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Diretrizes preliminares para o desenvolvimento de tecnologias de saúde digital em ensaios clínicos no Brasil

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“O prazer mais nobre é o júbilo de compreender” -
Leonardo da Vinci.

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RESUMO

RODRIGUES, Lídia Maria Lourençön. **Diretrizes preliminares para o desenvolvimento de tecnologias de saúde digital em ensaios clínicos no Brasil.** 2022. 95 f. Tese (Doutorado em Saúde Pública) - Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, 2022.

Na última década, a prática médica baseada em evidências tem sido auxiliada em larga escala por ferramentas informatizadas de apoio à decisão, visando reduzir a incerteza diagnóstica e terapêutica, complementando as ações do profissional de saúde. Com a evolução tecnológica, já é possível considerar esses sistemas como parte da intervenção clínica, tanto para o diagnóstico como para o tratamento de doenças. A literatura tem descrito a implementação de ferramentas e-health, ou seja, inovações tecnológicas na área da saúde como software, aplicativos, serious games, entre outros, como estratégia para melhorar o processo e a adesão ao tratamento. No entanto, ainda não há instrumento padronizado no Brasil que possa ser utilizado para guiar o desenvolvimento, desde a fase de pesquisa, e a implementação dessas ferramentas como intervenção em saúde, repercutindo também nos desfechos para o paciente. Com o intuito de investigar uma nova forma terapêutica e preventiva, baseada na intervenção com um sistema computacional, este trabalho propõe a criação de diretrizes-guia para o registro e a implementação de ferramentas e-health como intervenção clínica. A proposta aspira ser capaz de auxiliar na padronização do registro desde o estágio de desenvolvimento até a aplicação da ferramenta de e-health auxiliando no tratamento de doenças, relatando toda a experiência vivida na pesquisa e aplicando-a em um contexto de pandemia.

Palavras-Chave: Diretrizes de pesquisa; ensaios clínicos; *e-health*; saúde digital; Evidências de mundo real.

ABSTRACT

RODRIGUES, Lídia Maria Lourençön. **Preliminary guidelines for the development of digital health technologies in clinical trials in Brazil.** 2022. 95 p. Thesis (Doctorate in Public Health) - Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, 2022.

In the last decade, evidence-based medical practice has been supported on a large scale by computerized decision support tools, aiming to reduce diagnostic and therapeutic uncertainty, complementing the actions of the health professional. With technological developments, it is now possible to consider these systems as part of clinical intervention, both for the diagnosis and treatment of diseases. The literature has described the implementation of e-health tools, that is, technological innovations in the health area such as software, applications, serious games, among others, as a strategy to improve the process and adherence to treatment. However, there is still no standardized instrument in Brazil that can be used to guide the development, from the research phase, and the implementation of these tools as a health intervention, also impacting patient outcomes. With the aim of investigating a new therapeutic and preventive way, based on intervention with a computer system, this work proposes the creation of guidelines for the registration and implementation of e-health tools as a clinical intervention. The proposal aspires to be able to assist in the standardization of the record from the development stage to the application of the e-health tool helping in the treatment of diseases, reporting all the experience lived in the research and applying it in a pandemic context.

Key words: Research guidelines; Clinical Trials; e-health; Digital Health; Real World Evidence.

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1. Introdução e Motivação

O homem, ao longo da história, registra a sua evolução enquanto espécie utilizando-se de diversas técnicas, passando desde a pintura rupestre no período pré-histórico utilizada com o objetivo principal de anotar a vida cotidiana das caçadas animais, aos documentos técnicos de linguagem mais elaborada criados para contemplar as mais diferentes necessidades de documentação do homem moderno. O homem cientista não é diferente. Infelizmente, pesquisas realizadas sem uma padronização em seus relatos causam dificuldade na interpretação correta dos resultados e em sua replicação por outros pesquisadores em outros cenários. Elementos muitas vezes essenciais da metodologia dos estudos são omitidos ou mal descritos, o que limita o valor das diretrizes estabelecidas para a prática clínica.

Além de registrar seus feitos históricos, outra busca importante do homem tem sido a criação de máquinas munidas de inteligência artificial que se aproxime e até mesmo supere a capacidade do cérebro humano. Essa busca bastante ambiciosa tem cativado, principalmente, os profissionais ligados à área da saúde, que visionaram na computação o auxílio na realização de diagnósticos e tomada de decisões a respeito dos tratamentos aos seus pacientes, funções muito além das primeiras utilizações do computador para armazenamento e processamento de dados e conhecimentos.

No contexto de pandemia em que vivemos desde o ano de 2020, as tecnologias digitais estão cada vez mais sendo utilizadas para o apoio na tomada de decisão e resposta em saúde pública em todo o mundo, incluindo as ações de vigilância epidemiológica, diagnóstico de casos e rastreio de contatos, além de auxiliar na avaliação das intervenções remotas com base em dados de saúde coletados da população. A tendência é que a saúde se torne cada vez mais digital e que o uso das ferramentas de *e-health* auxilie no processo de formulação de regulação, avaliação e utilização das tecnologias digitais para o fortalecimento da gestão pública e suplementar frente à situações de crise em saúde (BUDD et al., 2020; GOSTIC et al., 2020).

A assistência à saúde e as pesquisas clínicas que envolvem tanto diagnósticos quanto tratamentos, necessitam de parâmetros teóricos e clínicos a serem seguidos, embasados em preceitos éticos, estabelecidos para pesquisas com seres humanos, e em evidências científicas. Sem a padronização de procedimentos e respaldo teórico adequado pode haver o

desfavorecimento à prestação de cuidados ao paciente, dando margem à práticas clínicas negligentes, imprudentes e/ou imperitas. Além de possibilitarem maior segurança aos profissionais que os utilizam, os protocolos direcionados ao ensino e pesquisa operacional são recursos vantajosos para o aumento da qualidade das pesquisas e serviços em saúde, para facilitar a avaliação e incorporação de novas tecnologias assistenciais e para garantir transparência nas informações e financiamento em saúde (PIMENTA et al., 2014).

Embora diversos estudos tenham sido realizados para testar tecnologias digitais enquanto complemento da intervenção clínica em tratamentos de saúde (LESTER et al., 2010; TETZLAFF et al., 2012; VODOPIVEC-JAMSEK et al., 2012; BELISARIO et al., 2013; LIU, 2013; SARNO, CANELLA e BANDONI, 2014; OLIVEIRA et al., 2017; YAN et al., 2017; BAKKER et al., 2019; DORST et al., 2019; BUDD et al., 2020; GEOGHEGAN et al., 2020; INAN et al., 2020; CHENG et al., 2021; MANTUA et al., 2021; RADIN et al., 2021; WANG et al., 2021), não há registro de uma proposta específica de diretrizes para pesquisa e implementação de investigações científicas – como os ensaios clínicos - com ferramentas de *e-health* no Brasil.

A comunidade científica tem, até o momento, como protocolos-guia para intervenções que utilizam inteligência artificial em saúde o CONSORT E-HEALTH (EYSENBACH, 2011), o CONSORT-AI EXTENSION (LIU ET AL., 2020) e o SPIRIT-AI (RIVERA ET AL., 2020), estabelecidos em contextos diferentes dos vivenciados em nosso país com relação ao desenvolvimento de tecnologias em saúde digital.

Dado o contexto, o objetivo deste trabalho é propor diretrizes preliminares para o desenvolvimento e implementação de ensaios clínicos com ferramentas de saúde digital no Brasil.

Apesar de sua aparente simplicidade, o que diferencia o protocolo proposto nessa tese das diretrizes já publicadas internacionalmente é seu desenvolvimento pensado para o cenário de tecnologia em saúde no Brasil e sua implementação realizada em tempo recorde no serviço denominado TeleSUS, um serviço de telessaúde do Sistema Único de Saúde (SUS) desenvolvido em resposta à pandemia da COVID-19 no Brasil, em março de 2020 (MINISTÉRIO da SAÚDE, 2020).

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2. Objetivos

2.1 Objetivo Geral

Propor diretrizes preliminares para o desenvolvimento de tecnologias de saúde digital para a utilização em ensaios clínicos no Brasil.

2.2 Objetivos Específicos

2.2.1 Validar um conjunto mínimo de itens e a metodologia de trabalho no desenvolvimento das diretrizes.

2.2.2 Implementar as diretrizes validadas no processo de desenvolvimento de uma ferramenta de saúde digital no Brasil.

3. Aspectos éticos

Todas as exigências éticas prescritas pela Resolução nº 510/2016 do Conselho Nacional de Saúde (CNS) e suas complementares foram sendo cumpridas no desenvolvimento deste trabalho. O projeto foi aprovado pelo Comitê de Ética em Pesquisa (CEP) da Faculdade de Medicina de Ribeirão Preto - FMRP/USP (CAAE: 14671019.2.0000.5440). Os participantes foram informados dos objetivos do estudo e da confidencialidade dos dados em termos de compromisso e de consentimento livre e esclarecido (TCLE) especialmente elaborados para essa pesquisa (APÊNDICE I). Cabe destacar que o uso das informações dos participantes nos sistemas de análise de dados foi realizado respeitando o sigilo e a não identificação, seguindo o vigente na Lei Geral de Proteção de Dados – LGPD do Brasil.

4. Métodos

4.1 Modelo do estudo

O estudo apresentado tem duas fases estabelecidas em seu percurso de desenvolvimento: a primeira, de criação e validação das diretrizes e a segunda, de implementação do construto.

A primeira fase trata-se de um estudo metodológico, envolvendo o desenvolvimento de método rigoroso e sistematizado de obtenção e organização de dados e condução da pesquisa. Tais métodos estão descritos detalhadamente em artigo já publicado pela autora dessa pesquisa (RODRIGUES ET AL., 2018), presente na seção de publicações.

A segunda fase da pesquisa trata-se de uma estudo epidemiológico descritivo-analítico de intervenção, com abordagem qualitativa e quantitativa. Essa fase contempla a implementação das diretrizes no desenvolvimento de uma ferramenta de saúde digital denominada TeleSUS, o serviço de telessaúde do Sistema Único de Saúde do Brasil.

4.2 População do estudo

Na fase de Criação e Validação do construto foram selecionados, por amostra intencional não probabilística, dez juízes especialistas nas áreas de saúde e/ou informática do Brasil, com experiência profissional acima de cinco anos e titulação mínima de Mestre.

Na fase de Implementação do protocolo, o desenho inicial foi concebido para sua utilização com os profissionais de saúde e informática que participaríam do desenvolvimento e utilização da ferramenta *MTBapp* com os pacientes internados no Ambulatório de Tuberculose do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo.

A ferramenta *MTBapp* (SANTOS et al., 2018), cuja publicação tem coautoria da presente pesquisadora, foi desenvolvida com o intuito de calcular a pontuação preditiva para meningite tuberculosa, a fim de apoiar as decisões clínicas dos especialistas na área. A fase de implementação estava prevista para ocorrer no período entre março/2020 e agosto/2020. Porém, com o advento da pandemia da COVID-19, a pesquisa não pode ser aplicada no referido

ambulatório que foi utilizado como base para internação e tratamento de pacientes com o coronavírus e fechado para a realização de quaisquer outras atividades.

Optou-se, portanto, pela adaptação da implementação do protocolo com os profissionais de saúde e informática envolvidos no contexto de desenvolvimento do serviço de telessaúde denominado TeleSUS - Serviço de Telessaúde do Sistema Único de Saúde - criado em parceria com o Ministério da Saúde e empresa privada vencedora da licitação para a operacionalização do serviço. Durante o desenvolvimento da operação, a presente pesquisadora foi responsável pela criação e atualização constante dos algoritmos clínicos do sistema e pela análise dos resultados das ações propostas.

O TeleSUS, cujas operações se iniciaram em abril de 2020 e se encerraram em julho do mesmo ano, foi concebido com o objetivo de orientar a população a respeito da infecção pela COVID-19 e monitorar casos suspeitos e confirmados da doença em todo o território nacional. A estratégia disponibilizou um serviço de atendimento pré-clínico de saúde, visando esclarecer a população sobre a doença e o momento necessário para procurar atendimento presencial. Também teve o importante papel de favorecer o isolamento domiciliar da população potencialmente contaminada e grupos de risco para a doença (na ausência de sinais de gravidade) e evitar o esgotamento dos serviços presenciais de saúde (MINISTÉRIO DA SAÚDE, 2020).

4.3 Construção das diretrizes

A construção das diretrizes preliminares, ou aqui também denominadas de "protocolo", se baseou nos instrumentos já existentes em literatura que sistematizam diretrizes e recomendações para a condução de ensaios clínicos, ainda que somente um desses instrumentos – o CONSORT E-HEALTH (EYSENBACH et al, 2011) e sua extensão CONSORT-AI EXTENSION (LIU ET AL., 2020) - especifique tópicos metodológicos importantes para pesquisas com ferramentas de saúde digital – ou *e-health* - na área da saúde.

Os principais instrumentos utilizados foram CONSORT Statement 2010 (MOHER et al., 2001) e suas extensões STRICTA 2010 (MACPHERSON et al., 2010), E-HEALTH (EYSENBACH et al., 2011) e CONSORT-AI EXTENSION (LIU ET AL., 2020); SPIRIT Statement 2013 (CHAN et al., 2013) e sua extensão o SPIRIT-AI (RIVERA ET AL., 2020);

TIDIER (HOFFMANN et al., 2014), QUOROM (MOHER et al., 1999) e STARD BLCM (KOSTOULAS et al., 2017). Também foram consultadas as plataformas de registro de ensaios clínicos certificadas pela Organização Mundial da Saúde (OMS) e pelo *International Committee of Medical Journal Editors* (https://www.who.int/ictrp/network/primary/en/), destacando-se o ReBec – Registro Brasileiro de Ensaios Clínicos (http://www.ensaiosclinicos.gov.br/) e o ISRCTN Registry (http://www.isrctn.com/), a fim de verificar quais aspectos de registro elas contemplavam. Após a coleta e análise do conhecimento sintetizado, o desenvolvimento do protocolo padronizado foi dividido em cinco passos mostrados na figura 01 abaixo.

O primeiro passo foi a realização de uma revisão sistemática nas bases de dados *PUBMED/MEDLINE, WEB OF SCIENCE*, SCOPUS, LILACS SciELO, utilizando os descritores previamente selecionados para dar origem ao protocolo. A metodologia utilizada na realização da revisão sistemática se encontra descrita em detalhes em artigo já publicado (RODRIGUES, 2018), presente na seção de publicações desta pesquisa.

O segundo passo foi o refinamento dos tópicos/questões a serem abordados na declaração do protocolo. Após a delimitação destes tópicos, o terceiro passo foi a validação do protocolo, ou seja, assegurar a revisão/avaliação da declaração estabelecida por pares de especialistas. O quarto passo foi a implementação, ou seja, a disseminação do protocolo, incluindo o local para teste piloto. Por fim, o quinto e último passo, denominado de Avaliação, foi composto pela análise dos resultados da utilização do protocolo e de sua qualidade enquanto instrumento de ensino.

Figura 01. *Pipeline* contendo os cinco passos para o desenvolvimento do protocolo.
Fonte: própria.

4.4 Validação das diretrizes

A metodologia para validação teve como objetivo verificar o grau de qualidade do instrumento proposto (POLIT, BECK, HUNGLER, 2011). Dentre os métodos disponíveis para validação de conteúdo de protocolos foi escolhido o Método Delphi (POLIT; BECK, 2011), que visa obter a maior concordância possível entre um grupo de especialistas sobre um tema, quando não há unanimidade de opinião ou informações contraditórias registradas na literatura científica (REVORÊDO et al 2015). Nesta pesquisa, o método foi adaptado para a modalidade *online*, via *internet*, e com ocorrência preestabelecida de no máximo três rodadas e uma reunião de consenso caso ainda houvesse divergências. Isso facilitou a interação entre os participantes do estudo e o pesquisador responsável, independentemente da localização geográfica (MUNARETTO, CORRÊA, CUNHA, 2013).

Os critérios incluídos na avaliação do instrumento foram Escopo e propósito, envolvimento dos Stakeholders (ou interessados), rigor no desenvolvimento, clareza na apresentação, aplicabilidade e independência editorial (BROUWERS, 2010). As partes interessadas incluíram profissionais de saúde, cientistas da computação, representantes da indústria, formuladores de políticas, informáticos de saúde, pacientes e financiadores.

Dez juízes especialistas nas áreas de saúde e/ou tecnologia da informação no Brasil, com experiência profissional superior a cinco anos, foram selecionados por meio de amostra

não probabilística intencional. A pesquisadora entrou em contato com os especialistas selecionados por e-mail, convidando-os a participar (APÊNDICE II) e enviando um *link* para o formulário a ser preenchido, por meio de questionário eletrônico (*Google Docs*), acompanhado da primeira versão das diretrizes (protocolo) elaborada, definindo o estudo, seus objetivos, orientações quanto ao preenchimento e a importância da avaliação do instrumento pelos especialistas.

Para ter acesso ao formulário contendo os itens da pesquisa a serem avaliados, os participantes foram orientados a clicar no *link* enviado por e-mail e concluir a avaliação em até 20 dias. Clicando no link, o participante era direcionado ao formulário com abertura imediata do Termo de Consentimento Livre e Esclarecido – TCLE. Somente após o preenchimento obrigatório do TCLE, indicando o consentimento em participar da pesquisa, as seguintes telas para avaliação foram disponibilizadas ao participante. Uma vez que os questionários foram aplicados eletronicamente, as respostas foram registradas diretamente em um banco de dados, evitando assim erros associados à intervenção do pesquisador no registro das respostas fornecidas.

Antes de iniciar a etapa de implementação do protocolo, a pesquisadora optou por não realizar nenhum tipo de capacitação individual dos participantes do estudo, com esclarecimento de dúvidas e/ou exemplos de aplicação prática do protocolo para evitar condicionar a maneira como cada um o utilizaria e, também, para extrair resultados mais fidedignos com relação à clareza, intuição, praticidade e fácil entendimento do instrumento proposto, primordialmente, para a utilização no ensino. O teste piloto realizado no ambiente de operacionalização do TeleSUS serviu como guia para garantir a verificação mais precisa da eficiência do protocolo na prática e a identificação dos ajustes necessários para um novo teste no futuro.

A intenção foi principalmente medir através de um questionário semiestruturado (APÊNDICE IV) elaborado, o quanto o protocolo auxilia os profissionais envolvidos e simplifica a construção de um processo de desenvolvimento de uma ferramenta de saúde digital para ser utilizada como intervenção em saúde.

É importante dizer que a proposta do protocolo não tem o intuito de automatizar técnicas e procedimentos de saúde, nem de substituir o profissional especialista, mas sim complementar e melhor gerenciar o atendimento ao paciente, agilizar os cuidados, reduzir custos e

proporcionar uma reflexão crítica aos pacientes com relação aos padrões de prestação de cuidados de saúde.

4.5 Análise estatística

As análises estatísticas foram feitas pelo programa IBM SPSS *Statistics* versão 22.0.0.0, a concordância entre os juízes foi avaliada pelo Índice de Validade de Conteúdo (IVC) (HYRKÄS, APPELQVIST-SCHMIDLECHNER e OKSA, 2003) e para a verificação de confiabilidade foi utilizado o Coeficiente Alpha de Cronbach.

Nesta pesquisa, foi considerada como concordância/discordância o resultado proporcional de peritos que julgarem o item como válido para o protocolo pelo total de especialistas da amostra, conforme cálculo abaixo. Para consenso, foi considerado o IVC superior a 0,80 (POLIT, BECK, 2006) e para o cálculo do IVC, em uma escala de sete pontos, as respostas de 5 a 7, onde 5 e 6 ("importante, porém não crítico") e 7 ("importante e crítico") serão consideradas como concordância, e as respostas de 1 a 4 ("não é importante/necessário") serão consideradas como discordância.

$$\textbf{IVC} = \frac{\text{Concordância}}{\text{Total de respostas dos especialistas}}$$

No cálculo do Coeficiente de Alfa de Cronbach para quantificar a confiabilidade do questionário, o valor mínimo aceitável para considerá-lo aceitável é de 0,7 (ALMEIDA; SANTOS; COSTA, 2010). Como os valores variam de 0 a 1, quanto mais próximo de 1, maior confiabilidade entre os indicadores, e vice-versa (FREITAS, RODRIGUES, 2005; TAVAKOL; DENNICK, 2011).

5. Resultados e Discussão

A seção de resultados e discussão é aqui apresentada em formato de artigos científicos publicados, submetidos e/ou elaborados, além de outros materiais desenvolvidos utilizando-se a metodologia proposta nesta pesquisa. Todas as publicações são apresentadas em língua inglesa.

O primeiro artigo científico publicado, derivado da presente pesquisa de Doutorado (Rodrigues et al., 2017), é apresentado na seção 5.1 e teve como objetivo descrever as etapas do desenvolvimento de um banco de dados de notificação de reações adversas (RA) para servir como padrão-ouro de um projeto até então pioneiro no país para o processamento automático de dados a partir da inclusão de sistemas de notificação eletrônica nos Sistemas de Informação Hospitalar (SIH). O artigo foi publicado logo no início do curso de Doutorado e foi por meio dele que as diretrizes nesta tese propostas para o desenvolvimento de ferramentas de saúde digital começaram a ser concebidas. O artigo traz um passo a passo detalhado para a criação do banco de dados de notificação de RA e preocupa-se em destacar a importância de o método de pesquisa estar registrado do início ao fim para possibilitar o desenvolvimento teórico e prático de métodos automatizados de farmacovigilância e avançar no estado da arte através da publicação de resultados pautados na qualidade dos estudos elaborados. Esta publicação foi intitulada "*Proposal of a gold standard database model of adverse drug reactions reports*". Além disso, o artigo foi submetido e aceito para apresentação oral no *CENTERIS / ProjMAN / HCist 2017 - Conference on ENTERprise Information Systems / International Conference on Project MANagement / Conference on Health and Social Care Information Systems and Technologies*, realizado em Barcelona, Espanha. O texto completo do artigo foi publicado na revista *Procedia Computer Science* (ISSN: 1877-0509) em seu volume 121 do ano de 2017 (doi: 10.1016/j.procs.2017.11.114), disponível em https://www.sciencedirect.com/science/article/pii/S1877050917323165.

O segundo artigo científico publicado (RODRIGUES et al., 2018) é apresentado na seção 5.2 e teve como objetivo descrever o desenho do projeto de pesquisa utilizado como base para a construção da tese de Doutorado. O artigo traz em detalhes a metodologia utilizada na realização da revisão sistemática que foi fundamental para o início do desenvolvimento das diretrizes propostas nesta pesquisa. Esta publicação foi intitulada "*Towards a standardized protocol for conducting randomized clinical trial for software*". Além disso, o artigo foi submetido e aceito para apresentação oral no *CENTERIS / ProjMAN / HCist 2018 - Conference on ENTERprise Information Systems / International Conference on Project MANagement / Conference on Health and Social Care Information Systems and Technologies*, realizado no Porto, Portugal. Assim, o texto completo do artigo foi publicado na revista *Procedia Computer*

Science (ISSN: 1877-0509) em seu volume 138 do ano de 2018 (doi: 10.1016/j.procs.2018.10.018), disponível em https://www.sciencedirect.com/science/article/pii/S1877050918316491.

O terceiro artigo científico publicado, derivado da presente pesquisa de Doutorado, (SANTOS et al., 2018) é apresentado na seção 5.3 e teve como objetivo descrever o desenvolvimento de um assistente virtual auxiliar ao tratamento do paciente com tuberculose por meio de um aplicativo em saúde com técnicas de inteligência artificial e acessibilidade para maior adesão à intervenção. A ferramenta foi pensada para validação utilizando-se as diretrizes concebidas nessa tese de Doutorado à época do referido artigo ainda em fase inicial do projeto. Esta publicação foi intitulada "*Proposal for the development of a mobile virtual assistant for treatment of tuberculosis*". Além disso, o artigo foi submetido e aceito para apresentação oral no *CENTERIS / ProjMAN / HCist 2018 - Conference on ENTERprise Information Systems / International Conference on Project MANagement / Conference on Health and Social Care Information Systems and Technologies*, realizado no Porto, Portugal, e está disponível em https://www.researchgate.net/publication/331399302_Proposal_for_the_development_of_a_mobile_virtual_assistant_for_treatment_of_tuberculosis.

O quarto artigo científico elaborado é apresentado na seção 5.4 e teve como objetivo realizar uma revisão sistemática de literatura a fim de identificar e descrever se há uma padronização na literatura para o desenvolvimento de *software* e/ou ferramentas de *e-health* antes do advento da pandemia da COVID-19. Foram pesquisados artigos que descrevessem o processo de concepção e desenvolvimento de um *software* e/ou ferramenta *e-health* para ser aplicada como intervenção clínica em saúde, independentemente do tipo de enfermidade alvo. Para o desenvolvimento da revisão, foram utilizadas as recomendações do protocolo de submissão de revisão sistemática PRISMA (MOHER, 2009). Como critérios de elegibilidade foram incluídos ensaios clínicos e estudos originais que descrevessem resultados relacionados ao uso de *software* e ferramentas *e-health* como intervenção clínica em pacientes (desfechos primários ou secundários). Os demais critérios de inclusão foram: data de publicação do estudo de 2010 a dezembro de 2018, intervenções a serem realizadas em crianças, adultos e/ou idosos e publicação em inglês, espanhol e/ou português. Foram excluídos estudos de revisão, editoriais, cartas ou comentários, capítulos de livros, dissertações e/ou teses e estudos em

animais. Optou-se por excluir o período de pandemia desta revisão por dois motivos principais: o primeiro para entender como o desenvolvimento das ferramentas de saúde digital era pensado antes da COVID-19 nos apresentar um cenário onde as atividades remotas de saúde tornaram-se amplamente necessárias, além de outros aspectos importantes em termos de avanços tecnológicos no espaço-tempo, e o segundo porque também se pretende realizar uma revisão sistemática apenas com artigos publicados de 2019 a 2022 e comparar as duas revisões posteriormente. Esta publicação foi intitulada "*Systematic review of existing methodologies for software development in healthcare before the pandemic*" e foi submetida ao periódico *Digital Medicine – Nature Partner Journals* (https://www.nature.com/npjdigitalmed).

O quinto artigo científico elaborado, e coração desta tese, é apresentado na seção 5.5 e teve como objetivo descrever as diretrizes preliminares para o desenvolvimento e implementação de tecnologias de saúde digital em ensaios clínicos no Brasil. Apesar de sua aparente simplicidade, o que diferencia o protocolo proposto nesta tese e explanado no artigo das diretrizes já publicadas internacionalmente é seu desenvolvimento voltado para o cenário de tecnologia em saúde no Brasil e sua implantação realizada em tempo recorde no serviço denominado TeleSUS, serviço de telessaúde da União Sistema Único de Saúde (SUS) desenvolvido em resposta à pandemia de COVID-19 no Brasil, em março de 2020 (MINISTÉRIO da SAÚDE, 2020). Esta publicação foi intitulada "*SACI Protocol: Preliminary guidelines for the development of digital health technologies for clinical trials in Brazil*" e foi submetida ao periódico *E-Health Telecommunication Systems and Networks* (https://www.scirp.org/journal/etsn).

O sexto artigo científico é apresentado na seção 5.6 e teve como objetivo avaliar a usabilidade de um sistema de telessaúde, medindo o grau de satisfação dos profissionais de saúde usuários, identificando fatores que influenciam positiva e negativamente na avaliação. Isso se faz necessário considerando-se a importância do TeleSUS, estratégia explanada no artigo, para os serviços públicos de saúde no Brasil. Esta publicação foi intitulada "*Usability evaluation of the TeleSUS digital health tool according to the perception of the user health professional*" e foi submetida ao periódico *E-Health Telecommunication Systems and Networks* (https://www.scirp.org/journal/etsn).

5.1 Artigo 1

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Proposal of a gold standard database model of adverse drug reactions reports

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- **Abstract**

During the post-marketing period, when the drugs are used by large populations and for longer periods of time, unexpected adverse reactions (AR) may occur, which changes the risk-benefit ratio of the drugs, requiring a Regulatory action. Most post-marketing AR requires a significant increase in health care and result in damage, often fatal, to the patient. Therefore, the early detection of AR in the post-marketing period is the primary goal of a health system, in particular, pharmacovigilance systems. The main objective of this article is to show the stages of the development of an AR notification database to serve as the "gold standard" of a pioneering project in Brazil to process data automatically from the inclusion of electronic reporting systems into the Hospital Information Systems (HIS).

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Keywords: Adverse reactions; database; pharmacoepidemiology.

1. Introduction

According to EU Directive 2010/84 (applied in July 2012), an Adverse Drug Reaction (ADR) is a harmful and unwanted response to one or more drugs and may occur due to medication errors, drug quality deviations, drug interactions and/or intoxications that produce causal links between the adverse reaction and the drug[1].

In Brazil, pharmacovigilance actions, aimed at early detection of adverse reactions and monitoring possible increases in their incidence, are carried out in a shared manner by the sanitary surveillance of the States, municipalities and the National Agency of Sanitary Surveillance - ANVISA, created in 1999 along with The National Pharmacovigilance System. Starting in 2008, the National Notification System for Health Surveillance (Notivisa) was created in order to store information on qualified adverse reactions directly in the database[2,3,4].

In Portugal, the National Pharmacovigilance System (NPS) was created in 1992 and later modified with the introduction of Regional Pharmacovigilance Units (RFU), autonomous units with the aim of disseminating topics related to pharmacovigilance, processing spontaneous reports of adverse drug reactions Medicines (ADR), to bring NPS closer to health professionals and users, and to ensure the safety and the safe use of medicines.

Pharmacovigilance systems should be able to assess the benefits and risks of a pharmacological product by ensuring that it maintains the quality, safety and efficacy compatible with its rational use[3].

Traditionally, ADR signal-detection methodologies analyze data from a single source, typically databases of voluntary notifications. An emerging belief in pharmacovigilance research is that combining information from multiple sources of data can lead to the most effective and accurate discovery of AR[8,9].

Depending on the data sources used, and how they are combined, it is believed that the resulting system could lead to increased statistical significance of the results and facilitate new discoveries that are not possible using isolated data sources. Although this hypothesis has already been preliminarily confirmed[5], further studies are needed.

Therefore, the objective of this paper is to describe the steps of the research on architecture for the construction of a database that is a reference for adverse drug reactions, from a detailed analysis of heterogeneous sources of data.

The main difference from our research project from the ones in the literature is we assume that the processing of large volumes of heterogeneous data (for example hospitalization and pharmacovigilance data) allows the creation of more effective pharmacoepidemiological

analysis systems capable of detecting ADRs that cannot be detected through the analysis of a single data source. This research considers the hypothesis that heterogeneity makes the analysis more powerful. Thus, in the absence of a reference standard for the detection of ADR, we must focus on the construction of this pattern from an analysis of heterogeneous data sources, disaggregating the analyses in space and time.

In the second section of this paper, we will present theoretical models used as reference for the construction of the proposed database model. Then, in the third section, we will describe the stages planned to build this model and the possible methods for its execution along with its analysis. At last, in the fourth section, 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

In this section, we present the necessary steps and theoretical elements for conducting this research.

2.1. Adverse Drug Reactions

An adverse drug reaction (ADR) is an unintended and undesired effect of a drug used in humans for diagnosis, therapy and treatments. Generally, the ADRs are expensive and fatal. Because of this, the World Health Organization (WHO) built an International Drug Monitoring Program and the United States Food and Drug Administration reinforced the security of monitoring of drugs[7].

Another important definition is about the Drug Related Problems, a heterogeneous group including ADRs. These problems interfere with the achievement of an optimal outcome in a patient's drug treatment. The Adverse drug events, injuries related to the use of a drug, include medication errors such as the incorrect doses prescript or administered without adjustment in the patients and the ADRs.

The Adverse Drug Reaction are a Public Health Problem and the cause of approximately 5% of the hospital admissions[5].Therefore, it is very important to detect and prevent the ADRs through pharmacovigilance as one of the ways of possibility of increasing Healthcare quality and decreasing its costs[6].

2.2. Pharmacovigilance

It is defined as the science/activities related to the detection, understanding and prevention of the adverse drug reactions and related problems[7]. Some ADRs are difficult to detect during phases of research before the drugs are ready for commercialization and occurring several years after its administration. Nacional and International Drug Regulatory Agencies

from around the world currently use spontaneous reporting as a continuous in the Pharmacovigilance methods.

2.3. Adverse Drug reactions (ADR) identification and coding information

We adopted the definition of ADR proposed by WHO already mentioned before and the database of two public hospitals considered in this study included information of diagnosis on the form of codes of ICD-9-CM (Portugal) and ICD-10-CM (Brazil). The diagnostic codes searched in this study were selected after a validation study performed in an earlier moment. For validation, we selected the diagnostic codes that allowed us to identify more cases of ADR suspects.

3. Research Methods

3.1. Building the Database

For the development of the database, we will use the data of two sentinel hospitals, HCRP-USP (Clinical Hospital of Ribeirão Preto – University of São Paulo), in Brazil, and São João Hospital in Portugal, prepared to report adverse reactions and technical complaints refer to health products.

Hospital admission data will be compared with data processing in the electronic medical records, clinical narratives, and associated examinations. Set the reference standard, it would become a retrospective study of the pharmacoepidemiology of adverse reactions for each region to understand the variations found.

To collect the data, the inclusion criteria are all hospitalizations occurred during the year 2015 that present the International Classification of Diseases (ICD), ICD-9 for Portugal' data and ICD-10 for Brazil's data, more favorable to adverse reactions according to the literature consulted[8,9,10].

The collected data will be mapped to the Concept Unique Identifier (CUI), aimed at their standardization, and transformed into Medical Dictionary for Regulatory Activities (MedDRA) coding, terminology developed by the International Conference on Harmonization (ICH), to standardize, at national and international level, the classification system of diverse reactions, nationally and internationally, making it possible to compare cases reported to the UFN and ANVISA with the cases detected through the selected ICDs.

Since the National Pharmacovigilance Systems covered are part of the World Health Organization (WHO) Adverse Drug Reactions (ADR) monitoring Program, they must meet certain requirements to code the AR and assign a degree of probability of their occurrence through "imputation of causality". The causality categories used in this study will be classified according to the system proposed by WHO-UMC[11].

3.2. Statistical Analysis

Statistical analyses will be done with the Chi-square test for categorical variables, Student's t-test for normally distributed continuous variables and Mann–Whitney for variables without normal distribution. The level of significance chosen by the moment is $p<0.05$. Methods of disproportionality analysis (DPA) will also be used for the data being analyzed. This measure will be used to classify "drug/event adverse" identified in the processing step.
Methods of analysis of disproportionality (ADP) in pharmacological surveillance represent the main class of analytical methods for the analysis of spontaneous reporting (SRS) data[12].

3.3. Design of the research project

In this paper, we decided to use this particular approach because it allows more elucidation on the impact generated by the building of a computerized database for ADR, providing benefits in the management of these events. We considered this approach the most suitable for bringing betters results.

The first step is to collect the data for the two sentinel hospitals involved in this study. From the separation of the cases reported in these hospitals we must compare the findings with a detailed processing of the contents of electronic medical records, clinical narratives and laboratory tests that in turn must be processed by natural language processing systems to extract drugs, diseases and symptoms.

Records will be processed automatically using tokenization, stemming, tagging, entity recognition and ontology interpretation. We use the General Architecture for Text Engineering (http://gate.ac.uk/) framework for text mining. GATE is considered one of the best tools for language processing and information extraction for text mining[13]. It allows the use of ontologies, tokenizer, and machine learning to classify information. GATE is also one of the most used applications in the medical field and was therefore elected in our approach. It has, however, some restrictions. Some plugins can only classify English. Therefore, to use Portuguese texts, it was necessary to get other tools that could classify Portuguese language in a more complete way for the language-dependent plugins in GATE. For this purpose, Freeling (http://nlp.lsi.upc.edu/freeling/), a tool that supports Tagging, Stemming and Entity Recognition in several languages, including Portuguese, was selected.

They will then be mapped to Concept Unique Identifiers (CUIs) defined by the Unified Medical Language System – UMLS[14] aiming at their standardization. In second place we must select the ICD hospitalizations that occurred in the year of 2015. After that, is important to compare the findings and also process the contents of electronic records, clinical narratives and laboratory tests. The next stage of the project is the data processing and the mapping for Concept Unique Identifiers. Therefore, we proceed to standardization of the data and transformation of the ADR into MedDRA, creating a detailed map of the hospitalizations' causes. After this stage we must remove the cases with probability "unclassifiable" and

"unlikely"[11] to happen and filter the data for the final result of the gold standard creation process.

Still at this stage of the research we must try new associations (not previously known) between drugs and ADR in these databases. However, it is important to stress that this phase of the research should work with a univocal relationship between notification and adverse reaction to a drug. Indeed, this will be important in order to make an exploratory analysis, based on pharmacoepidemiology of hospitalizations due to adverse reactions, since it is not expected that it will always be possible to have access to electronic medical records processing, including possible scenarios of maturity degree of adverse reactions in the hospital environment.

In Figure 1 (below), it is possible to observe the flowchart containing the steps defined for the development of the "Gold-Standard" database in order to guide a better understanding of them. The flowchart also describes the methods used in each stage.

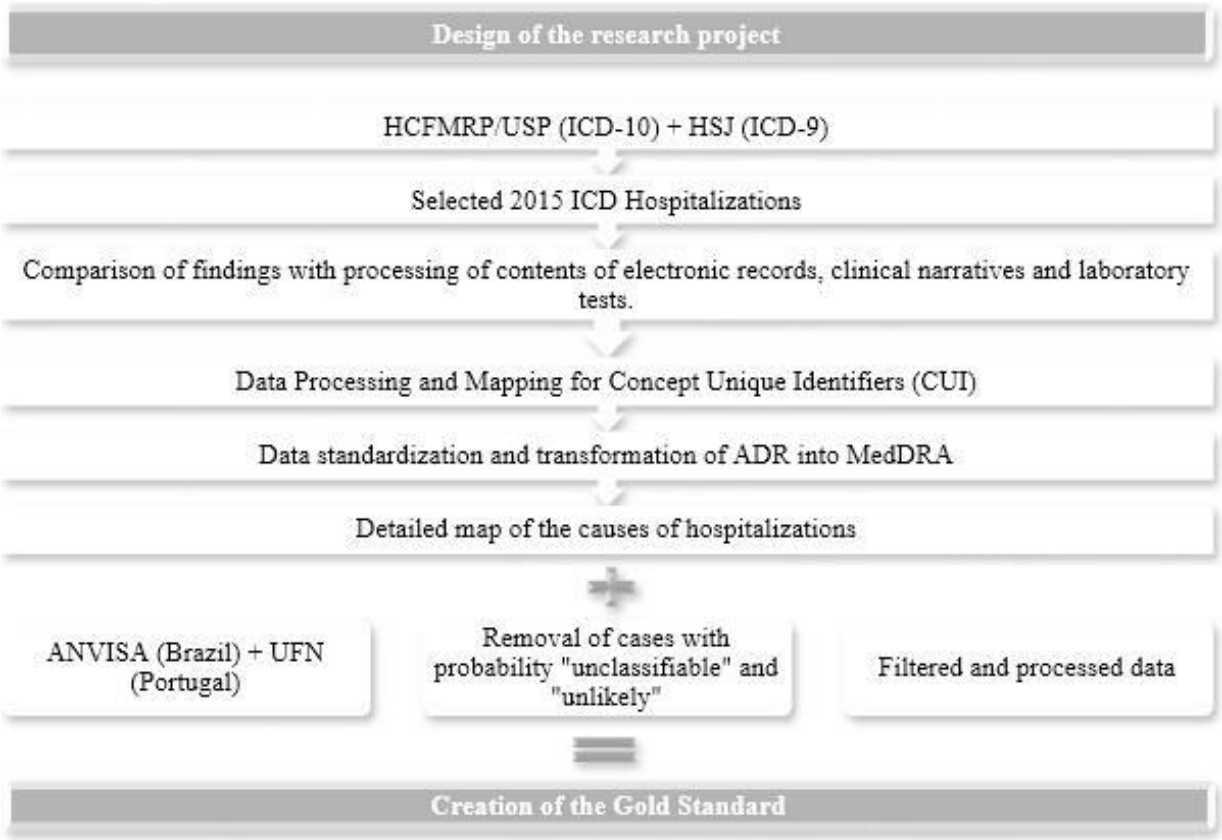

Figure 1 – Flowchart for the construction of the gold standard.

Based on the relationship between hospitalization and the medications that lead to the adverse reaction, a second phase of the research will be done in the database of the Regional

Observatory of Hospital Attention (ORAH / FMRP). In this case, we will be exploring all hospitalizations for the 38 health facilities in 26 cities that make up the region of Ribeirão Preto (DRS-XIII) that occurred in the selected period. This database contains information about the demographic profile of the patients, the main and secondary diagnoses; surgical, therapeutic and diagnostic procedures; the medical specialty of the treated case; dates of entry and exit; type of discharge and the source of payment.

Preliminarily we must make a descriptive study of variables selected to characterize care at the hospital level. These variables will be as follows: legal nature (public / private), volume of hospitalizations, time of hospitalization and size. Another attribute of the hospital to be studied will be the volume of hospitalizations in the intended period of the study, considering all the reasons for admission and not only the main diagnoses selected. This variable is considered as indicative of the complexity of the hospital and will be treated in its intra-annual variation to verify its stability and/or seasonality. The size of the hospital will be measured by the number of beds, which is also understood to be associated with hospital complexity. This preliminary study is important to characterize the region as to the heterogeneity of the data sources that will be studied.

The selection of these variables presupposes an audit of this database with respect to its quality of information. Also, all the variables will be evaluated with respect to inconsistencies and fill level, paying attention to underreporting, sub-registrations, typing errors (annotation) and degree of completeness per variable.

4. Conclusion

The main goal with this research is to show the steps for creating a safe and agile database which is a reference standard for the relation causes of hospitalization and adverse reactions to specific drugs. From a scientific point of view, this project will contribute to the theoretical and practical development of automated methods of pharmacovigilance and to progress in the state of art through publication of the results obtained. We believe that this proposal should be embraced as an effective methodology of pharmacovigilance that can complement other methodologies. The identification of ADRs through databases can increase our knowledge about it and lead us to their detection and more effectively prevention.

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5.2 Artigo *2*

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Towards a standardized protocol for conducting randomized clinical trial for software

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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.

Keywords: clinical protocol; clinical trial for software; evidence-based medicine.

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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 01 below presents the proposed steps for the development of the work.

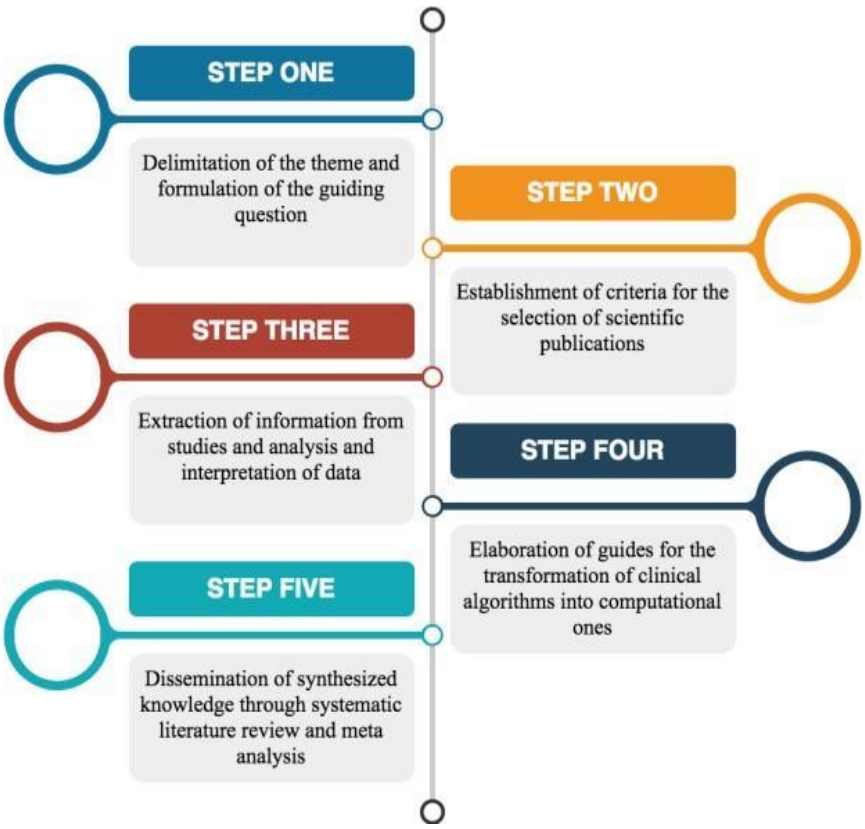

Figure 01. Flowchart of the research methodological steps.

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 02). 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.

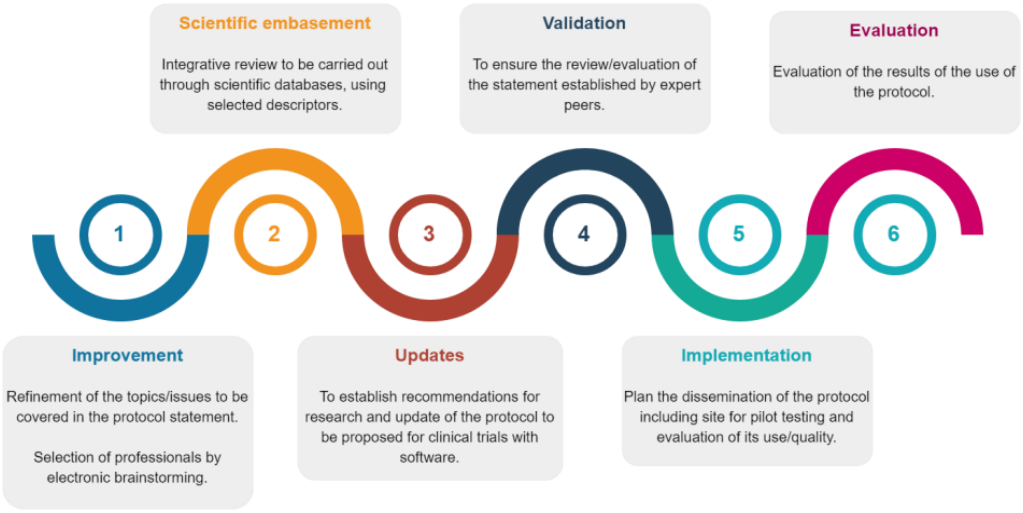

Figure 02. Pipeline containing six phases for the development of the standardized protocol.

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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5.3 Artigo 3

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HCist 2018 – International Conference on Health and Social Care Information Systems and Technologies

Conference Paper

Proposal for the development of a mobile virtual assistant for treatment of tuberculosis

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Abstract

Tuberculosis (TB) is a serious health problem in Brazil and in the world, affecting mainly developing countries. In order to improve this situation, we still need research that looks at operational points of view on the treatment of the disease and that contemplates changes and improvements in the technologies used. This article aims to describe the development of a virtual assistant that can assist patients in the treatment of tuberculosis through a mobile application with an Android operating system that uses artificial intelligence techniques as well as accessibility features that guarantee greater patient engagement. The operational analysis will allow to evaluate if the system increases the solvency of the proposed treatment. The analysis of the cost effectiveness of the process will guide the implementation or not of the same in the follow-up of tuberculosis.

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Keywords: Tuberculosis; Artificial Intelligence; Directly Observed Treatment.

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HCist 2018 – International Conference on Health and Social Care Information Systems and Technologies

1. Introduction

Tuberculosis (TB) is a chronic infectious disease that primarily affects the lungs. Every year, around 10 million new cases are reported worldwide, causing more than one million people to die[1]. In Brazil and in the world, tuberculosis is a serious public health problem, with

deep social roots, resulting from several intervening elements such as low family income, poor education, poor/nonexistent housing, large families, community densities, food malnutrition, alcoholism, diseases associated infectious diseases[2].

TB is a curable disease, and to be successful in treatment it is necessary to obey the principles of drug therapy: proper drug association, correct dosage and use for sufficient time. In the first weeks of treatment, the patient feels better and, therefore, needs to be advised by the health professional to perform the treatment until the end, regardless of the improvement of symptoms[3]. It is important to remember that irregular treatment can complicate the disease and result in the development of drugresistant strains, which is called multidrug-resistant tuberculosis (MDR-TB). The average duration of treatment is 6 months, with up to 18 months in cases of MDR-TB[4].

As a methodology to combat TB, today the Directly Observed Treatment short-course strategy (DOTS) is applied, which has as one of its principles the standardized treatment of short duration, directly observed and monitored in its evolution[5]. Representatives of the World Health Organization have insisted on its efficiency and reinforced its implementation in countries where tuberculosis represents a major public health problem, such as Brazil[6]. Seeking to improve the current performance of the application of the DOTS strategy, a mechanism is being implemented for the recording of the patient's medication intakes through a mobile platform called WebDOT[7].

An exploratory study by Crutzen et al. 2011[8] showed a large potential to reach a varied group of adolescents and to provide them with answers to their questions related to sex, drugs, and alcohol. We expect similar results when integrating a virtual assistant with the current WebDOT system, which will be able to solve the main doubts of the patients, provide guidance and collect patient information through conversations with a chatbot, equipped with artificial intelligence, natural language processing and accessibility features.

The main objective of this work, therefore, is to develop the virtual assistant that includes mechanisms of artificial intelligence and accessibility features through a smartphone with Android operating system, in order to allow remote monitoring of the patient, increase the engagement and the chance of success of the TB treatment, to facilitate the access and the dissemination of information to patients about their health. The virtual assistant will be integrated in the previously mentioned WebDOT platform, and SISTB[9], a pioneering patient management system to aid in the DOTS strategy, enabling the registration, monitoring and evaluation of TB patients and their contacts.

The remainder of this paper is organized as follows: the second section contains the description of methodological steps and the tools that will be used to carry out the project; section three contains the steps determined for the development of the mobile virtual assistant and, finally, session four presents the conclusion of the research and indicates possible future work to be developed on the subject.

2.Materials and methods

2.1Building the assistant: Base platform

The development of this virtual assistant will be based on the WebDOT, a Video DOTS (VDOT) platform developed in the scope of the SISTB in 2016. The WebDOT system was designed to fulfill the basic functions of recording and transmitting media files between the smartphone and a web platform contemplating the specificities in the treatment of TB[7].

2.2 Development tools

To create the virtual assistant will be employed the official integrated development environment of Android applications: Google Android Studio[12]. The languages that will be used in mobile programming are: Java[13] and for the creation of interfaces will be used the eXtensible Markup
Language (XML)[14]. The mobile application will communicate through a REST API (Representational State Transfer) to provide interoperability between computer systems on the Internet. developed in PHP[15] so that we can manage the analysis processes and manage the platform in a centralized way. The data will be kept in a database management system called MySQL[16].

The artificial intelligence responsible for identifying and returning the context of the patient's queries to chatbot will be done by a platform called LUIS[17], which will perform this data processing every time a new question is asked.

3.Results

Fig. 1 below illustrates how the various levels of the application will interact with a question sent orally by the patient and shows, briefly, what processes the virtual assistant will go through until the response is transmitted.

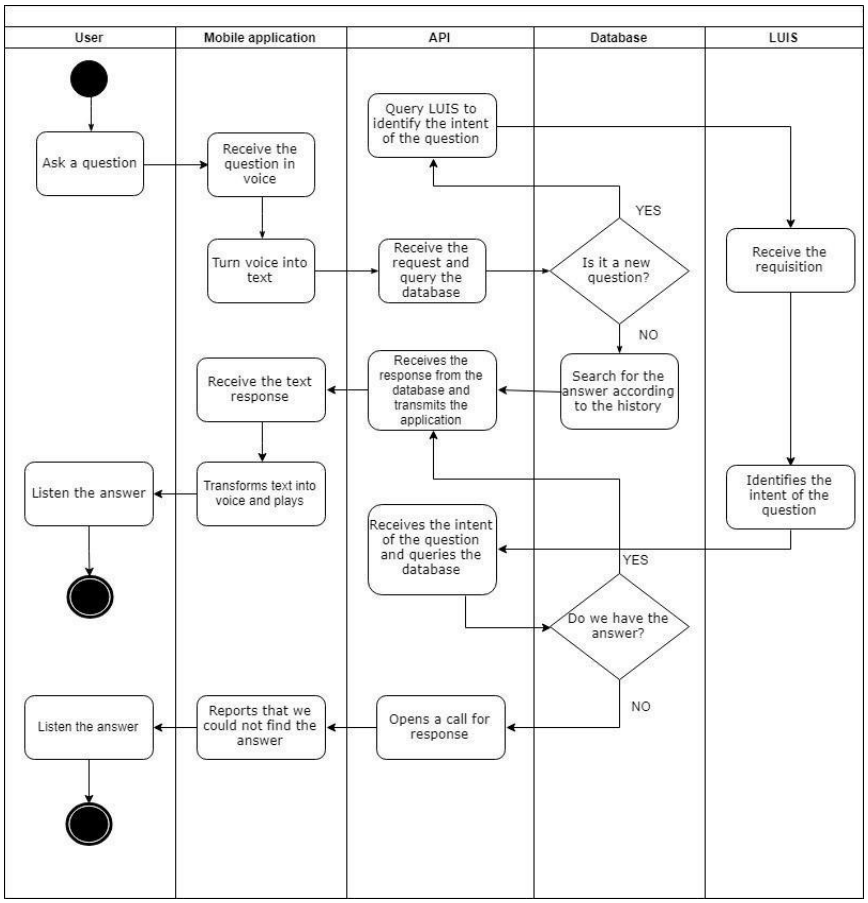

Fig 1. Interaction flowchart of the various software tools when the patient asks a question.

In this article, we decided to use this particular approach described step by step at Fig. 2 below. As first step, the needs of the patients and health professionals who will use the software will be raised beyond directly interviews with the users and compilation of bibliographical references for the literature review that will provide scientific background to the work. In step two will be developed a prototype of the virtual assistant for mobile device capable of interpreting patient interaction and return a response within the context created. In step three, the software will be improved until it is satisfactory in relation to the demand of patients and health agents. The fourth step will be to implement and deal with questions about accessibility and mechanisms to improve the user experience and step five will be to analyze the results obtained by using the virtual assistant. Finally, the last step will contemplate carrying out a costeffectiveness study of the process aiming at its application in public health.

Fig. 2. Flowchart for the construction and implementation of the mobile virtual assistant.

After performing the steps described above, the authors intend to carry out a validation process for the tool to confirm the accomplishment of all the previous steps and to guarantee the fulfillment of the needs specified by the users of the tool. According to literature[18] it is fundamental to apply techniques related to the validation of the mobile tool in order to identify possible adjustments to be made.

4. Conclusion and future work

In view of the complexity and importance of corroborating a change in the TB scenario, the virtual assistant project to assist medical treatment through a smartphone would open the possibility of making available in several types of devices a communication interface, accessible in a way intuitive, to accompany and respond to patients. This could improve the health situation of each patient, facilitating the collection of information in order to carry out the monitoring remotely and minimizing the impacts of the absence of a face-to-face follow-up in poor conditions environments.

The authors of this project intend to carry out the validation of the assistant in the health services for the treatment of tuberculosis in the city of Ribeirão Preto, state of São Paulo, Brazil, in the units and location specified earlier in this article. For this, a pilot study will be carried out with the tool, using a specific protocol, proposed by Lídia M. L. Rodrigues et al. 2018 (to be published), for software's clinical trials. In future work, we hope to understand what are the key features that can be implemented in a virtual assistant that increases the success rate of tuberculosis treatment, to know which profiles are eligible to use such technology, and to apply this tool in other scenarios to promote health.

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5.4 Artigo 4

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Systematic review of existing methodologies for software development in healthcare before the pandemic

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There are still few studies that describe the complete methodology for the software development in health research, fundamentally thinking about the teaching of undergraduate and graduate students who explore this topic in their studies. Among the reasons for this are the lack of standardization of methods and techniques for the development of technological tools for health, the difficulties in accessing technology in the most vulnerable populations, the adaptation and feasibility of software for different scenarios and the high costs. with technologies. On the other hand, the expansion of mobile technologies and the gradual increase in internet access have exponentially expanded the possibilities of communication and data transmission, which facilitates the insertion of health software in different scenarios around the world. It is observed that issues such as immediacy, portability, convenience, and interactivity/interoperability that technology provides make it increasingly possible to develop health promotion actions based on mobile devices. Even so, further studies are needed to evaluate the use of health technologies on a large scale and to discuss the standardization of their development. Our systematic search identified 19 publications meeting inclusion criteria. From these papers, we extracted data including the medical condition, concept of interest captured by the mobile technology, outcomes captured, and details regarding the sensors, algorithms, development of the e-health tool and study sample. The technologies developed ranged from online platforms, electronic messaging systems, interactive games to mobile applications. Regarding the type of study, there was variation between exploratory qualitative research, clinical trials, intervention studies and formative assessment studies. Although all studies present methodological steps in the software development stage, only 1.5% presented a detailed description of both the formation of the research groups and the stages and methods chosen for the development of the software, such as the language for writing source code, data storage, base operating system, among others.

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INTRODUCTION

An increasing number of clinical trials are being developed in which digital health tools are being used as a clinical intervention and as a platform for capturing data from study participants. With the rapid evolution of computational algorithms and artificial intelligence, especially after the advent of the COVID-19 pandemic in 2020, it was possible to analyze and convert a large amount of information stored in these devices into more assertive clinical decisions in the treatment of the patient and, consequently, in its clinical result.

Although data collection by digital health devices has numerous potential advantages, it is necessary to promote standardization in the development of these digital tools so that decision-making on which technologies to use for certain interventions is conducted more efficiently. The Clinical Trials Transformation Initiative (CTTI) recently published a set of recommendations for

improving the quality and efficiency of clinical trials through the appropriate use of mobile technology.

Among the topics covered are the development of endpoints, the implementation of decentralized trials, the application of digital technologies in clinical trials, among others (https://www.ctti-clinicaltrials.org/programs/mobile-clinical-trials).

To catalog the range of methods used in the development of e-health tools for use in clinical trials and to facilitate the use of data collected on mobile technologies, a systematic literature review was carried out, compiling a database of feasibility studies. The objective was also to identify if there is a standardization of methodologies for the development of health technologies and the efficient adoption of digital technologies in clinical research. The objectives of this paper are therefore to describe the methodology of our systematic scoping review and summarize key trends that emerged from the identified studies.

RESULTS

Screening

The systematic review of the literature had as a guiding question, formulated by the PICO method[1] is there a standardized methodology for the development of software for the health area?

Articles were searched that described the process of designing and developing a software to be applied as a clinical intervention in health, regardless of the type of target disease. The recommendations of the PRISMA systematic review submission protocol[2] were used.

The searches were updated until December 2018. As eligibility criteria, clinical trials and original studies were included that described results related to the use of software as a clinical intervention in patients (primary or secondary outcomes). The other inclusion criteria were date of publication of the study from 2010 to December 2018, focus on interventions to be performed in children, adults and/or the elderly, and publication in English, Spanish or Portuguese. Review studies, editorials, letters or comments, book chapters, dissertations and/or theses and animal studies were excluded.

We chose to exclude the pandemic period from this review for two main reasons: the first to understand how the development of e-health was thought before COVID-19 presented us with a scenario where remote health activities became largely mandatory in addition to other important aspects in terms of technological advances in space-time, and the second because it is also intended to carry out a systematic review only with articles published from 2019 to 2022 and compare both reviews at a later time.

To select the articles, a search was carried out in the PUBMED/MEDLINE, WEB OF SCIENCE, SCOPUS, LILACS and SciELO databases, using the bibliographic search terms: mhealth development; e-health development; software' development for clinical intervention, clinical trial and software, software as clinical intervention. Two of the review authors (L.R. and G.C.) independently analyzed the articles extracted from the database. A first evaluation was carried out, based on the titles and abstract of the articles, and those that did not meet the inclusion criteria or presented any of the exclusion criteria were rejected.

When a study could not be included or was rejected, the full text was analyzed in a second evaluation. In cases where there was no consensus between the two researchers who performed the analyses, the third author researcher (D.A.) was consulted for decision making.

To compare the data, a narrative synthesis of the selected studies was performed, which were presented according to the type of technology developed for health. Details of the studies were described, such as their design, name and type of software developed, description of the technology development process designed for intervention and description of the population involved, in terms of the number of subjects and their main characteristics. The diseases/field of study targeted by the software present in the included studies were described in terms of the type of disease/field for which the developed technology is intended.

As a result, the search revealed 1,653 articles in total. Of the 557 articles selected after reading the title and abstract, 514 were excluded in the first screening because they were review articles, editorials, letters or comments, book chapters, dissertations and/or theses or because they were not specifically about the desired topic. In a second screening of the 43 remaining articles, 6 were excluded because they did not explain in detail the stages of software development for health. 37 articles were selected for full reading of the manuscript. In the end, 19 articles were included in the study (figure 01).

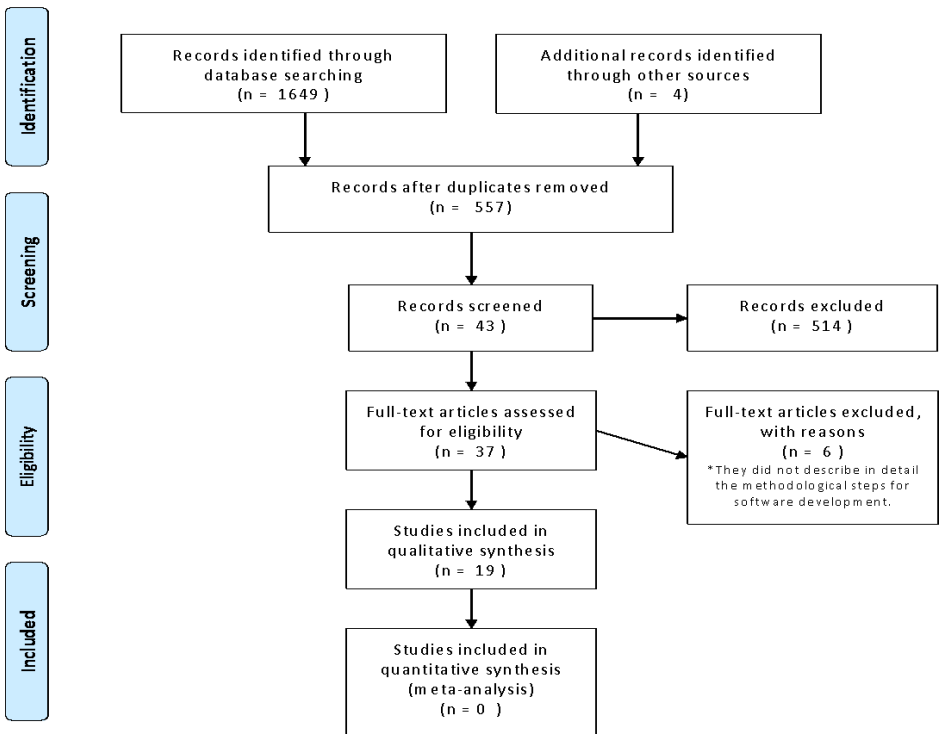

Figure 1. Adapted from Moher D et al. The PRISMA Group (2009).

Data Categorization

The studies were conducted both developed and developing countries[3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20], with emphasis (in quantity) for Netherlands, Brazil,

United States of America, Finland and Australia, with three, four and two articles each, respectively.

The analyzed studies addressed severe mental illness[1], diabetes mellitus[3,12] as disease/target field, adverse events of drug interactions in the elderly[4], stroke[5], vocal health[6], home care[14,15], coronary heart disease[7], bipolar disorder[8,10], smoking[9], aging[11], systemic arterial hypertension[13], cardiovascular disease[16], obesity[17], invasive pneumococcal disease[18] and heart failure[20].

The technologies developed ranged from online platforms, electronic messaging systems and interactive games to mobile applications. Regarding the type of study, seven studies were classified as exploratory qualitative, five as clinical trials, six as intervention studies and one formative evaluation study.

The number of individuals studied (samples) ranged from seven to 871. It was not possible to identify whether there was a predominance of sex among the study populations. All technologies evaluated showed positive effects on the intended outcomes, with great acceptance of the target population in relation to the software.

Although all studies present methodological steps in the software development stage, only seven[1,4,5,6,7,10,16] presented a detailed description of both the formation of the research groups and the steps and methods chosen for the development of the software, such as the language for writing the code- source, data storage, base operating system, among others. The importance of the methodological description in detail is highlighted, as there is no standardization for the development of technologies to be used as health interventions, which makes the creation and learning process difficult for students/professionals involved in research projects that have software as part of the patient's treatment and contributes to the decline in the quality of intervention tools and projects developed under this theme.

DISCUSSION

There are still few studies that describe the complete methodology for the software development stage in health research, fundamentally thinking about the teaching of undergraduate and graduate students who explore this topic in their studies. Among the reasons for this are the lack of standardization of methods and techniques for the development of technological tools for health, the difficulties in accessing technology in the most vulnerable populations, the adaptation and feasibility of software for different scenarios and the high costs. with technologies. Another difficulty to be raised is the accelerated evolution of existing technological components, which makes software obsolete quickly and increases the cost of systems for clinical interventions.

On the other hand, the expansion of mobile technologies and the gradual increase in internet access have exponentially expanded the possibilities of communication and data transmission, which facilitates the insertion of health software in different scenarios around the world. It is also observed that issues such as immediacy, portability, convenience, and interactivity/interoperability that technology provides make it increasingly possible to develop health promotion actions based on mobile devices. Still, further studies are needed to evaluate the use of health technologies on a large scale.

Due to what was observed in the studies, the need for multidisciplinary work for the development and application of new technologies can be mentioned, making independent

evaluation and review by each professional, effective interactivity between team members and the definition of specific individual goals. In this way, professionals favor usability, meeting all the needs of users who use the system.

As a final consideration, the limitations and methodological heterogeneity found in these studies make it difficult to compare them through meta-analysis, making it extremely important to standardize intervention protocols and the stages of development of software, so that it is possible to advance in the teaching of thematic.

METHODS

Conduct of the systematic scoping review

We do not restrict the scope of our research to a single therapeutic area or mobile technology. The complementary table below (table 1) brings the data collected from each of the analyzed studies and the search terms extracted from the publications. After searching the databases, the review process was carried out in several steps to select the publications for analysis. Two trained research analysts (L.R.; G.C.) independently reviewed each publication title respecting the inclusion criteria and following the PICOS structure (Population, Intervention, Comparison, Outcome; Study Design). Second, the reviewers reviewed the abstracts of other eligible publications to determine whether they met the inclusion criteria. When there was disagreement between two reviewers during any phase, the decision to advance a publication was resolved by a third reviewer (D.A). Finally, two reviewers reviewed the full text of each of the publications that passed the abstract screening step and established the final list of publications to be included.

To build the database, the pair of analysts (L.R.; G.C) extracted the data and categorized each publication according to the study design, the name and type of health technology developed, the disease for which the intervention tool is intended, the target population of the study, and the description of the methodological steps for the development of what we call software (digital health tool developed as a clinical intervention). Topics are described and standardized in Table 1.

Table 01. Characteristics of the studies included in the systematic review grouped into categories.

Authors and year; country	Study design	Software name and type	Disease and/or field for which the software is intended	Description of the target population for using the software in the testing phase	Description of the methodological steps in the research for the health-oriented software development stage
Beentjes et al., 2016; Netherlands.	Randomized controlled clinical trial of early clusters.	E-health tool that supports the Illness Management & Recovery (IMR) programme).	Severe mental illness (SMI).	Intervention mapping step: 52 Dutch individuals with SMI. Evaluation stage: 50 participants with SMI present in outpatient clinics and 50 participants with SMI hospitalized.	The six steps of the Intervention Mapping protocol by Bartholomew et al. (2011) were adopted. Study subjects (with SMI) joined the development group to address important and relevant issues for the target group. The group consisted of six subjects with GDM, an informal caregiver, two professionals familiar with the IMR, and two more researchers. Group discussions and brainstorming sessions were held. Decisions during the development process were based on qualitative assessments of the IMR program, structured interviews, development group discussion, and literature reviews. Five IMR experts reviewed these decisions and confirmed the results. The design of the e-IMR intervention was completed after pre-testing readability, usability and bugs and the intervention website was designed in order to increase ease of use by people with cognitive disabilities and less technology experience.
Bernhard et al., 2018; Germany.	Qualitative study with focus groups.	Shared patient-centric and web-based medication platform for patients with Diabetes Mellitus 2 (DM2).	Diabetes Mellitus 2 (DM2).	Patients with type 2 diabetes mellitus (n = 25), general practitioners (n = 13) and health assistants (n = 10).	The researchers used Atlas.ti (version 7.0.80, Scientific Software Development GmbH, Berlin, Germany), a qualitative software package to organize and code data collected from patients. The researchers met regularly during the study to discuss the selected categories and subcategories until consensus on the final set of categories was reached. Taking into account the number of focus groups reporting specific requirements, prioritization of requirements was possible. Altogether, from May to July 2013, 8 focus groups were held.
Böttiger et al., 2018; Finland.	Descriptive two-phase, qualitative, interventional study.	PHARAO (Online Pharmacological Risk Assessment) - decision system that provides a risk profile for adverse events associated with the combined effects of multiple drugs.	Adverse events of drug interactions in the elderly.	The PHARAO system was used 933 times in a total of 871 patients, 503 treated in geriatric wards and 368 in primary care. The mean age of patients was 84 years in geriatric care and 69 years in primary care.	The PHARAO project was developed and carried out by a group of specialists in pharmacology and clinical neurology, pharmacists and software developers. Specialists from other clinical disciplines, such as cardiology and nephrology, were consulted. The properties incorporated in the project were attributed considering adverse events relevant to elderly patients and their choice was based on the clinical experience of the professionals of the working group, on comments and questions received from end users of the databases and on the format of interactions. of drug pairs. The system was tested in a pilot study carried out with specialists in geriatrics and primary care to evaluate the system.
Cadilhac et al., 2018; Australia.	Formative assessment study.	iVERVE - Electronic messaging system designed for stroke survivors to support their recovery and secondary prevention goals after hospital discharge.	Cerebral Vascular Accident (CVA).	The system is ready to be tested in a randomized clinical trial with stroke patients.	The first phase of the project was a literature search on existing data from stroke survivors and theories of behavior change. Two working groups were established; one for the development of the electronic infrastructure and the other (comprising researchers, clinical experts and consumer representatives) to establish the patient-centered program. After defining the categories for the goal setting menu, relevant messages were developed and independently reviewed by experts to support and educate patients. An alpha approach test was carried out using the first 60 messages elaborated. The principal investigator

					and project coordinators were members of both working groups to ensure that competing work was complementary and that experience from one area could be used to inform the other.
Carlos et al., 2016; Brazil.	Qualitative, exploratory, experimental and applied study.	*VoiceGuard* - Application for mobile devices that assists in the care and management of vocal health.	Vocal Health.	The researchers intended to test the application with teachers from the Municipal Education Network of Fortaleza, but there have been no new publications so far.	The first step consisted of a literature review on the subject. The development of the application began in November 2014 at the Technological Innovation Laboratory of the University of Fortaleza – UNIFOR, with the help of a multidisciplinary team. For the development, the participatory interaction design by Preece et al. (2013). In the construction phase of the interactive version, the team used the best practices and tools from the areas of Human Computer Interaction and Software Engineering. The platform chosen for the application was Android. The last activity of the process was the usability assessment of the application by specialist professionals educated about the research objectives.
Carvalho et al., 2011; Brazil.	Qualitative, exploratory, applied study..	SCIADS (Intelligent Computer System for Home Health Care) - intelligent computer system to connect the patient at home and the health professionals, through the integration of several remote health monitoring devices.	Home care for patients with hypertension.	Patients with hypertension.	Residential Health Center (RHC) receives and processes patient data (physiological and activity) and environmental data collected by measurement devices and sensors to determine the patient's health status. Monitoring begins with the Care Plan, composed of a series of prescriptions prepared by the health professional who can, at any time, modify the original plan. SCIADS can also generate notifications to the patient, reminding him to comply with the defined procedures.
Chen et al., 2016; China.	Qualitative study, Clinical trial.	TAKEmeds – app to improve adherence to secondary prevention of coronary heart disease in China.	Coronary heart disease.	59 physicians participated in the needs assessment survey: six physicians were interviewed and four physicians were involved in the focus group discussion.	A survey and interviews were carried out to assess the needs of physicians and their patients. The working group relied on an application developer to design and test the pilot application and to develop the message bank and messaging system to be linked to the application. The design and development process lasted from July 2014 to May 2015. Based on survey feedback and interviews, the app design was finalized and the app developed in collaboration with the Kunshan Innovation Institute at Zhejiang University. The application was developed using Java language, on the server with Spring MVC and Hibernate framework, MySQL database with data encryption and on Tomcat6.0 þ Deployment Environment. Cache technology was adopted to store the data and the app interface was designed for Wechat, the most popular social media mobile app used in China. The trial version of the app was shared with researchers and clinicians for feedback before being put into practice.
Eiring et al., 2017; Norway.	Qualitative, exploratory, intervention study.	Health optimization system for patients with bipolar disorder.	Bipolar disorder.	78 potential users participated in one or more usability testing sessions: 39 laypersons, 23 adult patients, 5 nurses, 2 general practitioners and 9 psychiatrists.	For the construction of the system, the methods of shared decision making and multicriteria decision analysis (MCDA) were chosen, used in the project to model the system database, integrate inputs from several sources in a consistent way and to connect the system modules. main. The requirements analysis process included interviews and discussions with patients, healthcare professionals, hospital departments, and researchers investigating clinical decision support and patient decision measures. A literature review, a review of existing solutions, interviews with focus groups were carried out in order to raise the needs of users. A detailed analysis and description of how the system should work in clinical practice was developed. The system was built and maintained on Windows Server 2012 R2 using C#, JS programming languages and the Azure SQL Server 2016 database. The main programmer and project lead analyzed the initial requirements and built a working description of the project with a

					sufficient level of detail for system design. New descriptions were added, discussed and improved in the JIRA® project management tool throughout the project.
Gomide et al., 2016; Brazil.	Descriptive, qualitative, intervention study.	"Live without Tobacco" – an open source web-based intervention for smoking cessation.	Smoking.	Seven adult participants (over 18 years old) were regular smokers or were undergoing tobacco treatment. Participants were also required to use the Internet from a desktop or notebook computer for at least one hour per week.	The development of the intervention was divided into four phases, which corresponded to the versions in the development process: Pre-alpha, Alpha, Beta and Release Version. In the licensing and software selection stage, the researchers decided to use the GNU (General Public License) (FREE SOFTWARE FOUNDATION, 2007) and "freeware" for the entire development of the interventions, to allow the reproduction and adaptation of the intervention. To write the source code, Java JSF was used; to store the data, MySQL; and as an application server, Glassfish. The code was created in NetBeans IDE; images in Inkscape and Gimp; the video animation, in Blender and Openshot; and the flowcharts and initial content, in Dia and Libreoffice Writer. The content was written and developed on Debian-Linux based computers.
Hidalgo-Mazzei et al., 2015; Spain.	A three-phase, qualitative, multi-method study with a randomized clinical trial.	SIMPLe - smartphone application to monitor symptoms and signs, strengthening the self-management of bipolar disorder, in order to identify early symptoms and prevent relapses and hospitalizations.	Bipolar disorder.	74 adult patients undergoing treatment for Bipolar Disorder.	For the development of the application, periodic meetings were held during a year of a team of specialists in bipolar disorder, such as psychiatrists and psychologists, together with software engineers and graphic designers to discuss and determine the design of the online tool to monitor the signs and symptoms of bipolar disorder and to offer personalized psychoeducational content. Simultaneously, a web-based interface was developed to allow the mental care team to monitor the status of patients interacting with the application. Afterwards, the authors intend to conduct studies to evaluate the use, reliability and patient satisfaction with the software.
Jongstra et al., 2016; Netherlands, France e Finland.	Prospective, multinational, multicenter, prospective, randomized, intervention study.	HATICE - Interactive Internet Platform for Seniors: Healthy Aging through Internet Counseling.	Senescence.	41 people aged 65 or over used the platform for 8 weeks in the pilot study.	The conceptual framework of the interactive platform was based on Bandura's social-cognitive theory and Michie's taxonomy was used for standardized definitions of the behavior change aspects of the intervention. For the functional design of the platform, a systematic literature review and meta-analysis were performed. In parallel, four-hour brainstorming sessions were held with the researchers and software developers. Schemes of the platform's functionalities and architecture were developed and discussed with an expert in health communication among older people, an expert in online lifestyle change, a specialist in cardiology prevention and representatives of patient organizations (Dutch Heart Foundation and Dutch and Finnish Alzheimer Association). Ten focus groups were held with people who resembled the target population for the study (HATICE) where it was discussed how an internet platform could help people improve their lifestyle. Finally, the results of the meta-analysis, expert meetings and focus groups were incorporated into the final version of the functional design. The software was built using the Scrum method and a secure hosting environment was designed in accordance with strict Good Clinical Practice privacy regulations covered by local standard NEN 7510.
Mass et al., 2016; Netherlands.	Descriptive, qualitative, intervention study.	Eindhoven Diabetes Education Simulator (E-DES) - Educational diabetes	Diabetes.	The storyboards of the four game concepts were evaluated with 12 patients (mean age 60 years), a nurse and	For the development of concepts, user research, idea generation, evaluation and choice of concepts, storyboards and feasibility analysis for evaluation were carried out. The concepts and ideas developed were evaluated through group voting and analysis by the project team. Four concepts were developed by the multidisciplinary development team based on the results of user interviews. These user

		game following a user-centered design approach.		nutritionist from Máxima Medical Center, Eindhoven, Netherlands.	evaluations and a feasibility analysis served as input to a general evaluation and discussion by the development team, resulting in the final choice of concept for the elaboration of the educational game.
Mann et al., 2013; United States of America.	Descriptive, qualitative, multiphase study.	DASH Mobile: mobile lifestyle intervention system for the treatment of high blood pressure.	Arterial hypertension.	30 hypertensive patients.	For the development of the application, a multidisciplinary design team was assembled including skills in primary care, behavior change, nutrition, computer science, graphic design, human-computer interactions, usability, videography and informatics. University funding was also acquired for a pilot test project, execution of the modified project design and rapid cycle prototyping process, including use case development, was carried out. Subsequently, a software platform and wireless devices were chosen, including blood pressure cuff, weight scale and pedometer. Wireframes, storyboard video clips, smartphone emulator application (Eclipse) and usability testing of the prototype were developed. The researchers intend to carry out a pilot clinical trial with a sample of patients with hypertension.
Caballero Muñoz et al., 2013; Chile.	Longitudinal, quantitative-qualitative, randomized study.	Mobile electronic record for the home care of the bedridden patient. The purpose of the program is to improve the quality of care for the bedridden person and relieve the family and caregivers.	Home care for the bedridden patient.	152 bedridden patients (at home) of a CESFAM in Santiago.	For the development of the tool, data collection was carried out through focus groups, surveys with key informants in the community and analysis of bibliographic content. The project consists of 5 steps, the first being the determination of requirements, the second the development of protocols and mapping of the identified data, the third the development of the home patient care record system, based on web and mobile technology, the fourth the implementation of the system and the fifth usability tests and evaluation of the system and its modifications. To carry out the work, it was necessary to create protocols for home care and design a registration system in an ontological way, including the integrated workflow between each of the clinicians and with the family. The researchers conducted a literature search, conducted focus groups with experts in the care of elderly and bedridden patients and with the community, collected data from key informants, observed the needs of bedridden patients in the field, trained the community in terms of digital literacy and analyzed the clinical processes carried out during the home visit to identify patterns after consensus on requirements.
Neubeck et al., 2016; Australia.	Qualitative, multiphase, intervention study.	Web application integrated with electronic records in primary care for people with, or at high risk of, cardiovascular disease.	Cardiovascular disease.	Patients with (or at high risk for) cardiovascular disease.	The application development was carried out in four phases of an interactive process involving a multidisciplinary team of ten clinicians and academics (primary care physician, nurses and other health professionals), two consulting designers, a graphic designer, three software developers and 14 proposed end users to provide feedback on early development steps such as defining requirements after literature review, and refining the prototype for pilot testing.
O liveira et al., 2018; Brazil.	Qualitat ive descriptive study.	Lisa Obesidade - mHealth technology to assist in the prevention and control of obesity in adults in the light of health literacy.	Obesity.	Obese patients.	For the development of the technology, the user-centered participatory interaction design process was used, developed by a design professional, with the guidance of a master's nurse in public health, PhD professors in nutrition and a PhD professor in computer science. The process included the identification of user needs and the establishment of system requirements. Soon after, the design of possible solutions for such needs was carried out and the construction of the interactive functional prototype was carried out. The prototype design was carried out in the Photoshop tool. During development, brainstorming meetings took place to identify technical requirements and functions that the system should cover. Discussions among team members took place throughout the process.
Panatto et al., 2016; Italy.	Qualitative, exploratory, multiphase study.	Mobile app specifically designed to raise community awareness of invasive	Invasive pneumococcal disease (IPD).	Patients with pneumococcal disease.	The app is designed to be maximally functional and conceived according to user-centered design. Its content, layout and usability were discussed and formally tested during several workshops that involved key stakeholders, including IPD and information technology experts and potential end users.

		pneumococcal disease and its prevention.			After several workshops, it was decided that in order to make the app more interactive, its core should be a risk "checker" of acquiring IPD and should present a user-friendly risk communication strategy. The verifier was filled with risk factors identified through official Italian and international guidelines. After discussion of various drafts in the application, a prototype was created and submitted for usability evaluation by experts and users. Google Analytics was used to quantify online data traffic and determine user characteristics and interaction with the application.
Radhakrishnan et al., 2016; United States of America.	Descriptive, qualitative, intervention study.	Interactive digital e-health game (IDEG) to learn about heart failure (HF).	Cardiac insufficiency.	Participants aged 55 years or older and hospitalized with a diagnosis of HF.	For the development of the game prototype, an interdisciplinary team of nursing, computer game programming, usability and communication was assembled. Two rounds of usability assessments were conducted to interactively improve the usability of IDEG. The beta test of the game was carried out with 19 participants.
Reho et al., 2016; Canada.	Two-phase, multi-method, qualitative study.	SBIRT - Online Screening, Intervention and Treatment Referral Tool - Lifestyle and Education Parent Resource Information Program (RIPPLE).	Child obesity.	38 participants, being parents of children 12.5 to 5.5 years old (n=10), researchers (n=8) and graduate interns, focusing on pediatrics (n=20).	RIPPLE was developed in partnership with Evolution Health Systems, a company with a history of developing tools such as SBIRT. In two years, approximately 40 teleconferences were held with the company and about 10 face-to-face meetings of the team participating in the research. The multidisciplinary research team, together with provincial government stakeholders, developed the RIPPLE content based on bibliographic evidence of childhood nutrition, physical activity and sedentary behaviors. To enter data into the software, the research assistants, using a standardized protocol, measured the children's height and weight and entered these data in the graphical user interface. Using this data, the system screens children and provides objective, personalized feedback to parents, both numerically and visually.

Contemplated categories: authors, year of publication and country; study design, software name and type; disease/field for which the software is intended; description of the study population and detailed description of resarch methodological steps for the development of e-health.
Source: Research data.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article.

AUTHOR CONTRIBUTIONS

Conception/design – All authors; Data collection – L.R; G.C.; Data analysis and interpretation – All authors; Manuscript preparation – All authors; Final approval – All authors.

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5.5 Artigo 5

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SACI protocol: Preliminary guidelines for the development of digital health technologies for clinical trials in Brazil

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In the last decade, evidence-based medical practice has been supported on a large scale by computerized decision support tools, aiming to reduce diagnostic and therapeutic uncertainty, complementing the actions of the health professional. With technological developments, it is now possible to consider these systems as part of clinical intervention, both for the diagnosis and treatment of diseases. The literature has described the implementation of e-health tools, that is, technological innovations in the health area such as software, applications, serious games, among others, as a strategy to improve the process and adherence to treatment. However, there is still no standardized instrument in Brazil that can be used to guide the development, from the research phase, and the implementation of these tools as a health intervention, also impacting patient outcomes. With the objective of investigating a new therapeutic and preventive form, based on intervention with a computerized system, this work proposes the creation of guidelines for the registration and implementation of e-health tools as a clinical intervention. The proposal aims to be able to assist in the reporting standardization from the development stage to the application of the e-health tool helping in the treatment of diseases, registering all the experience lived in the research and applying it in the context of a pandemic.

Keywords: reporting guidelines; clinical trials; digital health; e-health

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Introduction

Man, throughout history, records his evolution as a species and knowledge using various techniques from cave painting to the most standardized technical documents currently available. The scientist man is no different. Unfortunately, research carried out without standardization in its reports causes difficulties in the correct interpretation of the results and in their replication by other researchers in other scenarios.

Often essential elements of study methodology are omitted or poorly described, which limits the value of established guidelines for clinical practice. Another main quest of man has been the creation of machines equipped with artificial intelligence that approach and even surpass the capacity of the human brain. This very ambitious search has captivated, mainly, professionals linked to the health area, who envisioned in computing the aid in carrying out diagnoses and making decisions regarding treatments for their patients, functions far beyond the first uses of the computer for storage and data processing and knowledge.

In the context of the pandemic in which we have been living since 2020, digital technologies are increasingly being used to support public health decision-making and response around the world, including epidemiological surveillance, case diagnosis and contact tracing, in addition to assisting in the evaluation of remote interventions based on health data collected from the population. The trend is for health to become increasingly digital and for the use of e-health tools to assist in the process of formulating regulation, evaluation, and use of digital technologies to strengthen public and supplementary management in the face of crisis situations in health[1,2].

Although several studies have been carried out to test digital technologies as part of clinical intervention in health treatments[3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,] there is no record of a specific proposal for guidelines for research and implementation of scientific investigations – such as clinical trials – with e-health tools in Brazil.

The scientific community has, to date, the CONSORT E-HEALTH[20], the CONSORT-AI EXTENSION[21] and the SPIRIT-AI[22] as guide protocols for interventions that use artificial intelligence in health, established in contexts different from those experienced in our country in relation to the development of technologies in digital health.

Given the context, the objective of this work is to propose preliminary guidelines for the development and implementation of digital health tools for clinical trials in Brazil. Despite its apparent simplicity, what differentiates the protocol proposed in this thesis from the guidelines already published internationally is its development designed for the health technology scenario in Brazil and its implementation carried out in record time in the service called TeleSUS, a telehealth service of the Brazilian Unified Health System (SUS) developed in response to the COVID-19 pandemic in Brazil, in March 2020[23].

Methods

The methodological study describes the development of a rigorous and systematic method of obtaining and organizing data and conducting the research. The approach chosen was qualitative and quantitative.

The construction of the preliminary guidelines, or here also called "protocol", was based on existing instruments in the literature that systematize guidelines and recommendations for conducting clinical trials, although only one of these instruments[21,21] specify important methodological topics for software research in healthcare. The main instruments used were CONSORT Statement[24] and its extensions STRICTA[25], E-HEALTH[20] and CONSORT-AI EXTENSION[21], SPIRIT Statement[26] and its extension SPIRIT-AI[22], TIDIER[27], QUOROM[28] and STARD BLCM[29].

Clinical trial registration platforms certified by the World Health Organization (WHO) and the International Committee of Medical Journal Editors (https://www.who.int/ictrp/network/primary/en/) were also consulted, highlighting if the ReBec – Brazilian Registry of Clinical Trials (http://www.ensaiosclinicos.gov.br/) and the ISRCTN Registry (http://www.isrctn.com/), in order to verify which registry aspects they contemplated. After collecting and analyzing the synthesized knowledge, the development of the standardized protocol was divided into five steps, whose implementation and evaluation steps will be explored in another publication.

The first step was to carry out a systematic review in the PUBMED/MEDLINE, WEB OF SCIENCE, SCOPUS, LILACS SciELO databases, using the descriptors previously selected to create the protocol. The methodology used to carry out the systematic review is described in detail in an article already published[30].

The second step was the refinement of the topics/issues to be addressed in the protocol statement. After the delimitation of these topics, the third step was the validation of the protocol, ensuring the review/evaluation of the statement established by peers of experts. The fourth step was implementation, including the pilot test site. Finally, the fifth and final step, called Assessment, consisted of analyzing the results of using the protocol and its quality as a teaching instrument.

Ethical approval

This study was approved by the Research Ethics Committee of the Faculty of Medicine of Ribeirão Preto, University of São Paulo (CAAE: 14671019.2.0000.5440). All the ethical requirements prescribed by the resolution nº 510/2016 of the Brazilian National Health Council (*Conselho Nacional de Saúde*; CNS) and its complementary are being fulfilled in the development of this work. All the necessary information about the study was provided to participants electronically prior to survey completion. Delphi participants provided electronic informed consent.

Validation of preliminary guidelines

Among the available methods for validating protocol content, the Delphi Method[31] was chosen which aims to obtain as much agreement as possible among a group of experts on a topic, when there is no unanimity of opinion or contradictory information recorded in scientific literature. In this research, the method was adapted to the online modality, via the internet, and with a pre-established occurrence of a maximum of three rounds and a consensus meeting in case there were still disagreements. This facilitated the interaction between the study participants and the responsible researcher, regardless of the geographic location.

The evaluation criteria included were Scope and purpose, involvement of Stakeholders (or interested parties), rigor for development, clarity in presentation, applicability, and editorial independence[32]. Stakeholders included healthcare professionals, computer scientists, industry representatives, policy makers, health informaticists, patients and funders.

Ten expert judges in the areas of health and/or information technology in Brazil, with professional experience of over five Years and minimum master's degree, were selected by means of an intentional non-probabilistic sample. The researcher contacted the selected experts by e-mail, inviting them to participate and sending a link to the form to be completed, via an electronic questionnaire (Google Docs), accompanied by the first version of the operational protocol, defining the study objectives, instructions regarding the completion and importance of the evaluation of the instrument by the specialists. To gain access to the form containing the survey items to be evaluated, the participant was instructed to click on the link sent by email and to complete the evaluation within 20 days.

By clicking on the link, the participant was directed to the form with immediate opening of the Free and Informed Consent Term – TCLE. Only after the mandatory completion of the TCLE indicating the consent to participate in the research, the following evaluation screens were made available to the participant. Once the questionnaires were applied electronically, the responses were recorded directly in a database, avoiding errors associated with the researcher's intervention in recording the responses provided. Two rounds were needed for expert consensus and figure 1 presents the flowchart of the process of validating the proposed guidelines using the Delphi Method.

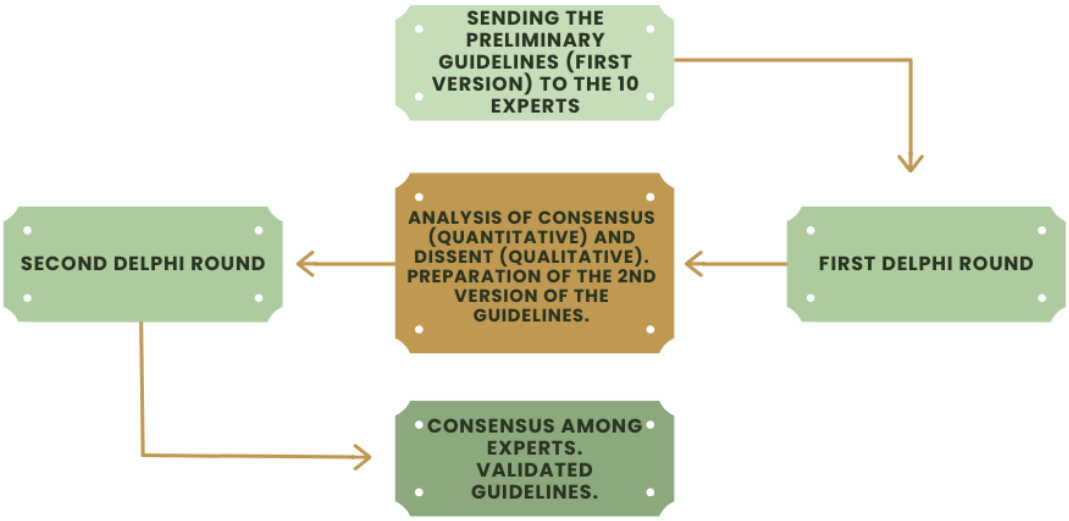

Figure 1 - Flowchart of the validation process of preliminary guidelines using Delphi Method.
Source: authors.

The profile of the expert judges participating in the validation of the guidelines in this research was balanced in relation to the degree of master and doctor, 40% and 60%, respectively, and the average age of the experts was 46.2 years, with one (10%) being in the age group from 30 to 39 years old, seven (70%) in the age group from 40 to 49 years old and two (20%) in the age group from 50 to 59 years old. Regarding the time of professional activity, it was observed that 40% of the specialists had between five and ten years of professional practice, another 40% between eleven and twenty years of experience and 20% had between twenty-one and 30 years of career.

Regarding the field of activity of the participants, it was observed that the specialists were distributed in 20% in the field of Higher Education, 30% in Scientific and Institutional Research, 30% in Medical Assistance and 20% in Public and Private Management in Health. It is important to highlight the number of specialists who work daily involved with telehealth services aimed at Primary Health Care, totaling half of the sample of judges consulted in this research.

The domains evaluated by the experts in the validation rounds of the guidelines proposed in this research and the degree of agreement between the judges in the process are shown in the following table (table 1).

Statistical analyzes were performed using the IBM SPSS Statistics program, version 22.0.0.0, the agreement between the judges was evaluated by the Content Validity Index (CVI)[33] and reliability verification was performed by Cronbach's Alpha Coefficient. The proportional

result of experts who judged the item as valid for the protocol by the total number of experts in the sample was considered as agreement/disagreement.

For consensus, a CVI greater than 0.80 was considered[34] and for the calculation of the CVI, on a seven-point scale, responses from 5 to 7, where 5 and 6 ("important, but not critical") and 7 ("important and critical") will be considered as agreement, and responses from 1 to 4 ("not important/necessary") will be considered as disagreement.

In relation to Cronbach's Alpha, a coefficient that measures the relationship between responses in a questionnaire through the analysis of the profile of the responses made by the respondents, in the first round, a Cronbach's alpha of 0.90 was obtained and in the second 0.93, indicating optimal internal consistency.

Table 1 - Results of CVI and Cronbach's α in each domain for the 1st and 2nd Delphi rounds.

	Evaluated domains	**CVI**	***Cronbach's Alpha Coefficient***
Delphi first round	Scope and purpose	0,95	0,60
	Stakeholders	0,97	0,73
	Rigor in development	0,91	0,75
	Clarity	0,95	0,67
	Applicability	0,97	0,65
	Editorial independence	1	0,80
	Total	0,95	0,90
Delphi second round	Scope and purpose	1	1
	Stakeholders	1	0,84
	Rigor in development	1	0,88
	Clarity	0,95	0,78
	Applicability	1	0,83
	Editorial independence	1	0,80
	Total	0,98	0,93

Source: research data.

Before starting the protocol implementation stage, the researcher chose not to carry out any type of individual training of the study participants, with clarification of doubts and/or examples of practical application of the protocol to avoid conditioning the way in which each one would use it and, also, to extract more reliable results in terms of clarity, intuition, practicality, and easy understanding of the proposed instrument, primarily for use in teaching. The pilot test carried out in the TelesSUS operational environment served as a guide to ensure the most accurate verification

of the efficiency of the protocol in practice and the identification of the necessary adjustments for a new test.

The intention was also to measure, through a semi-structured questionnaire designed especially for this research, how much the protocol helps the professionals involved and simplifies the construction of a process of developing a digital health tool to be used as a health intervention.

It is important to say that the protocol proposal is not intended to automate health techniques and procedures, nor to replace the specialist professional, but to complement and better manage patient care, streamline care, reduce costs, and provide critical reflection to patients. patients with respect to health care delivery standards.

SACI Protocol

The instrument was named Protocol SACI, acronym for "*Software as Clinical Intervention*", friendly to the teaching of Brazilian students and professionals alluding to a well-known character in Brazilian folklore – Saci Perêrê[35]. The intention was to develop the protocol in the form of text with tables, illustrated with figures and flowcharts and divided into sessions as shown in the figure below (figure 02).

The first section is dedicated to essential data referring to the research project developed. The second section is dedicated to important data for the initial meeting of the multidisciplinary team involved in the research project. The third section is dedicated to data on the development of the digital health tool and, finally, the fourth section is dedicated to data for project management, including the results of the patient intervention carried out with e-health.

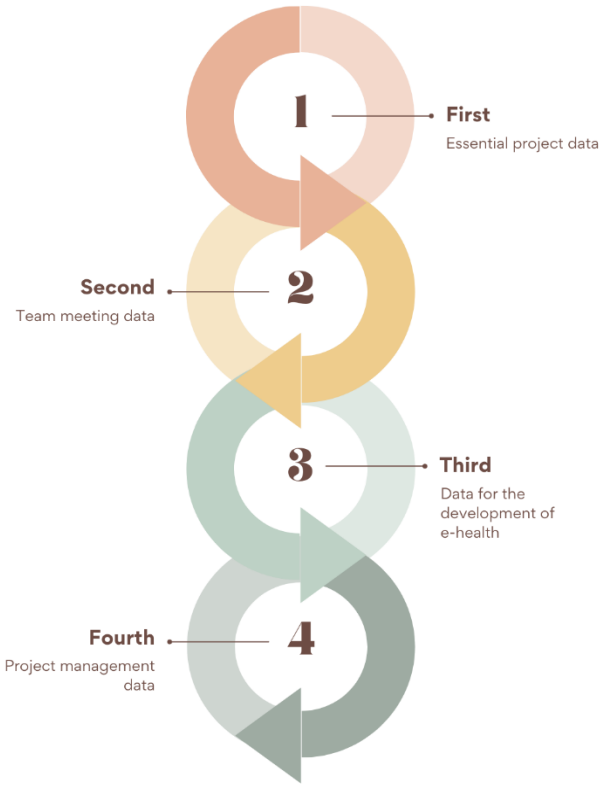

Figure 2 - Distribution of protocol items into four sections.
Source: authors.

The protocol checklist was designed in a table format (with a title involving the name and description of the checklist) consisting of the indication of each of the protocol sections and six columns, listed below and represented in table 02.

I. The column called "*Item*", where the study item for consideration must be referenced;
II. the column called "*Subitem*", where the composition of sub-items for each item presented in the previous column must be referenced, when applicable;
III. the column called "*Description*", where the description referring to the first two columns must be recorded in an essay form;
IV. the column called "*Reported (Yes/No)*", where it must be registered if there was an indication, referring to the previous columns, of the necessary information at the time of the research execution;
V. the column called "*Status (Completed/under discussion)*", where the status of the items and/or sub-items referenced in the previous columns must be indicated, according to the moment in which the research was carried out and
VI. the column called "*Space to write down the respective information*", where pertinent information regarding the research must be described, for each of the items addressed.

Table 2 – Organization of SACI checklist.

Protocol section indication						
Item	Subitem	Description	Reported	*Status*		Space to write down necessary information
			Yes / No	Concluded /	Under discussion	
			( ) ( )	( )	( )	

Source: authors.

During the construction of the protocol, some highlights were raised. It is necessary to pay attention to the fact that in interventions carried out with software, it is the patient/health professional who has control over the use of the technology, in terms of frequency and time of use. For this reason, it is extremely difficult to assess the actual results of these interventions and interpret the findings on their effectiveness, as many participants do not adhere to the proposed technologies and are not followed up for a long period of time.

Researchers, through metrics such as the number of logins in the software and the time spent in each session, can raise more reliable analyzes of the effectiveness of interventions in these trials, but it is important to provide additional and detailed information about these parameters, preventing, for example, that the user only logs in to the software but does not actually use it (establishing, for example, a maximum time for automatic logout), increasing the accuracy of the

analyses. Primary and secondary outcomes of the targeted intervention should also be described in detail, including the methodology for extracting the results.

Here, the importance of the analysis called ITT from the English “Intention to treat” or Analysis by intention to treat is highlighted. This analysis of results is based on the attribution of initial treatment and not on the one eventually received, precisely because of the difficulty in adhering to the interventions proposed throughout the studies. The ITT analysis recommends that participants be included in the analyzes even if they have not fully adhered to the research protocol, those who deviated from the protocol due to non-adherence or being removed from the treatment should still be kept in the analysis. The justification for this is that there is a need to estimate the allocation effects of an intervention during practice and not just the effects on the subgroup of participants who adhere to the first one[36].

Another highly recommended aspect is the creation of flow diagrams during the construction of the research and a friction diagram[20,21] facilitating the visualization of participants' behaviors and the influence of interventions with software in the patient care process.

The SACI protocol (PSACI) was lovingly conceived and improved to serve as a guide for researchers, mainly in the national territory, to conduct their studies under the theme of clinical trials with e-health. It is believed that these guidelines, as well as the few previous international publications with the same desire can have a positive impact on the quality of research reports carried out in Brazil and in the world with interventions based on new technologies, facilitating the learning of students and professionals, the replicability of studies, and the translation of the knowledge produced.

The first steps in clinical trials involve research registration, where the researcher must provide important data for the identification of his work. With that in mind, the first section of the protocol includes items on data that characterize the research project. In the second section of the PSACI, the items set out aim to include the fundamental information for the understanding of the study by all team members and for the alignment of expectations and possibilities during the formulation and execution of the work. Here, important issues are highlighted for understanding the scenario where the research is developed and the clinical algorithms to be considered.

For multidisciplinary teams composed of health professionals and IT professionals to be able to communicate more efficiently, it is important to raise questions about the functioning of the environment where the software will be implemented as an intervention, the protocols followed for patient care in this environment, the modus operandi of the professionals in the team in which the intervention will be applied and their expectations regarding the intervention's outcomes for each phase of the patient's treatment in which it is used. After extensive dialogues with students and professionals from both areas covered in this study, it is believed that these are the initial points of interest to clarify and align the work of multidisciplinary teams.

In the third section of the SACI protocol, the items provided aim to include fundamental information for the process of technological development of the software that will be used as a clinical intervention in the treatment of the patient. In addition to the aspects directly related to the development of the tool that must be described with precision, respecting the organization and quality of the final product, what distinguishes the protocol created here from other existing theories of software development is the genuine concern both in relation to its possible effects such as health intervention and the way in which information from the entire process of creation and

application of the tools is recorded, so that their reproducibility by other researchers is possible, facilitating the learning process and the dissemination of acquired knowledge.

It is understood that in the documentation phase of scientific research and in the phase of publication of the results, it is essential that the readers of the works can understand step by step how each stage of the development of new technologies was carried out, whether they are familiar with the topic or not. Adopting this attitude in scientific research contributes to the transparency of the work process and to the increase/assurance of quality both in terms of methodological aspects and in relation to the software itself.

In view of this scenario, we realized that in order to enable the creation of a software for health, as mentioned above, it is necessary to hold meetings with focus groups involving professionals specializing in the subject and to research information with key informants belonging to the place where the study is intended to be carried out. Using these strategies, it is possible to understand more clearly the needs of software users and to arrive more easily at the determination of requirements, also recognizing the importance of systematizing clinical and administrative processes and representing the workflow of professionals, including behavioral and environmental variables, in providing patient care. To this end, it is recommended that the first contact of students/professionals in the informatics and computing area for the development of tools is with patient care planning information.

When planning the intervention, the multidisciplinary team must consider the health situation of the patient involved with the implementation of the technology, observing physiological aspects and other clinical procedures to which he is already submitted in traditional care. With these aspects in mind, the third section of the protocol includes a checklist to verify that the important aspects were considered in the process of technological development of the digital health tool.

The fourth and final section of the SACI protocol is aimed at aspects of research project management, with the greatest emphasis being given to managing the digital health tool development process, involving domains of communication, management, implementation and project completion.

Table 3 – SACI protocol items list.

I. Essential project data		
Item	***Subitem***	***Recommendation***
1. Study title		Brief descriptive title. If possible, provide information about the intervention to be performed in the study (for example the name or type of).
2. Study objectives	Justification for carrying out the study	Describe the main objectives of the study. Provide a brief theoretical background and/or justification for its realization.
3. Methods	Study design Study population Intervention Ethical Aspects Statistical analysis	Describe which study model and approach were chosen, inclusion and exclusion criteria for the study population and techniques for selecting subjects, data collection locations, data storage sources, and recording/output platforms and analysis of the collected data. Describe in detail: i) type of technology chosen (mobile, text messages, teleservice, among others); ii) how the intervention will take place in the study participants with details for each selected group, including activities to support and support treatment adherence carried out during the intervention; iii) place where the intervention is intended to be carried out (ambulatory, hospitalization, home care, among others); iv) expected time of intervention (start and end date); v) expected number of interventions or dosage (how many times a day, week, month, among others) It is strongly recommended to record the changes made to the intervention since its initial proposal, facilitating the subsequent comparison between what was planned and what happened in reality. It is strongly recommended to describe the procedures performed for the randomization of the clinical trial and for data analysis, including statistical methods. Submit the research for approval by the Ethics Committee of an accredited Teaching and Research institution and prepare a Free and Informed Consent Form for the study participants, ensuring the confidentiality and security of their personal data.

4. Results	Population groups Data collect Intervention outcomes Intervention damage Complementary results	Describe variations in the initial and final number of participants in the groups, demographic, epidemiological and clinical characteristics, reasons for loss and/or exclusion of subjects. Detail the outcomes of the intervention for each group of participants and the harms of the intervention, if any. Record complementary results, such as subgroup analysis, adjusted analysis, or other results extracted from the intervention that may complement the study findings.
II. Data for team meeting		
Item	***Subitem***	***Recomendation***
5. Level of Health Care	Primary, Secondary or Tertiary Health Care	Record the level of Health Care where the intervention will be implemented, specifying whether in basic health units, home care, units with a family health strategy, emergency care units, outpatient care and/or medium and high complexity hospitals.
6. Clinical algorithms	Clinical care protocols	Record what and how are the care protocols or clinical algorithms practiced at the target location for the implementation of the intervention. Develop an algorithm incorporating digital health technology into the clinical routines and algorithms of the service where the tool will be implemented together with professionals involved in the daily provision of health care. Carry out a comparison of results between traditional intervention and intervention plus the digital health tool.
7. Team involved in implementation	Students, healthcare professionals, patients	Register who will use, in practice, the digital health tool during the health intervention. Register necessary training for those who will use the tool.
III. Data for the development of the digital health tool		
8. Development methodology		Describe in detail the methodology used for the development of the software, the technology chosen for the development and the architecture of the system and data operation.
9. Requirements		Describe the essential elements used to define software requirements. Describe, if applicable and possible, the needs and expectations of users in relation to the developed tool.

10. *User experience Design* (UX)		Describe the steps designed for user interaction with the tool from the first use to the evaluation at the end of use. Describe the opinions and suggestions issued by users at the beginning and at the end of the implementation of the tool.
11. Data storage and management	Database model Deployment manager system	Describe what definitions for the database model and management system to implement.
12. Auxiliary equipment		Describe whether any auxiliary communication or information recording equipment will be used connected to the tool to obtain and/or exchange patient data.
13. Interoperability, security and reliability		Describe in detail the approach taken to issues of system interoperability and security and reliability in the transit of electronic clinical data and documents.
IV. Project Management Data		
14. Start of planning	Project Structure	Describe the methodology chosen for project management and the steps to be taken to fulfill the product management scope, considering its restrictions and assumptions. Study the feasibility of the product and carry out a financial planning resulting from its implementation.
15. Execution	Schedule User engagement and focus	Describe in detail the schedule of actions planned for the project development time, according to the defined methodology, specifying those responsible for each activity. It is strongly recommended that in the project execution stage, the management focus is on the user, constantly promoting actions for their engagement/adherence to the use of the developed tool and their feedback on non-use, if it occurs.
16.Monitoring		Periodically describe the results of the meetings with the research team and the results extracted in the field. It is strongly recommended to record difficulties of any nature related to the project reported throughout the process by users.
17. Project closure		Create project closure reports with the collected information and data analysis, recommended in this checklist and a lessons learned report to be consulted with each new research to be developed.

Source: Research data collection.

Final considerations: the value of registration and information

We believe that the guidelines suggested here, as well as those that already exist in international literature and that contribute so much to the quality of scientific research in health, will promote a healthy exercise of reflection regarding the importance of a well-prepared record of scientific information and compliance in manuscripts submitted to the available journals.

The guidelines were conceived mainly as a teaching tool, as a guide for novice researchers to build their way in the development of research, focusing on the quality of the product and the well-being of the patient involved in the study.

The judges participating in this study and the authors of this study believe that the constituent items of the SACI protocol are useful in this objective and start a good path for future discussions in the national literature.

The authors are aware that the construction of a list of minimum items is not enough to improve the completeness of scientific reports, but they believe that the initiative is a starting point for the creation of more specific instruments in the national literature for the encouraging more transparent reports for teaching, increasing the possibilities of reproducibility of higher quality research and medical-scientific evidence.

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5.6 Artigo 6

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Evaluation of the usability of a telehealth system for COVID-19 according to the perception of the user professional

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Abstract

With the advent of the pandemic, the Brazilian Ministry of Health structured in record time the Telehealth Service of the Unified Health System called TeleSUS, an ecosystem based on the intensive use of information technology involving automated mechanisms and a personalized health care center at distance. In addition to constant evaluations carried out in the service as a public health strategy, at clinical and epidemiological levels, the team involved in the project was also concerned with evaluating the system developed to enable the operation of remote care, from the conception of the organization of health actions to the technological development of the digital health tool. The objective of this study was to carry out an evaluation of a telehealth system, measuring the degree of satisfaction of users of health professionals regarding its usability and identifying factors that positively and/or negatively influence the evaluation.

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Introduction

The year 2020 was marked by the discovery of an infection originating from a modification of the virus called SARS-Cov2, which had an impact of sufficient size to the point of being considered a Pandemic. Near ubiquity and cross-species transmission are specific features of coronaviruses. Still, the rapid dispersion, the varied incubation period, not yet fully identified forms of transmission, asymptomatic carriers, absence of herd immunity and high morbidity and mortality related to SARS-CoV2 are some of the factors that concern physicians and scientists worldwide[1]

It is known whether the main route of transmission of the virus is by inhalation of contaminated droplets (aerosols) and by contact with contaminated hands and nasal, oral and ocular mucosa[2]. Faced with the growing pandemic chaos, defense and prevention measures involve, in addition to early diagnosis, isolation of the infected patient, monitoring of their contacts, as well as suspected and confirmed cases, social isolation and quarantine[3].

The confinement, combined with the impact of the crisis on health systems and the risks inherent to exposure to the virus, demanded behavioral adaptations never seen in history, demanding almost instantaneous changes, and still ongoing, in this new pandemic scenario.

In this context, telehealth and telemedicine gain a prominent role in meeting many demands in the health area, contributing to the reduction of the risk of transmission of the coronavirus in different scenarios in the world[4,5,6,7,8]. Given the scenario, the Ministry of Health of Brazil listed some measures to respond to the fight against the pandemic in the country. In order to support the population in the adoption of preventive practices, guarantee assistance for mild cases and coordinate care for the most severe cases, it was essential to use remote assistance strategies, placing Telehealth and Telemedicine as central points in this strategy.

In partnership with a private company that won the bidding process for the execution of the proposed services, the telehealth service of the Unified Health System called TeleSUS was structured in record time, an ecosystem based on the intensive use of information technology involving automated mechanisms and a central personalized service at a distance. Through Telehealth, there was teleservice by qualified and trained nursing professionals for remote care and clinical triage of the patient, in the presence of symptoms of COVID-19, all guided by clinical algorithms referenced and based on scientific literature.

According to each identified risk situation, different guidelines were offered to the patient as well as promotion and prevention guidelines, home isolation for cases and household contacts, with provision of self-declaration, guidance on the use of medication, referral to the most appropriate health service. health, among others, in addition to returning calls for all severe symptomatic cases.

During the period of operation of the services (April to July 2020) more than 970 thousand individuals throughout the national territory were assisted by TeleSUS and more than 85% of those assisted did not need to seek a face-to-face health service to solve their problem of health, staying at home under the program's self-care guidelines.

In addition to constant evaluations carried out in the service as a public health strategy, at clinical and epidemiological levels, the team involved in the project, of which the present author was part, was also concerned with evaluating the system developed to enable the operation of remote care, from the conception of the organization of health actions to the technological development of the digital health tool. To this end, among other strategies, the researcher used the context as a pilot test of the guidelines developed in her Doctoral research for the registration of clinical trials containing digital health tools, yet to be published.

It is known that health information systems are not limited to the technology they use, but to the care environment in which they are inserted, the profile of system users and the type of data that must be stored[9].

In order to design systems considered to be of good usability, it is necessary to understand factors of different natures such as psychological, organizational, ergonomic and social that will determine how people use the systems effectively[10]. From there, the development of tools must translate this interaction, reaching the pillars of efficiency, effectiveness and safety when using them.

To evaluate the system, the instrument chosen was the System Usability Scale (SUS)[11] with ten questions that measure the usability of products and services, applicable to mobile and clinical systems, hardware, websites, among others. The instrument is quick to apply and generates a single score on an intuitive and easy-to-understand scale, in addition to its good reliability and references that support its interpretation.

In this sense, considering the importance of the system for public health services in Brazil and for helping managers and professionals in health decision-making, the objective of this study was to carry out an evaluation of a telehealth system, measuring the degree of satisfaction of user health professionals regarding its usability and identifying factors that positively or negatively influence the evaluation.

Methods

It is a cross-sectional analytical descriptive research with a quantitative and qualitative approach. The project was approved by the Research Ethics Committee (CEP) of the Faculty of Medicine of Ribeirão Preto - FMRP/USP (CAAE: 14671019.2.0000.5440).

Data were analyzed in MS Excel 2019 16.0.11929.20198 and statistical tests of correlation of variables were applied, when necessary. Ten professional health and information technology specialists involved in the development of TeleSUS, with more than five years of academic training and a minimum Master's degree, were selected for the study. Participants were invited to fill out the electronic instrument (System Usability Scale) and registered in the system with a login and password to fill in the data, consult and/or correct it, if necessary. Data completion was carried out between January and April 2022.

The questionnaire was divided into two stages, the first containing demographic data such as gender, age, education and professional area, and the second containing the ten questions of the System Usability Scale instrument, graded using a 5-point Likert scale: 1- “strongly disagree”; 2- “disagree”; 3-“neutral/neither agree nor disagree”; 4-"agree" and 5-"strongly agree".

To find the answer value, a single number, it is necessary to use the test calculation methodology: for odd questions (numbers 1, 3, 5, 7 and 9) it is necessary to subtract 1 from the score that the user answered. For even questions (number 2, 4, 6, 8 and 10) you must subtract 5 from the score that the user answered. Then, add the values of the ten questions and multiply by 2.5. Questionnaire results can range from 0 to 100. The system is then rated according to the score received as <20.5 (worst imaginable); from 21 to 38.5 (poor); 39 to 52.5 (median); 53 to 73.5 (good); 74 to 85.5 (excellent) and 86 to 100 (best imaginable/possible).

Results and discussion

All users selected for the study answered the questionnaire (n=10). The profile of the participants was mostly female (70%), 40% with a Master's degree and 60% with a Doctor's degree and an average age of 46.2 years, being a user (10%) in the age group of 30 to 39 years, seven (70%) in the age group from 40 to 49 years and two (20%) in the age group from 50 to 59 years.

Regarding the time of professional activity, it was observed that 40% of the specialists had between five and ten years of professional practice, another 40% between eleven and twenty years of experience and 20% between twenty-one and 30 years of career. Regarding the area of activity, most were distributed between Medical Assistance (30%) and Scientific Research (30%) and the rest in Health Management (20%) and Higher Education Teaching (20%).

In the final score obtained by the System Usability Scale instrument, the mean total score was 84.6, with a standard deviation of 14.2, a minimum value of 42 and a maximum of 100, which classifies it as excellent in usability by the metric established in the construct.

In the analysis of the association by the Spearman coefficient and the Kruskal-Wallis test of the instrument's score with the variables education, age group and professional area, no statistically significant correlations were found (p-value=0.201; p=0.613; p =0.511, respectively).

Considering the relative values obtained as answers to the instrument's questions it was possible to verify that the system developed for TeleSUS presents the usability attributes recommended by Nielsen, which are the ease of learning, efficiency in use, ease of memorization, low error rate and subjective user satisfaction[10,12].

In addition to the usability assessment carried out through the SUS instrument, the researcher verified, along with the telehealth service system development process, items referring to the objectives, needs and expectations of the professionals who use the system through its developed checklist (SACI, still to be published). The delay in correcting errors in filling in patient data in the system was identified as a point of attention once the call was opened to the development team. A highlight raised by the participants was the user support offered by the system on a 24-hour help platform, with direct communication to support in a quick and resolute way and with an intuitive interface for filling.

Throughout the technology development process, concepts and theories relevant to telehealth[13] were analyzed, comparing them at different stages of the life cycle of a solution for the purpose of remote health care. Since its conception, the stages of technological development, implementation, integration and operation were permeated based on real world needs and the intended outcomes for patients using the system, causing a positive impact in the face of the COVID-19 pandemic scenario experienced in the All the world.

The system was evaluated with excellent usability by the user professionals for observing fundamental issues related to the Telehealth Model built for the provision of services and included seven essential domains in its composition: the identification of the population's health needs, the definition of the technologies used with the choosing the solution that best meets the presented scenario, the legal and ethical responsibility with health data, the acceptability of the patient and the professional user of the technology, the constant monitoring and auditing of the system, indicators and political aspects[14].

It is expected, in the future, that new assessments will be carried out with a larger number of populations and that services and systems like this will be increasingly present in the reality of countries like Brazil, where the geographic distance limits the offer of services in basic and specialized health in a large part of the national territory.

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6. Considerações finais

A autora acredita que as diretrizes aqui sugeridas, bem como os artigos aqui elaborados e publicados derivados das mesmas, promoverão um exercício saudável de reflexão sobre a importância de um registro bem elaborado das informações em pesquisa científica.

As diretrizes foram concebidas principalmente como uma ferramenta de ensino, como um guia para pesquisadores iniciantes construírem seu caminho no desenvolvimento dos estudos, com foco na qualidade do produto e no bem-estar do paciente envolvido no estudo.

Os juízes participantes e os autores desta pesquisa acreditam que os itens constituintes do protocolo SACI são úteis nesse objetivo e abrem um bom caminho para futuras discussões na literatura nacional.

Os autores ainda estão cientes de que a construção de uma lista de itens mínimos não é suficiente para sanar o problema a respeito da completude dos relatórios científicos, mas acreditam que a iniciativa é um ponto de partida para a criação de instrumentos mais específicos na literatura nacional para o incentivo à transparência nos relatórios de pesquisas clínicas, aumentando as possibilidades de reprodutibilidade dos estudos e produzindo evidências médico-científicas de maior qualidade.

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Apêndice I – Termo de consentimento livre e esclarecido para o comitê de avaliadores

UNIVERSIDADE DE SÃO PAULO
HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DE RIBEIRÃO PRETO

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO (Comitê de Avaliadores)

O(a) senhor(a) está sendo convidado(a) a participar voluntariamente do projeto de pesquisa intitulado: ***Proposta de protocolo para registro e realização de ensaio clínico randomizado para software***.

Esta pesquisa faz parte do projeto de Doutorado da aluna **Lídia Maria Lourençön Rodrigues,** do Programa de Pós-Graduação em Saúde Pública da Faculdade de Medicina de Ribeirão Preto/USP, orientada pelo **Prof. Dr. Domingos Alves,** docente do Departamento de Medicina Social da Faculdade de Medicina de Ribeirão Preto/USP, e tem por objetivo a construção de uma proposta de protocolo para facilitar e padronizar o registro e realização de ensaios clínicos tendo *software* como intervenção clínica central.

O estudo deste tema justifica-se pela necessidade de construir conhecimento e aumentar a qualidade das pesquisas no âmbito de desenvolvimento e aplicação de novas tecnologias para auxílio ao diagnóstico e tratamento em saúde.

Caso o(a) senhor(a) concorde em participar deste estudo, será convidado(a) a colaborar no processo de **validação do protocolo** que consiste em responder algumas questões sobre o escopo e propósito do protocolo, o envolvimento dos Stakeholders (ou partes interessadas), rigor para desenvolvimento, clareza na apresentação, aplicabilidade e independência editorial. O protocolo desenvolvido visa proporcionar qualidade no registro das pesquisas que envolvem software como intervenção clínica ao paciente e foi construído para ser um instrumento útil, fácil e prático de ser utilizado pelos profissionais e estudantes envolvidos com a utilização de novas tecnologias em saúde, tornando-as cada vez mais seguras aos pacientes e trazendo melhores resultados às intervenções em saúde, além de facilitar o processo de registro das etapas de desenvolvimento da tecnologia desde sua concepção até a sua aplicação final. O instrumento utilizado para a avaliação será o AGREE II (AGREE Next Steps Consortium, 2009). O tempo estimado despendido com sua avaliação é em torno de 30 minutos.

Sua participação na pesquisa não lhe acarretará ônus financeiro e não implicará em remuneração ou qualquer vantagem financeira decorrente de sua contribuição. O(a) Senhor(a) será esclarecido (a) sobre qualquer aspecto relacionado à pesquisa, se assim desejar, a qualquer momento. É garantido o seu direito de não aceitar participar ou de retirar sua permissão a qualquer momento, caso o processo de avaliação lhe provoque qualquer desconforto, sem nenhum tipo de prejuízo ou retaliação por sua decisão. Se por eventualidade, alguma dúvida ou mal-estar lhe acometer, estaremos disponíveis para lhe auxiliar.

Gostaríamos de esclarecer que seu nome e dados pessoais serão mantidos em sigilo e as informações que o(a) Senhor(a) nos fornecer serão confidenciais e utilizadas apenas para as análises deste estudo, sendo armazenadas em um banco de dados acessível somente aos pesquisadores do projeto. Tais informações serão muito úteis para compreendermos a melhor forma de propor um protocolo padronizado para pesquisas com *software* em saúde e poderão ser publicadas e/ou apresentadas com objetivo científico, mantendo sempre a confidencialidade dos dados referentes à identificação dos participantes. O(a) Senhor(a) também poderá se manter

atualizado(a) sobre os resultados da pesquisa, assim que os mesmos forem do conhecimento dos pesquisadores.

Os procedimentos adotados nesta pesquisa obedecem aos Critérios da Ética em Pesquisa com Seres Humanos conforme **Resolução no 466/2012 da Comissão Nacional de Ética em Pesquisa (CONEP)**. Nenhum dos procedimentos utilizados aqui oferece riscos à sua dignidade e/ou integridade física, sendo limitados a riscos como desconforto, cansaço ou aborrecimento ao responder a avaliação proposta. Em casos excepcionais, será oferecido suporte psicológico especializado. Caso haja danos decorrentes dos riscos previstos em legislação, o pesquisador assumirá a responsabilidade pelos mesmos, de acordo com as Leis vigentes no país.

Se precisar de algum outro tipo de esclarecimento sobre o estudo, o(a) senhor(a) pode entrar em contato com os pesquisadores responsáveis através dos dados disponíveis abaixo:

Prof. Dr. Domingos Alves
Docente do Departamento de Medicina Social da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo.
Endereço de e-mail: quiron@fmrp.usp.br
Telefone celular: (16) 99601-1595

Lídia Maria Lourençön Rodrigues
Mestre e Doutoranda pelo Departamento de Medicina Social da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo.
Endereço de e-mail: lidia.rodrigues@usp.br
Telefone celular: (16) 99775-7979

Caso o(a) Senhor(a) necessite de mais esclarecimentos referentes aos aspectos éticos da pesquisa, por favor entre em contato com o **Comitê de Ética em Pesquisa do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto - Universidade de São Paulo** através dos dados disponíveis abaixo. Para melhor entendimento, um Comitê de Ética em Pesquisa (CEP) é composto por um grupo de pessoas que são responsáveis por supervisionar pesquisas em seres humanos que estão sendo feitas na instituição e tem a função de proteger e garantir os direitos, a segurança e o bem-estar de todos os participantes de pesquisa que se voluntariam a participar da mesma.

Comitê de Ética em Pesquisa em Seres Humanos do Hospital das Clínicas e da Faculdade de Medicina de Ribeirão Preto – Universidade de São Paulo

Presidente: Dra. Márcia Guimarães Villanova
Localização: Subsolo do Hospital das Clínicas da FMRP/USP
Horário de Funcionamento: 08h às 17h, de segunda a sexta-feira
Endereço de e-mail: cep@hcrp.usp.br
Telefone: (16) 3602-2228
Endereço eletrônico para maiores informações: https://site.hcrp.usp.br/comite-de-etica/

Agradecemos sua colaboração e colocamo-nos à disposição para os esclarecimentos que se fizerem necessários.

Este termo é impresso em duas vias, sendo que uma ficará com o(a) senhor (a) e a outra com o pesquisador responsável. Caso o(a) senhor(a) concorde em participar desse estudo, por favor, assine, date e rubrique as duas vias do documento.

Ribeirão Preto, _____ de _____ de _____.

Nome do participante: _____.

Assinatura do participante: _____.

_____
Lídia Maria Lourençön Rodrigues
Pesquisadora responsável

Apêndice II – Carta convite à participação para o comitê de avaliadores

Carta Convite - Comitê de Avaliadores
(Validação do Protocolo)

Prezado(a) Sr.(a):

Esta validação é parte do projeto de pesquisa de meu doutorado que envolve a construção de um protocolo para o registro e realização de ensaios clínicos tendo um *software* como intervenção central. Este projeto será apresentado ao Programa de Pós-Graduação em Saúde Pública da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo. Este instrumento, se validado, será aplicado aos profissionais e estudantes participantes de pesquisa que envolve o desenvolvimento de um aplicativo que auxilia no diagnóstico médico da meningite tuberculosa, denominado MTBapp, no ambulatório de Tuberculose do Hospital das Clínicas da Faculdade de Medicina, Universidade de São Paulo.

O protocolo contemplará uma lista de itens a serem observados e registrados durante a construção do *software* voltado à área da saúde, sendo divididos em três grandes blocos, com dissertativas objetivas de resposta binária (Sim ou Não) e espaço para complementos que se fizerem necessários segundo julgamento de cada pesquisador que o utilizar. Também há um espaço inicial a ser completado com os dados específicos de cada pesquisa que utiliza-se do protocolo como apoio para registro.

Desta forma, solicito sua colaboração na avaliação do conteúdo do protocolo por meio do preenchimento de instrumento padronizado, disponível no *link* enviado por *e-mail*.

Agradeço pela sua valiosa colaboração,

Cordialmente,

Lídia Maria Lourençön Rodrigues – Doutoranda

Prof. Dr. Domingos Alves – Orientador

Apêndice III - Termo de consentimento livre e esclarecido para os profissionais da saúde

UNIVERSIDADE DE SÃO PAULO
HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DE RIBEIRÃO PRETO

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO II (ESTUDANTES E PROFISSIONAIS DA SAÚDE E/OU INFORMÁTICA)

O(a) senhor(a) está sendo convidado(a) a participar voluntariamente do projeto de pesquisa intitulado: ***Proposta de protocolo para registro e realização de ensaio clínico randomizado para software***.

Esta pesquisa faz parte do projeto de Doutorado da aluna **Lídia Maria Lourençön Rodrigues**, do Programa de Pós-Graduação em Saúde Pública da Faculdade de Medicina de Ribeirão Preto/USP, orientada pelo **Prof. Dr. Domingos Alves**, docente do Departamento de Medicina Social da Faculdade de Medicina de Ribeirão Preto/USP, e tem por objetivo a construção de uma proposta de protocolo para facilitar e padronizar o registro e realização de ensaios clínicos tendo *software* como intervenção clínica central.

O estudo deste tema justifica-se pela necessidade de construir conhecimento e aumentar a qualidade das pesquisas no âmbito de desenvolvimento e aplicação de novas tecnologias para auxílio ao diagnóstico e tratamento em saúde.

Caso concorde em participar deste estudo, o(a) senhor(a) inicialmente será convidado(a) a preencher o protocolo desenvolvido com as informações a respeito de sua experiência durante as etapas de pesquisa, elaboração e implementação de um *software* em saúde. Esse instrumento de ensino foi anteriormente validado e pretende auxiliar operacionalmente no desenvolvimento de ensaios clínicos tendo o *software* como intervenção central a ser avaliada. O protocolo foi construído para ser um instrumento útil, fácil e prático de ser utilizado pelos profissionais e estudantes envolvidos com a utilização de novas tecnologias em saúde, tornando-as cada vez mais seguras aos pacientes, principalmente no âmbito metodológico da elaboração das propostas de pesquisas, e trazendo melhores resultados às intervenções em saúde, além de facilitar o processo de registro das etapas de desenvolvimento da tecnologia desde sua concepção até a sua aplicação final. Após a utilização do protocolo, o(a) senhor(a) será convidado a responder um questionário a respeito de como foi a sua experiência durante o desenvolvimento de sua pesquisa, elaborado especialmente para o presente trabalho.

Sua participação na pesquisa não lhe acarretará ônus financeiro e não implicará em remuneração ou qualquer vantagem financeira decorrente de sua contribuição. O(a) Senhor(a) será esclarecido (a) sobre qualquer aspecto relacionado à pesquisa, se assim desejar, a qualquer momento. É garantido o seu direito de não aceitar participar ou de retirar sua permissão a qualquer momento, caso o processo de utilização do protocolo lhe provoque qualquer desconforto, sem nenhum tipo de prejuízo ou retaliação por sua decisão. Se por eventualidade, alguma dúvida ou mal-estar lhe acometa, estaremos disponíveis para lhe auxiliar.

Gostaríamos de esclarecer que seu nome e dados pessoais serão mantidos em sigilo e as informações que o(a) Senhor(a) nos fornecer serão confidenciais e utilizadas apenas para as análises deste estudo, sendo armazenadas em um banco de dados acessível somente aos pesquisadores do projeto. Tais informações serão muito úteis para compreendermos a melhor forma de propor um protocolo padronizado para pesquisas com software em saúde e poderão ser publicadas e/ou apresentadas com objetivo científico, mantendo sempre a confidencialidade dos

dados referentes à identificação dos participantes. O(a) Senhor(a) também poderá se manter atualizado(a) sobre os resultados da pesquisa, assim que os mesmos forem do conhecimento dos pesquisadores.

Os procedimentos adotados nesta pesquisa obedecem aos Critérios da Ética em Pesquisa com Seres Humanos conforme **Resolução no 466/2012 da Comissão Nacional de Ética em Pesquisa (CONEP)**. Nenhum dos procedimentos utilizados aqui oferece riscos à sua dignidade e/ou integridade física, sendo limitados a riscos como desconforto, cansaço ou aborrecimento ao responder ao protocolo proposto. Em casos excepcionais, será oferecido suporte psicológico especializado. Caso haja danos decorrentes dos riscos previstos em legislação, o pesquisador assumirá a responsabilidade pelos mesmos, de acordo com as Leis vigentes no país.

Se precisar de algum outro tipo de esclarecimento sobre o estudo, o(a) senhor(a) pode entrar em contato com os pesquisadores responsáveis através dos dados disponíveis abaixo:

Prof. Dr. Domingos Alves
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Endereço de e-mail: lidia.rodrigues@usp.br
Telefone celular: (16) 99775-7979

Caso o(a) Senhor(a) necessite de mais esclarecimentos referentes aos aspectos éticos da pesquisa, por favor entre em contato com o **Comitê de Ética em Pesquisa do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto - Universidade de São Paulo** através dos dados disponíveis abaixo. Para melhor entendimento, um Comitê de Ética em Pesquisa (CEP) é composto por um grupo de pessoas que são responsáveis por supervisionar pesquisas em seres humanos que estão sendo feitas na instituição e tem a função de proteger e garantir os direitos, a segurança e o bem-estar de todos os participantes de pesquisa que se voluntariam a participar da mesma.

Comitê de Ética em Pesquisa em Seres Humanos do Hospital das Clínicas e da Faculdade de Medicina de Ribeirão Preto – Universidade de São Paulo

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Telefone: (16) 3602-2228
Endereço eletrônico para maiores informações: https://site.hcrp.usp.br/comite-de-etica/

Agradecemos sua colaboração e colocamo-nos à disposição para os esclarecimentos que se fizerem necessários. Este termo é impresso em duas vias, sendo que uma ficará com o(a) senhor (a) e a outra com o pesquisador responsável.

Consentimento pós-informado:

Declaro que concordo em participar na qualidade de voluntário do projeto de pesquisa "Proposta de protocolo para registro e realização de ensaio clínico randomizado para software", após estar clara e devidamente informado sobre os objetivos do estudo e os termos de minha participação. Assino o presente Termo de Consentimento Livre e Esclarecido em duas vias, que serão assinadas também pelo pesquisador responsável pelo projeto, sendo que uma das cópias se destina a mim (o participante) e a outra ao pesquisador.

As informações fornecidas aos pesquisadores serão utilizadas na exata medida das finalidades do projeto de pesquisa, sendo que minha identificação será mantida em sigilo e sob a responsabilidade dos proponentes do projeto.

Não receberei nenhuma remuneração e não terei qualquer ônus financeiro (despesas) em função do meu consentimento espontâneo em participar do presente projeto de pesquisa.

Independentemente deste consentimento, fica assegurado meu direito a me retirar da pesquisa em qualquer momento e por qualquer motivo, sendo que para isso comunicarei minha decisão a um dos proponentes do projeto, acima citados, dos quais ficarei com os contatos.

Ribeirão Preto, _____ de _____ de _____.

Nome do participante: _____.

Assinatura do participante: _____.

_____
Lídia Maria Lourençön Rodrigues
Pesquisadora responsável

Apêndice IV - Questionário semiestruturado para os estudantes e/ou profissionais selecionados na fase de implementação do protocolo

1) O(a) senhor(a) poderia descrever o quão fácil/difícil foi realizar o compêndio de informações necessárias para dar início à construção do *software*?
2) O(a) senhor(a) teve dificuldades ao realizar o registro das informações de seu estudo? Se sim, qual a natureza (origem) de tais dificuldades?
3) O(a) senhor(a) teve dificuldades durante o processo de desenvolvimento do *software*? Se sim, qual a natureza (origem) de tais dificuldades?
4) O(a) senhor(a) se recorda dos tópicos que foram discutidos em reunião inicial com a equipe multiprofissional envolvida no desenvolvimento do *software*? Se sim, por favor, especifique.
5) O(a) senhor(a) se recorda das decisões e prioridades que foram tomadas em reunião inicial com a equipe multiprofissional envolvida no desenvolvimento do *software*? Se sim, por favor, especifique.
6) O(a) senhor(a) se recorda de quantas reuniões focais com a equipe multiprofissional foram necessárias para a explicação e o entendimento do algoritmo clínico apresentado por todos os membros da equipe? Se sim, por favor, especifique.
7) O(a) senhor(a) se recorda qual o método de gestão adotado para seu estudo? Se sim, por favor, especifique.
8) O(a) senhor(a) se recorda do tempo gasto desde a concepção da ideia do *software* até a finalização do produto para implementação no serviço de saúde? Se sim, por favor, especifique.
9) O(a) senhor(a) acredita que o software, em sua versão final, atendeu a todas as necessidades e expectativas dos membros da equipe multiprofissional? Por favor, justifique sua resposta.
10) O(a) senhor(a) acredita que a aplicação do *software* auxiliou positivamente no tratamento do paciente? Por favor, justifique sua resposta
11) O(a) senhor(a) acredita que a análise de resultados após a implementação do *software* foi, de alguma forma, simplificada e/ou facilitada pelo acesso às informações, por meio do Protocolo SACI, durante o processo de desenvolvimento de seu estudo? Por favor, justifique sua resposta.
12) O(a) senhor(a) possui alguma sugestão ou alteração para ser considerada no Protocolo SACI?

Anexo I – Prova de submissão do artigo 4

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Detailed Status Information

Manuscript #	NPJDIGITALMED-04169
Current Revision #	0
Submission Date	29th May 22 20:03:53
Current Stage	Manuscript Received
Title	Systematic review of existing methodologies for software development in healthcare before the pandemic
Running Head	Software development in healthcare
Manuscript Type	Review Article
Collections	N/A
Word Count	5904
Corresponding Author	Dr Lídia Maria Rodrigues (lidia.rodrigues@usp.br) (University of São Paulo)
Contributing Authors	Guilherme Catanante , Inácia da Silva , Rui Pedro Rijo
Authorship	Yes
Abstract	There are still few studies that describe the complete methodology for the software development in health research, fundamentally thinking about the teaching of undergraduate and graduate students who explore this topic in their studies. Among the reasons for this are the lack of standardization of methods and techniques for the development of technological tools for health, the difficulties in accessing technology in the most vulnerable populations, the adaptation and feasibility of software for different scenarios and the high costs. with technologies. On the other hand, the expansion of mobile technologies and the gradual increase in internet access have exponentially expanded the possibilities of communication and data transmission, which facilitates the insertion of health software in different scenarios around the world. It is observed that issues such as immediacy, portability, convenience, and interactivity/interoperability that technology provides make it increasingly possible to develop health promotion actions based on mobile devices. Even so, further studies are needed to evaluate the use of health technologies on a large scale and to discuss the standardization of their development. Our systematic search identified 19 publications meeting inclusion criteria. From these papers, we extracted data including the medical condition, concept of interest captured by the mobile technology, outcomes captured, and details regarding the sensors, algorithms, development of the e-health tool and study sample. The technologies developed ranged from online platforms, electronic messaging systems, interactive games to mobile applications. Regarding the type of study, there was variation between exploratory qualitative research, clinical trials, intervention studies and formative assessment studies. Although all studies present methodological steps in the software development stage, only 1.5% presented a detailed description of both the formation of the research groups and the stages and methods chosen for the development of the software, such as the language for writing source code, data storage, base operating system, among others.
Subject Terms	Health sciences/Health care/Health policy Scientific community and society/Scientific community/Research management
Competing interests policy	There is no conflict of interest
Clinical Trial	No
Applicable Funding Source	No Applicable Funding

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Editor Assigned	29th May 22 20:03:53
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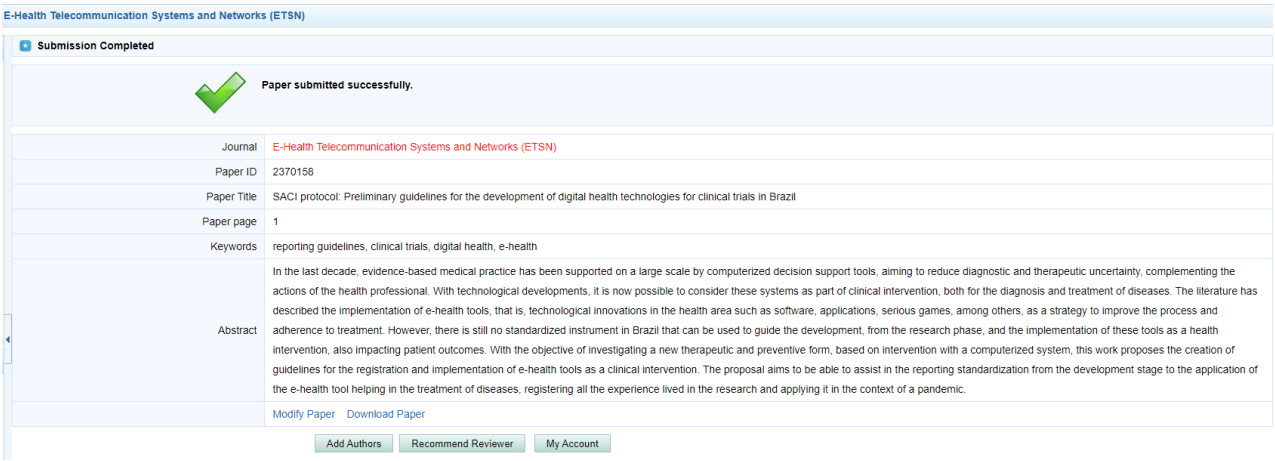
Anexo II – Prova de Submissão do artigo 5



E-Health Telecommunication Systems and Networks (ETSN)

Submission Completed

Paper submitted successfully.

Journal	E-Health Telecommunication Systems and Networks (ETSN)
Paper ID	2370158
Paper Title	SACI protocol: Preliminary guidelines for the development of digital health technologies for clinical trials in Brazil
Paper page	1
Keywords	reporting guidelines, clinical trials, digital health, e-health
Abstract	In the last decade, evidence-based medical practice has been supported on a large scale by computerized decision support tools, aiming to reduce diagnostic and therapeutic uncertainty, complementing the actions of the health professional. With technological developments, it is now possible to consider these systems as part of clinical intervention, both for the diagnosis and treatment of diseases. The literature has described the implementation of e-health tools, that is, technological innovations in the health area such as software, applications, serious games, among others, as a strategy to improve the process and adherence to treatment. However, there is still no standardized instrument in Brazil that can be used to guide the development, from the research phase, and the implementation of these tools as a health intervention, also impacting patient outcomes. With the objective of investigating a new therapeutic and preventive form, based on intervention with a computerized system, this work proposes the creation of guidelines for the registration and implementation of e-health tools as a clinical intervention. The proposal aims to be able to assist in the reporting standardization from the development stage to the application of the e-health tool helping in the treatment of diseases, registering all the experience lived in the research and applying it in the context of a pandemic.
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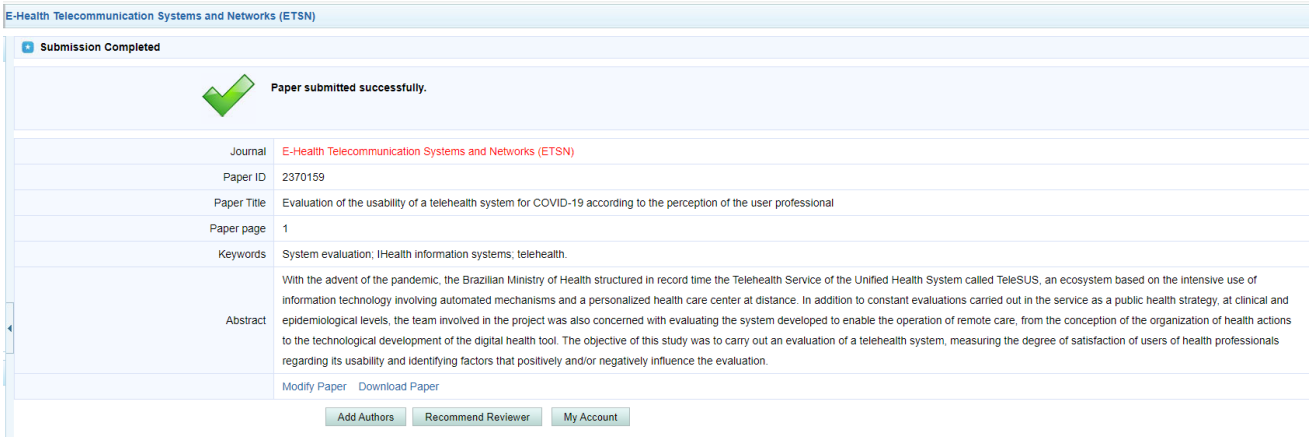
Anexo III – Prova de Submissão do artigo 6



E-Health Telecommunication Systems and Networks (ETSN)

Submission Completed

Paper submitted successfully.

Journal	E-Health Telecommunication Systems and Networks (ETSN)
Paper ID	2370159
Paper Title	Evaluation of the usability of a telehealth system for COVID-19 according to the perception of the user professional
Paper page	1
Keywords	System evaluation; IHealth information systems; telehealth.
Abstract	With the advent of the pandemic, the Brazilian Ministry of Health structured in record time the Telehealth Service of the Unified Health System called TeleSUS, an ecosystem based on the intensive use of information technology involving automated mechanisms and a personalized health care center at distance. In addition to constant evaluations carried out in the service as a public health strategy, at clinical and epidemiological levels, the team involved in the project was also concerned with evaluating the system developed to enable the operation of remote care, from the conception of the organization of health actions to the technological development of the digital health tool. The objective of this study was to carry out an evaluation of a telehealth system, measuring the degree of satisfaction of users of health professionals regarding its usability and identifying factors that positively and/or negatively influence the evaluation.
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