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Towards a standardized protocol for conducting randomized clinical trial for software

Lídia Maria Lourençõn Rodrigues^{a,*}, Inacia Bezerra de Lima^b, Luiz Ricardo Albano dos Santos^a, Valdes Roberto Bollela^a, Maria Manuela Cruz-Cunha^c, Rui Pedro Charters Lopes Rijo^d, Domingos Alves^a

^aRibeirão Preto Medical School, University of Sao Paulo, Ribeirao Preto, Brazil.

^bSchool of Nursing of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

^cSchool of Technology, Polytechnic Institute of Cávado e Ave, Barcelos, Portugal.

^dSchool of Technology and Management, Polytechnic Institute of Leiria, Leiria, Portugal.

Abstract

In the last decade, evidence-based medical practice has been aided on a large scale by computerized decision support tools, aimed at reducing diagnostic and therapeutic uncertainty, complementing the actions of the health professional. With the technological evolution, it is already possible to consider these systems as part of the clinical intervention, both for the diagnostic stage and for the treatment of diseases. This article proposes the creation of a specific clinical trial protocol to evaluate the effects of the software as clinical intervention in different medical settings. The proposal is unprecedented and extremely relevant in the scientific literature and able to standardize from the development stage to the application of the software aiding in the treatment of diseases.

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* Corresponding author. Tel.: +55 16 997757979.

E-mail address: lidia.rodriques@usp.br

1. Introduction

Since the earliest days of computing in human evolutionary history, one of the main pursuits has been the creation of an artificial intelligence (AI) that could approach the rational capacity and intelligence of the human brain. This very ambitious pursuit has mainly attracted the professionals related to the health area who envisioned, in the computer aid for diagnoses and decision making regarding the treatments to their patients. The implementation of an AI-based computer system is aimed at supporting medical decision-making by defining, together with professionals, better medical procedures for each case presented and preliminary analysis of the procedures proposed for each patient [1] [2].

The so-called randomized clinical trials are epidemiological experiments that seek to investigate new therapeutic and preventive forms by randomly allocating subjects of the research and a comparison test between cause and effect to assess an interaction between them[3]. They are used on a large scale and mostly to verify the effectiveness of new medicinal products in the safest possible way[4]. Because they are of great clinical relevance, clinical trials are registered in specific platforms to allow access to information on the products researched and their effects, contributing to the transparency in research and the strengthening of ethical values that involve the scientific studies with human beings[3][4].

However, no Resolution or registration platform has specifications when health intervention is fundamentally about software. Therefore, the objective of this paper is to describe the steps of the research for the proposal of creation, development, and validation of a protocol for software clinical trials as a reference for the international scientific literature. The main difference from this research project from the ones in literature is although some studies have been carried out to test the clinical intervention of software in health treatments [5][6][7][8][9][10][11][12], there is no record of a specific proposal of a standardized protocol and description of phases for the accomplishment of these scientific investigations and for the adequacy of clinical trials fundamentally using software.

In the second section of this paper, we will present theoretical models used as reference for the construction of the proposed standardized protocol. Then, we will describe the stages planned to build this protocol and, at last, we will present a brief description of the importance of the presented work and the possible ramifications in scientific and health management that it may constitute.

2. Background

To appreciate the content of this proposal, we will briefly describe the thematic focuses that will be addressed during the project, detailing, therefore, some of the theoretical elements that should be taken as basis in this research.

2.1. Artificial Intelligence: Brief Considerations

The emergence of Artificial Intelligence occurred in 1956, in the United States, during a conference at Dartmouth College[1][13][14]. The intention was to make the computer programs could use work methodologies based on the way humans think and solve their problems. Artificial Intelligence systems should therefore be able to store, apply, and acquire knowledge through experience for problem solving[15]. Medical applications based on artificial intelligence are represented computationally by paradigms such as clinical algorithms, databases with analytical functions, mathematical models, pattern recognition and decision analysis[13]. They can, for example, issue warnings for contraindication to clinical and medication behaviors and important changes in patients' general health conditions, as well as to preserve the knowledge of specialists in certain areas[16].

2.2. Health Information Systems

Given the speed of the technological advance in the development of auxiliary equipment for the diagnosis and medical treatment, the need arose and the opportunity to integrate the medical science with the computer science in order to better qualify the services rendered in health. The application of the computational knowledge in the routines of the health services brought an intense change in the management of the assistance and in the access to sources of information relevant to the clinical practice, approaching the professional and the patient himself from the care of his illness.

The so-called Decision Support Systems (DSS) are created and implemented due to the need to integrate functions and improvement processes in the organization's control, responses and coordination, allowing information to flow between the sectors that understand it[17][18]. The application of these systems can be done in different ways and for different purposes, among them, to send alerts to doctors about patient's health status, to retrieve information, to find safer diagnosis (diagnostic aid), to make therapeutic decisions and to interpret medical images[14].

The main advantages of expert systems over traditional models are the attribution of expert knowledge, possibility of use by a large number of people, better performance and consequent productivity, elimination of errors arising from human activity, among others[19][20]. According to Ganesh (2015)[21], the relationship established between the doctor and the patient is irreplaceable and negative interferences in this relationship can lead to mistaken conclusions. Therefore, a Medical Decision Support System only assists in the diagnosis and conduct to be adopted and cannot replace any specialist in any area of practice.

2.3. Why apply clinical trial for software?

The advantages of applying clinical trials studies are the reduction of systematic errors, the greater reliability of the study due to the selection of patients without interference from other pathologies, the possibility of determining statistically significant differences between the study groups, indicating the effect of the treatment, the identification of the main differences between traditional interventions and new interventions, objectively defining why software as a complementary clinical intervention is important and should be incorporated into present and future healthcare settings.

The literature has pointed out the result of primary digital clinical interventions with software in the treatment of different diseases[22][23][24][25][26][27][28]. Pharmaceutical companies such as Science 37, Pfizer, Sanofi and *TransCelerate BioPharma* are also making progress with digital clinical trials since 2012 considering in the process from the participant recruitment to their adherence to treatment. The approach was premature in the first years but in the year of 2015 Sanofi and *eClinicalHealth* announced the VERKKO (phase 4 trial), an investigation targeting a cloud-connected glucometer with 60 participants through Facebook platform, following the necessary check-ins of their system. It's important to think about how to do these "Digital clinical trials" considering as first step figuring out what you need to develop the software and then creating a pipeline as a guide that will lead to more apps for health management.

3. Research Methods

3.1. Design of the research project

It is a quantitative, transversal, prospective, descriptive and evaluative research on the applicability of a healthcare technology. Protocols are systematically structured instruments for guiding the decisions of health professionals and users about the adequate assistance in different clinical scenarios, based on scientific evidence, evaluations of health technologies and health economics, always aiming at the quality of services provided[29]. To reach the objectives proposed in this study, the literature review was selected as a research method, in order to synthesize the results of scientific research on the subject and to provide a deeper understanding about the object of study. The following steps were taken:

- Delimitation of the theme and formulation of the guiding question;
- Establishment of criteria for the selection of scientific publications;
- Extraction of information from studies and analysis and interpretation of data.

The criteria adopted for the selection of scientific papers were the development and/or validation of a protocol and the use of software as a clinical intervention and to improve patient adherence to the medication and to present a complete text available online. The search and analysis of the literature has occurred using the descriptors "*clinical protocol*" and "*protocol for clinical trial with software*". The steps to be followed in the future are:

- Elaboration of guides for the transformation of clinical algorithms into computational ones;

- Dissemination of synthesized knowledge through systematic literature review and meta-analysis.

The figure 1 below presents the proposed steps for the development of the work.



Figure 1. Flowchart of the research methodological steps.

4. Results and discussion

4.1. Building the Protocol

After the collection and analysis of the synthesized knowledge and as a result of this proposal so far, we decided to divide the development of the standardized protocol in six phases shown in the bottom pipeline (Figure 2). The first phase will be for refinement of the topics/issues to be covered in the protocol statement, carrying out an electronic brainstorming through the selection of a group of health, informatics professionals and users of health services in outpatient clinics. After delimiting these topics, an integrative review will be carried out through scientific databases, using the previously selected descriptors. The third phase is to establish recommendations for research and update of the protocol; the fourth phase is the validation by expert peers. The fifth phase is the implementation, i.e., plan the dissemination of the protocol, and the sixth and last phase is called Evaluation.

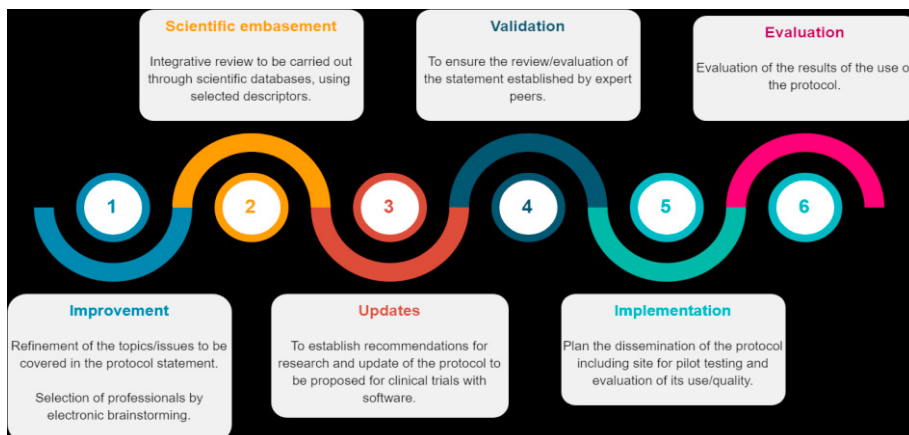


Figure 2. Pipeline containing six phases for the development of the standardized protocol.

In order for the developed protocol to conform to Clinical Trial type studies, the main international statements and recommendations will be consulted for the realization and registration of this type of research, among them the Consort protocol[30] and the Spirit Statement[31]. The intention is to develop the protocol in the form of text, illustrated and divided into sessions and subscriptions. The pre-selected protocol domains are the Scope and Purpose, Involvement of Stakeholders, Rigor for Development, Clarity in Presentation, Applicability and Editorial Independence. The instrument for evaluating the quality of the protocol will be the Appraisal of Guidelines for Research and Evaluation - AGREE II[32] and making adjustments recommended by the judges. Statistical analyzes will be done by the IBM SPSS Statistics version 22.0.0.0 program and concordance between judges will be evaluated by the Content Validity Index (IVC)[33].

Then, the protocol will be forwarded to a specialized professional, for the revision of the Portuguese language and translation into the English language, and a biomedical informatics professional for the computerization of the protocol and application of technologies such as machine learning and artificial intelligence. Finally, the authors intend to carry out a pilot study with the applications developed in the LIS denominated MTBApp (still to be published), for the diagnosis of tuberculous meningitis, and WebDot[34], application to record the medication taken by the patient under treatment for tuberculosis. It is worth mentioning that the standardized protocol proposal does not have the intuition to automate health techniques and procedures nor to replace the professional specialist.

5. Conclusion and future work

The development of the standard protocol proposed here will obey rigorous methodological steps that contemplate the findings of the international scientific literature and the experiences of the subjects involved in this research. Subsequent studies will be conducted to evaluate the impact of the use of the protocol in clinical software trials. The authors believe in the premise that we should envision a better world and develop new health systems that transform health into wellness and the patient into a collaborative designer of health care platforms.

6. Ethical considerations

The guidelines of Resolution nº. 466/12 of the National Health Council regarding research with human beings will be fulfilled and the study will be submitted to the Research Ethics Committee of the Medical School of Ribeirão Preto/University de São Paulo for proper appreciation.

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