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MEMORANDUM

FROM EXCLUSION TO INCLUSION. IMPROVING CLINICAL RESEARCH IN VULNERABLE POPULATIONS

Berlin-Brandenburg Academy of Sciences and Humanities

berlin-brandenburgische
AKADEMIE DER WISSENSCHAFTEN

Berlin Brandenburg Academy of Sciences and Humanities (BBAW)

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Herausgeber: Der Präsident der Berlin-Brandenburgischen Akademie der Wissenschaften

Redaktion: Christopher Hank und Ute Tintemann
Grafik: angenehme gestaltung/Thorsten Probst
Druck: Brandenburgische Universitätsdruckerei u. Verlagsgesellschaft Potsdam mbH

ISBN: 978-3-939818-45-8

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FOREWORD

Therapeutic care for vulnerable populations – meaning patient groups such as underage children and the mentally ill that have limited or no capacity for giving informed consent – is severely lacking. Thus, for example, a great portion of pharmaceuticals used in the treatment of children and youth have not been specifically designed for these groups, which often results in side effects that are disproportionate to those associated with such medicines when used by adults. Moreover, vulnerable populations are at times faced with having no therapies at all for some of their ailments, such that children and dementia sufferers, for example, are often considered to be "therapeutic orphans". It is therefore urgent that clinical research be carried out among vulnerable populations in order to improve their therapeutic possibilities.

The *Clinical Research on Vulnerable Populations* Research Group – a cooperative effort between the Berlin-Brandenburg Academy of Sciences and Humanities (Berlin, Germany) and the European Academy of Technology Assessment (Bad Neuenahr, Germany) – has set itself the task of analyzing the state of clinical research on vulnerable populations so as to be able to develop suggestions for improving future research of this kind. The results of this work are presented in the following memorandum, which seeks to portray the state-of-the-art in this domain while also assessing the strengths and weaknesses of contemporary ethical and medical perspectives related to it. The memorandum is primarily oriented towards those in the relevant scientific disciplines who can benefit from obtaining an *informed consensus* regarding the current state of the discussions taking place around this topic.

Under vulnerable persons are understood those who, due to illness and legal or other reasons, have limited or no capacity for informed consent. It is above all in connection with the treatment of such persons as probands in the development of diagnoses and therapies via clinical research that difficult ethical and legal questions arise. In fact, the concrete spur for the present research developing into the interdisciplinary study that it has become was the introduction in 2007 of the EU regulation on child pharmaceuticals (1901/2006), which obliges pharmaceutical companies in the EU to also test medicines with new ingredients, indications, doses, or dosage forms on children. Furthermore, at the moment there is a proposal circulating in the EU Parliament concerning the replacement of existing regulations (2001/20/EC) on the clinical testing of medicinal products, so the topic addressed by the present document is clearly still timely.

The two central, normatively opposed, ethical and legal problems related to the clinical study of vulnerable populations are the following:

I. Persons who do not have the capacity for informed consent are entitled to special moral and legal protection because, among other things, they usually lack the discernment and/or legal competence to defend themselves against being misused. Especially shaky here is how to adequately explain the concept of "informed consent" in this context.

II. Were all persons not having the capacity for consent to be excluded in principle from diagnostic and therapeutic test situations, then it would not be possible to produce medicines that have actually been tested on particular target groups, such as children. This situation has set in motion a debate over whether individuals or their legal guardians are morally obliged to consent to participate as probands in, e.g. in double-blind studies which would in the end not likely be of direct benefit to themselves but have a collective health benefit only. Although such an incorporation of members of vulnerable populations into medical studies is not permitted by the existing laws of a large part of the world, an ethical debate about this issue should be conducted unprejudiced. In this vein, it must also be clarified whether the ignoring of individual preferences in other life situations (e.g. national defense, natural disaster management) has normative similarities with the present topic.

In any case, it seems obvious that the morally and legally entrenched entitlement to special protection for potential research probands from vulnerable populations and the also morally and legally mandated demand to conduct research related to such groups – both set in a tense, antinomic relationship – have not yet found a satisfactory solution.

Taking into account all of the issues mentioned so far, recommendations for a legally sound and medically feasible development of clinical research on probands from vulnerable populations are included at the end of this memorandum, including reference to notable gaps in existing legal statutes. The recommendations provided here are rather general, because it seems more sensible to articulate an overview of what kind of conditions and options could enable vulnerable populations to receive the most benefits from clinical research than to focus on overly concrete solutions in that direction.

Bad Neuenahr-Ahrweiler/Berlin, April 2014
Carl Friedrich Gethmann

VORWORT

Die therapeutische Versorgung vulnerabler Populationen, d.h. von nicht oder nur eingeschränkt einwilligungsfähigen Patientengruppen wie zum Beispiel Minderjährigen und einem Teil der psychisch Kranken, ist mangelhaft bzw. verbesserungsbedürftig. So ist zum Beispiel immer noch ein erheblicher Teil der bei Kindern und Jugendlichen verabreichten Pharmazeutika nicht speziell für diese zugelassen, was unverhältnismäßig häufig zu Nebenwirkungen und insgesamt zu nicht befriedigenden therapeutischen Ergebnissen führt. Darüber hinaus gibt es in vulnerablen Populationen für viele Krankheiten überhaupt keine Therapien, so dass zum Beispiel Kinder und Demenzkranke als „therapeutische Waisen" angesehen werden müssen. Es ist daher eine dringende Aufgabe, klinische Forschung in vulnerablen Populationen zu fördern und damit die therapeutische Situation der Betroffenen zu verbessern.

Die gemeinsam von der Berlin-Brandenburgischen Akademie der Wissenschaften und der Europäischen Akademie Bad Neuenahr GmbH getragene interdisziplinäre Arbeitsgruppe *Klinische Forschung in vulnerablen Populationen* hatte es sich zur Aufgabe gemacht, die Situation der klinischen Forschung an vulnerablen Populationen zu analysieren und Vorschläge für eine Verbesserung dieser Forschung zu entwickeln. Sie präsentiert die Ergebnisse ihrer Arbeit in dem vorliegenden Memorandum. Es reflektiert den *state of the art* und bewertet die Stärken und Schwächen der gegenwärtig vertretenen ethischen und medizinischen Standpunkte. Das Memorandum richtet sich in erster Linie an die einschlägigen wissenschaftlichen Disziplinen, um im Sinne eines *informed consensus* über den aktuellen Stand der Diskussion zu informieren.

Unter vulnerablen Personen werden solche Personen verstanden, die aus krankheitsbedingten und/oder rechtlichen Gründen nicht oder nur eingeschränkt einwilligungsfähig sind. Vor allem im Zusammenhang mit der Beteiligung solcher Personen als Probanden an der Entwicklung medizinischer Diagnostik und Therapie im Rahmen klinischer Forschung werden schwerwiegende ethische und juristische Fragen aufgeworfen. Konkreter Anlass, das Thema zum Gegenstand einer interdisziplinären Studie zu machen, war eine im Januar 2007 in Kraft getretene EU-Verordnung über Kinderarzneimittel (1901/2006), durch die pharmazeutische Unternehmen in der Europäischen Union verpflichtet werden, Medikamente mit neuen Wirkstoffen, Indikationen, Dosierungen und Darreichungsformen auch in Studien mit Kindern zu prüfen. Zudem wird zur Zeit ein Vorschlag für eine Verordnung des Europäischen Parlaments über die

klinische Prüfung von medizinischen Produkten, die die bisherige Verordnung 2001/20/EC (GP) aufheben wird, im Europaparlament beraten, so dass die hier diskutierte Thematik immer noch aktuell ist.

Die beiden zentralen, normativ gegenläufigen, ethischen und rechtlichen Probleme klinischer Studien in vulnerablen Populationen sind:

I. Nicht einwilligungsfähige Personen haben Anspruch auf einen besonderen moralischen und rechtlichen Schutz, unter anderem, weil sie sich nicht aus eigener Einsicht und/oder rechtlicher Zuständigkeit gegen Missbrauch schützen können. Besonders prekär ist in diesem Zusammenhang, den Begriff der „informierten Einwilligung" zu explizieren.

II. Würde man nicht einwilligungsfähige Personen allerdings grundsätzlich von diagnostischen und therapeutischen Testsituationen ausnehmen, könnte es keine spezifischen Medikamente beispielsweise im Rahmen der Kinderheilkunde geben, die an entsprechenden Personengruppen getestet sind. In diesem Zusammenhang ist eine Debatte darüber in Gang gekommen, ob Individuen beziehungsweise ihre rechtlich autorisierten Vertreter mit Blick auf kollektive Gesundheitszwecke moralisch verpflichtet sein könnten, etwa im Rahmen von Doppelblind-Studien „fremdnützig" als Probanden eingesetzt zu werden. Obwohl eine derartige Indienstnahme von Mitgliedern vulnerabler Populationen durch die geltende Rechtslage in weiten Teilen der Welt ausgeschlossen sein dürfte, sollte die ethische Debatte offen geführt werden. In diesem Zusammenhang ist auch zu klären, ob die Nichtbeachtung des individuellen Willens in anderen Lebenszusammenhängen (Landesverteidigung, Katastrophenschutz o. ä.) erlaubt, normative Vergleichsgesichtspunkte zu gewinnen. Offenbar stehen der moralisch und rechtlich verbürgte Anspruch auf besonderen Schutz von Forschungs-Probanden aus vulnerablen Populationen und die ebenfalls moralisch und rechtlich abgesicherte Forderung gerade für diese Patientengruppen mehr Forschung zu betreiben, in einem Spannungsverhältnis, für dessen Auflösung bislang keine befriedigenden Lösungen gefunden worden sind.

Empfehlungen für die moralisch gerechtfertigte und medizinisch sinnvolle Weiterentwicklung der klinischen Forschung an Probanden aus vulnerablen

Populationen werden am Ende des Memorandums ausgesprochen. Zudem werden auch Lücken im derzeitigen Rechtsrahmen angesprochen.

Die Empfehlungen sind sehr allgemein gehalten, weil es weniger darum gehen sollte, konkrete Handlungsanweisungen zu vermitteln als vielmehr die Bedingungen und Optionen aufzuzeigen, unter denen ein Einbezug vulnerabler Populationen in die klinische Forschung zum Wohle der Betroffenen ermöglicht werden kann.

Bad Neuenahr-Ahrweiler/Berlin im April 2014
Carl Friedrich Gethmann

1 INTRODUCTION

The therapeutic situation of vulnerable populations – such as minors, the mentally ill, and intensive-care patients – is unsatisfactory. A large proportion of the pharmaceuticals given to minors, for example, are designated "off-label" (i.e. without a paediatric indication approved by a drug regulatory agency), which may be a sign that there is not sufficient data to support safe and effective use for children. What seems even more worrying is that for many conditions there is no validated therapy available, leaving patients as "therapeutic orphans". It is, therefore, an urgent task to foster clinical research for vulnerable populations and to discuss the medical, ethical, legal and economic problems involved.

In the context of clinical research, we underline that vulnerable populations should be even more entitled than others to special protection, as these groups are exposed to a greater risk of having their rights violated. Therefore, those responsible for protecting such rights and interests need to specify the kinds of protection required. Obviously, there is a tension between the morally and legally backed entitlement to special protection for research probands from vulnerable populations and the equally morally and legally justified claim for more research on such patient groups. Up to now, no convincing solutions for these challenges have emerged. The present memorandum is addressed to an interested expert audience and aims at a careful analysis of the current state-of-the-art of clinical research on vulnerable populations, evaluating prominent ethical and medical positions as well as the current regulatory framework.

Before going more deeply into this topic, it needs to be mentioned that there is considerable debate about formulating a suitable definition of the term 'vulnerable populations'. In this paper, we use the term in a narrow sense to denote groups of people with restricted or missing capacity for decision-making because of limitations in their mental (i.e. cognitive, intentional or emotional) capacities, due to

- developmental and/or pathological processes or
- external factors, such as imprisonment or poverty and other social factors.

From the variety of factors that can cause vulnerability, it follows that clinical research among different patient groups faces quite different obstacles, depending on the respective vulnerabilities. Developing recommendations for improving clinical research in vulnerable populations is not a matter of across-the-board solutions.

Rather, much will depend on targeted group-by-group approaches addressing specific vulnerabilities. In the following sections, the problems of performing clinical research on three vulnerable populations – minors, mentally ill, and critically ill patients – will be discussed in detail via relevant examples.

1.1 VULNERABLE POPULATIONS HAVE A RIGHT TO RESEARCH …

Societies are generally assumed to have an obligation to help those of its members that are in need. However, there is considerable disagreement about, amongst other issues, the extent to which this help should be given. At least in Western welfare states, that is, most European countries, a well-developed healthcare system offering substantial benefits for almost all of its citizens is a de facto part of the social responsibility to help individual members in need. It does not need much argument to see that implementation of a healthcare system should not be limited to providing currently existing remedies but should also include strategies for improving healthcare to cover currently unmet health needs. To initiate and subsidise health research is therefore part of a society's moral obligation to help those of its members whose health needs are not met.[1]

It is a matter of basic justice that no societal group, including vulnerable populations, should be excluded from the potential benefits of health research, meaning that *our societies have a moral obligation to find ways to safeguard health research for vulnerable populations*. Many international agreements[2] reflect such moral considerations and infer that, as part of this special protection, vulnerable populations are entitled to the highest attainable standard of health and that no individual should be deprived of his/her right of access to such healthcare services. This can be interpreted to mean that vulnerable populations have the right to the best available treatments, including medicines, to meet their therapeutic needs. Among the general population, ensuring the highest attainable standards of medical therapy as part of healthcare relies in part on being able to access proper, scientifically researched, information concerning the efficacy, safety and quality of medicines. *Based on this premise, we assume that in such societies there is an entitlement to ultimately receive effective and safe, evidence-based care, not just state-of-the-art standard therapies.*

1 To what extent a society should subsidise research and how resources should be distributed between different branches of the healthcare system – let alone between healthcare and other public sectors such as education – is open to debate but lies outside the focus of this article.

2 For example the Convention on the Rights of the Child.

One consequence of this line of thought is that society has an obligation to meet the healthcare needs of vulnerable populations through interventions of proven efficacy and safety, though this may also appear to conflict with the parallel obligation to protect vulnerable populations from research risks. However, this tension can be redefined as a broader obligation of society to provide access to research participation to its vulnerable members to ensure they are not deprived of the benefits of biomedical research. Hence, there is a need to ensure that the procedures regulating research participation provide protection without creating barriers. In practice, this means that it is a violation of the general obligation of care and protection of vulnerable populations not to provide treatments they need which already exist for other populations or to provide them with an existing treatment (e.g. medicine) without knowing the correct dosage and whether the treatment is safe and effective for use in that population. In other words, vulnerable populations have the right to benefit from research-based treatments to improve their health, but restrictions on research among these populations have to be strictly adhered to, and studies that are not specifically qualified must be avoided.

1.2 ... BUT NOT A DUTY TO PARTICIPATE

Relevant codices and regulations can be summarised as affirming a right to limitation of research in accordance with a research participant's rights, especially the rights of self-determination and bodily integrity. However, due to the fact that the capacity to consent is restricted or impaired in vulnerable persons, the predominant view as laid down in existing guidelines is that research participants, especially those from vulnerable populations, must be protected from possible harms of research (Hübner 2003).

In liberal societies, competent individuals are allowed to take considerable risks if they have consented to them, such as, smoking, mountaineering or participating in a potentially risky research project. Though participating in medical research is undoubtedly more honourable than, for example, entering the death zone of Mount Everest without extra oxygen, both activities are morally permissible if done with consent.

Clearly, the problem with patients from vulnerable populations is that many of them have a limited or even missing capacity to properly consent, so that

decisions for such patients to participate in research projects need to rely on surrogate consent given by a parent or other authorised person. There is considerable dissent about the extent to which it is justified to expose vulnerable persons to risk due to research. A majority of experts argue that parents and other patient representatives have the right to give surrogate consent to research if it is reasonable to expect a risk-benefit-relationship in favor of a more or less substantial benefit for the participant. This seems to be in line with the general rule that parents are allowed to make even risky decisions, such as on education, if they are in the presumed interest of the child. A further problem emerges, however, when considering research with no expected direct individual benefit. Here, most experts assume that authorised persons are morally obligated to deny consent in case of probably more than minimal risk for the research subject. The issue of surrogate consent surely deserves more attention, but it is fair to conclude that on moral grounds the patient's legal representative should give surrogate consent for research participation only to a very limited extent.

Large areas of medical research – such as attempts to clarify disease mechanisms or investigate drug action – are valuable in the sense of potentially leading to new therapies. Nonetheless, though valuable in the sense of likely generating social benefits, such research is not usually in the direct interest of research subjects. In the case of vulnerable populations, legal representatives – in line with the above-outlined logic – can hardly give consent that their wards may participate in such research. More recently, however, there have been attempts to claim that it is in the interest of vulnerable populations that more research be conducted in certain areas, even if this involves risks for participants (Mastroianni & Kahn 2001). Some authors even argue that there is not only a right to conduct research on vulnerable populations, but a duty to do so. Odd or even repugnant as this argument may seem to the reader, we are aware of certain conditions under which individuals – including children and other vulnerable subjects – can be obligated (voluntarily or against their will) to participate in the interest of the public. Examples here include expropriations or the compulsory medical examination and treatment of patients with contagious diseases. The duty to tolerate such intrusions is usually justified by referring to a state of emergency. Though such an argument seems to be plausible in principle, it actually entails certain problems, as shall be briefly illustrated.

An example of obligation to give reasonable emergency aid is the following: If you take a walk along the seashore and see a child in danger of drowning, you have the duty to help this child, even if this involves a certain risk for you,

such as because you are a bad swimmer or because there are very high waves. Characteristic for this obligatory emergency aid is that person A takes a certain risk in order to help person B who is in danger of being seriously harmed. With respect to clinical research on participants from vulnerable populations, such a situation is only partly comparable, however, because the vulnerable person can be both the person in danger and the person taking the risk – thereby potentially assuming a double burden. Moreover, arguing in terms of current emergency situations may seem somewhat awkward with respect to the great part of clinical research that is designed to help future patients. Therefore, other strategies to justify a solidarity obligation to tolerate research need to be discussed. Further thought is required as to whether one can more convincingly justify a *supererogatory* act: a morally advisable but not mandatory solidarity obligation. Furthermore, one might explore whether an obligation to tolerate research can be justified in terms of *long-term responsibility* instead of emergency aid. Compare this, for example, with financial burdens citizens are obliged to assume now in order to avert potential harm for future generations.

It remains doubtful whether any of these arguments can convincingly establish a duty for individuals from vulnerable populations. Nevertheless, the above considerations indicate that representatives of such individuals may, in the case of minimally risky research, consent to the participation of their wards, even if there is no clear direct benefit to be expected.

1.3 LACK OF RESEARCH PROBANDS

A main concern for researchers both in academia and industry continues to be that of finding sufficient numbers of test subjects from among vulnerable populations. On the one hand, there is growing demand for clinical research and, therefore, for more probands. On the other hand, parents and legal guardians frequently do not like the idea of their offspring or protectees taking part in clinical research and are often not susceptible even to good arguments such as that patients are nowhere better monitored than in a state-of-the-art clinical trial. This reservation cannot be simply overcome by more extensive consent procedures but rather requires the building personal and trusting relationships between legal guardians and researchers. Research in bioethics can help better understand both the strengths and limitations of our current models for recruiting vulnerable populations to participate in research. A critical aspect here is to examine the factors and circumstances contributing to the decision of relatives

to enrol their beloved children or demented family members in research projects and, in parallel, to elucidate credible motivations for test persons to participate.[3] Cultural and social factors also play an important role, as, for example, it has been traditionally more difficult to enrol ethnic minorities in research in the USA. Systematic assessment of the motivating factors for research participation in different cultural and economic contexts would aid in better understanding the process and may generate more effective approaches for recruiting research participants.

1.4 CHALLENGES ARISING FROM THE GLOBALISATION OF RESEARCH

In countries providing universal healthcare there appears to be considerably less willingness to consent to research, due to external motivations such as access to treatment. The common tendency of relatives in the Western world to not expose their beloved ones to a perceived risk is natural, though not very socially responsible, and clinical researchers have adjusted to this situation by increasingly moving trials overseas. There are also other reasons for conducting research in economically developing countries and emerging markets: foremost being that it is usually less expensive to carry out clinical trials in these settings. As such research is often performed in order to meet regulatory requirements for marketing medications in developed countries, this situation can raise the concern of possible exploitation of research participants in developing countries who are not likely to benefit directly from research outcomes. The worry, thus, is that the trial requirements for market authorisation of pharmaceuticals imposed by regulators give rise to an unfair distribution of the burdens and benefits of research (Nuffield Council 2002, Petryna et al. 2006, Petryna 2009).

In fact, a large proportion, though certainly not all, of global research is conducted in accordance with relevant legal regulations, and clinical data generated outside the Western world are regularly accepted for market authorisation in developed countries. The pharmaceutical industry is sometimes criticized for neglecting its corporate citizenship and moral obligations. It is highly

3 The current, rather limited data for research in minors indicate that the primary motivation for parents is the pursuit of high-quality care for their children, better understanding of their child's illness, or free treatment (Rothmier et al. 2003, Vitiello et al. 2007). A motivating factor for participating in non-therapeutic research is often monetary compensation, while altruism is less frequently reported (McCarthy et al. 2001). However, these data may be specific to particular healthcare systems, in which access to quality care can be difficult or impossible for certain segments of the population to obtain. Moreover, for other vulnerable populations different reasons may prevail.

controversial though to what extent such obligations exist and what their potential content could or should be. The notion of corporate citizenship and moral obligations should not be confounded with compliance with applicable laws. The responsibility for legal frameworks that fail to prevent morally unwanted consequences is not in the hands of the companies acting under them, but rather in the hands of those who give legitimacy to such frameworks.[4]

In sum, in developed countries research participants from vulnerable populations are an increasingly scarce resource, due to increasing ethical awareness of the need to protect them from abuse. The trend of globalising clinical research poses medical ("validity of research"), moral ("acceptability") and legal ("control") problems that need intensive discussion. However, the globalisation of research should be seen not only as a problem, but also as an opportunity to expand the basis upon which high quality (both scientifically and morally) clinical research to the benefit of vulnerable populations can be conducted. One factor to take into account when research is organised by investigators from a developed country, but conducted in a developing country, is whether and how the research addresses the health needs of the developing country. Research that is relevant to both the developed and developing country is more likely to be justifiable than studies that have little relevance to the latter.

1.5 THE REGULATORY FRAMEWORK[5]

A variety of normative regulations prescribe the content, extent and mode of the protection of research participants against risks, including major guidelines such as the Helsinki Declaration of the World Medical Association of 1964 and its revisions, the French or the Danish Research Law, and, in particular, the first international legally binding instrument concerning biomedical research, the European Convention on Biomedicine and Human Rights of 1997 (Oviedo Convention) and its Additional Protocol on Biomedical Research of 2005, which is accompanied by an Explanatory Report.

4 It would be naive, however, to deny the problematic role of lobbying in framing regulations. See, for example, Nuffield Council on Bioethics (2002); Macklin (2001a, 2001b).

5 The authors would like to thank Tade Matthias Spranger (Bonn) for valuable advice on the legal aspects of clinical research that he gave on several occasions during our project.

A first step was taken by the Helsinki Declaration, the leading guideline for medical research since 1964, which included the possibility of research with incompetent patients under the following conditions:

- "a legally authorised representative" had given informed consent,
- "the research is necessary to promote the health of the population represented", and
- "this research cannot instead be performed on legally competent persons". (now in § 27)

A later revision further added (in § 29) the possibility of including patients without consent, "including proxy or advance consent", however, "only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population" (World Medical Association 2008).

In the 1990s, some expert bodies[6] in Germany developed specific rules for research with patients who do not have the capacity to consent. The proposals of 1995, put forward by a group of psychiatrists and lawyers (Helmchen & Lauter 1995) triggered the 1997 statement by the Central Ethics Committee at the Federal Chamber of Physicians on "the protection of patients without competence to consent in research" (Zentrale Ethikkommission bei der Bundesärztekammer 1997). This statement divided research according to four different groups of incompetent patients: 1) medically indicated but experimental treatments with a direct potential individual benefit for participating patients themselves, i.e. single-case trials (*Heilversuche*), 2) research with at least a *future* potential individual benefit for participating patients, i.e. with respect to the further course of the disease or later relapses, 3) research with no (or at least no direct) potential individual *benefit* for participating patients, but with benefit for other patients with the same disease or condition or the same age, i.e. a so-called *group-specific benefit*, and 4) research on incompetent patients that falls outside the parameters of these defined groups, which is then deemed unacceptable.

6 Arbeitskreis "Forschungsbedarf und Einwilligungsproblematik bei psychisch Kranken" (Helmchen and Lauter 1995); Arbeitskreis medizinischer Ethikkommissionen (DÄ 1996, C 2209); Kommission für Ethik in der ärztlichen Forschung der Philipps-Universität Marburg (Freund & Heubel 1997).

Furthermore, the statement added new criteria to the existing ones for research with patients in groups 2 and 3, stipulating that such research is justified only if 1) it cannot be performed on patients *with competence* to consent, 2) it is expected to result in *essential new knowledge* on assessment, clearing up causes, preventing or treating a disease, 3) it is expected to have an *acceptable risk-benefit* ratio, 4) a legal guardian who has appropriate knowledge of the patient gives informed consent, 5) the patient does not exhibit *refusal behaviour*, 6) a competent ethics committee has given a *positive vote*, and 7) additionally for group 3 research, it must be expected to pose *no more than minimal* risks or burdens.

At the same time, in 1997, the European Council elaborated and published the Convention of Human Rights and Biomedicine (CHRB), which deals inter alia with this controversial problem through the special conditions laid out in Article 17 for research with patients who are not competent to give informed consent. In particular, paragraph 2 of Article 17[7] triggered heated public discussion.[8] Human rights activists strongly opposed the specified rule that such research can be permissible not only as research with indirect potential individual benefits for the involved patients themselves, but – even if with strict limitations and as an exception – with benefit also or only for other patients of the same age or with the same disorder or condition. In other words, there must be a group-specific benefit.

In a 2003 hearing of the Ethics Committee[9] of the German Federal Parliament, controversial positions regarding the acceptability of research with incompetent patients were again laid out in plain terms. However, the Steering Committee on Bioethics of the European Council recently delivered a Draft Additional Protocol to the Convention which, by way of exception, allows group-specific research with no more than minimal risks and burdens as additional protective criteria to all other criteria mentioned above (Council of Europe 2005).[10]

7 CHRB, Art. 17, 2: "The research has the aim of contributing [...] to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition." This broad formulation includes research as defined in groups 2 and 3 of the CEC statement mentioned above.

8 In Germany in the 1990s, this debate was highly emotional (de Wachter 1997).

9 Enquète-Kommission Ethik und Recht in der Medizin.

10 This was published in 2005 for ratification by the European member states. However, the Additional Protocol can be ratified only by states that had already signed the CHRB itself (Klinkhammer 2006). The Protocol can be downloaded from www.aerzteblatt.de/plus0405.

The Additional Protocol to the CHRB, published in 2005, dealt (in § 19) with urgently needed research with incompetent patients in *emergency* cases and called for protective criteria to be determined by law, in addition to those mentioned previously, and for arrangements to be made for cases where informed consent could not be obtained in time, even from an authorised person.

A significant public health problem is pharmaceutical research done with children, which has now been recognised, first in the US in the late 1990s and then in the European Union. To improve the health of children, special paediatric legislation and regulations have been adopted both in the US and the EU. The EU Paediatric Regulation (EU 1901/2006), which came into force in 2007, aims at increasing high-quality research into medicines for children, promoting the development and authorisation of such medicines, and improving information on medicines designed for children, while avoiding unnecessary studies on children. Children as a vulnerable population will be discussed in more detail in the following section.

Another development worth mentioning is that the protective powers of ethics committees are being strengthened.[11] In Germany, the change from having an ethics committee with a purely advisory function to one with decision-making powers increased the responsibility of ethics committees and gave their votes a binding character, while also making them liable to examination by administrative law courts. It should also be pointed out that international guidelines such as the Helsinki Declaration or the European Convention define terms relatively vaguely in order to make international compromises possible. However, allowing regional interpretations on the basis of local acceptance of such ambiguous terms impedes their standardised international use.[12] Therefore, at least for reasons of international comparison, the harmonisation and standardisation of terms and rules in major sets of guidelines would seem desirable.

11 Perhaps it would be better to leave the full responsibility for ethical conduct of research with the researcher, while the responsibility of the EC should be to evaluate the ethical arguments for conducting the research and to control its performance.

12 Even adherence to basic rules of the European Convention is not certain, as is shown by the fact that Germany as well as the United Kingdom did not sign the Convention, albeit for opposite reasons (Helmchen 2004), although the Convention states that every signatory power is obliged to adhere to the Convention's rules as a minimum but is allowed to use stronger regulations.

2 CLINICAL RESEARCH ON CHILDREN

2.1 INTRODUCTION

As we have been arguing, the inevitable tension between society's need to acquire generalisable new knowledge for improving health and the need to use some of its members as research participants is especially acute in the case of vulnerable populations. Minors (here defined as individuals less than 18 years of age) constitute a vulnerable population for several reasons. The child, by reason of its physical and mental immaturity, needs special safeguards and care, including appropriate legal protection, before as well as after birth. The normal growth, development and maturation of a child are especially vulnerable to many external factors, including diseases, malnutrition and the effects of xenobiotics such as medicines. On the other hand, it is precisely this very growth, development and maturation, which make children vulnerable, that also make it in many ways difficult or even impossible to treat children on the basis of experience and data collected from adults.

Following a history of lack of attention to the specificities of children's differences from adults, their vulnerability and special need for protection and care were finally recognised in the Convention on the Rights of the Child, adopted by the United Nations General Assembly on 20 November 1989, and ratified by most countries. Well-known therapeutic disasters of the late 1950s exclusively involving children (e. g. sulfisoxazole or chloramphenicol) dramatically demonstrated simultaneously the vulnerability of children and the need for research to understand the effects of medicines before they can be used in clinical practice.[13] These tragedies led to the development of laws and regulations that required demonstration of efficacy and safety before a medicinal product could be allowed to enter the market. They also dramatically demonstrated that children are not just small adults and that treatment of children with medicines has to take into account developmental differences and not merely the smaller size of children.

Until recently, the large majority of available medications were not approved for use by children as the appropriate studies to prove their efficacy and safety in pediatric populations had not been conducted. So, despite the right of children to enjoy the highest attainable standards of health and healthcare services, as promised by the Convention on the Rights of the Child, no child anywhere has ever had the same level of access to and quality of medicines to meet their

13 For an overview on these developments, see Ross (2006), especially chapter 1.

medical needs as adults living in similar circumstances have had. The predictable consequence has been that in industrial countries about half of all children are treated with unlicensed or "off-label" medicines.

Children are also vulnerable as research subjects because, depending on the developmental stage of their cognitive abilities, they cannot often appreciate the implications of research participation or properly weigh the risks and benefits of research procedures. Furthermore, even if they are able to fully understand all these elements, their capacity to make balanced and independent decisions is still immature, thus making them vulnerable to the risk of being manipulated by others. Especially vulnerable are children who suffer from conditions such as autism, cognitive disabilities and mood and psychotic disorders that impair their cognitive abilities, including their capacity to concentrate, apply logical thinking, or relate to others in a developmentally appropriate way. These children can be considered to carry a "double vulnerability" with respect to research participation.

The effects of a medicine, both beneficial and harmful, depend on the dose of (exposure to) the medicine, on the way a person's body handles the medicine (disposition) and on their response to it. For optimal benefit, a medicine should be given in a dose that is large enough to provide maximal therapeutic effect but low enough to avoid adverse effects. Both overdosing and underdosing should be avoided.

During a child's development, the ability in newborns to eliminate medicines is initially very low but increases rapidly to reach adult values by their first birthday. During the next few years of life (toddlerdom), the elimination of medicines actually tends to be more rapid than in adults. The decline to adult values occurs during puberty. There are some significant exceptions to this general rule, but in practice the consequence is that newborns need a dose of medicine that is smaller than an adult dose, reduced in proportion to the difference in body size. In young children, however, the dose in relation to body weight needed is, in general, larger than in adults. Giving a child medicine based on adult data, without proper information on the required dosage, is likely to lead to overdosing in newborns and small infants and underdosing in young children. While toxicity resulting from overdosing is better understood and more feared, lack of effect due to underdosing is a much more frequent, but mostly unrecognized, problem of paediatric therapy, when not based on solid data from clinical trials.

This leads to the conclusion that, although medical care of children is in good part informed by data derived from studies in adults, the specific characteristics of the developing organism can result in fundamental differences in the effects of medication and other biomedical interventions, with implications for both efficacy and safety. There are, for example, of drugs that are toxic at a particular stage of development, or that are effective in adults, but less so in children (Stephenson 2005, Vitiello 1998). The history of medicine is replete with instances of unexpected adverse reactions to therapeutics given to young children, thus documenting that the attempts of utilising exclusively adult data to inform child treatment have failed. Likewise, studies in young animals, though helpful, cannot fully substitute for research in humans. The moral foundation of child research rests therefore on the realisation that, unfortunately, there is no valid alternative to conducting research experiments directly involving children, if we want to provide safe and effective medical interventions to paediatric populations.

There is evidence that systematic research involving children has led to major advances in the treatment of serious diseases, such as child leukaemia, whose prognosis was once inevitably fatal and is now frequently favourable (Pui & Evans 2006). Remarkable, though less dramatic, progress has occurred in evaluating the efficacy, safety, pharmacokinetics, and range of therapeutic doses for paediatric use for many medications that had been originally developed for adult use. Thanks to these research efforts, children, who were once called "therapeutic orphans" due to the dearth of relevant scientific data, can now in some countries receive evidence-based treatment for a growing number of medical conditions (Hoppu et al. 2012, Roberts et al. 2003).

The importance of child research extends beyond knowing standard information about drug disposition in the body and safety. Preventive and treatment interventions early in life have a potential for benefit that is often much greater than in adult years. Basic research in the last few years has documented that many of the disorders that become evident in adult or later life have their onset at the molecular and cellular level in childhood. Conditions such as schizophrenia, mood disorders, or metabolic and cardiovascular diseases are now being reframed as developmental disorders, due to evidence that the underlying pathological mechanisms are already underway early in life, even if clinical manifestations may not appear until much later (Cannon et al. 2008). Even for Alzheimer's disease, generally considered a disease of old age, there are preliminary hints that the brain may already show specific changes early in life (Shaw et al. 2010).

The implications of such findings are multifold and raise important ethical and practical issues about the proper utilisation of this information while avoiding stigmatisation and discrimination. The findings also offer the possibility of developing early interventions that could correct pathological processes during development and, thus, fundamentally change the trajectory of illnesses and improve life-long outcomes. To achieve these goals it is necessary to conduct research involving children. Because the clinical manifestations of such illnesses have not appeared yet and some of interventions may produce adverse effects, determining the risk-benefit ratio for a particular study can be difficult and marred by uncertainty. This situation is especially challenging when an intervention is targeted at risk factors rather than a particular illness, which cannot be predicted with full certainty. For example, recent research on the prodrome of schizophrenia has identified some characteristics of youths who are at high risk of developing schizophrenia because of a combination of family history and behavioural manifestations. Both pharmacological and psychosocial interventions are being tested in this particular population in order to prevent the onset of schizophrenia. The risk of conversion to schizophrenia, however, appears to be about 35% over a two-year period, thus raising concerns about both stigmatisation and unnecessary exposure to intervention for most of these youths (Woods et al. 2009).

As their organisms are experiencing rapid development, children may be more sensitive to the adverse effects of experimental interventions. In particular, it is often difficult to estimate the possible long-term consequences of early life exposure to pharmacological or psychosocial interventions. This element of uncertainty cannot always be fully dispelled, although it can in part be compensated for by the greater potential for benefit that early interventions may entail. Indeed, if the pathological trajectory of an illness can be therapeutically modified early in life, the entire prognosis can improve, with the possibility of beneficial lifelong impacts. Thus, the vulnerability of the developing organism to medical interventions translates into both a higher risk for harm and a greater potential for benefit.

Research/clinical trials on children

Clinical trials on children are a special challenge in many ways, again strongly influenced by growth and development. The small physical size of newborns makes all interventions, including taking blood samples, challenging.

In addition, the small blood volume of a newborn severely limits the quantity safely available for sampling. These factors allow for only a minimum number of carefully planned samples to be taken and require very sensitive assay methods for analysis of samples. Meanwhile, assessment of subjective symptoms, which in adults is done through questionnaires and interviews, is not possible until a child reaches a level of development where they are able to communicate in an understandable way and express subjective feelings. A good example is the assessment of pain related to interventions or in trials of analgesics.

2.2 CHILDREN AS RESEARCH SUBJECTS

Over the years, ethical concerns about research participation of children have resulted in regulations based on three general approaches: I) ensuring that the balance between risks and potential benefits of a research project be clearly favourable to the child; II) for research projects that do not offer the expectation of a direct benefit, allowing child participation only if the risk can be considered *minimal* or no greater than a *minor increase over minimal risk*; and III) requiring in all cases permission by a competent adult with parental authority, in addition to assent from the child when this is developmentally feasible. Exceptions to these situations can be entertained, but are subject to higher levels of scrutiny and review.

Similarities between the US and European principles and regulations indicate that there is substantial agreement among experts in bioethics and research. However, although the fundamental principles upon which the current regulatory approach to child research rests are generally accepted as ethically sound, and no practically valid alternatives have been proposed, there has been an ongoing debate as to how to interpret and apply the regulations to specific research projects. In particular, determining whether a research procedure involves only minimal risk, a minor increase over minimal risk, or more than a minor increase over minimal risk can result in significant variability, even among experts. The need to develop more effective diagnostic and therapeutic interventions for children is urgent, and advances in genetics and other basic biomedical disciplines can provide new opportunities for clinical research. It appears, therefore, timely to analyse the scientific, bioethical, and regulatory premises of child participation in research.

The workgroup presenting the present memorandum has conducted an interdisciplinary review of current ethical and regulatory approaches to child research participation with the aim of acquiring a better understanding of current needs and identifying strategies for improving both the scientific and ethical value of paediatric research. Our analysis has been articulated in sequential steps regarding topics such as rationales for direct child participation in research, the need for scientific rigor in selecting research studies, and the practical circumstances under which child participation can be considered ethically acceptable, which will be elaborated on in the following subsections.

2.3 WHEN IS RESEARCH IN MINORS JUSTIFIABLE?

Human research should be employed when it is necessary for acquiring important knowledge to understand, treat, or prevent illness and so to advance human health (Emanuel et al. 2000). If potential knowledge is not important or can be obtained through non-human research, such as research in vitro or using animals, it becomes difficult to justify experiments using humans. These general principles are even more relevant in the case of child research participation. The importance of posing relevant research questions is, therefore, a critical element for ethics determination. In fact, if a research project is merely driven by commercial purposes and does not address a clinically significant need, enrolment of children becomes ethically questionable, especially if the research participation involves the risk of adverse effects. In practical terms, such a situation may arise in the case of me-too drugs, that is, in the development of compounds that duplicate already available medications with no prospect of innovation or significant improvement.

If the research question is deemed to be indeed important, the next ethical requirement is that the research methods be scientifically valid in order to meet the aims of a study. An implication of this is that science and ethics are inextricably linked in justifying a research project. Research on children should be allowed only when it can be expected that the study design and methods are likely to deliver informative and significant results. Unfortunately, this does not always happen, as shown by a number of studies that are too small in sample size or whose methods are too limited to be truly informative.

In any case, the risks of participation must be deemed acceptable. In order to make such a determination, current regulations distinguish between research

with a prospect of direct benefit to participants and that which does not offer such a prospect. "Prospect" here means a concrete probability or likelihood of benefit and not a distant, unlikely possibility. A "direct" benefit is a specific health benefit that accrues to a child as a consequence of their exposure to research procedures. A general feeling of satisfaction at having contributed to research and helping scientific progress does not count as a direct benefit. Determining whether a particular study offers a prospect of direct benefit is typically made at study entry. A study that randomises children to receive treatment or no treatment can be considered to offer a potential benefit to each participant, because each participant has a chance of receiving treatment. However, alternative interpretations of this understanding are in evidence. In fact, in general there is considerable variation among ethical committees reviewing the same protocols (Stark et al. 2010, Sha et al. 2004).

Determining whether a risk-benefit ratio is favourable to children participating in research is another area where ethical committees and experts can disagree with regard to specific projects. In fact, a number of elements can contribute to the risk factors of a particular study, and these are not solely limited to the actual risks of research interventions and procedures. It must be taken into account that children entering a research protocol may give up, at least temporarily, the opportunity of receiving alternative, potentially beneficial treatments. Thus, the impact of restricting therapeutic options for the duration of research participation is an important factor to take into account.

Research without the prospect of direct benefit to participants generally includes research to better understand the normal or abnormal biological structures or mechanisms of the human body and its functioning. Usually, this type of research does not generate information that is immediately useful to the research participant. Exceptions can apply when specific conditions may be diagnosed or more precisely characterised so that more targeted therapeutic interventions can be applied. However, if no direct benefit to the research participants can be anticipated, the ethical acceptability of a research project depends on whether the risk is considered within the limits of "minimal risk" or, for research that is specifically relevant to the medical condition of the participant, "no greater than a minor increase of minimal risk". Minimal risks are, in such cases, usually defined as being no greater than those normally encountered in daily life or during routine physical or psychological examinations or tests of a healthy child. These determinations require a great deal of interpretation, and there is ongoing debate about how to define minimal risk standards vis-à-vis other risks commonly encountered

in daily life (Wendler et al. 2005). As "ordinary life" varies substantially across the global spectrum of cultural and socio-economic contexts, the boundaries of "minimal risk" can either present substantial variability or represent an idealised, context-independent concept. While indexing minimal risk to ordinary life may look like a pragmatic and practical approach, this interpretation has been criticised as being insufficient for research risk determination (Ross & Nelson 2006).

2.4 ETHICAL IMPLEMENTATION OF CHILD RESEARCH

The foundation of biomedical research ethics lies upon the core principles of beneficence, justice and autonomy, which inform the actual implementation of research projects deemed to be scientifically valid and appropriate for child participation (Koelch & Fegert 2010). Paediatric research is necessary for improving child health, but conducting research on children is more challenging than on adults, and this difficulty results in a shortage of children participating in research – a factor that significantly limits progress (Caldwell et al. 2004).

Parental informed consent

An essential requirement for child research participation is parental permission, which is formally documented by signed, informed consent. For informed consent to occur, it is necessary that the relevant information be provided in accessible language and that the information be received, processed and retained by the intended user. Traditionally, researchers and ethical committees have focused on the comprehensiveness of the consent form by making sure that it contains all important information about the voluntariness of research participation, research risks, and alternatives. Less attention has been paid to ensuring that this information is actually understood by those digesting it (Tait et al. 2003, Vitiello 2008).

Research has documented that, if adequate time is spent by researchers to explain the aims and procedures of a study, parents can reach a sufficient level of understanding to make properly considered decisions about it (van Stuijvenberg et al. 1998, Vitiello et al. 2005, Vitiello et al. 2007). Not surprisingly, the higher the educational background of the parent, the greater the level of understanding. Consistent with data regarding adult research, in child research there is also evidence that parents have difficulties appreciating that treatment research differs from clinical care, in that it has to follow protocols that usually constrain

individualised care. Parents, like adults participating in research, tend to inaccurately attribute therapeutic intent to research ("therapeutic misconception") (Vitiello et al. 2005 and 2007).

The availability and comprehensiveness of information and the capacity to understand it are prerequisite for informed consent, but not sufficient. A prospective research participant, or the parent(s) or caregiver(s) in the case of children, must process information logically; evaluate potential benefits and risks of research participation, including with respect to possible alternatives; and make an independent decision without undue influence from others or external circumstances. For these reasons, evaluating capacity for informed consent is quite a complex process. Specific assessment instruments have been, however, developed and are being tested for validity and feasibility (Koelch et al. 2010).

Child informed assent

In addition to parental permission, ethical standards and current regulations require that childen – when possible in light of of their level of cognitive development – be explained the purposes and procedures of a study, together with the basic rights of research participants, and be asked to provide assent for participation. In the absence of cognitive disabilities, most children aged seven or above are able to understand many, if not necessarily all, of the aspects of research and, thus, can express their opinion on them (Whittle et al. 2004). Such a perspective recognises that the capacity of a child to give assent is not an all-or-nothing condition, but rather exists along a continuum, with greater understanding accruing as the child grows. Although girls develop, on average, an earlier capacity for understanding and retaining research-relevant information (Vitiello et al. 2007), existing data indicate that, by age 16, most youths of both sexes are able to understand and retain as much information about research participation as their parents. It remains, however, to be determined whether adolescents can properly process such information and use it for independent decision-making.[14]

14 The *Arbeitskreis Medizinische Ethik-Kommissionen* has drawn up a proposal for informing and obtaining the informed consent of children and young people, which can serve as a model solution for research (www.ak-med-ethik-komm.de).

Choosing research designs and methods that minimise risk

Research design and assessment methods strongly influence the potential balance of benefits and risks. Designs that minimise exposure of participants to potentially ineffective interventions are, consequently, clearly preferable. In this context, the issue of placebo use has been the subject of an ongoing and lively debate.

Recognising and managing conflict of interest

Much of pharmacological research, on both adults and children, is funded by pharmaceutical companies, which have a financial interest in showing that their products are effective and safe. Hence, there can be an intrinsic risk of conflict of interest in such research. Indeed, there is evidence that industry-sponsored treatment studies are more likely to report favourable outcomes (Turner et al. 2008). Especially troublesome are particular instances where certain sponsoring companies have not published negative results of studies on antidepressants in children that did not support their claims of efficacy and safety (Whittington et al. 2004). Such practices are clearly a serious threat to the ethical integrity of research activities and represent a violation of the duty that researchers have towards research participants and society at large to pursue scientific aims, unfettered by financial concerns. When research participants are children, it is especially important to ensure that all potential conflicts of interest are properly identified and managed.

Recently, both regulatory agencies and scientific editors have taken a number of corrective actions against such potential research abuses. All clinical trials funded for regulatory purposes must be registered and summaries of results made public. In parallel, most journals now require that clinical trials being reported must be registered in a public database (Zarin & Tse 2008). While these corrective actions are very likely to have positive impacts, the databases of many clinical studies remain "proprietary", meaning that they are owned by their sponsor(s), which are often pharmaceutical companies. Thus, the question arises as to whether it is ethically justifiable to expose vulnerable populations, such as children, to research procedures for generating privately owned data that may not be accessible to all researchers. Data sharing among researchers has become a common requirement for publicly funded research. Arguably, this should also be considered for privately funded clinical research, at least when it is based on the participation of vulnerable populations.

3 CLINICAL RESEARCH ON THE MENTALLY ILL

Mental disorders may undermine the basic prerequisite of conducting research with humans: the capacity to give informed consent to participation in research projects (Helmchen 2013). Therefore, clinical research in patients with mental disorders encounters two major problems:[15] 1) protection of incompetent[16] patients and 2) assessment of capacity to consent.

3.1 PROTECTION OF INCOMPETENT PATIENTS

The public debate on research with vulnerable people has been dominated by a concern that human dignity and autonomy are being violated by instrumentalising incompetent mentally ill people for research, using people who are viewed as vulnerable due to their incapacity to defend their own rights.[17] However, there are also good reasons for conducting research on such patients, particularly those with new morbid states, such as apallic syndromes, or with an increasing number of states such as emergency cases in need of intensive care or demented patients.[18] Such reasons are based on adhering to the principle of welfare by developing or optimising therapies, in conjunction with the principle not harming patients through unproven measures, that is, through non-evidence-based treatments (Rittner 2007). Therefore, for all cases, each medical consideration regarding research with such incompetent patients is imperatively interwoven with ethical questions. The following sections discuss some key proposals for solving this dilemma.

15 These considerations are based on i) Helmchen (2002); ii) Helmchen (2005), iii) a systematic PubMed search and evaluation of the scientific literature for three years (2005–2007/8), including recent analyses and reviews (Helmchen 2012, Petrila 2006, Saks & Jeste 2006, Vollmann & Winau 1996).

16 In the following, the term "incompetent" explicitly does not mean handicapped but rather has the specific meaning of incompetence to give informed consent.

17 A positive definition of vulnerability as "unconditional obligation of rescue with the best possible methods" is an exception in the literature (Rittner 2007).

18 Demographic change, with a sharp increase in the numbers of elderly people and the particular frequency of dementia became major reasons for discussing the inherent ethical problems of research with such vulnerable patients, beginning in the 1980s and leading to the development of rules to deal with these problems (Helmchen et al. 1989, Hodge 1989, Kendell 1989, Langley 1989, Levine 1986).

3.2 ASSESSMENT OF CAPACITY TO CONSENT IN THE MENTALLY ILL

The range of the problem: Capacity to consent is impaired particularly frequently in cases of severe mental illness; this is, however, the very area of mental disorders having an especially strong need for research to improve the deplorable fate of its victims. Incapacity to consent can also be caused by a wide range of medical or somatic diseases, disorders and conditions (Palmer et al. 2005, Vollmann et al. 2003)[19] and can be impaired transiently or persistently depending on the state of the respective disease.[20] Pars pro toto emergency cases are also included here, such as acute cardiovascular insults, poisoning, polytraumata or severe brain injuries, for example, following a stroke (especially if it has caused aphasia), mostly in patients treated in intensive care units.

Although states of incompetence can be associated with many medical conditions, the following order of selected diagnoses reflects the different frequencies – coma > dementia > schizophrenia > depression and minor mental disorders > other somatic diseases (Appelbaum 2006, Vollmann et al. 2003) – capacity to consent must be assessed in each individual case, because this capacity depends mainly on individual characteristics and the stage and severity of disease.

Lack of standardised and practicable instruments: In contrast to the logical procedure, historical events developed in reverse order: First rules to protect incompetent subjects from being potentially harmed during research were developed, and then the process of assessing competence to give consent has gained importance over the past few years.[21] The reason for this is that, from a theoretical point of view, construing competence had seemed to be a clear procedure, whereas the protection of human beings in research activities has always been problematic, because progress in modern medicine is based on research (Helmchen & Winau 1986). However, the more medical research expanded to also include patients with questionable or no competence to consent, the more the practical problems of assessing this competence became evident.[22]

19 Because the respective problems regarding minors will be dealt with elsewhere, we will confine our argument to corresponding questions for adults.

20 "Across diagnoses, cognitive capacity, physical functioning, and a diagnosis of mental illness have the greatest impact on decision-making capacity, with level of education also having an impact." (Candilis et al. 2008, p. 350).

21 D.C. Marson, a leading author in the specialist field of consent assessment, proposes "an enormous intergenerational transfer of wealth" as a reason for "the greatly expanded incidence and importance of capacity assessment of older adults", e.g. for questioning the capacity to make a valid last will (Moye & Marson 2007).

22 An indication of this late development may be that the only corresponding remark in the

Being able to correctly assess competence to consent is ethically relevant, because incorrect estimation can either lead to questionable consent being given by an incompetent patient or can end up discriminating against a competent patient by denying him/her the right to participate. However, the technique currently used is only a more or less rough clinical estimation based on impressions. At best, the patient will be asked for him/her *understanding* of the information they were given about a planned research project, meaning here to repeat in him/her own words what will be done (aim, procedure, expected benefits and risks), why it will be done (rationale) and what it means for him/her (appreciation). At present, standardised tests such as the McArthur Test Battery are time-consuming and insufficient in their specificity (Vollmann et al. 2003, Breden & Vollmann 2004). Moreover, there is little agreement regarding different instruments for evaluating capacity to consent (Guerra et al. 2007), though at present instruments for quick assessment are under development which should be able to be performed in five minutes.[23]

Consequences: There are at least two methods in use to overcome the difficulties of competence assessment in research with possibly incompetent patients:

- changing the threshold for accepting given consent as valid and
- differentiating types of consent according to specific research projects.

Both ways of dealing with competence assessment, which have been validated through empirical investigation of various elements of the consent procedure, will now be discussed in more detail.

1. *Changing the threshold for accepting given consent as valid:* A characteristic of the first method is related to the general statement included in scientific publications that all participants have given (written) informed consent, though the

Additional Protocol of the CHRB can be found in Article 14, paragraphe 3: "Where the capacity of the person to give informed consent is in doubt, arrangements shall be in place to verify whether or not the person has such capacity." The corresponding number 79 of the Explanatory Report states that it is the responsibility of researchers to report to the ethics committee how they will examine capacity. But no practicable test of capacity is available, and almost no scientific publication gives information on how capacity to consent was assessed. Therefore, a leading author in the field seems to be right when he states: "Assessment of decision-making capacity in older adults is an emerging area of practice and research" and has "become a distinct field of study" (Moye & Marson 2007).

23 University of California San Diego Brief Assessment of Capacity to Consent (UBACC) (Jeste et al. 2007); Capacity to Consent to Treatment Instrument (CCTI) (Okonkwo et al. 2007, Duron et al. 2013).

procedure for assessing competence is very rarely described. Therefore, it usually remains unclear whether competence to consent has been validly assessed. Even recent publications on research with dementia patients give as their only specification that the patients had "mild or moderate" states of dementia as well as sometimes providing the range of the MMSE score being, for example, 16–26 (Hock et al. 2003). However, a "mild or moderate" state of dementia says almost nothing about the capacity to consent of an individual patient, and in patients with MMSE scores below 20 there is doubt about their capacity (Karlawish et al. 2005), and this should be tested specifically. The results of specific investigations into the validity of consent are in line with such doubts.

Such examples could be assumed to result from a change of definitions or thresholds.[24] In particular, the threshold for assuming lack of capacity to consent may have been changed: either moved upwards, with the result of accepting an only questionable or impaired capacity as valid, or moved downwards, meaning impairment of capacity may be assumed, with the consequence of appointing a legal guardian for a competent person. This potential for changing the threshold calls for more empirical research in order to control the validity of routinely assessed capacity to consent.

Even if demented patients who are probably incompetent have agreed to what has been proposed to them, caution should be taken in interpreting this as assent, not least because, as some studies have revealed, of the role of the emotional and social dimensions of informed consent (Sugarman et al. 2007), meaning that a patient's decision may be influenced by the situational context (Hellström et al. 2007).

Therefore, it would be more transparent and ethically acceptable if, in accord with high standards of competence, possibly or probably incompetent patients were to be declared incompetent and studies be performed under the protective premise of obtaining consent not only from the patient – in the form of assent or only as acquiescence – but also from an authorised person. However, as is the case in Germany, judges can refuse to appoint a legal guardian for a research intervention with no direct potential individual benefit, in compliance with the law that such guardians (*Betreuer*) only have the competence to act exclusively in the best interest of the individual patient. A simpler, but to date scarcely used,

24 In the hearing of the Federal Parliament mentioned above, there was a question about the danger that exclusively group-specific research would be declared to be a therapeutic trial.

means of obtaining consent is for competent patients themselves to authorise a person having their confidence for later decisions (i.e. if they become incompetent) concerning research.

2. *Differentiating types of consent:* An alternative method differentiates consent in terms of 2.1) specific research questions and 2.2) various standards of consent, while also seeking to assess 2.3) validity of consent. Empirical findings in this domain include the following:

2.1 *Consent specificity:* Capacity to consent is not absolute but only relative to the point in question; that is, it may exist with regard to one topic but not to another at the same time in the same person. Furthermore, it is not a stable feature of a person but may change over time. Therefore, it is crucial to obtain consent for participation in a concretely formulated research project, and it must be valid here and now. Since mental abilities are not static, enhancement of the patient's capacity is a reasonable aim (see 4.i). Some authors emphasise the clinical experience that capacity to consent may be related to the specifics of a research project, such as treatment of acute stroke, elective cataract surgery on demented or geriatric patients,[25] or regarding dementia. Demented patients incapable of giving independent consent themselves may be deemed capable of appointing a proxy regarding research consent.xxvii Correspondingly, it was found that laypersons at risk of dementia support surrogate consent for research (Kim et al. 2005).

2.2 *Consent standards:* Analysis of the consent process has revealed differences in both the quality and expression of consent. Major components of consent are evidencing a choice, understanding, reasoning, and appreciating information (Grisso & Appelbaum 1995, Helmchen 1995, Vollmann 2000). Evidencing a choice is considered a minor standard, whereas understanding represents a major standard. If all of these abilities exist simultaneously, then the person is considered to be at the highest standard. Furthermore, there is flexible gradation among the various forms of evidencing a choice,

25 "Laypersons at heightened risk of Alzheimer's disease discriminate among research scenarios of varying risks and burdens. They are supportive of surrogate consent-based research even when risks and burdens are significant to the subjects; these opinions appear to be based in part on their assessment of risks as well as on their general attitude toward biomedical research." (Kim SYH et al. 2005, p. 1395) Kim et al. proposed "a rationale for assessing the capacity to appoint a proxy and then described a novel interview instrument for assessing the capacity to appoint a proxy for research consent" (Kim & Appelbaum 2006, p. 469).

including consent as an informed autonomous decision, assent as adherence to a proposal, acquiescence as tacit agreement, or lack of refusal.

Applying the highest standard of consent would eliminate a great portion of the mentally ill as potential probands as well as many potential probands with other medical diseases and even some healthy persons, or would require a legal guardian for them to consent to research. Therefore, a question should be raised concerning which standard of evidencing a choice is appropriate, especially with regard to the risk-benefit ratio of a research project. Lower standards of consent are presumably implicitly and frequently used in clinical practice. However, ethically it is preferable to determine explicitly for each research project which standard of consent would be ethically acceptable, such as a lower standard being appropriate only in minimal risk studies.

2.3 *Consent validity:* All sources of consent may be flawed: the patients themselves, their advance directives, or authorised persons. Comparing this state of affairs with the example given above involving persons with increased risk of dementia authorising others to give consent to participate in research (Kim et al. 2005), it is worth considering how accurately such investigations represent real situations.

Measures to improve the validity of consent: In order to meet the highest standard of full capacity to consent, various procedures have been investigated to 1) improve impaired capacity, 2) substitute it through an advance directive, or 3) substitute it via valid consent of a proxy.

1. Enhancing patient capacity to consent: According to Ritchie & Portet, "[p]ersons with cognitive dysfunction are commonly excluded from making decisions about the implementation of cognition-enhancing treatments although they wish to do so" (2006, p. 570). Various procedures for enhancing capacity to consent have been proven to be efficacious (Flory & Emanuel 2004), not only in cases of schizophrenia (Appelbaum 2006, Carpenter et al. 2000) but also dementia (Mittal et al. 2007). For example, the procedure of "experienced consent", meaning patients experiencing research by participating in a one-week try-out, has been seen as promising (Welie & Berghmans 2006). However, a systematic review of 42 trials using this method yielded "only limited success. Having a study team member or a neutral educator spend more time talking one-to-one to study participants

appears the most effective available way of improving research participants' understanding; however; further research is needed" (Flory & Emanuel 2004, p. 1593). One study found that contextualised cognitive training "improved cognitive abilities specific to the abilities trained and continued five years after the initiation of the intervention" (Willis et al. 2006, p. 2805).

2. Advance directives: Advance directives with regard to research are feasible but perhaps do not assist the consent decisions of a patient or proxy (Stocking et al. 2007). They are apparently scarcely used though they are recommended (Korczyn 2007). Consequently, "three major international documents on medical research – the CHRB (ETS 164), its Additional Protocol (ETS 195), and Directive 2001/20/EC on Clinical Trials on Medicinal Products– give conflicting messages on the legal status of advance directives in medical research" (Lötjönen 2006, p. 235; FEAM, 12.05.2011).

3. Educating authorised persons:[26] Clinical scientists "must be prepared to educate patients and family members about dementia and research, determine each potential subject's competence to consent, and ensure that decisions about participation are in accordance with the best interests of the subject. Ethical conduct of clinical trials of new antidementia therapies will require that everyone involved understands the values and beliefs that guide their decision-making and the potentially conflicting roles facing the clinician-scientist" (Fisk 2007, p. S32).

This is important because "proxies […] themselves have biases about their loved ones and their potential for participating in research" (Beattie 2007, p. 27), and there seems to be "poor agreement between the decisions made by surrogates and patients." It is also said that "[s]urrogates' decisions would have resulted in the patients having far more treatment than the patients would have wanted" (Li et al. 2007, p. 46). Consequently, "[f]urther study is needed on measures such as facilitated discussions, advance directives and the difficulties that surrogates face, in order to improve the accuracy of surrogates' decisions and respect of patients' autonomy" (Li et al. 2007, p. 46).

The role of spouses of persons with dementia as potentially responsible gatekeepers for excluding people with dementia from participating in research needs further consideration, "with particular reference to the appropriateness of viewing consent as a primarily cognitive, universalistic and exclusionary event

26 Next of kin, authorised proxies, legal guardians.

as opposed to a more particularistic, inclusive and context relevant process" (Hellström et al. 2007, p. 608).

In addition, it should be mentioned that interviews with caregivers about ethical concerns concerning drug treatment in dementia patients showed that "problematic consequences of an early diagnosis and the creation of unreasonable hope did not appear" and "problems concerning rising awareness of cognitive decline were not found" (Huizing et al. 2006, p. 869).

All of these measures have yielded conflicting results and are in need of further empirical as well as theoretical research. However, one consequence is clear: the implementation of each of these measures demands time on the part of personnel.

4 CLINICAL RESEARCH IN CRITICALLY ILL PATIENTS

4.1 INTRODUCTION

Critical illness is an acute and unexpected life-threatening event caused mainly by severe infections and sepsis, organ failure, stroke, cerebral bleeding, neurological disorders, trauma through accident or burn, and complications after surgery or medical treatment. Intensive care medicine has become the key issue in the treatment of critical illness. Nowadays, hospital deaths occur in most cases in the intensive care unit (ICU). Thus, from an epidemiological and economical healthcare point of view, critical illness and severe sepsis have to be considered important topics to be addressed. Convincing and experimentally proven concepts have shown the gut to be a the potential origin of systemic inflammation and sepsis and a starter for the development of multiple organ failure. There is, however, a considerable gap between concepts and evidence-based interventions. Further research is needed in order to narrow this gap and improve patient outcomes. Treatment of critical illness remains controversial and has not seen significant improvement over the past decade. From the perspective of the healthcare system, it is mandatory that the treatment of critical illness should be based on high-quality medical care (Weimann et al. 2013).

In most intensive-care studies, the inclusion of a patient has to occur within 24 to 72 hours of the onset of acute critical illness. Regarding the design and protocol of a study, this is a reasonable procedure, because in the case of a highly inflammatory life-threatening disease, a longer delay in treatment intervention might hide potential beneficial effects. At this stage, the critically ill patient is usually unconscious, narcotised on a ventilator, and therefore unable to give informed consent. Inclusion of these patients is possible only when permission is given by a legally authorised representative.

4.2 CONSENT SUBSTITUTES

In Germany, a legal representative has to be assigned by law. This means that German law does not per se foresee the spouse, children or relatives of a critically ill patient becoming a representative for informed consent. In most cases, there is neither previous assignment of a representative by patients themselves nor documented willingness to be included in clinical trials. Therefore, a legal representative has to be officially assigned by a special court (*Betreuungsgericht*).

Usually, this procedure takes more than 72 hours and, therefore, presents an obstacle for the inclusion of participants. Local courts have no standard procedure for "fast tracking" this process, especially concerning cases of potential inclusion in clinical trials. Consequently, a legal representative is not always available to sign an informed consent form (ICF) within the deadline for enrolling a patient. It is common practice in many medical centres to already begin with a study, indicating the date on a fax sent to the court to request approval from the relative or independent physician as the start date for permission to participate. In this way, the ICF may be signed before the court has officially approved the legal representative. Some local courts indicate that it is possible to run a study and include patients. However, no official document from the court is made available to confirm this procedure. Another option is to request approval from a local ethical committee to start conducting a study when it is evident that approval of a court will not be received in time. It is our view that inclusion in a study should be in the interest of patients and in agreement with their potential willingness. This should be anticipated even in cases where an intervention is not lifesaving but just a beneficial side effect in a treatment bundle aimed at curing a patient. Taking the assumed interest of patients in receiving improved treatment into account, the practice in some institutions of sending a fax to the local court requesting assignment of a representative as quickly as possible seems to us to be more than is actually required.[27] Next to gaining approval from an ethical review board, the "Heidelberg Procedure", which was developed for acute stroke patients, prescribes early informing of local courts about research trials and protocols. This may be considered a proposal for informal means of cooperation with regard to the inclusion of patients into clinical trials.

It is our view that inclusion in a clinical study may also be justified if the intervention is not lifesaving but does contain the likelihood of a beneficial side effect in a treatment plan aimed at curing the patient. Balancing the benefit risk and burden for the patient is part of what is considered during the review by the Research Ethics Board.

27 Compare, for example, Erwin Deutsch's comment on the German Drug Law (AMG), 3rd ed. 2010, p. 448: "Potential willingness of a patient with severe disease may be anticipated, if the clinical trial offers the chance of curative treatment."

4.3 PSYCHOLOGICAL BARRIERS

There are several psychological barriers that can inhibit patient inclusion. Identifying suitable candidates for a study in accordance with inclusion criteria clearly requires the commitment of intensive care unit staff physicians and can depend on their personal convictions concerning clinical research in intensive care patients. If staff members conducting research lack motivation, they will simply not consider enrolling a patient. Furthermore, inclusion criteria may be misinterpreted, and inclusion times may be exceeded. An additional aspect is an increase in workload, starting with a difficult conversation with a patient's relative representative, who has first of all to be informed about a life-threatening situation. In cases of life-threatening illnesses, there may be a psychological barrier to raising the issue of participation and informed consent for a clinical trial at the same time. However, communication of this kind is essential for informed consent. The quality of such discussions is crucial and will depend on a physician's personal convictions regarding the importance of a study and his or her capacity to convey the necessary information in a trustworthy way to the patient's representative. If the physician fails to inspire confidence in the medical treatment added by a study intervention, informed consent is not likely to be obtained. Moreover, it is very difficult to explain to laypersons the scientific principle of randomisation. If there is a potential benefit with calculable risk through an intervention, the control group will find it hard to accept its role as being random. A further obstacle is that patients' personal convictions and beliefs with regard to clinical research are very often unknown. In most cases, the question of being included in a prospective randomised clinical trial (PRCT) will not have been previously discussed in a family or with representatives assigned by a patient. Written information may be very complex (or even incomprehensible) for laypersons, and there is not really sufficient time for consideration before informed consent has to be given. Though it is widely agreed that coercion or undue pressure on patients or their representatives is not acceptable, in practice it is not easy to avoid any psychological pressure concerning the decision to be made *and* the need to include the patient within the required timeframe. Special training in communication may help to prepare staff physicians for this difficult task.

Most dropouts from studies occur through formal violations of established protocol, starting in the inclusion period. At times this is due to the problem of staff members being inadequately informed about the details of a protocol, especially when a study nurse is not available. The risk of violating a protocol is considerably higher in case of low inclusion rates, which may occur in multicentre trials.

In order to avoid dropouts, continuous briefings and updates from local clinical investigators and staff are essential. The support of a study nurse is a basic requirement and minimises the risk of violating a protocol. Ideally, this nurse should be completely familiar with the staff and with specific standards and procedures. As mentioned previously, the extra workload involved may act as an obstacle for ward physicians, given their already limited time resources when on duty. There may also be personal limitations and barriers concerning the issue of inclusion in a study when communicating with patient family members, surrogates, or advocates. In multicentre trials, a ward physician usually does not receive any personal scientific or material appreciation. In most cases, only the clinical investigator – very often the head of department – will be listed as a co-author in published results. For the staff physician, non-material incentives could include appreciation of the attending and head of department – usually the local investigator – in view of prospects, for example, for their academic careers or co-authorship. Financial bonuses are likely to considerably motivate staff physicians or whole teams. Incentives schemes should be further discussed, though there is widespread moral concern about abuse in this domain.

The potential benefits of a study for a participant should be unequivocal. As explained above, it may be hard to explain the principle of randomisation to an assigned surrogate. On the other hand, the potential extra workload, involving procedures that are not part of daily work, for example, the special preparation of study drugs or lab chemistry at the weekend, may also considerably inhibit participant recruitment. It is recommended that ethical review boards require from applicants that a budget for this extra workload be available before approving a study.

In 2008, supported by the German Federal Ministry of Education and Research (BMBF), a network of coordination centres (KKS) for the organisation of clinical research was established in Germany. By 2014, 18 centres were collaborating in the network, all of them located at university hospitals. A special focus of the University of Leipzig Centre for Clinical Studies is a special partnership with affiliated academic hospitals in order to organize research activities and to facilitate participation of major community hospitals in multicentre trials. The Centre for Clinical Studies (*Zentrum für Klinische Studien,* ZKS) holds training courses for physicians and study nurses several times a year. In winter 2010/2011, a new MSc degree course for Clinical Research and Translational Medicine has been started.

5 FROM PROTECTION BY EXCLUSION TO PROTECTION BY INCLUSION: RECOMMENDATIONS FOR SHIFTING THE EMPHASIS OF CLINICAL RESEARCH TO THE BENEFIT OF VULNERABLE POPULATIONS

In the 1960s and 70s, severe incidents involving unexpected side effects from pharmaceuticals revealed grave shortcomings in the standards of clinical drug research. In several of these incidents, children were the prime victims. As a reaction to these events, a moral and regulatory framework for clinical research with human subjects was developed, the central principle of which was and still is that any research procedure requires informed consent of test persons. Naturally, many individuals from vulnerable populations, such as children, the mentally ill, or intensive care patients, cannot give consent or can do so only to a limited degree. The difficulties of obtaining informed consent in vulnerable populations and the high level of protection they require has led to disproportionally less clinical research being produced for vulnerable populations than for the majority of patients with non-limited capacity to consent.

Though proper protection of vulnerable populations is without question mandatory, it appears that the strong focus on preventing harm has been realised mainly by setting high standards for the enrolment of such populations in clinical research projects. But the result has been a considerably less than satisfactory therapeutic situation for vulnerable populations in comparison with that for the non-vulnerable majority.

It is our hope that, through a careful and responsible evolution of existing frameworks of clinical research, the current tendency to protect vulnerable populations by excluding them from clinical research might eventually shift towards offering better protection to these patients by including them in research projects, thereby letting vulnerable populations benefit from medical progress more than has been the case so far.

5.1 SOCIETIES ARE MORALLY OBLIGED TO IMPROVE THE UNSATISFACTORY THERAPEUTIC SITUATION OF VULNERABLE POPULATIONS.

It does not need much argument to see that the implementation of a healthcare system should not be limited to providing currently existing remedies but should also include research strategies for improving healthcare to cover currently

unmet health needs. *We assume, therefore, an entitlement to evidence-based state-of-the-art disease management and not only to state-of-the-art standard therapies, based on empirical experience.* Consequently, as a matter of justice, vulnerable populations are also entitled to treatment to cover their healthcare needs through appropriate healthcare interventions, including medicines that have been shown to meet the generally accepted (scientific/regulatory) criteria of safety, efficacy and quality. However, in comparison to the therapeutic situation for other patient groups, vulnerable populations are substantially underprivileged. Our argument so far comes down to the claim that *our societies have a moral obligation to find ways to safeguard health research for vulnerable populations.* In the US and Europe, this situation is reflected in current legal regulation on orphan drugs and paediatric research.

5.2 ASSESSMENT TOOLS FOR DETERMINING THE CAPACITY TO CONSENT OF PROSPECTIVE TEST PERSONS ARE UNDERDEVELOPED AND NEED IMPROVEMENT.

Many test persons from vulnerable populations are limited in their capacity to consent. Enrolling such patients in research efforts must include attempts to obtain their consent or assent or, in cases of incapacity, the consent of legally authorised persons (parents or legal guardians). Assessment tools can help to achieve greater participation. However, there is still a lack of scientifically proven and practicable standardised tests, which needs to be overcome by further research.[28]

5.3 THE LIKELY BENEFIT OF RESEARCH PROJECTS IN COMPARISON TO EXISTING THERAPIES SHOULD BE MORE CRITICALLY ASSESSED.

The scientific quality of research design in vulnerable populations is at present rigorously controlled by licensing authorities and ethics committees. This stringent control is, amongst other things, especially important if a pool of potential research participants is too small to be able to carry out all proposed research studies in a particular domain. (This is, for example, the case in child and adolescent psychiatry.) There are, however, persistent concerns related to studies testing

28 The goal should not be seen as ending up with just one "master test". A plurality of situation- and/or patient-specific tests would probably be more adequate.

so-called "me-too" drugs, that is, pharmaceutical compounds that are slightly altered versions of drugs already marketed successfully by competing companies. In view of the limited availability of test persons from some vulnerable populations, it is problematic when research projects aimed at developing new therapies have to compete with research projects duplicating already established therapies. Though it seems that licensing authorities and ethics committees are attentive to this problem and frequently do not accept such studies, we would like to emphasise that very careful reasoning for new clinical research studies is of utmost importance in view of limited patient populations: not specifically qualified research interventions should be avoided.

5.4 ADVANCE DIRECTIVES

Mentally ill patients who have still maintained (e.g. in early stages of neurodegenerative diseases) or regained the capacity to consent after an episode of illness should be encouraged to draw up an advance directive for medical interventions, including possible participation in a research project.

5.5 RISK-BENEFIT EVALUATION IS DIFFICULT AND MARRED BY UNDERDEVELOPED METHODS AND UNCERTAINTY.

Benefits and risks are often undefined legal terms and should be explicitly defined in as clear terms as possible in each specific research design. Moreover, it would be advisable to develop and implement structured procedures that would help to make these evaluations more transparent and reliable (Hüppe & Raspe 2011).

In view of the uncertainties of risk-benefit assessments, safe validation of consent could be ensured by following a three-step evaluation of the requirement of acceptability of potential risks and burdens in relation to the expected benefits of a research intervention (Helmchen in press):

First, researchers must give reasons as to why they consider the relationship of risks and burdens of their planned research interventions to be acceptable, here meaning reasonable and justified.

Second, *research ethics committees* need to evaluate this relationship with regard to existing legal and ethical norms and professional expertise, and they should give reasons – at least in research studies with vulnerable subjects – not only when rejecting research applications, but also when accepting them, particularly concerning the ethical considerations of the applying researcher(s).

Third, potential *research participants* or their legal guardians have to evaluate the institutionally approved set of potential risks, burdens, and inconveniencies in relationship to the expected benefits of a research study in light of their own personal idiosyncrasies, interests and values. If they find the relationship individually acceptable, then they may consent to participate.

5.6 EDUCATING RESEARCHERS

Researchers, as well as medical students and patient groups, should be educated systematically on the ethical implications of clinical research. All regulations should be observed thoroughly in order to not lose the trust of either research participants or the general public in the validity of research, which is a basic requirement for successful recruitment of vulnerable individuals. Moreover, it might be advisable to engage patient representatives earlier on in the process of planning research studies.

5.7 THE MOTIVATING FACTORS FOR LEGAL REPRESENTATIVES TO ENROL THEIR PROTECTEES IN CLINICAL RESEARCH PROJECTS SHOULD BE SYSTEMATICALLY ASSESSED, INCLUDING A DEBATE ON MORALLY AND LEGALLY JUSTIFIED INCENTIVES FOR STIMULATING RESEARCH PARTICIPATION.

A main concern for researchers both in academia and industry continues to be that of finding sufficient numbers of vulnerable populations as test persons. Especially in countries providing universal healthcare, representatives are less prone to give consent because of external motivations such as access to treatment. The common tendency of representatives in the Western world to not expose their beloved ones to a perceived risk is a fact that investigators have to adjust to.

Research in bioethics can help better understand both the strengths and limitations of our current models for recruiting vulnerable populations to participate in research. One critical aspect is to examine the factors and circumstances contributing to the decision of representatives to enrol their protectees in research protocols, and, in parallel, to elucidate the motivations of test persons participating. Relevant factors are the pursuit of high-quality care, better understanding of their protectee's illness, free treatment, monetary compensation, and, less frequently, altruism. Since research in this field is still in its early stages, we propose a systematic assessment of motivation for research participation in different cultural and economic contexts in order to gain more knowledge that may help to set up effective recruitment schemes that can be adapted to the interests and needs of potential test persons.

5.8 TRUST IS A CRUCIAL ISSUE IN THE SUCCESSFUL RECRUITMENT OF TEST PERSONS.

It is our belief that a shift to more clinical research in vulnerable populations cannot be effected only by changing laws and regulations. An issue of utmost importance is that of establishing an atmosphere of trust between researchers and the representatives of patients lacking capacity to consent. This is important not only at the institutional level, to enable cooperation between the scientific community and patient groups, but also at the level of recruiting test persons by establishing communication between researchers and/or research nurses and patient representatives. To achieve this, *more emphasis should be laid on creating a trustful climate of cooperation between the two sides. These considerations should already be taken into account when setting up a research design, and researchers should be trained in establishing a trustful atmosphere for communicating with prospective test persons and their representatives.*

5.9 THE GLOBALISATION OF CLINICAL RESEARCH SHOULD BE RIGOROUSLY CONTROLLED AND CRITICALLY ASSESSED, IN ORDER TO MINIMISE RISKS AND OPTIMISE OPPORTUNITIES.

The globalisation of clinical research has increased rapidly over the past years. Reasons for this point towards lower costs for conducting research projects in less economically developed countries, with at times more rapid progress being made, but also fewer difficulties in enrolling sufficient numbers of test persons

there. This development raises concerns with respect to adequate control and quality of research carried out outside the developed countries. Licensing authorities – such as the FDA and EMA – are developing strategies for coping with these challenges. Though there is every reason to critically observe the ongoing globalisation of clinical research, it should not be forgotten that this process not only means shifting research from one place to another, but can also result in an increase in the total number of research projects, which would indeed be welcome in view of the discussed limitations of clinical research in developed societies. Furthermore, conducting high-quality clinical research presupposes the establishment of a research infrastructure which can also be deemed to be beneficial for the future development of health care and health research in developing countries.

5 SCHUTZ DURCH INKLUSION UND NICHT DURCH AUSGRENZUNG: EMPFEHLUNGEN FÜR EINE SCHWERPUNKTVERLAGERUNG KLINISCHER FORSCHUNG ZUM WOHL VULNERABLER POPULATIONEN

In den 1960er und 70er Jahren offenbarten einige ernsthafte Zwischenfälle mit unerwarteten Arzneimittelnebenwirkungen schwere Mängel in Bezug auf die damaligen Anforderungen an klinische Forschung und die Zulassung daraus resultierender Arzneimittel. In vielen dieser Fälle waren vor allem Kinder betroffen. Als Reaktion auf diese und andere Ereignisse, bei denen Mitglieder vulnerabler Populationen geschädigt wurden, kam es zur Entwicklung von weitgehenden ethischen und juristischen Rahmenbedingungen für die klinische Forschung mit menschlichen Probanden. Das zentrale Prinzip hierbei war und ist es immer noch, dass jedes Forschungsverfahren die Einverständniserklärung des Probanden erfordert. Viele Mitglieder vulnerabler Populationen wie Kinder, ein Teil der psychisch Kranken oder Intensivpatienten können gar nicht oder nur eingeschränkt ihre Zustimmung erteilen. Die Schwierigkeiten bei der Einholung der Einverständniserklärung von vulnerablen Populationen und deren hohe Schutzbedürftigkeit führten dazu, dass die Durchführung klinischer Forschung an vulnerablen Populationen im Vergleich zur Mehrheit uneingeschränkt einwilligungsfähiger Patienten noch schwieriger wurde und dadurch unverhältnismäßig wenige klinische Studien durchgeführt wurden.

Obwohl ein angemessener Schutz vulnerabler Populationen ohne Frage zwingend ist, scheint es, dass die starke Fokussierung auf die Schadensvermeidung vor allem dazu geführt hat, dass hohe Hürden für die Aufnahme vulnerabler Populationen in klinische Forschungsprojekte errichtet wurden. Dies führte zu einer weniger zufriedenstellenden therapeutischen Situation für die vulnerablen Populationen im Vergleich zu der nicht betroffenen Mehrheit.

Unsere Hoffnung ist, dass eine sorgfältige und verantwortungsvolle Weiterentwicklung der bestehenden Rahmenbedingungen für die klinische Forschung die aktuelle Tendenz, vulnerable Populationen durch Ausschluss aus der klinischen Forschung zu schützen, sich mittelfristig dahingehend entwickelt, dass diesen Patienten besserer Schutz geboten werden kann, indem sie in Forschungsprojekte einbezogen werden und somit mehr als bisher vom medizinischen Fortschritt profitieren.

5.1 GESELLSCHAFTEN SIND MORALISCH VERPFLICHTET, DIE UNBEFRIEDIGENDE THERAPEUTISCHE SITUATION VULNERABLER POPULATIONEN ZU VERBESSERN.

Es ist leicht einzusehen, dass die Aktivitäten im Gesundheitswesen nicht auf die Bereitstellung der derzeit vorhandenen Heilmittel beschränkt sein, sondern auch Forschungsmaßnahmen zur Verbesserung der Gesundheitsversorgung umfassen sollten, um bisher ungedeckte gesundheitliche Bedarfe zu erfüllen. Wir fordern deshalb eine evidenzbasierte, dem Stand der Forschung entsprechende Krankenversorgung und nicht nur eine auf die state-of-the-art Standard-Therapie beschränkte Versorgung, die lediglich auf empirischer Erfahrung beruht. Folglich haben zur Wahrung der Gesundheitsgerechtigkeit vulnerable Populationen gleichermaßen einen Anspruch darauf, dass die Behandlung ihre gesundheitlichen Bedürfnisse durch Maßnahmen der Gesundheitsversorgung abgedeckt wird, einschließlich von Arzneimitteln, die den allgemein anerkannten (wissenschaftlichen/rechtlichen) Sicherheits-, Wirksamkeits- und Qualitätskriterien entsprechen. Im Vergleich zur therapeutischen Situation anderer Patientengruppen sind vulnerable Populationen derzeit jedoch wesentlich benachteiligt. Wir vertreten die Ansicht, dass unsere Gesellschaften eine ethische Verpflichtung haben, Wege zu finden, um die Gesundheitsforschung für vulnerable Populationen zu gewährleisten. In den USA und in Europa spiegelt sich dies in den aktuellen gesetzlichen Regelungen zu Arzneimitteln für seltene Krankheiten und zur pädiatrischen Forschung wider.

5.2 DIE METHODEN ZUR ERMITTLUNG DER EINWILLIGUNGSFÄHIGKEIT POTENZIELLER TESTPERSONEN SIND NICHT AUSREICHEND AUSGEREIFT UND SOLLTEN VERBESSERT WERDEN.

Die Aufnahme von Patienten in ein Forschungsprojekt bedarf der Zustimmung oder Einwilligung der potenziellen Testperson und – wie bei Testpersonen aus vulnerablen Populationen häufig – im Falle der Einwilligungsunfähigkeit, der Einwilligung der gesetzlich autorisierten Personen (Eltern, Vormund oder Betreuer). Geeignete Methoden zur Beurteilung der Einwilligungsfähigkeit können helfen, mehr Probanden zu gewinnen. Allerdings gibt es immer noch einen Mangel an wissenschaftlich erprobten und praktisch anwendbaren standardisierten Tests, der durch weitere Forschung behoben werden sollte.[29]

29 Das Ziel sollte nicht sein, am Ende nur einen „Master-Test" zu haben. Eine Vielzahl von situations- und/oder patientenspezifischen Tests wäre wahrscheinlich angemessener.

5.3 DER WAHRSCHEINLICHE NUTZEN VON FORSCHUNGSPROJEKTEN IM VERGLEICH ZU VORHANDENEN THERAPIEN SOLLTE KRITISCHER BEURTEILT WERDEN.

Die wissenschaftliche Qualität des Designs von Forschungsvorhaben, die vulnerable Populationen einbeziehen, wird von Zulassungsbehörden und Ethikkommissionen streng kontrolliert. Diese strenge Kontrolle ist unter anderem vor allem dann besonders wichtig, wenn der Pool der potenziellen Studienteilnehmer zu klein ist, um alle vorgeschlagenen Studien durchführen zu können. (Dies ist z. B. in der Kinder- und Jugendpsychiatrie der Fall). Es gibt anhaltende Bedenken in Bezug auf Studien mit sogenannten Analogpräparaten, d.h. pharmazeutischen Wirkstoffen, bei denen es sich um eine nur leicht veränderte Version bereits auf dem Markt befindlicher Präparate konkurrierender Unternehmen handelt. Angesichts der eingeschränkten Verfügbarkeit von Probanden aus einigen vulnerablen Populationen ist es problematisch, wenn Forschungsprojekte zur Entwicklung neuer Therapien mit Forschungsprojekten konkurrieren, die bereits etablierte Therapien duplizieren. Obwohl es scheint, dass die Zulassungsbehörden und Ethikkommissionen sich dieses Problems bewusst sind und solche Studien häufig nicht akzeptieren, möchten wir betonen, dass eine sorgfältige Begründung neuer klinischer Studien im Hinblick auf die begrenzt verfügbaren Patientengruppen von großer Bedeutung ist: Nicht speziell als geeignet ausgewiesene Forschungsmaßnahmen sollten vermieden werden.

5.4 PATIENTENVERFÜGUNGEN

Psychisch kranke Patienten, die noch einwilligungsfähig sind (z. B. im Falle neurodegenerativer Erkrankungen) oder die ihre Einwilligungsfähigkeit nach einer Krankheitsepisode wiedererlangt haben, sollten dazu ermutigt werden, eine Patientenverfügung für medizinische Eingriffe, einschließlich der möglichen Teilnahme an einem Forschungsprojekt, aufzusetzen.

5.5 DIE NUTZEN-RISIKO-BEURTEILUNG VON FORSCHUNGSVORHABEN IST SCHWIERIG UND WIRD DURCH EINE UNTERENTWICKELTE METHODIK ZUSÄTZLICH ERSCHWERT.

Nutzen und Risiken sind oft unbestimmte Rechtsbegriffe und sollten in jedem konkreten Forschungsdesign explizit und so klar wie möglich definiert werden.

Darüber hinaus wäre es ratsam, strukturierte Verfahren zu entwickeln und umzusetzen, die dazu beitragen, diese Beurteilungen transparenter und zuverlässiger zu machen.

In Anbetracht der Unsicherheiten der Nutzen-Risiko-Beurteilung könnte eine Einwilligung durch eine dreistufige Evaluierung der Akzeptabilität potenzieller Risiken und Belastungen im Verhältnis zu den erwarteten Vorteilen einer Forschungsmaßnahme abgesichert werden:

Zunächst muss der Forscher begründen, warum er das Verhältnis der Risiken und Belastungen seiner geplanten Forschungsmaßnahme akzeptabel, d. h. angemessen und gerechtfertigt, findet.

Zweitens muss die Forschungsethikkommission dieses Verhältnis mit Blick auf die rechtlichen und ethischen Normen und den medizinische Forschungsstand bewerten. Zumindest bei Studien mit nicht einwilligungsfähigen Probanden sollte dazu eine ausführliche Begründung gehören – und zwar nicht nur im Falle der Ablehnung des Forschungsantrages, sondern auch im Falle der Annahme, insbesondere im Hinblick auf die ethischen Überlegungen des antragstellenden Forschers.

Drittens muss der potenzielle Forschungsteilnehmer oder sein gesetzlicher Vertreter das durch die Forschungskommission akzeptierte Verhältnis zwischen potenziellen Risiken, Belastungen, Unannehmlichkeiten und erwartetem Nutzen der Studie im Hinblick auf seine persönlichen Präferenzen, Interessen und Werte bewerten. Wenn er/sie das Verhältnis für sich individuell akzeptabel findet, kann er/sie die Zustimmung zur Teilnahme geben.

5.6 AUFKLÄRUNG DER FORSCHER

Forscher aber auch schon Medizinstudenten sollten systematisch über die ethischen Implikationen klinischer Forschung unterrichtet werden. Alle ethischen und rechtlichen Vorgaben müssen konsequent beachtet werden, um nicht das Vertrauen des Forschungsteilnehmers und der Öffentlichkeit in die Forschung und damit eine Grundvoraussetzung für die erfolgreiche Rekrutierung von vulnerablen Personen zu gefährden. Darüber hinaus könnte es ratsam sein, Patientenvertreter bereits früher in den Planungsprozess von Forschungsstudien einzubeziehen.

5.7 DIE FAKTOREN, DIE GESETZLICHE VERTRETER BEWEGEN, FÜR IHRE SCHÜTZLINGE IN DIE TEILNAHME AN KLINISCHEN FORSCHUNGSPROJEKTEN EINZUWILLIGEN, SOLLTEN SYSTEMATISCH UNTERSUCHT WERDEN – UND EINE DISKUSSION ÜBER ETHISCH UND RECHTLICH GERECHTFERTIGTE ANREIZE ZUR FÖRDERUNG DER TEILNAHME EINSCHLIESSEN.

Ein Hauptanliegen der Forschung sowohl der Wissenschaft als auch der Industrie ist weiterhin, eine ausreichende Zahl von Mitgliedern vulnerabler Populationen für die Teilnahme an klinischer Forschung zu finden. Besonders in Ländern mit allgemeiner Gesundheitsversorgung sind die gesetzlichen Vertreter vulnerabler Patienten wenig geneigt, ihre Einwilligung aufgrund äußerer Motivation, wie z. B. Zugang zu Behandlung, zu erteilen. In solchen Staaten geht der Trend dahin, dass die Patientenvertreter ihre Angehörigen keinem als solchem wahrgenommenen Risiko aussetzen.

Bioethische Forschung kann dazu beitragen, die Stärken und Schwächen unserer aktuellen Modelle für die Rekrutierung vulnerabler Populationen zur Teilnahme an Forschungsprojekten besser zu verstehen. Dabei sind in jedem Fall die Faktoren und Umstände zu untersuchen, die zur Entscheidung der Vertreter beitragen, für ihre Schützlinge in Forschungsprojekte einzuwilligen, und parallel dazu, die Motivation der teilnehmenden Probanden zu klären. Relevante Faktoren sind ersten Erkenntnissen zufolge das Streben nach hoher Pflegequalität, ein besseres Verständnis der Krankheit des Schützlings, kostenlose Behandlung, finanzielle Entschädigung und – seltener – Altruismus. Da die Forschung in diesem Bereich noch in den Kinderschuhen steckt, schlagen wir vor, die Motivation für die Forschungsteilnahme in verschiedenen kulturellen und wirtschaftlichen Kontexten systematisch zu untersuchen, um so nähere Erkenntnisse zu erlangen, die dazu beitragen können, wirksame Rekrutierungsmethoden zu implementieren, die an die Interessen und Bedürfnisse möglicher Testpersonen angepasst werden können.

5.8 VERTRAUEN IN DIE FORSCHUNG IST UNVERZICHTBAR FÜR DIE ERFOLGREICHE REKRUTIERUNG VON PROBANDEN.

Wir sind der Überzeugung, dass eine Ausweitung der klinischen Forschung mit vulnerablen Populationen nicht nur durch eine Änderung von Gesetzen und Vorschriften bewirkt werden kann. Von größter Bedeutung ist die Schaffung eines Vertrauensverhältnisses zwischen Patienten mit fehlender Einwilligungsfähigkeit,

ihren Vertretern und den Forschern. Dies ist sowohl auf der institutionellen Ebene wichtig, d. h. im Hinblick auf die Zusammenarbeit der scientific community mit Patientengruppen, als auch auf der Ebene der Probandenrekrutierung, d. h. im Hinblick auf die Kommunikation zwischen Forscher und/oder Pflegepersonal und dem Patientenvertreter. Um dies zu erreichen, sollte mehr Wert auf die Schaffung eines vertrauensvollen Klimas der Zusammenarbeit zwischen beiden Seiten gelegt werden. Diese Überlegungen sollten bereits beim Entwurf des Forschungsdesigns angestellt werden und die Forscher sollten zur Schaffung einer vertrauensvollen Atmosphäre in der Kommunikation mit den potenziellen Testpersonen und ihren Vertretern geschult werden.

5.9 DIE GLOBALISIERUNG DER KLINISCHEN FORSCHUNG SOLLTE STRENG KONTROLLIERT UND KRITISCH BEWERTET WERDEN, UM RISIKEN ZU MINIMIEREN UND CHANCEN ZU OPTIMIEREN.

Die Globalisierung der klinischen Forschung hat in den letzten Jahren stark zugenommen. Gründe hierfür sind u.a. niedrigere Kosten für die Durchführung von Forschungsprojekten, zum Teil deren schnellere Durchführung, aber auch geringere Schwierigkeiten bei der Rekrutierung einer ausreichenden Zahl von Probanden. Diese Entwicklung wirft Fragen mit Blick auf die angemessene Kontrolle und Qualität von Forschungsprojekten auf, die nicht in Industrieländern durchgeführt werden. Zulassungsbehörden – wie FDA und EMA – entwickeln Strategien für die Bewältigung dieser Herausforderungen. Obwohl es allen Grund gibt, die fortschreitende Globalisierung der klinischen Forschung kritisch zu beobachten, sollte nicht vergessen werden, dass Globalisierung in diesem Sinne nicht nur eine Verlagerung der Forschung von einem Ort zum anderen bedeutet, sondern auch zu einem Anstieg der Gesamtzahl von Forschungsprojekten führen kann – was hinsichtlich der diskutierten Einschränkungen der klinischen Forschung in Industrieländern durchaus willkommen wäre. Darüber hinaus setzt die Durchführung hochwertiger klinischer Forschung die Einrichtung einer Forschungsinfrastruktur voraus, die auch als vorteilhaft für die künftige Entwicklung der Gesundheitsversorgung und Forschung in den jeweiligen Ländern angesehen werden kann.

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GLOSSARY

Benefit
Direct Benefit: Research with potential individual benefit for research participants.

Indirect Benefit: Research with no direct but rather a potential future benefit for participating patients.

Group-specific Benefit: Benefit for other patients with the same disease or condition or of the same age.

Clinical Research
Any investigation done on human subjects intended to determine the clinical effects of medicinal products and to identify adverse reactions.

Informed Assent
In the absence of a capacity for giving informed consent, some patients, i.e. older children, can understand and assent to medical interventions, even if they lack the (legally defined) capacity for informed consent.

Informed Consent
Communication between a patient and physician that results in the patient's authorization to undergo a specific medical intervention. Capacity to consent can be impaired persistently or transiently by a wide range of medical conditions.

Minimal Risk
Minimal risk is usually defined as a risk no greater than those normally encountered in daily life or during routine physical or psychological examinations or tests. These determinations require a great deal of interpretation, and there is ongoing debate about how to define minimal risk standards vis-à-vis other risks commonly encountered in daily life.

Risk-Benefit Ratio
An acceptable risk-benefit ratio is an agreed upon precondition of clinical research. However, risk-benefit evaluation is difficult and marred by underdeveloped methods and uncertainty. Benefits and risks are often undefined (legal) terms and should be explicitly defined in as clear terms as possible in each specific research design.

Single Case Trial
Medically indicated but experimental treatment with a direct potential individual benefit for the participating patients themselves.

Vulnerable Population
Groups of people with restricted or lacking capacity for decision-making due to limitations in their mental (i. e. cognitive, intentional or emotional) capacities, resulting from a) developmental and/or pathological processes or b) external factors, such as imprisonment or poverty and other social factors.

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ACKNOWLEDGEMENTS

The authors would like to thank the following people for discussions, suggestions and encouragement that they contributed to the Research Group.

Elisabeth Weisser-Lohmann (FernUniversität Hagen); Michael Kölch (Chief Physician Child- and Adolescent-Psychiatry, Vivantes Clinic, Berlin); Andreas Suchanek (HHL Leipzig, Graduate School of Management, Chair of Economic and Business Ethics); Tade Matthias Spranger (IWE Bonn); Norbert Konrad (Institute of Forensic Psychiatry, Charité Berlin); Donald Mattison (National Institute of Child Health and Human Development, Washington D.C.); Robert "Skip" Nelson (Senior Pediatric Ethicist, Office of Pediatric Therapeutics, FDA); Urban Wiesing (University of Tübingen, Institute of Ethics and History of Medicine); Armin Sablotzki (Chief Physician of the Clinic for Anaesthesiology, Intensive-and Pain-Therapy, St. Georg Clinic Leipzig); Laila Narouz-Ott (Bayer AG, Berlin); Markus Jensen (Bayer Vital GmbH); Heike von Lützau-Hohlbein (President of the German Alzheimer Society e.V.)

ISBN 978-3-939818-45-8