms, the situation is unfortunately less favourable in practice. In reality, despite the fact that Law n. 6/2004 requires the nomination of a supporting administrator within sixty days, various difficulties arise in practice that drastically extend this timeframe [54]. This situation makes it very difficult to conduct clinical trials in Italy that involve subjects incapable of expressing consent.

Emergency situations

It is a well-known fact that emergency situations exist in which it is legitimate to intervene even without valid consent. Italian law recognises five such reasons: (1) a public health emergency, (2) a clinical emergency, (3) patient incapacity, (4) patient relinquishment or waiver, or (5) the "therapeutic privilege" (*i.e.* a situation in which the physician, either at his own discretion or at the patient's request, withholds information that could compromise acceptance of the proposed treatment, in virtue of his primary duty as a physician to care for each patient as best he can and to safeguard the patient's interests).

The legality of actions performed under emergency conditions is addressed by article 54 of the Italian Criminal Code. Regarding the "state of necessity", it says that "if a person committed a deed because he was obliged to by the need to save himself or another person from an imminent danger of serious harm that was neither voluntarily caused by him nor otherwise avoidable, he is not punishable, provided

that the deed is proportionate to the danger” [55]. The United States Code of Federal Regulations contains similar provisions in which the waiver of consent during an emergency is acceptable [56]. It should be apparent, however, that emergency conditions are quite rare in clinical research trials: emergency is, by its very nature, episodic [57].

Proposals for the obtainment of informed consent from incapacitated subjects in research trials

It is important to keep in mind several considerations from the previous sections in order to develop proposals for facilitating the obtainment of valid informed consent from incapacitated subjects participating in clinical trials. They can be summarized as follows:

- a physician has the duty to perform interventions necessary for meeting the primary needs of persons in his or her care;
- medical actions require valid informed consent that, in the case of incapacitated subjects, must be provided by a legal representative;
- only a small number of incapacitated patients in Italy actually has a legal representative, and the waiting periods for naming a representative when there is a need for urgent intervention are longer than the urgency allows.

Based on paragraph 4 in article 405 of the Italian Civil Code, once a petition has been submitted, the tutelary judge can adopt *ex officio* “urgent provisions for the care of the concerned person and for the preservation and administration of his assets” [50]. Furthermore, as already mentioned, Law n. 6/2004 [51] requires physicians to petition the tutelary judge for the nomination of a supporting administrator. The law does not explicitly allow a health-care worker to go directly to the tutelary judge seeking direct authorisation to carry out medically necessary treatments on an incompetent patient lacking legal representation. Nevertheless, some authors think that “this is legally possible in light of spirit and purpose of Law n. 6/2004 and particularly in virtue of the core principles of our Constitutional Charter and the entire legal system currently in force” [58, 59]. From a legal point of view, this process is an important resource for physicians faced with a need to act not only in urgent situations but also in the routine care of persons lacking a legal representative. In the case of clinical experimentation, however, leaving the decision to participate in clinical research trials up to a tutelary judge’s pronouncement alone casts serious doubt on the some of the basic and unanimously recognized demands of clinical research ethics [60]. Other solutions are therefore necessary.

In Italy, the issue of informed consent from persons affected by dementia was also addressed by the National Health Council (Consiglio Superiore di Sanità) at the request of the Italian Medicine Agency (Agenzia Italiana del Farmaco). On 10 July 2007, the Italian Medicine Agency turned to the National Health Council in order to address an issue that

had arisen in the wake of regulations that the same Agency established regarding the pharmacological treatment of mental illness in patients with dementia [61]. A requirement for valid informed consent was established together with the allowance of off-label drug prescriptions. The resulting problem is clear: since the patients are affected with dementia, most of them are not able to provide valid consent [62, 63]. In this case, the issue is not clinical experimentation *per se* but routine pharmacological treatment; however, there is a fine line between treatment and experimentation in the use of off-label drugs. On 23 October 2007, the National Health Council responded with an opinion reemphasising the need to obtain valid informed consent as required by regulation [64].

On 13 December 2007, the Italian Drug Agency sent a new request to the National Health Council on the same topic, this time explicitly focusing on clinical trials. The National Health Council responded on 10 July 2008 with an opinion titled “Requests for informed consent from patients with dementia needing pharmacological treatment in clinical experimentation” [65]. In its opinion, the National Health Council reaffirmed the need to respect the regulations currently in force that require informed consent from a legal representative or supporting administrator in order to conduct trials involving mentally incapacitated patients. At the same time, the National Health Council recognized that such conditions often constitute an insurmountable obstacle to clinical trials given the extensive time it takes to name a legal representative or supporting administrator. This difficulty has negative consequences for the patients themselves, who could benefit from such trials. In this light, the National Health Council encouraged revising the regulations and following the example set by other countries.

Modifications to article 5 of Legislative Decree n. 211/2003 have been proposed on various occasions in the interest to allowing certain other individuals – in the absence of a legal representative – to express informed consent on behalf of incapacitated subjects for participation in clinical trials [25]. Specifically, some suggest that the individuals listed in article 408 of the Civil Code as preferable candidates for supporting administrator should be allowed to express consent without explicit appointment by a tutelary judge: spouse (not legally divorced), stable cohabitating partner, father, mother, child, brother, sister, or any relative not more distant than fourth degree [50, 51]. This approach has already been adopted in other situations in Italy.

For example, article 23 of Law n. 91/1999 [66] states that the following individuals can present legitimate written opposition to organ removal: spouse (not divorced) or cohabitating partner more uxorio, or, where not applicable, children of legal age, or, if there are none, parents. The list of individuals in article 408 of the Civil Code [51] and those in Law n. 91/1999 [61] are clearly quite similar. The list of preferred in-

dividuals to take on the role of supporting administrator in the Civil Code was also included in the law proposal regarding advance directives for medical treatment in the version approved by the Social Affairs Committee in the House of Representatives on 12 May 2010 [67]. This document addressing medical treatment will become an important reference point in addressing the issue and it would be surprising if the individuals who are allowed to consent to the enactment and interruption of medical treatment were not allowing to make decisions regarding participation in clinical trials. Certain clarifications will clearly be necessary to avoid contradictions between Legislative Decree n. 211/2003 [25] and the new document regarding advance directives for treatment [67]. The "Outline for a law proposal containing regulations for clinical trials and other health-care matters" presented by the Minister of Health, Ferruccio Fazio, to the Council of Ministers on 16 July 2010 does not directly address the issue of clinical trial participation for subjects incapable of providing informed consent.

The document does stipulate, however, that decrees for its application on specific questions be adopted within nine months of its enactment in order to simplify the authorisation procedure for clinical trials. It is therefore probable that this ministerial initiative will also lead to legislative action on the matter.

Acknowledgements

This article has been written as a part of the project "Nosographic revision of vegetative states: application of behavioural analysis methods in the study of subjects in coma and vegetative state".

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of his study.

Received on 12 August 2010.

Accepted on 4 October 2010.

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