

Informed consent from cognitively impaired persons participating in research trials: comparative law observations

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Summary. This article addresses the ethical requirements to be considered when conducting clinical trials involving human subjects whose mental condition limits their ability to understand the information and to express fully autonomous and informed consent. It does not address other categories of vulnerable persons, such as children, or advanced directives concerning end-of-life care. There are many ethical issues entailed in clinical trials involving subjects with mental disabilities: how to obtain informed consent, balancing risks and benefits, balancing individual benefits with collective scientific and social interests, legal representation and many more. This article focuses on the issues surrounding the concept of minimal risk and the relationship between informed consent and risk. These issues are addressed with particular emphasis on the regulations adopted by the European Union and the federal government of the United States of America. The conclusion proposes a list of working criteria.

Key words: bioethics, informed consent, human research, legislation, mental disability.

Riassunto (*Il consenso informato nel caso di soggetti con disabilità mentale che partecipano alla sperimentazione clinica: osservazioni di diritto comparato*). L'articolo riguarda i requisiti di etica da considerare quando si intendano effettuare sperimentazioni cliniche con soggetti in condizioni mentali tali da non poter né comprendere pienamente le informazioni relative al trattamento proposto, né esprimere un consenso sufficientemente consapevole, autonomo ed informato. Non viene invece fatto riferimento ad altre categorie cosiddette "vulnerabili" (come, ad esempio, i bambini), né alle disposizioni anticipate, date in condizioni di consapevolezza, per il rifiuto di trattamenti negli stati terminali di malattia. I problemi di etica da affrontare per l'esecuzione di sperimentazioni cliniche con soggetti affetti da disabilità mentali sono molteplici: modalità del consenso informato, bilanciamento tra rischi e benefici, bilanciamento tra benefici individuali e interessi scientifici e sociali collettivi, rappresentanza legale e molti altri. Nell'articolo sono discussi in particolare i problemi relativi al cosiddetto "rischio minimo", ai livelli di accettabilità del rischio, nonché al consenso informato in relazione al rischio. Tali problemi sono discussi con riferimento specialmente alle normative comunitarie nell'Unione Europea e alle normative federali negli Stati Uniti d'America. Nelle conclusioni è proposto un elenco di criteri operativi.

Parole chiave: bioetica, consenso informato, ricerca sull'uomo, legislazione, disabilità mentale.

INTRODUCTION

In this article, expressions such as "cognitively impaired persons" and "decisionally impaired persons", rather than "demented persons", are preferred for two main reasons. First, "dementia" and similar terms often have a negative or derogatory connotation [1]. Second, "dementia" in a medical sense is too restrictive: it leaves out other cognitive alterations, from mild impairment to complete unconsciousness, which are included in the more general category of "cognitive impairment".

Research with decisionally impaired subjects raises many ethical and procedural concerns. Some of

them are common to all types of research, regardless of the question of competence, yet they differ here in terms of their extent and characteristics. In particular, subjects with cognitive impairment are more vulnerable to coercion [2] and may lack capacity to provide informed consent [3], which is a multifaceted issue [4, 5]. In a previous article [6] we briefly discussed the historical development of the debate and certain aspects of legal representation and proxy consent. This article discusses several aspects of informed consent in relation to risk-benefit assessments and offers a concise comparison of European and American regulations.

HISTORICAL DEVELOPMENT

Concerns about clinical research involving persons with cognitive impairment have received significant attention in the second half of the twentieth century [7]. Several cases of research abuse were revealed after World War II [8], many of which involved decisionally impaired subjects [9]. These cases became the stimulus for several codes, declarations and reports on the ethics of research on human subjects [10]. The Nuremberg Code [11] is considered the first of many [12], most of which also deal with questions affecting vulnerable persons in general: the physically disabled, the mentally disabled and persons otherwise unable to provide consent.

A literal interpretation of the Nuremberg Code would preclude all research involving persons unable to consent; however, several later codes and declarations, such as the Ethical Principles and Guidelines for the Protection of Human Subjects of Research [13] by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, the International Ethical Guidelines for Biomedical Research Involving Human Subjects [14] by the Council for International Organizations of Medical Sciences (CIOMS), and the more recent versions of the Declaration of Helsinki [15] by the World Medical Association, allow such research under certain conditions [16]. In accordance with widely accepted professional and ethical principles, examples of these conditions include the following: persons lacking sufficient capacity to consent must not be involved in research that could be conducted with competent subjects; authorisation by a legal representative must be obtained; research can be permitted only when it provides meaningful benefits, particularly if benefits are not otherwise available to the subjects; and so forth [17].

The question of participation in research lacking the prospect of direct benefit is one of the most controversial [18]. There is general agreement that in the absence of a specific advance directive authorising participation and surrogate consent, no incapable person should be involved in research with moderate or high risks if the research is not expected to benefit the person directly [19]. Similarly, there is a general consensus on the authority of surrogates to consent to research only when it involves no more than minimal risk [20]. Advance directives are usually accepted on these conditions [21], but there is debate regarding research with a "minor increase over minimal risk" [22]. According to the National Bioethics Advisory Commission's report on adults with decisional impairment, research involving more than minimal risk and no expected benefit is prohibited unless the subject has previously created a specific advance directive or unless the research has been approved by a special panel [23].

One straightforward approach to protecting vulnerable research subjects is to require that incapacitated adults be enrolled in research only when their participation is necessary to answer the scientific

question posed. This requirement has been defined as the "necessity clause" [24], but evaluating such necessity is not easy. In every research trial with cognitively impaired subjects, investigators would have to explicitly justify the need to enrol subjects who are unable to provide informed consent. Acceptability must therefore be assessed on a case-by-case basis.

ASSESSMENT OF CAPACITY: AN OVERVIEW

Before addressing the problem of informed consent and risk-benefit assessments, a brief discussion on assessing capacity will be useful. In British English the term "competence" is used primarily in the clinical context to indicate the person's mental capacity and the term "capacity" can be used to indicate both clinical and legal capacity. In American English, on the other hand, "competence" generally indicates both clinical and legal capacity whereas "capacity" refers only to clinical capacity [25]. Despite these subtle differences, "capacity" and "competence" are typically considered synonymous and interchangeable and their usage in this article follows suit.

Adults are presumed competent to make autonomous decisions [26]. According to the Report of the International Bioethics Committee (IBC) on Consent by the United Nations Educational, Scientific and Cultural Organization (UNESCO), "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" [27].

In the legal context, a judgment of incapacity is made by formal judicial ruling and rendered in the context of the person's ability to make specific decisions (*e.g.*, medical decisions or management of finances) [28]. In the clinical context, a diagnosis of illness causing dementia is not sufficient to assess decisional capacity: diagnosis alone is inadequate to distinguish individuals who are able to provide valid informed consent from individuals who are unable to do so [29]. Therefore, a diagnosis is neither necessary nor sufficient to determine whether an individual needs greater safeguards than those already in place for research subjects in general. As a result, the person obtaining the subject's consent for a medical intervention or research trial must determine that the person has sufficient capacity to give it. Moreover, researchers and ethics committees should consider the need for an independent assessment of capacity, which should be documented.

Actual decision making capacity varies continuously. It may change from incapacity to full capacity depending on many circumstances. It may vary not only between diagnoses but also within a diagnosis, depending on the type and severity of the illness. It often fluctuates over time as well. Conversely, the determination of capacity is discontinuous: health pro-

professionals usually make “yes” or “no” determinations about the subject’s capacity to consent. Similarly, ethics committees often make categorical determinations about both capacity and risks (*e.g.*, “minimal risk” or “greater than minimal risk”). Though an individual’s actual decision making capacity may vary, he or she must be judged capable or incapable of consenting. This decision is a clinical judgment.

The level of capacity required to consent varies according to the type and complexity of the decision: as complexity increases, required capacity increases; however, people lacking the capacity to make complex decisions may be able to make simpler choices. In the medical setting, patients commonly manifest reduced decision making capacity in some areas but retain full capacity in others. In other words, the threshold for incapacity varies depending on what task an individual is asked to perform. For example, persons in the early stages of cognitive impairment may be unable to provide consent for a complex clinical trial, yet retain the ability to appoint a trusted family member or friend as a representative. Furthermore, individuals lacking the capacity to give informed consent may be capable of assent, which is a less demanding standard of authorization [30].

Appropriate thresholds are difficult to determine. Consequently, capacity assessments are made on a case-by-case basis. There are four commonly used standards of capacity, which have been proposed in various contexts and adopted by the American Psychiatric Association [31] and other scientific societies and institutions: 1) the ability to make a clear choice, communicated by a “yes” or “no” decision; 2) the ability to understand key information, meaning that the person can state what the research procedures involve and any other information required for proper consent; 3) the ability to comprehend the situation and its probable consequences; and 4) the ability to rationally handle information.

In the case of research on human subjects, these four standards mean 1) the ability to communicate a “yes” or “no” decision, 2) the ability state what the research procedure involves and any other information required for proper consent, 3) the ability to comprehend what research participation entails and its probable outcomes, and 4) harmony between the decision and any moral, religious or other beliefs. The first three standards focus on the outcome, while the fourth focuses on the process. The first and the second are applicable to all research, the third generally applies to any research involving greater than minimal risk, and the fourth becomes more critical at less favourable risk-benefit levels.

The manner in which these standards are assessed is an important matter for which several tools are available, but it is not the subject of this article. By way of example, readers are encouraged to investigate the writings of Thomas Grisso and Paul S. Appelbaum, who have expounded their views and proposed practical criteria for capacity assessment both in guides [32] and scientific articles [33].

MINIMAL RISK

The notion of “minimal risk” is controversial [34]. According to the Additional Protocol [35] to the Convention on Human Rights and Biomedicine [36], risk is said to be minimal if it is expected “to result, at the most, in a very slight and temporary negative impact on the health of the person concerned”, and the burden is said to be minimal if it is expected that “the discomfort will be, at the most, temporary and very slight for the person concerned” (article 17).

The Code of Federal Regulations states that in a situation of “minimal risk”, “the probability and magnitude of harm or discomfort anticipated in research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests” [37]. According to the Code of Federal Regulations, research involving a minor increase over “minimal risk” that does not offer a prospect of benefit for the child-subject may still be justifiable under the following conditions: a) “the intervention or procedure presents experiences to subjects that are commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations”; b) “the intervention or procedure is likely to yield generalizable knowledge about the subjects’ disorder or condition”; and c) “adequate provisions are made for soliciting assent of the children and permission of their parents or guardians” [37]. According to numerous authors, these same conditions can be reasonably applied to adult subjects incapable of providing valid informed consent despite the ongoing debate about interpreting the risk level [38, 39].

The interpretation of “minimal risk” is also important to the distinction between standard medical care and clinical research participation [40], which has major implications for decisionally impaired subjects. The “therapeutic misconception”, which was defined in 1982 by Appelbaum and co-authors as the situation in which persons participating in clinical research mistakenly believe that its primary purpose is therapeutic [41], is already a danger for persons with full capacity, so extra caution must be taken to protect the decisionally impaired.

EUROPEAN POLICIES AND REGULATIONS: KEY POINTS ABOUT CLINICAL TRIAL RISKS

The Council of Europe has adopted several documents addressing the treatment of persons with cognitive impairment. Recommendation R(99)4 of the Committee of Ministers to Member States on Principles Concerning the Legal Protection of Incapable Adults emphasizes that competence should be held as the central concern when dealing with mentally impaired individuals [42]. According to principle 3 of the Recommendation, “1. The legislative framework should, so far as possible, recognize that different degrees of capacity may exist

and that incapacity may vary from time to time. Accordingly, a measure of protection should not result automatically in a complete removal of legal capacity. However, a restriction of legal capacity should be possible where it is shown to be necessary for the protection of the person concerned. 2. In particular, a measure of protection should not automatically deprive the person concerned of the right to (...) consent or refuse consent to any intervention in the health field, or to make other decisions of a personal character at a time where his or her capacity permits him or her to do so". Principle 12 stipulates that "there should be adequate procedures for the investigation and assessment of the adult's personal faculties", though no reference is made to what these should be or the standards that should govern them. Principle 22 states that whenever an adult is capable of giving informed consent, even if he or she is guarded by protective measures, the intervention may only be carried out with his or her consent.

Other key documents from the Council of Europe include Recommendation no. R(90) 3 of the Committee of Ministers to Member States Concerning Medical Research on Human Beings [43], the White Paper on the Protection of Human Rights and the Dignity of People Suffering from Mental Disorder, Especially Those Placed as Involuntary Patients in a Psychiatric Establishment [44], Recommendation Rec (2004) 10 of the Committee of Ministers to Member States Concerning the Protection of Human Rights and the Dignity of Persons with Mental Disorder and its Explanatory Memorandum [45]. Particularly important are the 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 [36] and the Additional Protocol on the Convention of Human Rights and Biomedicine Concerning Biomedical Research [35]. The main point of reference within the European Union is 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 [46].

All of these documents emphasize the unique protection owed to adults with mental disorders; however, the problem of assessing and preserving decisional competence seems to have been avoided. In fact, the Convention on Human Rights and Biomedicine [36], the Additional Protocol [35] and the European Directive [46] do not approach the matter of participation from a standpoint that requires an assessment of decisional competence prior to surrogate decision making; rather, they assume surrogate decision making as the starting point. A minor reference to the issue is made in Article 14(3) of the Additional Protocol [35], where it simply

states that "arrangements shall be in place to verify whether or not the person has such capacity", yet it does not elaborate on what form the arrangements might take or what criteria they must abide by.

Furthermore, there appears to be some incoherence within the European guidelines on capacity. In 2000, the Council of Europe's White Paper [44] suggested that the concept of mental capacity was inadequately articulated in Europe and in need of development. The Council of Europe suggested that persons with cognitive impairment should be protected from involvement in non-therapeutic clinical trials even when they do consent. In the absence of a formal assessment of capacity, however, this vaguely paternalistic [47] approach seems to presume incompetence, which would not be coherent with the widely accepted "presumption of competence" principle [27], with its "view to the preservation of the autonomy" of minors and adults who are incapable of consenting "with regard to interventions affecting their health", which was actually recognized by the same Council of Europe [36, 48].

Directive 2001/20/EC [46] is based primarily on the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) [49]. It went into effect on May 1, 2004. It was intended to harmonise the different laws, regulations and administrative rules concerning clinical trials in member states. It does not address all kinds of human research, but rather a limited subset of clinical trials, and specifically trials that study the safety and/or efficacy of pharmaceuticals. It does not cover studies involving biological pharmaceuticals or medical devices. Article 3 of the Directive contains a list of general protections for individuals involved in such clinical trials.

Article 5 of the Directive deals with "clinical trials on incapacitated adults not able to give informed legal consent" and proposes some solutions to the problems raised by this kind of research (see Appendix 1). It provides a list of further conditions (in addition to general principles) required for research involving incapacitated persons. The aim is to reconcile two needs: protecting persons who are incapable of giving consent from risks, distress and exploitation on the one hand, and finding new therapies for many diseases that affect such persons on the other.

A few problematic aspects arise here. Article 5 posits a criterion based on a risk-benefit threshold: patients must benefit from the test drug enough to outweigh the risks of not receiving the test drug. Alternatively, there must be evidence that the drug test entails no risk (which is very unlikely). In other words, the researcher must expect the test drug to be better than the standard treatment available. If this is so, then the criterion of clinical equipoise is not satisfied [50]. A violation of the criterion of equipoise constitutes a violation also of the Declaration of Helsinki [15], the Additional Protocol [35] to the Convention on Human Rights and Biomedicine [36] and many other documents.

Therefore, the words “no risk” in article 5 can probably be interpreted in a practical rather than literal sense to mean “no serious risk”. Otherwise any treatment would be precluded. This interpretation is consistent with the Convention on Human Rights and Biomedicine [36] and its Additional Protocol [35] (which recommend “minimal risk and minimal burden” as a limit) and with Good Clinical Practice [49] (which affirms that the risks and impact should be low and minimized). This “minimal risk” position has also been adopted by the US Common Rule, which allows for a “minor increase over minimal risk” [37].

AMERICAN POLICIES AND REGULATIONS: KEY POINTS ABOUT CLINICAL TRIAL RISKS

There are no comprehensive federal standards on decisional competence as of yet. While health care professionals are usually better equipped to measure competence than judges, assessments made by psychiatrists or other health care professionals are not legally binding: in most jurisdictions, only a court can decide whether a person is incompetent. Criteria for the definition and assessment of competence vary across jurisdictions.

In 1981, federal regulations established a national legal framework regarding research on adult human subjects. These regulations comprise the Federal Policy for the Protection of Human Subjects (FPPHS) and were adopted by sixteen US federal agencies in 1991. They have come to be defined as the “Common Rule” [37].

Subpart A of the Common Rule is the primary source of regulations for research on human subjects, clarifying the requirements for informed consent. There are probably at least two shortcomings with regard to its treatment of the participation of mentally impaired persons in clinical trials. The first is the presumption that any potential research participant is decisionally competent unless proven otherwise without providing the means to prove otherwise: competence requirements and assessment criteria are not specified. The second is that in paragraph 46.116, parts (a) 1-8 and (b) 1-6 (see Appendix 2), the discussion is framed in terms of how the researcher is to satisfy his legal “duties” to the potential participant, with little concern for the participant’s lack of medical training and understanding of the research process. In other words, some points seem designed to offer legal protection to the clinician and/or researcher rather than to the mentally impaired subjects recruited for their studies.

Although these two shortcomings may accentuate the relationship inequalities between researcher and participant, it should also be recognised that paragraph 46.116 does reaffirm numerous legal protections for the research participant, such as the prohibition on terms of consent that would waive the participant’s legal rights.

CONCLUSIONS

Research with cognitively impaired persons: a need and a challenge

In the *Neurological disorder public health challenges* Report, WHO describes dementia as a top-level health care challenge in modern societies [51]. Aging certainly has an impact on the prevalence of dementia, and at present there are 650 million people in the world over the age of 65, 400 million of whom live in the poorest countries. The number has been estimated to increase to 1.2 billion by 2025 [52]. Worldwide, 25% of individuals display one or more mental or behavioural disorders during the course of their lifetime [53]. In response, many countries have implemented noteworthy national policies with regard to mental illness. In France, a national policy was adopted on February 1, 2008 [54] after careful consultation [55]. On February 2, 2011, the United Kingdom published a new long-term mental health strategy for England based on six main “shared objectives” [56].

The data attest to the need for therapies, and therefore research [57], directed toward persons with mental illnesses, intellectual disabilities and age-related illnesses. Nevertheless, the inclusion of cognitively impaired persons in clinical trials continues to raise many ethical and legal issues [58]. It is therefore not surprising that complete and definitive policies and legal frameworks are rarely successful. Regulations seldom provide a univocal definition of mental disability or precise criteria for adequate informed consent, especially when the research involves vulnerable subjects [59].

Since studies involving impaired subjects are highly complex, it is unlikely that a single policy or law will adequately address every type of research. In fact, a single approach to so many different kinds of research would be inappropriate. Though regulations will probably remain insufficient in many respects, particularly with regard to risk-benefit assessment, more specific regulations would do much to strengthen the existing protections for decisionally impaired subjects.

General criteria regarding capacity, informed consent and risks

The main ethical concerns raised by research involving subjects with cognitive impairments are the potential exploitation of such individuals and, except in situations of mild impairment, the difficulty of obtaining valid consent [60]. Guidelines and checklists are available from several institutions to help navigate this process – Appendix 3 provides a checklist by the Alzheimer’s Society [61] – but there are still no complete or definitive criteria.

By way of conclusion, then, taking into account the various institutional documents discussed here, the following is an unpretentious attempt to devise a list of criteria for including cognitively impaired persons in clinical trials. This tentative and incomplete list deals only with capacity, informed consent and risk. Its purpose is practical; hence, general eth-

ical requirements (*e.g.*, respect for dignity, etc.) are not mentioned. Many of the criteria listed apply to all types of research, but are particularly important for studies involving subjects with cognitive impairments.

I) Capacity assessment and informed consent

- obtaining informed consent from a research participant is an early, ongoing and integral component of what should be trusting relationship between investigator and subjects;
- protocols should include a description of how informed consent will be obtained;
- researchers should assume a person has capacity unless proved otherwise;
- a formal plan for capacity assessment is necessary in protocols involving mentally impaired subjects;
- a person who lacks capacity is not necessarily incapable of making all decisions;
- capacity assessment should occur after the initiation of dialogue but prior to signing the informed consent document;
- competence is relative to the type and complexity of the treatment decision at hand. Some impaired patients are competent to make simple treatment decisions but incompetent to make complex ones, which may require balancing risks and benefits and alternative treatments;
- individuals who lack capacity to give informed consent might be capable of assent (a less demanding standard of authorization);
- decision making capacity should include the ability to comprehend the difference between clinical care and clinical research in order to avoid the “therapeutic misconception”;
- just as individuals with cognitive impairments are often unable to provide valid consent for research, they are similarly unable to withdraw from research. However, dissent is widely accepted as a sufficient basis for withdrawing from research;
- additional independent assessments can provide further safeguards. Assessment of capacity to consent by independent, qualified professionals is often considered decisive when studies pose greater than minimal risk;
- an independent clinician to manage clinical care separately from research care is recommended for high-risk studies with vulnerable subjects;
- attention is often directed toward assessing decisional capacity prior to research participation. Attention should also be given to the protection of subjects who are able to provide informed consent at the beginning of a study but who then lose the capacity during the research;
- educational interventions frequently improve decision making capacity.

II) Risk assessment and informed consent

- the interests and welfare of the persons who participate in research shall prevail over the interest of society or science;

- the safeguards chosen should depend on the level of risk posed by the research and the nature and magnitude of the subject’s decisional impairment;
- levels of risk that are justified in medical care might not be justifiable in clinical research;
- thresholds for competence to make treatment decisions should be graduated. The threshold for competence should be more demanding as the risks of an intervention, the uncertainty of its benefits, the complexity of the research increase.

III) Role of proxies and informed consent

- surrogate consent is acceptable for some research;
- like patient-volunteers, surrogates may be subject to the therapeutic misconception. Careful consent forms help avoid the therapeutic misconception;
- individuals who are likely to lose capacity may prepare an advance directive at the time of enrollment, which includes assigning a surrogate decision maker who will take on an increasingly active role in decision making as the subject declines.

IV) Roles and duties of ethics committees

- when research institutions provide a bioethics consultation service, the review of research protocols before submission to the ethics committee can provide useful improvements to the research protocols;
- ethics committees shall pay attention to the scientific quality of the protocols and the processes are especially important;
- ethics committees that regularly review research protocols involving adults with decisional impairment should include multiple representatives: persons with scientific and clinical expertise, persons with patient expertise, family members and advocacy group members;
- evaluation by an ethics committee and analysis on a protocol-by-protocol basis is particularly important for studies involving cognitively impaired persons;
- conflict of interest statement;
- there are no potential conflicts of interest or any financial or personal;
- relationships with other people or organization that could;
- inappropriately bias conduct and findings of this study.

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 this study.

Submitted on invitation.

Accepted on 4 October 2011.

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Appendix 1.

From: European Parliament and Council of the European Union 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 [46]

Article 5.

Clinical trials on incapacitated adults not able to give informed legal consent.

In the case of other persons incapable of giving informed legal consent, all relevant requirements listed for persons capable of giving such consent shall apply. In addition to these requirements, inclusion in clinical trials of incapacitated adults who have not given or not refused informed consent before 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 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;
- (c) 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;
- (d) no incentives or financial inducements are given except compensation;
- (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; and
- (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.

Appendix 2

From: Department of Health and Human Services, National Institutes of Health, Office for Human Research Protections "The Common Rule. Title 45 (Code of Federal Regulations). Part 46 (Protection of Human Subjects)" [37]

46.116. General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

- (a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:
 - (1) a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
 - (2) a description of any reasonably foreseeable risks or discomforts to the subject;
 - (3) a description of any benefits to the subject or to others which may reasonably be expected from the research;
 - (4) a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
 - (5) a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
 - (6) for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
 - (7) an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
 - (8) a statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- (b) Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:
 - (1) a statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
 - (2) anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
 - (3) any additional costs to the subject that may result from participation in the research;
 - (4) the consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
 - (5) a statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and
 - (6) the approximate number of subjects involved in the study.
- (c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:
 - (1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
 - (2) The research could not practicably be carried out without the waiver or alteration.
- (d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:
 - (1) the research involves no more than minimal risk to the subjects;
 - (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;
 - (3) the research could not practicably be carried out without the waiver or alteration; and
 - (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.
- (e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.
- (f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

Appendix 3.

From: Alzheimer's Society, "Volunteering for Research into Dementia" [61]

Before taking part in any research, the person with dementia and their carer should consider the following points:

I) General

- What is the purpose of the research?
- What does the research involve for the person with dementia and will they benefit from participating?
- Will the carer be involved and if so how?
- Where will the research take place, with how many sessions and over what period of time?
- How will confidentiality be maintained?
- Who will have access to questionnaires and will this information be destroyed once the research is complete?
- Will any necessary transport be arranged and paid for?
- Are there plans to tell people about the results of the research and, if so, how and when?

II) Health-related research

- Has the research been approved by a research ethics committee?
- Is the research likely to cause any discomfort or distress?
- If the research involves treatment what are the risks and likely side-effects?
- If the research involves treatment that appears to benefit the person with dementia can they continue with the treatment once the research is completed?