Ethical and legal implications for technological devices in clinical research in Europe^{*}

Flowchart design for ethical and legal decisions in clinical research

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ABSTRACT

In recent years engineers developing new technologies with assistive or medical purposes have become aware that to create acceptable and usable solutions they need to involve final users, patients and stakeholders in the design, development and evaluation of systems as well as in the device certification processes. Involving stakeholders in such processes has several ethical and legal implications. It has become evident that it is still difficult for engineers in Europe to know which ethical and legal processes should be carried out as they have not been previously trained in these issues during their studies.

This article is a review of the laws, standards and recommendations applicable in Europe concerning human involvement in new technologies research, with the aim of helping researchers in the region in question to identify the ethical and legal issues that could arise during those tasks. This review has been carried out in response to the identified need on the part of technological researchers.

The design of a flowchart is presented as a summary of the interpretation of the documentation reviewed with the aim of helping the researchers to take the ethical and legal decisions that apply to research involving humans.

The flowchart presented has been validated with various research projects in which the authors have participated. The proposed conceptual design can be used for taking decisions, but it is suggested that a tool based on this design be built with the aim of making decision taking easier for researchers in this area.

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Interacción '21, September 22–24, 2021, Málaga, Spain

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ACM ISBN 978-1-4503-7597-9/21/09.

<https://doi.org/10.1145/3471391.3471403>

CCS CONCEPTS

• Applied computing ~ Health informatics • Social and professional topics ~ Medical information policy • Human-centered computing ~ User studies

KEYWORDS

User studies, informed consent, privacy, ethical committee, competent authority.

ACM Reference format:

Ainara Garzo and Nestor Garay-Vitoria. 2021. Ethical and legal implications for technological devices in clinical research in Europe: Flowchart design for ethical and legal decisions in clinical research. In *XXI International Conference on Human Computer Interaction (Interacción '21)*, September 22–24, 2021, Málaga, Spain, 8 pages. <https://doi.org/10.1145/3471391.3471403>

1 Introduction

User involvement in design activities, such as software engineering, has been taking place for some time. The final user participation process in the design and evaluation of products can be found under different names such as, among others, Participatory Design, Contextual Design, User Centered Design (UCD), Human-Computer Interaction, Human-Factors, User eXperience or User Involvement [1]. Nowadays, considerable effort is being devoted to design and develop usable, well accepted, easy to use and ergonomic systems, processes and devices which relate to users' real needs. According to the ISO 9241 family, Human-Centered Design (HCD) is used instead of UCD, to refer to the stakeholders' involvement in the design and development of systems. The aim of this approach is to apply techniques that make the systems ergonomic and usable, which improve the productivity, accessibility and wellbeing and reduce stress and inherent risks [2]. Hence, HCD is a process and a set of techniques which are used in order to create new solutions, including products, services, spaces, organizations and ways of interaction [3,4]. The target users who are going to employ the new solution are at the center of the process. First, users' needs, wishes and behaviors are analyzed in order to find the desired

outcomes. Once these are identified, possible solutions are designed taking feasibility and viability into account. It also has to be said that when medical devices are developed, especially if software is included, the harmonized norm 62366 relating to usability must be applied [5], thus HCD techniques are also very useful to ensure compliance with this norm.

The use of HCD techniques has several ethical implications, as mentioned by Garzo and Garay-Vitoria [6]. There are several recommendations regarding participants' involvement such as the Declaration of Helsinki [7] which has been used as a reference point in the scientific community in research with humans for many years or the Belmont report [8]. Moreover, the Oviedo convention document has been made an international legally binding instrument for the protection of humans in the biomedical field [9]. This agreement protects the rights and the dignity of humans with respect to biological and medical applications.

This work has been divided into the following tasks: 1) identify the need; 2) define the objectives and review the literature accordingly; 3) design a solution; 4) validate the solution. In the following lines, the motivation for the review is explained. Subsequently, a summary of the reviewed documents relating to the ethical and legal implications for stakeholder involvement has been drawn up. The design of a flowchart to solve the identified problem is proposed according to the previous conclusions, including a brief validation. Finally, we conclude with suggested future research lines and opportunities for this proposal.

2 Problem identification

Human involvement in the design and development of products and services has several ethical implications. Although some universities are aware of this and prepare the engineers on the ethical aspects involved before any research with humans takes place [10,11], this is not usual nor mandatory in most European universities for engineers or researchers with a technological background. They are aware that technological developments require the involvement of humans in experiments, even more so in technological medical device design and development, but there are knowledge gaps concerning the ethical issues, and the documentation regarding this information is complex and spread out over several reports.

Other researchers also agree on the gap between ethics and human-centered practices, and some research has been done and proposals been made with regard to Artificial Intelligence technologies, for example [12]. Some European projects such as DIH-HERO [13], Satori [14], Inbots [15] or Wearable Robots [16], for example, have also been analyzing the ethical and legal issues as well as the necessary standards, best practices or recommendations to ensure the safety, security and ethical treatment of patients during the research.

In the DIH-HERO project a total of 43 semi-structured interviews were carried out with representatives from France, Germany, Italy, Poland, Serbia, Spain, Switzerland, the Netherlands and UK,

in which 14 small and medium-sized enterprises also participated. The aim of those interviews was to collect information about the awareness and application of standards related to quality, safety, security, environmental care, ethical, legal and socio-economic issues, among others, related to health robotics. The conclusion was that interviewees considered that best practices in healthcare robotics were not yet well documented, collected, structured, harmonized or promoted. During this project, a flowchart was proposed to summarize the documentation applicable in each case, something which was welcomed by the participants.

3 Review on ethical and legal implications

Nowadays, it is well accepted that any research involving humans must be evaluated by an Institutional Review Board (IRB) or an ethical committee [17]. Any ethical committee activities will include at least the following ones [18]:

- a) Evaluate the qualification of the principal investigator and research team, as well as the project feasibility;
- b) Ensure that methodological, ethical and legal aspects and risks/benefits for the study are balanced;
- c) Review that user data or samples can be properly traced, also taking into account additional regulations, such as Regulation 2016/679, also known as GDPR [19];
- d) Develop good-practices and/or manage conflicts according to any applicable ethical principles;
- e) Coordinate the activity with other boards;
- f) Ensure the evaluated projects and personal data confidentiality.

However, additional ethical and legal issues must also be taken into account when humans are involved in research, as has been previously outlined by authors [6]. Additionally, in the Directive 93/42/CEE there is an important section about medical devices used in research with humans in which the technical specifications and the obligations of the researchers are detailed [20]. It is mentioned therein that any research must follow the recognized ethical principles and has to be approved by the corresponding ethical committee and also by the competent authority of the country in which the research will be carried out. The role of the competent authority is at least, to ensure that the medical device complies with the minimum safety specifications when used by or with a human, to evaluate the risks in order to know whether risks are offset by benefits for participants, and to evaluate whether the study is sufficiently relevant from a scientific point of view. Most countries of the European Union have their own competent authority [21]. The new Regulation 2017/745 on medical devices came into effect repealing this Directive on May 2021 after some delay due to the impact of the COVID-19 pandemic [22,23]. In the case of the medical devices in research, both documents have some similarities, but the new Regulation reinforces the relevance of carrying out experimentation with medical devices before launching them on the market and then monitoring them when they are on the

market. This Regulation also mentions the relevance of protecting vulnerable participants such as children, pregnant women, the elderly or immuno-compromised people, as the effects of the trials on these groups could be considered especially negative.

With respect to the obligatory nature of obtaining the endorsement from an Ethical Committee in order to carry out research with medical devices, Regulation 536/2014 relating to clinical tests with medication for human use can be found [24]. This regulation came into effect in April 2016 in every member state of the European Union. Although its title may suggest that this Regulation is not applicable for this study, the same guidelines should be used while carrying out research with medical devices used by humans. In this case, the vulnerable groups are considered to be not only children or pregnant women, but also, any subject who might have problems to understand the research processes or very specific procedures involved in the clinical research. In those cases, a justification of the target group must be included, and an ethical evaluation would be mandatory according to this regulation.

In addition to the presented legislation, the harmonized standard ISO 14155 related to good clinical practice is a reference document [25]. This standard includes information regarding the ethical aspects that must be taken into account when designing a study, the need to obtain the ethical committee approval and the description of the requirements for this purpose, and the most appropriate informed consent process for the study. Other factors are also presented such as risk assessment, the data gathering notebook design, the researchers' manual, the monitoring of adverse effects, etc. moreover, several guidelines regarding the carrying out of these activities are given.

The International Conference on Harmonization should also be mentioned, which is a board regarding technical requirements for pharmacists to be applied in humans [26]. This group has developed several good clinical practice regulations that are recognized worldwide. The regulations were drawn up with clinical trials with drugs in mind, but almost all the recommendations should be applied in a similar way in any research with medical devices. Recommendations and laws also refer to rights to privacy and dignity, as these are considered as fundamental for humans.

The 95/46/CE European Directive has also been the point of reference in Europe in recent years with regard to personal data protection [27]. On the 25th of May of 2018 the new Regulation 2016/679 came into force repealing the named Directive and with the aim of unifying European personal data treatment and fostering the free movement of this data between the members of the European Union [19]. However, in the new Regulation, some sections may be subject to various changes depending on each member state. Some important issues relating to this Regulation have implications for personal data collection when participants take part in research. The new Regulation is also very sensitive with regard to personal data transfers to countries outside the European Union and in its Chapter V the restrictions concerning

that issue are explained, detailing that explicit consent must be requested for any data transfer after informing the subject of the possible risks thereof.

3.1 Conclusions of the legal and ethical implications for research with humans

A summary of the reviewed documentation is explained in the following lines:

- Participation in a research project must be voluntary, participants will be properly informed and may withdraw at any time without having to provide a reason.
- The risk-benefit must be balanced and correctly justified.
- Any research involving humans must be supervised by a competent and multidisciplinary entity to evaluate the related ethical considerations. That entity will be an ethical committee or an IRB. In the case that the research also involves a medical device, this must be notified to or approved by a competent authority.
- Vulnerable groups such as children, people with cognitive impairments, etc. should not take part in the research, unless the research is based on that target group. In that case, their participation will be properly justified and ethically supervised by an external group.
- The research results must be shared with the scientific community according to the best-practices on research, protecting the participants privacy.
- An informed consent process is mandatory for any research with humans which includes information regarding risks and benefits. Explicit consent, preferably written, will be requested from participants.
- In the case that a legal tutor is required in the informed consent process due to cognitive impairments or because children are involved, for example, the participant's acceptance must be also taken into account.

Regarding the personal data treatment, the summary of the applicable legislation is as follows:

- Do not record any personal data other than that which is strictly necessary.
- In the case that personal data treatment is necessary, consider the following points:
 1. Record the minimum necessary for the required purpose.
 2. Demonstrate that the subject affected has approved the data treatment. Accordingly, express consent will be needed.
- Informed consent related to data collection and treatment must include information about: 1) the data that will be collected and the purpose of its collection; 2) the data treatment controller and data protection officer; 3) the

purposes of the treatment; 4) the legal basis for the processing; 5) the recipients of the personal data including third party countries or international organizations where applicable; 6) the envisaged time limits for erasure of the different categories of personal data; 7) the existence of the right to request the controller for access to, rectification and/or erasure of personal data and restriction of the personal data treatment; 8) the right to lodge a complaint with a supervisory authority.

- Any data collection for research purposes should: 1) respect fundamental rights and freedoms; 2) respect the principle of data minimization; 3) include pseudonymization to avoid personal identification when possible; 4) comply with other relevant legislation such as the existing legislation on clinical trials, if applicable; 5) protect the rights and freedoms of the data subject first, even if the data is of general interest.
- Member States may add some limitations over the Regulation relating to health, biometric or genetic, or scientific research data, such as in Spain [28] or Germany [29].

It was possible to find several proposals for the preparation of an informed consent document for any research involving humans [30–32]. As a summary of the reviewed documents and legislation it is recommended that the following information be included in this document:

1. A research summary including procedure information, objectives, benefits and the time that will be required of the participant.
2. Risks, discomforts or adverse events foreseen and the minimization measures.
3. Opportunity to be informed after participation.
4. Personal data treatment, including the time that the data will be stored as well as the information presented above.
5. Contact information of the research team, signature and date.

There must be sufficient information on the informed consent document to take the decision of whether to participate, and it must be written in understandable language according to the participants' capabilities [33].

A research procedure could be rejected by an ethical committee or IRB if risks and benefits are not balanced, the procedure or humans' participation is not well justified, or the methodology is not completely defined. In any case, the group who supervise the procedure will ask additional information and make some recommendations about the reviewed ethical considerations with the aim of helping the researchers to improve the procedure and enhance the participants' involvement.

4 Conceptual design

A flowchart has been designed with the aim of providing a tool which summarizes the regulations, norms and recommendations reviewed in this study (see Figure 1).

To build this concept design the process for the ethical and legal approvals needed in Spain, the UK, Germany, Denmark, Poland and Switzerland have been also included, as DIH-HERO project partners from those countries participated by facilitating the information corresponding to their countries. To apply the flowchart, first researchers have to indicate whether humans are involved in their study. Next, and depending on the characteristics of the study, several questions have to be answered in a given order and there are several possible outcomes:

- a) Supervision by an ethical committee is not considered essential in the study when there is no personal data treatment, when humans are not directly involved in the trials, or when participants are not required to use any medical software or device, or when using any software or device, participants are not vulnerable and no risk (either physical, or psychological) is expected such as, for example, using a computer or a mobile phone for completing an anonymous survey. However, it is recommended that an ethical committee be contacted to clarify any doubt.
- b) The study is considered a research project involving humans and therefore Ethical Committee approval is required in the case that personal data are being collected and/or managed and/or any device or software not considered a medical device is being used by the participants, or if participants are part of a vulnerable target group and/or if any risk (physical and/or psychological) is foreseen for the participants during the research.
- c) The study is considered to be observational research and there is a need for Ethical Committee approval when humans are involved, medical devices and/or software that have CE markings are used and are going to be used according to the described instructions and the research follows the usual clinical practice.
- d) Otherwise, the study is considered a clinical research which needs Ethical Committee approval, in addition to the approval or the notification (depending on the medical software or device characteristics, see Figure 1) of the competent authority. In all cases, the competent authority must be also informed about any relevant adverse events.

When humans or their personal data are involved in research, informed consent, which an Ethical Committee must supervise, is also needed. In the case that research with a medical device is performed (considered clinical research) registration in a public data-base is recommended, such as the World Health Organisation [34], U.S. National Library of Medicine [35], or Swiss National Clinical Trials Portal [36].

The letters 'CE' that appear on the products mean they have been assessed to meet high safety, health, and environmental

protection requirements. In the case of medical devices, the CE marking is the way in which a manufacturer indicates that a device conforms with the applicable requirements set out in Directive 93/42/CEE [20] and/or Regulation 2016/679 [19] concerning medical devices and other applicable Union harmonization legislation.

5 Validation

The presented flowchart (Figure 1) was designed according to the reviewed legislation and feedback received from the Spanish competent authority [37]. It has been applied in several research projects in which the authors have participated, and which involved human participation in technology evaluation. In this section some projects are presented as flowchart validation.

The aim of the Sentient project carried out within the FIK private financing program [38] was to develop a system which adapts the environment (temperature, lighting, sounds, ...) according to the user emotions defined by Ekman [39]. This type of system was identified as intrusive, and therefore to create an acceptable technology some exploratory focus groups and interviews were carried out with the elderly participants and their caregivers [40]. Participants' data were collected, and according to the flowchart, the supervision of an ethical committee was required. In this case, the Healthcare Ethical Committee from Ingema, the research center involved in the participants' recruitment, approved the methodology used [40,41].

Figure 1: Flowchart to summarize the ethical and legal decisions for human involvement in technology evaluation according to existing laws and regulations in the European Union.

The CogLaboration European project, was financed under the Seventh Framework European Programme [42]. A control law based on Dynamic Movement Primitives was implemented to control a robotic system composed of a robotic arm equipped with an anthropomorphic hand [43]. This control system was developed for industrial and home settings. The last set-up application was evaluated with a group of elderly people. Participants were requested to exchange different daily life objects with the robotic system and to fill in a questionnaire after the task [44]. In this project, humans were involved, and the device in use was under development. However, this device was not considered a medical device due to the defined intended use. During the trial, some personal data of the participants were recorded, and some risks were foreseen such as possible collisions or bumps between participants and the robot, which were avoided by ensuring a sufficient distance was maintained during the exchange. According to the flowchart, Ethical Committee approval was required, and in this case, the local Ethical Committee approved this experimentation.

The aim of the iFree project, locally financed through the ADINBERRI program [45], was to identify new ways to measure the frailty of the elderly using different technological systems including some DAVID Spine devices [46] and an Equimetrix prototype [47]. Several users, with different degrees of frailty participated to measure their balance using Equimetrix and their cervical and lumbar mobility and range of movement and strength using DAVID Spine Devices with the objective of matching the collected data with frailty status evaluated with standard scales. In this project the correlated data gathered in these devices has been used in order to identify the degree of frailty of future users. As Equimetrix is considered a medical device prototype, the corresponding ethical committee and competent authority approvals were requested prior to starting with participant recruitment, as outlined in the presented flowchart.

MERLIN is a project that has received funding from EIT Health¹ [48]. In this project a clinical evaluation was carried out using the MERLIN system, which consists of the ArmAssist robotic system based on serious games, merged with the Antari Home Care telecare platform [49]. The system has been evaluated by 9 post-stroke patients, at the Reina Sofia Hospital in Cordoba (Spain) [50] and by 12 patients at the University Medical Center in Groningen (The Netherlands) [51]. As the MERLIN system is considered a medical device prototype and thus did not have CE certification, the approval of the corresponding ethical committee and the competent authority was required, as stated on the presented flowchart. In this case, the approval was requested in both countries in which the trials were organized (Spain and the Netherlands) before starting patient recruitment.

6 Discussion

¹ EIT Health is supported by the European Institute of Innovation and Technology (EIT), a body of the European Union receives support from the European Union's Horizon 2020 Research and innovation programme.

Proposed conceptual design aims to help researchers to take decisions on the ethical and legal approval needed to carry out any research involving humans in technological evaluations, including medical devices. This flowchart can be easily applied to research with technological devices involving humans. Before initiating human involvement, it is suggested that researchers answer the questions shown in the flowchart in Figure 1, in order to determine the ethical and legal approval needed in each case. The same approach used for the presented projects used for the flowchart validation could be used for any additional research.

The flowchart design presented has been validated with projects in which the authors have participated and it is set out in such a way as to have enough flexibility and validity to cope with future changes in the legislation, and to enhance researchers' understanding of the reviewed legislation.

In this review, it should be mentioned that one of the key issues in the new European Regulation on medical devices is to give greater importance to research with medical devices before they enter the market, as it has been found that there is a lack of studies of this kind. The Regulation also pretends to motivate the publication of the results in order to register and make traceable any study with medical devices.

6.1 Limitations and future work

The work presented has some limitations that must be mentioned. First, the concept design has only been validated in projects in which the authors had participated, thus it is mainly Spanish legislation which has been reviewed. Only in one of the cases could the applicable legislation in the Netherlands be validated. Thus, in future, additional validation for other European countries is proposed, which could be an onerous task due to the complexity of the different languages used around Europe.

Second, this work is only a concept design of a flowchart that could be used in decision taking. Several researchers have already used it and they were faced with some problems such as deciding if the device they were using was a medical device or not, how to check the CE marking, or the definition of intended use or usual clinical practice. However, no formal evaluation has been carried out. With the aim of addressing the aforementioned problems it was proposed to build a software prototype to help decision making in each case along with the recording of the corresponding information arising from evaluations involving humans.

7 Conclusions and future work

The present manuscript presents a flowchart as a summary of the analysis carried out regarding the recommendations, legislation and regulations within the European Union that apply to research with new technologies involving humans.

This work also includes some recommendations for a research protocol description and informed consent process development, including personal data management.

The flowchart presented has been designed to address different researchers' needs, including the DIH-HERO partners and stakeholders. The flowchart was presented to the research community in a webinar organized by the DIH-HERO project consortium [52]. A tool has been also designed and built to help researchers understand and read the flowchart and, while doing so, resolve the identified problems [53]. This approach will help us to gather additional information regarding the usefulness and limitations of this conceptual design.

In the future, this flowchart will be updated in order to be used in several European countries, depending on their particular legislation.

ACKNOWLEDGMENTS

Special thanks to DIH-HERO partners for their help on the documentation interpretation for each country. The authors would also like to thank the volunteers who participated in the interviews.

This work was supported by the Department of Education, Universities and Research of the Basque Government (grant-number IT980-16); and the DIH-HERO European project which has received funding from the European Union's Horizon 2020 research and innovation programme (grant-number 825003).

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