Ethics of clinical research with mentally ill persons

Article *in* European Archives of Psychiatry and Clinical Neuroscience · January 2012

DOI: 10.1007/s00406-011-0287-2 · Source: PubMed

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ArticleTitle	Ethics of clinical research with mentally ill persons	
Article Sub-Title		
Article CopyRight	Springer-Verlag (This will be the copyright line in the final PDF)	
Journal Name	European Archives of Psychiatry and Clinical Neuroscience	
Corresponding Author	Family Name	**Helmchen**
	Particle	
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Schedule	Received	6 July 2011
	Revised	
	Accepted	20 December 2011

Abstract

This article describes *ethical, legal and professional* components of the two core requirements of clinical research: informed consent and risk–benefit relationships. It deals particularly with the ethically relevant reasons, criteria, procedures and validity of (1) the informed consent process, (2) the relationship between benefits and risks, and as a requirement of its assessment: (3) standards and (quasi quantitative) criteria of benefits and risks and/or burdens of a research intervention. These requirements will be discussed with specific reference to research interventions in mentally ill patients, and particularly in those who are incompetent to consent. (4) The analysis concludes by demanding a strong adherence to the ethical rules of clinical research in order to protect participants and preserve the trust of both the patients and the public and (5) yields in a set of recommendations.

Keywords (separated by '-')	Ethics of psychiatric research - Mentally ill subjects - Incapacity to consent - Standards of benefits and risks - Risk–benefit relationship
Footnote Information	The text is related to discussions in the Interdisciplinary Working Group “Clinical research in vulnerable populations” … conclusions is only with the author.

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Eur Arch Psychiatry Clin Neurosci
DOI 10.1007/s00406-011-0287-2

ORIGINAL PAPER

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Abstract This article describes *ethical, legal and professional* components of the two core requirements of clinical research: informed consent and risk–benefit relationships. It deals particularly with the ethically relevant reasons, criteria, procedures and validity of (1) the informed consent process, (2) the relationship between benefits and risks, and as a requirement of its assessment: (3) standards and (quasi quantitative) criteria of benefits and risks and/or burdens of a research intervention. These requirements will be discussed with specific reference to research interventions in mentally ill patients, and particularly in those who are incompetent to consent. (4) The analysis concludes by demanding a strong adherence to the ethical rules of clinical research in order to protect participants and preserve the trust of both the patients and the public and (5) yields in a set of recommendations.

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Clinical research

A broad view of clinical research comprises all (biological or physical, psychological and social) types of interventions in patients with the objective of gaining new knowledge about causes and conditioning or risk factors (of the development, manifestation, course and outcome) of diseases, their (primary, secondary and tertiary) prevention, treatment and care, including rehabilitation and palliation. Related topics are human genetics [1] epidemiological research on human diseases [2], public health research [3] as well as translational research [4, 5]. Clinical research is understood as the intervention in human beings, which aims by scientific methods systematically to supraindividual knowledge, and thereby goes beyond the individual benefit of the participating person. Such research intervention is ethically acceptable only

- if the informed consent is valid, and
- if its risk–benefit relationship is reasonable and justified.

The latter criterion includes the fact that the research must be scientifically correct because research is unethical per se that—due to methodological reasons—cannot yield a valid result and therefore burdens the research participants in vain.

Research with patients who are specifically vulnerable due to their incapacity to give consent is ethically acceptable only as a last resort if there are no other ways to resolve important clinical questions. This is clearly stated in the Declaration of Helsinki 2008 [6]:

> § 27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research

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Article No. : 287 | ☐ LE | ☐ TYPESET
MS Code : EAPC-D-11-00093 | ☑ CP | ☑ DISK

cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

§ 29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population…

Informed consent

All medical interventions in human beings must be authorised personally by the concerned individual. This is particularly important for a research intervention because it aims not only at the benefit of the individual but also or even only at the benefit of others.

Benefit for others in the context of medical research is improved medical knowledge for better diagnostics, treatment or care of all other human beings as potential patients, i.e. the social value of clinical research, or—more restricted—for other patients with the same disease as that of the research patient, i.e. a group-specific value. This may be the only benefit of research interventions with only questionable or no individual potential benefit for the participating patients, e.g. in validating a diagnostic measure, or in assessing potential risk or conditioning factors or causes of a disease.

Therefore, the basic precondition for research with human beings is their voluntary and valid informed consent. However, the voluntariness may be jeopardised by conditions such as imprisonment, poverty or personal dependency [7], the validity may be impaired by insufficient information, its inadequate understanding or incapability to make decisions.[1] The first mentioned external factors may influence mainly the intentional dimension of the capacity to consent, but they can be changed; the last mentioned factor of incapacity to consent is mainly related to the cognitive dimension of consent and must be compensated by protective measures.

Populations with such risk factors are termed as vulnerable populations. Mentally ill persons are a vulnerable population. Their specific vulnerability is given by the risk that their competence to consent may be impaired or does not exist at all, and that their vulnerability may be increased by being institutionalised, personally dependent or poor. In all such conditions, they are at risk to be used without authorisation for other than their own benefit.

Sometimes unauthorised use of a person is called instrumentalisation in the Kantian view that "an actor uses a person 'merely as a means' for his own purposes (whether 'egoistic' or 'altruistic'), and the person who by consequence of this action is inhibited to act on its own purposes ('its own ends')". However, often the normative implications and limitations of this term are not reflected [8].

The underlying concept of informed consent is that the consenting research participant makes the objective of the research intervention on his own. However, practice is more or less distant from this concept, particularly in incompetent patients, for example, in minors or in mentally ill people. Therefore, some ethicists did consider the research participation of incompetent subjects as unacceptable, for example, the authors of the German Research Regulation of 1931 [9] or of the Nuremberg Code of 1947 [10]. However, clinicians know that there exists a demand for improving the ill condition of these populations, and the conviction is growing that these populations have the right to participate in research that may yield helpful research results for them (e.g. [11–17]) by preventing them from becoming therapeutic orphans [18] or more specifically from successful developments against the mental disorder that causes their incompetence.

Examples:

- Patients with acute psychotic states such as manic episodes or delirium tremens usually are incapable of valid consent; however, immediate treatment is necessary and must be improved. A randomised controlled trial with the non-pharmacological intervention of viewing videotape of themselves while experiencing delirium tremens in order to reduce the relapse rate in alcohol-dependent patients used a "deferred" consent, that is, a retrospective consent [19]. A "deferred" consent procedure has been developed for research with emergency patients without capacity to consent [20, 21].
- In age-associated dementias, the research demand is evident because the underlying neurodegenerative process is not treatable to date. But the disease destroys the capacity to consent, slowly but inevitably—and thereby an essential prerequisite for its investigation in patients with dementia. The treating physician who informs the patient about the disorder in the beginning of the clinical course should also stimulate the patient to write an advance directive, including a consideration with regard to a potential participation in a research intervention.
- Capacity to consent is often reduced in patients with acute strokes [22]. However, therapy must be implemented as early as possible, that is, at a time when no

[1] The terms capability or capacity or competence to consent are used as equivalent in this text although in some countries capacity to consent is understood as a medical term and has to be differentiated from the legal term competence.

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authorised person may be available to substitute the consent of the patient. This ethical dilemma is particularly relevant in badly needed research with these patients in order to improve the existing therapeutic measures. Incapacity to consent and narrowness of timing are major ethical and legal challenges of such research. But solutions for ethically acceptable procedures have been developed by neurologists together with lawyers and courts [12].

- Mentally ill persons with suicidal intentions usually are excluded from clinical research studies, due both to the risk of realisation of their intentions and to their questionable or restricted capacity to consent. But there exists a demand for better suicide preventing interventions. An inherent specific ethical problem is the "possibility of imminent suicide risk associated with patients' right to discontinue the study treatment" [17].

Since these groups should not be excluded from research, they need protective measures such as a substituted informed consent, informed assent if possible [23], a relationship of benefits to risks clearly in favour of benefits, and "there is additional need for appointed representatives who monitor research and for legal obligations to compensate for any injuries suffered" [24]. There are also some warnings that exceptions from the protection rules, particularly to waive the requirement of (at least substituted) consent, for example, in emergency research or in some cases of research interventions with only minimal risks [25] as in newborn screening programs [11], could be taken too permissively [26].

Details and open questions of the informed consent process such as embedding it into the development of the physician–patient relationship, improving the patient's capacity to understand and to consent, particularly the assessment of the capacity had been dealt with elsewhere [27–29]. Recently, a broad range of instruments for a standardised assessment of the capacity to consent have been developed, but up to now, their application is limited by a restricted practicability or unproven validity or specific indications for only some dimensions of the capacity to consent [30, 31]. Some of them focus not only on understanding of information but also on both intentional and emotional influences on the capacity to consent and that of attitudes of relatives and carers as well as of personal dependency from them. However, there exist some doubts that all these dimensions of the capacity to consent can be adequately represented by a scale. Therefore, assessment of the capacity to consent requires taking great care, circumspection and responsibility. Even if the capacity to consent is impaired, the researcher should try to get at least an assent as an expression of respect for the patient and as a trust-building measure, whereas a dissent of an incompetent patient must be respected in any case. Particularly, patients after having remitted from an episode of mental illness and/or with regained capacity to consent as well as patients in early stages of a progressive neurodegenerative disease still with capacity to consent should be encouraged and empowered to develop an advance directive for medical interventions in situations to be expected in the future, for example, relapses/recurrences or worsening of their illness, in which their capacity to consent may be impaired. If possible and acceptable with regard to the value profile of the patient, he/she should be asked to include a statement on a possible participation in a research project in his/her advance directive [32].

Information on the appropriateness of the risk–benefit relationship of the research intervention to the potential research participant (or his authorised guardian) is a core requirement for gaining a valid consent.

Appropriateness of the benefit–risk relationship

This ethical core requirement of a clinical research intervention means that the relationship between its potential benefits and risks is reasonable and justified and does not violate good customs.

Because usually there do not exist unequivocal criteria of risks and benefits as well as clear rules for the assessment of their relationship to each other, the guess of a risk–benefit-relationship is influenced by the individual and social context of the decision makers, for example the members of an IRB or ethics research committee; this means e.g. that they will not decide against the good customs or ruling moral norms of their community. This argument may make relative the worldwide validity of basic moral norms such as human and civil rights. Therefore, it is of course a dangerous argument, but it is reality. At least, decision makers should be aware of it.

Without these preconditions, a research intervention is not permissible, even if competent probands consent to participate in the research intervention. On the other hand, also risky interventions, if reasonable and justified, or those without a potential direct individual benefit may be ethically justified if competent persons consent, for example, in Phase I trials in healthy people. However, it is a difficult task to find an acceptable balanced relationship[2] in cases with only a

[2] Simonsen [33] "The wording 'fair balance' is occasionally used by the European Court of Human Rights when there is a reasonable relationship between legitimate but conflicting interests, typically between the individual and the society at large." "During the last decade there has been a move from ethical and professional norms towards the adoption of legally binding norms in this field, both internationally and nationally in Europe".

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future or no direct potential individual benefit but potential risks such as objective material risks—not to mention a risk of compromising the dignity of the research participant.

According to different kinds of thinking on and sometimes almost meaningless vagueness of the term human dignity [34, 35], here the basic value of human dignity will not be referred to as an absolute and abstract value but to only one of its specific meanings in dealing with the suffering of mentally ill individuals, i.e. the concept of "inherent" dignity which all human beings have as human beings. Accordingly respect for the dignity of each mentally ill individual manifests itself especially in recognising his or her capacities as well as limitations, particularly those of the individual capacity to consent. This is relevant because its incorrect assessment either leads to an invalid consent and leaves the responsibility for decisions with an incompetent patient or else discriminates against a competent patient.

But, "risk–benefit ratios often cannot be calculated, even roughly; and that even if they could, ethical experiments don't need to have favourable risk–benefit ratios" [36]. The final report of the US National Bioethics Advisory Commission (NBAC) [37] stated in 2001: "An IRB may approve a research proposal only if it judges that the risks are reasonable in relation to potential benefits. This judgement may be an IRB's single most important and difficult determination, because it ensures that when research participants voluntarily consent to participate in a research study, they are offered a 'reasonable choice'" (quoted from [33]). Unfortunately, as the NBAC notes: "current regulations do not further elaborate how risks and potential benefits are to be assessed, and little additional guidance is available to IRBs" [38]. A fundamental difficulty is that both potential risks and benefits can be established only as probabilities, for example, as "probable", "possible" or "cannot be excluded". Furthermore, these probabilities may vary between individuals, for example, with regard to the individual everyday risks. In addition, the strength of risks (and benefits) often can be only roughly guessed as, for example, mild, moderate and severe. Accordingly, the assessment of the risk–benefit relationship as reasonable may be influenced by normative values and conventions [26]. This is particularly relevant because "there does not exist any operationalisable criterion for the decision that this benefit has the strength of that risk. Furthermore, there is no way to calculate the benefit for society against the risk for an individual without further assumptions" [39].

Example

Even a simple example may illustrate the complexity and difficulties of decision making with regard to the appropriateness of risks and benefits on: the individual level versus benefits and risks on the social level: the individual benefit of recovering from the illness as quickly as possible may interfere with the social benefit of gaining knowledge, e.g. by a delay of recovery if the individual belongs to a pure placebo control group.

But, according to the law, researchers and ethics committees have to assess the risk–benefit relationship of a research intervention. Therefore, they should give their arguments for their assessment, and particularly should "say that certain risks are not acceptable in the sense that they cannot be negotiated" [39]. In the past decades, some procedures have been proposed in order to attenuate this difficulty by standardisation of the assessment [40]. In any case, it is a task of clinical researchers to convey the meaning of probabilities and the risk–benefit relationship in a way that the potential research participants can understand.

Due to the difficulties of this judgement Research Ethics Committees (RECs) tend to avoid such in-depth evaluation of the risk–benefit relationship and focus on other aspects of the study, such as the consent process as Simonsen found out in his 3-year observational study of Swedish RECs [33].

The evaluation of the appropriateness of the benefit–risk relationship is of special importance in research interventions with patients whose capacity to consent is impaired due to mental disorders or whose voluntariness may be hampered by the before-mentioned external factors because occasionally the risk of exploitation of such patients may be greater than in competent patients. A careful evaluation implies a clear understanding of the uncertainties in establishing

- potential benefits
- potential risks and/or burdens and/or inconveniences

for the participating individual as well as for other present or future patients (social value).

Standards of benefits and risks

Both benefits and risks have to be considered on the individual as well as on the social level.

Benefits

Social benefit

All clinical research aims for scientifically based knowledge with the final objective to improve the treatment and care of ill people (in best case successfully also for the

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participating individuals). The important *social value* of this objective is evidenced by legal norms such as:

- the social law (SGB V) [41] in Germany provides that insurance companies are permitted to pay only for medical interventions with established economic efficacy and advisability, and correspondingly
- physicians are obliged to prescribe only indicated, effective and economical interventions. Furthermore, the demand for scientifically based medical knowledge, for example, particularly with regard to the frequent off-label use of drugs ("orphan drugs") in minors, is also indirectly evidenced by laws and guidelines;
- laws, for example, the German Drug Law (AMG), the European Guideline for Good Clinical Practice (ICH-GCP-Guideline E6) in 1996/Directive 2001/20/EC Directive 2001/20/EC on clinical trials [42], which became part of national laws in some European countries, for example, in Germany by the 12th amendment of the Drug Law in 2004 [43], guidelines of the drug licensing authorities, particularly the US Food and Drug Administration (FDA) [44], the European Medicines Agency (EMA) [45] or national authorities such as the German Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) [46] or the Schweizerisches Heilmittelinstitut Swissmedic [47]. In addition, the standards of national institutes for quality assessment influence the clinical testing of drugs, for example, the National Institute for Health and Clinical Excellence (NICE) [48] in the United Kingdom, or the Institut für Qualitätssicherung und Wirtschaftlichkeit (IQWIG) [49] in Germany.

Reasons for these regulations with regard to the social value of scientifically based knowledge are

- ethically, the demand of distributive justice to reimburse only effective medical interventions; they are also intended as protection for ill people from taking ineffective treatments with the risk of deterioration of the untreated disease;
- financially, the continually limited resources requiring an economic stake of the resources.

Consequently, it is a societal demand to prove scientifically the "efficacy" (or "effectiveness" under conditions of clinical routine), and the "efficiency" of medical interventions, that is, the relationship of therapeutic effectiveness to its costs, both medically in terms of side effects and risks and particularly economically in terms of financial burdens [50]. These complex requirements may imply the risk of keeping new treatment options for a relatively long time out of the reach of regular care. Nevertheless, the societal demand must, of course, be fairly balanced with the protection of the individual research participant against risks, burdens and inconveniences, particularly in vulnerable individuals.

The reason for considering the social value of needed research also in vulnerable populations is mainly that these populations are seen to have the right to participate in the progress of evidence-based medical interventions against their disorders and handicaps, because the evidence-based knowledge on other than the specific condition of a vulnerable population may be not valid for their specific condition and cannot be transferred.

Examples:
antipsychotic drugs with unknown interactions in multimedicated psychotic patients with somatic diseases, or antidepressant drugs in multimorbid multimedicated demented patients, or if drugs are prescribed or even must be prescribed for suicidal patients, but conditions characterised by suicidal ideation or behaviour are usually excluded in RCTs under current ethical standards, or if psychosocial interventions are related to specific mental handicaps.

Individual benefits

However, due to the legally founded conviction in liberal western societies that no human being is obliged to sacrifice himself for the community,[3] the practice of clinical research is dominated not by this social value of clinical research but by the impression of *individual benefits* of the participating research subjects such as

- to get a better intervention that is more effective, acts more rapidly, or has less side effects than the existing standard intervention;
- to satisfy his or her altruistic feelings of solidarity with other ill people, for example "Most respondents continue to participate in the ESPRIT study in hopes of benefiting personally. The majority also recognized that by participating in ESPRIT they were contributing to helping others; they experienced pride regarding this contribution and considered it an important reason to continue to participate" [51];
- to get some money [52] or other privileges.
- Further motivational factors are a feedback about the own illness and its state, feeling autonomic and self-determined and the wish, that other people will have a better understanding of their mental state.
- Particularly in incompetent patients with mental illness, the motivation of their carers and guardians is important; it has been evidenced for research interventions

[3] "In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests." (§ 6, Declaration of Helsinki/Seoul 2008) [6].

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that aim to an improvement of the ill person's quality of life and/or lessen the burden for the carer [53, 54].

Standards of benefit

Benefit can be determined more precisely only in reference to something such as reduction in symptoms or suffering or increase in quality of life. *Individual* benefit may comprise welfare or well-being as well as the best interest of the research participant, that is, both subjectively experienced benefits and objective benefits seen from outside. *Social* benefit is related to the gain of knowledge.

Reduction or increase in more complex concepts such as suffering or quality of life are clearly more difficult to be operationalised as a requirement for the assessment of the size of a benefit. Terms such as the "prospect" of benefit, or a "direct", "important" or "significant" benefit for the participating research subject or the gain of "essential" knowledge are not clearly defined or—as undetermined terms of law—not definable at all and thereby open for subjective interpretations. Such specifying criteria of benefit may be understood as:

- "Direct" and "immediate" benefits are used synonymously. However, "direct" benefit may be understood as an effect caused by the intervention, "immediate" benefit as an effect connected by time to the intervention. The use of the term "direct" benefit suggests that there may exist also indirect forms of benefit, for example, the development of a new treatment based on the cause of the ill condition that had been discovered by the research intervention. "Few existing accounts disagree over how this crucial concept of 'direct' benefit should be defined. This disagreement raises concern over whether those who cannot consent, including children and adults with severe dementia, are being adequately protected". It is suggested "that the extant definitions of direct benefits either provide insufficient protection for research subjects or pose excessive obstacles to appropriate research" [55].
- "Prospective" or "potential" benefit indicates an anticipated or expected benefit. Because it is a probability assessment it should be graded accordingly at least as possible or as probable.
- "Strength" of a however defined benefit could be assessed as questionable, detectable or evident.
- "Collateral" benefit was proposed for other than causal effects of the research intervention, that is, effects related to the participation or performance of the study, for example, an "inclusion benefit" by intensified medical monitoring [40].
- "Important" or "essential" or "significant" benefits are particular vague terms and open for different interpretations by (different) clinicians or researchers. However, the term provides a necessary range for interpretation because the newness of a progress of knowledge and also its practical usefulness often is difficult to evaluate and to recognise quickly.
- "Therapeutic research" was assumed as a potential benefit in contrast to "non-therapeutic research". However, this distinction is problematic because the border between these two types of research is often not clear. The distinction is especially problematic with regard to the therapeutic misconception [56]. Therefore, we prefer the ethically more relevant and clear term "with" or "without potential individual benefit" [57].

Risks, burdens and inconveniences

If an individual participates in a needed and legally required research study for the best of all—then, of course, this individual must be protected against risks and burdens of the research intervention. A variety of normative regulations prescribes the content, extent and mode of this protection of research participants against risks, for example, in major guidelines such as the Helsinki Declaration of the World Medical Association from 1964 and its revisions [6], the French or the Danish Research Law, and particularly the first international legally binding instrument concerning biomedical research, the European Convention and Human Rights of 1997 (Oviedo Convention) on Biomedical Research [58] and its Additional Protocol of 2005 [59] (which is accompanied by an Explanatory Report [60]).

Social risks

Not only benefits of research interventions for society should be considered but also some social risks, for example, if research interventions imply considerable risks or do not precisely follow the (scientific, ethical and legal) regulatory requirements, and thereby lead to incidents or invalid results and undermine the necessary trust of the public; this may prolong or even prevent the recruitment of individuals for research interventions that aim at the gain of needed knowledge.

Example:
Especially in psychotherapy research it seems difficult to separate the psychotherapist's empathy and understanding of the individual from the researcher's necessary objectivising and reductionistic approach as is exemplified by research in "neuropsychotherapy". "Harmful objectivation", "premature generalisation"

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and "misuse of objective data" are of specific ethical concern [61].

A particular risk are leaks in the confidentiality of individual research data. This breach will increase the mistrust of the public and reduce its readiness to participate in research.

To control these risks by evaluating the scientific quality of the research project, of its performance, and of the investigator(s) is the primary task of the research ethics committee (REC) (see "Assessment of the risk–benefit-relation"). The more the REC considers this evaluation the less the risks for the research participants will be. However, a positive vote of the REC does not remove the responsibility from the researcher, which has recently been emphasised again with regard to psychotherapy research [62].

Individual risks

The heading of individual "risk" comprises (1) predominantly objective threats to the proband, for example, unwanted side effects of the intervention; prolongation of suffering or worsening of the disorder due to the withhold of a specific treatment in a in placebo-control group, and in a broader sense also dispositions for unwanted effects, for example, pharmacogenetic or allergic dispositions or those that are related to noncompliant personalities, as well as (2) mainly subjective burdens and inconveniences of an individual specific nature, for example, by a too strong rigor of the research procedures or a feared risk such as stigmatisation, particularly in depressed patients and drug abusers which may demotivate potential research participants. Therefore, the individual should be specifically explored with regard to his/her sensitivity to both physical and mental risks and burdens, which may be specifically related to the intervention.

Standards of risks and burdens

In order to make risks comparable, some gradations have been proposed and are used. However, these gradations are fairly vague, rough and not at all quantitative. Nevertheless, some efforts have been made to standardise risks by more or less clear definitions and vivid examples.

Strength of risks is described by a broad range of grading terms[4] such as "without the danger of impairment",[5] minimal risk, minor increase of minimal risk, "not insignificant risks",[6] "serious risk to health", "possible irreversible damages",[7] risks of unacceptable dimensions".[8]

Probability is the other important dimensional standard but—by its inherent nature—can also be determined only with uncertainties, at best within a defined range. At least a gradation according to "cannot be excluded", "possible" and "probable" should be made.

Absolute upper limits of risks for research participants are irreversible impairments and death. Standard limits for research with incompetent patients are no more than "minimal risk", "minor increase of minimal risk" and "direct prospective benefit" [64]. "Minimal risk": it is a decisive criterion of protection of incompetent research participants. However, there exist different interpretations of "minimal risk" as (1) The US regulations allow institutional review boards (IRBs) to approve a given research intervention in incompetent patients only if "it poses no more than "minimal" risk, defined as the risks encountered in daily life or during the performance of routine examinations or tests (46.102)" [64]. But, "in the absence of empirical data, IRB members may assume they are familiar with the risks of daily life and with the risks of routine examinations and tests and rely on their own intuitive judgment to make these assessments. Yet intuitive judgment of risk is subject to systematic errors, highlighting the need for empirical data to guide IRB review and approval of pediatric research…. Current data on the risk of mortality in healthy children suggest IRBs are implementing the federal minimal risk standard too cautiously in many cases" [65]. On the other hand this vagueness have led also to a warning against a softening the minimal risk criterion [11]; (2) Furthermore, standards of minimal risk with regard to risks of daily life will vary according to age, in minors [66] as well as in old adults. Due to such difficulties it was proposed to drop the standard of daily living [67]. (3) With regard to the minimal risk criterion of comparability with "routine examinations" the Central Ethics Committee at the German Federal Board of Physicians stated that the standard of a minimal risk corresponds with

4FL01 [4] Page numbers in the following 4 footnotes are all from [63].

5FL01 [5] Switzerland (Steffen et al. p. 383): in non-therapeutic research.

6FL01 [6] Oesterreich (Kopetzki, p. 236): The guardian must get the approval of the court. The consent of a guardian without powers for clinical trials is inadmissible. 6FL02 6FL03

7FL01 [7] Tschechien (Cisarova et al. p. 402): No more than minimal risk is defined by the exclusion of permanent deterioration. Canada-Northern Territory (Naffine, p. 270) "a psychiatric patient can only participate in research if it "will not be detrimental to the best interest of that patient". 7FL02 7FL03 7FL04 7FL05

8FL01 [8] Denmark (Hybel, p. 493): as such the Danish Research Law regards risks that go beyond the risks of the disease. 8FL02

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e.g. "taking body liquids or tissues in small quantities in the context of necessary diagnostic measures or operations with no additional risk for the patient. Also certain physical investigations (e.g. sonography, transcutaneous tissue measures) or psychological investigations (e.g. interviews with questionnaires, tests, observations of behaviour) belong to this group" [68].

"Minor increase above minimal risk": with children "who have some disorder or condition": the US Federal Code restricts research to no more than a minor increase over minimal risk, unless potential harms are offset by potential benefits to them, as in therapeutic studies [69]. However, it is unclear what a "minor increase" means [70]. Due to different interpretations of the criterion "minor increase over minimal risk" and its lack of clarity the extension from minors to adults or elderly patients incompetent to consent seems unacceptable at present in cases without potential direct benefit but should be explored with regard to a higher level of protection.

The limits of the minimal risk criterion in research with incompetent participants are unclear as is evidenced by the fact that "According to the Council of Europe's European Convention on Human Rights and Biomedicine, such research may be approved only if it entails no more than 'minimal risk and minimal burden'. In contrast, in a more recent document offering guidance on the application of the clinical trials directive with regard to trials with minors, the European Union recommends allowing 'a minor increase over minimal risk' in case of benefit for the group of children with the same disease" [71]. The US Common Rule [72] states in its subpart D more precisely that "45 CFR 46.406, permits research posing a minor increase over minimal risk and no prospect of direct benefit but expected to yield vital knowledge about the subjects' disorder or condition". Furthermore, a higher level of protection is given by the requirement of "federal review and approval of the Secretary of Health and Human Services under 45 CFR 46.407" if "other children [will be included] in research posing a minor increase over minimal risk and no prospect of direct benefit requires" [73]. However, the ambiguities of language in these regulations have led to heterogeneous interpretations by IRBs and call "for a national consensus on the interpretation of federal regulations" [74].

Thus, research without potential individual benefit in—both healthy and ill—incompetent individuals is either seen as not permissible or only as an exception and limited by the standard of no more than minimal risk, if the participant's consent is substituted by an authorised person. In ill-incompetent minors, a minor increase in minimal risk will be accepted if a vital knowledge about the participant's disorder is anticipated, even if no potential individual benefit can be expected. Definitions of these standards are open for interpretation, less for minimal risk, more for minor increase in minimal risk and most for "vital" benefit.

Assessment of the risk–benefit relation

The assessment of the strength and probability of potential risks and burdens as well as of potential benefits and particularly its relation to each other is the crucial step in evaluating the acceptability of a research intervention. Due to the mentioned fact that strengths and probabilities of risks and benefits mostly can be only roughly guessed and the relation of benefits to risks even in the individual, but much more between the individual and society, some authors have developed matrices in order to explicate the components of the guesses and standardise this process [40, 75, 76].

Example:
In studies with more than minimal risks, as in vaccination studies, the ethics committee has to decide whether the risk–benefit-relationship of such therapeutic research would be ethically acceptable in patients with a presently almost untreatable disease such as Alzheimer's dementia with a fatal outcome (as it is argued for in oncological trials in patients with final stages of carcinomas) but at liberty to the risk–benefit-assessment of the authorised persons.

Thereby, different standards for the evaluation have been developed as is evidenced by a recent controversy between representatives of the "equipoise" standard (e.g. [74] and those of a "net-risks-test" [38]. This controversy has been discussed in depth [77].

Equipoise is regarded as a moral prerequisite of the trial because it combines the principle of research ethics (the honest null hypothesis) with the principle of medical ethics (the best possible care, or no inferior treatment) in comparison research, i.e. randomised clinical trials. It says that the research study should be conducted only if there is substantial uncertainty among experts about the relative value of benefits or risks of one treatment versus another [78, 79]. Studies in which intervention and control are thought to be non-equivalent violates the uncertainty principle [80, 81]. "The equipoise-criterion allows an essentially more precise estimate of the benefit of medical research than the up-to-now general risk–benefit-estimate" [82]. However, this criterion has been criticised because it "conflates the sound methodological principle that RCTs should begin with an honest null hypothesis with the questionable

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ethical norm that participants in these trials should never be randomised to an intervention known to be inferior to standard treatment" Wendler [64]. Thereby equipoise may provoke a therapeutic misconception, i.e. misunderstanding a medical research intervention as individual medical care [83]; furthermore it is seen as unreasonably restrictive and may inhibit necessary and well reasoned research. Therefore, a net-risk-test has been developed which focuses on assessing the risks and benefits of a research intervention and justifies morally the research only by the net-benefit for the research participant [38].

Trust

Despite of both the social demand of clinical research and possible or even probable individual benefits up-to-now medical interventions are often based not on scientifically proven evidence but only on empirical evidence [84], for example, by clinical experts' published but uncontrolled efficacy of interventions and thereby sometimes used as standards, and the experience of the treating physician, for example, with multi-medication in multi-morbid or chronically ill [85], or in therapy-resistant patients. Reasons among others comprise difficulties of scientific methodology on the one hand, and uncertainties about possible risks and research refusing convictions or feelings of potential participants on the other hand.

Examples of difficulties and ethically questionable implications of research methodology may be: (1) a methodologically necessary rigor, e.g. selection criteria for a sample of multimorbid and multi-medicated patients may come across with the practicability of patient recruitment, or may conflict with the well-being of the participant, or (2) the objectives of "industry sponsors aiming at licensing and marketing drugs may weaken the usefulness of the findings to EBM" [86], or (3) the assessment of the risk–benefit-relationship may be influenced subjectively due to unclear standards and procedures [81, 87–89].

Therefore, more practicable standards of benefits and risks as well as more objective standards of the benefit–risk assessment are badly needed.

A major factor on the side of the public may be a lack of trust [90]. Public awareness of other aims of clinical research than gain of knowledge, e.g. market interests of industry, or personal interests (uncontrolled scientific curiosity, career, money) of researchers, biases (e.g. publication bias, selective reporting of findings, and distorted interpretation of results) or undue and even hidden and inadmissible influence of industrial sponsors [91–93] up to phrasing guidelines [94], or on ethically questionable behaviour of researchers, or even frauds in science, or personal bad experience with clinical settings and physicians will foster a sceptical or avoidant attitude of society towards clinical research. Loss of trust is a societal risk which hamper or even prevent the gain of helpful knowledge for the community.

Therefore, it is a further demand to take steps against uncontrolled or dubious influences on clinical research, and above all to take thorough care of patients participating in research, for example, taking seriously their welfare, interests and wishes. It includes a careful information of the potential research participant and/or his authorised guardian not only of possible benefits of the research intervention, but also on its potential risks and burdens, including the benefit–risk relationship.

Connell et al. [53] conclude from their interviews with caregivers of patients with Alzheimers dementia: "to maximize the perceived benefits of research participation, potential participants should have access to regular personal contact with staff, information about health status changes in the care recipient, and the short-term and long-term results of the research studies in which they are participants."

Recommendations

1. Informing the patient is not only a legal must but much more a chance to develop trust.[9] But it needs time and should be considered in planning the research study. Particularly, vulnerable research participants should be empowered at least to assent to the research procedure besides the substituted informed consent by authorised persons.
2. Mentally ill patients with still maintained (e.g. in early stages of neurodegenerative diseases) or regained capacity to consent after an illness episode should be encouraged to develop an advance directive for medical interventions including a possible participation in a research project which is—according to national regulations—related to his/her disease.
3. Assessment of competence to consent is needed to be sure of the validity of consent. However, there is still a lack of scientifically proven and practicable

[9] "The patient who is armed with information, who wants to ask questions, should be seen as an asset in the process of care and not an impediment to it." (Donaldson, cited by Maclean [95]).

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standardised tests, which should be overcome by further research. Nevertheless, the assessment remains the responsible obligation of the clinical researcher.

4. Consent should not only be related to the relevant matter in question but also be graded in relation to potential risks: the threshold for accepting the competence to consent should be higher with higher risks.
5. Benefits and risks are undetermined terms of law and should be determined explicitly as clear as possible in each specific research design.
6. With regard to the uncertainties of the assessment of potential risks and burdens in relation to the expected benefits of a research intervention, a safe validation of its acceptability should be observed by a three step evaluation:

   - First the *researcher* has to give reasons for why he considers the relationship of risks and burdens to the expected benefits of his planed research intervention as acceptable, that is, as reasonable and justified.
   - Then, the *Research Ethics Committee* (*REC*) has to evaluate this relationship with regard to legal and ethical norms and professional expertise, and should give reasons—at least in research studies with vulnerable subjects—not only for refusal but also in case of acceptance of the research application and particularly of the ethical considerations of the applying researcher.
   - Finally, the potential *research participant* or his legal guardian has to be informed about the arguments of the institutionally approved relationship of potential risks, burdens and inconveniences to the expected benefits of the research study. Then, he or she has to evaluate this relationship with regard to his personal idiosyncrasies, interests and values. If this relation is acceptable for him or her he or she may consent to participate.

7. Researchers should be educated systematically on the ethical implications of clinical research.[10] All regulations should be observed thoroughly in order to not loose the trust of both the research participant and the public into research, which is a basic requirement of successful recruitment of vulnerable individuals.

Acknowledgments Special thanks goes to Prof. Urban Wiesing for his constructive, thoughtful, stimulating and clarifying comments.

Conflict of interest The author declares that he has no conflict of interest.

[10] Recently, a workshop of the European Science Foundation made clear that "there is an urgent need to develop consistent education in conduct of research (RCR)" [96].

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Journal : Large 406 | Dispatch : 26-12-2011 | Pages : 12
Article No. : 287 | ☐ LE | ☐ TYPESET
MS Code : EAPC-D-11-00093 | ☑ CP | ☑ DISK