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Ethical Aspects of Vulnerable Group of Patients in Clinical Trials

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Abstract

The current publication aims to review and analyse the ethical aspects and regulations to protect the category of vulnerable patients, as defined in the European legislation. These patients need special protection and require more detailed approach throughout the clinical trials' life cycle.

Keywords: clinical trials, vulnerable patients, ethical aspects, informed consent

1. Introduction

According to the National Institutes of Health USA, the number of clinical trials shows a stable trend for growth. Nearly 28% of all clinical trials worldwide are conducted in Europe [1]. It is therefore important that clinical trials are regulated legally and monitored with needed level of detail. They must also comply with the ethical standards that promote respect for human beings and protect their health and well-being.

Often, researchers included patients who are vulnerable and need special protection. The chapter aims to provide an overview of the ethical issues in clinical trials with vulnerable patients.

Based on European legislation, specifically Regulation (EU) No. 536/2014 of the European Parliament and Council and ICH GCP E6 (R1), several categories of so-called vulnerable groups of patients might be defined:

1. Pregnant or breastfeeding women
 2. Minors
-

3. Students and employees
4. People suffering from multiple chronic conditions or terminally ill
5. Ethnic minorities
6. Older people
7. Military
8. People affected by mental health disorders

Each of the listed groups has its specific need, which has to be taken into consideration. While standard requirements towards clinical trials life cycle are outlined in European legislation, some ethical issues related to the vulnerable groups of patients need to be also part of ethical codes of conduct or local legislation. These include additional requirements related to the objectives of the study, risk-benefit assessment, strict adherence to the study protocol and additional steps in the course of obtaining informed consent.

It is important to constantly improve access to treatments available for vulnerable groups. Therefore, medical products of significant clinical value should be appropriately studied for their effects in these specific populations. Vulnerable groups of patients require more detailed approach and in cases when the legislation does not provide needed level of detail or is outdated, ethical issues outlined in the chapter could be taken into consideration by members of ethics committees and investigational staff.

2. Clinical trials on women of reproductive age, pregnant or breastfeeding

Until the early 1990s of the twentieth century, the inclusion of women of reproductive age in clinical trials Phases I and II is very limited. One of the reasons behind this is FDA's 1977 guideline, which recommended excluding women with childbearing potential from participating in early phases of drug trials. The recommended exclusion was broadly applied to any 'premenopausal female capable of becoming pregnant', but explicitly did not apply to women with life-threatening diseases [2]. The results of such a major limitation were:

- the rights of sick women were limited, as they cannot get timely treatment with more effective drugs;
- the efficacy of many medical products on the women was unknown, although they were prescribed both men and women.

Thus, in 1993, under pressure from the public and the scientific community, FDA issued 'Guidelines for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs', according to which women should be allowed to determine for themselves the appropriateness of participating in early clinical trials [2].

In 1998, experts from the World Health Organisation (WHO) and United Nations (UN) issue a report 'Women and Health Mainstreaming the Gender Perspective into the Health Sector' [3]. The report concludes women need to be included in clinical trials, but their participation must be accompanied by informed consent.

Thus, the inclusion of women of **reproductive age** in clinical trials remains a pivotal issue. Ethical committees must ensure proportional participation of both sexes in order to obtain reliable trial data; however, the inclusion of women in the study should only take place when drug safety data is available and measures to protect women's and future offspring's health are undertaken. Women should receive information about the risks on their reproductive system and contraception methods during the study. They should immediately inform the medical team in the event of planned or already occurred pregnancy.

Studies on **pregnant women** should only be conducted in cases when the required data cannot be obtained from another patient's categories and when the purpose of the study corresponds to the mother's and foetus's health needs with minimal risk. It is mandatory that the informed consent is obtained, and information about possible consequences for the health of the women, foetus or future child is promptly communicated.

Studies related to monitoring **pregnancy, childbirth and the postpartum period** are usually conducted to evaluate the standards and pathologies during pregnancy, childbirth, postpartum and breastfeeding periods. Some of them are targeting diseases arising during pregnancy (hypertension, diabetes, etc.). In cases when a standard therapy does not work, it is necessary to conduct experimental treatment. In cases when the benefit is minimal and the risk for a woman or foetus is indefinite or high, the testing should be stopped. However, provided that the test drug is vital for a pregnant woman, her consent may be sufficient to implement the experimental therapy—even if the risk to the foetus is unknown or exceeds the minimum.

There are no specific guidelines for the inclusion of **breastfeeding women**. Nonetheless, the ethical committee should pay close attention to the safety of the health of breastfed children (mother's own child or the one who gets the breast milk). Medical team should regularly take samples from the breast milk and monitor the composition and protein component in colostrum or milk.

As defined by European legislation, along with standard requirements, additional conditions should be in place for a clinical trial on pregnant or breastfeeding women. Some of them are as follows:

- The clinical trial is required to indicate a direct benefit for trial subject (pregnant or breastfeeding woman, or her embryo or child). The benefit should outweigh the risks involved.
- If the research involves a breastfeeding woman, additional actions need to be taken to ensure no negative impact on child's health.

In cases where there is no direct benefit for the trial subjects (pregnant or breastfeeding woman, or her embryo or child), a clinical trial can only be allowed:

- if it cannot be conducted on other patient groups;
- if it contributes greatly to obtaining results which could be beneficial to pregnant or breast-feeding women, or other children or embryos;
- if it holds minimal risk to the subjects [4].

3. Clinical trials on minors

In paediatrics, it is often that methods and therapies are applied based on studies conducted on adults. But the results in children are not always the same. Therefore, the treatment for children needs to constantly improve and enhance based on clinical trials conducted on children population. However, the best interests of the child should be a primary consideration.

According to the Convention on the Rights of the Child adopted by the UN General Assembly in 20 November 1989, the children have the same rights as adults. Thus, clinical trials on children should meet the same requirements needed for such trials on adults. However, due to children's vulnerability, they require special care and additional protection of their interests. It is essential to obtain informed consent, assess the risks to the child and minimise the fear and pain during the study.

There are two main concepts on the child's participation in a clinical trial:

- Informed consent
- Assent

For the first time, the term assent is mentioned in the Declaration of Helsinki, which states that when a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative [5].

Prior including a child into a clinical trial, his assent needs to be obtained. If such is missing, this fact, along with reasonable explanations of the same, needs to be noted in the Informed Consent of child's parents or legally authorised representative. Child's assent alone is not sufficient; it should always be accompanied with the informed consent of the parents. If a child reaches age of legal competency during the trial, his informed consent should be obtained and enclosed to the study documentation.

However, the degree of child's involvement in the decision depends on its age and maturity. Ethical committee can determine the age of the child when it can give consent to participate. This decision should comply with the local laws. Only the child's age, however, is not determinative of whether it is capable of giving consent to participate. The level of development, intellectual ability and experience may also be decisive. In all cases, trial information provided to a child needs to be adapted to its age and mental maturity.

The ethical expertise usually assesses and determines the risks and the benefits of clinical trials. The main principle is that the best interests of the child shall be a primary consideration. In practise, risk assessment on children depends on many factors. For example, taking a small quantity of blood from a child suffering from haemophilia creates risk, significantly exceeding the minimum. Children suffering from a chronic disease usually perceive easier various medical treatments. So they are at less risk compared to children who have no similar experience in illness.

During clinical trials on children, it is important to reduce and mitigate painful manipulations, by applying effective methods of pain reduction—usage of corresponding equipment and personnel trained or experienced in working with children.

Clinical studies on minors would also include some additional requirements:

- No incentives or financial benefits are allowed. The only exception that can be considered is a compensation for expenses directly related to the clinical trial.
- The medical condition being treated occurs only in minors population.
- The clinical trial aims to validate data already collected on adult population to confirm it can be applied in minors.
- The clinical trial relates directly to a medical condition of a child.

4. Clinical trials on students and employees

When attracting healthy volunteers, it is imperative that they take the decision to participate in a clinical trial on their own and without pressure. They should receive all needed information related to the trial and declare their voluntary informed consent. Volunteers are usually compensated for their time, discomfort and possible risks. Thus, ethical commission is to make sure that these cash compensations are not unreasonably high and that attracted patients are not from category that is easily persuaded and influenced (*people with low incomes or without education*).

Healthy volunteers are usually patients in Phase I clinical trials. The task of this phase is to evaluate drug's safety, determine a safe dosage range, pharmacokinetics and side effects.

The researcher should consider possible action in the event that a patient volunteer gets sick or hurt during the tests. These actions must be thoroughly listed in the informed consent form:

- Whether the patient will receive medical treatment and at whose expenses in case he gets sick or hurt during the course of the study
- Primary point of contact in case of injury
- Opportunity to withdraw from the clinical trial at any time without having to provide any justification

The participation of **students and employees** in clinical trials is widely discussed. There are two ethical issues: whether the decision to participate was completely voluntary and privacy concerns.

On the one hand, students' and employees' participation in clinical trials conducted on campus puts under question the free nature of this decision. The student/employee may decide to participate in the study with the idea that his/her participation will be beneficial for the learning process or work conditions (better grades, good recommendations, etc.). Conversely, there is concern that non-participation in the study may have a negative impact on relations with the teaching staff or employer.

On the other hand, the ban on students' and employees' participation in clinical trials limits their right of choice. Therefore, the Good Clinical Practice highlights the requirement to investigator to recruit patients-volunteers exclusively through advertisement of a general nature and not through individual approach to minimise any coercion or pressure in decision-making.

Another ethical concern is data privacy issue. The researched should guarantee protection and confidentiality of personal data of the participants. This may not be so easy to achieve if study involves students or employees of medical institution which conducts the trials. In this case, there is a conflict of interest as participants in the study are students or employees, and the investigational staff is the employer.

5. Clinical trials in emergency situation and on people suffering from incurable diseases

In general, clinical trials with patients who require emergency treatment or intensive therapy differ from studies with patients in stable condition. These differences are mostly related to the problem of obtaining informed consent—the patient has blurred consciousness, unresponsive or unconscious, lack of time and opportunity to discover his legal representatives.

Ethical standards and legislation allow informed consent to be missing in cases where the patient's life is in danger, and alternative ways of treating are missing. In all cases, however, the informed consent shall be sought after the performed emergency intervention to continue the participation of the subject in the clinical trial.

If the patient or his/her legal representative does not give consent, he/she has the right to object to the use of data collected from the clinical study.

The situation is different in clinical trials and treatment of deadly diseases. They suggest another category of patients—terminally ill. Such trials are of a great importance, as often there are no alternative types of patients that might be involved due to this is not justified from the ethical stand point.

It should be borne in mind that it is possible terminally ill patients wrongly to suggest that participation in testing is a necessary condition to receive medical care and that it is better to

receive any medical care than nothing. Some terminally ill patients consider their participation in the trial as an opportunity to be helpful to others. It is therefore important that they are properly informed and do not participate in the trial based on false assumptions.

Nowadays the topical question is around participation of terminally ill patients in Phase I clinical trials from, as medicines in this phase can be dangerous (e.g. a new kind of chemotherapy). Despite the researcher's willingness to be helpful and give positive results of the tests, the patient may not improve or even get worse. For this reason, it is very important for the patient to be thoroughly informed the potential risks and benefits of the research, without giving unnecessary hope. Study participants must be informed whether their participation or non-participation in the study is a prerequisite for treatment in a hospital, and whether the stay in hospital is at patient's cost.

The AIDS epidemic boosts new kind of demand—access to investigational drugs. Many terminally ill patients are willing to take investigational drugs in a clinical trial because there is no other way to get them—they are either not available or too expensive.

In the United States, there are several examples of treatment use of investigational drugs. In 1976, the 'Group C' treatment was established by agreement between FDA and the National Cancer Institute. The purpose of the programme is to distribute investigational drugs to oncologists to treat cancer under studies outside the controlled clinical trial. Another expanded access concept is so-called Parallel Track policy announced by FDA in April 1992, which permits wider access to new drugs for AIDS/HIV-related diseases [6].

In Europe, 'Compassionate use' programmes allow a medicinal product, without marketing authorisation, to be given to patients with a life-threatening disease when no alternative authorised treatments exist. The European Regulation 726/2004/EC provides directions to 'compassionate use' programmes in the European Union. It states that patients must have a chronic or life-threatening disease, and the medicinal product must be undergoing assessment in a clinical trial or be in the marketing authorisation stage. However, details around authorisation procedures are still missing and ultimately the programmes are governed by individual member states [7].

6. Clinical trials on ethnic minorities

Ethical standards suggest unbiased approach to selecting patients—inclusion or exclusion criteria should not be based on gender, race or ethnicity. Most diseases are applicable to all populations, so the researcher must include the most diverse types of patients. This way the results obtained in the course of the study may be useful for all people who are at risk for a disease being treated. The researcher should provide clear justifications on inclusion or exclusion of specific populations.

Yet there are diseases that often occur in certain ethnic groups. For example, sickle cell disorders are more common among people whose ancestors have lived in tropical and subtropical regions. In such studies, the inclusion of patients from specific ethnic minority is a must.

Exclusion or under-representation of ethnic groups would be unfair approach, as thus they are deprived of the equal benefits of treatment during the study.

An example of abuse and racial discrimination is The Tuskegee Study of Untreated Syphilis in the Negro Male (1932–1972). The purpose of this study was to observe the natural progression of untreated syphilis in rural African-American men in Alabama, US.

Usually, clinical trials with homogeneous populations are cheaper. The more diverse the group of test patients is, the more variables occur throughout clinical study live cycle. Ultimately, all this leads to additional costs. Therefore, in cases where patients represent a homogeneous group, the study results should be applicable for the same group and not for the population in general.

When attracting ethnic minorities, investigator and ethics committee should ensure that:

- patients representing ethnic minorities are not exposed to additional risk;
- in cases when representatives of minorities are poor or illiterate, their rights are protected and there is no coercion or undue incentives for their participation in the clinical trial;
- documentation is in a language understandable to the minority patients.

Different racial and ethnic groups experience disease and respond to treatments differently. Therefore, it is important that various populations participate in clinical trials to ensure that the treatments and interventions are going to be relevant to those populations.

7. Clinical trials on older people

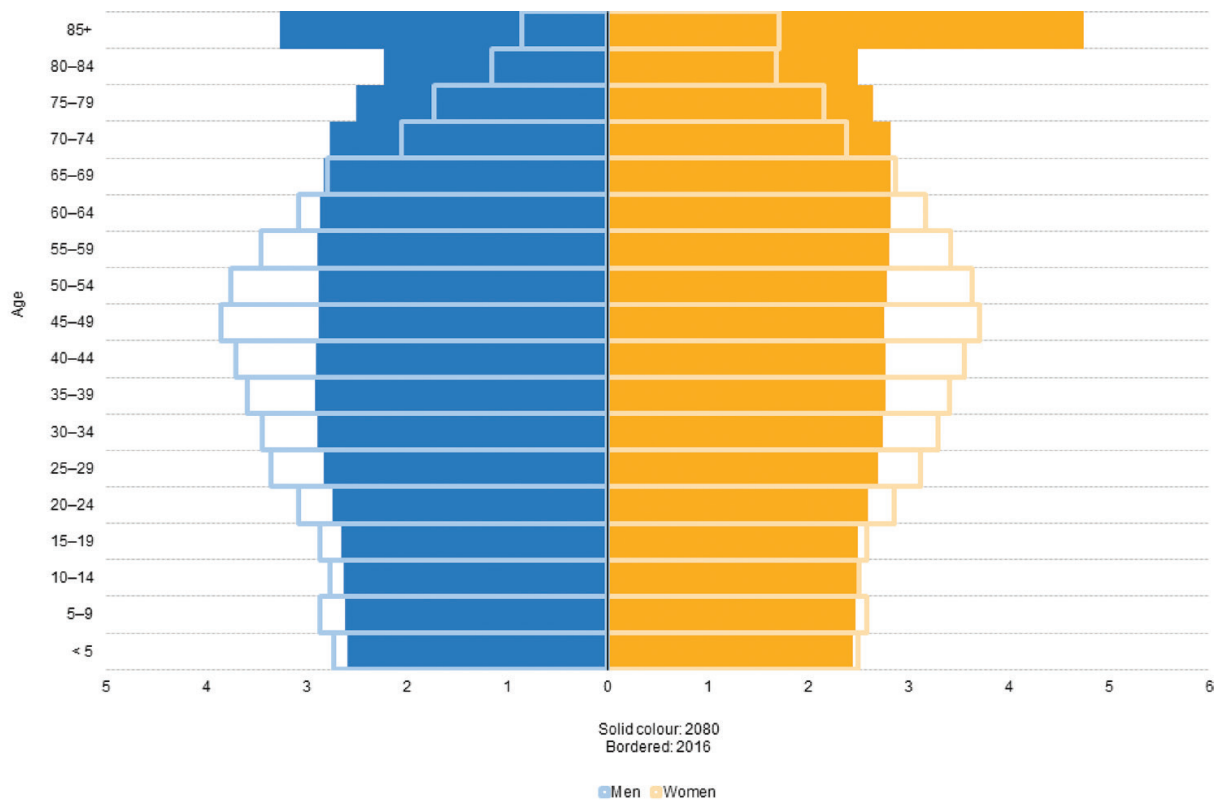
Population ageing is a long-term trend which began several decades ago in Europe [8]. The older population (aged 65 years and over) is constantly increasing. As seen on **Figure 1**, European population is projected to continue to age. And therefore, the importance of additional research on diseases typical for older people is becoming increasingly important.

In general, there is no certain age, after which the patient involvement is not recommended. Yet some researchers avoid recruitment of older patients because of certain difficulties they entail. Older people tend not to respect the regime of medications, have difficulties to the specific requirements of the study, especially when they are in conflict with their daily life (diet, daily regime, etc.).

Older people often have problems seeing and hearing, which means more time and effort to explain the purpose and conditions of the study. They tend more often to interrupt their participation in the trial, suggesting larger initial screening of patients.

Despite the above-mentioned complications, participation of older people in clinical trials is absolutely necessary and very important given the overall ageing of the population.

But can the elderly make a conscious choice? It has been known that the elderly people usually perceive new information worse than younger ones. Older people have a bad memory,



Note: 2016: estimate, provisional. 2080: projections (EUROPOP2015).
 Source: Eurostat (online data codes: demo_pjangroup and proj_15npms)

Figure 1. Population pyramids, EU-28, 2015: provisional; estimate. 2080: projections (EUROPOP2013) (% of the total population). Source: Eurostat (online data codes: demo_pjangroup and proj_13npms).

and show lower performance in some cognitive functions—hearing, vision, and reaction time. Thus, older people need more time to absorb and understand a similar volume of mental work than people in younger age.

Thus, in order to ensure that old patients understand and remember information and requirements regarding the study, the researcher is advised to split the procedure of obtaining informed consent in two parts. The purpose of the second part is to verify and confirm whether the old patient understands and remembers the information obtained in the first meeting. Patients who cannot remember important facts about the study should not participate in the trial.

8. Clinical trials on military

In the past, military participation in clinical trials has been quite common for many reasons—controlled diet, easy access to patient homogeneity of the population, etc. But the number of clinical trials conducted in the past in accordance with the norms and principles of Good Clinical Practice is comparatively small.

Examples of some of these studies include radiation exposure, mustard gas experiments and lysergic acid diethylamide (LSD) testing in non-volunteer human subjects [9], not to mention human experimentations before and during the World War II.

The ethical problem with clinical trials on military population is obvious—the military are in a position of subordination and dependency. There are methodological challenges associated with these clinical trials:

- Age range limitation does not allow to determine a strategy for prevention and treatment of the general population.
- Limited duration of the study group. Often, this is associated with the period of military service or contract, as well as frequent redeployments in other locations or divisions.
- Density of settlement contributes to high levels of disease in acute respiratory tract infections.
- Specific conditions of life style and daily regimen during military service may be a factor that could affect the test results.

Thus, clinical studies on military should be initiated and conducted with the consent of the ethical committee only in cases where the data cannot be collected from the civilian population or purpose of the test is the prevention or treatment of conditions and/or diseases peculiar to military population.

An example is the study of the probiotic foods with *Lactobacillus bulgaricus*. Effect of the probiotic foods with *Lactobacillus bulgaricus* was investigated on 56 sailors from the Bulgarian Submarine fleet and 60 pilots from the Air Force of Bulgaria, who were put to extensive mental and physical pressure. There are lots of clinical studies of the use of probiotic food containing *Lactobacillus bulgaricus* as a nutritional support and a part of the medical treatment in 60 cases of severe intoxication accompanied by poly-organic insufficiency. As a result, these probiotic foods were included in the regular diet of the pilots from the Air Force of Bulgaria, sailors from the Submarine fleet of Bulgaria and of commandos [10].

9. Clinical trials on people affected by mental health disorder

Clinical trials involving patients with psychosocial or cognitive disorders, as well as those suffering from drug or alcohol addiction bring up an ethical question—if these patients are able to make their own rational decisions.

People with intellectual or psychosocial disorders are deprived of their legal capacity and put under some form of guardianship. There are two main guardianship models: full and partial. People under partial guardianship keep their main civil rights but certain capacities are transferred to a legal representative, such as financial affairs. Those under full guardianship, on the other hand, lose almost all of their civil rights.

There are European countries where guardians besides other life spheres are also empowered to take decisions on behalf of the individual in regards to health care. Guardian's consent may

result in hospitalisation or medical interventions. This is considered as voluntary, even though the consent from the individual concerned is not present. The interventions might even be against the individual's expressed will, however in a legal sense will still be considered as voluntary. In other European countries, guardians or other legal representatives cannot make health care decisions. However, non-consensual interventions in the psychiatric field are still possible in most countries if a doctor finds them necessary and a court confirms the same.

European legislation outlines additional protection requirements towards inclusion of incapacitated patients into clinical trials:

- The informed consent of the legal representative has been obtained; consent must represent the subject's presumed will and may be revoked at any time, without detriment to the subject.
- Information received during the informed consent process should be adequate in view of the patient's capacity to understand it.
- No incentives or financial inducements are given except compensation.
- There are grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risk at all.
- The clinical trial is essential with respect to incapacitated subjects and data of comparable validity cannot be obtained in clinical trials on persons able to give informed consent, or by other research methods.
- The incapacitated patient should take part in the informed consent procedure as far as possible [4, 11].

In the past years, the so-called paradigm shift in disability policy is widely discussed. This is a shift from the deprivation of legal capacity to the right to support for exercising legal capacity.

Such example is a person diagnosed with Down's syndrome applying for a certain service. If he/she is provided information in easy-to-read format and adequate time and support, he/she may be able to understand pros and cons of the service and choose whether or not to use it. In this situation, no disability arises. However, if information is provided in standard language and no additional effort taken to explain it in a manner adequate to person's condition, disability becomes a fact. The paradigm shift calls for legal, attitudinal and environmental changes [12].

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