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Review Article

Aspects of vulnerable patients and informed consent in clinical trials

Aspekte schutzbedürftiger Patienten sowie der Einwilligung nach Aufklärung in klinischen Prüfungen

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Abstract

Scope: To discuss the rationale behind informed consent in clinical trials focusing on vulnerable patients from a European and German viewpoint.
Methods: Scientific literature search via PubMed, Medline, Google.
Results: Voluntary informed consent is the cornerstone of policies regulating clinical trials. To enroll a patient into a clinical trial without having obtained written and signed consent is to be considered as a serious issue in the conduct of a clinical trial. Development of ethical guidance for physicians started before Christ Era with the Hippocratic Oath. Main function of consent, as articulated in all guidelines developed for clinical research, is to facilitate an individual's freedom of choice, respect autonomy, and thus to ensure welfare of the participants in clinical trials. Minors are unable to provide legally binding informed consent, this issue is addressed through a combination of parental permission and minor's assent. Illiteracy is a critical problem that affects all corners of our earth; it has no boundaries and exists among every race and ethnicity, age group, and economic class. New strategies to improve communication with patients including the use of videotapes or animated cartoon illustrations could be taught. Finally the time with the potential participant seems to be the best way to improve understanding.
Conclusion: Discovery of life saving and life enhancing new treatments requires partnership that is based on good communication and trust between patients and researchers, sponsors, ethics committees, authorities, lawyers and politicians so that vulnerable patients can benefit from the results of well controlled clinical trials.

Keywords: informed consent, vulnerable patients, minors, illiteracy

Zusammenfassung

Ziel: Diskussion der Aspekte der Einwilligung schutzbedürftiger Patienten nach Aufklärung zur Teilnahme an klinischen Prüfungen aus europäischem und deutschem Blick.
Methoden: Wissenschaftliche Literaturrecherche via PubMed, Medline und Google.
Ergebnis: Das freiwillige Einverständnis ist ein Eckpfeiler aller Regularien von klinischen Prüfungen. Einen Patienten in eine klinische Prüfung aufzunehmen, ohne zuvor die mit seiner Unterschrift versehene schriftliche Einverständnis eingeholt zu haben, ist als schwerwiegendes Fehlverhalten anzusehen. Die Entstehung ethischer Leitlinien begann bereits vor christlicher Zeitrechnung mit dem Hippokratischen Eid. In allen danach für die klinische Forschung entwickelten Leitlinien wird verdeutlicht, dass eine Hauptfunktion der Einwilligung nach Aufklärung die Sicherstellung der Willensfreiheit ist, um auch so das Wohl der Teilnehmer in klinischen Prüfungen sicherzustellen. Minderjährigen ist es nicht möglich ein diesbezüglich bindendes Einverständnis zu geben, dieses Problem wird durch eine Kombination von elterlicher Zustimmung

sowie soweit möglich der Einwilligung des Minderjährigen adressiert. Analphabetismus ist betreffs der informierten Einwilligung ein kritischer Aspekt, der die ganze Welt betrifft. Er existiert in allen Gesellschaften, allen Bevölkerungsschichten und in jeder Altersgruppe. Um die Kommunikation mit diesen Patienten zu verbessern, können neue Strategien mittels Verwendung von Videotapes oder animierten Illustrationen und Trickfilmen gelehrt werden. Letztlich scheint die mit dem potentiellen Teilnehmer verbrachte Zeit der beste Weg zu sein, um die Verständigung zu verbessern.

Schlussfolgerung: Die Erforschung lebensrettender und lebensverbessernder neuer Behandlungen erfordert eine Partnerschaft, die auf guter Kommunikation und Vertrauen zwischen Patienten und Forschern, Sponsoren, Ethikkommissionen, Behörden, Juristen und Politikern basiert, damit auch schutzbedürftige Patienten ohne Einschränkung von den Ergebnissen kontrollierter klinischer Prüfungen profitieren können.

Schlüsselwörter: Einwilligung nach Aufklärung, schutzbedürftige Patienten, Minderjährige, Analphabetismus

Introduction

In this paper we are discussing the rationale behind informed consent in clinical trials focusing on vulnerable patients from the European and German viewpoint.
After a short view into general aspects of informed consent, important milestones of the development for guidance for physicians will be presented. A brief look into general aspects of vulnerable patients will lead to minors, their parents and illiteracy in particular. Ethical and practical challenges of the use of informed consent in daily routine of physicians have nearly similar impact and challenges in clinical trials. While focusing ethical and regulatory aspects on Europe and Germany a global view will show that we can learn from the rest of the world as well.

Informed consent – general aspects

Voluntary is the cornerstone of policies regulating clinical trials. However, there are situations where a written informed consent is impossible to obtain, such in a case from ill or injured patient who is unconscious and unable to communicate or from children who do not have the legal capacity to provide informed consent. Participation of vulnerable patients in clinical trials raises an ethical and legal dilemma which typically won't be associated with average intelligent adults in good mental health. In Neonates, young children or comatose patients it is manifested, that they are unable to give consent for their participation in a clinical trial. Either parents or their legal representative(s) function as surrogates of the child and have to give their consent in case they agree to the child's trial participation. For an unconscious or comatose patient a legal representative has to sign the informed consent form. Similar to patients able to give consent, a signed and dated consent form has to be provided from them and the informing process through the investigator has to be documented in the patients' source data.
The ICH Guideline for Good Clinical Practice [1] defines informed consent as a process by which a subject or his legal representative voluntarily confirms his or her willingness to participate in a particular trial after having been informed about all aspects of the trial that are relevant to the subject's decision to participate. informed consent is documented by means of a written, signed and dated informed consent form [1]. The informed consent process relies on three principles [2], [3]:

- Adequate information is provided, generally, what a reasonable person would want to know in order to decide
- Participants comprehend the information
- Consent is given voluntarily

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki [4], [5]. Prior to the beginning of the trial, the investigator should have the Ethics Committee's (EC) written approval of the written informed consent form and any other written information to be provided to subjects. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information that may be relevant to the subject's consent becomes available. Any revised written informed consent form and written information should receive the EC's approval in advance of use. The subject or the subject's legal representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented [1]. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial. None of the oral and written information concerning

the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legal representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as possible and should be understandable to the subject or the subject's legal representative and the impartial witness, where applicable. Before informed consent may be obtained, the investigator or a person designated by the investigator should provide the subject or the subject's legal representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legal representative. Prior to a subject's participation in the trial the written informed consent form should be signed and personally dated by the subject or by the subject's legal representative and by the person who conducted the informed consent discussion [1].

After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject or the subject's legal representative, and after the subject or the subject's legal representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to and apparently understood and that informed consent was freely given [1]. Prior to participation in the trial, the subject or the subject's legal representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legal representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent. A non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form. Non-therapeutic trials may be conducted in subjects with consent obtained from a legal representative in case the following conditions are fulfilled [1]:

- The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.
- The foreseeable risks to the subjects are low.
- The negative impact on the subject's well-being is minimized and low.
- The trial is not prohibited by law.
- The approval of the EC is expressly sought on the inclusion of such subjects and the written approval covers this aspect.

In emergency situations, if prior consent of the subject is not possible, the consent of the subject's legal representative, if present, should be requested. If prior consent of the subject is not possible and the subject's legal representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere with documented approval from the EC to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements has to be available. The subject or the subject's legal representative should be informed about the trial as soon as possible and consent to continue should be requested [1]. Per definition of the ICH GCP Guideline a legal representative for such patients is an individual, juridical or other body authorized under applicable law to consent, on behalf of a prospective individual, to the individual's participation in the clinical trial.

Development of guidance for physicians

The Hippocratic Oath, named after the physician Hippocrates (460–370 BC), is considered to be the first fundamental wording of medical ethics. It is an oath historically taken by doctors swearing to practice medicine ethically. The Hippocratic Oath (gr. orkos) is one of the most widely known of Greek medical texts, it requires a new physician to swear upon a number of healing gods that he will uphold a number of professional ethical standards [6].

In Roman law (428 AD) the relationship between patient and physician has not been legally binding. The exchange between achievement and payment has been regulated for the case of success [7], [8]. During the high middle ages the relationship physician-patient was regulated by 'healing contracts': a physician had to heal the patient, only in case of success the payment to the physician was permitted [9].

A change could be observed during the first half of the 17th century, when therapy and pharmaceutical medication obtained more relevance and the liability of the physician was no longer limited to success of treatment. Sir Ajlouni presented a historical document on 'legal informed consent' recorded during the Ottoman Empire in the 17th century, but this document does not meet the basic standards of the concept of informed medical consent, it is a contract to ensure that the physician will not be held responsible for death, rather than an attempt to seek informed consent from an educated and autonomous patient [10], [11], [12].

A broad range of ethical issues concerning informed consent became apparent as early as the 19th century;

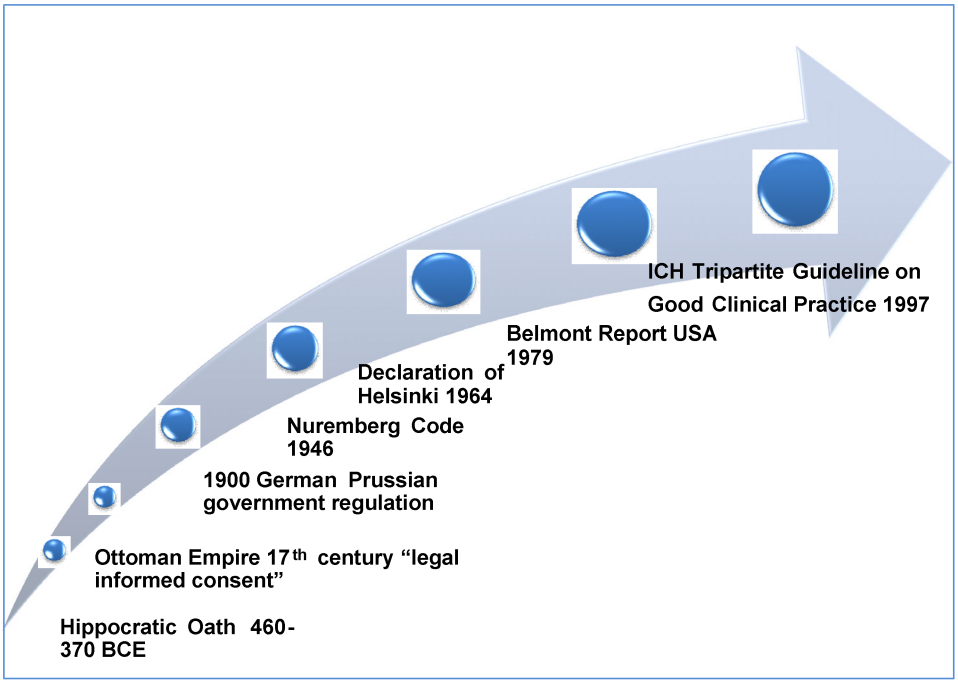

Figure 1: Milestones of important documents in clinical research (own illustration)

the Directive of the Prussian Minister of a German Government regulation on human experiments [13] is probably the earliest official regulation of informed medical consent in the Western world. It was issued after patients were injured in non-therapeutic research [13]; these injuries evoked critical public and professional discussion and a debate in the Prussian parliament [13]. Minors and individuals not competent due to other reasons were generally excluded from non-therapeutic research, since they could not give a valid informed consent in the underlying model of autonomy. Other pronouncements on the importance of consent in medical research are to be found in the early 20th century in Germany [14], [15].

The Geneva Declaration of the Rights of the Child 1923 is the name given to a series of related children's rights proclamations [16]. The first was adopted by the International Save the Children Union, Geneva and endorsed by the League of Nations General Assembly on November 26th, 1924 as the World Child Welfare Charter [17].

In 1931 the German Minister 'Reichsminister des Innern' released a Directive on Human Experimentation: 'Richtlinie des Reichsministers des Inneren vom 28. Februar 1931'. The Deutsche Reich forbids innovative therapy unless the subject or his legal representative has unambiguously consented to the procedure in the light of relevant information provided in advance and the protection of vulnerable persons and the responsibility as well as the necessity of a trial protocol are regulated [18] (Figure 1).

As direct result of the medical experiments on thousands of concentration camp prisoners, the Nuremberg Code was established in 1949, stating that "The voluntary consent of the human subject is absolutely essential", making it clear that subjects should give consent and that the benefits of research must outweigh the risks [4], [19]. Although it did not carry the force of law, the Nuremberg Code was the first document which advocated voluntary participation and informed consent.

The Declaration of Geneva [20] was adopted by the General Assembly of the World Medical Association at Geneva in 1948 and amended in 1968, 1984, 1994, 2005 and 2006. It is a 'declaration of physicians' dedication to the humanitarian goals of medicine. The Declaration of Helsinki (DoH) [5]: In 1964, the World Medical Association established recommendations guiding medical doctors in biomedical research involving human subjects. The declaration provides guidance for international research ethics and defines rules for research combined with clinical care and non-therapeutic research. The Declaration of Helsinki was revised [21] most recently in 2008 [22].

In 1974 the National Commission for the Protection of Human Subjects in the United States developed the National Research Act for the Protection of Human Subjects of Biomedical and Behavioral Research, which was charged to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. The commission drafted the Belmont Report, a foundational document for the ethics of human subjects' research in the United States [23].

The Belmont Report from 1979 is an important historical document in the field of medical ethics. It stressed that each patient group should be evaluated separately and a subject's wishes should be taken into account to the greatest extent possible. A third party should be appointed to act on behalf of the subject and thus substitute his consent. The report recommended the role of Ethics

Table 1: Important documents in clinical research

1948	The Declaration of Geneva	Adopted by the General Assembly of the World Medical Association at Geneva in 1948 and amended in 1968, 1984, 1994, 2005 and 2006. It is a declaration of physicians' dedication to the humanitarian goals of medicine, a declaration that was especially important in view of the medical crimes which had just been committed in Nazi Germany. The Declaration of Geneva was intended as a revision of the Oath of Hippocrates to a formulation of that oath's moral truths that could be comprehended and acknowledged modernly [20]
1948	Nuremberg Code	The Nuremberg Code was established in 1948, stating that "The voluntary consent of the human subject is absolutely essential" making it clear that subjects should give consent and that the benefits of research must outweigh the risks [4]. Although it did not carry the force of law, the Nuremberg Code was the first document which advocated voluntary participation and Informed Consent and it was the motor for the international guidelines. However, the Nuremberg Code had a number of shortcomings. Research involving incompetent persons such as children or adults with cognitive impairments was not allowed [4], [19].
1964	The Declaration of Helsinki (DoH	In 1964, the World Medical Association established recommendations guiding medical doctors in biomedical research involving human subjects. The Declaration governs international research ethics and defines rules for research combined with clinical care and non-therapeutic research. The Declaration of Helsinki was revised most recently in 2008 [5], [21], [22].
1979	The Belmont Report	The Belmont Report stands for Ethical Principles and Guidelines for the protection of human subjects of research. In 1979 it has been created by the former United States Department of Health, Education, and Welfare which was renamed to Health and Human Services entitled: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, authored by Dan Harms, it is an important historical document in the field of medical ethics. The report was finalized on April 18th1979 and got its name from the Belmont Conference Center where the document was drafted [2], [3].
1990	ICH Tripartite of GCP	Harmonization of regulatory requirements was pioneered by the European Community (EC), in the 1980s, as the EC (now the European Union) moved towards the development of a single market for pharmaceuticals. The success achieved in Europe demonstrated that harmonization was feasible. At the same time there were bilateral discussions between Europe, Japan and the US on possibilities for harmonization. It was, however, at the WHO Conference of Drug Regulatory Authorities (ICDRA), in Paris, in 1989, that specific plans for action began to materialize. Soon afterwards, the authorities approached the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) to discuss a joint regulatory-industry initiative on international harmonization, and ICH was conceived. The birth of ICH took place at a meeting in April 1990, hosted by the European Federation of Pharmaceutical Industries and Associations (EFPIA) in Brussels. Representatives of the regulatory agencies and industry associations of Europe, Japan and the US met, primarily, to plan an International Conference but the meeting also discussed the wider implications and terms of reference of ICH. At the first ICH Steering Committee (SC) meeting of ICH the Terms of Reference were agreed and it was decided that the Topics selected for harmonization would be divided into Safety, Quality and Efficacy to reflect the three criteria which are the basis for approving and authorizing new medicinal products [1].
2001	Directive 2001/20/EC	The EU-Directive 2001/20/EC had major impact on this Amendment and can be regarded as a mother of the German 12th AMG Amendment. Until 2001 clinical research in Europe was regulated by a variety of rules and regulations in the different member states. A need to harmonize led to a meeting with representatives from academia, industry, regulatory bodies and European Union (EU) and the development of the clinical trial European Directive 2001/20/EC. The Directive 2001/20/EC was implemented into European drug laws of all member states by 2004. The German 'Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen (GCP-Verordnung - GCP-V)' serves to implement the EU Directive 2001/20/EC [1].

Committees in ensuring that sufficient information will be disclosed to the subjects. Moreover it is stressed that investigators should avoid the use of vulnerable subjects when possible [23], [24].
The International Conference on Harmonization (ICH) published guidelines governing clinical trials. An important one is the ICH Tripartite Guideline E6 from 1996, last published in 2002 [1], a Note for Guidance on Good Clinical Practice (GCP, CPMP/ICH/135/95). Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected; consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible (Table 1).

Vulnerable patients – general aspects

The word 'vulnerable' has its origins in the Latin verb 'vulnerare', 'to wound'. It refers to a person's state of being liable to succumb, as to manipulation, persuasion or temptation. ICH GCP Guideline E6 [1] defines vulnerable subjects as individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished people, and patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent [1].
The more protection trial participants need and especially patients whose decisional competence seems to be questionable, the more difficult it is for others to take decisions on their behalf about whether or not they should participate in the clinical trial. Many people enrolled in clinical trials can be considered vulnerable, and such trials often raise concerns because of the diminished ability of vulnerable patients to consider and protect their own interests. Which patients are vulnerable and what are the criteria for a patient to be unable to give consent? Does it only belong to legal capacity? Beauchamp [25] notes to legal competence, that legal capacity as a category distinct from psychological capacity. Some patients, such as precocious minors, may have psychological ability, but no legal capacity. Some patients may have legal capacity without psychological capacity. To say that someone is legally competent is to say that no-one is justified in the authorizing interventions in the person's affairs or in acting on his/her behalf [25]. Claimed is here, that legal capacity can exist in the absence of decisional capacity and vice versa. Finally the physician judges and decides about the competence of an adult potential trial subject.
Still, therapeutic research for these diseases in patients unable to give consent is meaningful and equally important, such as which interventions are effective, which have no impact, and which do more harm than good. The guarantee for the protection of the individual intended to be treated, belongs to another individual, which is related to a community and therefore is not violated in case the human being has to comply regardless of his interests [26]. This makes clear that self-interest is not the only criterion for the guarantee for protection of the human dignity in the area of medical research. For clinical research with patients unable to give consent therefore is clarified, that it is permissible to look for a well-balanced concept between protection of dignity of patients unable to give consent and the goal of our community and the researcher – to help a group of other ill people [27], [28], [29].

Vulnerable patients – minors

Children have not attained the legal age for consent to treatment or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted. They are both, vulnerable subjects in need of protection from research risks and a neglected class that needs better access to the benefits of research. Based on the EU Directive [30], German drug law regulates in § 40 (4) and § 41 (2) clinical trials on children. In respect of a clinical trial on minors, the medicinal product must be intended to diagnose or prevent diseases in minors and the use of the medicinal product must be indicated in accordance with medical knowledge for the purpose of diagnosing or preventing diseases in the minor. The medicinal product is indicated if its administration to minors is medically indicated. Clinical trials performed on adults cannot be expected to produce satisfactory test results according to medical knowledge, the consent is granted by the legal representative after being informed. It must correspond to the minor's presumed will where such a will can be ascertained. Before the start of the clinical trial, the minor shall be informed by an investigator who is experienced in dealing with minors about the trial, the risks and benefits as far as possible. It has to be taken into account the minor's age and mental maturity. Should the minor declare or express in any other way that he/she does not wish to take part in the clinical trial, this must be respected.
The determination of the levels of risk and the associated potential benefits are the basis for ethical approvability. In the following examples, levels of risk are considered to be in balance with the benefit for a trial with the pediatric population [31].

- Minimal risk, which could be defined as probability of harm or discomfort not greater than that ordinarily

encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- Minor increase over minimal risk, with benefit to individual or benefit to the group, and with the benefit to risk balance being at least as favorable as that of available alternative approaches.
- Greater than minor increase over minimal risk with benefit for the individual that is especially favorable in relation to available alternative approaches for the individual's condition.

With regard to benefit for the group, it is also emphasized in the European Convention on Human Rights and Biomedicine which states in its article 17.2 "Exceptionally and under the protective conditions prescribed by law, where the research has not the potential to produce results of direct benefit to the health of the person concerned, such research may be authorized [...]" if:

1. "The research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, 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";
2. "The research entails only minimal risk and minimal burden for the individual concerned; and any consideration of additional potential benefits of the research shall not be used to justify an increased level of risk or burden".

With implementation of the Directive 2001/20/EC clinical research in minors is now extended from direct benefit for the individual to benefit for the group of affected patients in the European Union. Parents have an important role if their children shall be included in a clinical trial: It is a challenge for an investigator to illustrate the benefit for the single or group of patients. To explain to them that their severely ill child could possibly receive placebo in a placebo controlled trial, and to explain the complexity of a placebo controlled trial does not make it easier. Parents have to be fully involved in the process and to feel that they are sufficiently informed.
According to Regulation (EC) No 1901/2006, the term pediatric population refers to the part of the population aged between birth and 18 years. Age of assent can/is to be determined by Ethics Committees and has to be consistent with local legal requirements, which differ with an extreme variance in all countries and regions worldwide due to different regulations, cultures and religions. According to the EU Directive 2001/20EC in addition to any other relevant restriction, a clinical trial on minors may be undertaken only if [30]:

- The informed consent of the parents or legal representative has been obtained and consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor.
- The minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits.
- The explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator.

Parents – representatives

The informed consent process for the pediatric population is different from a trial with adults. The Clinical Trials Directive 2001/20/EC Article 4 requires the informed consent of the legal representative, it must represent the minor's presumed will and may be revoked at any time, without detriment to the minor. Article 4(a) of the Clinical Trials Directive 2001/20/EC requires that the specific and written informed consent of parent/legal representative must be sought prior to enrolling a child in a trial. Consent in line with the Clinical Trials Directive should be obtained from the parent(s)/legal representative(s) at the same time as assent is sought from the child. Information should be given by an experienced investigator, or his adequately trained delegate, to each parent, or the legal representative(s), on the purpose of the trial and its nature, the potential benefits and risks. They also have to know the names of the investigators(s) who are responsible for conducting the trial with background professional information (such as education, work experience) and get direct contact details (telephone and e-mail) for further information regarding the trial. The parent/legal representative(s) should be given sufficient time and necessary information to consider the benefits and risks of involving the child in the clinical trial. The role of the physician changes from solely being the treating doctor to an investigator, who in addition conducts the clinical trial often per contract with a sponsor. However, the investigator should not take part in the decision making, but should ensure that the information has been understood and that there has been enough time allowed to come to a decision. The investigator must make sure that children know what will happen to them during the study, the risks and benefits and that they may withdraw their assent at any time. Obtaining assent gives children a role in shared decision making and reminds us that children should be treated with dignity and respect. Assent of the minors themselves is required when they are able to understand the nature, importance and consequences of the clinical trial. There is no possibility to conclude from earlier expression of their presumed willingness to take part in a clinical trial. This imposition indeed is justifiable only with the guarantee of a very high protection. Depending on their age they should provide a signature and the participation must correspond to the assumed will of the little subject.

Some studies about cognitive development and decision making in juveniles show that, according to the measures used, children above age fourteen are, in general, as capable as adults to make decisions [32]. while children below age eleven lack many capacities which are necessary to make decisions [33]. Some children in the middle group (ages eleven to fourteen) have the capacity to make decisions, while others have not [32]. However it is worth noting that children will have less background knowledge about medicine than adults and thus may require considerably more instruction to achieve adequate understanding. In addition they may lack a general context of life experiences by which to judge the risks and benefits of the proposed treatment. The EU Directive 2001/20 EC states, that every effort should be made to understand and respect differences of opinions between the child and his/her parents or legal representative. Objections raised by a child at any time during a trial should be considered: Here emerges a dilemma for the investigator and the parents/legal representative/s) on how to deal with this situation. There are varying views belonging to this topic and research is needed to address the paucity of empirical data concerning the informed consent process in pediatric clinical research. Research on the interaction between investigators, children and stressed parents who have to decide on trial participation of their ill child could also be very valuable in order to support them if needed.

Children's assent

Assent refers to the minor's agreement to participate in the clinical trial, after being provided with information appropriate to its age and cognitive abilities. The term of assent is not explicitly included in the Clinical Trials Directive 2001/20/EC, which only requires that the minor's will should be considered. Assent should be understood in the context of Article 4(c) of the Clinical Trials Directive as the expression of the minor's will to participate in a clinical trial. The capacity of a child to make voluntary informed decisions, i.e. to assent, evolves with age, maturity and previous experience of life and illness. While assent may not be possible in all age groups (e.g. neonates) or in all research conditions (e.g. research in emergency situations), the information process provided to the child and the child's response should be documented in the source data. If the minor is in a position to comprehend the nature, significance and implications of the clinical trial and to form a rational intention in the light of these facts, then his/her assent should also be required. An opportunity for a counseling session should be offered, not only to the legal representative but also to the minor. The clinical trial may only be conducted if it subjects the person concerned to as little burden and other foreseeable risks as possible. Both the degree of burden and the risk threshold must be defined specifically in the trial protocol and monitored constantly by the investigator [33].

Illiteracy

Purely illiterate persons cannot read or write in any capacity, for all practical purposes. In contrast, functionally illiterate persons can read and possibly write simple sentences with a limited vocabulary, but cannot read or write well enough to deal with the everyday requirements of life in their own society. In many parts of the world, patients and their relatives lack education and/or they do not read and write well enough to understand health information, including typical informed consent information that would be provided to them by the investigator, when deciding to be enrolled into a study or not. The German Alphabund [34] defines functional illiteracy: "exists when the written skills of adults are lower than those which are the minimum and considered a matter of course to cope with day-to-day requirements in society. [...] If a person cannot read one or several items of information directly contained in a simple text so that the sense is understood and/or the person is at a similar skills level when writing." UNESCO talks about functional illiteracy when full command of reading, writing and math's skills is lacking [34]. In many parts of the world, patients and their relatives lack education and/or they do not read and write well enough to understand health information, including typical informed consent information that would be provided to them by the investigator, when deciding to be enrolled into a study or not. Illiteracy is a critical problem that affects all corners of our earth; it has no boundaries and exists among every race and ethnicity, age group, and economic class [35]. This silent epidemic of people unable to read threatens over 796 million adults worldwide [35]. Although attending school until the age of 16 is mandatory in Germany, around 7,5 million of over 80 million people in Germany are still functional illiterates [36], [37]. They may have gone to school for years, but they read and write so poorly that it's hard for them to lead a normal life. Illiteracy was long ignored in Germany or dismissed as a problem in poorer, less developed countries. Indeed, most of the world's 800 million illiterates live in developing countries. But particularly since the PISA studies carried out by the Organization for Economic Cooperation and Development (OECD) showed that pupils here lag far behind their peers in other highly developed countries, educators and the public have realized that many schoolchildren find it tough to write correct German [38]. Extremely low literacy rates are concentrated in three regions, South and West Asia, Sub-Saharan Africa, and the Arab states, where one-third of the men and half of the women are illiterate. Africa, as a whole continent, has less than a 60% literacy rate. Over two-thirds of the non-literate adults populate the following countries: India, China, Bangladesh, Pakistan, Nigeria, Ethiopia, Indonesia, and Egypt. Staggering numbers show that India alone has over 440 million illiterate citizens [35].

If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent

discussion before enrolment into a clinical trial [1]. After the written informed consent form and any other written information to be provided to subjects is read and explained to the subject/legal representative, and after the subject/legal representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject/legal representative, and that informed consent was freely given by the subject/legal representative [1]. The consent form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. A video tape recording of the consent interview is recommended [39].

Sufficient time should be allowed for questions to be asked and answered, both by the subject, and by the person obtaining consent to ensure the subject comprehends the consent information. The responsibility of ensuring that a potential subject understands the research and the risks and benefits involved falls upon the investigator and not upon the potential subject.

It is critical to the consent process that the investigator not only fields questions but also asks questions. Asking questions can further the discussion, elicit questions from the potential subject, prompt the potential subject to think more carefully about the study, and help the investigator decide whether the person has adequately understood the study. Useful questions will be open-ended and non-directive. Rather than asking for yes or no answers, they ask for explanation because these questions often can be answered in a variety of ways, and do not already contain the correct answer. Open-ended questions are often introduced with "what", "where", "how often", "when", and "please describe" [40].

Examples of open-ended questions are:

"Just so that I'm sure you understand what is expected of you, would you please explain to me what you think we're asking you to do?"

"Describe in your own words the purpose of the study."

"What more would you like to know?"

"What is the possible benefit to you of participating in this study? What are the possible risks?"

"Can you describe what the alternatives to participation in this study are?" [40]

A method of informed consent for illiterate populations has been described in the Lancet [41] where audiovisual documentation of oral consent (video and audiotape recording and photography (ADOC) has been developed which consists of written and oral steps. To document the consent process and prevent falsification, oral steps were documented by audio recording, video recording, and photography (triple media recording [TMR]). The documents describing the study, the planned consent procedure and consent form were submitted with the study protocol to the relevant legal and ethical authority. All records were labeled and stored. ADOC, or similar standardized procedures designed with the same principles, enables valid informed consent to be obtained from illiterate populations for participation in clinical research, and should be available as an alternative to written and signed consent where needed [41].

There are many aspects of clinical trials that those living in developing countries do not understand. Work done in Kilifi, Kenya, suggests that misunderstandings have contributed to concerns and rumors, which potentially undermine ethical aspects of research and local trust in the institution [42]. To address the challenge of informed consent for this population, the World Medical Association, the South African Medical Association, the Steve Biko Centre for Bioethics in Johannesburg and some pharmaceutical companies partnered with Books of Hope, a literacy empowerment program that seeks to empower illiterate populations. In 2005 a 'Speaking Book' has been launched for illiterate people to explain the fundamentals related to participating in a clinical trial. The Speaking Book is a book that uses cartoons in addition to text, which is spoken when the corresponding button is pushed for that page. It uses visual messages accompanied by sound and the recorded text serves as a script. Contrary to radio and television, the Speaking Book does not depend on access to electricity or proximity. In 2008 approximately 4,500 books were distributed in South Africa and Speaking Books are called a World Changing Idea [35]. One is titled: What it means to be part of a clinical trial [35].

Discussion

The main function of consent, as articulated in all guidelines for clinical research, is to facilitate an individual's freedom of choice, respect autonomy, and thus to ensure welfare of the participants in clinical trials. To enroll a patient into a clinical trial without having obtained written and signed consent is to be considered as a serious issue in the conduct of a clinical trial. However, there are some circumstances where it is very difficult to obtain properly informed consent. Considering informing minors when parents differ in their opinion or no parents or legal representatives are available, which would be the most unethical thing to do: To try to answer a relevant question without consent? To never conduct the trial so that no one knows the right way to solve a specific problem, with the added possibility that children will continue to receive suboptimal care? This issue needs to get attention from lawyers and Ethics Committees. The question if shared decision making really adds protection to the minor could not be answered and further research on that issue can be recommended.

Considering if a signature of a child really is necessary, German drug law asks for informed consent if the minor is capable of understanding the nature, significance and implications of the clinical investigation. The signature of

the minor can be one interpretation of the law. In case it only should protect the investigator from a possible accuse then it does not add protection of the minor and does not reflect that the investigator informed the minor in an appropriate way.

The complete informed consent process combined with enhanced education and counselling materials can lead to good comprehension of informed consent issues. Strategies to improve communication with patients including the use of videotapes, group discussions, simulations or animated cartoon illustrations like for instance the Speaking Book [35] could be taught. Video clips about patients' rights could be arranged in different waiting areas of the institutions. The exposure to these materials could make it simpler for them to recognize when they are being invited to be part of a research trial [43]. These products probably can overcome illiteracy and because they can transmit a very clear message with the inclusion of cartoons in the communication. For patients who are illiterate and those who inform that their verbal agreement can be regarded as consent a signature on an informed consent form might be not applicable. The investigator could document the patient's verbal consent into the patient file similar to the process when a minor gives assent.

The increasing width of information, not only related to medically related interventions, but also to items such as data protection, lets the informed consent forms often increase to a voluminous leaflet [44]. The conditions for vulnerable patients informed consent are manifold and the requirements could be tailored to their needs. Ethics Committees, investigators lawyers and sponsors could cooperate and think about a reform of the document in limiting the length of consent form and structure the required information in a question & answer style. A quote from a US case may illustrate this point: "A physician violates his duty to his patient ... if he withholds any facts which are necessary to form the basis of an intelligent consent by the patient ... [but] ... the patient's interest in information does not extend to a lengthy polysyllabic discourse on all possible complications. A mini-course on medical science is not required ... " [45].

A single worldwide standard for obtaining informed consent in clinical research studies may be difficult to achieve as long as the legal and ethical requirements in the cultures differ from each other. Several authors have addressed different approaches to improve the patients' comprehension of experimental treatments, the time with the potential participant or legal representative seems to be the best way to improve the understanding [32], [46], [47] and this cannot be replaced by an information sheet, which adds hardly something to the protection of the patients' wellbeing itself. Educational programs on informed consent could already be integrated very early during university days into the curricula of human medicine, pharmacy, science related to pharmacological research and law. Possible topics of a training program on informed consent:

- Background and history of informed consent
- Aspects of clinical research with vulnerable patients, minors, illiterates
- Local laws and ICH-GCP Guidelines
- Students could be encouraged to place themselves in the position of a patient e.g. a child or an unconscious patient → role plays with feedback on their performance from their counterpart
- Communication techniques and hands-on training with model informed consent Form, psychological conversation techniques, e.g. on how to explain exactly which elements of treatment and care are research and are therefore optional
- Alternatives to leaflet such as the Speaking Book

In 2011 the European Commission launched a high-level expert group on literacy [48], [49]. We would like to encourage the organization and support of such a campaign in order to achieve improvement of literacy rates.

Notes

Competing interests

The authors declare that they have no competing interests.

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Authorship

The authors assure that the work completed is their own and that no other sources or assistances for those stated have been used. The co-author has read and approved the final manuscript.

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