

e-Informed Consent in Clinical Trials – ethical considerations

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Abstract: This article is dedicated to analyze the possible impact of e-informed consent on clinical trials. The development of e-communication, telemedicine and e-Health, as well as the increasing number of clinical trials has required a new modality to inform and educate patients. Considering the importance of the informed consent from the patients' point of view, we analyse the developing standards in this field and the way in which we can improve the current practices and strategies in order to establish a set of ethical recommendations useful for researchers, clinicians and, not in the least, patients.

Key Words: clinical trials, informed consent, e-communication

1. Introduction

Bioethics is defined by Warren Thomas Reich as a “systematic study of the moral dimensions - including moral vision, decisions, conduct, and policies—of the life sciences and health care, employing a variety of ethical methodologies in an interdisciplinary setting.” [4, 14]

The development of a system of medical ethics is not only absolutely necessary, but also an ever more complex approach in the context of medical progress. [19]

Human being, as a central element in the medical field, is not a simple subject of the activities specific to the clinical trials, but the most important beneficiary of the research.

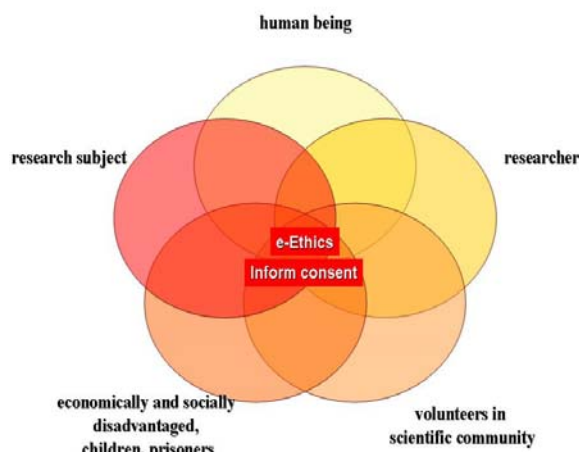


Fig.1 – e-ethics

During clinical trials researchers have an ethical and legal obligation to give subjects proper information in

order to make them able to decline or grant their consent to participate in the trial. In the last years clinical research become very sophisticated with a lot of procedures and technology involved and as a consequence the amount of information provided to the participants increased being more and more complex, often confusing, exceeding the patients' reading capacity.

This paper is part of a project that intends to implement the e-informed consent (e-IC) as a standard procedure in the clinical trial development.

It is also a pleading for the use of electronic communication, including binding electronic signatures, to gain informed consent (IC) from patients as a way to provide comprehensive, understandable information presentation to the patients to decrease costs, improve disclosure, and decrease time constraints on physicians. [17]

Along time a series of documents have been issued including the ethical norms accompanying the human activities, including the ones in the research area. The most known are: Magna Charta Libertatum, Habeas Corpus Act, Bills of Rights or Helsinki Declaration. The European Council elaborated a number of documents aiming at the standardisation of the research activities, the humanisation of the scientific rigour, the placement of man in the centre of the value system, as well as the decrease of risks and abuses on human subjects in the area of scientific research. [22, 23, 24]

As underlined by Henk A. M. J. Ten Have and Annique Lelie at Nijmegen Catholic University: “we all approach the moral dimension of the world from a set of prior understandings; they form the basis of our interest in what at first seems odd and strange to us, requiring us

to continuously reconstruct the moral meaning of our lives.” [21]

2. Demand for new approach in IC process



Fig.2 – Informed consent

There is an increasing need to improve the information communication process necessary for a good understanding of the patients participating in clinical trials. [3, 11]

Legally, the clinical investigators and the patients' advocacy need to prove without doubt that a person was informed about and understood what their voluntary participation in a clinical trial required. [9]

No legislation focuses specifically on the use of electronic media or electronic signature in the informed consent process. There has been a physician movement to use new technologies for informed consent, based on the theory that these technologies enhance the potential to achieve the consent.

Informed consent is a process not only a document that has to be read and signed by the participant.

As a document, the IC offers a summary of the clinical trial: “the aims and methods of the research, the expected duration of the subject participation, the benefits that might reasonably be expected as an outcome of research to the subject or to others, any risk to the subject, associated with study, maintenance of confidentiality of records, responsibility of investigators, provision of free treatment for research related injury, compensation of subjects for disability or death resulting from such injury, freedom of individual to participate in and withdraw from research at any time without penalty or loss of benefits to which the subject would otherwise be entitled”, etc. [7]

The beginning of the informed consent process consists in a conversation between the clinical

investigator and the patient, who is presented the option to participate in the clinical trial.

Depending on the patient's desire, two ways could be followed: the patient takes the IC document at home to study it alone or together with the family, or s/he reads the IC at the clinical centre.

If the patient decides to enter the trial, the patient gives his/her official consent by signing the document. The patient will receive a copy of document latter used it as an information source about the procedures, rights and obligations as a participant during the trial.

The informed consent process continues with on-going explanations to the patient, offering appropriate answers to his/her possible questions that will help the patient to “make educated decisions about whether to begin or continue participating in a trial”. For sure the IC document alone is not a guarantee that a patient fully understands what participation means. Therefore, before the patient takes a decision, the research team will discuss with him/her the study's procedures, risks and benefits, rights and obligations. After the patient grant the consent to be enrolled, the research investigators will give him/her continuous updated new information that may affect their status. “Before, during, and even after the trial, you will have the opportunity to ask questions and raise concerns. Thus, informed consent is an ongoing, interactive process, rather than a one-time information session”. [10]

The informed consent process reaches its purpose only if patients understand the information presented by the IC document or medical team.

In the last 10 years of research practice, the IC has evolved from a simple to a rather long document (more than 20 pages), with a large amount of complicated information describing many procedures difficult to understand. This may be relevant for the study development but irrelevant from the viewpoint of the patient's consent.

A challenge of this process is the fact that a great number of less instructed or middle age/elderly patients not having or losing the reading exercise really find the study of this document exhausting. They give up after the first pages, saying “My doctor knows best”. The patients too easily consent to participate in the trial because the doctor has told them that they can. [15]

The problem requires more time to be allocated by the clinical investigator in providing each subject with an adequate amount of detailed information. However, the extra time necessary for this does not usually exist (generally it is about lack of time, time constraints on physician-patient interaction) and sometimes investigators choose the easy way, which leads to serious deviation from the good clinical practice conduct.

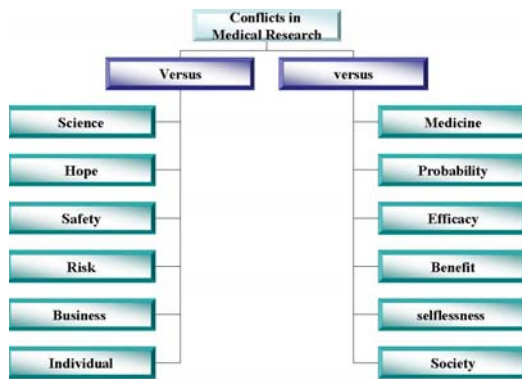


Fig.3 – Conflicts in medical research

Other challenges of the acquisition of valid informed consent are: variation in the ability of patients to comprehend and retain information that IC document/physicians disclose, irrational decision making by patients, and the current environment of health care delivery. The prevalent managed-care structure places constraints on physicians' time with patients and may contractually give financial incentive for limiting the delivery of medical services and access to subspecialists. The contractual incentives between physicians and managed-care organizations may alter a physician's advice to a patient, creating a need for unbiased information to ensure that informed medical decision making occurs when a patient is confronted with a complex clinical trial choice. The limited time for physician-patient interaction diminishes the opportunity for a detailed discussion and exacerbates the limitations caused by the differences in abilities among patients. [13]

First of all, the simplification of the informed consent document is mandatory for the good of the subjects.

Therefore, new and new recommendations and guidance must be done for developing the documents in an ethical way. The recommendations have followed three goals: "to make the forms more useful and understandable to people who want to participate in clinical trials; to aid investigators in developing better informed consent documents; and to assist Institutional Review Boards (IRBs) in reviewing the documents and ensuring their quality". [10]

3. e-tools for e-informed consent

In order to prevent/solve these problems a computer generated program could be a useful tool.

An electronic media audio-video interactive presentation IC or interactive web-based IC presumes to give benefits to investigators and subjects alike and could be introduced as a supplement to the paper-based informed consent IC process.

The possible benefit of interactive medical web sites or media presentations is to help patients attain the

knowledge and understanding necessary to discern complex medical information. Accessing an interactive web site or watching a multimedia presentation educates viewers about clinical trials procedures through text, illustrations, photographs, and animation.

The efficacy of an e-IC program has to be evaluated in some feasibility studies, with subjects from different centres suffering of different medical conditions. Some centres will use the e-IC to supplement the paper-based IC, others will use only a standard paper-based IC. Participants from all centres will also receive a face-to-face consultation with a member of the research team.

Does the use of an e-IC as an e-learning tool achieve the goals of educating the patient while freeing up the medical practitioner and thereby reducing medical costs?

It should be verified how the patients and the research team embrace the new e-IC technology and if institutional ethics committees fully accept the use of this innovative approach to IC. Additional outcome will include the effectiveness of the software in delivering the interactive video presentations, the reliability of the involved hardware components (i.e., Tablet PCs, headphones to listen to the audio without being disturbed) and the estimation of the impact of the use of this technology on costs.

The goal is to develop an application used for presenting the e-learning modules and also track the progress of each subject through the information process in real time with full consideration of 21 CFR Part 50 requirements for adequate IC. [2]

We consider that the Tablet PCs have combined optimal mobility with ideal user friendliness. Viewers will be able to use the Tablet PCs offline or online, mostly in the waiting room, and did not require a keyboard or a PC mouse.

By incorporating photographs of the clinical centre and study team, the presentation will be personalized and the viewer becomes familiar with team members and this will strengthen the subject-researcher relationship, which is considered a powerful tool for promoting subject retention.

After the subject has completed the e-IC session, the site personnel through the specific feature will transmit the tracking data to the server allowing individual centres, data management or the sponsor to retrieve numerous real-time reports.

The presentations could also be customized to collect some data about the patient, e.g. collecting gender information. Once the gender of the subject has been captured in the session management screen, gender-specific versions of the presentation are delivered (e.g., female patients would be offered sections on contraceptive precautions during the trial).

Also the program could provide for each subject a 21 CFR Part 11-compliant e-signature, and a PDF format of the text IC form including the signature, that could be printed out in one of the printers at the site. The patient could then receive a signed copy immediately, while another copy will be placed in the medical record. The development of e-IC technology to be used in clinical trials should respect certain requirements such as: the programmers' capability to create multimedia content for clinical trials and have extensive experience in this role, quality control measures must be set-up, in-depth knowledge of pertinent regulations must be demonstrated (e.g., HIPAA, 21 CFR Parts 11 and 50). [8]

The video content as animated slideshows, which might satisfy e-learning requirements for rapidly changing content, will be available in a library section and also a study-specific section that includes all elements of the paper IC document. The reference library could contain optional clips that cover information on disease management, background information on clinical trials, and other relevant topics.

The standardization of the e-IC information and delivery will be archived through an identical video presentation, with the exception of a brief site-specific welcome clip.

Near the end of the video session, subjects will be asked to complete a series of true/false questions to verify their comprehension. As a feedback tool in the trial version of the program, an e-questionnaire will be built into the application for both patients and site team to rate the usability of the technology and its associated tools in the pilot trial.

The interactive software will offer a testing feature that enables a patient and a physician to jointly confirm the patient's understanding, approval, and informed acceptance of the clinical trials procedure. Physicians may use the testing features to identify the areas in which more discussion must occur to achieve informed consent, based on a short analysis of the conflict in the medical research.

The usefulness of the e-IC technology will be assessed at least in part by results from standardized questionnaires evaluating the interest of patients in participating in clinical trials using e-IC. The usefulness of e-IC as a source of valid information and involved hardware have to be rated (from "very low" to "very high"), by scores for quality of the content (from "bad" to "very good"), completeness of content (from "incomplete" to "complete"), appropriate duration of the presentations (from "too short" to "too long"), usefulness of navigation tools, language used, and the Tablet PC itself (from "very low" to "very high"). Three aspects will be evaluated: the investigators' opinion about the e-IC, the influence of the personal discussions with the patient on the informed consent process and the

time spent compared to the time required by the normal text-based consent.

Published studies report that alternative methods for obtaining IC such as multimedia systems are considered to provide substantial benefit to subjects. [12] Similarly, Eilenberg et al. reported on patients using interactive Web-based IC with high satisfaction rates. [6]

4. Ethics and e-informed consent

As stated by Selye, scientists are with good reason worried by their own ethics, conduct to work and fellows. Great enthusiasm and ambition to attain perfection in any field are so consumptive that man has left little room for other feelings and manifestations, becoming a highly specialized machine, precisely directed to a certain goal [5].

The informed consent is 'based on autonomy, individually authorizing a medical intervention or research involvement. As a social rule, this is the legal way of gaining consent in institutions.' [20]

The figure below suggests that the informed consent is part of the ethical elements involved in the clinical development. e-IC raises a number of ethical questions common to the consent obtained through classical means, but it also presents elements particular to the way in which it is obtained through electronic means. [16]

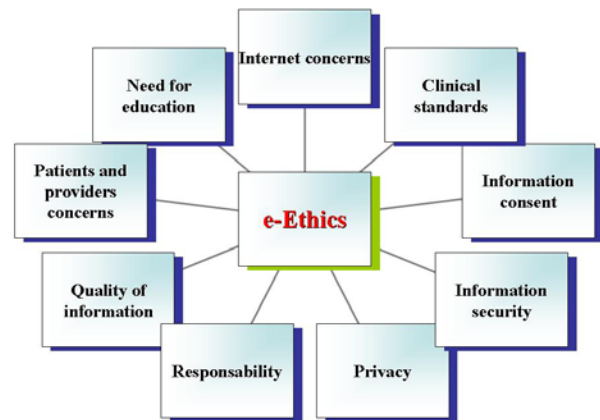


Fig.4 – e-ethics

The informed consent has to be gained voluntarily, by competent persons who have had access to every bit of information, such as the treatment effects, the anticipated results and possible risks.

5. Conclusions

The informed consent is both an ethical doctrine, deriving from the principles of showing respect and observing one's rights to self-determination, and a legal doctrine, legally imposed and having minimal standards

to be followed, the conditions of renouncing the IC being, ethically, rather restrictive.

The current paper-based IC process is highly regulated. Using e-IC can be considered a breakthrough in improving IC without impacting the current paper-based system. e-IC can overcome the above mentioned disadvantages in the existing paper-based processes. A very important advantage of the applied e-learning tool will be the evidence documentation of the IC and understanding process.

e-IC helps researchers to obtain an easier to understood informed consent through an interactive multimedia computer based tutorial.

Interdisciplinary research is increasingly engaged in the ethical regulation of the interconnection among different research activities, while the medical bioethics experience, positive or not, has to reflect itself in this research, which has directly or indirectly repercussions on the human existence. [18]

The fact is perfectly emphasised in a 2001 USA National Bioethics Advisory Commission report, subtitled Education as the key to promoting local responsibility: *“It is unrealistic to think that ethical obligations can be fully met without guidance and resources. To help researchers and IRBs fulfil their responsibilities, the federal government should promote the development of education, certification, and accreditation systems that apply to all researchers, all IRBs members and staff, and all institutions.”* [1]

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