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Ph.D. student Daniel PURCARU

e-Informed Consent in Clinical Research

- Summary of PhD thesis -

Scientific tutor

Prof.univ.dr. Liliana ROGOZEA

BRAȘOV, 2014

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Also, we would like to invite you to attend the public presentation of the PhD thesis.

Thank you.

CONTENTS

Motto

"An autonomous person signing a consent form without reading it or understanding it is qualified to give informed consent, but failed in doing so"

Prof. Ruth Faden - Biomedical Ethics, Johns Hopkins Berman Institute
Phil. Tom Beauchamp, Kennedy Institute of Ethics (1986)

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Keywords: informed consent, clinical research, multimedia, internet

Introduction

Topicality and necessity of the theme

Improving the process of informed consent in clinical research is a constant preoccupation of the regulating authorities in the field, a challenge for the professionals and a requirement from the participating patients.

The clinical study of the medication with therapeutic benefit has become a complex field, with a highly sophisticated activity. Clinical research involves numerous investigation methods, medical procedures and technologies, as well as a certain quantity of information offered to the ever increasing number of participants; all these being ever more complicated, sometimes confusing, and potentially exceeding the patients' capacity to read and respectively, understand and remember. There is an increasing need to improve the information-communication process, with a view to ensuring a better understating, necessary to the patients participating in the clinical research, so that a valid aware informed consent might be obtained.

The state-of-art discoveries in information technology and Internet offer the opportunity of developing a new method to obtain the informed consent, in the context of an electronic medical system, through an online multimedia interactive platform, for instructing the subjects, with a view to their participating in clinical studies.

Given the complexity increase of the clinical studies, there is interest and there are requests, from both the sponsors and clinical-research organizations, as well as from the doctors (investigators) and patients to use the new technologies in order to obtain the informed consent, as well as to unequivocally prove that the subjects were informed and they understood the requirements of their voluntary participation in the clinical study.

Objective of the research

The general and main objective of the thesis is the improvement of the informed-consent process in the clinical research on the medication, searching, identifying and implementing the most appropriate *method* to obtain a valid informed consent.

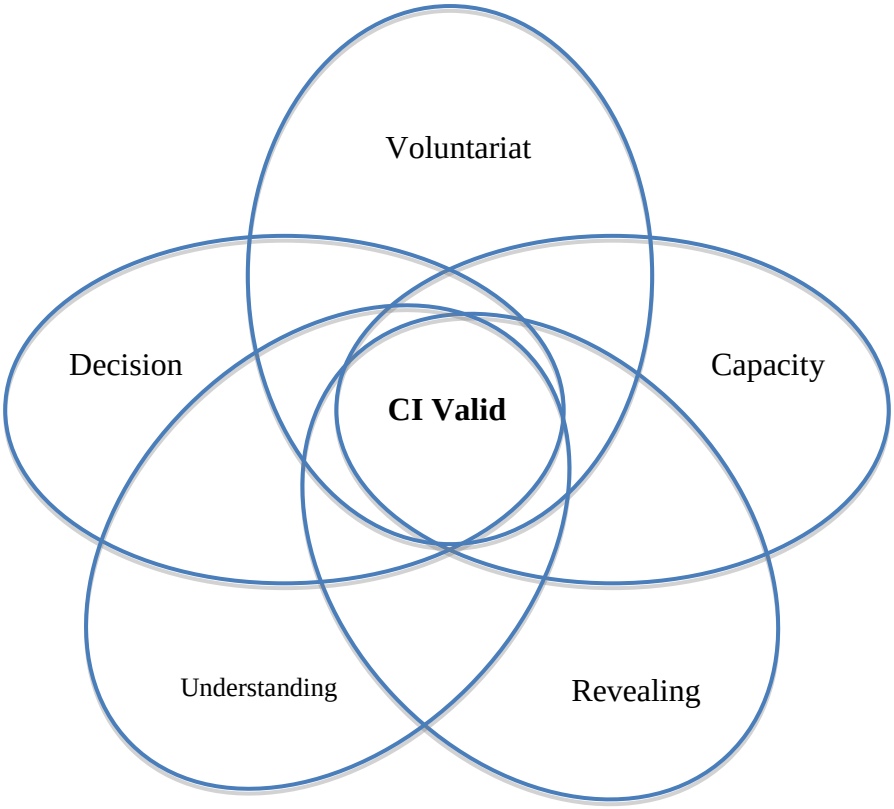
This work presents the developed *instruments* (means), adequate both to the clinician investigators and to the subjects in the process of informed consent, highlighting the

implementation of the electronic system of communication-evaluation-learning, in the current clinical research practice, as well as the results obtained from implementing such a system.

I. GENERAL PART

1. The concept of informed consent in clinical research

Informed consent is a documented process. It is a *process* of lifelong presentation/information/learning of all relevant aspects of the clinical study to the person who voluntarily confirms his/her wish to participate or not. The *decision* of the informed consent is documented by a written form, signed and dated.



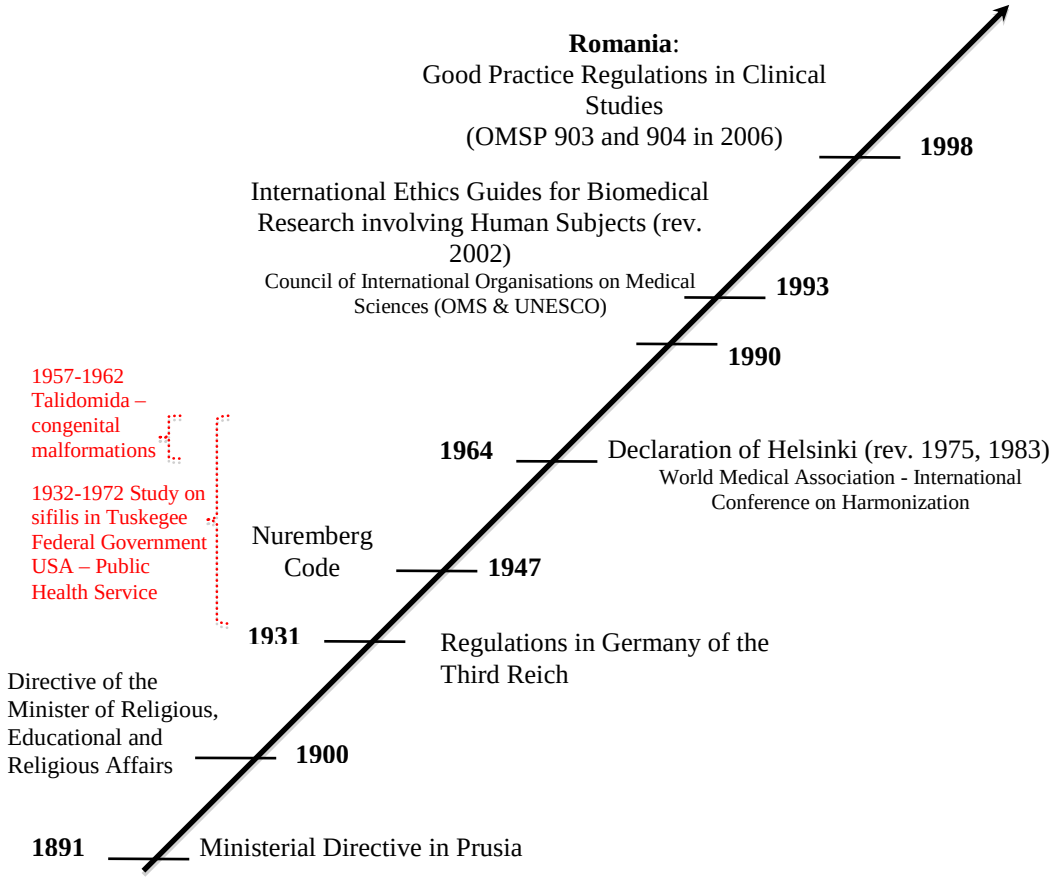
Basic components of a valid informed consent (CI)

The respect towards the patient's autonomy and the protection from harm and prejudices are extremely important, both in clinical care and in clinical research (Pierce 2003). Nevertheless, clinical care and clinical research are different. The main purpose of clinical care is to bring benefits to the patient. Instead, the main purpose of the research is to obtain new knowledge; the prospective patients being those who mostly avail from the benefits of this research (Truog et al. 1999). In this way, the standard of informed consent, in clinical care or in

research might be different, depending on the context or on the risk level. In practice, clinical research is much more severely controlled by regulating codes and avails itself of greater supervision from the ethics committees or from the institutional reviewing committees, compared to informed consent in clinical research (US National Institutes of Health 2004).

2. Development and history of informed-consent regulations in clinical research

The Nuremberg Code of 1947 is regarded as the first document imposing ethical regulations, on human experimentation, based on informed consent. However, the researches of professors Jochen Vollmann and Rolf Winau indicated that the basic concepts of informed consent had been formulated long before the Second World War and the Nazi crimes in Germany (Vollmann & Winau 1993). Nowadays, there is a set of common ethical principles, internationally defining the procedure of informed consent, adopted by the legislation of each participant country.



Major landmarks in regulating clinical research

3. Limitations of informed consent in clinical research

In over 10 years of activity in the field of the clinical research on medication and as a result of the study on the current situation of the informed-consent process, a series of observations have been made, grouped into three categories, which have become **premises** of the doctoral research, as follows:

In terms of the ***informed consent document***, it has evolved from a short to a long document, frequently exceeding 20 pages, containing a great volume of complex information which describes procedures difficult to understand, in spite of its facile language (Baker & Taub 1983; LoVerde, Prochazka & Byyny 1989; Henry et al. 2009; Hopper, Ten Have & Hartzel 1995; Meade & Howser 1992). The strategies meant to improve the informed-consent documents have been reviewed, resorting to a simple language. Recommendations have been made, for the discussion between investigator and patient, with a view to improving communication and understanding, and to increasing the level of satisfaction in the informed-consent process. The described studies have shown that improving the informed-consent documents, by systematically raising the lexical-syntactic readability or by the intervention of the working groups, leads to a better understanding of these documents by the subjects, regardless of the used method (Sharp 2004; Paris et al. 2005; Christopher 2007; Dunn et al. 2002; Agre & Rapkin 2003; Agre et al. 2003; Paris et al. 2010).

In terms of the ***clinical study subjects***, there is a lack of interest, on their part, in the activity they will attend (Corbie-Smith et al. 1999). They comply with the calendar and the procedures of the study, yet they are not highly interested in the nature and objectives of a clinical study. In the current research practice, a challenge is that a certain number of less instructed/educated or aged patients, or who have lost the exercise of easy reading, consider the study of the document quite fatiguing. Even if the document is read by a doctor, the patients' attention will often wander, or, if the document is individually read by the patient, (s)he will proceed superficially, skimming the text, as (s)he would if (s)he read an agreement of utilities, to be signed. There are subjects with a low level of understanding, remembering and, respectively keeping in mind the information; and some patients are not so motivated to understand (Cox, Fallowfield & Jenkins 2001; Joff et al. 2001; Appelbaum et al. 1987). They are only interested in the final result (cure or improvement of their state), even if they are aware or informed this is not a guarantee.

Even if, legally, the failure or the lack of understanding do not lead to invalidating the consent, ethically, for the patient's good, a method should be used, which might certify the latter has gained full understanding.

One of the purposes of this study was to transform the informed consent in fully aware consent, a significant difference being implied between the two terms under discussion.

Moreover, within the doctoral research, there was also aimed at noticing whether the subjects, after understanding the nature of the clinical study and its implications, succeed in assuming, on their own initiative, without any constraint, their incumbent part from the medical activity conducted in an organized framework, strictly monitored by experts. The participation in clinical studies means not only the potential therapeutic benefit of the medical act (which may be absent) or the free investigations, medication and free consultations; but also, and especially, the voluntary contribution to obtaining results that might benefit other persons, too; and, likewise, the evolution of medical science. Secondary, beside the possibility to experiment a new therapy, the persons involved in such activities acquire a sense of usefulness, by their contribution to the scientific community. Nevertheless, all these benefits can also be reached within the limits of the medical-field ethics, expressing thereby consideration and respect for the subject of the research.

With respect to the ***investigators***, one problem is that they frequently do not have the time to present all necessary information and explanations. Another problem is that, sometimes, they take the easy path and accept the "transfer" of the decision to the patients, as the latter give their assent much too easily, saying: "- Doctor, you know better what I should do!" or " – Doctor, I trust you completely!". This trust is welcome, due to its great healing potential by the placebo effect, yet it may lead to abuses.

Starting from the aforementioned observations, the question has raised: "*How can the informed-consent process be significantly improved?*".

4. Informed consent in clinical research, in informatics era

The attempts to improve the informed-consent document have shown that this is hard to achieve because, on one hand, the document content is strictly legislated (by the guide of good practice in clinical research), and there is a great volume of information offered to an ever increasing number of participants; and, on the other hand, as regards the text, there is not much to be done to the language, terminology and readability, given that they are under the permanent supervision and assessment of the experts in the development of such documents, and of the legislating authorities.

The analysis on the level of the current research in terms of electronic communication, with a view to obtaining the valid informed consent highlighted multimedia and interactivity as means to enhance attention, motivation, learning and understanding. Many researches focused on the use of the media services, in order to deliver the consent-related information (Agre et al. 2003; Campbell et al. 2004; Dunn et al. 2002; Henry et al. 2009; Jeste et al. 2008; Karunaratne et al. 2010; Kass et al. 2009; Strevel et al. 2007). Nevertheless, most of these researches on

informed content gave inconsistent results (Cohn & Larson 2007; Dunn & Jeste 2001; Flory & Emanuel 2004; Jeste et al. 2008; Ryan et al. 2008). Henry James and collab. (2009) complain of the "*relative insufficiency of the data in the fundamental, rigorous and conceptual studies*" (page 1), which creates a barrier in the use of multimedia services in informed consent (Henry et al. 2009); Flory, Wendler and Emmanuel (2007) claim that informed consent must turn into an evidence-based practice (Flory, Wendler, & Emanuel 2007). The cognitive theory of multimedia learning (Mayer 2001) and the technology-mediated learning (Mahoney et al. 2002; Wan, Wang & Haggerty 2008; Alavi & Leidner 2001) were applied in the design of the created multimedia system, in order to help those studying to use more efficiently their working memory in selecting, organizing and integrating the information; which results in a more efficient learning process.

The Internet has also transformed clinical research. Currently, numerous clinical studies in the field of medication resort to the Internet and Information Technology, in order to register the patients' screening, to carry out randomizing, to allot and account for the medication, to monitor safety, by recording the possible adverse events or health alterations, to collect the efficacy-related data at the patients' domicile or at the medical centre, to close the databases (Barrett et al. 2001). The patient's audio-visual information improves knowledge and understanding, without raising anxiety (Luck et al. 1999; Mason et al. 2003), influences behaviour (Sherafat et al. 2003) and helps patients make the decision to participate in the clinical study (McGregor 2003).

Yet, the consent procedures can be significantly improved; and a possible solution to solve the lack of control upon the reading of the informed-consent documents by the subjects, to verify the understanding and to raise the satisfaction in the informed-consent process is to create an interactive multimedia platform, namely to use a computerized electronic format, with a view to obtaining informed consent.

II. PERSONAL RESEARCHES AND ACCOMPLISHMENTS

In order to achieve and implement the e-consent, there has been created **MICONOS (**its name comes from abbreviating **Multimedia Interactive CONsent Operating System),** an online interactive informatics *innovating* system, destined for informing and verifying the understanding of the patients, in the process of informed consent, with a view to participating in clinical studies. The audio-visual multimedia system (images, video, text and sound) with its instruments and functionalities, is an originality element, because, in the medical field, there are

electronic platforms for informed consent, implemented with limited functionalities (only "e-learning"-type information) for dental or surgical procedures; yet not for clinical research.

5. Cross-sectional prospective observational study of patients' behaviour during the informed consent process

The observational study of the patients' behaviour, during the informed-consent process anticipated the ascertaining and experimental researches on the impact of the informed-consent document on electronic support, compared to the printed format, on the informed consent, in full awareness.

The hypothesis has been enunciated that the behaviour of the patients participating in a clinical study, to ask questions or not, as well as their quality, may be an indicator for their interest, knowledge of the facts and understanding of the information submitted in the consent documents.

The objective was the analysis of the patients' behaviour until signing the informed consent form.

Scheme of the informed-consent procedure

The study results have shown that, of the total of 68 participants, most of them (24) asked no question, and the others asked between 1 and 4 questions; and, of the 92 questions: (20,6%) referred to the gist of the clinical studies, (72,8%) targeted the form of the studies and (6,6%) had no connection with the clinical study. This attitude may be a sign of no or insufficient interest, knowledge of the facts or understanding. Therefore, it is recommended to use, within the informed-consent process, some helping tools, meant to stimulate the patients' interest in what will happen throughout the clinical research, to keep their attention focused on the presented information and to assess, in understanding the communicated notions.

6. Studies of the electronic informed consent document compared with the printed format in the aware informed consent process

The researches supposed creating comparative groups of subjects who should undergo the informed-consent process in electronic format (multimedia informatics system) under the real conditions of effective participation in clinical studies (not simulated), which is another element of originality, differentiating the current study from other previous studies.

The general **objectives** of the conducted researches derived from their purpose:

1. To identify the individual and contextual factors which influence the subjects' level of satisfaction in the informed-consent process.
2. To submit an applicative model, meant to improve the informed-consent process, by the creation of an online interactive multimedia platform for the "electronic informed consent".

The specific objectives were:

1. To develop three research tools:
    - for assessing the comprehension of the present information;
    - for assessing the subjects' level of satisfaction in the informed-consent process;
    - for assessing the level of exercise, as regards the informed consent, knowingly.
2. To design and implement an online interactive multimedia platform, as regards the "electronic informed consent".
3. To analyze the relations existing between the subjects' level of understanding the presented information and their degree of satisfaction in the informed-consent process.
4. To assess the impact of an online interactive multimedia platform, in terms of "electronic informed consent" on the level of understanding and awareness in the informed-consent protocol.

The following **hypotheses** were stated:

1. The high level of understanding the submitted information is allegedly strongly associated with the rise in the subjects' level of satisfaction, with respect to the multimedia format versus paper.
2. The number of errors in the information process for informed consent can allegedly be explained by the combination of the most important aspects that facilitate the comprehension of the information.

3. The relation between the levels of understanding related to the presented information is allegedly influenced by the efficiency of the multimedia platform; therefore, the use of the multimedia platform is strongly associated to the rise in the level of exercise of the consent, in full awareness.
4. The level of understanding with regards to the presented information is allegedly influenced by the efficiency of the multimedia platform; therefore, the use of the multimedia platform is strongly associated to the rise in the subjects' level of exercise of the consent.

The **material** and the **methods** of the researches conducted in order to assess the efficacy and the satisfaction in using MICONOS in the current practice of clinical research required the following stages:

1. Ascertaining research – for identifying the individual and contextual factors of influence in understanding, satisfaction and full awareness;
2. Pilot study - for:
    - testing the research instruments and modifying them in case of need (if the test results proved significant, this means that the instruments were accurate and measured what they intended to measure; and if the test results proved insignificant, they had to undergo modifications);
    - setting the measure of the group under study, in order to reject the null hypothesis (the absence of the relations among variables) and to obtain statistically valid results, which may be extrapolated over the population referred to;
3. Experimental research – for establishing the causal relations between the variables under study, respectively between the interactive multimedia platform and the understanding, the satisfaction and the full awareness in the informed-consent process;
4. The comparative impact study of the interactive multimedia platform vs. classical study among the medical staff (described in chapter 7) – for validating the multimedia platform and the associated instruments among the medical staff.

The researches were conducted in the period February 2012 - March 2014, at the Department of Clinical Studies of the *Clinic Neomed* in Brasov. They included 362 patients, who were going to participate in clinical studies of Dyslipidemia (308); BPOC (44) and Nasal Polyposis (10) and 40 doctors. The patients were divided into 3 groups, based on the received information format (multimedia or printed) with a view to obtaining the informed consent, in this way: a control group, which only studied the document on paper support (NH-122 patients); and two experimental groups, which used the multimedia platform, before (HIMM-120 patients) or after (HDMM-120 patients) which read the printed document. The research also included a validation stage of the created instrument (interactive multimedia platform) among the doctors, who were an

important part in the clinical-research process. Knowing the impact of the online platform of informed-consent among the specialists who might be involved in clinical studies was targeted; they becoming subjects of the described research and being divided into 2 groups (multimedia: 20 and paper: 20). The methods of research were the survey-based inquiry and the study of the databases, representing the number of correct answers, respectively the total number of errors made by the subjects after the application of the survey assessing the understanding of the presented information, or the answers to the questions in the feedback (satisfaction) questionnaire, their presentation in printed format respectively multimedia platform.

The participants' consent (patients and doctors) was obtained for data collection and analysis.

The statistical analysis was made with the software G*Power 3.1 and SPSS 19, for the factorial analysis, multiple linear regression, test of significance t, test of association $\chi 2$.

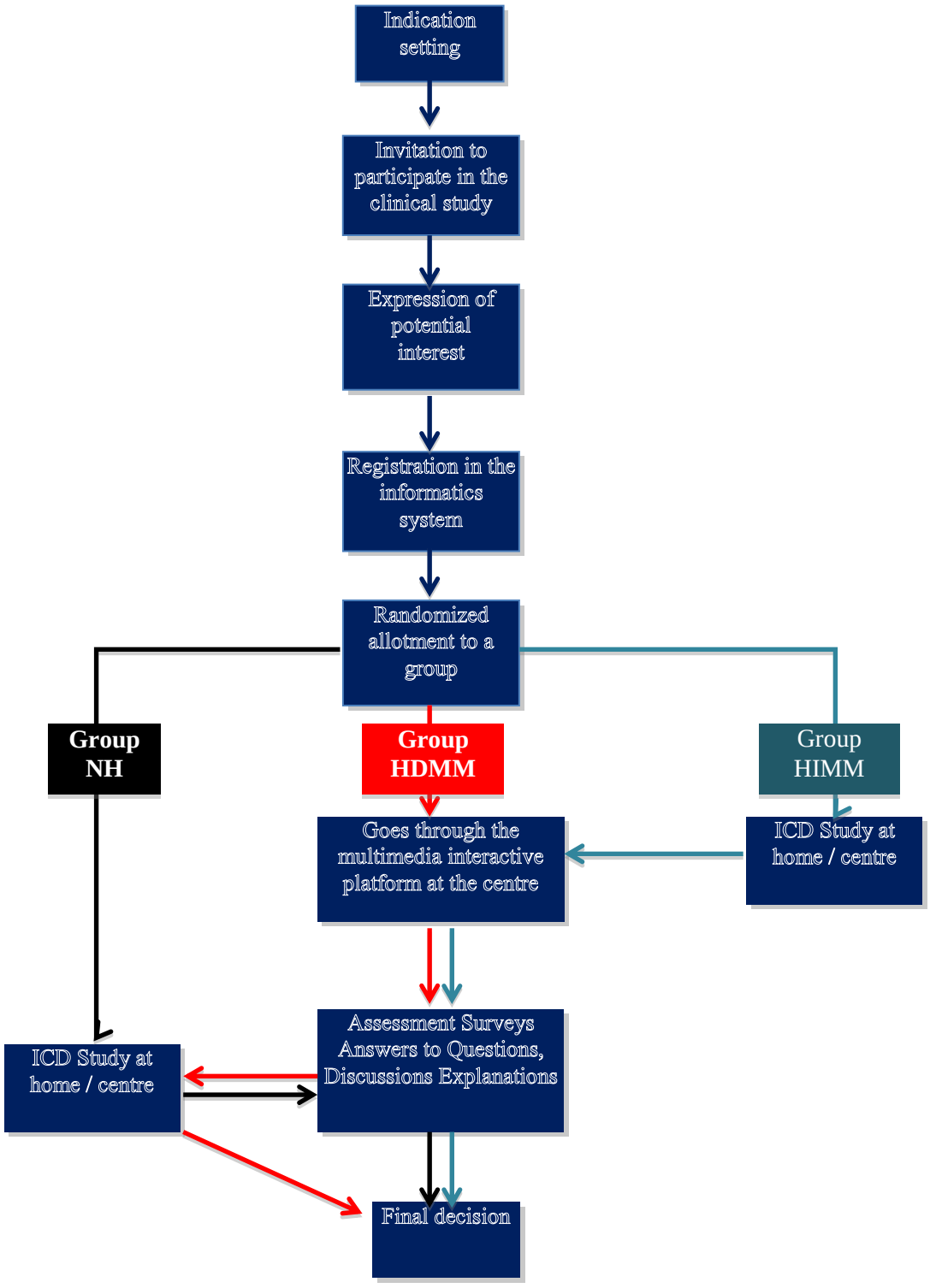
MICONOS, the interactive multimedia system, allows recording the clinical studies in various countries, in numerous medical centres, with dozens of investigators and hundreds or even thousands of enrolled patients. The web platform resorts to the PHP, Java Script and Adobe Flash technology. The databases are MySQL. The MICONOS system operates as online component of the field:

www.eu-consimt.info.

This allows for the system to be accessed from anywhere, not requiring the installation on one's personal computer.

The main characteristics of the software are:

- it is a unitary system, allowing the use of a standardized preparation protocol;
- it has multicentric character – the same software is applicable in several medical centres, even if the patients' information activity can be performed on the level of the medical centres where they are enrolled;
- it has multinational character- the system allows for the same protocol to be implemented in different countries; therefore the patients will be trained in their language of choice;
- data centralization – the system provides the same data to the registered users, depending on the permitted level of access;
- traceability – any change can be tracked, detected;
- the complying security rules – the system ensures the security and confidentiality of the data, complying with the legislation in force and the regulations of the clinical studies.



Informed consent procedure

The main obtained **results** have been grouped based on the researches they originated from, in this way:

1. The results of the analyses from the ***pilot study*** have shown that, in order to test the research instruments, the total number of subjects necessary for the investigation is 128. The proportion of representativeness between the population of the research and the population of the pilot study should be of 3 to 1. Consequently, the number of subjects necessary for the

research is of 384. Actually, 22 of the subjects decided to leave the study before its being finalized. This aspect did not influence the anticipated results, as the chosen proportion of subjects allowed this deviation. The most important results from the testing of the instruments developed in the pilot-study were:

- the modification of three items in the survey assessing the subjects' satisfaction in terms of the used format, respectively printed document versus multimedia platform, one for a better discrimination of the participants' choices, the second and the third for the manner of composing the response scale. The survey assessing the comprehension of the presented information underwent no modifications, as it raised no problem.

The analysis of the subjects' needs regarding the improvement of the quality of the informed-consent process, in full awareness, by correlations between the total number of errors and the level of satisfaction of one of the presentation formats, has revealed the following significant aspects:

- the less the subjects commit errors, the more they regard as adequate the format of the presentation afferent to the consent (p=0,001);
- the more the subjects prefer reading the document in printed format, the more the number of errors is higher or increases (p=0,004). The analysis results show that the data are in favour of the multimedia platform;
- the more the subject is aware that the chosen format facilitates the comprehension of the information, the less (s)he commits errors (p=0,021);
- the more the subject reckons that the chosen format is easily readable, the less (s)he commits errors (p=0,001);
- the more the subject reckons that the chosen format is easily usable, the less (s)he commits errors (p=0,002).

2. The interpretation of the data collected in the pilot study enabled drawing favourable conclusions to continuing the research, on a larger scale, over the overall group of subjects, in the framework of the ***ascertaining – correlational study***, having and confirming the following results as consequential:
   - the less the subjects commit errors, the more they regard as adequate the format of the presentation afferent to the consent (p=0,0001);
   - the less the subjects commit errors, the more they appreciate the presented format, along with the discussions with the investigating doctor (p=0,026);
   - that the subjects having committed a low number of errors deem that this kind of presentation has raised their interest in the participation in the clinical study (p=0,024);

- the more the subjects commit errors, the more they regard the presentation of the information as difficult (p=0,0001).

The ascertaining research aimed at forming a clear image on the influence of the analyzed factors on the dependant variable. As a consequence, the influence of the created level of satisfaction on understanding the information has become conspicuous, by its being proven. This image was the onset of an experimental approach.

3. Within the ***experimental research of an interactive multimedia platform in the process of informed consent in the clinical research,*** a program with several hypostases as regards the evaluation of the level of exercise of the informed consent was implemented. There has been verified whether by manipulating the information presentation format (multimedia versus paper) in the information procedure for the participation in clinical studies, we have obtained significant differences in the level of exercise of the consent, in full awareness, the following significant results being obtained from the comparisons between the groups of participants:
   - the subjects consider the multimedia format as highly interesting compared to the paper format, the declared level of satisfaction being considerably higher (p=0,001).
   - the multimedia group, compared to the printed format group, deems, as an average, that the afferent presentation raises their interest in the participation in clinical studies (p=0,015).
   - the multimedia platform is perceived by the subjects in the experimental groups as highly efficient, facilitating the comprehension of the information, much above the average of the group with informed consent presented on paper format (p=0,003).
   - the subjects regard as much easier to follow the presentation of the information on (computer, tablet) than to read a written document (p=0,0001).
   - the group having received the multimedia format for information presentation tends to undertake the decision to participate in the clinical study (p = 0,001).
   - the group having received the multimedia format for information presentation tends to appreciate as higher, the degree of responsibility in the following stages of the clinical stage (p = 0,001).
   - the group having received the multimedia format for information presentation tends to consider as benefits from the participation in the clinical study, also the contribution to medical scientific community, in addition to the medical checkups, free medication, appreciated by the other group (p = 0,01).

7. Comparative study of the interactive multimedia platform impact vs. classical format among medical staff

With respect to the differences between the perceptions of the two informed-consent presentation formats, there were clear differentiation situations of the interviewed doctors satisfaction degree between the :

- the doctors who consider that the patients' interest in clinical studies will rise are those having received the multimedia format. Likewise, most of those having received the paper format are convinced that the form of presentation represented by the printed document of the informed consent will not raise the patients' interest in clinical studies ($p<0,01$).
- the doctors claim that the free discussions with the patient and the free discussions plus multimedia as presentation format are the best information methods for the patients ($p=0,81$ shows insignificant differences between the two groups, due to a similar tendency in both groups).
- the doctors who regard the presentation format as highly efficient are those having received the multimedia format ($p=0,002$).

8. Final conclusions

This doctoral thesis has fulfilled the initially set objectives and displays the following general conclusions:

1. The insufficient interest, understanding or full awareness is a consequence of the informed-consent process in the clinical research on the medication. This determined the creation of a new multimedia format.
2. The audio-video interactive multimedia platform and the survey assessing the understanding concentrate the attention and capture the interest in studying the information. They are essential pieces in the mechanism of understanding, respectively of assimilating the knowledge; therefore, the developed instruments are an approach to obtain real consent, in full awareness.
3. The main advantages of MICONOS are: comfort of use; high level of multi-sensory stimulation (auditory, visual, reading-writing); control on the listening/reading of all provided information on the clinical study, not allowing the participant to overlook them; additional information (text/audio/video) clarifying some notions/procedures; by the survey assessing the level of understating and by the system of activity reports, it allows the investigators to know in real time the subjects' errors of understanding.

4. The presence of the survey assessing the understanding, integrated in the platform, enhances the motivational level and raises the subject‘s responsibility, in terms of his/her own involvement.
5. The subjects having undergone first through the interactive audio-video multimedia platform have obtained a smaller number of errors in the evaluation of the understanding of the presented information and display higher autonomy, in the exercise of the informed consent.
6. The presentation format, the information method, the user friendliness of the information source and the duration of the presentation are a nodal point in the prediction model for the small number of errors.
7. The use of the multimedia platform is significantly and strongly associated with the rise in the subjects' level of satisfaction related to the presentation format in print versus multimedia.
8. The level of satisfaction of the subjects having used the multimedia platform has a strong impact on the level of understanding of the information; therefore, it is one of the important aspects to be pursued by the researches in terms of informed consent in full awareness.
9. A rise was observed in the awareness degree of the personal and collective benefits obtained after the clinical study of the medication in the case of those who had the possibility to consult the multimedia platform whenever and wherever.
10. A higher influence was noticed, of other close relatives (family) in the subjects' life, or of the doctor /investigator, on making the decision to participate in the group of the subjects informed by written document than in the group having undergone the multimedia process.

9. Discussions. Original contributions. Future research directions. Results dissemination

A review of the literature on informed consent, in MEDLINE on improved medical consent (Flory& Emanuel 2004; Kucia & Horowitz 2000; Fitzgerald et al. 2002; Stiles et al. 2001; Coletti et al. 2003; Carpenter et al. 2000; Agre et al. 2003) has shown scepticism regarding the value of such multimedia instruments; yet the obtained results here indicate they may be efficient, when they are correctly integrated in the consent process. Therefore, this demonstration has not been in terms of human interaction vs. technology, bur rather human interaction vs. technology-aided such interaction. This suggests that, by the use of the multimedia procedures and by the repetition of the missed information, the understanding of the consent-relation

information, in many patients' case, may be raised to a level enabling full awareness. Thus, a number of persons who do not adequately understand the research protocol when the relevant information is supplied by usual methods, can display adequate understanding if the same information is presented in a manner compatible with the user.

The results of the conducted researches illustrate that the multimedia consent procedures are feasible and efficient in improving the capacity to consent, in full awareness, to the clinical research. The limitations of the current legal printed consent forms have been long documented and are well known to researchers, participants and members of the Ethics Committees. It is time for innovation in the informed-consent process, as the rapid expansion of the available multimedia instruments provides the investigators with the opportunity to go beyond the barriers of the printed forms. The Ethics Committees should encourage the investigators to use new approaches in unveiling the consent information. In this light, given the added value of the multimedia consent procedures, the investigators who conduct a clinical study involving protocols of high risk among the potentially vulnerable subjects should consider the inclusion of the multimedia consent processes in the discussion and process of global consent, with a view to ensuring an adequate understanding of the information by each participant. The electronic consent has not been designed with the intention to replace, but supplement the interaction researcher-patient involved in the consent process.

A limitation of the conducted researches is that they have not covered the whole palette of factors influencing the subjects' satisfaction and the understanding level of information. The research efforts focused on the most important variables and the analysis of all individual factors was absent, as well as the influence of the institutional factors and the socio-cultural context.

The Doctoral Thesis contains: 247 pages, where of 197 pages (79%) personal contributions, 45 graphics, 35 figures, 60 tables. The Bibliography has 204 titles.

Personal and original contributions

1. Contributions with synthetic character

- ***Related to the scientific content:*** there were identified the existing problems in the informed-consent process in clinical research and solutions were proposed, to this affect. The conducted researches proved the significant improvement of the informed-consent process in the clinical research on the medication by the use of the interactive multimedia platform.

2. Contributions with theoretical and experimental character

- Cross-sectional observational prospective study of the patients' behaviour during the informed consent process;
- Ascertaining research regarding the identification of the individual and contextual factors, which influence the understanding, satisfaction and the full awareness;
- Pilot study;
- Experimental research on the use of an interactive multimedia platform, in the process of informed consent in clinical research;
- Comparative impact study of the interactive multimedia platform vs. the classical format, among the medical staff.

3. Contributions with curricular scientific character

- Elaboration of the scientific-research reports within the doctoral research program;
- Completion of the doctoral thesis;
- Study of the current state of the researches in the field of informed consent in clinical research.

4. Novelty of the Doctoral Thesis:

- Creation and implementation of an innovating online interactive informatics system (in Romania, there is no similar system put into practice and, internationally, they are in an early stage of use) destined for informing and verifying the patients' understanding in the informed-consent process, with a view to their participating in clinical studies.

5. Usefulness of the research results

- In scientific terms: the results obtained from the conducted researches prove the value of the electronic informed consent in clinical studies. The conducted assessments have brought further knowledge and proofs, in support of the interactive multimedia platform

in the informed-consent process in clinical research.

- In didactic terms: this platform can be used as means of training/educating the future investigators or by other members of the research team in the informed-consent process.
- In applicative terms: the efficacy of the electronic format was tested and implemented (multimedia informatics system) in the informed-consent process under the conditions of real situations of effective participation in clinical studies (not simulated). In this way, the system proved functional and may be further used, in the clinical trials on medication, after its being endorsed by the competent authorities.

6. Enhancement and dissemination of the research results in the scientific academic environment

- Publication and participation in scientific events: the results of the conducted research materialized in publishing 7 papers and defending 6 papers within national and international conferences
- Accomplishment of the scientific-research reports in the framework of the scientific training programme
- Completion of the Doctoral Thesis.

Future research directions

As likewise explained in the "Methods" section, no potential participant was excluded based on a low educational level; however, as some clinical studies specifically target persons with a very low cognitive functional level, the possibility for the multimedia instruments to play an important part in improving the capacity to consent, requires specific empiric attention, by subsequent researches.

The use of the Internet-based informed consent fulfils the patient-education objectives, while liberating the doctor, thus reducing the medical costs; nevertheless, an electronic system has costs in advance and its maintenance requires staff and materials which lead to administrative costs. These aspects will have to be carefully evaluated by studying the economic impact on the electronic informed consent in clinical research.

With regards to the future use of the platform MICONOS and of the survey assessing the understanding, an audit will be required in order to verify the conformity of fulfilling all the requirements for the electronic systems, as well as the compliance with the norms of good clinical practice in research (GCP). Moreover, the authorities should legislate their integration as part of the informed-consent process in clinical studies.

Electronic informed consent can be also used when training the medical staff who can be

involved in conducting trials or even in obtaining an adequate consent in common medical practice and not only in clinical research.

Dissemination of results

The results of scientific researches contained in this doctoral thesis were presented in national and international conferences and were published in journals, as it follows:

Crt No	Publication	Cat	F.I	Year	Vol	No	Pg	Title	Authors	ISSN
ARTICLES PUBLISHED IN ISI JOURNALS										
1	PLOS ONE	ISI	3.534	2014	9	10	1-6	Informed Consent: How Much Awareness Is There?	Daniel Purcaru, Adrian Preda, Daniela Popa, Marius Alexandru Moga, Liliana Rogozea	1932-6203
2	Revista Română de Bioetică	ISI	1	2014	12	2	37-46	Informed Consent and e-Communication in Medicine	Lorena Dima, Angela Repanovici, Daniel Purcaru, Liliana Rogozea	1583-5170
3	Rom J Morphol Embryol	ISI	0.723	2014	55	2	719 - 722	Biomedical Research - Opportunities and Ethical Challenges	Liliana Rogozea, Daniel Purcaru, Florin Leasu, Codruta Nemet	1220-0522
ARTICLES PUBLISHED IN B+ JOURNALS										
4	Bulletin of the Transilvania University of Brasov	B+	-	2012	5(54)	1	107 - 112	Informed Consent in the Informatic Era	Daniel Purcaru, Anca Purcaru, Liliana Rogozea	2065-2216
5*	Acta Medica Transilvanica	B+	-	2015	In press	1	-	Interactive Informed Consent in Clinical Research	Daniel Purcaru, Florin Leasu, Ioana Nicolae, Anca Purcaru, Liliana Rogozea	2285-7079
ARTICLES PUBLISHED IN JOURNALS IN DATABASES										
6	Jurnal Medical Brasovean	B	-	-	8	1	81-85	Evolutia Consimtamantului Informat în Cercetarea Clinică	Daniel Purcaru, Onisai Lazar, Anca Purcaru, Liliana Rogozea	1841-0782
ARTICLES PUBLISHED IN EXTENSO IN INTERNATIONAL CONFERENCES										
7	WSEAS AIASABEBI '11 Proceedings	Proceeding conferinta indexata BD		2011	-	-	366 - 371	e-Informed Consent in Clinical Trials-Ethical Considerations	Daniel Purcaru, Onisai Lazar, Anca Purcaru, Liliana Rogozea	1790-0832

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Crt No	Conference	Place	Period	Pres Type prez	Publication Type	Paper title	Authors
ARTICLES PUBLISHED IN ABSTRACT IN NATIONAL CONFERENCES							
1	a XLI-a Reuniune Nationala de Istoria Medicinei	Brasov, Romania	27-29 octombrie 2011	lucrare	în progr. conf.	Repere istorice ale consimţământului informat în cercetarea clinică de la origini până în prezent	Daniel Purcaru, Liliana Rogozea, Anca Purcaru, Lazar Onisai
2	a VIII-a Conferinţă Naţională de Bioetică	Cluj-Napoca, Romania	13-16 octombrie 2012	lucrare	rezumat	Este consimţământul informat în deplină cunoştiinţă de cauză?	Daniel Purcaru, Lazar Onisai, Liliana Rogozea
3	a IX-a Conferinta Nationala de Bioetica	Iasi, Romania	24-26 octombrie 2013	poster	rezumat	Îmbunătăţirea procesului de consimţământ informat în cercetarea clinică	Daniel Purcaru, Liliana Rogozea
COMMUNICATIONS PRESENTED IN PROGRAMS IN INTERNATIONAL CONFERENCES							
4	Third Cambridge Consortium for Bioethics Education	Reid Hall, Paris, France	19-21 June 2013	lucrare	în progr. conf.	An Interactive Approach to Teaching Ethics: A Case Study	Liliana Rogozea, Daniel Purcaru
5	Fourth Cambridge Consortium for Bioethics Education	Reid Hall, Paris, France	23-25 June 2014	lucrare	în progr. conf.	Informed Consent: An E-Learning Model	Daniel Purcaru, Daniela Marinescu, Anca Purcaru, Liliana Rogozea
PARTICIPATIONS IN INTERNATIONAL CONFERENCES							
6	Second Cambridge Consortium for Bioethics Education	Reid Hall, Paris, France	11-13 Aprilie 2012	-	-	-	-
7	International workshop	Cluj-Napoca, Romania	7-9 noiembrie 2012	-	-	-	-

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Electronic Informed Consent in Clinical Research

e-Informed Consent in Clinical Research

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Abstract

The state-of-art innovations in information technology and Internet provide the opportunity to develop a new method to obtain informed consent, in the context of the increasing complexity of the clinical studies, in order to unequivocally prove that the subjects were informed and have understood the implications of their voluntary participation in the clinical study. An applicative model was achieved, with a view to improving the informed-consent process, by creating MICONOS an online interactive multimedia platform, for the "electronic informed consent". The researches conducted with a view to establishing the feasibility and efficacy of this platform were based on its being tested under the conditions of real situations of effective participation in clinical (not simulated) studies, on a group of 362 subjects and 40 physicians. The research results proved the value of the interactive multimedia consent procedures, towards improving the capacity to consent in full awareness to the clinical studies. The assessments brought additional knowledge and proofs, in support of the use of the interactive multimedia platform, in the process of informed consent, in clinical research.

Keywords: informed consent, clinical research, multimedia, internet

Rezumat

Ultimele inovaţii în tehnologia informaţiei şi internet oferă oportunitatea dezvoltării unei noi metode de obţinere a consimţământului informat în contextul creşterii complexităţii studiilor clinice pentru a dovedi fără dubiu că subiecţii au fost informaţi şi că au înţeles ce presupune participarea lor voluntară în studiul clinic.

A fost realizat un model aplicativ pentru îmbunătățirea procesului de consimțământ informat prin crearea MICONOS o platformă multimedia interactivă online pentru „consimțământul informat electronic”.

Cercetările efectuate în vederea stabilirii fezabilității și eficacității acestei platforme s-au bazat pe testarea ei în condițiile unor situații reale de participare efectivă în studii clinice (nu simulate), pe cohortă de 362 de subiecți și 40 de medici.

Rezultatele cercetărilor efectuate au demonstrat valoarea procedurilor de consimțământ multimedia interactive în îmbunătățirea capacității de a consimți în cunoștință de cauză la studiile clinice.

Evaluările efectuate au adus un plus de cunoștințe și de dovezi în sprijinul utilizării platformei multimedia interactive în procesul de consimțământ informat în cercetarea clinică.

Cuvinte cheie: consimțământ informat, cercetare clinică, multimedia, internet

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