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Issues of Ethics in Geriatric Clinical Research

Katsa Maria Efthymia[1], Daratsianou Maria[1] and Tzavella Foteini[1]

Abstract

Introduction: Clinical trials made in geriatric population, regarding health issues disease require the establishment and the compliance of specific ethical principles. **Purpose:** To describe the basic ethical principles for clinical research in geriatric population. **Methods:** A literature review took place in the electronic database "PubMed", "Google Scholar" and "WHO" during the period 1989-2016. Criteria for articles exclusion were languages different from English and Greek, as well as articles in which there was no full access. Finally, 32 were included. **Results:** The Code of Nuremberg and later the Helsinki Declaration contributed to establish ethical principles in clinical research in humans. Regarding the research in elders, it remains ambiguous if they can be characterized as a vulnerable group. In any case, four basic bioethics principles which are needed to be followed: autonomy, justice, beneficence and non-maleficence. Some special issues of clinical trials in geriatric population are: the equal right for participation, the informed consent, the right of withdrawal without consequences, the protection of personal data and the protection from possible damages. **Conclusion:** In order to ensure the ethical dimension of these studies, it is required to take into account the fundamental rights and the principia of Nuremberg Code and Helsinki Declaration.

Keywords: clinical research, clinical studies, geriatric population, ethics, deontology, law.

1 Introduction

The Nuremberg Code (1947) and the Declaration of Helsinki (1964) offered the legal framework for establishing ethical principles in human research studies.

[1] Department of Nursing, Faculty of Human Movement and Quality of Life Sciences, University of Peloponnese, Sparta, Greece

Their primary aim was the human benefit and safety, with the Informed Consent Form (Informed Consent Document / ICD) holding an essential role in ensuring this [1,2].
In a clinical research the subject is human himself who is protected by ethical rules, in order not only to contribute to the science evolution but also to benefit himself after participating the study. Typical examples of scientific progress in which the role of human participation was crucial, are the cardiovascular surgery, organ transplants, vaccines development and specialized genetic therapies [1,3, 4].
Medical research on the natural aging, elderly health issues-diseases and pharmacological or other alternative forms of intervention in geriatric patients require the establishment of specific standards and participation requirements for the protection of this vulnerable group of patients. In addition to the clinical studies conducted for the prevention and treatment of physical diseases, many researches are directed in order to study the possible psychological factors which are related to the memory, cognition, and generally the personality of aged people. At the same time researches, regarding the social programs and their effectiveness in senior people, are conducted [5].

2 Methods

The literature review was based on the search of data from electronic databases: PubMed and Google Scholar. The articles used in this review included research studies and reviews, referring information about ethics and for the conduction of clinical studies made in geriatric population. The criteria for the exclusion of articles were languages different from English and Greek and articles for which there was no access to the full text. The selection of articles was limited in time from 1989 to 2016, using as key words: clinical research, clinical trials, clinical studies, geriatric population, ethics, deontology, law. Totally, forty (40) articles were found but thirty two (32) were studied for the current review because they were not available as full texts. Sixteen (16) legal framework's references regarding the studied theme were also taken into consideration.

3 Results

3.1 Main conceptual issues

Scientific procedure is a controlled observation that is taking place through an experiment [6]. The circumstances under which an experiment is carried out are created and controlled by the researcher, who tries to minimize or even restrict the external factors that could affect the outcome.
In the health sector, as noted above, the contribution of clinical studies, drug testing in human subject, [7] was important so as to improve the quality of life of society.
The Nuremberg Code (1947) was the first step for establishing ethical principles in

the humans' research. This code was imposed by the criminal researches that were conducted by the Nazis during World War II which were characterized not only unethical but also trampled every human right and the meaning of the scientific research itself [1].

The Declaration of Helsinki following the Nuremberg Code, is concentrating on the clinical studies and was expressed for the first time by the World Medical Association in 1964, having been adjusted for several times. The Declaration of Helsinki is regarding the promotion of humans' health, a basic human right. A prerequisite for the conduction of a clinical research which safeguards the participation in it, is the completion of the consent form by the participant volunteer himself or by the authorized representative [2,8,9,10].

As *elders* are defined people aged over 65 years. This conventional categorization has resulted in a highly heterogeneous group with important variations in physical and mental health. Once in the mid-1990s, an attempt was made for the re-categorization with an age basis having as a target the most appropriate description of the aging stages according to table 1 [11]

The elderly as a vulnerable group: Aging does not always characterize a person as inherently vulnerable. The NBAC (National Bioethics Advisory Council) does not consider the elderly as a vulnerable group of the population, although they have high potential for mental or physical harm alongside with children and women. Instead, the Agency for Research and Quality (AHRQ, Agency for Healthcare Research and Quality) part of the US Department of Health and Human Services), explicitly states that the vulnerable sections of the population may be at risk due to age, health, functional status, the possible coexistence of a chronic or incurable disease, evidence which may in fact apply to the elderly [5].

Autonomy is the ability and capability of a person to take decisions according to his benefit or desires. In the case of elderly the phenomenon of "roles reversal." often occurs. Specifically, the child assumes the role of the father or the mother of the elderly person taking also all the responsibilities arising from this role. Significant differentiation of this reversal is that this unnecessary decisions taking for the parent is considered unethical for the child. Besides, according to the principle of autonomy, any person is entitled to take the decisions on his own, except in the case that he is documented not able to do so (coma, etc. advanced stages of dementia) [12].

3.2 Basic bioethics principles

The four basic bioethics principles, also characterized as principia, that have to regulate the clinical research are: the principle of autonomy, the principle of justice, the principle of beneficence and the principle of non-maleficence. In the clinical research every researcher owes to support the person's autonomy and the right of self-determination while protecting in parallel the people with a reduced ability of taking autonomous decisions. With the principles of beneficence and non-maleficence the benefits are maximized and the risks are minimized always in favor of the participants. Finally, the justice principle ensures the fair distribution

with regards to benefits and hazards as a result of participating in the research [13].

3.3 Ethics committees

European Union has introduced some specific principals regarding the timetable for assessing a clinical trial proposal and the variety of issues which the committee ought to take into consideration. In this way, a degree of uniformity and harmonization has been achieved in all countries of European Union [14].

In Greece ethics issues in the scientific research of biomedical sciences are studied, examined and ensured by the «National Bioethics Committee», the National Committee for Ethics for Cclinical Sstudies and a series of committees that are housed in hospitals, universities and other institutions. In 1992 the 2071/92 law enabled the establishment of the National Council of Medical Ethics at the Ministry of Health Care and Social Security while the law 2519/1997 predicts special particles at hospitals which protect the patients' rights. (see legal framework)

In 2005 the National Bioethics Committee had a meeting so as to examine the ethical and social issues of its responsibility related to the establishment and operation of the Committees of Ethics in the biomedical research. Amongst others in the terms of this meeting it was found that the particles that have been established according to the 2519/1997 law were insufficient to cover the needs of control of ethics in the biomedical research as it is imposed by the international standards. An important step for solving this problem is the national law framework for the research that was formed by the 3653/2008 law which has as a purpose the methodical forwarding and promotion of research in Greece including research activities in the biomedical science. Basic point of this law is the establishment of the National Institute of Research and Technology for the evaluation of research proposals and several research programs. (see legal framework)

The framework of the ethics of research has been rapidly developed internationally over the last decades having as a goal to prevent the repetition and recurrence of mistakes and atrocities of previous eras but also to promote the scientific research and thus the scientific knowledge. Basic condition for success is that each researcher knows that no code of behavior, no ethical committee even no law adjustment can protect himself and more importantly the subject of the research such efficiently as the deep understanding, the admission and the approval of the fact that ethics and ethical approved behavior are his duties [15,16].

A significant example of an immoral research was the American government research (U.S. Public Health Service), Tuskegee Clinical Study for syphilis which lasted from 1932 till 1972 in which 600 poor Afro-American men participated. In this research not only the commitments for free medical treatment, food and burial treatment were kept but also even though that in 1947 penicillin was discovered It wasn't granted to the patients. Later on when this criminal attitude of the

researcher was made known, one of the consequences was also the negative and suspicious stance of the ethnical minorities for participating in clinical researches. Much lately in 16 of May in 1997 the president of the US Bill Clinton apologized publicly for this attitude of the American government health services [17,18].
Another, also negative example which took place in New York's Jewish Chronic Disease Hospital, in July 1963 regarded 22 elderly and helpless patients. Dr. Chester Southam and his collaborators injected live cancer cells, claiming research purposes, without informing the patients [19, 20].
In clinical research in general and thus in the more specialized geriatric clinical research basic rights of the participants which need to be protected are a) the right to participate in safe and valid scientifically researches b) the right not to be physically or psychologically harmed c) the right to keep the confidentially of the personal data d) the right for autonomous participation and e) the right for complete and constant information about the research in which they participate [21].

4 Discussion

4.1 An equal right to participate

Over the last century, huge steps were made towards the effective management of chronic diseases through biomedical innovations, studies for the promotion of health and diseases prevention, alongside with an enhanced understanding of pharmaceutical therapies and genetic determined health factors. However, these evolutions haven't helped equally all the population age groups. Inequalities are perpetuated due to the fact that participation of elderly in the research procedures is still low even though these people are holding the biggest health burden, showing high percentages for cancer, cardiovascular diseases, arthropathy, Parkinson disease and dementias.
Equal participation in clinical tests according to age is of vital importance for ensuring the safety and effectiveness of new therapies. Basic reason due to which medicine has to be tested also at older people is the differentiation they present in their pharmacokinetic and pharmacodynamics properties in contrast with adults. This results to important differentiations in the effectiveness and adverse effects. Moreover, in contrast with younger adults the behavior of the elderly is characterized by particularities that have to do with their age such as multi-morbidity and polypharmacy, increasing the risk of side effects and interactions between medicines [22].
Some gaps of policy and ethics have been spotted in literature which lead to unequal access to clinical tests and have to do mostly with phyletic origin and age. Adults of a greater age have to encounter a combination of obstacles including age racism ,companion diseases, economic restrictions, lack of insurance and generally aspects of communication problems (e.g hearing problems, low vision, mobility problems, cognitive weaknesses) have to be included [23].

An effort is being made so that the participating population of patients-volunteers in each clinical research program is representative of the population of target patients. As it is noticed in the current directive ICH E7, the disease assessment has to be combined with age, intake of other medicine and the coexistence of different diseases. Taking into account the increasing quota of geriatric population and an increasing recognition of its complexity it would be advisable to include more than hundred (100) patients with a different medical history to draw reliable results. It should be noted that in the group of patients with a geriatric profile, there exist in general more women than men due to their higher life expectancy. If there are disqualification criteria, there would be automatically more women with an exclusion of some special cases such as prostate diseases [24].

4.2. Informed consent, right of withdrawal and confidentiality

The scientific identity of researchers contains also their ethical obligation for defending the rights of the people that participate in researches. A consequence of this is the respect towards the autonomy of the subjects, for taking effortless decisions relevant to the choice for participating or not in a study, while in parallel the basic information for making this decision easier has to be available to them.

The fundamental right of voluntary participation in a research has a double meaning if the right of the person, which was chosen as a subject of a research, to accept this participation is defended, while in parallel his right to either withdraw from the procedure whenever he wants or ask for complementary information [25] is maintained.

The aware consent is considered to be the main mechanism for protecting the interests, the prosperity and the rights of the participants in the therapeutic or the researching action. In the international guidelines for awareness in clinical research, it is referred that "the decision for participating in a clinical study has to be in written form with a date and signature while it needs to be taken freely after being thoroughly informed for the nature, importance, consequences and hazards that are stemming from it. This document is completed by the person itself who is able to give his consent or when the person is not able to give this consent by its legal representative. If the interested person is not able to provide a written consent then a verbal consent is given with the presence of at least one witness". The witness who is referred to in this definition has to be unassociated with the members of the research team [26].

From all the above it is concluded that there has to be a signed consent from all the people of greater age which are of course able to consent or refuse this consent. A simple, short and easily understandable form-printed matter of consent helps the readability and understanding of data from the elderly participant. Special importance has to be paid to people with visual or other sensorial disorders so that the visual and hearing aids will be provided. Finally the usage of a simple tool or questions for checking the understanding of information from the elderly patient is advised. The researchers have to devote adequate time for the provision of information and the ensuring of acquiescent opinion of the elderly

patient according to the valid legislation. Additionally, the elderly have to be encouraged to ask questions and discuss whatever matter of concern for them. It is important to be understood that the consent is a dynamic continuous procedure and thus hasn't to be restricted by the existence of a signed document which is provided before the start of the study. In practice, in the procedure there could be included for example a short informative conversation during the duration of each visit between the elderly patient and the researcher who also has to protect their rights even if this has to be against their research [1].

Elderly patients and in some cases their legal representatives have to be aware of their right to refuse participation in a clinical test. The refusal for consent for participating has to lead to no consequences or discriminations. Inviolable rule is the fact that the participant has the right to withdraw from the research for whatever reason even a completely personal one without any consequence. In addition he has the right to continue the previous program of health treatment or even an alternative pharmaceutical treatment with which he feels safer. It has thus to be satisfied that his withdrawal will not affect any future therapy. In the case of a consent which is withdrawn in the middle for example of anesthesia the instant stop of the procedure may not be possible since the health of the elderly people participating may be in danger. It has to be pointed out that in case of a participant withdrawal the researcher still is responsible for reporting incidents relative with the test according to the pharmacovigilance law [26].

During the duration of their participation in a clinical research elderly patients and their legal representatives have to have the chance to watch the progress of the research having as an exclusion only cases where the research is characterized as clinical inappropriate or violates the right of the participant in privacy so that they would be able to decide a possible withdrawal every moment.

The subject should not accept any kind of pressure or coercion so that these rights may be valid. The meaning of coercion may include on the one side intimidations and threats for possible penalties that may be imposed with the denial of participation or the decision for the stop of it and on the other side promises for big rewards especially when it has to do with people that belong to low economic classes. The subjects have to receive special assurances that whatever their decision may be it won't affect their relationship with the researcher or the provision of health care [27].

According to Francis Bacon "Knowledge is power" and science is the best way to conquer knowledge). So in the case where people are bound to participate in a research their knowledge provides them the power to decide autonomously if they will take part in the study or not. The transparency during the provision of information and the sincere answers to all the inquires of the participants are a moral obligation of every researcher who owes to inform the possible subjects of his research regarding the procedure that will be followed, the subjects and their obligations and the goal of the research [28,29].

In order to ensure the respect to the autonomy of the person and his right for self-determination, the participants will have to be completely informed and

encouraged to ask questions for every possible subject that troubles them. Otherwise the participation in a research has to be considered as violation of their rights and their consent invalid.

Another important issue that is related with the clinical research is confidentiality and maintenance of secrecy which is an important rule in every ethical code. According to the general principle that governs the confidentiality in research, the data can be used only for the purposes of the specific research to which the subjects consented. It is a fact that the principle of confidentiality as it is in general applied in the health sector, often acts restrictively also for the researchers taking into account that the researcher owes to respect the right of the subjects for confidentiality and not to transmit the information he collects to third parties even if it has to do with research purposes. An exception is the cases where all these information have to be published for the achievement of a higher purpose, such as the protection of public health or the protection of life and safety of a man [12].

4.3 Protection from damages

In Article 24, paragraph 2 c) of the Medical Ethical Code it is stated that the research in humans is permitted only when "The hazards to which the human is exposed are disproportionally small compared to the possible benefits from the research" while in article 26 paragraph 2 a) of the same Code it states that the doctor-researcher and thus every member of the research team owes to "consider its highest duty the protection of life, dignity of the person participating in the research and this protection is of higher priority compared to the interest of the science of the society". (see legal's framework references)

Taking into account these two articles it is concluded that in order to have a research taking place the balance between possible dangers and benefits for the subjects has to be kept. Explaining, none of the participants has to be exposed to a risk of damage which is not covered by the possibility of a bigger benefit [30] while the meaning of a minimal risk has to be also taken into account. According to the United States Department of Health, Education, and Welfare (HEW) the meaning of minimal risk suggests that the person that participates in the research is not likely to suffer some damage which will threaten him in his everyday life [31].

The meaning of danger and damages is extremely wide and has to do with negative physical, psychological, legal, economic and social consequences that the subjects may undergo during or after the completion of the research. Therefore it has to do with dangers that have to be avoided not only by the researchers that carry out quantitative but also by researchers who carry out quality researches, either therapeutic or not. For this reason in a discussion carried out by the British Medical Association amongst its members it was concluded that the discrimination between therapeutic or not researches and it was suggested that every research has to offer a satisfying analogy of benefits and dangers for damages [32].

4.4 Legal framework

The legal framework according to which clinical tests are carried out to elderly patients includes the following European regulations and directives:

1. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. OJ L 121, 1.5.2001: 34
2. Directive 2001/83/ec of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. Official Journal L - 311, 28/11/2004 : 67 - 128.
3. Directive 2003/94/EC of the European Commission of 8 October 2003, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.Official Journal of the European Union.14.10.2003. L. 262 : . 22-26.
4. Clinical trials - Regulation EU No 536/2014 of the European Commission of 16 April 2014 for ensuring the identical rules for conducting clinical trials throughout the EU. Official Journal of the European Union 27.06.2014. L 158: 1-76.
5. Regulation (EC) No 726/2004 of the European Parliament and of the Council laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.2004R0726— EN— 06.07.2009 — 004.001.
6. Directive 2005/28/EC of the European Commission of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. Official Journal of the European Union 9/04/2005. L 91 : 13-19.
7. Pharmacovigilance regulations (EMA 2 /07/2012, comprised of Directive 2010/84/EU and Regulation
8. CH Guideline for Good Clinical Practice (E6), CPMP/ICH/135/95. (www.ema.europa.eu/pdfs/.../ich/013595en.pdf)
9. ICH Studies in Support of Special Populations: Geriatrics, Questions and answers (july 6, 2010). Web site: http://www.ich.org. : 1-5.
10. ICH 2008. Final concept paper E7 (R1). Studies in support of Special Populations Geriatrics. Revision of the ICH E7 Guidelines. 23/10/2008. : 1-5
11. ICH Studies in Support of Special Populations: Geriatrics, Questions and answers (july 6, 2010). Web site: http://www.ich.org. : 1-5.
12. (EU)1235/2010.http://ec.europa.eu/health/documents /new_en.htm
13. CHMP Guideline on conduct of Pharmacovigilance for medicines used by the geriatric population (June 2006) EMEA/CHMP/PhVWP/235910/2005- rev.1
14. Detailed guidance on the collection, verification and presentation of adverse

reaction reports arising from clinical trials on medicinal products for human use (revision 2) as required by Article 18 of Directive 2001/20/EC.
15. Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (revision 1) as required by Article 8 of Directive 2001/20/EC.Feb. 2006: 1-34.
16. Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (revision 2), as required by Article 9 of Directive 2001/20/EC.Oct.2005: 1-56.

5 Labels of figures and tables

Table 1: Aging stages

65 – 74 years old	**premature elderly**
75 – 84 years old	average elderly
above 85 years old	mature elderly
above 95 years old	Centenarian

6 Conclusion

The conduction of specialized clinical tests on elderly is necessary due to the different pharmacokinetic and pharmacodynamics of this population group. In the meantime the general principles of ethics have to be taken into account that stem from tree fundamental rights, the three pillars as Hirsh called them : autonomy (of the person), benefactions (benefiting and not causing damage) and justice (fair distribution of the obstacles and benefits of the research).
Always the following have to be checked:

- The implementation of unnecessary tests in elderly.
- The necessity of including the elderly for achieving the goals of the research and the benefits of the participants themselves.
- The appropriateness of each age group for the participation in the research and the reception of pharmaceutical creations
- If the initial case is based on relevant publications and experimental works
- If the quality of the research helps for getting reliable results.

- The side effects of the preparations in the elderly.

References

[1] F.Tzavella, "Deontological problems in clinical research: The Informed Consent Document", Arch Hel Med, Vol. 27, no. 2, 2010, pp. 230−238.
[2] L. Kopelman, "Children as research subjects: a dilemma", J Med Philos, Vol. 25, December 2000, pp. 745–64.
[3] M. Brazier, "Exploitation and enrichment: The paradox of medical experimentation", J Med Ethics, Vol.34, March 2008, pp.180–183.
[4] J. Kimmelman, "Battling a thousand points of might", Hastings Center Report, Vol. 39, January – February 2009, pp. 3.
[5] S. Walsh, "Conducting Research with the Elderly: Ethical Concerns for a Vulnerable Population", Southern Online Journal of Research Nursing, Vol. 9, No. 4 http://www.resourcenter.net/images/snrs/files/sojnr_articles2/Vol09Num04Art03.pdf
[6] P. Galanis, "Clinical Trials", Archives of Hellenic Medicine; Vol. 29, No. 4, 2012 pp.489–507.
[7] World Medical Association (WMA), "Declaration of Helsinki. Ethical principles for medical research involving human subjects", WMA, Inc, October 2000 (amendment).
[8] S. Edwards, M. McNamee, "Ethical concerns regarding guidelines for the conduct of clinical research on children", J Med Ethics, Vol.31, June 2005, pp.351-354.
[9] Council for International Organizations of Medical Sciences (CIOMS), "International ethical guidelines for biomedical research involving human subjects", Geneva, 2002.
[10] British Medical Association (BMA), "Medical ethics today; the BMA's handbook of ethics and law" (2nd ed), London: BMA, 2004.
[11] GJ. Caranasos, "A more opportune description of the stages of aging", J Am Geriatr Soc. Vol. 41, No. 8, 1993, pp. 888.
[12] AJ. Rosin, Y van Dijk, "Subtle ethical dilemmas in geriatric management and clinical research", J Med Ethics. Vol. 31, 2005, pp.355-359.
[13] L. Dunn, S. Misra,"Research Ethics Issues in Geriatric Psychiatry", Psychiatr Clin North Am. Vol. 32, No. 2, June 2009, pp. 395–411.
[14] A. Hedgecoe, F. Carvalho, P. Lobmayer, F. Raka. "Research ethics committees in Europe: implementing the directive, respecting diversity", J Med Ethics, Vol. 32, No. 8, 2006, pp.483–486.
[15] R. Northway, "Commentary", Nurse Researcher: Vol 10, no 2,2002, pp.4-6
[16] F. Fotis, D. Katopodi, G. Pafyla, "Ethical dilemmas in the management of health services", 2007. http://www.medtime.gr

[17] A. Caplan, "When Evil Intrudes", Hastings Center Report, Vol. 22, No. 6, 1992, pp.29-32.
[18] S. Reverby, "Ethical Failures and History Lessons: The U.S. Public Health Service Research Studies in Tuskegee and Guatemala", Public Health Reviews, Vol. 34, No. 1, 2012. http://www.publichealthreviews.eu/upload/pdf_files/11/00_Reverby.pdf
[19] L. Caplan, "The meaning of the Holocaust for Bioethics", Hastings Center Report, Vol. 19, No. 4, 1989, pp.2-3.
[20] B.Lerner, "Sins of omission--cancer research without informed consent", N Engl J Med, Vol 351. No.7, 2004, pp. 628-30.
[21] AC. Denson, A. Mahipal, "Participation of the elderly population in clinical trials: barriers and solutions", Vol. 21, No.3, 2014, pp.209-214.
[22] P. Wrobel, M. Dehlinger-Kremer, I. Klingmann, "Ethical Challenges in Clinical Research at Both Ends of Life", Therapeutic Innovation & Regulatory Science. Vol. 45, 2011, pp.189-105.
[23] A. Herrera, S. Snipes, D. King, I. Torres-Vigil, D. Goldberg, and D. Armin, "Weinberg Disparate Inclusion of Older Adults in Clinical Trials: Priorities and Opportunities for Policy and Practice Change", Am J Public Health, Suppl.1, 2010, pp.105-112.
[24] ICH Studies in Support of Special Populations: Geriatrics, Questions and answers, 2010. Web site: http://www.ich.org. : 1-5.
[25] E. Pucci, N. Belardinelli, G. Borsetti, D. Rodriguez, M. Signorino, "Information and competency for consent to pharmacologic clinical trials in Alzheimer disease: an empirical analysis in patients and family caregivers" Alzheimer Dis Assoc Disord. Vol. 15, No. 3, 2001, pp.146–154.
[26] S. Quallich, "The practice of Informed Consent. Urologic Nursing" Vol. 24, No. 6, 2005, pp.513.
[27] RL. Bushardt et al. "Polypharmacy : misleading but manageable" Clin. Interv. Aging, Vol. 3, No. 2, 2008, pp.383-89.
[28] ME. Tinetti, SA. Studensky, "Comparative Effectiveness Research and Patients with Multiple Chronic Conditions" NEJM, Vol. 364, No. 26, 2011, pp.2478-81.
[29] J.M. García. "Scientia Potestas Est – Knowledge is Power: Francis Bacon to Michel Foucault", Neohelicon, Vol 28, No 1, 2001, pp. 109-121.
[30] Kennedy & Grubb. Medical Law. Butterworths; 3 edition.
[31] D. Mutasingwa, G. Hong, R. Upshur, "How applicable are clinical practice guidelines to elderly patients with comorbidities?", Can Fam Physician, Vol. 57,No. 7, 2011, pp.253-62.
[32] D. Wendler. "The Ethics of Clinical Research", The Stanford Encyclopedia of Philosophy (Fall 2012 Edition), Edward N. Zalta (ed.), URL = <http://plato.stanford.edu/archives/fall2012/entries/clinical-research/>.