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TOWARDS PARTICIPANT-CENTRIC ELECTRONIC INFORMED CONSENT IN CLINICAL RESEARCH

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LIST OF ABBREVIATIONS

ACT EU	Accelerating Clinical Trials in the European Union
CASP	Critical Appraisal Skills Programme
CFR	Code of Federal Regulations
COREQ	Consolidated Criteria for Reporting Qualitative Research
CTD	Clinical Trials Directive
CTEG	Clinical Trials Expert Group
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
DPO	Data protection officer
EC	Ethics committee
EDPB	European Data Protection Board
EFCNI	European Foundation for the Care of Newborn Infants
eIC	Electronic informed consent
eIDAS	Electronic identification and trust services for electronic transactions in the internal market
EMA	European Medicines Agency
ePIC	Electronic personalized informed consent
EU	European Union
FDA	U.S. Food and Drug Administration
FIMEA	Finnish Medicines Agency
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HCP	Health care professional
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act of 1996
HMA	Heads of Medicines Agencies
HRA	Health Research Authority
IC	Informed consent
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use
IMP	Investigational medicinal product
INC	International Neonatal Consortium

ISO	International Organization for Standardization
MHRA	Medicines and Healthcare products Regulatory Agency
MMAT	Mixed Methods Appraisal Tool
PI	Principal investigator
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RRI	Responsible Research and Innovation
SUS	System usability scale
US	United States
WHO	World Health Organization
WMO	Medical Research Involving Human Subjects Act

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GENERAL INTRODUCTION AND OBJECTIVES

1 General introduction

1.1 The origins of informed consent in bioethics

The principle of informed consent (IC), a fundamental tenet in bioethics, is shown to be an evolving process. It was introduced in research practices in the 20th century and has been further shaped by various international standards and regulations (1-6). As an introduction, we provide a brief history of IC to understand its origins and its evolution, with a particular reference to the major ethical guidelines and regulations.

1.1.1 The Nuremberg Code

Horrific medical experiments were conducted on concentration-camp inmates shortly after World War II. The so-called 'Doctors' trial' or 'Medical Case' was the first of a series of 12 war crimes trials (1). As part of the judgement, the United States (US) Military Tribunal formulated conditions for conducting 'permissible medical experiments', which became known as the Nuremberg Code (2, 7). The Nuremberg Code states, among other requirements, that "*the voluntary consent of the human subject is absolutely essential*". In addition, the human subject should have adequate knowledge and comprehension to make an informed decision on whether or not to participate in a medical experiment. Therefore, information related to the "*nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment"* should be provided to the human subject (2). Although the Nuremberg code in its whole has not been adopted as law, it has served as a milestone for the protection and welfare of human subjects involved in medical research (8, 9). Nevertheless, physicians were of the opinion that the Nuremberg Code was irrelevant to their own practices as it was promulgated by judges in the context of cruel experiments (10, 11). Due to this criticism, subsequent efforts were made to develop alternative standards regarding the conduct of medical research (11).

1.1.2 The Declaration of Helsinki

The Declaration of Helsinki, having its origins in the Nuremberg Code, was adopted by the World Medical Association General Assembly in 1964 (3, 12). It has been revised multiple times; with the most recent revision in 2013 (3, 11, 12). The Declaration acknowledges the duty of physicians to protect the rights and welfare of human subjects involved in medical research, including research on identifiable material or data from human origin, and therefore highlights a number of requirements

related to IC (3). The fundamental elements of IC, as outlined by the Declaration of Helsinki, are described below.

Voluntary nature – The human subject's choice must have been freely made without undue influence. Therefore, physicians should be cautious to seek IC from human subjects with whom a dependent relationship has been established. In this particular case, the Declaration of Helsinki advises to involve a qualified individual who does not have this relationship to obtain the human subjects' consent. Moreover, refusal to take part in a study or withdrawal from a study should not negatively impact the physician-human subject relationship (3).

Type of information – The Declaration of Helsinki sets out the type of information that must be provided to human subjects involved in medical research: "*Each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal*.". Additionally, attention should be paid to the information needs of individual human subjects and to the manner the information is delivered. Moreover, all human subjects need to have the possibility to be informed about the outcome and results of the research study (3).

Documentation – After ensuring that human subjects have understood the information, their IC must be documented. According to the provisions of the Declaration of Helsinki, the human subjects' freely-given IC must be obtained, preferably in writing. If their consent cannot be in writing, the non-written consent has to be witnessed and documented (3).

Competence – When human subjects are incapable of providing their IC for taking part in medical research, for example when physically or mentally impaired, the IC should be obtained from their legally authorized representative. Involvement of these human subjects in a research study can only be allowed if, amongst others, there is a "*likelihood of benefit for them*" or when the study is "*intended to promote the health of the group represented by the potential subject*". In case it is not feasible to acquire the IC from their legally authorized representative, for example due to unavailability, participation in the study can proceed without IC on several conditions, such as the approval of the study by an ethics committee (EC). However, IC must be obtained from their legally authorized representative as soon as possible. If human subjects who deemed incapable of providing their IC are

able to express their permission to study participation, the physician must seek their assent in addition to the IC of their legally authorized representative (3).

1.1.3 THE BELMONT REPORT

In 1932, the US Public Health Service initiated the 'Tuskegee study', which continued for 40 years, to investigate the natural course of untreated syphilis in black males. When penicillin came on the market in the early 1940s to effectively treat syphilis, it was not offered to the study participants (13, 14). In addition, there is a lack of evidence that IC was obtained from these males taking part in the 'Tuskegee study' (15). To avoid repetition of these ethical lapses in other medical studies, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established (16). In 1979, the Commission published the Belmont Report in which fundamental ethical principles are defined, including IC. According to the Belmont Report, the IC process entails the following components: information, comprehension, and voluntariness (4).

Information – The Belmont Report pays special attention to how much study-related information and what type of information should be conveyed to human subjects. According to the Report, it is challenging to agree on the standard regarding the amount and sort of information to be provided to subjects. Therefore, the standard of the 'reasonable volunteer' is proposed: "*The extent and nature of information should be such that persons, knowing that the procedure is neither necessary for their care nor perhaps fully understood, can decide whether they wish to participate in the furthering of knowledge. Even when some direct benefit to them is anticipated, the subjects should understand clearly the range of risk and the voluntary nature of participation.*" (4).

Comprehension – The Belmont Report considers the methods used to deliver the study-related information to the human subjects, next to the information itself, as of utmost importance. In addition, the Report highlights that it is key to tailor the presentation of the information to the individual human subject's needs and that special attention should be paid to subjects whose comprehension may be limited, such as the mentally impaired (4).

Voluntariness – Finally, the Belmont Report emphasizes that human subjects should voluntarily agree to take part in a research study. Therefore, their IC should be obtained "*free of coercion and undue influence*" (4).

1.1.4 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: guideline on Good Clinical Practice

In 1990, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was established to respond to the pharmaceutical industry seeking global markets (17, 18). The ICH aims to harmonize obligations for the development and authorization of safe, effective, and high-quality pharmaceuticals (19). With regard to clinical trials, the first version of a Good Clinical Practice (GCP) guideline (i.e., ICH E6(R1)) came out in 1996, having its origin in the Declaration of Helsinki (5, 20). GCP is an international ethical and scientific standard that aims to protect the safety, rights, and well-being of human subjects involved in clinical trials. According to GCP, IC is "*a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate*". Prior to the start of a clinical trial, the voluntary given written, signed, and dated IC must be obtained from the human subject. Additionally, GCP crafted the elements the human subject needs to be informed about by using understandable language (5). In 2016, the ICH E6(R2) addendum was released to foster implementation of more efficient approaches to the conduct of clinical trials (20). In addition, since the development of ICH E6(R2), clinical trials have continued to evolve in view of new trial designs and emerging technologies (21). To this end, the ICH E6(R3) Expert Working Group published a draft version of the updated GCP principles in 2021, addressing the use of technologies in clinical trials; for example, to inform participants and to obtain their consent (22).

1.1.5 Clinical Trials Regulation

The Clinical Trials Regulation (CTR) was adopted in 2014 and entered into application on 31 January 2022 (6, 23). This directly binding legislative act aims to ensure greater harmonization for the assessment and supervision of clinical trials throughout the European Union (EU) (6, 23, 24). For example, the CTR introduced the Clinical Trials Information System (CTIS), functioning as the single European entry point for sponsors to submit clinical trial applications (25). As a result, the submission, assessment, and authorization processes of clinical trials are centralized in a single platform (26). Moreover, the CTR requires sponsors to submit a lay summary of the trial results to the CTIS to increase transparency of clinical trial information (6, 25). The CTR highlights that the provisions laid down in this Regulation are in line with the Declaration of Helsinki and the GCP principles, hereby creating the link between the ethical standards in research involving human subjects and the legal rules for conducting clinical trials (6). With regard to IC, the CTR defines that human subjects need to provide their written, dated, and signed IC after being truly informed of all the pertinent aspects of a particular trial. In

addition, extensive focus is being directed towards obtaining the consent from minors or subjects incapable of providing consent for taking part in a clinical trial.

1.2 Informed consent as a legal ground for the processing of personal data

The General Data Protection Regulation (GDPR) is the leading regulatory act at European level to protect human subjects' rights in relation to the processing of their personal data (27, 28). Personal data are considered information that can be directly or indirectly linked to a human subject. According to the GDPR, data processing must be legitimated on one of the legal bases as described in Articles 6(1) and 9(2), such as IC, regarding the processing of non-special and special categories of personal data, respectively. The GDPR highlights that clear and plain language must be used when informing human subjects about various aspects; for example, the purpose and legal basis for data processing, the categories of recipients, and the period of data storage (28). However, questions have been raised regarding the degree of specificity of IC. Recital 33, although not adopted in the provisions of the GDPR, states that "*It is often not possible to fully identify the purpose of personal data processing for scientific research purposes at the time of data collection. Therefore, data subjects should be allowed to give their consent to certain areas of scientific research […]*", thereby opening up the possibility towards broad consent which is highly debated in biomedical research (29-32). The Article 29 Data Protection Working Party – now European Data Protection Board (EDPB) – was tasked with providing practical guidance on several topics outlined by the GDPR in order to facilitate compliance (32-34). With regard to this Recital, the EDPB specified that the IC must include a well-described purpose for data processing. In case these purposes cannot be specified within a research project, human subjects can provide their consent for general purposes and subsequently, when the research study advances, consent for next steps can be obtained. In addition, the EDPB highlights that when special categories of personal data (e.g., health data) are processed, Recital 33 requires a high level of scrutiny (32, 34). According to the GDPR, IC should be freely given by data subjects (28). However, with regard to clinical research, an imbalance of power may exist between these subjects and the controller; for example, when these subjects have a poor health status and taking part in a clinical study may be the last opportunity to improve their health condition. For these cases, the EDPB has stated that IC is not an appropriate legal basis for data processing (34, 35).

1.3 The transition to electronic informed consent: the story so far

The IC process has historically been based on paper-based documents. Nevertheless, current paper-based IC forms (ICFs) often contain specialized medical and legal terminology in a static approach, and therefore, may be ineffectual in achieving the primary goal of IC: truly informing the research

participants (36, 37). Various systematic literature reviews have shown that the extent to which participants understand the study-related information does not lead to truly IC (36-38). As a result, there may be the risk of not adhering to study requirements or dropping out because of false expectations (39, 40). Furthermore, other challenges remain; for example, related to ensuring correct documentation of signed ICFs or recontacting research participants to obtain their consent upon study amendments (41-43). As a result, due to the increasing complexity and the dynamic nature of modern clinical research, paper-based IC has been stretched to its limits (44-46).

The digital era has shifted the focus from paper-based ICFs to other strategies to inform research participants and to obtain their consent, such as involving multimedia or making use of test/feedback interventions (47). In 2021, the European Medicines Agency (EMA) published a draft 'Guideline on computerised systems and electronic data in clinical trials' in which the use of electronic informed consent (eIC) is addressed. According to the EMA, eIC refers to "*the use of any digital media (e.g. text, graphics, audio, video, podcasts or websites) to firstly convey information related to the clinical trial to the trial participant and secondly document IC via an electronic device (e.g. mobile phones, tablets or computers)*" (Figure 1) (48). Similarly, the U.S. Food and Drug Administration (FDA) and the Department of Health and Human Services Office for Human Research Protections issued guidance concerning the use of eIC in clinical investigations in 2016. This guidance provides various recommendations; for example, related to the presentation of information, the use of electronic signatures, and the ethical review process of eIC (49). Generally, the eIC process can take place on-site when the research team and the research participants are at the same location or it can take place remotely (e.g., at the research participants' home). According to the ICH E6(R2) GCP guideline, research participants or their legally acceptable representative should have sufficient opportunity to ask questions and to discuss the study-related information before consenting (5). Therefore, it should be noted that eIC is meant to run alongside rather than to replace the face-to-face contact between the research team and the research participants, which can be established on site or through video-mediated communication (50, 51).

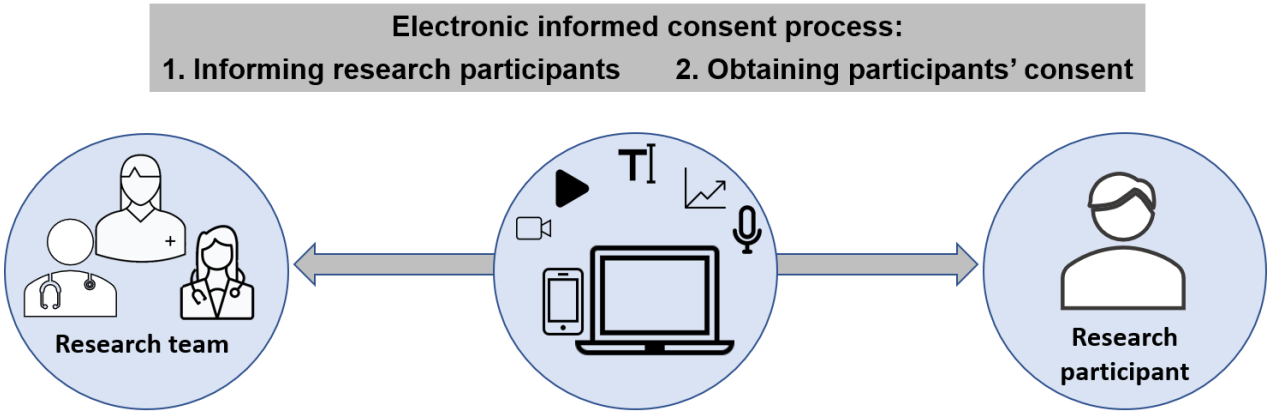

***Figure 1**. The eIC process*

Compared to paper-based ICFs, eIC could offer various advantages for stakeholders involved in clinical research such as ECs, physicians, regulators, sponsors, and research participants. By exploiting technology, study information can be conveyed tailored to the research participants' preferences (52). For example, participants could select a format to receive study-related information that suits their own learning style such as audio or video (53-55). Offering a personalized approach may promote research participant engagement by putting participants at the center of decision-making (52, 56). As seen in the literature, eIC can improve the participant's understanding of study-related information compared to paper-based ICFs (57-59). In addition, eIC may facilitate interaction over time between research participants and the research team during or after a study; for example, to reconsent upon study amendments (52). eIC could also offer other potential benefits, such as improving version control of ICFs and reducing regulatory inspection findings by offering an electronic audit trail that provides a record of consent-related activities (51, 60). Furthermore, informing research participants and obtaining their consent remotely may allow for a greater reach of clinical studies and increased participant diversity (61, 62). For these reasons, sponsors and contract research organizations indicate to shift towards eIC in the near future (63).

To date, a growing number of eIC initiatives in the context of biomedical research have been launched by nonprofit and for-profit organizations. However, the lack of access to detailed information on these initiatives makes it challenging to fully understand the state of the art in this rapidly growing field. Nevertheless, Table 1 provides some examples of eIC initiatives on the market. Dynamic consent, a particular type of eIC, has mainly been investigated and developed in response to the alleged consent problem within biobanking and prospective cohort studies (64, 65). Dynamic consent enables research participants to provide and revoke their consent regarding the future use of their samples and data

over a long period of time and to follow-up the activities of the biobank (31, 64, 65). The use of eIC can also be extended to research contexts outside of biobanking (66). For example, various eIC systems have been developed for clinical studies, some of them using features related to personalization and/or long-term interaction (67-69).

***Table 1**. Examples of nonprofit and for-profit initiatives with regard to eIC*

Nonprofit eIC initiatives
• TransCelerate, an organization involving the world's leading biopharmaceutical companies, issued guidance on eIC in order to provide stakeholders with insights to facilitate implementation of eIC in clinical research (51, 70).
• Sage Bionetworks conducted the mPower study in which they investigated the feasibility of remotely collecting information about changes in symptom severity related to Parkinson's disease. Using the mPower app, participants received study-related information about the study and provided their consent electronically, after passing a quiz evaluating their understanding of information (71).
• The Rare UK Diseases Study (RUDY), a prospective cohort study, made use of dynamic consent to allow the research participants to change their consent options (e.g., related to the use of their samples and data). In addition, the researchers returned lay summaries to the participants who contributed data and/or samples (72).
• The Cooperative Health Research in South Tyrol (CHRIS) study, promoted by the Institute of Biomedicine of Eurac Research and the South Tyrolean Health Authority, made use of dynamic consent (73). Through this dynamic consent, participants are able to control the extent of their participation in research over time; for example, related to data sharing, the return of results, or recontacting for taking part in further studies (74, 75).
For-profit eIC initiatives
• The Signant SmartSignals eConsent application, developed by SignantHealth, consists of various functionalities such as reconsenting participants (76, 77).
• The contract research organization ICON developed an eIC system taking into account recommendations outlined in the abovementioned guidance issued by the FDA and the Department of Health and Human Services Office for Human Research Protections (69, 78). For example, various multimedia features were implemented in this eIC system (78).
• Drugdev, an IQVIA company, developed an eIC system which makes use of features such as graphics, quizzes, and linked terms producing pop-up boxes that further explain particular terms (79, 80).

1.4 DESIGNING ELECTRONIC INFORMED CONSENT WITH AND FOR STAKEHOLDERS

Literature suggests that digital technologies are often designed without adequately understanding the end users' needs (81, 82). However, it is of utmost importance to design technological applications such as eIC with the end users' interests as a priority to be successful in real use (83, 84). Over the years, the design of new technologies has shifted the focus from designing for stakeholders to designing with stakeholders (85, 86). Participatory design draws from a variety of traditions and disciplines such as software engineering, architecture, and sociology (86, 87). It is commonly defined as a "*set of theories, practices, and studies that involve end users as full participants in activities leading to software and hardware computer products and computer-based activities*" (86). More concretely, participatory design can be brought down to three core concepts: (i) having a say, (ii) mutual learning, and (iii) co-realization. First, stakeholders who will be affected by a design outcome must have the possibility to have a substantive say in order to affect the design of a particular technology. Therefore, the participatory design process should involve stakeholders having a range of competencies about the technology and its context of use. Second, mutual learning refers to the two-way learning process between designers and end users (88). Users who are considered 'domain experts', knowing best the practices and context into which the technology will be implemented, learn about the design and the potential a particular technology can offer while designers strive to learn about the experiences, concerns, and desired aims of the users (88, 89). Third, co-realization relates to the active involvement of end users in visualizing and prototyping ideas. The emphasis in co-realization is on iteratively prototyping and evaluating technical artifacts to make users' ideas tangible and concrete in order to support them to experience the future rather than relying solely on their imagination (88, 90).

2 RATIONALE OF THE PROJECT

Despite the increasing interest in eIC to supplement or replace the traditional paper-based IC process, widespread adoption in clinical research is lacking behind. For example, results of a recent survey conducted by the TransCelerate's Modernizing Clinical trial Conduct Initiative revealed that the majority of TransCelerate's member companies has limited or no experience with eIC in clinical research (91). Therefore, its opportunities remain largely unfulfilled due to several barriers in the ethical, legal, regulatory, user interface, and technical domains. More concretely, familiarity with eIC is lacking. Researchers expressed concerns about how to present eIC to ECs, and also EC members themselves face uncertainty owing to the lack of experience with eIC (50, 92, 93). Moreover, there is uncertainty in the legal and regulatory fields due to the lack of support and harmonization of legal requirements (50, 91). Despite some eIC systems already on the market making use of features related to personalization and/or long-term interaction between the participants and the research team, there is a lack of detailed scientific insights related to a co-designed personalized and long-term eIC system, involving end users as full partners throughout the design process. To this end, more research is needed to investigate how eIC should be personalized (i.e., tailored to research participants' needs) and how and for which reasons long-term interaction should be established.

Although considerable research has been devoted to single aspects important for eIC, rather less attention has been paid to integrated information of these scientific domains. Therefore, it is vital to balance the relevant domains to better inform, empower, and engage research participants. To this end, this PhD project is embedded in the multidisciplinary 'Electronic personalized informed consent' (ePIC) research project (KU Leuven funded C2 project) that aims to create guidance for developing a participant-centric eIC application in clinical research. More specifically, technical research is conducted by DistriNet. In addition, the ePIC project can rely on the Centre for IT & IP Law, the Centre for Biomedical Ethics and Law, and the Meaningful Interactions Lab for legal, ethical, and user interface support, respectively. This PhD project reports studies undertaken in view of the ethical, legal, regulatory, and user interface domains which serve as a contribution to the general objective.

3 OBJECTIVES AND OUTLINE OF THE DISSERTATION

The overall aim of this PhD project is to provide recommendations for developing and implementing a participant-centric eIC application in clinical research, considering the ethical, legal, regulatory, and user interface domains. To achieve the overall aim, the following four sub-objectives, as displayed in Figure 2, are identified:

1. To explore the ethical, legal, regulatory, and user interface perspectives of stakeholders on eIC ***(part 1)***;
2. To define eIC requirements with research participants ***(part 2)***;
3. To test and evaluate eIC modules, co-developed with DistriNet based on requirements ***(part 3)***;
4. To inform the creation of a European regulatory framework on eIC ***(part 4)***.

Part 1 comprises three chapters. **Chapter 1** reports the results of a systematic literature review on the ethical, legal, regulatory, and user interface perspectives of relevant stakeholder groups to assist responsible implementation of eIC in biomedical research. In **Chapter 2** we conducted semi-structured interviews with key stakeholders in the field to investigate the potential advantages and challenges of a personalized and long-term eIC system for the current clinical research process. **Chapter 3** zooms in on a particular case study. More concretely, the results of semi-structured interviews with health care professionals are reported on the use of eIC in clinical research involving neonates.

Part 2, consisting of two chapters, focuses on defining eIC requirements with research participants (i.e., participants who had taken part in a clinical study). **Chapter 4** elucidates how an eIC interface can be effectively personalized, based on the participants' needs and how such an interface can establish valuable longitudinal interactions between research participants and the research team. More concretely, research participants were involved in co-creation workshops, semi-structured interviews, and a focus group discussion and were offered a key role in the design of a participant-centric eIC application. In **Chapter 5** the results of provocative interviews with research participants are described which further inform the design of eIC. To open up the debate on various aspects related to trust, personalization, and long-term interaction, a number of situations, which were informed by insights from Part 1, were presented to and discussed with the participants.

Part 3 provides insights into the usability of a co-designed eIC module by (potential) research participants as well as into stakeholders' views on the practical implementation of such an eIC module in their daily practice. We integrated all the insights obtained in Parts 1 and 2 to design, together with Distrinet, a personalized and long-term eIC module. By testing the usability of such a module, the

potential for a successful and user-friendly eIC application is more likely. Through usability testing and semi-structured interviews conducted with key stakeholder groups, we set out recommendations for the design and implementation of a user-friendly personalized and long-term eIC application in **Chapter 6**.

Part 4 consists of three chapters. Through a survey disseminated to various stakeholder groups, **Chapter 7** provides insights into these stakeholders' experiences with alternative consenting methods, such as eIC, before and during the COVID-19 pandemic. Furthermore, insights into how stakeholders experience any regulatory or legal support for eIC implementation in clinical research are presented. **Chapter 8** portrays the legal and regulatory landscape of (electronic) IC in the EU and is based on an analysis of European and national legislation and guidelines as well as consultations with medicines agencies of various countries. In **Chapter 9** the views of key stakeholders are described with regard to the development and content of a European guidance framework related to the implementation of eIC in clinical research. Based on the results of semi-structured interviews and focus group discussions, of which the topic guide was informed by Part 1, some recommendations for the creation of such a European guidance framework are put forward.

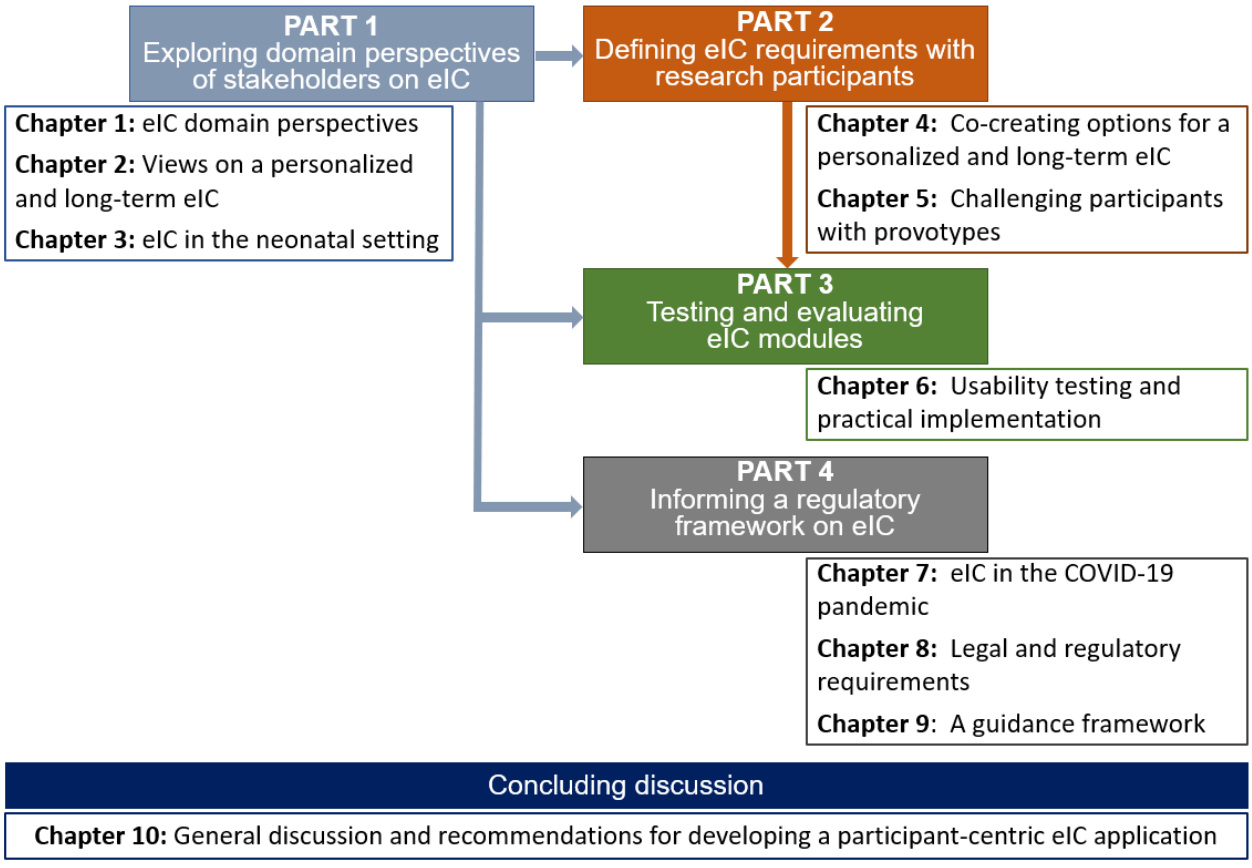

***Figure 2**. Schematic overview PhD project*

PART 1:
EXPLORING ETHICAL, LEGAL, REGULATORY, AND USER INTERFACE PERSPECTIVES OF STAKEHOLDERS ON ELECTRONIC INFORMED CONSENT

CHAPTER 1:
IMPLEMENTATION OF ELECTRONIC INFORMED CONSENT IN BIOMEDICAL RESEARCH AND STAKEHOLDERS' PERSPECTIVES: SYSTEMATIC REVIEW

This chapter is published as:

De Sutter E., Zaçe D., Boccia S., Di Pietro M.L., Geerts D., Borry P., Huys I.

Implementation of electronic informed consent in biomedical research and stakeholders' perspectives: systematic review

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1 ABSTRACT

Background: Informed consent is one of the key elements in biomedical research. The introduction of electronic informed consent (eIC) can be a way to overcome many challenges related to paper-based informed consent; however, its novel opportunities remain largely unfulfilled due to several barriers.

Objective: We aimed to provide an overview of the ethical, legal, regulatory, and user interface perspectives of multiple stakeholder groups in order to assist responsible implementation of eIC in biomedical research.

Methods: We conducted a systematic literature search using Web of Science (Core collection), PubMed, EMBASE, ACM Digital Library, and PsycARTICLES. 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) guidelines were used for reporting this work. We included empirical full-text studies focusing on the concept of eIC in biomedical research covering the ethical, legal, regulatory, and user interface domains. Studies written in English and published from January 2010 onward were selected. We explored perspectives of different stakeholder groups, in particular researchers, research participants, health authorities, and ethics committees. We critically appraised literature included in the systematic review using the Newcastle-Ottawa scale for cohort and cross-sectional studies, 'Critical Appraisal Skills Programme' for qualitative studies, 'Mixed Methods Appraisal Tool' for mixed methods studies, and Jadad tool for randomized controlled trials.

Results: A total of 40 studies met our inclusion criteria. Overall, the studies were heterogeneous in the type of study design, population, intervention, research context, and the tools used. Most of the studies' populations were research participants (i.e., patients and healthy volunteers). The majority of studies addressed barriers to achieving adequate understanding when using eIC. Concerns shared by multiple stakeholder groups were related to the security and legal validity of an eIC platform and usability for specific groups of research participants.

Conclusions: eIC has the potential to improve the informed consent process in biomedical research compared to the current paper-based consent. The ethical, legal, regulatory, and user interface perspectives outlined in this review might serve to enhance the future implementation of eIC.

2 INTRODUCTION

Obtaining informed consent (IC) is a fundamental ethical practice in biomedical research. It is the process of providing meaningful information to the potential participant in order to enable an autonomous well-informed decision on whether or not they wish to participate in the research study (3, 6, 94). Moreover, IC may serve as one of the legal grounds for processing personal data, as described in articles 6 and 9 of the General Data Protection Regulation (28). The primary goal of IC is to truly inform potential research participants or their representatives about different aspects such as the study design, study procedures, the risks and benefits, treatment options, participants' responsibilities, and the right to withdraw as well as information regarding data processing (3, 6, 28). Therefore, information must be available in lay terminology and in a language understandable to the participants (3). Long and cumbersome paper-based IC documents are the result of the increasing complexity of clinical research and the multitude of legal and regulatory requirements to satisfy IC needs (44, 45, 95). Regulatory requirements refer to those related to the regulatory approval of medicines (96). Available evidence has shown that research participants lack understanding of the key concepts of research studies (38, 95). For this reason, many attempts have been made to improve the understanding of research participants (47).

Owing to innovations in information technology, different strategies to consent have been developed, ranging from involving multimedia to the implementation of quizzes (47). Research on the use of different multimedia formats to present information and improve research participants' understanding is gaining popularity (47, 54, 97). Recently, the U.S. Food and Drug Administration (FDA), in collaboration with the Office for Human Research Protections, issued guidance (49) concerning electronic informed consent (eIC) in order to provide a shared and harmonized approach. eIC refers to electronic systems which may incorporate multimedia in order to convey information and to obtain IC. In this guidance, recommendations are described covering several aspects related to eIC such as the presentation of information, the use of electronic signatures, identity verification, FDA inspections, and the review process by ethics committees (ECs) (49). The development of an eIC platform, enabling participants to give and manage their eIC, could offer several opportunities. First, it could facilitate long-term interaction with research participants in cases where reconsenting for follow-up studies is required or for providing research results. Second, it may truly inform research participants in an interactive, tailored approach based on the individual's information needs (52).

Considerable research has been devoted to single aspects important for eIC; however, rather less attention has been paid to integrating information from several important scientific domains such as

ethical, legal, regulatory, and user interface domains. It is vital to balance the relevant domains in order to create an eIC platform that better informs, empowers, and engages research participants (50, 93). In the field of research, the EC plays an important role as it is responsible for reviewing study protocols to ensure that they meet the ethical, legal, and regulatory requirements of the country where the research is being conducted, paying attention to the applicability of international norms and standards (3). However, it remains unclear to what extent ECs are familiar with eIC and how they will handle eIC. Moreover, the involvement of research participants in the design of an eIC platform is of utmost importance as they fulfill a central role in biomedical research. Personalized human-centered design enables understanding of the participants' experiences and incorporation of their feedback to facilitate a participant-centered eIC platform (98).

Despite an increasing number of studies relevant for eIC, a comprehensive overview of these studies across the ethical, legal, regulatory, and user interface domains is lacking. Hence, the primary outcome of this systematic review was to provide a descriptive overview of the perspectives of different stakeholder groups (i.e., researchers, research participants, health authorities, and EC members) in these different domains with regard to eIC in biomedical research. The secondary outcome aimed to provide recommendations to assist responsible implementation. Insights of this review may serve as the foundation to design an eIC platform, thereby taking scientific steps forward in view of the international state-of-the-art.

3 METHODS

This systematic review was reported according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement (99). The corresponding review protocol is registered in the 'International Prospective Register of Systematic Reviews' (PROSPERO CRD42020158979).

3.1 SEARCH STRATEGY

The electronic databases of Web of Science (Core collection), PubMed, EMBASE, ACM Digital Library, and PsycARTICLES were searched in order to retrieve potential eligible studies. The searches for all databases were performed November 14, 2019. A search string for PubMed was developed and consisted of 'Medical Subject Headings' terms and free-text words. The search string was adjusted for use in the other electronic databases. All search strings were verified by a health sciences librarian. These search strings consisted of keywords such as electronic (informed) consent, dynamic (informed) consent, e-consent, digital (informed) consent, interactive (informed) consent, online (informed) consent, multimedia, and telemedicine. The search was restricted to studies published in English after

January 1, 2010. This timeframe was justified by the fact that eIC in biomedical research gained popularity only in the last decade and that technology has evolved quite rapidly. The full search strategy for all databases can be found in Appendix A.

3.2 STUDY SELECTION AND CRITERIA

All study types (i.e., qualitative, quantitative, and mixed methods) that discussed the concept of eIC in biomedical research covering the ethical, legal, regulatory, and user interface domains were included. Perspectives of stakeholders, in particular research participants (i.e., patients and healthy volunteers), researchers, EC members, and health authorities were considered relevant. We excluded nonempirical studies and abstracts. All studies retrieved from the search strategy were imported to EndNote X9 (Clarivate Analytics) and duplicates were removed. The remaining studies were uploaded to Rayyan (Qatar Computing Research Institute) software. Two researchers (EDS and DZ) independently performed the first screening based on titles and abstracts. In a second step, studies with full texts available were carefully reviewed by two researchers (EDS and DZ) and disagreements were resolved by consensus. When the full texts were not available, the corresponding authors were contacted. The reference lists of the included studies were hand searched for additional studies.

3.3 DATA EXTRACTION AND ANALYSIS

Data extraction was performed independently by two researchers (EDS and DZ) and was subsequently checked. A dedicated Excel (Microsoft Inc) data extraction form was used retrieving the following information for each eligible study: study identification (first author, title, publication year); study characteristics (study period, country, design, objective, scenario); stakeholder group (research participants, researchers, EC members, health authorities); tool used to collect information (survey, focus groups, interviews); intervention (a description of the eIC platform); domain being assessed (ethical, legal, regulatory, or user interface); and ethical, legal, regulatory, or user interface perspectives regarding eIC.

Two researchers (EDS and DZ) carried out data analysis together using Excel. A combination of deductive and inductive thematic analysis of the ethical, legal, regulatory, and user interface perspectives was used, reporting different concepts and the main findings associated with them. Thematic analysis was conducted according to the six-phase approach described by Braun and Clarke (100). During the first phase, notes were created on the ethical, legal, regulatory, or user interface perspectives found in literature. These notes were valuable for the creation of initial codes in the second step. During the third step, we clustered these codes to generate broad concepts. Thereafter,

the concepts were thoroughly reviewed and were defined in the fourth and fifth step. In the sixth and last step of this approach, we provided a descriptive overview to summarize the concepts found in literature (100). Within these concepts, studies reporting similar findings were grouped together in order to provide a concise overview of results.

3.4 Quality assessment

Two researchers (EDS and DZ) assessed the quality of all included studies. Based on the study design, the 'Critical Appraisal Skills Programme' (CASP) for qualitative studies (101), 'Mixed Methods Appraisal Tool' (MMAT) for mixed methods studies (102), and Jadad tool for randomized controlled trials (103) were used. MMAT and CASP were used to criticize study aspects such as the aim and the methodology of the study (101, 102). These aspects were evaluated using a categorical scale (i.e., yes, indeterminate, or no), and thereafter, we converted the number of positive assessments into percentages. The quality of randomized controlled trials was assessed by considering the randomization, blinding, dropouts, and withdrawals. Randomized controlled trials could receive up to 5 points using the Jadad tool (103). The Newcastle-Ottawa scale for cohort studies and an adapted version of this scale for cross-sectional studies were applied. Using the Newcastle-Ottawa scale, cohort and cross-sectional studies were evaluated using the following quality parameters: selection of study groups, comparability of study groups, and ascertainment of the outcome. Moreover, this scale also assessed the statistical test used in cross-sectional studies. Scores ranged from 0 to 9 for cohort studies and from 0 to 10 for cross-sectional studies (104, 105).

4 Results

4.1 Search results

Our search strategy produced a total of 9984 studies. After the screening process (Figure 3), 40 studies were included in the final analysis.

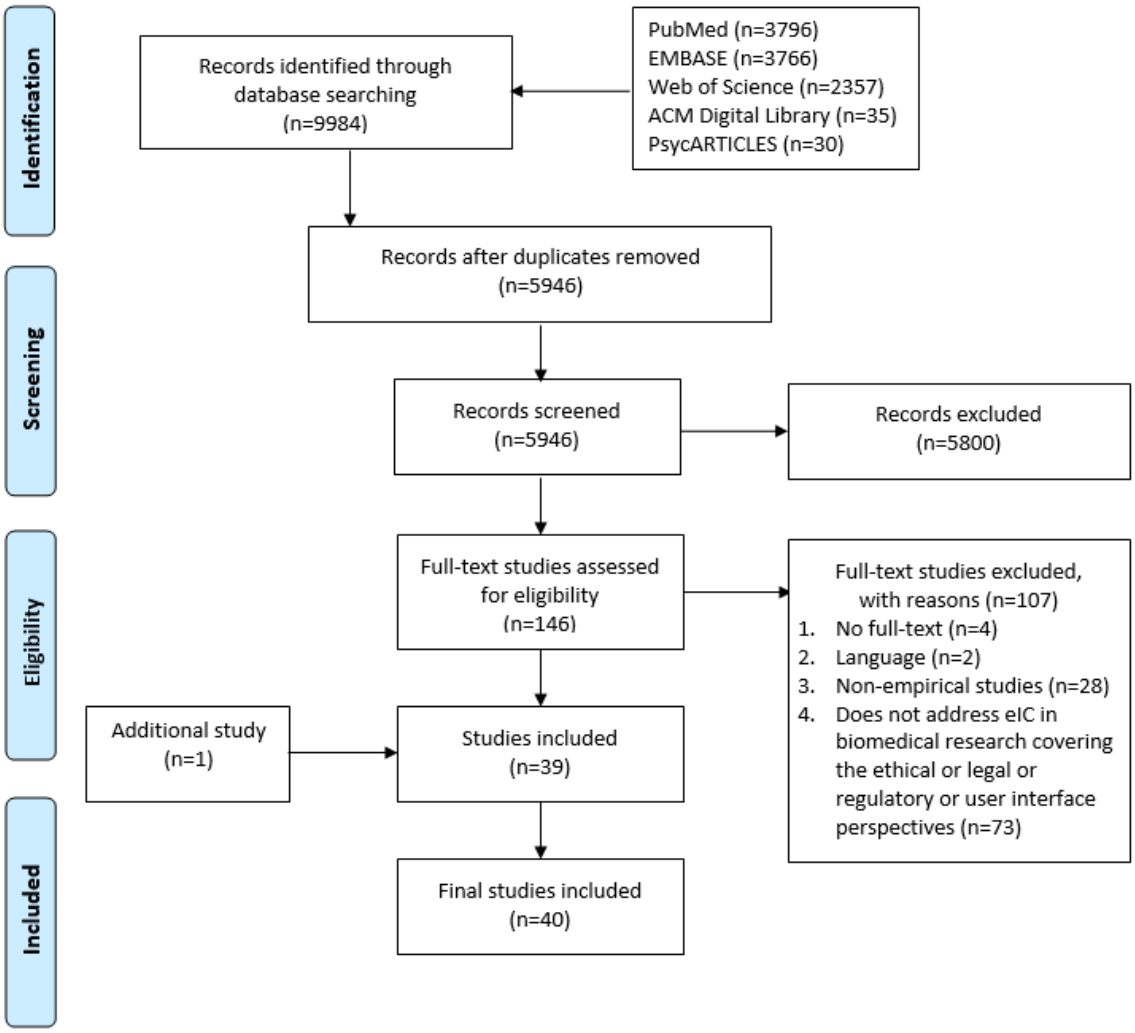

Figure 3. *PRISMA flowchart of the systematic review*

4.2 CHARACTERISTICS OF INCLUDED LITERATURE

Appendix B summarizes the main characteristics for each study. The majority of studies were conducted in the United States (27 studies), followed by the United Kingdom (3 studies). There was 1 study each in Ireland, Korea, Canada, Australia, Spain, Germany, and Denmark; 3 studies reported results from several countries. The designs of the studies included 10 randomized controlled trials, 10 mixed methods studies, 10 cross-sectional studies, 9 qualitative studies, and 1 cohort study. Most stakeholder groups involved in the studies were represented by research participants (26 studies), followed by researchers (2 studies), and EC members (1 study). In 11 studies, more than 1 of these categories, including health authorities, were involved. As for the characteristics of the research participants, 22 studies included different age categories (range 18-88 years), 3 studies each were conducted in young and elderly populations, and only 1 study was conducted in children. No

information regarding age was reported in 5 studies involving research participants. When the information was provided, we noticed that, in 12 studies, the majority of research participants had a college degree or more, in 8 studies the majority of research participants had less than a college degree, and in 2 studies there was an equal distribution in education level of the research participants. Meanwhile, in 12 studies there was no information regarding the education level of the research participants. Studies were conducted in both female and male populations, except 4 studies that only included either women or men. The tools used to collect relevant information varied, based, also, on the study design. Appendix C shows an overview of the intervention, scenario, and tools used.

4.3 Quality assessment

The quality of the included studies varied widely. Among the randomized controlled trials, only 3 studies (58, 106, 107) received a quality score of 3. Quality scores of 2 and 1 were provided to 1 study (59) and 6 studies (57, 108-112), respectively. The qualitative studies ranged from satisfying 80% or more of the quality criteria (6 studies) (61, 113-117) to satisfying 50% to 60% of the quality criteria (3 studies) (118-120). Moreover, 3 mixed methods studies met 80% or more of the quality criteria (93, 121, 122), 6 studies met from 57% to 71% of the quality criteria (50, 123-127), while 1 met only 43% of the quality criteria (128). The only cohort study had a quality score of 7 (129), while the quality scores of cross-sectional studies were assessed to be 4 (130-133), 5 (92, 134-137), and 6 (138).

4.4 Domain perspectives

Perspectives of the ethical, legal, regulatory, and user interface domains were reported using 6 concepts: format, impact on understanding, acceptability, security and trust, storage, and content. Due to the cross-disciplinary nature of these perspectives, they were not reported for each domain individually as each of these concepts touches on 2 or more domains.

4.4.1 Format

A range of aspects related to the format were identified in the literature review. The majority of research participants, researchers, members of the EC as well as health authorities believed that the ability to incorporate audio, video, or graphics in eIC is a distinct benefit, especially for vulnerable groups (50, 59, 93, 112, 116, 120, 122, 124-126, 134). Patients who were older adults, for example, expressed the usefulness of graphics and audio (122). Research participants mentioned in a focus group that video and graphics may be more effective than written text in conveying information (93). Moreover, patients involved in a study of Simon et al. indicated that audio narration could be of help for research participants with poor eyesight or limited literacy (116). However, participants argued for

caution because background music and sound effects could be an added distraction (127). In contrast, video was considered a multimedia element that might hold participants' attention more than a paper-based IC could (112). Important to consider is the length of the video, since research participants highlighted that a 5-minute video was too long (112). The use of graphics, including icons, was appreciated by all involved stakeholder groups (50, 59, 93, 116, 120, 122, 124-126, 134). For instance, the implementation of a progress bar was advised by researchers to indicate the different steps of the eIC form (120). A pilot study involving children highlighted the entertainment of graphics, making the eIC platform a pleasure to use (125). On the contrary, adult patients with fragile X syndrome, a genetic disorder causing intellectual impairment, had difficulty understanding aspects of clinical research such as blinding and randomization explained by several animations (124).

Furthermore, hyperlinks were identified as an important aspect of the format by participants and researchers (93, 120, 133). Hyperlinks could be used as a video link between researchers and participants in order to combine an online with a face-to-face consent process (133). Moreover, patients engaged in focus groups elicited hyperlinks as an encouraging way to seek additional information (93). Nevertheless, it should be noted that only 20 out of 491 patients (4.1%) involved in a randomized controlled trial clicked on 1 or more hyperlinks (106). Members of the EC and health authorities advised avoiding the use of hyperlinks to webpages that may modify their content (50).

Researchers and EC members as well as research participants criticized having extensive content during usability analysis of eIC platforms (57, 131). Research participants advised using a bullet point format with access to additional information if desired (57, 59, 127). Simple, concise language should be used to encourage a sufficient level of understanding (50, 59, 117, 127). The possibility of marking information that participants did not understand was considered useful and was viewed as an opportunity to enhance the discussion with the research staff (50). Nonetheless, research participants and researchers emphasized not losing the personal connection between researcher and participant (50, 127).

Moreover, eIC offers the possibility to give information in several languages by using subtitles or translated text. Although many factors influence participant recruitment, researchers and research participants believed that eIC may facilitate recruitment, particularly in rare disease research (61). By translating the content of eIC into different languages, information is available for a large number of individuals regardless of their geographical setting (61, 130).

Little information was provided about the choice of the device when using an eIC platform. Two studies, both of them using touchscreen formats, reported incorrect end user input (128, 130). Researchers entered incorrect medical record numbers and patient names containing spelling errors (130). A similar case with research participants was reported; in this particular study, several participants accidentally removed their signature, which contributed to the majority of errors when using touchscreen devices (128). Moreover, research participants who were older adults reported that they would need training to be able to use a tablet-based consent process (122).

4.4.2 IMPACT ON UNDERSTANDING

eIC may have an impact on the understanding of research participants by implementing a quiz, before signing the consent, to assess the participants' level of comprehension (59, 61, 116, 121, 132). However, research participants argue for caution (to not make it feel like a test) (127). In addition, interactive technology and a printed consent form offer the opportunity to review information giving participants the time to learn about the research (50, 93, 114, 116, 127). Patients considered a paper-based form more permanent and suggested implementing a printout option in the eIC technology (116). In addition, Vanaken et al. reported that some research participants preferred to take a printed version of the IC document home (50). Hence, the pressure to give consent immediately was decreased (93). An extensive amount of studies investigated barriers related to the use of eIC which could prevent research participants from achieving a reasonable level of understanding (50, 57-59, 106, 107, 110-112, 116, 117, 121, 122, 125, 126, 129, 130, 132, 136, 137). For the majority of studies, no barriers were reported (57-59, 106, 107, 110-112, 121, 125, 129). For example, patients with mental disorders, of whom the majority had a primary level of education, were able to make well-informed decisions by using eIC (129). Moreover, patients with schizophrenia had better understanding of disclosed information when using eIC compared to when using paper-based IC (111). In a few studies, barriers impeding adequate comprehension were reported by research participants, researchers as well as EC members regarding people with limited computer literacy, visual or auditory impairment, and regarding the lack of access to computers or internet (50, 116, 117, 122, 130, 136, 137). Other reported barriers to achieving adequate understanding were the attitudes of research participants looking for additional information after reading a very concise IC and the use of graphics that may be unclear (124, 126, 132).

4.4.3 ACCEPTABILITY

Some researchers had concerns regarding approval of eIC as an alternative consent process by ECs (93, 137). In addition, ECs themselves expressed uncertainty about the impact of the audio-visual aspects

on the ethical review process and the review duration (50, 92, 137). The ability to confirm the identity of research participants consenting remotely may be challenging, especially for researchers (134). In general, varying perceptions were reported regarding the use of electronic signatures. Although the majority of EC chairpersons enrolled in a study by Kane et al. did not encounter submissions of IC documents containing electronic signatures, a large number of involved chairs would approve it (92). However, researchers and members of ECs were unsure about compliance with local regulations (50, 92). Some representatives of health authorities supported the use of electronic signatures while others were concerned about data privacy (50). With respect to the research participants and their representatives, a study by Haussen et al., involving legal authorized representatives of whom 21 out of 53 representatives (40%) had a low educational status, stated that for these subjects there is an increased chance of preferring a paper-based IC (136).

4.4.4 SECURITY AND TRUST

Research participants stressed the importance of trust in the authenticity of eIC to share health data and to agree to take part in the study (113). This went hand-in-hand with security of the eIC platform, which was a main concern for all stakeholders (50, 57, 113, 116, 117, 119, 127, 137). A secure platform may enable the transfer of files, which researchers considered an important factor in biomedical research (134). Chhin et al. reported that the eIC platform that they developed could only be accessed by using individual user accounts and passwords (130). Moreover, researchers mentioned the need for providing sufficient information on privacy aspects to potential research participants (120). According to research participants, eIC may enhance trust in research because of the possibility of returning research information by using innovative technology (115). Nevertheless, Harle et al. conducted a randomized controlled trial with patients receiving a standard, interactive-only, or interactive trust-enhanced eIC (106). Trust-enhanced messages were implemented containing additional information on data protections, regulations, and training of the research staff. They indicated there was no effect from the inclusion of these trust-enhanced messages on data sharing, satisfaction, and understanding (106).

4.4.5 STORAGE

According to multiple stakeholders, electronic storage of consent details constitutes a notable benefit by enabling researchers to have a trustworthy and traceable overview of the consent status of participants (50, 61). For example, eIC can support online withdrawal, together with documentation of the reasons for withdrawal (118, 123). Moreover, online storage improves version control which might reduce the number of adverse inspection findings by the health authorities. Nevertheless, health

authorities voiced concerns that IC forms may be inaccessible during an inspection (50). An important feature for researchers and the EC is to have the ability to control access for specific consent documents (134). According to research participants, access to their own health information is a key benefit of participation (123). Research participants requested more transparency regarding the use of their data (115, 135). They expressed the right to control the sharing and use of their private health information (114, 119). Moreover, eIC enables researchers to update participants frequently with information about preliminary results, follow-up studies, and main outcomes (61). Nevertheless, the majority of patients with mental disorders, involved in a study by Sundby et al., stated that they would prefer direct contact with the research staff for receiving genomic information concerning serious or life-threatening conditions (138).

4.4.6 CONTENT

The usefulness of additional content elements such as definitions was articulated in a focus group involving research participants who were older adults (122). Moreover, exposing research participants to social annotation, such as comments generated by end users on several aspects of the eIC form, was considered important to feel adequately informed (108). However, the emotional force communicated in social annotations has an influence on research participants' perceptions with regard to information given in eIC. Research participants exposed to positive valence annotations indicated feeling less informed than participants receiving a combination of positive and negative valence annotations (109). Various studies provided insights into a personalized approach of an eIC platform(50, 114, 135, 138). Research participants stated that they would like to receive personalized elements and tailored information such as the display of their name in the eIC form or the impact of their contribution on a specific research question (50, 114). Moreover, Kim et al. conducted a study using an eIC platform in which research participants were allowed to modify their preferences for data sharing. In this study, research participants indicated that a personalized approach could enable participants' eagerness for data sharing for research purposes (135). Furthermore, researchers appreciated the possibility of research participants indicating what kind of information they would like to obtain (138).

5 DISCUSSION

5.1 IMPORTANCE OF UNDERSTANDING IN ELECTRONIC INFORMED CONSENT

The majority of studies paid particular attention to understanding, considering that it is seen as a crucial point in enabling participants to give their IC. In some studies the majority of participants had

a high level of education (57, 59, 112, 116, 121-123, 125, 132, 136, 138). It should also be noted that a number of studies assessing comprehension did not report the education level of their participants (107, 108, 128). Therefore, there might be additional barriers for less educated participants to achieving an adequate level of understanding. If research participants are not adequately informed about a research study, they may be disappointed due to misconceptions of the benefits. As a result, researchers may face increased dropout. Moreover, research participants may distrust ECs when they do not put the research participant at center when reviewing an eIC. Literature reported that eIC could improve understanding through the opportunity to check participants' level of comprehension by using quizzes before electronically signing the consent form (59, 61, 116, 121, 132). The implementation of a quiz may prevent research participants from immediately agreeing to participate in research, not allowing the content to be reviewed thoroughly. Nevertheless, meta-analysis of different IC interventions conducted by Nishimura et al. showed a significant higher understanding for paper-based enhanced consent forms including simplified text and facilitated reading level (47). A non-significant increase of understanding was observed for multimedia interventions. These enhanced consent forms and multimedia approaches were compared with a control consent process that consisted of a paper-based IC or an already enhanced IC (47). It would, therefore, seem that further research is needed to explore the effect on understanding of an eIC platform including all of these aspects, considering the education level, age, health status, and health literacy of the participant.

5.2 Particular attention to specific population groups

Several studies included in this review reported concerns about access to eIC for specific population groups (50, 116, 117, 122, 136, 137). From an ethical point of view, different population groups need to have the opportunity to be represented in biomedical research. The possibility for several population groups to take part in a research study may, first, broaden their access to treatments, and second, positively impact the generalizability of research results. Adequate support is required for participants with, for example, no or limited computer literacy. Obtaining IC in people with mental disorders remains a challenge that may be overcome with eIC. Health authorities believe that vulnerable populations, which are often underrepresented in clinical research, might benefit (50). However, it is important to highlight that only a limited number of studies included vulnerable groups who may have particular requirements (58, 110, 111, 122, 124, 125, 138). In only 1 pilot study, perceptions of children regarding the use of graphics were evaluated (125). Recommendations cannot be inferred from this pilot study because they require verification in further research. Generally, eIC platforms are intended to be used by multiple dissimilar target groups. The target population varies in literacy, education, age, health condition, and many other factors. Therefore, preferences for

designing a usable interface may deviate across the type of end users. Visual factors, such as the font size or the use of graphics, will differ for research studies involving older adults, children, or visually impaired participants.

5.3 Personal connection

Attention needs to be paid to not losing the personal connection between research participants and research staff. eIC has the opportunity to supplement the existing paper-based consent process but is not meant to replace it. For example, research participants may prefer the paper-based consent document or eIC facilitated by a discussion with the research staff to enable an informed decision. To enhance trust in research or in the authenticity of an eIC platform, the personal connection may play an important role. Moreover, eIC has the potential to inform research participants about early findings, but participants involved in a study by Sundby et al. preferred having direct contact with the research team if this information was related to life-threatening conditions (138). In addition, the online consent form should provide participants with a link that they can enter to withdraw their consent any time they desire. Nevertheless, for several types of medication, it is dangerous to abruptly stop (139). For this reason, the interaction between the research participant and the research team is of utmost importance to prevent withdrawal symptoms by giving all necessary information. In general, a lack of face-to-face communication may lead to misunderstanding with regard to several aspects of a research study.

5.4 Guidance framework

Acceptability of eIC by the health authorities was unclear (50, 92). Therefore, analysis of the legal framework regarding different aspects of eIC is required to determine the restrictions in certain jurisdictions. More research is needed to explore the legal aspects related to eIC across several countries. In addition, uncertainty exists about the review process of eIC by ECs (50, 92, 137). Due to the lack of experience, it remains unclear how the evaluation process of ECs will be impacted. It would thus be of interest to investigate which aspects of the eIC process ECs would consider for evaluation. General consensus on the review process of ECs is required to facilitate harmonized review for multicentric studies in which multiple ECs are involved. In addition, researchers need to receive clarification on which materials they need to submit to ECs. A guidance framework could reduce the burden of researchers and ECs concerning the preparation and review of eIC and could ensure protection of the rights, safety, and welfare of human participants.

5.5 PRIVACY BY DESIGN

Notable concerns were expressed by several stakeholders regarding security of eIC platforms, and thus data privacy (50, 57, 113, 116, 117, 119, 127, 137). Because eIC establishes the opportunity to give consent remotely, capture of an electronic signature and proof of identity are challenging. Researchers and ECs raised concerns about low compliance of electronic signature with local regulations. These concerns may strengthen reluctance to implement and use eIC platforms in biomedical research. In order to secure the platform, potential security threats need to be identified to counter them in security software. It is of utmost importance to implement the highest standards in security and privacy design to prevent fraudulent use of participants' health data. Moreover, clarifying the integrated security and privacy aspects to the research participants is valuable to reduce these concerns. A breach of privacy could, for research participants, lead to job loss or consequences related to their insurance. Moreover, researchers could be held responsible for misconduct. ECs and health authorities could also be held responsible, as they did not look into the security of the eIC platform when reviewing or inspecting. In previous years, the failure to obtain and document the consent of research participants was part of frequent FDA inspection failures (140). Owing to online storage, eIC may contribute to, for example, better version control and documentation of the consent process (50, 61). Nevertheless, controlled access systems need to be implemented to restrict access for stakeholders for different types of content in order to respect the privacy of the participants.

5.6 USABILITY

Noteworthy is the discrepancy between quantitative and qualitative usability testing. Despite the mention of hyperlinks as an important feature of the user interface in a qualitative focus group study (93), this feature was barely used in a randomized controlled trial evaluating different eIC platforms (106). These results suggest using an iterative design cycle starting with an evaluation of what participants would consider as useful in the user interface, after which a usability analysis should be performed. It is crucial to involve research participants when designing an eIC platform to create a user-friendly and acceptable system. This will support researchers in ensuring an adequate number of participants in order to detect potentially important clinical findings. Moreover, although research participants indicated preferring concise information in consent forms, attention needs to be paid to participants who are not motivated to seek additional information (50, 59, 117, 127). Specific measures are needed if input of researchers or research participants is required when using eIC in order to prevent errors. Potential errors are related to devices used by biomedical research stakeholders and the amount of manual input required. The use of touchscreen devices might invoke more inadvertent actions from accidental touches on the display, compared to those from the use of computers. The

implementation of a quality assurance procedure is highly recommended in order to avoid incorrect end-user input.

5.7 Inclusivity

Language aspects may complicate obtaining IC, and thus recruitment. It requires additional effort to involve research participants whose primary language is not frequently used in the IC process. To make the IC process more inclusive, subtitles or translated text can be used in eIC. Additionally, intercultural mediation can be considered to reduce the adverse outcomes of language barriers. An intercultural mediator can be part of the eIC process to assist the linguistic interpretation of information in the eIC (141).

5.8 Toward personalized electronic informed consent

An eIC platform provides an important means for modifying consent preferences. eIC can be tailored to participants' needs to address their preferences. In this way, participants may change different aspects such as which information they would like to receive, how they prefer to be contacted, and how often they wish to be contacted. Research participants indicated that access to their personal health data is an important motivation to participate in research studies. By enabling a personalized approach in the eIC platform, research participants can indicate whether they would like to receive this information. Moreover, eIC can be personalized for different kind of diseases. Patient preferences can vary for disease-specific IC. Participants with delicate health conditions may, for example, require additional information related to the study and may not be eager to share their data. Personalization may improve research participants' engagement and understanding. However, attention needs to be paid to the review process of such personalized eIC in order to avoid a time-consuming process. Further research that considers several types of end users is recommended, as eIC must be tailored to different population needs. Moreover, eIC provides the possibility of updating research participants with information on an ongoing research study. Nevertheless, it needs to be investigated how an eIC platform can be personalized and how longitudinal interaction can be assured.

5.9 Recommendations

The ethical, legal, regulatory, and user interface perspectives were converted into recommendations to facilitate implementation of eIC in biomedical research. The recommendations are based upon the 6 concepts reported in the results and are shown in Table 2.

Table 2. *Recommendations to guide implementation of eIC in biomedical research*

Concept	Description
Format	• Implement audio, video, graphics (i.e., icons, progress bar), and hyperlinks. Note: do not add audio that may distract participants, consider the length of the video, create understandable graphics, and avoid hyperlinks to webpages with dynamic content • Use simple, concise language and implement a bullet point format. Note: provide access to additional information if desired • Give the possibility to research participants to highlight information that is difficult to understand in order to facilitate the discussion with the research staff • Depending on the research study, make eIC available in multiple languages by using subtitles or translated text • Implement a quality assurance process to check the input of the end user
Impact on understanding	• Pay attention to the personal connection between the research participants and the research staff (also refers to security and trust) • Implement quizzes to assess the participants' level of comprehension. Note: do not let the quizzes feel like an evaluation • Give the possibility to review information by using interactive technology or the printed eIC form • Guarantee adequate support for people with limited computer literacy, visual/auditory impairment and people who do not have access to internet or computers
Acceptability	• Collaborate with health authorities and ECs to create a framework for reviewing and implementing eIC
Security and trust	• Implement controlled access systems for several stakeholder groups and pay attention to a secured eIC platform. Note: provide sufficient information to potential research participants about privacy aspects of the platform • Make sure that the secure transfer of files is possible between stakeholder groups
Storage	• Provide online storage of the IC • Support online withdrawal with documentation of the reasons for withdrawal • Pay attention to transparency regarding the use of participants' health information and their right to control the sharing and use of this information • Implement the possibility to update research participants frequently with information about preliminary results, follow-up studies and main outcomes
Content	• Implement definitions • Implement social annotations but mind the emotional force • Implement a personalized approach (e.g., by letting the participants indicate what kind of information they would like to receive)

5.10 LIMITATIONS

Our systematic review only included literature published in English. As a consequence, selection bias could have been introduced because it is possible that information specific to the ethical, legal, regulatory, or user interface domain of eIC in languages other than English was not identified. Another limitation was that the methodological quality of the included studies was rated overall as moderate which needs to be considered when interpreting the reported findings. Most of the studies had small sample sizes, which could be an issue for the generalizability of results. The studies included in the review had a high level of heterogeneity among them, which is the reason why a descriptive analysis was conducted. The differences in study designs, research fields and contexts, populations, and tools used to assess the results may have impacted the findings reported by each study.

6 CONCLUSIONS

This systematic review highlights different opportunities and challenges for responsible implementation of eIC in biomedical research. eIC provides the possibility of enforcing a personalized approach and supporting a longitudinal interaction with research participants. Findings suggest that eIC may have a beneficial impact on the consent process as long as some requirements are fulfilled. Special attention needs to be paid to specific population groups and to personal interaction with research staff. Future high-quality research, especially using randomized controlled trials, is required to provide information that may encourage the use of eIC for vulnerable groups.

CHAPTER 2:
PERSONALIZED AND LONG-TERM ELECTRONIC INFORMED CONSENT IN CLINICAL RESEARCH: STAKEHOLDER VIEWS

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Personalized and long-term electronic informed consent in clinical research: stakeholder views

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1 ABSTRACT

Background: The landscape of clinical research has evolved over the past decade. With technological advances, the practice of using electronic informed consent (eIC) has emerged. However, a number of challenges hinder the successful and widespread deployment of eIC in clinical research. Therefore, we aimed to investigate the views of various stakeholders on the potential advantages and challenges of eIC.

Methods: Semi-structured interviews were conducted with 39 participants from 5 stakeholder groups from across 11 European countries. The stakeholder groups included physicians, patient organization representatives, regulator representatives, ethics committee members, and pharmaceutical industry representatives, and all were involved in clinical research. Interviews were analyzed using the framework method.

Results: Interviewees identified that a powerful feature of eIC is its personalized approach as it may increase participant empowerment. However, they identified several ethical and practical challenges, such as ensuring research participants are not overloaded with information and offering the same options to research participants who would prefer a paper-based informed consent rather than eIC. According to the interviewees, eIC has the potential to establish efficient long-term interactions between the research participants and the research team in order to keep the participants informed during and after the study. Interviewees emphasized that a personal interaction with the research team is of utmost importance and this cannot be replaced by an electronic platform. In addition, interviewees across the stakeholder groups supported the idea of having a harmonized eIC approach across the European Member States.

Conclusions: Interviewees reported a range of design and implementation challenges which needs to be overcome to foster innovation in informing research participants and obtaining their consent electronically. It was considered important that the implementation of eIC runs alongside the face-to-face contact between research participants and the research team. Moreover, interviewees expect that eIC could offer the opportunity to enable a personalized approach and to strengthen continuous communication over time. If successfully implemented, eIC may facilitate the engagement of research participants in clinical research.

2 INTRODUCTION

The informed consent (IC) process in clinical research refers to informing a potential research participant of all the pertinent aspects of a clinical study by presenting the information in a IC document (5). However, lengthy and complex paper-based IC documents have been proven to be ineffectual in providing information in an understandable manner to research participants (38, 142). As a result, researchers have attempted to make the IC process more engaging and informative (47). Presently, there is a popular shift towards using digital technologies. Available research shows that more than 80% of clinical research sponsors will implement electronic informed consent (eIC) in the short term (63).

eIC is regarded as a promising alternative to paper-based IC in clinical research (52, 66). For instance, by offering tailored information based upon the preferences of research participants, it places them centrally and this may result in a more active engagement (52, 61). Moreover, eIC could enable a long-term interaction with research participants by facilitating ongoing communication with the research team during and after a research study (61). This interaction with research participants may be beneficial for informing the participants of updates to the IC due to new research requirements or other unforeseen circumstances, or to provide them with research results (52). Throughout this manuscript, eIC refers to an interactive online-based IC application which could facilitate interactions over time and could enable a personalized approach, adapted to research participants' needs.

Within the European Union, the conduct of clinical research is governed by a large number of legal instruments, such as the Clinical Trials Directive (CTD) which will soon be replaced by the Clinical Trials Regulation (CTR) (6, 143, 144). Moreover, the General Data Protection Regulation (GDPR) lays down the foundation to protect research participants' rights in relation to the processing of their personal data (28). Under the CTD and the CTR, written IC needs to be obtained for participation in clinical research, while the GDPR allows a written statement, including in electronic form, to obtain research participants' IC for data processing (6, 28, 144). Moreover, the Regulation on electronic identification and trust services for electronic transactions in the internal market (eIDAS Regulation) describes that "*a qualified electronic signature shall have the equivalent legal effect of a handwritten signature*" (145). However, this Regulation is not specifically focused on obtaining participants' eIC in the context of clinical research (145, 146). Therefore, compliant use of eIC to convey information and to obtain research participants' consent is a matter of ongoing debate. National laws concerning the use of eIC in clinical research are highly variable across European countries (146). Some national laws do not

mention eIC; for example, in Spain or Finland. Examples of the legal acceptance of eIC in some countries included in this manuscript are presented in Table 3.

Table 3. *Examples of the legal acceptance of eIC in the context of clinical research participation*

European country	Is it legally allowed to use eIC in clinical research?
Austria	eIC can be used in clinical trials (147).
Belgium	A guidance document was developed by a working group on IC, specifying the needs and restrictions when using eIC in interventional clinical trials (148).
The Netherlands	The Netherlands allow only a paper-based signature. Nevertheless, the Medical Research Involving Human Subjects Act is currently under revision to include the use of electronic signatures (149).
The United Kingdom	The Health Research Authority and the Medicines and Healthcare products Regulatory Agency published a joint statement on the use of eIC in clinical research (150).

Next to the uncertainties regarding compliant use of eIC, a number of other issues remain that are important to resolve in order to achieve the trustworthy implementation of eIC in clinical research. Specifically, there is a need for structured insights regarding how an eIC platform (through which research participants are able to manage their eIC) may be effectively personalized and also on how the long-term interactions may be established. A complete overview of the aspects of an eIC platform that are acceptable to personalize is currently lacking (151). With regard to the long-term interactions, it is necessary to determine which results may be shared with the research participants via eIC. In addition, the impact of eIC on the clinical research process, as well as on the review processes of ethics committees (ECs) and regulators, needs to be addressed. Moreover, the management of an eIC platform requires clarification. The hosting party will be responsible for the correct storage of data and access control and thus, needs careful consideration. This study aims to investigate these issues by collecting the views of multiple stakeholders: physicians, patient organization representatives, regulator representatives, EC members, and pharmaceutical industry representatives. The study has one main research question: What are stakeholders' views on the potential advantages and challenges of eIC for the current clinical research process?

The insights provided by these different stakeholder groups may support the development and responsible implementation of interactive eIC approaches that will stimulate research participants to be more empowered and informed.

3 METHODS

This study is reported in accordance with the 'Consolidated Criteria for Reporting Qualitative Research' (COREQ) checklist (Appendix D) (152).

3.1 APPROACH

Semi-structured interviews were conducted to seek the views and experiences of various stakeholder groups across Europe and the United Kingdom regarding (electronic) IC in clinical research. An interview guide was developed based upon a systematic literature review and the research aims (151). This systematic literature review identified that more research regarding the personalization of an eIC platform and the long-term interaction with research participants was required. In addition, several other issues remained, such as those related to the hosting of an eIC platform. Some questions were slightly different for each stakeholder group (Appendix E). Questions on the current paper-based IC process were included to explore potential strategies for enhancing the implementation of eIC. Specific eIC-related questions were also added. The interview questions were tested in three pilot interviews. The interview guide was provided in advance to interviewees upon request.

3.2 INTERVIEWEE SELECTION AND RECRUITMENT

Semi-structured interviews were conducted with people from 5 stakeholder groups: pharmaceutical industry representatives, patient organization representatives, regulator representatives, EC members, and physicians. Patient organization representatives and physicians involved in different disease areas were recruited. Moreover, we included physicians who work in academic institutions, as well as those who work in the pharmaceutical industry. Interviewees were recruited through purposive sampling and snowballing where existing interviewees suggested potential recruits. Potential interviewees were identified by exploring stakeholder websites and existing literature with regard to eIC or upon referral by the research group's network. Interviewees were eligible for inclusion when they (i) were active in a European country, (ii) had fluent proficiency in English or Dutch, and (iii) were familiar with (electronic) IC in clinical research. An invitation containing the IC for the interview study was mailed to suitable interviewees. Recruitment continued until data saturation was achieved. In total, 39 interviews were conducted with representatives of the pharmaceutical industry (n = 8), of patient organizations (n = 7), of regulators (n = 5), physicians (n = 6), and EC members (n = 13, of whom n = 4 were also physicians). Interviewees across the stakeholder groups were working in Austria, Belgium, Finland, Germany, Latvia, Lithuania, the Netherlands, Portugal, Slovakia, Spain, the United Kingdom, or were active at a pan-European level.

3.3 Data collection

Interviews took place between March and September 2020 and were conducted by using Skype for Business or other electronic means if preferred by the interviewee. All interviews were conducted by the same researcher (EDS). At the start of each interview, the interviewer introduced herself and described the aim of the interview study. Interviewees were always provided with the definition of eIC as issued by the U.S. Food and Drug Administration (FDA) to emphasize that both providing study-related information to participants and obtaining their consent occur via electronic means (49). Interviews were conducted in Dutch or English and were digitally audio-recorded. The interviews were 20–60 min long. Only the interviewer and the interviewee were present during the interview.

3.4 Data analysis

Interviews were analyzed by applying thematic analysis, according to the framework method (153). Pseudonymized audio-recordings were transcribed verbatim by a third-party and by the interviewer (EDS). The transcripts were thoroughly read by EDS who made reflective notes related to the content of the transcripts and, if necessary, listened to some parts of the audio-recordings again. Subsequently, NVivo software was used to code the transcripts by applying a combination of an inductive and deductive approach. The latter was based upon themes integrated in the interview questions. The first two transcripts were coded independently by EDS and F. Vanendert (FV) or B. Coopmans (BC). The coded transcripts were compared, and the assigned codes were grouped into broader categories by using a coding tree (Appendix F). As a result, a working analytical framework was developed. Hereafter, one researcher (EDS), using NVivo, applied this analytical framework to the other transcripts. The coded text was exported from NVivo to Microsoft Excel in order to create a framework matrix. In this matrix, the transcripts were summarized for each code and each interviewee to allow for comparison between and within different stakeholder groups. The data obtained was then interpreted.

4 Results

4.1 Current paper-based informed consent process

4.1.1 Advantages

Many interviewees indicated that paper-based IC involves a face-to-face conversation with a health care professional, such as a physician. They underlined that the face-to-face contact between research participants and the physician is a crucial part of the paper-based IC process. Firstly, it facilitates the verification of research participants' identity and secondly, the interviewees believed that the

presence of a physician is necessary to convey the consent options to the research participants and ensure that they are adequately informed.

> "*A health professional can easily determine from the body language and the eye contact of study participants whether they are really ready to participate or not and whether they still have doubts or questions.*" (14, EC member)

These interviewees believed that the paper-based IC document was the traditional method of providing information to research participants, and due to this, the paper-based form is manageable for the majority of participants. Moreover, the interviewees agreed that as the paper-based document is a fixed document, it offers the research participants the opportunity to discuss the research study with family members, friends, or a general practitioner. It allows the research participants to review what they have consented to after signing the IC. In addition, paper-based IC enables research participants to highlight certain parts of the document and compose further questions.

4.1.2 CHALLENGES

The majority of interviewees across the stakeholder groups recognized that paper IC documents are often very long and complex to read and understand. The information described in the IC often contains a specialized medical and legal terminology. As a result, it is not always clear to the research participants what is expected from them.

> "*There is the issue of the informed consent being rather lengthy nowadays. Not only understanding, but also reading through everything and concentrating on everything might be more of an issue, maybe even more than understanding the document.*" (4, regulator representative)

Nevertheless, all EC members asserted that the reading level of the IC document is reviewed when assessing a research protocol. Their assessment of the language used is based upon their own experiences or perspectives, and they do not have concrete tools to easily identify the readability of the information.

Another challenge raised by the interviewees was related to ensuring the documentation was correct and to the storage of the paper-based IC. Archiving was considered challenging for both the research participants and the research sites due to repository and document retrieval difficulties. Several

physicians and regulator and pharmaceutical industry representatives indicated that paper-based IC is associated with various documentation issues, such as signatures on incorrect IC versions or the erroneous placing of signatures on the document.

Several interviewees remarked that a paper-based IC is static and, thus, is not tailored to the needs of the research participants.

> "*Patient preferences at one particular time will not necessarily be the same throughout a study and the only way for patients to change their mind during a study is to withdraw from it rather than to change an option.*" (3, physician)

Moreover, it was argued that establishing a long-term interaction between research participants and the research team is complicated. It was considered to be burdensome for the research team if the need arose to recontact research participants to obtain reconsent or present a lay summary. It also placed time and logistical demands on the research participants to make additional visits to the research site in order to sign new versions of the IC document.

4.2 ELECTRONIC INFORMED CONSENT PROCESS

The majority of interviewees reported they did not have experience with eIC; however, a few interviewees have gathered practical experience or have been involved in theoretical discussions about eIC. If relevant, we have indicated which answers stemmed from experienced interviewees.

4.2.1 PERSONALIZATION

a) Functionalities

When interviewees were asked how they would personalize an eIC platform, several functionalities were suggested (Table 4).

Table 4. *Stakeholders' proposals regarding the functionalities of a personalized eIC platform*

- Present a first layer of information that is essential for participation in the research study, followed by a second layer that offers more specific information to those who are interested (e.g., by using hyperlinks or by hovering over a word)
- Enable the research participants to indicate if, how, and for which reasons they would like to be recontacted. For instance, for receiving information regarding the status of the research study, the results, amendments, studies that will take place in the coming months, etc.
- Enable the research participants to change the layout (e.g., font size) and highlight information
- Provide research participants with the option to choose between audio or video content (particularly in case of hearing or visual impairment)
- When implementing a quiz to assess research participants' comprehension, automatically redirect them to the relevant information/specific topic when they have answered incorrectly
- Provide the possibility to implement metrics that allow physicians to monitor various variables (e.g., how long did it take for research participants to read a certain topic)
- Offer the ability for physicians to stratify groups and provide adapted information (e.g., only give information about pregnancies and breastfeeding to women with a childbearing age)

b) Advantages of a personalized approach

Some interviewees stated that a personalized approach is the strength of eIC. They mentioned that eIC enables research participants to adapt how they would like to receive information about the research study based on their preferences.

> "*As it concerns voluntary participation, research participants need to have the possibility to indicate their preferences.*" (2, physician)

Some EC members and regulator and patient organization representatives highlighted that a personalized approach may partly solve the issue of flooding the participants with a large amount of information by adapting the information to the needs of the participants.

> "*I think a tiered approach is a very good option as there is very often too much information in the consent form, so that it sometimes really makes the most important information obscure.*" (4, regulator representative)

Furthermore, some interviewees believed that a personalized approach is very valuable for both the research participants and the physicians. Research participants are able to receive tailored information increasing their empowerment and enabling more focused conversations with the physician.

Personalization also stimulates individuals to be more engaged and better informed according to their needs.

> "*A personalized approach would be more tailored to the particular situation of research participants. I think it would help to understand the information.*" (3, regulator representative)

c) Challenges of a personalized approach

Several regulator representatives had reservations about personalized eIC platforms. They stated that, from a legal point of view, every potential participant needs to receive all the relevant information pertaining to a research study in order to make an informed decision. Many other interviewees across the stakeholder groups agreed and mentioned that it must not be allowed that some participants have access to more information than other participants. Personalization can also be an issue when both a paper-based IC and eIC are offered during a specific research study. Research participants receiving a paper-based IC should also have the opportunity to read the additional information. Another concern that was raised related to the amount of additional information that participants could choose to receive.

> "*You need to make sure that the research participants will not be overwhelmed with information.*" (4, physician)

Moreover, questions arose regarding how to present information in a correct and tailored manner to the research participants. According to EC members and pharmaceutical industry and regulator representatives, it would be challenging and time-consuming to develop such a personalized eIC platform. To make it feasible, one pharmaceutical industry representative advised that a template for a personalized eIC platform, which already offers the different functionalities, be developed. The pharmaceutical industry representatives also thought that it would be challenging for ECs to review a personalized eIC platform.

Some interviewees mentioned that not all research participants are able to manage the responsibility of indicating their preferences themselves. One physician raised the point that if the research participant has too much responsibility and freedom, it could affect the quality of the study. Another physician, having had practical experience with an eIC platform, stated that personalization complicates the IC process because verification of who has given permission for which aspects is required. However, this may be done automatically.

"*In a modern age, checking the preferences of the participants is done electronically by using automated pathways.*" (3, physician)

4.2.2 LONG-TERM INTERACTION

Stakeholders agreed that eIC offers the possibility to establish a long-term interaction between research participants and the research team. One of the abovementioned functionalities of a personalized eIC platform states that the decision to maintain a longitudinal relationship with the research team lies with the research participant. Moreover, it was agreed that eIC can facilitate continued contact with participants for research purposes as electronic devices were considered to be a convenient method of approaching participants. It was believed that the potential to recontact participants easily is valuable as research is dynamic in character and, therefore, it is not always feasible to anticipate all of the research requirements in advance. One pharmaceutical industry representative argued that being able to recontact participants easily would be beneficial to scientific research.

"*It would be an advantage for scientific research. There would be more flexibility in what you can do with already collected data.*" (2, pharmaceutical industry representative)

Interviewees raised the point that the long-term interaction may be used to inform the research participants of various aspects of the research study. Two patient organization representatives asserted that patients sometimes do not know, or remember, that they are participating in a research study. Therefore, they advised that repeated IC discussions are set up or that feedback is provided from the study center on regular basis. Similarly, an EC member also voiced the opinion that it would be valuable to set up a repeated IC discussion, particularly if it concerns a long-term study. Contact with the participants may also be maintained in order to inform them of updates to the IC. As a result, the participants are not necessarily required to go to the research site physically in order to sign a new version of the IC. Information regarding the status of the research study or the various steps involved in the research process may also be shared with the research participants. It was highlighted that this information would be valuable to inform participants about the different phases and the duration of the drug lifecycle to avoid any misunderstanding.

"*Lay persons usually have no idea how long it takes to develop a drug and to get it on the market. Sometimes they have the feeling that there is one study and when the study is successful, the medication will be available tomorrow.*" (11, EC member)

An eIC platform may also be used to return the results of the research study to the participants. The views of the various stakeholders about the type of results that may be returned and their considerations on this matter are shown in Figure 4. Several patient organization representatives stated that research participants have the right to receive the results of the research study in which they have taken part. Therefore, they advocated that it should be up to the research participants to decide which type of results they would like to receive through the eIC platform. Nevertheless, one physician and one regulator representative stated that it is not appropriate to return results via an electronic device. They were convinced that a clinical consultation is necessary to convey these results to the research participants. Other interviewees indicated that information not related to serious health conditions of the research participants may be shared easily via the eIC platform. However, research participants should be able to contact the research team if they have questions and require further explanation.

> "*An electronic platform is not an excuse to not give participants the information they need, and which they need face-to-face.*" (3, pharmaceutical industry representative)

Type of results	Considerations
• Lay summaries • Interim results • Results of additional investigations (e.g., blood sampling)	• Research participants should have the option to contact the research team • Results without large consequences for the research participant may be returned • Results should be validated by a Scientific Steering Committee • Patient experts should be included in the preparations for returning results

Figure 4. *Stakeholders' views on the type of results that could be returned and their considerations*

Moreover, some interviewees were convinced that an institutional policy, discussed and agreed upon by all relevant stakeholders, should be established to prevent differing practices of returning information from study to study.

Several interviewees were of the opinion that information needs to be returned in an understandable and participant-friendly manner in order to prevent harming the participants. Therefore, it was argued that a deeper reflection of which results may be returned and how this information may be interpreted by a lay person is needed. One patient organization representative advocated for a patient expert to be included when preparing for the return of information.

4.2.3 TYPES OF CLINICAL RESEARCH STUDIES

Interviewees agreed that eIC may be implemented quite broadly. The views of the stakeholders on the study population and the study type for which eIC may be used are presented in Figure 5. In addition, it was mentioned that eIC is beneficial for conducting research during the COVID-19 pandemic as it reduces visitations to research sites.

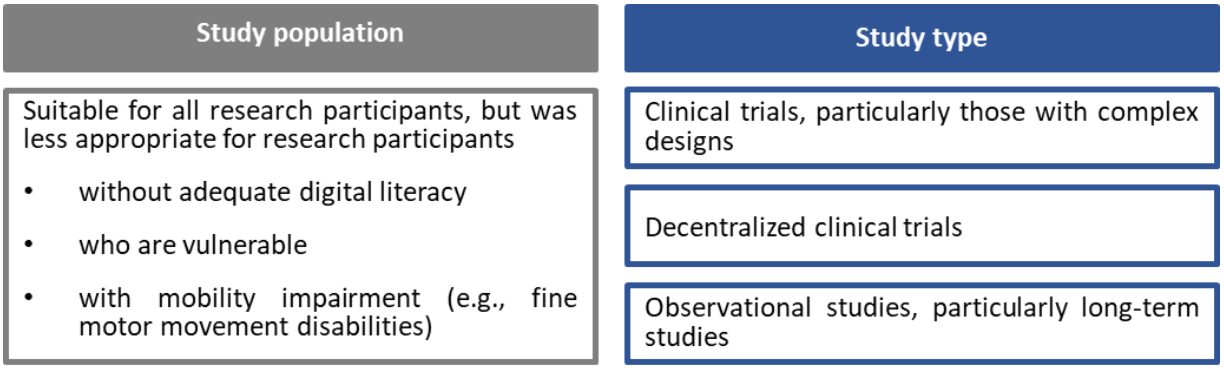

Figure 5. *Stakeholders' views on the use of eIC in clinical research*

Interviewees raised the point that research participants must not be excluded from a particular clinical research study due to a lack of digital literacy. Therefore, they advocated for research participants to always be offered the possibility to read and sign a paper-based IC instead of an eIC. It was considered important to promote participation, particularly for those with unmet medical needs, as participation in a clinical study may be the last opportunity for some research participants to improve their health-related condition.

The physicians and pharmaceutical industry representatives, who already have had experience with eIC, mentioned that they used eIC in different study populations and therapeutic areas. Moreover, one pharmaceutical industry representative indicated that eIC was rapidly being accepted by research participants.

4.2.4 IMPACT ON CLINICAL RESEARCH STUDIES

a) Recruitment, dropout, and understanding

The perspectives of the interviewees regarding the impact that eIC could have on recruitment, dropout, and understanding are presented in Table 5.

Table 5. *Perspectives of stakeholders on the potential impact of eIC on recruitment, dropout, and understanding*

Recruitment	Dropout	Understanding
Positive impact	**Positive impact**	**Positive impact**
• Would be facilitated, especially for rare diseases	• Frequent updates could keep participants interested	• Interactive tools could facilitate comprehension and retention of knowledge
• More diverse population	• Participants could have a better understanding of what to expect	• Implementation of metrics could support physicians when explaining the research study
Negative impact	**Negative impact**	**Negative impact**
• Could widen the digital gap	• Electronic systems could be too complicated	• Information overload
• Would be difficult to establish a relationship of trust	• Participants may stop participating due to less personal contact	

Various interviewees were of the opinion that the implementation of eIC in clinical research studies could have both a positive and a negative impact on the recruitment and dropout of research participants. However, one pharmaceutical industry representative, already having had experience with eIC, noted that the impact on recruitment and dropout is difficult, or time-consuming, to quantify. Similarly, interviewees expected that eIC could have both a positive and negative impact on the understanding of research information. Nevertheless, two EC members and one physician were of the opinion that eIC would not impact understanding.

> "*I do not see the difference of understanding the information between electronic informed consent and the paper-based informed consent form. If there are problems to understand, they will occur in both formats.*" (13, EC member)

Interviewees posed the notion that the use of eIC could have a negative influence on the contact between the physician and research participants, and this could adversely affect recruitment and drop-out. They emphasized that an electronic platform cannot replace the personal interaction between the physician and the research participant. However, they mentioned that eIC can supplement the oral explanation given by the physician. Moreover, it was mentioned that the decision of a research participant to take part in a study is sometimes based upon a relationship of trust that is developed with the physician, which may be more easily established through personal contact.

"*The process of informing the participant should be more or less the same as with paper-based.*" (2, regulator representative)

b) Documentation and storage

All stakeholder groups agreed that using eIC will probably improve the process of signing and dating IC. eIC has the potential to disable errors, such as recording an incorrect date, and therefore, it will support quality assurance. Interviewees also believed that it is easy to securely store eIC, for example by enabling password protection. However, interviewees across stakeholder groups identified that the primary challenge of implementing eIC is the protection of the research participants' privacy during storage. It was mentioned that eIC platforms need to be adequately secure in order to avoid confidentiality infringements. Moreover, one regulator representative thought that European servers should be used to store the data, preferably in the country where the data is collected and used.

Regarding inspections, the regulator representatives stated that they must be able to track who has handled the data. In addition, they would thoroughly investigate the eIC platform during inspections in order to assess if it could damage the rights of the research participants. To end, they mentioned that they will require proof that the eIC will be accessible for at least 25 years, as is stated in the CTR.

4.2.5 IMPACT REVIEW PROCESSES

EC members and regulator representatives believed that the use of eIC platforms may slow down their processes of reviewing study protocols initially, particularly when eIC platforms become widely employed. They mentioned that they would have to consider additional aspects compared to those of the paper-based IC. For example, proof regarding compliance of electronic signatures with the applicable legislation, or a statement confirming face-to-face contact between the participant and physician, would be required. However, EC members and regulator representatives stated that if a robust platform, checked by an independent party, was used, then the ECs could immediately trust the platform, and this would result in an accelerated assessment.

"*One unique platform will streamline the assessment. If the platform is already validated and accepted by regulators then it would be quite easy.*" (3, regulator representative)

Nevertheless, it was strongly corroborated that guidelines would be useful to determine the quality criteria for an eIC platform and this would facilitate the reviewing process.

Two EC members, who already had developed experience with reviewing an eIC platform, reported different views. The first EC member argued that an eIC platform was challenging to review and control, whereas the second EC member did not experience major differences from the review process of a paper-based IC. Several pharmaceutical industry representatives acknowledged that it is not clear how they should submit eIC to ECs and whether the ECs would like to have access to the platform. In addition, one EC member mentioned that ECs in several countries are independent, and this could have a negative impact on a harmonized review process.

> "*A more centralized approach regarding ethics committees would be better. Then you could have a library with approved electronic informed consent material and that would be very helpful.*" (7, EC member)

4.2.6 HOSTING AN ELECTRONIC INFORMED CONSENT PLATFORM

Interviewees who have had previous practical experience with eIC platforms, used those offered by private vendors or academic institutions. The other interviewees reported differing opinions on who should be responsible for hosting an eIC platform; however, it was widely agreed that it should not be the sponsor. Three possibilities for eIC platform hosts arose out of their responses. The first was that a regulatory body should host the platform, preferably at a European level.

> "*There would be variations of the platform in each country, unless it is agreed at the European level. It could be hosted by a centralized body such as the European Medicines Agency and you could have a single identical platform in all countries.*" (3, regulator representative)

The second possibility was that an eIC platform be hosted by the principal investigator, as he or she was already responsible for managing the paper-based IC documents. Nevertheless, the investigator would need to have a ready-to-use platform to ease the administrative burden. The third possibility was that a trusted center, controlled by a regulatory body, hosts the platform. It was considered crucial that it be a center that would hold the participants' trust. Moreover, managing an eIC platform goes hand in hand with its financing. For all of the abovementioned possibilities, it was suggested that the hosting of an eIC platform be financed independently.

4.2.7 TOWARDS HARMONIZATION

Several interviewees advocated for the development of a European eIC platform. It was mentioned that when a research site conducts multiple clinical research studies at the same time, it would be more user-friendly to use a single platform. Moreover, one pharmaceutical industry representative believed that eIC platforms created by commercial vendors will never be accepted by all the clinical research stakeholders. Also, it would be very challenging for physicians if there were numerous eIC platforms.

> "*When physicians would participate in five clinical trials at the same moment, they would have to adjust themselves to these different platforms.*" (9, EC member)

Nevertheless, the interviewees raised several challenges related to this harmonized European approach. First, the legal requirements between Member States differ. For example, some Member States still require a wet-ink signature for study participation. Second, the development of IT in the various research sites or hospitals within each Member State differs. Interviewees noted that eIC could be integrated into established systems such as e-Health. Nevertheless, these systems may not always support the integration of eIC. Third, future participants, as well as other stakeholders involved in clinical research, need to accept this single European eIC platform. For example, sponsors may prefer to retain their own method of collecting IC or have already invested in eIC platforms.

Moreover, pharmaceutical industry representatives stressed the need for a European guidance for the implementation and use of eIC in clinical research. They were convinced that one of the reasons holding back the adoption of eIC is the lack of such a guidance. This guidance could provide a framework for harmonization across European Member States.

> "*We are conducting trials in 20 European countries. It is not feasible to have different electronic informed consent systems for these countries.*" (5, pharmaceutical industry representative)

5 DISCUSSION

This manuscript presents the opinions of various stakeholders regarding the potential advantages and challenges of eIC. Whereas previous research has mostly focused on investigating potential opportunities of eIC or assessing participants' understanding when using eIC, this study has taken a more precise approach on how an eIC platform can be effectively personalized and how the interaction over time can be guaranteed. Therefore, this study adds to the scarce empirical literature on

personalization and the longitudinal interaction in the context of eIC. In addition, this study identified interviewees' divergent views with regard to the hosting party of an eIC platform and the impact of eIC on the clinical research process. The various key findings that emerged from this study need to be considered when designing or implementing eIC in clinical research.

5.1 Enhancing the informed consent experience

Several interviewees highlighted that paper-based IC documents are difficult to understand due to the scientific and legal nature of the information and emphasized the importance to present information in an understandable and engaging manner to research participants. eIC can assist in this by making use of video, audio, or graphics to convey information to participants, which is considered more effective than written text (151). Nevertheless, a small number of interviewees were convinced that eIC would not influence the understanding of research participants compared to that of a paper-based IC. Similarly, other research has shown that eIC does not necessarily result in the enhanced understanding of research participants (47). Therefore, in addition to multimedia interventions, more needs to be achieved in order to support a more readily understandable eIC. Efforts should be directed to involve patients in the design of eIC. For example, Ramos et al. involved patients to design and test an eIC interface. In this way, patients can provide feedback on several aspects of this interface, such as the ease of use or the presentation of information (126). Moreover, a widely accessible library could be established that will store multimedia elements which present information, not related to a specific study (154). This library could be used for designing eIC in a participant-friendly way. Interviewees agreed that eIC could be used in a wide range of clinical research studies. However, research participants should always be given the choice between eIC and a paper-based IC. If eIC would be used remotely, participants can prefer a paper-based IC because they lack digital literacy or do not have access to electronic devices. However, offering both eIC and paper-based IC may increase the workload of the researchers or the sponsor.

5.2 Personal contact

Personal contact between the research participant and physician was valued highly. According to some interviewees, the decision of a potential participant to partake in a research study relies on a relationship of trust developed with the physician, which is in line with the available literature (155, 156). Dellson et al. showed that the decision of patients to participate in a clinical trial is guided by the doctor-patient relationship and the trust that they have in the physician rather than by the information provided in the IC document (155). Interviewees were of the opinion that using eIC would negatively impact personal contact. However, a review found that the implementation of digital health

technologies, such as eIC, may result in increased personal contact between the research participant and physician. If eIC would result in a more efficient way of working for physicians, they have more time to inform participants and to answer their questions (157).

5.3 AN INTERACTIVE CONSENT INTERFACE

Interviewees widely agreed that eIC can support the establishment of long-term interactions between the research team and research participants. Some interviewees suggested that these long-term interactions could be used to continuously educate participants. For example, the study requirements, that participants need to comply with, may be emphasized by having repeated IC discussions (158). The strengthening of continuous communication with participants during a research study may have a positive impact on participant compliance with these requirements (142). Additionally, interviewees mentioned that an eIC platform can also be used to provide generalized or individual results related to the research study. However, concerns were reported about how the results would be interpreted by lay individuals. Therefore, when using eIC, it is advisable to involve patient representatives who are able to develop or review the information that will be returned to research participants (159).

In addition, some interviewees indicated that a personalized eIC platform could empower research participants. Nevertheless, several obstacles related to personalization were discussed. For example, it was acknowledged that caution should be taken to not overwhelm research participants. Research has found that overloading research participants with information can impact their capabilities regarding making healthcare decisions (160). Therefore, the structure for how information is presented is important; for example, switching between brief and detailed content. Information may be offered in layers: a first layer offering essential information, followed by a second layer that allows research participants to access additional information if preferred (154). An interactive eIC system allows research participants to indicate how they would like to be involved. However, interviewees indicated that not all research participants are able to set their own preferences. Some research participants may not have the capacity to make sound health-related decisions as their health literacy is limited (161). Moreover, when too much responsibility is given to research participants, who may be facing other challenges, there is a risk that they feel too pressured to adapt an eIC platform based on their preferences.

5.4 A HARMONIZED ELECTRONIC INFORMED CONSENT APPROACH ACROSS EUROPEAN MEMBER STATES

Interviewees supported harmonization across European Member States and beyond regarding eIC. However, they indicated that establishing a harmonized approach would be challenging. For example, some Member States, such as Hungary, are reluctant to use eIC in clinical trials (162). Several interviewees showed a preference for developing and using a European eIC platform. This would benefit EC members and regulator representatives when assessing study protocols or conducting inspections. Nevertheless, there were divergent views about who should manage this platform. Interviewees expressed confidence in regulatory bodies, physicians, and trusted centers to perform the role of hosting party. Moreover, the management and financing of a European eIC platform cannot be considered separately. For example, there are costs associated with maintaining the system as well as with the personnel responsible for controlling the access of the different user groups.

5.5 STUDY LIMITATIONS

Although this qualitative study provides valuable information for the implementation of eIC, it has some limitations. Qualitative research does not allow for the generalization of results. Moreover, a self-selection bias may have been introduced because it is possible that participants who are more interested in eIC agreed to take part in this study. It is also important to recognize that the majority of interviewees did not have practical experience with eIC, and therefore, some questions remained theoretical. However, in the event that eIC was implemented in the daily practice of the stakeholders, these views may change. Nevertheless, this qualitative study identified the perception of interviewees without practical experience regarding eIC.

6 CONCLUSIONS

This qualitative study indicates that stakeholders expect several advantages to a personalized eIC platform that enables long-term contact between researchers and research participants. However, for effective and widespread eIC implementation, several challenges need to be overcome. Attention needs to be paid to the preferences of the research participants regarding contact with the research team and the choice between eIC or a paper-based IC. Moreover, interviewees expressed the wish to establish a harmonized eIC approach across the European Member States.

CHAPTER 3:
CLINICAL RESEARCH IN NEONATES: REDESIGNING THE INFORMED CONSENT PROCESS IN THE DIGITAL ERA

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1 ABSTRACT

Background: Currently, many initiatives are devoted to optimizing informed consent for participation in clinical research. Due to the digital transformation in healthcare, a shift toward electronic informed consent (eIC) has been fostered. However, empirical evidence on how to implement eIC in clinical research involving neonates is lacking.

Methods: Semi-structured interviews were conducted with 31 health care professionals active in Belgium or the Netherlands. All health care professionals had experience in conducting clinical research involving neonates. Interviews were audio-recorded, transcribed, and analyzed using the framework method.

Results: Interviewees generally supported the use of eIC in clinical research involving neonates. For example, eIC could enable parents to receive study feedback via the eIC system. Requirements were expressed for parental involvement to decide on which feedback would be appropriate to return. Moreover, experts specialized in presenting information and designing electronic systems should be involved. Broad consensus among health care professionals indicates that the face-to-face-interaction between parents and the research team is vital to establish a relationship of trust. Therefore, it is necessary that the use of eIC runs alongside personal interactions with the parents. Concerns were raised about the accessibility of eIC to parents. For this reason, it was suggested that parents should always be given the possibility to read and sign a paper-based informed consent form or to use eIC.

Conclusions: Health care professionals' views indicate that the use of eIC in clinical research with neonates may offer various opportunities. Further development and implementation will require a multi-stakeholder approach.

2 INTRODUCTION

Conducting clinical research in pediatric patients has been proven challenging due to economic, clinical, and ethical considerations (163). As a result, these patients may receive medicines outside their marketing authorization, considering their limited clinical evidence pertaining to the efficacy and safety (164, 165). Over the past years, it has been widely acknowledged that medicinal development for pediatric populations is needed to protect their welfare (163). In 2007, the Pediatric Regulation came into force in the European Union, establishing a framework to support research and development of medicines for pediatric therapeutic needs (166). According to an ex-post evaluation, this Regulation has boosted the conduct of pediatric clinical research (167). In addition, the International Neonatal Consortium (INC) was established in 2015 under a grant from the U.S. Food and Drug Administration (FDA) (168). The INC, a global collaboration of key stakeholders such as regulatory agencies, academic researchers, neonatal advocacy groups, pharmaceutical companies, and neonatal nurses, aims to foster the therapeutic toolbox for neonates (169). Unique challenges are related to the conduct of neonatal research. For example, parental decision-making may be impaired when urgently enrolling a neonate with life-threatening conditions in a research study. Therefore, parents could be approached in the antenatal period to convey information on postnatal study enrolment (170).

From an ethical point of view, each participant involved in clinical research needs to be adequately informed during the informed consent (IC) process about what the research study entails. This process is vital to safeguard the participants' well-being, health, and rights (3). When research is conducted in neonates, the IC process needs to inform their legally designated representative(s), often the parents, enabling them to decide on participation in the best interest of their child (6). In the Netherlands, both parents need to sign the IC (171). Similarly, both parents need to sign the IC in the United States, except if the institutional review board considers the permission of only parent sufficient. This may concern clinical investigations that do not involve greater than minimal risk or minimal risk with the prospect of direct benefit for the child (172). However, conflicting approaches to Belgian legal instruments such as the Civil Code and the Law of 7 May 2004 on experiments on human beings emerged (173, 174). Based upon article 373 of the Civil Code, some suggest that only one parent has to provide IC if both parents are living together. According to the Law of 7 May 2004, IC needs to be obtained from both parents, on the condition that parents have joint custody of their child. As a golden mean, some advise to obtain the signature of at least one parent at the time of recruitment and the written authorization of the other parent along the conduct of the study (175). In the United Kingdom, the IC from only one parent is required (176).

However, obtaining IC from parents whose neonate is critically ill may be challenging (165, 177, 178). For example, parents can feel emotionally distressed or the mother can experience interfering medical conditions such as preeclampsia or post-anesthesia (165, 177, 179). Parents are often overwhelmed and may have a poor understanding of the study-related information when being under time pressure (178, 180). As a result, they may feel incapable to decide about their neonate's participation in a research study (180). Key points suggested to improve the IC process are antenatal awareness and discussion, training of those seeking IC, continuing two-way communication, and clear and well-regulated information (180-182). Related to these key points, advances in technology have resulted in new opportunities to enhance the paper-based IC process (47). According to the FDA, electronic informed consent (eIC) is defined as "*The use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent*" (49). eIC offers the possibility to present information in a more informative and engaging way by using multimedia tools (151). Moreover, an eIC system, allowing parents to manage their eIC, could enable researchers to remain in contact with parents over time. For example, study results can be provided to the parents on regular basis, parents can revisit their consent decision or repeated IC discussions can be set up. Additionally, an eIC system could be tailored to the parents' needs and to the research endeavor (61, 64). Nevertheless, stakeholders, such as research participants and researchers, voiced concerns about access of eIC to specific population groups and data privacy (151).

Currently, paper-based IC is still widely used in neonatal research. Less attention has been given to the implementation or use of eIC in clinical research involving neonates (183, 184). For this reason, this study aims to investigate health care professionals' (HCPs) perspectives, as one of the relevant group of stakeholders, on the current paper-based IC process and how this process could be improved by using eIC. Moreover, this study investigates how an eIC system should be designed to enable responsible implementation in clinical research in neonates. The following research questions are addressed in this study:

1. What are HCPs' views on the current IC process?
2. What are potential advantages and disadvantages of using an eIC system in clinical research involving neonates?

3 METHODS

3.1 PARTICIPANT SELECTION AND RECRUITMENT

Semi-structured interviews were conducted with HCPs (i.e., physicians and nurses) from both university and non-university hospitals located in Belgium and the Netherlands. Participants were selected through a combination of purposive sampling and snowballing. Purposive sampling implies the identification and selection of potential participants who are able to provide insights into the topic of interest (185). Additionally, snowballing sampling was used whereby potential recruits were identified from suggestions made by existing interviewees. Participants fulfilled the inclusion criteria when they were experienced in seeking parental (electronic) IC for a neonate's participation in clinical research, were fluent in English or Dutch, and were active in Belgium or the Netherlands. An invitation mail was sent to suitable participants, including the IC of the interview study and the interview guide (Appendix G). All participants provided IC prior to participation in this study. Participants were recruited until data saturation was reached.

3.2 CONDUCT

An interview guide was derived based on the research questions and a systematic literature review (151). At the time of conducting this review, no empirical literature was available with regard to the use of eIC in neonatal research. Therefore, it needs to be investigated how an eIC system can be effectively adapted to parents' and HCPs' needs and how ongoing communication with parents can be established during and after a research study (151). The interview guide was piloted in two interviews and consisted of questions related to the IC process and specifically, the use of paper-based IC forms (ICFs) and eIC. The pilot interviews, conducted with HCPs, were not included in the qualitative analysis. Moreover, open discussion was encouraged to gain an in-depth understanding of interviewees' perspectives. All interviewees received the interview guide in advance in order to prepare themselves for the interview. Interviews were conducted via teleconference from October 2020 until January 2021. Interviews were 30–60 min long. At the start of each semi-structured interview, an electronic slideshow was used to introduce the interviewer, the aim of the study, and to provide the definition of eIC, as issued by the FDA (49). This definition was used to inform interviewees that both conveying information and obtaining parents' signature occur via electronic means when using eIC. Interviews with Belgian and Dutch HCPs were conducted by two researchers (BC and FV, respectively) and were supervised by another researcher (EDS). All interviews were conducted in Dutch and were audio-recorded. Moreover, Dutch quotes were translated to English upon inclusion in the manuscript.

3.3 Analysis

The qualitative data analysis utilized a thematic analysis framework (153). Researchers (BC and FV) immersed themselves in the data by transcribing the interviews, reading the transcripts, and re-listening to the audio-recordings. The first two transcripts were coded independently by three researchers (BC, EDS, and FV) and were subsequently compared. Interviews were coded deductively based upon themes of the interview guide. Additionally, inductive codes were created when critically observing the data. Deductive and inductive codes were grouped into broader categories in order to create a coding tree using NVivo software (Appendix H). This coding tree was then applied independently to the other transcripts by two researchers (EDS and FV or BC). The coded data were compared and were charted in a framework matrix. Hereafter, the data obtained were interpreted, outcomes were described, and quotes of individual interviewees were added for further clarification.

4 Results

In total, 31 interviews were conducted. An approximately equal number of HCPs active in Belgium and the Netherlands took part in this qualitative study (Table 6). Results of the interviews are structured according to the categories identified during analysis: involvement of parents during the IC process, current paper-based IC process, and eIC process.

Table 6. *Descriptive characteristics of the interviewees*

Characteristics	Number of interviewees
Country	
Belgium	16
The Netherlands	15
Stakeholder group	
Neonatologist	25
Pediatrician	3
Study nurse	3

4.1 Involvement of parents during the informed consent process

Generally, HCPs asserted that parents are involved during the IC process by discussing the study information with the HCP.

"*It is marvelous how parents, whose neonate is fragile, are willing to participate in a research study.*" (HCP-BE 4)

Nevertheless, according to the majority of HCPs, some parents make the decision for their neonate to partake in a study based on their relationship of trust with the HCP rather than deliberative weighing of the study information. It was indicated that parents' involvement in the IC process is negatively influenced by a low socioeconomic status and an inadequate understanding of study information. Moreover, the majority of HCPs believed that the timing of seeking IC is not optimal. Distressed and vulnerable parents, who are already overloaded with questions and fear regarding their child's health, may not always have the capacity to process study information. Therefore, HCPs aim to focus on antenatal counseling to facilitate an informed decision, in particular when women have a high risk of premature birth. Even then, seeking IC can be overwhelming to parents.

"*Parents are often shocked by the premature birth of their child, next to a medical problem for which the child has to be treated."* (HCP-BE 12)

From an ethical perspective, Belgian HCPs consider it of utmost importance that both parents sign the ICF. It was raised that collecting parents' signatures is the best way to ensure dual parental permission for their neonate to participate in clinical research. However, almost all HCPs argued that gathering both signatures is often practically challenging. For example, when fathers need to resume work after their paternity leave.

"*If it concerns a research study somewhat later in the disease process, we experience that fathers already go back to work and therefore, it is challenging to obtain their signature.*" (HCP-NL 2)

It was considered essential that HCPs convey information pertaining to a research study to both parents, in particular if it concerns an interventional study. An interventional study is associated with various uncertainties with regard to the benefits and the long-term risks. Therefore, it is of great importance that both parents are adequately informed by the HCP to enable a well-informed decision on their neonate's study participation. One HCP believed that if parents would sign the IC separately, they would be less influenced by each other's decision. Nevertheless, HCPs took it for granted that both parents act in their child's best interest.

4.2 CURRENT PAPER-BASED INFORMED CONSENT PROCESS

Overall, HCPs considered the IC process as a valuable approach of informing parents about a research study. The majority of interviewees recognized that the face-to-face contact between parents and the responsible HCP is vital to establish a relationship that involves trust. Some HCPs voiced that the decision to partake in a research study is based upon the oral explanation of study information provided by the HCP rather than by thoroughly reading the paper-based ICF.

> "*When orally explaining the study to parents, I am able to personalize the information based on parents' needs.*" (HCP-NL 4)

Nevertheless, concerns were voiced that parents may be subjected to undue pressure to freely decide on their neonate's study participation. Because the responsible HCPs are often the researchers, their roles are conflated. Additionally, HCPs are able to determine from nonverbal language whether parents are adequately informed and are able to provide truly IC. If parents would have additional questions, HCPs can immediately answer these during the face-to-face contact.

The majority of HCPs agreed that the written, paper-based ICF contains all study details. For this reason, it enables parents to review study information on their own pace. Nevertheless, it was argued that ICFs are very long and scientific and legal in nature and, therefore, often incomprehensible.

> "*I notice that some informed consent forms are very extensive. I experience that parents often do not read the full document.*" (HCP-BE 3)

Another challenge raised by HCPs is that a paper-based ICF often gives rise to improper storage and documentation, such as signing incorrect IC versions. Moreover, ICFs need to be manually scanned into the neonates' electronic health record. In the end, parents often need to be recontacted to provide or to ask for further consent, due to new research requirements, and this is considered an administrative burden on the research team. One HCP raised the point that when parents are recontacted after finishing the research study, some do not remember that their child took part in the study.

4.3 ELECTRONIC INFORMED CONSENT PROCESS

4.3.1 POTENTIAL ADVANTAGES AND DISADVANTAGES

HCPs agreed that an eIC system could inform parents in an interactive way. For example, a question and answer session could be implemented to assess parents' level of understanding. Moreover, the use of multimedia was considered a distinct benefit to convey information. By implementing video or graphics, information can be made visually attractive. HPCs believed that an eIC system could support data integrity by guaranteeing that eIC is correctly managed. For example, an audit trail could be integrated to log who performed a certain action and when. In addition, it was believed that the data entered in the eIC system could be automatically exchanged with the electronic health record, and thus, adequately stored.

Some HCPs thought that the use of eIC would result in less personal interaction with parents. Therefore, it was raised that the eIC process must be a combination of personal contact and electronically reviewing study information and signing the eIC. Some HCPs highlighted that remotely signing eIC could facilitate obtaining both parents' signatures. Moreover, telemedicine technology could be integrated, enabling to remotely video conference with parents.

> "*Personal contact helps to explain the study details and the value the study may have for the neonate.*" (HCP-NL 5)

Moreover, parents need to have the opportunity to ask questions related to the research study. Several HCPs remarked that parents could indicate, via the eIC system, that they have further questions. Based on the type of questions, HCPs could choose to answer these questions remotely or during a physical consultation. One HCP indicated that it would not be feasible to quickly respond when parents would be worried or if information would be unclear.

Generally, HCPs did not experience a major impact of the COVID-19 pandemic on the IC process. Several HCPs mentioned that they inform the parents about their neonate, who receives inpatient neonatal care, on a daily basis. For this reason, there is no need to schedule additional contact moments with parents to discuss study information.

> "*Neonates who are involved in a research study are very often hospitalized in the neonatal intensive care unit so there is already face-to-face contact with the parents. As a result, COVID-19 did not have a negative impact on the informed consent process.*" (HCP-BE 9)

However, when the mother was infected with COVID-19, IC was obtained by phone or signed ICFs were stored in sealed plastic bags and processed several days after signing. In addition, only HCPs who took care of the neonate were allowed to visit the unit and, thus, other HCPs who conducted research were not able to have a face-to-face conversation with parents. Therefore, HCPs indicated that it would be beneficial to organize the IC process via an electronic device. Another HCP raised that eIC could facilitate providing information to parents, during and after the COVID-19 pandemic. It was believed that the pandemic has driven fundamental change in healthcare delivery.

> "*Before the COVID-19 pandemic, the use of telehealth was not common in practice due to several barriers and now it turns out that it is widely adopted. It will be the same with electronic informed consent.*" (HCP-NL 13)

Concerns were raised about the accessibility of eIC to parents. One HCP mentioned that an unfavorable socioeconomic environment of the pregnant mother is an important determinant for premature delivery. As a result, some women who are admitted to the neonatal intensive care unit will lack digital literacy.

> "*It is important that parents who do not have access to the internet are also able to let their child participate in a research study.*" (HCP-BE 16)

Therefore, HCPs believed that alternative solutions need to be foreseen, such as a paper-based ICF or electronic devices which can be offered to parents to review study information. Moreover, concerns were reported about how eIC should be submitted to the ethics committees (ECs).

4.3.2 ACCESSIBILITY TO AN ELECTRONIC INFORMED CONSENT SYSTEM

HCPs were asked how long an eIC system should be available to parents. Their key concerns and needs with regard to the accessibility to an eIC system included the following:

- If the eIC system is used only to inform parents and to obtain their consent, it should be accessible until the final analysis of research data. If the system is also used to facilitate the establishment of a long-term interaction with parents (e.g., to provide results), it should be longer accessible.
- The accessibility depends on the type of research study. For example, if it concerns a study with a long follow-up period, the eIC system should be longer accessible in comparison with a study without follow-up.

- There should be a contact point in case parents would have questions after the end of the research study.
- If maintenance of the eIC system is too costly, parents should have the option to download data and store these data themselves.
- Children have the right to know in which study they have taken part. Therefore, they should have the possibility to retrieve information about the study and the study outcomes. For example, if a subject has medical issues several years after study participation, it can be valuable to access the eIC system to refresh knowledge about the study.

Additionally, some HCPs mentioned that it would be valuable to understand the frequency parents, or the study subjects themselves, access the eIC system after participation in the research study.

4.3.3 INTERACTIVE INFORMED CONSENT

a) Long-term interaction

As reported by HCPs, an eIC system could facilitate maintaining contact with parents during or after the research study. It was considered a great opportunity to provide feedback on the study, such as study results, via an electronic device. Establishing a longitudinal interaction between parents and the study team may benefit transparent communication. According to HCPs' experiences, parents are willing to receive the general study results as well as the individual results of their neonate. One HCP raised that disclosing results is still not a common practice, although parents have the right to receive these. It was also mentioned that individual results related to a neonate should be conveyed during a clinical consultation, in particular if it concerns sensitive information.

Many HCPs indicated that the principal investigator should, together with the EC, decide which results can be shared. Moreover, it was considered important to involve parent representatives to discuss which information may be relevant and appropriate to share during or after the research study. HCPs were convinced that information must be returned in lay language. It was also indicated that the use of an eIC system must not be at the expense of face-to-face conversations with parents to further explain the results.

> "*It is of utmost importance that parents think together with health care professionals and members of the ethics committee about which information can be returned. Moreover, feedback can be asked to parents on how the electronic informed consent system can be improved.*" (HCP-NL 11)

Because an eIC system could facilitate continued contact with parents, they can be easily recontacted if additional consent needs to be obtained due to unforeseen circumstances. Moreover, the system could enable parents to complete surveys during the course of the study. Parents may receive a pop-up alert indicating that new information is available or that surveys need to be completed.

b) A personalized interface

HCPs were of the opinion that a personalized interface is meaningful for both the parents and the HCPs. Interviewees were asked how they would personalize an eIC interface. Opportunities for adapting the interface to parents', study subjects', and HCPs' needs were identified (Table 7).

Table 7. *Overview of opportunities for a personalized eIC interface according to HCPs*

Parents could be able to:
• Choose the language in which they would like to review study information • Choose the format in which they would like to review study information, e.g., visuals, graphics, text only • Access additional information if preferred. For example, hyperlinks to official websites may be implemented. • Receive a copy of eIC, e.g., by email • Set preferences on how they wish to communicate with HCPs. For example, parents may be able to indicate if they would like to discuss study information with the HCP in person or remotely. • Set preferences to establish a long-term interaction • Complete a question and answer session to assess their comprehension. Parents can be redirected to information related to a specific topic when they have answered incorrectly.
HCPs could be able to:
• Check if parents read the study information
Study subjects could be able to:
• Have an overview of clinical studies in which they have previously taken part

Few HCPs questioned whether information could be adapted to parents' education level. Nevertheless, concerns were raised about the ethical and practical applicability. Parents in the neonatal intensive care unit may experience psychological and emotional distress. Therefore, some HCPs advised to develop an eIC system including user-friendly information.

> "*Not every woman who has given birth will be motivated to use electronic informed consent and to review complex information.*" (HCP-NL 7)

For this reason, some HCPs recommended to include diverse experts specialized in presenting information and designing interfaces.

It was widely agreed that all parents need to receive the same amount of information. Based upon their preferences, they can decide to access additional information. Parents could also be able to indicate preferences to establish a long-term interaction. For example, they could choose to receive study results, information about the study status, or updates to eIC via an electronic device.

> "*Some parents will not look back at the electronic informed consent system, while others are really interested. If they are informed about the progress of the study, it will improve study involvement.*" (HCP-BE 5)

4.3.4 IMPLEMENTATION AND HOSTING

Several HCPs mentioned that an eIC system should be compatible with various systems already integrated in the hospital infrastructure. Because hospitals may use different technologies, integration was considered challenging. Moreover, it was raised that the practical implementation of an eIC system would be an important factor to have a successful and well-used system. Therefore, relevant stakeholders should be involved to learn about their practical considerations regarding such a system. The majority of HCPs indicated that the study team should be responsible for hosting an eIC system. However, the end responsibility is with the principal investigator. Moreover, technical support should be offered when required. Some other HCPs believed that the hospital itself or an independent party must be responsible for hosting the system. It was also indicated that it would be better to have a European initiative.

> "*It would be better to have a European approach. In this way, there is no need to use systems that work differently, especially when multicentric studies are conducted.*" (HCP-BE 8)

5 DISCUSSION

This qualitative study aimed to assess the opinions of Belgian and Dutch HCPs involved in clinical research in neonates with regard to the current paper-based IC process and a potential shift to eIC. Belgium has, across European countries, one of the highest number of clinical trials per inhabitant (186, 187). Also in the Netherlands many clinical trial applications are submitted to the relevant regulatory authorities yearly, especially in comparison with its neighboring country Germany (187). Generally, Belgian and Dutch HCPs were satisfied with the current paper-based IC process to inform

participants about several aspects of a research study. Drawbacks were related to the complex terminology used in an ICF and documentation and storage challenges. Potential advantages of eIC, suggested by HCPs, included the possibility to use multimedia to convey study information, the facilitation of data integrity, and the exchange of data with the electronic health record. Moreover, an interactive eIC system, enabling a personalized approach and establishing longitudinal interactions, was valued highly by the HCPs. However, some HCPs were concerned about the accessibility of eIC to parents and the impact of eIC on the personal interaction with parents.

5.1 Implementation of electronic informed consent

Only one interviewed HCP had gathered practical experience with eIC. The question may raise which challenges hinder the widespread adoption of eIC in clinical research involving neonates. Next to these reported by HCPs, such as the use of eIC by parents who lack digital literacy, other challenges could be in place. For example, compliance with national requirements could be challenging. In the Netherlands, the Medical Research Involving Human Subjects Act states that a written, dated, and signed IC is needed to participate in scientific research (188). This Act is currently under revision to include the use of electronic signatures, which is not yet allowed (149). On a Belgian level, a guidance related to the use of eIC in interventional clinical trials was recently issued (148). The creation of this guidance was coordinated by the Clinical Trial College, an independent body within the Federal Public Service Health, Food Chain Safety and Environment, and developed in collaboration with representatives of the Belgian Association of Research Ethics Committees, the Belgian Association of the Innovative (Bio)pharmaceutical Industry, and patient organizations (189). This guidance provides a framework when using eIC in interventional clinical trials. For example, the research subject should always have the choice between signing a paper-based ICF or signing electronically (148). Another challenge could be related to the compatibility of eIC systems to interface with software already implemented in the research sites. Resources must be invested to strive for interoperability, which may be costly for a site. Interoperability allows two or more systems to electronically exchange data, and is considered essential for digital innovations for future medicine (190).

5.2 Parental involvement

Interviewees widely agreed that parents prefer to receive general results related to the research study and individual results relevant to their neonate, which is in line with the available literature. Greenberg et al. found that parents appreciate the return of results of the study in which their child has taken part (191). According to interviewed HCPs, parents can be involved to decide on relevant and appropriate information to be shared via an eIC system. The European Foundation for the Care of

Newborn Infants (EFCNI) recommends to involve parent representatives during the research process to learn from their experiences related to a specific disease or service. The EFCNI strives to collaborate with parent representatives in various, consecutive phases of the research process, from study protocol development until the dissemination of research results (192). In addition, the INC aims to inform clinical research by collecting the perspectives of parents who have experience with participation of their neonate in a research study (193). Some HCPs were of the opinion that user-friendly information should be used to inform parents. Therefore, it is essential to involve parents, next to experts in human-computer interaction, when setting up an eIC system. For example, it is important that the information will not overwhelm already traumatized parents whose neonate is fragile. In addition, HCPs believed that the research site needs to foresee electronic devices which parents can use to review study information and to sign the IC electronically. The use of digital technologies could result in the creation of digital vulnerable groups, also called the digital divide (194). Therefore, it is crucial that the usability and the user-friendliness are adequately assessed and improved by involving parents in the design of eIC, considering their education level or health literacy (195).

5.3 A DYNAMIC SYSTEM

HCPs mentioned that antenatal counseling is of great value to support an informed decision. Golec et al. confirm that strengthening continuous communication with parents is important. It would be optimal to start the IC process early on and communicate until after the intervention (170). Another study, researching parents' views of whom their child has taken part in longitudinal studies, found that parents would like to regularly receive information during the conduct of the study (196). HCPs expect that an eIC system could facilitate ongoing communication with parents during or after the research study. An eIC system, enabling dynamic interactions over time, can update parents about the outcomes of the study or can invite them for a clinical consultation (61). In addition, it is considered important that parents are continuously educated about the study details and their rights (170). When long-term contact is established between parents and the research team via an eIC system, it could help to remind parents of their child's participation in a research study, which may be forgotten (197). As formulated by the interviewed HCPs, it could be up to the parents to indicate how they would like to receive information. The eIC interface should give parents sufficient control to adapt it based on their needs, while being cautious to avoid burdensome practices (29). HCPs indicated that the trusting relationship with parents is one of the main reasons to consent, which is in line with the available literature. For example, it was reported that information written in the ICF did not always support parents' understanding (198). Similarly, HCPs raised that IC documents are often difficult to understand, due to scientific and legal information. HCPs have a legal and ethical duty to convey the

necessary information to parents (3, 6). By using eIC, the same information needs to be provided to parents. However, this information can be provided by using various multimedia formats, as indicated by the interviewed HCPs. This finding was also observed in a systematic review. According to some research participants, multimedia could be more effective to convey research information in comparison to written text. Additionally, the use of simple, concise language and the implementation of a question and answer session were recommended to support parents' understanding (151).

5.4 The use of electronic informed consent during the COVID-19 pandemic

According to HCPs, eIC could be beneficial during the COVID-19 pandemic. For example, eIC decreases the risk of being exposed to the virus and the use of personal protective equipment that needs to be used when approaching COVID-19 infected parents in the course of the IC process (199). The Central Committee on Research Involving Human Subjects, a competent authority in the Netherlands, issued a guidance on conducting clinical research during restrictive measures due to the COVID-19 pandemic (200, 201). This guidance states that, if study medication is directly sent to research subjects' home, the subjects need to provide IC for the use of their personal information. IC can be provided orally and confirmed by mail (200). The Belgian guidance, published by the Federal Agency for Medicines and Health Products, mentions that "*Any validated and secure electronic system already used in the investigation for obtaining informed consent can be used as per usual practice and if in compliance with national legislation*", which is in line with the guidance issued by the European Medicines Agency (202, 203). Moreover, other countries issued guidance about the management of clinical trials during the COVID-19 pandemic. For example, Hungary explicitly states that the use of eIC is forbidden (162). The FDA guidance, on the 'Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency', refers to eIC as a valuable approach to obtain the IC of a hospitalized patient who is in isolation (204).

5.5 Strengths and limitations

To our knowledge, this study is the first seeking to investigate the perspectives of Belgian and Dutch HCPs with regard to eIC in clinical research involving neonates. A strength of our study is that interviewed HCPs were equally recruited from Belgium and the Netherlands. Interviews were conducted by two junior researchers (BC and FVE) but were supervised by another researcher (EDS) who had previous experience in conducting semi-structured interviews. To minimize variability between interviews, an interview guide was used. The design of this interview guide was informed by the conduct of a systematic literature review. Additionally, the trustworthiness of the interview study was enhanced by two researchers who independently coded all interviews.

Qualitative research does not aim to provide results with a universal validity, but rather to provide insights into HCPs' perspectives about (electronic) IC. Therefore, caution should be taken when generalizing results. Selection bias might have occurred because the majority of HCPs were contacted by using the research group's network. Moreover, it may be possible that HCPs who are more interested in eIC decided to participate in this interview study. Only 1 interviewed HCP did have experience with eIC. Other perspectives may arise if HCPs would use eIC in practice. However, we were able to gain insights in how stakeholders expect that eIC would influence the conduct of clinical research involving neonates.

5.6 Future perspectives

This qualitative study provides insights into HCPs' perspectives on the use of eIC in clinical research involving neonates. Future research should focus on investigating parents' views to better understand the value of eIC in a stressful situation. Furthermore, attention must be paid to how study information can be effectively communicated to parents. Participatory design can be used to involve parents throughout the design process of an eIC system to better understand their needs. By involving parents in the design, the system will be co-created and the potential for success will be more likely.

6 Conclusions

Overall, Belgian and Dutch HCPs were positive toward the implementation of eIC in clinical research involving neonates. Ideally, the eIC process should be a combination of face-to-face conversations with an HCP and electronically reviewing research information and providing consent. Moreover, opportunities for a personalized interface were identified, as well as HCPs' views and concerns regarding a longitudinal relationship with parents during and after a research study. However, the implementation of eIC requires further research and goes hand in hand with the involvement of parents themselves.

PART 2:
DEFINING ELECTRONIC INFORMED CONSENT REQUIREMENTS WITH RESEARCH PARTICIPANTS

CHAPTER 4:
CO-CREATION WITH RESEARCH PARTICIPANTS TO INFORM THE DESIGN OF ELECTRONIC INFORMED CONSENT

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Co-creation with research participants to inform the design of electronic informed consent

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1 ABSTRACT

Objective: This study aimed to provide recommendations for a personalized electronic informed consent interface that is adapted to research participants' needs and could enable a longitudinal interaction between the participants and the research team.

Methods: The co-creation process consisted of three co-creation workshops, one focus group discussion, and four semi-structured interviews. In total, 24 participants, who had taken part in four disparate clinical studies in Belgium, were involved. Descriptive statistics and qualitative content analysis were applied to analyze the survey data and audio-recordings.

Results: Varying perceptions on the type and amount of information described in an informed consent form were reported. Other findings were related to the structure and presentation of information, setting preferences for data sharing, and electronically signing new informed consent versions. Regarding the long-term interaction, most of the participants wanted to receive progress updates, including the results, of the study in which they had taken part. They proposed to receive a notification, preferably via email, in case new information is made available on the electronic informed consent interface.

Conclusions: To optimally support the design of an electronic informed consent interface, it is key to understand the research participants' needs. Study findings suggest that an electronic informed consent interface may be a promising technological application to interactively provide study-related information and to keep participants informed during and after the clinical study.

2 INTRODUCTION

The 'Global strategy on digital health 2020–2025', put forth by the World Health Organization, aims to facilitate the development and adoption of person-centric digital health technologies to promote citizen empowerment (205). In the context of health-related research, electronic informed consent (eIC) may empower participants, by informing them according to their needs, to make a well-grounded decision on whether or not to participate in a clinical study (206, 207). As described by the U.S. Food and Drug Administration, eIC refers to "*the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent*" (49). Moreover, eIC opens the opportunity to establish longitudinal communication between research participants and the research team (208). For example, participants could indicate which information they would like to receive during the course of the study (52, 75). In recent years, there has been increasing interest in eIC applications. In 2017, TransCelerate, a nonprofit organization which aims "*to collaborate across the global biopharmaceutical research and development community*", issued guidance to facilitate the implementation of eIC in clinical research (51, 70). Moreover, various for-profit and nonprofit organizations have developed or implemented such applications in clinical studies (76, 80, 208-210).

When developing technological applications such as eIC, it is of utmost importance to understand the end users' needs. Therefore, end users should be involved during the design process (211, 212). Participatory design, defined as "*a set of theories, practices and studies related to end users as full participants in activities leading to software and hardware computer products and computer-based activities*", is considered a useful approach in the development of technological applications (86, 90). Co-creation, a participatory design practice, refers to interactions between the end users and the researchers that aim to produce a mutually valued outcome, based upon a rich dialog. It has the potential to contribute to participant-centric technological applications by engaging participants in an innovation process (212, 213). By focusing on the creativity, needs, and concerns of end users, an application can be co-constructed to suit its context (214).

A systematic literature review and semi-structured interviews conducted with various stakeholders involved in clinical research, such as ethics committee members and investigators, revealed a general interest in eIC, as it allows for personalization of information and for ongoing communication with the research team (151, 207). Yet, to design such a personalized and long-term eIC interface, investigating research participants' opinions would add a significant value toward a participant-centric eIC design.

To this end, we used a co-creation process involving participants who had taken part in diverse clinical studies. The aim of this study was to co-create solutions regarding (i) how an eIC interface can be effectively personalized, based on the participants' needs and (ii) how such an interface can establish valuable longitudinal interactions between research participants and the research team.

3 METHODS

3.1 GENERAL STUDY DESIGN

To understand participants' views on how they would personalize the informed consent form (ICF) of the clinical study in which they had taken part and how they would establish a potential long-term interaction, co-creation workshops were conducted. Each participant involved in a co-creation workshop is considered an "*expert of his/her experience*" (212). By using tools for ideation and expression, participants are provided with an active role during the design process (212, 215). The tools used during our co-creation workshops enabled participants to individually reflect on their needs which were then collaboratively discussed. In addition, a focus group discussion, not using the tools for ideation and expression since no individual preparation was required, and semi-structured interviews were conducted to enrich the data generated during the workshops (216). The original, paper-based ICFs of the clinical study in which the participants had taken part guided the discussion related to personalization. In doing so, participants were asked to reflect on study-related information they were already familiar with.

3.2 PARTICIPANTS AND RECRUITMENT

Research participants were eligible to participate if they had taken part in a clinical study, ranging from a qualitative to an interventional design, and were at least 18 years old. Moreover, participants needed to be Dutch-speaking to allow for in-depth discussions during the co-creation workshops, focus group discussion, or semi-structured interviews. Participants were recruited by the research teams responsible for the clinical study. More concretely, recruitment was undertaken at Leuven, Belgium, by the KU Leuven Academic Center for General Practice, the KU Leuven Clinical Pharmacology and Pharmacotherapy unit, and the Center for Clinical Pharmacology at the University Hospitals Leuven. The recruiting parties provided an invitation letter to potential participants. Those who were interested in participating contacted the researcher (EDS). Informed consent (IC) was obtained from all participants prior to participation in the co-creation workshop, focus group discussion, or semi-structured interview. Afterward, the participants received a gift voucher. Recruitment continued until

theoretical saturation was achieved, meaning that no new insights were emerging during data analysis (217).

3.3 CONDUCT AND DATA COLLECTION

The co-creation workshops, focus group discussion, and semi-structured interviews took place between May and December 2021 and were conducted in Dutch via Microsoft Teams. The co-creation workshops and focus group discussion were about 3 h long whereas the semi-structured interviews lasted for 30–45 min. The conduct of these qualitative methods was moderated by the same researcher (EDS). In each focus group discussion and co-creation workshop, participants who had taken part in the same clinical study were involved. Moreover, all semi-structured interviews were conducted with participants involved in the same study. Prior to the co-creation workshop, focus group discussion, and semi-structured interview, participants received a survey by email. This survey aimed to sensitize the participants to the paper-based ICF of the clinical study in which they had taken part. By sensitizing the participants, we implicitly encouraged and motivated them to reflect on the content of the ICF in the light of their personal context (218). This survey included a five-point Likert scale to evaluate the importance of each topic (e.g., the course of the study, study procedures, and potential benefits and risks) mentioned in the ICF. Participants were asked to score the information on the following scale: not at all important—not important—neutral—important—very important. In addition, the survey comprised questions regarding the participants' demographics (i.e., age, gender, and highest education level) and regarding whether the participant felt adequately informed for participation in the clinical study. The completed survey was returned to the researcher in the days leading up to the conduct of the workshop, focus group discussion, or semi-structured interview. At the start of each interaction, the researcher introduced herself, described the aims of the study, and emphasized that participants should not be concerned with technical or legal limitations, or limitations related to the paper-based format when suggesting new ideas or solutions.

3.3.1 CO-CREATION WORKSHOPS

The co-creation workshops proceeded in two stages: the first stage focused on the personalization of the IC whereas the second stage focused on the long-term interaction between participants and the research team. In the days leading up to the workshop, participants were provided via email with the tools for ideation and expression, in the form of two worksheets (i.e., on personalization and on the long-term interaction). The worksheet related to personalization, used during the first stage of the workshop, included two questions for each topic mentioned in the ICF of the study in which the participants had taken part: (i) "*How would the informed consent form better suit your needs?*" and (ii)

"*Which additional information would you have required at the beginning or during the clinical study?*". During the workshops, participants were first asked to individually write their ideas or perspectives down, using the worksheet, after each topic described in the ICF. Subsequently, participants were prompted to share their ideas in group, which provided the opportunity to generate new ideas and to exchange experiences. As the paper-based ICFs discussed during the co-creation workshops were 12–27 pages long, the forms were divided into three or four parts. Hence, multiple iterations of the individual reflection and group discussions were performed. The second stage of the co-creation workshop focused on the long-term interaction between research participants and the research team. Using the second worksheet (Figure 6), participants were given an individual exercise to reflect on (i) the aspect(s) for which they would like to maintain contact with the research team during or after the clinical study, (ii) why they selected these aspects, and (iii) how they would integrate their suggestion(s) in an eIC interface. To clarify what a long-term interaction could entail, some suggestions, identified using the available literature, were provided in the worksheet (Figure 6) (151, 207). Participants were encouraged to come up with as many ideas as possible. Hereafter, their ideas were discussed in a group discussion. All group discussions were digitally audio-recorded.

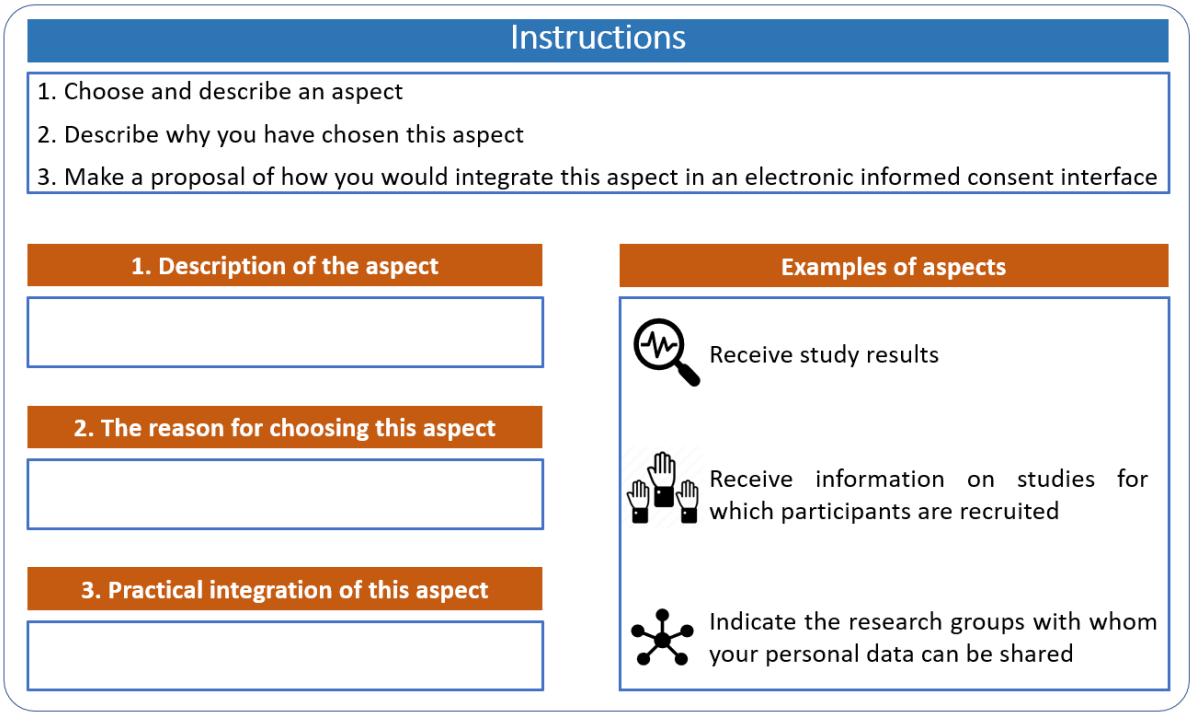

Figure 6. *Worksheet regarding the long-term interaction*

3.3.2 *Focus group discussion and semi-structured interviews*

Similarly, during the semi-structured interviews and the focus group discussion, participants were asked to reflect on how the ICF of the clinical study in which they had taken part could be adapted to their needs and how they would like to establish a long-term interaction. Hence, similar to the co-creation workshops, participants were asked the following questions about personalization: (i) "*How would the informed consent form better suit your needs?*" and (ii) "*Which additional information would you have required at the beginning or during the clinical study?*". Related to the long-term interaction, participants were asked to reflect on the tasks listed in the worksheet displayed in Figure 6. The ICFs discussed during the semi-structured interviews and the focus group discussion were those of qualitative studies and were two and nine pages long, respectively. The conduct of the semi-structured interviews was similar to the co-creation workshops, except for the group discussions. During the focus group discussion, participants did not make use of the worksheets as they did not individually prepare the tasks regarding personalization and the long-term interaction. The interviews and the focus group discussion were digitally audio-recorded.

3.4 Data analysis

The data were obtained from the answers to the survey and from the audio-recordings. Descriptive statistics were used to summarize participants' answers to the survey questions. The audio-recordings were analyzed according to the framework method (153). The researcher (EDS) familiarized herself with the data by conducting the co-creation workshops, the focus group discussion, and the semi-structured interviews, and by transcribing the audio-recordings verbatim. A combined deductive/inductive approach was used to code the first two transcripts. The worksheets related to personalization and the long-term interaction, as well as available research, informed the creation of deductive codes (207). Inductive codes were created based on observed patterns. Both deductive and inductive codes were grouped and subsequently, a preliminary coding tree was created (Appendix I). This coding tree was applied to the other transcripts by using NVivo (released in March 2020) and was further refined. Afterward, the coded data were summarized into a framework matrix and were then interpreted. Quotes were translated to English upon inclusion in this manuscript.

4 Results

Recruitment resulted in 24 individuals volunteering for the study. We organized three co-creation workshops (n=15, of three, four, and eight participants each), one focus group discussion (n=5), and four semi-structured interviews. Participants were recruited from four clinical studies, of which one was sponsored by a pharmaceutical company. The co-creation workshops included participants (i.e.,

healthy volunteers) who had taken part in an interventional clinical study about COVID-19 (n=12) or migraine (n=3). The focus group discussion and semi-structured interviews involved participants of a qualitative study about insomnia (i.e., healthy volunteers; n=4) or inflammatory bowel disease (i.e., patients; n=5). Participant demographics are displayed in Table 8.

Table 8. *Participant demographics*

Characteristics	**Participants (n=24)**	
	n	**%**
Age range (years)		
21-39	13	54
40-59	4	17
60-75	7	29
Sex		
Male	15	63
Female	9	38
Education		
High school	3	13
Bachelor's degree	8	33
Master's degree	13	54

4.1 SENSITIZING SURVEY

The survey, used as a sensitizing tool, enabled us to gain insights into the importance participants give to the information described in the ICF of the clinical study in which they had taken part. Overall, the majority of participants rated the information as (very) important. All participants considered information related to the course of the clinical study and what is expected from them (very) important. In addition, the results indicate that all but one participant were sufficiently informed about the aspects of the study. The latter participant argued that the ICF, more than 10 pages in length, was too long to read and understand, and advised to include concise and well-structured information.

4.2 PERSONALIZATION

During the co-creation workshops, focus group discussion, and semi-structured interviews, participants were asked to describe how they would tailor the ICF of the clinical study in which they had taken part to their needs. Their answers related to the type and amount of information, the structure and presentation of information, signing new IC versions, and data sharing and sample reuse.

4.2.1 TYPE AND AMOUNT OF INFORMATION

Many participants mentioned that the ICF presented clinical information in an understandable manner. Nevertheless, some participants raised that the ICF was too lengthy, containing redundant information, and was not attractive to read. In addition, a few participants admitted that they did not fully read the ICF before signing it because of the trust they have in the research team. They were of the opinion that an ICF is primarily a legal document that must contain all study-related information, and thus, seemed to be an attorney's contract. As a result, it required efforts to read and to understand the (non-medical) information mentioned in the ICF. For example, each ICF contained information about data protection. The majority of participants indicated they did not pore over this type of information and mentioned that it would be mainly participants with a legal background who are able to understand this. Moreover, some participants mentioned that the legal information, for example, related to data protection, is not important to them.

> "*The importance of information is dependent on the type of study in which I am taking part. If my blood samples would be collected, as part of an interventional study, I would pay more attention to information related to data protection.*" (P24)

Varying perceptions were reported on the amount of information required in an ICF. Various participants raised that some information was already well-known, and therefore, may be omitted from the body of the ICF. Examples of such information are definitions of the terms 'randomization' or 'double-blinded'. Nevertheless, additional information was required by some participants. They, for instance, preferred a more detailed explanation of the health condition for which the intervention is investigated in the clinical study. These participants suggested that, in an eIC interface, additional information could be provided when hovering over specific words or they advised to include a hyperlink, allowing research participants to access updated and detailed information about this health condition.

4.2.2 STRUCTURE AND PRESENTATION OF INFORMATION.

To create a user-friendly (electronic) ICF, the participants raised several suggestions. First, the implementation of a scheme or a table was considered an added value to notice important information (e.g., information related to the course of the clinical study and what is expected from the participants) at a glance. Second, it was suggested to present necessary and additional information in the first and second layers, respectively. A layered approach could solve the issue of flooding the participants with information and could help them to differentiate essential from explanatory information. For example,

it was proposed to list the definitions of the terms 'randomized' or 'placebo-controlled' as explanatory information. Third, it was advised to format the text using font options (e.g., italic and bold font) and bullet points, in order to enable participants to screen the information. Fourth, in some ICFs discussed during our qualitative study, a summary was included which was considered valuable. Similarly, a participant who had taken part in another clinical study, of which the ICF did not include a summary, argued that one page that summarizes the most important points must be included.

> "*If you read a lengthy document, it is not always clear what the most important information is.*" (P3)

Fifth, it was suggested to integrate visuals, such as a figure or a video fragment, to clarify study-related information.

> "*Information could be conveyed via multimedia formats, which would be mainly interesting for participants who are visually oriented.*" (P6)

Finally, some participants advised to implement a decision tree for information related to pregnancy, contraception, and interaction with other drugs. Such a decision tree could allow the integration of information reflecting the participants' medical history and demographics, such as their gender or age. These participants raised that, based upon the implementation of such a decision tree, they would be able to receive personalized information. For example, only women of childbearing potential would receive information about pregnancy.

4.2.3 SIGNING NEW INFORMED CONSENT VERSIONS

Some participants had to reconsent several times to reaffirm their decision to participate upon study amendments. It was considered burdensome to make additional visits to the research site to sign new ICFs. As a result, these participants suggested signing these ICFs electronically. One participant raised that the COVID-19 pandemic had accelerated the digitalization process, and therefore, did not understand why it was not possible to make use of electronic signatures in the context of health-related research.

> "*It requires some efforts to provide the research team with a signed informed consent version. Therefore, I would prefer to sign it electronically.*" (P15)

Some participants considered it important to easily notice the changes in the new IC version and advised to highlight these. Moreover, they were of the opinion that it was confusing to receive different paper-based IC versions and raised the point that it would be helpful if the research team could store the previous versions at the research site. It was also mentioned that if participants would be informed about new IC versions electronically, it would be sufficient to receive the changes only.

> "*I need to be informed about the changes only and do not need to receive the full informed consent document.*" (P7)

4.2.4 DATA SHARING AND SAMPLE REUSE

The ICF of a particular clinical study described that in case the study would reveal information clinically relevant to the participant's health, this information would be shared with his/her general practitioner. Participants who had taken part in this study mentioned that it is important to keep their general practitioner informed. Nevertheless, they suggested receiving a notification when such information would be shared. In another ICF, participants could tick boxes to indicate their preferences regarding data sharing, which was considered valuable.

> "*The consent form states that participants should be aware that any clinically relevant data obtained during the study will be shared with their general practitioner. I would prefer to tick a box to explicitly consent for my personal data to be shared with my general practitioner. In addition, I would like to be informed about what type of data is shared exactly.*" (P2)

Moreover, this ICF listed that the participants' samples could be used for the purposes of genetic research in the context of the health condition investigated in this particular study. According to one participant, it was unclear if there would be sufficient control, for example by the government, on what happens with these samples. This participant was surprised that his initial consent to participate in the study was also valid to use his samples in further genetic research. Some other individuals commented that a research participant should have trust in the research team to handle his/her personal samples correctly.

> "*The researcher signs the informed consent in good conscience. Therefore, it is important to hold trust in the researcher that he/she handles participants' personal data properly.*" (P12)

4.3 LONG-TERM INTERACTION

All but one participant showed a positive attitude toward a longitudinal relationship with the research team. This particular participant (P11) mentioned that the information described in the ICF sufficed to be truly informed about the study. Many participants stated that they would like to be able to indicate if, how, for which reasons, and for which duration they would like to establish this longitudinal relationship. It was raised that an eIC interface, enabling a long-term interaction, offers a largely untapped opportunity to bring science closer to research participants. Nevertheless, some participants thought that the type of information shared longitudinally would be impacted by legal or scientific restrictions.

4.3.1 PROGRESS UPDATES AND STUDY RESULTS

A longitudinal aspect suggested by almost all participants related to updates concerning the progress of the clinical study and the results. It was acknowledged that, although it may take several years, it would be interesting to receive the final study results. Some participants raised that they had taken part in the clinical study because of their interest in the field and to advance scientific research rather than for the financial compensation. Therefore, they considered it an opportunity to receive the study results. Nevertheless, some participants also raised concerns about how the results would be presented. They voiced the opinion that if they would receive an academic journal article, the results may not be understandable.

It was also considered valuable to receive individual test results, such as results of scans or biochemical tests conducted on the participant's samples, or in particular the results of the genetic test (if performed). A particular participant (P2) mentioned that returning individual test results could offer lessons for participants in their health management.

> "*I think that the results of a baseline scan or test can be shared with the participant, and this information may be interesting if one of the participants would suffer from health problems later on.*" (P2)

However, another participant disagreed and stated that it is not necessary to be kept informed about these individual investigations and considered it to be burdensome for the research team.

> "*It would be a huge cost and would place time demands on the research team if they have to keep participants informed about additional research conducted on our samples.*" (P16)

Some participants, who had taken part in an international clinical study, raised that they would like to be informed about adverse events, related to the investigational medicinal product, that take place in other countries. One participant mentioned that, during the course of the study, he was actively looking for updates about the investigational medicinal product in scientific journals.

> "*If there is important news related to the investigational medicinal product, I would like to be informed via email or text message.*" (P10)

Nevertheless, several other participants advocated that it would not be useful to receive information about events that occur in another setting, and considered it important to have trust in the research team to inform the participants about important events. Another participant added that if there were any questions, they could always be posed to the research team.

4.3.2 Overview of studies

Participants suggested a couple of more aspects they would like to be informed about. Several participants would like to establish a longitudinal relationship to receive information about new clinical studies for which participants are being sought. Nevertheless, it was considered valuable if they could indicate for which type of studies, for example related to a specific health condition, they would like to be informed.

> "*I am interested in clinical studies related to a specific health condition, and therefore, it would be useful to have an oversight of these studies for which participants are being recruited.*" (P18)

Some participants mentioned that they already received invitations to participate in clinical studies via email, which was considered useful. Nevertheless, they raised the point that these invitations often referred to studies including participants of a specific sex or age category. They advised to receive invitations for studies they are eligible for only, which may be done automatically based upon the participants' personal data. In this way, the research site could immediately target the eligible population when recruiting. Next to future studies, some participants highlighted that they would like to have an overview of the studies in which they had previously taken part. They suggested that an eIC interface would enable them to navigate throughout their studies, accompanied by the study results.

4.3.3 *Practical integration*

When participants were asked how they would practically integrate the aspects in an eIC interface, almost all of them stated that they would like to receive a notification when new information is available, preferably via email. Several participants mentioned that they would not always think about logging in to an eIC application, and therefore, wanted to receive notifications. Another suggestion made by some participants was to receive a newsletter of the study on a regular basis. This newsletter could also inform participants that new information had been made available on the eIC interface. Moreover, it was suggested to integrate a chat feature into an eIC interface which participants could use to contact the research team directly in case of questions about the information.

According to some participants, it should be avoided to create a new account to access the eIC interface. They preferred that such an eIC interface would be integrated into established systems because of their professional and security properties. For example, these participants mentioned that they were already using systems that store medical information and inform them about updates.

> "*If you would integrate electronic informed consent in an existing application, I would directly associate it with professionality and security.*" (P1)

5 Discussion

This study aimed to explore how an eIC interface could be personalized and could establish longitudinal interactions, based on the research participants' needs. The combination of co-creation workshops, a focus group discussion, and semi-structured interviews allowed us to facilitate data richness regarding participants' experiences related to their study participation, and more specifically the ICF. The qualitative methods provided participants with the opportunity to discuss how they would tailor the (electronic) IC process to their needs. We further identified that almost all participants would like to maintain a longitudinal relationship with the research team, mainly to receive the (final) study results. Options to personalize an eIC interface ranged from customizing the information mentioned in an ICF to signing new IC versions electronically. Through the provision of various qualitative methods, we made a series of suggestions that may be considered when designing an eIC interface.

First, several participants, especially subjects who had taken part in interventional clinical studies, were of the opinion that the ICF of the study is very long and complex to understand. The IC process in clinical research is tightly regulated. The information that must be conveyed to participants is laid down in ethical codes and regulations, such as the Declaration of Helsinki and the Clinical Trials Regulation

(CTR) (3, 6). Nevertheless, existing literature showed for example that the length of ICFs used in some of the major COVID-19 vaccine trials could be reduced by at least 50% while still complying with the applicable legislation (219). In this respect, the results obtained in the present study also show that a lengthy, static ICF may not be the best approach to truly inform the participants about a study, according to their needs. Similarly, a cross-sectional study conducted at study sites in seven Asia-Pacific countries showed that research participants wanted to be informed about most topics of the ICF content required. Some of these participants required more information about particular topics. Nevertheless, this cross-sectional study found that participants preferred to read an ICF no longer than 12 pages (220). Some advantages could be found in an eIC interface that presents tailored information, fortified by using simplified and concise language, which may reduce the length of the eIC (219, 221). In addition, a personalized eIC can be considered an added value to the verbal elucidation provided by the research team. According to stakeholders involved in clinical research, a personalized eIC interface could result in more focused conversations with the research team (207).

Second, participants expressed the need to better structure the information. According to Schneiderman et al., one of the eight golden rules of interface design is to strive for consistency (222). Therefore, it is advised to standardize the formats and colors used in the eIC interface. Moreover, structured information could shorten the ICFs. For example, if multiple study drugs are used, it is suggested to list duplicative side effects of these drugs only once, by adding a statement describing that all drugs can cause side effects such as fever, instead of listing them for each drug separately (223). This idea also highlights that special attention must be paid to the creation of an information architecture in which the information is structured and categorized in a coherent and usable way. For example, key concepts may be illustrated by using graphics (224). The 'Strategic Initiative for Developing Capacity in Ethical Review (SIDCER)', defined as "*a network of independently established regional fora for ethical review committees, health researchers and invited partner organizations from the Asia and Western Pacific region, former Russian states, Latin America, Africa, and North America*", defined three principles to assist researchers in developing an enhanced ICF (225, 226). One of these principles is to convey information to participants in a simple format; for example by using illustrations, by placing the core information into boxes, or by highlighting keywords in color (226). Moreover, also the user experience must be investigated (227). During usability testing, end users perform tasks that represent the user activity, and thus, will be performed during the course of using an eIC application in practice (228). Based on the results generated during usability testing, potential issues of an information architecture, including structured and categorized information, can be uncovered before implementing the application in clinical research (229).

Third, all but one participant favored establishing a longitudinal interaction with the research team during and after the clinical study, mainly to receive study results. An eIC interface could allow participants to set their preferences regarding the type of information they would like to receive electronically. The CTR already specifies that the sponsor must include a summary of the clinical trial results, understandable to a lay person, in the EU database in order to make them publicly available (6, 230). Similarly, in the United States, the Food and Drug Administration Amendments Act requires the submission of results to the ClinicalTrials.gov trial registry for certain types of clinical trials (231, 232). Yet, based on the results of our study, it seems that the majority of participants is not aware of these databases or would prefer to be notified when new information becomes available. Therefore, if an eIC application could send automated alerts to inform participants about new information, it would be valuable to also include these lay summaries in an eIC application. However, it would be important to inform research participants that it can take years before study results are made public. For example, in the case of phase I trials, it can take up to 30 months from the end of the trial before the lay summary is made public (233). In addition, a longitudinal interaction may be used to electronically remind participants about study visits or to provide them with certain types of questionnaires they have to complete (234).

Finally, participants of one particular study needed to reconsent several times. Although the Belgian IC template for interventional clinical trials in adult patients suggests including a table with the revision history, it was not clear to some participants what exactly had been changed in the ICF (235). Therefore, an eIC interface could provide a clear overview of all IC versions signed by the participant, while clearly indicating the changes. Moreover, teleconsultations could be integrated into an eIC interface, allowing the researcher to remotely video conference with the participant to explain these changes and to answer potential questions (236).

5.1 Strengths and limitations

One of the main strengths of this study is the involvement of participants, who had taken part in a clinical study, in a co-creation process. The limited number of participants in each co-creation workshop and focus group discussion allowed us to pay attention to each individual while still having the opportunity to discuss the participants' ideas in a group (218). Another strength relates to the diversity of the participants included, given that they had taken part in clinical studies with a different design, sponsored by academia and the pharmaceutical industry. Finally, the multidisciplinary team that was involved in the design of this qualitative study is an important additional asset. Nevertheless, a limitation of this study is that it included participants who had taken part in a clinical study in Belgium

only. It may be that ICFs are designed differently in other countries. Moreover, our study involved a small, relatively well-educated sample of participants, and thus, the results may not be generalizable. A lack of generalizability has become inherently associated with qualitative research. However, the main objective of qualitative research is to gain in-depth insights into participants' opinions in order to formulate suggestions rather than to make statements with universal validity.

Next, the group nature of the co-creation workshops and the focus group discussion may have hampered certain participants from freely expressing their experiences. However, this limitation was mitigated by additional individual interviews. Finally, it should be noted that the analysis of the qualitative data was conducted by one researcher as opposed to multiple researchers, meaning that no cross-check was performed (153). Nevertheless, the use of the other stages of the framework method, described by Gale et al., and the availability of existing literature to inform the coding process minimized subjective interpretation of the data (153, 207).

5.2 Future perspectives

This study presents the views of participants who had taken part in four clinical studies. To gain more knowledge about the feasibility of participants' suggestions in daily practice, follow-up studies should be conducted. For example, the perspectives of data infrastructure organizations and health care professionals involved in clinical research could be explored.

6 Conclusions

This co-creation approach enabled us to understand how research participants, who had taken part in a clinical study, would adapt the ICF of this study to better suit their needs and how they would establish a longitudinal interaction with the study team. As a result, this qualitative study offers a set of key considerations for the design of a participant-centric eIC interface. We identified varying perceptions related to the personalization of the ICFs, suggesting the need for a tailored interface. In addition, an eIC interface could allow participants to indicate which information they would like to be longitudinally informed about, such as the study results. Future research opportunities lie in the design and usability testing of such an eIC interface.

CHAPTER 5:
USING PROVOCATIVE DESIGN TO FOSTER ELECTRONIC INFORMED CONSENT INNOVATION

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Using provocative design to foster electronic informed consent innovation

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1 ABSTRACT

Background: The development of technological applications in clinical research, such as electronic informed consent (eIC), is on the rise. The involvement of end users throughout the design process of eIC is of utmost importance to improve the current informed consent process.

Methods: Using a provocative design, we conducted interviews with 30 clinical research participants. Provotypes were used as a starting base to discuss various aspects relevant to eIC. By providing a medium to encourage divergent thinking, participants' views and concerns were solicited. Thematic analysis was undertaken using NVivo.

Results: The majority of participants placed trust in the principal investigator or the hospital to perform the role of eIC hosting party. Differing opinions were reported on the amount of information required related to stakeholders' access to an eIC system, and thus, to participants' personal data, to enable trust in an eIC system. Nevertheless, this study indicates a general willingness of participants to share personal data with physicians and pharmaceutical companies on an international level, and to receive requests for new research studies via an eIC system. Participants suggested to tailor an eIC system based upon their preferences, for example, regarding whom they want to share their personal data with. Moreover, they expressed a desire to choose how they can contact the research team, and to indicate which study-related information they would like to receive electronically. In addition, positive opinions were voiced on the integration of a test to assess participants' understanding before providing their eIC.

Conclusions: Following a research through design approach, insights have been generated which inform the design of eIC. Provotypes were designed to help participants think beyond what is familiar to them. Study findings revealed that not all situations were perceived as provocative, because of participants' motivation to advance scientific research and the trust they place in the research team. Nevertheless, the use of provocative design resulted in additional insights, generated by clinical research participants, which could be considered in the further design of eIC.

2 INTRODUCTION

Digital health, such as health information technology or telemedicine, is becoming increasingly part of our healthcare system and holds huge promise for improving patient-centered care (237-240). If purposefully designed, digital health applications can promote the quality of health services and ultimately, citizens' welfare (241). In the context of clinical research, substantial interest has been paid to electronic informed consent (eIC). For example, the European Medicines Agency issued guidance during the COVID-19 pandemic, specifically addressing the use of eIC to inform participants and obtain their consent (202). eIC holds great potential to encourage research participant engagement in the informed consent (IC) process (151). Over time, IC forms (ICFs) have become lengthy documents, containing in-depth legal and scientific information, which are often complex to read and understand by research participants (44, 95). According to various stakeholders involved in clinical research, eIC could allow a personalized approach and could establish ongoing communication between participants and the research team (151, 207). For example, participants could be able to indicate for which reasons they would like to be recontacted via an eIC system or a test could be implemented to assess their comprehension (207).

End users have been traditionally considered passive recipients of digital health (242). As a result, digital technologies were seldom developed by using human-centered design principles, which is considered a key factor to achieve successful implementation (243-245). However, during the past years, the interest has grown to involve end users in the design of digital technologies (243, 246). Collaborating with end users aims to facilitate the development of technologies that serve the end users' needs (247). With regard to clinical research, it is essential that clinical research participants should play a key role in the design of an eIC system (82).

To inform the design of an eIC system, provocative design can be used to elicit feedback from end users. Provocative design intentionally provokes end users to generate detailed reactions by triggering their creativity and bringing them out of their comfort zone (248, 249). As a result, divergent ideas related to the design of an eIC system may be generated (250). Various types of provocation are described in literature. For example, aesthetic provocation refers to the visual characteristics of the design, functional provocation challenges the ways of interacting with the design, and conceptual provocation is related to the concepts the design tries to challenge (251, 252). The conduct of provocative design is facilitated by the use of provocative prototypes, also referred to as provotypes, which are considered design artefacts (253). Provotypes visualize issues or perspectives considerably further than spoken words, and therefore, aim to overcome barriers related to unlocking end users'

thinking (253). To define opportunities for a user-friendly eIC system, we aim to investigate how provotypes might trigger and shape the views of clinical research participants on different aspects relevant to the design of eIC. Moreover, we aim to gain insights into the importance participants give to particular ethical and legal requirements. The opinions provided during this study may inform the design of a participant-centric eIC system in clinical research.

3 METHODS

3.1 DESIGN

This manuscript builds on results from previous research related to eIC (151, 207). Previous research has shown that research participants stress the importance of trust in the authenticity of eIC, which goes hand in hand with the party that should ideally host an eIC system (151). Therefore, participants' views regarding the hosting party were investigated. Additionally, the amount of information that participants would like to receive regarding stakeholders' access to an eIC system and, thus, to participants' personal data, were also addressed. The first and second provotypes aimed to deepen understandings on what participants value in the design of an eIC system that would hold their trust. Other challenges for the design of eIC lie in the personalization and long-term interaction aspects. Therefore, our provotypes challenged participants on i) being searchable for future research studies, ii) being electronically informed about study-related information, iii) how to contact the principal investigator (PI) during the course of the study, iv) providing reconsent, v) the responsibility they might have when indicating their preferences, and vi) the implementation of questions to assess their understanding of study-related information. In total, eight provotypes were used in this study that may conceptually or functionally provoke participants and touch upon the themes of trust, personalization, or the long-term interaction. Provotypes, created with the software program Figma, presented various situations, ranging from provocative (i.e., intended for critical reflection) towards prototypical (i.e., intended to test a certain design direction). A detailed description and visualization of the provotypes can be found in Table 9 and Appendix J, respectively. These provotypes were used during interviews with participants who have taken part in a clinical trial. Participants interacted with these provotypes as if it would concern a real eIC system. For example, it was pretended that participants needed to log-in in order to access the different situations. During each interview, the eight provotypes, including the various situations, were shown in the same order, starting from the most provocative design and ending with the most prototypical design. After each situation, the participant's opinion was asked. At the end of the interview, the participant's demographic data (i.e., age and highest education level)

were collected. Moreover, it was clearly explained that some situations might not be correct from an ethical and legal point of view in order to avoid confusion.

Table 9. *Description of the provotypes presented during the interviews*

Provotype 1: Hosting an eIC system Participants were shown four different interfaces. Each interface mentioned that a certain party is responsible for hosting an eIC system, and thus, for correctly storing participants' personal data and guaranteeing their privacy. Hosting parties included i) a pharmaceutical company, ii) the Belgian government, iii) the PI, and iv) the hospital that has been conducting the clinical trial in which the participant has taken part.
Provotype 2: Amount of information about stakeholders' access to an eIC system Participants were shown four different interfaces. On each interface, it was mentioned that an eIC system stores participants' personal data such as their name, address, date of birth, and medication history. Additionally, interfaces included the following messages: i) "We cannot tell you who has access to your personal data.", ii) "Only persons with legitimate rights have access to your personal data.", iii) "The Belgian government has access to your personal data when conducting inspections. The government will conduct inspections if deemed necessary, for example if there is a complaint related to the study. The principal investigator has access to your personal data when consulting your electronic health record. The evaluating ethics committee does not have access to your personal data. The task of the ethics committee is to protect the rights of the participants who take part in a clinical study. They verify if your rights are respected. The sponsor of this study does not have access to your personal data. The sponsor is responsible for the preparation of the research protocol, taking an appropriate insurance, receiving approval for conducting the study of the relevant authorities/ethics committees, and registering the study in a publicly available register.", and iv) "The Belgian government and the principal investigator have access to your personal data.".
Provotype 3: Being searchable for future research studies Participants were shown three different interfaces. On each interface, it was mentioned that an eIC system stores participants' personal data such as their name, address, date of birth, and medication history. Participants were informed that their data will be shared with i) physicians all over the world, ii) a specific pharmaceutical company, and iii) physicians of the hospital that has been conducting the clinical trial in which the participant has taken part, and that they could contact them when they need participants for a new research study. All interfaces indicated that participants are able to indicate for which particular type of research (e.g., for research in a particular health condition) they would like to be contacted.
Provotype 4: Being electronically informed about study-related information Participants were shown one interface on which five pop-up messages appeared one after another. These messages included the following information: "The recruitment of this study has been finished. The study will start soon." or "New results of the study in which you are taking part are available. Please consult these results." or "There is a new informed consent version available. Please consult this new version.". Some messages appeared twice.

Provotype 5: Contacting the PI during the course of the study Participants were shown three different interfaces. Interfaces included the following messages: i) "If you have questions about this clinical study, you can only contact the chatbot. The chatbot is a software program that will help you further.", ii) "If you have questions about this clinical study, you can only contact the principal investigator via the chat.", and iii) "If you have questions about this clinical study, you can only set-up a video consultation with the principal investigator.".
Provotype 6: Providing reconsent Participants were shown three different interfaces. Interfaces included the following messages: i) "There is a new informed consent version available which you can consult. You will automatically agree to this version and do not need to take any action.", ii) "There is a new informed consent version available which you can consult. The changes are highlighted. If you agree, please sign this version electronically.", and iii) "There is a new informed consent version available which you can consult. The changes are highlighted and additional information is provided on why these changes were necessary. If you agree, please sign this version electronically.".
Provotype 7: Participants' responsibility when indicating their preferences Participants were shown two interfaces. On the first interface, it was mentioned that participants could be informed about the further course of the clinical trial via an eIC system, and that they could indicate their preferences regarding the type of information they would like to receive. The second interface included various options participants could choose. Options included: i) the status of the study, ii) final study results, iii) preliminary study results, iv) results of additional investigations (e.g., blood sampling), and v) a new informed consent version.
Provotype 8: Implementation of questions to assess participants' level of understanding Participants were shown four different interfaces. Interfaces included the following messages: i) "Please answer the questions below. You must answer all questions correctly before you can sign the informed consent. If you need more information to answer a question, please consult the principal investigator. This system will not provide any feedback or additional information on your answers, except whether all questions were answered correctly. If you give an incorrect answer to one or more of the questions, you will be excluded from the study. You get one single attempt.", ii) "Please answer the questions below. You must answer all questions correctly before you can sign the informed consent. If you need more information to answer a question, consult the principal investigator. This system will not provide any feedback or additional information on your answers, except whether all questions were answered correctly. You can retry as many times as you want.", iii) "Please answer the questions below. You must answer all questions correctly before you can sign the informed consent. If you need more information to answer a question, you can click the 'Tell me more' button. For any questions that are answered incorrectly, you will receive additional explanation. You can retry as many times as you want.", and iv) "Please answer the questions below if you want to get insights in how well you understand the study in which you would like to take part. It is NOT necessary to answer all questions correctly before you can sign the informed consent. If you need more information to answer a question, you can click the 'Tell me more' button. You can retry as many times as you want, or click 'skip' to sign immediately."

3.2 Recruitment

Recruitment was done in Leuven, Belgium, by the Department of Gastroenterology and Hepatology and the Department of Endocrinology at the University Hospitals Leuven, as well as the KU Leuven Vaccinology Center (LUVAC), through purposive sampling. Additionally, the researcher herself (EDS) recruited subjects at the Department of Endocrinology at the University Hospitals Leuven. Participants were eligible for inclusion if they were over 18 years old, were Dutch-speaking, and had experience with taking part in an observational or an interventional clinical trial. Participants with prior trial experience were selected so they could better empathize with the situations we presented them with. The recruiting parties provided an invitation, by email or in person, to potential participants. The invitation contained information on why they were invited to participate, the objectives and course of the interview study, the evaluation of the study by the Ethics Committee Research UZ/KU Leuven, the compensation participants would receive after participation, and the contact details of the researcher. If interested, participants could contact the researcher by email or phone. Written IC was obtained from each participant before the start of the interview. Afterwards, they received a gift voucher of 25 euro. Recruitment ceased once data saturation was achieved.

3.3 Data collection and analysis

Interviews were conducted either face-to-face or by using Microsoft Teams, according to the preference of the participant, between July and September 2021. All interviews were conducted by the same researcher (EDS). When interviews were conducted remotely, the participant was given control of the researcher's screen in order to interact with the provotypes. Interviews lasted between 30 and 60 minutes, were conducted in Dutch, and were digitally audio-recorded. Thematic analysis was performed in accordance with the various stages of the framework method, described by Gale et al. (153). A description of each stage is presented in Table 10. Dutch quotes were translated to English upon inclusion in this manuscript.

Table 10. Description of the framework method stages

Stages	Additional explanation
1. Transcription	Pseudonymized audio-recordings were transcribed a verbatim by a third-party.
2. Familiarization with the interview	The researcher (EDS) thoroughly read the transcripts, made reflective notes, and relistened to the audio-recordings, if necessary.
3. Coding	The researcher (EDS) coded 2 transcripts via a hybrid deductive and inductive approach. The provotypes presented during the interviews informed the creation of deductive codes while inductive codes were created based upon observed patterns.
4. Developing a working analytical framework	Codes sharing similarities in content were grouped into categories, creating a working analytical framework.
5. Applying the analytical framework	The researcher (EDS) applied the working analytical framework, also referred to as the coding tree (Appendix K), to the other transcripts by using NVivo software.
6. Charting data into the framework matrix	The data were charted into the framework matrix. Microsoft Excel was used to summarize the data from each code and transcript.
7. Interpreting the data	The data were interpreted to identify similarities and differences between the data.

4 RESULTS

In total, 30 interviews using a provocative design were conducted with participants who have taken part in various clinical trials: i) an interventional vaccine trial (n=12), ii) an interventional trial in the field of inflammatory bowel disease (n=10), and iii) an observational trial in the field of diabetes (n=8). Participants' characteristics are shown in Table 11. Results of the interviews were reported for each provotype related to trust, long-term interaction, and personalization.

Table 11. *Participant demographics*

Characteristics	Interviewees (n=30)	
	n	**%**
Age range (years)		
20-39	8	27
40-59	7	23
60-83	15	50
Sex		
Male	17	57
Female	13	43
Education		
High school	10	33
Bachelor's degree	15	50
Master's degree	5	17

4.1 TRUST

4.1.1 HOSTING AN ELECTRONIC INFORMED CONSENT SYSTEM

Generally, participants expressed confidence in a pharmaceutical company, the Belgian government, the PI, and the hospital where the clinical trial is conducted to perform the role of hosting party. It was argued that each party must comply with the applicable legislation regarding data protection. There were participants who expressed preferences for the PI and the hospital to host an eIC system. However, few participants indicated that they participate in a trial to advance scientific research, and that they do not take the hosting party in consideration. Moreover, it was believed that receiving information about the hosting party could foster clinical trial transparency. To this end, it is recommended to provide specific information about the department – within the Belgian government, the hospital, or the pharmaceutical company – that would be responsible for hosting the system.

Initially, several participants had reservations about a pharmaceutical company as hosting party, due to their profit-seeking behavior. Nevertheless, these participants highlighted that the efforts of pharmaceutical companies to speed up the process of bringing COVID-19 therapeutics to the market had a positive impact on the trust they have in the industry. The Belgian government was considered the most neutral party to host an eIC system. Participants indicated that they are already familiar with the use of applications hosted by the government, for example, to fulfil tax obligations or to receive a COVID-19 vaccination certificate. Therefore, they raised the point that they can trust the government. Nevertheless, it was raised that the government as hosting party of an eIC system sounded strange at first. According to the participants, it would be reasonable that the hospital would host an eIC system. Participants' medical information is documented in electronic health records that are stored in the hospital. Therefore, participants believe that the hospital has sufficient safeguards in place to adequately protect their data. Finally, almost all participants expressed confidence in the PI of the clinical trial in which participants have taken part.

> "*Because I have developed a relationship of trust with the principal investigator, this person can be put in control of my personal data.*" (P19)

Nevertheless, one participant asserted that it would not be feasible for one person to host an eIC system. Moreover, it is more likely that the PI would, due to the lack of IT skills, outsource the hosting to another department or organization.

4.1.2 LEVEL OF DETAIL ON ACCESS INFORMATION

Generally, participants did not agree with the first interface, which states that it is not possible to provide information on access of stakeholders to the participants' personal data. It was highlighted that this situation is not acceptable and does not result in an eIC system that would hold the participants' trust. Moreover, questions arose regarding the reason why it is not possible to provide the necessary information. Several participants argued that additional information about stakeholders' access was preferred, whereas only a few other participants were confident that only the necessary persons would access their personal data. Participants were more positive towards the second interface, specifying that only persons with legitimate rights have access to participants' personal data. Nevertheless, participants stated that they must be able to read more specific information about the persons with legitimate rights. Therefore, there were participants who expressed preferences for the third or fourth interface that includes minimal and detailed information about stakeholders' access to participants' personal data, respectively. Some participants noted that, because of the relationship of trust that is developed with the clinical research team, the minimal information is sufficient, whereas others argued that detailed information is necessary to enable trust in an eIC system. Therefore, some participants advised to offer all necessary information.

> "*Although the detailed information is time-consuming to read and process, it must be made available to all participants.*" (P29)

Moreover, it was advised to structure the information, for example by using bullet points, and to specify the department of the Belgian government that could access participants' personal data.

4.2 LONG-TERM INTERACTION

4.2.1 BEING SEARCHABLE

This provotype sought to investigate participants' preferences for sharing personal data and being contacted for new research studies. There were participants who wanted to share their personal data with physicians all over the world, the pharmaceutical industry as well as physicians of the hospital that has been conducting the study in which the participant has taken part. Participants tended to consider being contacted by these parties for new research studies as desirable. Moreover, it was considered valuable that participants are given the choice to indicate for which type of studies they can be contacted. Various interviewees saw this as an opportunity to participate in a study that could further the research field of the condition that affects them.

"*I would immediately volunteer to participate in a study related to diabetes to advance research in this health domain.*" (P26)

However, some participants raised the concern that they do not want to be overloaded with requests, and therefore they stressed the need to set preferences for being notified. For example, participants could be offered the possibility to set a limit on the notification frequency or to indicate how they would like to be contacted. Other considerations on this matter are shown in Table 12.

Table 12. *Participants' considerations on being searchable*

• When personal data is shared with physicians all over the world or with a pharmaceutical company, larger clinical studies can be conducted to advance scientific research. • Concerns were raised about the differing privacy rules at a global level. • When personal information is shared only with physicians of the hospital that has been conducting the study in which the participant has taken part, possibilities are limited from a scientific point of view. • A desire was expressed to be able to tailor preferences about whom participants want to share their personal data with. • Trust in a new research study, conducted by foreign physicians or a pharmaceutical company, may be positively impacted by discussing the study with the participant's treating physician. • Specific information must be provided on the name of the pharmaceutical company.

4.2.2 BEING ALERTED ABOUT NEW INFORMATION

Some participants indicated that the pop-up messages, describing that new study-related information is available, help to capture their attention. It was suggested that these messages could include a link that automatically redirects participants to more detailed information. Nevertheless, showing multiple pop-up messages one after another was considered annoying and overwhelming. In order to avoid a disorganized overview of new information, participants advised to use an inbox-like format rather than pop-up messages.

The majority of participants asserted that they would forget to undertake the action of logging in to an eIC system to verify if new study-related information has been made available. It was believed that a notification, such as an email, can be sent to participants, alerting them that new information can be accessed on an eIC system. As a result, participants are given the choice on whether or not to consult

the information. Nevertheless, participants prefer some control over the type and frequency of notifications they receive.

Moreover, participants raised the issue that they are already using a health-related application that sends notifications about new information in their medical dossier or medical appointments. Therefore, they indicated that it would be valuable to integrate the clinical study-related information, and thus, an eIC system, into established systems.

4.2.3 CONTACT WITH THE PRINCIPAL INVESTIGATOR

Participants indicated that it could be possible to obtain support through a chatbot. It was considered a good starting point to inform participants on a continuous basis. Participants mentioned that a chatbot could respond to frequently asked questions related to the conduct of clinical studies. Nevertheless, the personal contact between the participants and the research team was valued highly. Therefore, participants raised that if they have specific questions that require further explanation, they must have the possibility to contact the research team.

> "*If you engage in taking part in a study, you do not want to receive automated responses that do not address your question.*" (P2)

Participants agreed that the utilization of a chat feature can support the direct interaction with the PI. Chat integration allows the participants to discuss questions with a trustworthy person who has medical expertise. Participants indicated that not only the PI, but also another member of the research team, can answer their questions.

> "*The research team is informed about my medical background and is able to provide specific study-related information.*" (P20)

Nevertheless, participants required clarification on when it would be possible to chat with the research team. Moreover, some participants mentioned that they are unaccustomed to the interaction with others over technology, and therefore, prefer a face-to-face conversation.

Video consultations were considered as real-time interactions between the participants and the PI. It was raised that a video consultation enables participants to capture the body language and facial expression of the PI. Similar to the chat function, participants required clarification on when a video

consultation could be scheduled. One person highlighted that, when an appointment must be booked, additional efforts are required to ask for clarification. Additionally, some participants were concerned that conducting video consultations would result in an increased workload for the PI.

Some participants stated that if only one option is provided to contact the PI or the research team, it would adversely affect participants' willingness to take part in a particular study. Therefore, they advised to offer several options. Generally, participants indicated that their preferences depend on the importance of their questions and their familiarity with technology. If it concerns a non-urgent question, it can be asked via chat, email, or on the participant's next medical visit. However, in emergency situations where a participant has developed acute symptoms during the course of the study, there must be the possibility to call the PI or the research team.

4.2.4 SIGNING NEW VERSIONS OF ELECTRONIC INFORMED CONSENT

It was raised that automatically agreeing to a new eIC version, as mentioned in the first interface, is a convenient option. Participants expressed confidence in the research team, and therefore, believed that it would concern ethically sound modifications. Nevertheless, several participants voiced the opinion that it is not acceptable to automatically agree to a new eIC version and questioned the need to read the new version in case of automated approval.

> "*Why would I consult the new electronic informed consent version if it has been automatically accepted?*" (P12)

These participants emphasized the importance of indicating their agreement through a clear affirmative action, for example by ticking a box. Moreover, they advised to transparently communicate the modifications of the new eIC version. For this reason, they agreed with the second interface, stating that the changes of the new eIC version are indicated. Because it often concerns lengthy ICFs, participants raised that they should be able to immediately notice the changes.

The third interface, mentioning that additional information on the modifications is provided, was appreciated by the majority of participants. Some participants raised that they still have the option on whether or not they access the additional information.

> "*You could have the choice to access the additional information. It would also be interesting for the research team to monitor how many participants have read that information.*" (P25)

Nevertheless, it was considered burdensome for the research team. Therefore, they advised to provide only additional information if the research team deems it necessary. Finally, participants highlighted that it is important to mention that if they would have questions about the new eIC version, they have the possibility to contact the research team.

4.3 PERSONALIZATION

4.3.1 RESPONSIBILITY

Generally, participants did not feel personal responsibility to express their preferences regarding the type of study-related information they would like to receive. They reported that their involvement is encouraged by indicating which information they would like to be informed about, and mentioned that the added value of eIC is the access to additional study-related information.

> "*Because participants may have different interests, it is valuable that it can be indicated which information someone wishes to receive.*" (P4)

Almost all participants were interested in receiving study results. More concretely, they were willing to receive the final results and considered the preliminary results as redundant. However, concerns were raised related to the understandability of the results. Differing perceptions were reported on the willingness to receive information on the status of the study or additional investigations. For the latter, one participant mentioned that it would be useful to be informed in case of deviating results only. Finally, the majority of participants wanted to receive new IC versions electronically. They felt that receiving the information digitally could promote environmental sustainability.

4.3.2 QUESTIONS TO ASSESS PARTICIPANTS' LEVEL OF UNDERSTANDING

Generally, participants were positive towards the implementation of a test into the eIC process to assess their understanding of study-related information. These questions require them to reflect on what the study entails and to consult the study team if additional clarification would be required. Participants emphasized the importance of understanding the study conduct and implications before being enrolled in the study. They believed that the implementation of questions can depend on the type of study. For example, a test was considered more valuable for interventional rather than for observational studies because of the higher safety risk, related to the intervention, posed to study participants. Additionally, participants stressed the need to mention the aim of the questions: creating

awareness of study-related information. Moreover, they highlighted that they must be informed, in advance, that they need to complete questions and when they have to do so.

Participants widely disagreed with the first interface, indicating that they have only one single attempt to answer all questions correctly. According to the participants, unintentional errors are often likely be part of a question session, depending on the type and difficulty of questions. Therefore, it was raised that having one attempt would adversely affect recruitment. Participants also indicated that it is not acceptable to exclude patients with a specific disease who consider a clinical trial as an opportunity to improve their health condition. The first interface also described that participants could consult the PI to receive additional information to answer a question. However, some participants thought that it is not always feasible to reach the PI and acknowledged that they do not want to disturb the PI.

The second interface offered participants the possibility to retry as many times as they want to answer all questions correctly. Nevertheless, participants advised to set a limit on the number of attempts in order to avoid gambling.

> "*If you have not understood the information, it is useless to answer the questions multiple times.*" (P14)

Moreover, it was suggested to receive additional explanation when a question would be answered incorrectly, as presented on the third interface. Additionally, this interface enables participants to click the 'Tell me more' button before answering the question, which participants considered valuable. Nevertheless, if the additional information would not suffice, participants want to have the possibility to contact the research team.

When participants were shown the fourth interface, stating that it is not necessary to answer all questions correctly before signing the IC or that questions can be skipped, they believed that in some situations the questions would not be completed. For example, if it would concern a patient who lacks energy or if a long and time-consuming questionnaire needs to be filled out. Nevertheless, participants were of the opinion that, if the questions would be skipped, clinical research participants may not be aware of their responsibility when taking part in a study.

5 DISCUSSION

User involvement has become a widely accepted principle in the development of user-friendly technologies and is considered crucial to improve the quality of digital health (246). However, limited literature exists on human-centered design to inform the creation of an eIC user interface (151). Nevertheless, the importance of engaging clinical research participants in the design of an eIC interface cannot be understated. They are in a unique position to share their experiences about taking part in a clinical study. Recognizing the need to involve clinical research participants in the design process of a participant-centric eIC system is what resulted in the study described in this manuscript. Our study confirms that participants can reflect on several situations in order to explore future eIC design possibilities. Provotypes, putting forward more or less provocative situations relevant to the design of eIC, were a useful strategy to engage participants in an open discussion. The following key considerations for the design of an eIC system can be made based on our results.

5.1 TRUST

The majority of participants showed a preference for the PI or the hospital to perform the role of hosting party, as confidence was expressed that they handle participants' personal data properly. Similarly, another qualitative study involving various clinical research stakeholders found that the PI, a regulatory body, or a trusted center, controlled by a regulatory body, could be responsible for hosting an eIC system (207). A scoping review has shown that trust in digital health depends on a variety of factors. For example, the reputation of the service provider can act as an enabler or impediment to have trust in technologies (254). Several participants highlighted that a pharmaceutical company is motivated by profit and therefore, expressed more trust in public institutions, which is in line with the available literature. A cross-sectional study conducted among patients showed that their willingness to participate in a clinical study depends on the institution that is sponsoring the study. These patients indicated to be more willing to participate in a study sponsored by a public institution rather than a pharmaceutical company (255).

According to Beauchamp and Childress, respect for a person's autonomy is one of the principles that lies at the core of biomedical ethics (256). Nevertheless, study findings suggest that some participants felt indifferent towards the impairment of their autonomy once a relationship of trust has been developed with a specific professional or institution. For example, some participants agreed to not being able to make an autonomous decision about whether or not to accept a new eIC version because of the trust they have in the research team. Within health-related research, trust is a prominent factor between the study participant and the research team (257). For this reason, making a technological

application, such as eIC, trustworthy is critical to support this participant-research team relationship that involves trust.

5.2 Control and transparency

The provocative interfaces used in our study aimed to openly explore various themes. Participants did not always agree with statements mentioned on these interfaces, for example, related to automatically agreeing to a new eIC version or being searchable by specific parties. Therefore, it seems that some participants want to be offered a certain level of control to take decisions, such as indicating with whom they want to share their data with and for which type of studies. The concepts of control and transparency are inextricably linked. Transparent information needs to be conveyed to participants to address potential concerns they may have and is considered important to garner a justified trust in eIC (115, 258). When purposefully designed, eIC affords the opportunity to establish a transparent information exchange: it may enable participants to control their decisions, based on their wishes, and to receive understandable information over the course of the study.

5.3 Flexibility

Generally, participants' preferences differed regarding the type and amount of study-related information they would like to access. Additionally, participants wanted to have various options to contact the research team. These divergent views require the need for the design of a flexible eIC interface that can be tailored to the participants' wishes. In doing so, eIC may overcome the static character of a paper-based ICF, which is one of its stumble blocks (207). Existing literature shows that the information participants consider important for their decision to participate in a clinical study differs (220). A flexible approach can accommodate these differences, for example, by offering a layered eIC model. The first and second layer can convey essential and more detailed information, respectively (207). Moreover, by enabling participants to indicate which aspects of a clinical study they would like to be informed about, they may have more control over their involvement in this study (207, 259).

5.4 Informed decision

Each participant may have differing preferences, values, and goals which can impact the process of making an informed decision on enrolling in a clinical study. A flexible eIC interface can aid participants in accessing study-related information based on their needs and interests. Moreover, to ensure that participants understand the information, it has been suggested to integrate a test in the eIC interface to assess their comprehension (151, 207). Generally, participants involved in this qualitative study

were positive towards the implementation of a test. However, it is recommended to design an eIC interface providing access to additional information and answer feedback during and after completion of the test, respectively. Wilbanks et al. designed an eIC interface in which a test was implemented (260). In initial studies, participants needed to answer all questions correctly whereas in subsequent studies, participants could also enroll when one or more questions were incorrectly answered (123, 261). Wilbanks described that the latter approach is mainly appropriate for lower-risk observational studies (261). Similarly, participants involved in our study voiced that the importance of a test depends on the type of study.

5.5 Strengths and limitations

eIC has received little attention from a user-centered design perspective. Therefore, this study's main strength lies in engaging clinical research participants, as one of the important end users of an eIC system, in the design of an eIC interface. Provocative interviews are qualitative in nature and, therefore, provide subjective evidence that may not be generalizable. Nevertheless, our study design aimed to involve participants who have taken part in diverse types of clinical studies to reduce specificity. Additionally, we noticed that participants' ages ranged from 20 to 83 years, resulting in a heterogeneous sample. Nevertheless, it should be mentioned that the recruitment of participants was conducted in Belgium only. All interviews were conducted by the same researcher, reducing the variability between interviews. Participants' experiences with taking part in a clinical study, and more specifically with the IC process, was highly relevant to inform the design of an eIC interface. However, it is important to recognize that they provided views in a hypothetical setting, which may not reflect their decisions in more naturalized circumstances. In addition, it should be noted that the coding of the data was performed by one researcher. Although no independent coder verified the code assignment, the use of the other stages of the framework method and the availability of existing literature to inform the coding process minimized subjective interpretation of the data (153, 207).

6 Conclusions

To assist responsible implementation of eIC in clinical research, it is important to put study participants' desires and concerns at the forefront. This manuscript describes the involvement of study participants in the design process of eIC. Through provocative design, participants are triggered to creatively reflect on situations related to trust, personalization, and the long-term interaction. Findings point to the importance of trust, control and transparency, flexibility when designing eIC systems, and making an informed decision. These findings will contribute to the design of a participant-centered eIC system.

PART 3:
TESTING AND EVALUATING
ELECTRONIC INFORMED CONSENT MODULES

CHAPTER 6:
TESTING AND PRACTICAL IMPLEMENTATION OF A USER-FRIENDLY PERSONALIZED AND LONG-TERM ELECTRONIC INFORMED CONSENT IN CLINICAL RESEARCH: MIXED METHODS STUDY

This chapter is based on:

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Testing and practical implementation of a user-friendly personalized and long-term electronic informed consent in clinical research: mixed methods study

Manuscript in review

1 ABSTRACT

Background: Over the years, increasing interest has been shown in electronic informed consent (eIC) in clinical research. The user-friendliness of an eIC application and its acceptance by stakeholders have a central role in achieving successful implementation.

Objective: This study aimed to identify insights for the design and implementation of a user-friendly personalized and long-term eIC application, based on a usability study with (potential) research participants and semi-structured interviews with stakeholders on the practical integration of such an application in their daily practice.

Methods: An eIC prototype was evaluated and refined through usability testing among Belgian citizens and iterative redesign. Based upon a digital literacy questionnaire, a heterogeneous sample of participants was established. Participants needed to complete a series of usability tasks related to personalization and long-term interaction with the research team while using the 'think aloud' technique. In addition, usability tests involved completing the system usability scale (SUS) questionnaire and taking part in a semi-structured feedback interview. Furthermore, semi-structured interviews were conducted with ethics committee members, health care professionals, and pharmaceutical industry representatives, active in Belgium and involved in clinical research. Thematic analysis was undertaken using NVivo software.

Results: In total, three iterations of usability tests were conducted with 10 participants each. Each cycle involved some participants who reported having low digital skills. The SUS scores related to the tasks on personalization and long-term interaction increased after each iteration and reached 69.5 (SD=8.35) and 71.3 (SD=16.1) out of 100, respectively, which represents above-average usability. Semi-structured interviews conducted with health care professionals (n=4), ethics committee members (n=8), and pharmaceutical industry representatives (n=5) identified the need for an eIC system that can be easily set up. For example, a library could be established, enabling stakeholders to easily provide background information about a clinical study, presented in the second layer of the interface. In contrast, some functionalities, such as informing participants about new studies through an eIC system, were not considered useful by stakeholders.

Conclusions: This study provides insights for the implementation of a user-friendly personalized and long-term eIC application. Study findings show that usability testing is key to assess and increase the user-friendliness of an eIC application. Although this eIC system has the potential to be usable by a

wide audience, low-literate participants may not be able to use it successfully, arguing for additional participant support or other alternatives to an eIC system. In addition, key lessons emerging from the interviews include ensuring the application is easy to implement in practice and is interoperable with other established systems.

2 INTRODUCTION

Digital technologies are rapidly transforming society across many sectors, including the health sector. Since many years, digitalization of healthcare has been a priority for the European Union (262, 263). One of the objectives of the 'EU4Health program', adopted as a response to the COVID-19 pandemic, is to strengthen health systems by advancing digital transformation (263). This transformation holds the potential for improving patient centeredness and goal-oriented healthcare (264). For example, mobile health services may be used to send reminders to patients, monitor the patients' vital signs on a real-time basis, or enable patients to access medical information and communicate with health care professionals (HCPs) (265, 266).

The design of digital technologies is one of the critical factors that can influence successful implementation (245, 267). To increase ease of use and adoption, it is crucial to actively involve end users in the design process to translate their knowledge into new ideas and to co-create a technology that meets the end users' needs (212). Usability testing is part of the overall user-centered design process, consisting of iterative cycles of understanding the context of use and defining user requirements as well as designing and evaluating solutions to meet these requirements. According to the International Organization for Standardization (ISO) standard 9241-11, usability is defined as the "*extent to which a system, product or service can be used by specific users to achieve specified goals with effectiveness, efficiency and satisfaction in a specified context of use*". This ISO standard also highlights that the combination of the type of users, goals, and the context should be considered in the usability of digital technologies (268). Usability testing, an established technique in user-centered design, aims to improve the user-friendliness by detecting design flaws in interface elements or areas that need further improvement (269).

In the context of clinical research, the informed consent (IC) process is considered a basic principle of research ethics (3). To date, this process has mainly involved paper-based IC forms (ICFs), setting forth the pertinent aspects of a clinical study. Due to the digital transformation, a shift towards electronic IC (eIC) has been made. eIC refers to informing research participants and obtaining their consent electronically (48). It provides research participants the opportunity to learn about the study through a personalized approach, based upon their preferences, and to establish a long-term interaction with the research team during and after the study; for example, to return results or to provide participants with new IC versions upon study amendments (151, 207, 270). Digitalizing IC may also offer advantages for other stakeholders involved in clinical research. For example, eIC could decrease the administrative burden for research sites or could result in fewer inspection findings (51). Nevertheless, the trend

toward a digital future in clinical research requires the need for reinventing the modus operandi of these stakeholders (207, 271).

To date, various eIC applications, only some of them using personalized and long-term elements, have been developed by profit and nonprofit organizations (68, 76, 80, 121, 208, 209, 272, 273). However, only a small fraction of eIC applications have published their usability evaluation results (68, 121, 272, 273). Therefore, this study contributes to the dearth of literature on usability testing of a personalized and long-term eIC, a critical step in its user-centered design process. This study aimed (i) to investigate the usability of a co-designed personalized and long-term eIC prototype with (potential) research participants, and (ii) to seek the views of ethics committee (EC) members, HCPs, and representatives of the pharmaceutical industry on the practical integration of this eIC prototype in, and its influence on, their daily practice. Results may support the design of a user-centered eIC application and may assist responsible adoption of a personalized and long-term eIC application in clinical research.

3 METHODS

A mixed methods design was employed, consisting of (i) usability tests with (potential) research participants and (ii) semi-structured interviews with EC members, HCPs, and representatives of the pharmaceutical industry. In both study parts, a prototype implementation of an eIC system was used. Ethical approval for this study was obtained from the EC Research UZ/KU Leuven (ref. number S66313).

3.1 PROTOTYPE DEVELOPMENT AND DESCRIPTION

A user-centered design process was undertaken to design an eIC prototype. More concretely, the design of this prototype was informed by a systematic literature review, semi-structured interviews with various stakeholder groups involved in clinical research, and a co-design process with participants who had taken part in a clinical study (151, 207, 270, 274). Based upon this research, we identified various elements related to personalization and long-term interaction, such as presenting multiple layers of information or enabling the participants to indicate for which reasons they would like to establish a longitudinal interaction (Appendix L). Only the elements that we believe would add value compared to already existing eIC applications were implemented in the eIC prototype. The prototype, a client-side web application written in React, presented information of the Dutch paper-based ICF of a clinical study conducted in Belgian hospitals. This prototype has the main feature to inform (potential) research participants about study-related information, based on their preferences. To this end, participants can access additional information by consulting the second information layer of the interface (Figure 7). In addition, participants are able to mark study-related information they have

questions about, that may be further discussed during a video consultation with a member of the research team. With a particular focus on long-term interaction between the participants and the research team, other features were implemented such as enabling participants to indicate how and for which reasons they would like to be recontacted (e.g., to receive study results), to change preferences regarding data sharing, to review and sign new IC versions, and to withdraw from the study. A detailed description and visualization of the prototype, as used in the first iteration of usability testing, can be found in Appendix M.

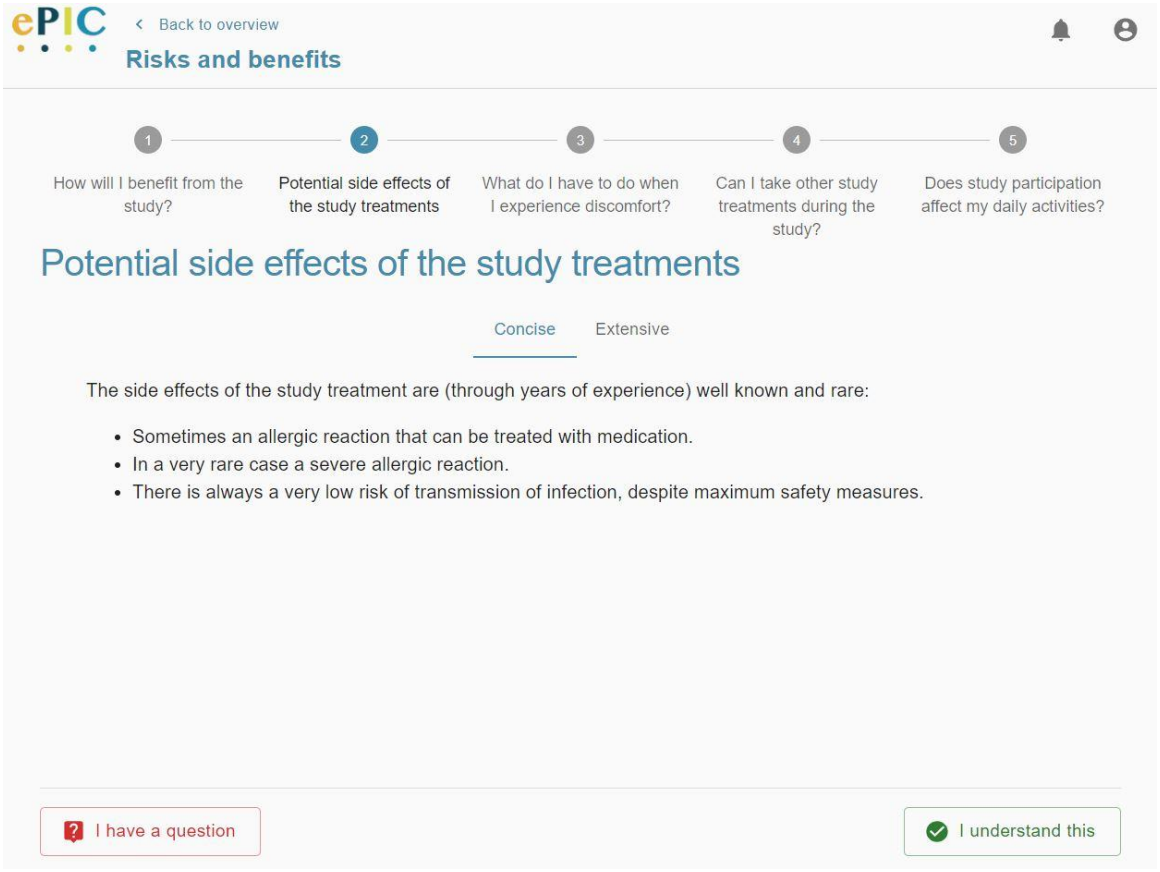

Figure 7. *Screenshot of the eIC prototype in the first iteration: multiple layers of information. Participants can navigate between the concise and extensive layers to hide or access additional information, respectively. If the information is not clear, participants can indicate that they have questions using the buttons at the bottom of the screen.*

3.2 USABILITY TESTING

3.2.1 PARTICIPANT SELECTION AND RECRUITMENT

Participants for usability testing were recruited via patient organizations and through active community outreach such as local community events. Potential participants were provided with flyers containing information on the eligibility criteria of the participants, the course of the study, the compensation for study participation, and contact information of the researcher. Individuals eligible for inclusion needed to be fluent in Dutch and aged 18 years or older. Those who were interested in participating contacted the researcher to express their interest. Hereafter, interested participants were asked to fill out a survey including demographic questions (e.g., age and highest education level) and questions related to digital literacy in order to establish a heterogeneous sample in the usability evaluation process (Appendix N). This survey, provided to the participants via email or regular mail, was based on the Belgian survey on 'Information and Communication Technologies (ICT) usage in households and by individuals' (275). After the establishment of a heterogeneous sample, the researcher provided the selected participants with the paper-based ICF of this study. All participants provided written consent before participation in a usability test. For each iteration, other participants were recruited to assure that they did not have experience with the previous eIC prototype.

3.2.2 PROCEDURE AND DATA COLLECTION

Iterative cycles of usability tests were used to evaluate and refine the eIC prototype following each cycle. After each iteration, the findings were discussed with the research team to further refine the prototype. Usability tests took place between April and July 2022 and lasted up to 60 minutes. Depending on the preference of the participant, usability tests were conducted face-to-face or by using Microsoft Teams. In case of remote usability testing, the participant was given control of the researcher's screen to interact with the eIC prototype. At the start of each usability test, the context and aims of this study were explained. In addition, some instructions were provided to the participants (Appendix O). Hereafter, participants were asked to perform specific tasks, without any pre-acquired knowledge of the eIC prototype, that users may perform when using the application in practice. The given tasks, related to personalization and long-term interaction, varied slightly between the iterations, depending on the changes made to the prototype (Appendix P). The tasks prepared for the first iteration were tested in three pilot usability tests. In case of a remote usability test, the participant was provided with the tasks via email or regular mail in the days leading up to the usability test. Participants were encouraged to think aloud while performing these tasks, meaning that they had to state out loud and explain their actions. Gaining insights into their reasoning when undertaking specific

actions may result in redesign recommendations (276). During each usability test, we collected performance measures such as the number of errors and moments of confusion. In addition, subjective measures were collected (e.g., participants' spontaneous comments). After each task, we had focused discussions, for example about specific errors made. After the tasks on personalization as well as the tasks on long-term interaction, the participant filled out the system usability scale (SUS). The SUS contains 10 statements for which participants must indicate the strength of their agreement with the statement, ranging from 1 (strongly disagree) to 5 (strongly agree) (277). Audio- and screen-recordings were made during each usability test.

3.2.3 DATA ANALYSIS

During each iteration, a summary sheet was created, containing the number and type of errors made by participants and the number of times they needed help (if applicable). This summary sheet, combined with listening to and watching the audio- and screen-recordings, respectively, informed the redesign of the eIC prototype. To be able to report the findings adequately, thematic analysis was used to analyze the qualitative data (153). First, all audio-recordings were transcribed verbatim. Second, NVivo software was used to code the first two transcripts thematically via a mixed deductive-inductive approach. The creation of deductive codes was based upon the tasks whereas inductive codes focused on the functionalities of the eIC prototype that needed to be redesigned. Hereafter, deductive and inductive codes were categorized, resulting in a working analytical framework. Subsequently, this framework was applied to the other transcripts and was then further refined. Finally, the coded data were charted in Microsoft Excel to create a framework matrix.

The SUS was scored according to the best practices described by Brooke, with the score for each statement ranging from 0 to 4 (277). The score from odd statements (i.e., statement 1, 3, 5, 7, and 9) is calculated as the scale position minus 1. For even statements (i.e., statement 2, 4, 6, 8, and 10), the score is calculated as 5 minus the scale position. The sum of both scores is then multiplied by 2.5 to obtain the overall SUS value.

3.3 SEMI-STRUCTURED INTERVIEWS

3.3.1 INTERVIEWEE SELECTION AND RECRUITMENT

Semi-structured interviews were conducted with people from three stakeholder groups: EC members, HCPs, and pharmaceutical industry representatives. Interviewees were eligible for inclusion if they (i) were involved in clinical research, (ii) had fluent proficiency in Dutch, and (iii) were active in Belgium.

A purposive sample of interviewees was identified by exploring stakeholder websites and via the network of the research group. In addition, snowball sampling was used whereby interviewees suggested potential recruits. An invitation, including the IC of this study, was mailed to suitable interviewees. Recruitment continued until data saturation was achieved, meaning that no new insights were observed in the data. All stakeholders provided written IC before taking part in an interview.

3.3.2 PROCEDURE AND DATA COLLECTION

Interviews were conducted with multiple stakeholders to explore qualitative insights regarding the practical implementation of the eIC prototype in their daily practice. Interviews took place between June and September 2022 and were conducted by using Microsoft Teams. Interviews were conducted in Dutch, lasted between 23 and 50 minutes, and were digitally audio-recorded. All interviews were conducted by the same researcher (EDS). An interview guide was developed based upon the research aims (Appendix Q). At the beginning of each interview, the definition of eIC as issued by the European Medicines Agency was provided to interviewees to familiarize them with the term 'eIC' (48). Hereafter, the interviewee was guided through the eIC prototype while being asked questions related to personalization and long-term interaction. In addition, the interview guide included questions on the impact of such a prototype on their daily practice.

3.3.3 DATA ANALYSIS

The analysis of the semi-structured interviews was similar to the abovementioned qualitative analysis of the usability tests (153). However, the creation of deductive codes was informed by themes integrated in the interview guide whereas inductive codes were created based upon observed patterns.

4 RESULTS

Three iterations of usability testing were conducted with 10 participants each (30 in total). Each iteration involved some participants who reported having little experience with computers or tablets (Table 13). In addition, 15 interviews were conducted with EC members (n=8, of whom two EC members were present at a single interview), HCPs (n=4), and representatives of the pharmaceutical industry (n=5, of whom two representatives were present at a single interview). All investigators were based in the same hospital. EC members and representatives of the pharmaceutical industry were active in five different Belgian ECs and three different companies, respectively. We first present the main results on personalization and long-term interaction emerging from the usability tests and the

semi-structured interviews, followed by stakeholder views on other practical elements related to eIC implementation.

Table 13. *Demographic and computer use characteristics of participants involved in usability testing*

Characteristics	**Iteration 1 (n=10)**	**Iteration 2 (n=10)**	**Iteration 3 (n=10)**
	n	**n**	**n**
Age range (years)			
18-39	3	2	2
40-59	2	0	3
60-79	5	8	5
Sex			
Male	7	7	6
Female	3	3	4
Education			
Secondary school not completed	0	0	1
Secondary school	3	3	6
Bachelor's degree	4	2	2
Master's degree	3	3	0
Other	0	2	1
Employment status			
Student	0	1	0
Employed (full time, part time…)	5	1	5
Retired	5	8	5
Having a computer or tablet at home with internet access			
Yes	9	10	10
No	1	0	0
Types of purposes for which this computer or tablet is used *(multiple answers possible)*			
Internet banking	8	9	6
Seeking information	9	9	8
Sending / receiving emails	8	8	7
Consulting social media	6	6	4
Listening to music	6	6	4
Other	3	3	2
Frequency of using this computer or tablet			
(Almost) every day, and even multiple times a day	8	8	5

(Almost) every day, but not multiple times a day	0	1	2
At least once a month, but not every week	1	1	2
Less than once a month	0	0	1
Types of activities carried out in the last 12 months *(multiple answers possible)*			
Transferring files between computers, tablets, or other devices	5	6	3
Installing software or applications (apps)	6	6	4
Changing the settings of any software programs	2	0	1
None of the above	6	3	6
Types of software activities carried out in the last 12 months *(multiple answers possible)*			
Copying or moving files or folders	6	7	4
Using word processing software	7	7	5
Creating presentations or documents integrating text, pictures, tables, or charts	5	4	1
Using software to edit photos, video, or audio files	4	3	2
Writing code in a programming language	1	2	0
None of the above	2	2	4

4.1 SYSTEM USABILITY SCALE

The SUS scores regarding the tasks on personalization (i.e., tasks 1-5) and on the long-term interaction (i.e., tasks 6-8) are listed in Table 14 and 15, respectively. As shown in these tables, the SUS score increased after each iteration. The final SUS was rated with average scores of 69.5 (SD=8.35) and 71.3 (SD=16.1) out of 100 for personalization and long-term interaction, respectively. A score above 68 is considered above-average usability (278).

Table 14. *SUS scores related to personalization of the eIC prototype*

	Iteration 1, mean (SD)	**Iteration 2, mean (SD)**	**Iteration 3, mean (SD)**
1. I think that I would like to use this system frequently	3.2 (0.92)	4.2 (0.63)	3.5 (0.71)
2. I found the system unnecessarily complex	3.2 (0.79)	2.5 (0.85)	2.0 (0.47)
3. I thought the system was easy to use	3.0 (0.82)	3.5 (1.2)	3.8 (0.63)
4. I think that I would need the support of a technical person to be able to use this system	2.9 (1.3)	2.8 (1.6)	2.8 (1.2)
5. I found the various functions in this system were well integrated	3.1 (0.88)	3.7 (0.82)	4.3 (0.48)
6. I thought there was too much inconsistency in this system	2.0 (0.82)	2.6 (1.4)	2.0 (0)
7. I would imagine that most people would learn to use this system very quickly	2.7 (0.95)	3.2 (1.1)	3.9 (0.74)
8. I found the system very cumbersome to use	2.9 (0.74)	2.3 (1.3)	2.1 (0.32)
9. I felt very confident using the system	3.3 (0.95)	3.4 (1.1)	3.7 (0.68)
10. I needed to learn a lot of things before I could get going with this system	2.9 (1.1)	2.7 (1.3)	2.7 (0.68)
Total SUS score	53.5 (16.8)	62.8 (19.4)	69.5 (8.35)

Table 15. *SUS scores related to a long-term interaction established by the eIC prototype*

	Iteration 1, mean (SD)	**Iteration 2, mean (SD)**	**Iteration 3, mean (SD)**
1. I think that I would like to use this system frequently	3.5 (0.85)	4.4 (0.70)	4.0 (0.82)
2. I found the system unnecessarily complex	3.1 (0.88)	2.3 (1.3)	2.1 (0.88)
3. I thought the system was easy to use	3.3 (1.1)	4.1 (0.88)	3.7 (0.82)
4. I think that I would need the support of a technical person to be able to use this system	2.7 (1.4)	2.1 (1.3)	2.3 (1.1)
5. I found the various functions in this system were well integrated	3.6 (1.1)	3.5 (0.85)	4.1 (0.57)
6. I thought there was too much inconsistency in this system	2.3 (1.2)	2.1 (1.2)	1.7 (0.68)
7. I would imagine that most people would learn to use this system very quickly	2.7 (1.1)	3.1 (1.2)	3.7 (0.95)
8. I found the system very cumbersome to use	2.6 (1.1)	2.0 (0.82)	2.0 (0.67)
9. I felt very confident using the system	3.5 (1.1)	3.6 (0.70)	3.7 (0.68)
10. I needed to learn a lot of things before I could get going with this system	3.1 (1.2)	2.1 (1.5)	2.6 (1.3)
Total SUS score	57.5 (19.5)	70.3 (17.3)	71.3 (16.1)

4.2 PERSONALIZATION

The personalization features of the eIC prototype concern the display of information at different levels of detail and handling questions and unclarities about this information.

4.2.1 USABILITY TESTING

a) Offering information in layers

The eIC prototype did not present all information at once but placed some information in a second layer, requiring an extra interaction to retrieve it. Participants involved in usability testing were asked to consult certain information presented in such a second layer. This task revealed usability issues in all iterations. In the first iteration (Figure 7), the majority of participants was not able to find this information promptly when navigation through a particular information section. One participant (P7) said: "*I did not notice that more detailed information could be consulted*". Following this iteration, some modifications were made to draw more attention toward this feature, namely (i) by adding an outlined button, including an icon, at the bottom of the interface that participants could also use to switch between concise and extensive information, and (ii) by adding icons in the text buttons 'Concise' and 'Extensive' at the top. However, these changes did not have a positive impact on the performance of this task in the second iteration. In this second iteration, multiple participants voiced that "*they had not seen that the button 'Extensive' was displayed on the interface*". Therefore, it was decided to simulate a tab-like interface by moving the topmost buttons to the left side of the interface, using outlined buttons rather than text buttons, and changing the text label of these buttons to 'Concise information' and 'Extensive information' (Figure 8). As a result of these actions, all but three participants found the required information in the third iteration. In line with the previous iterations, these three participants indicated that they were not aware that additional information could be accessed.

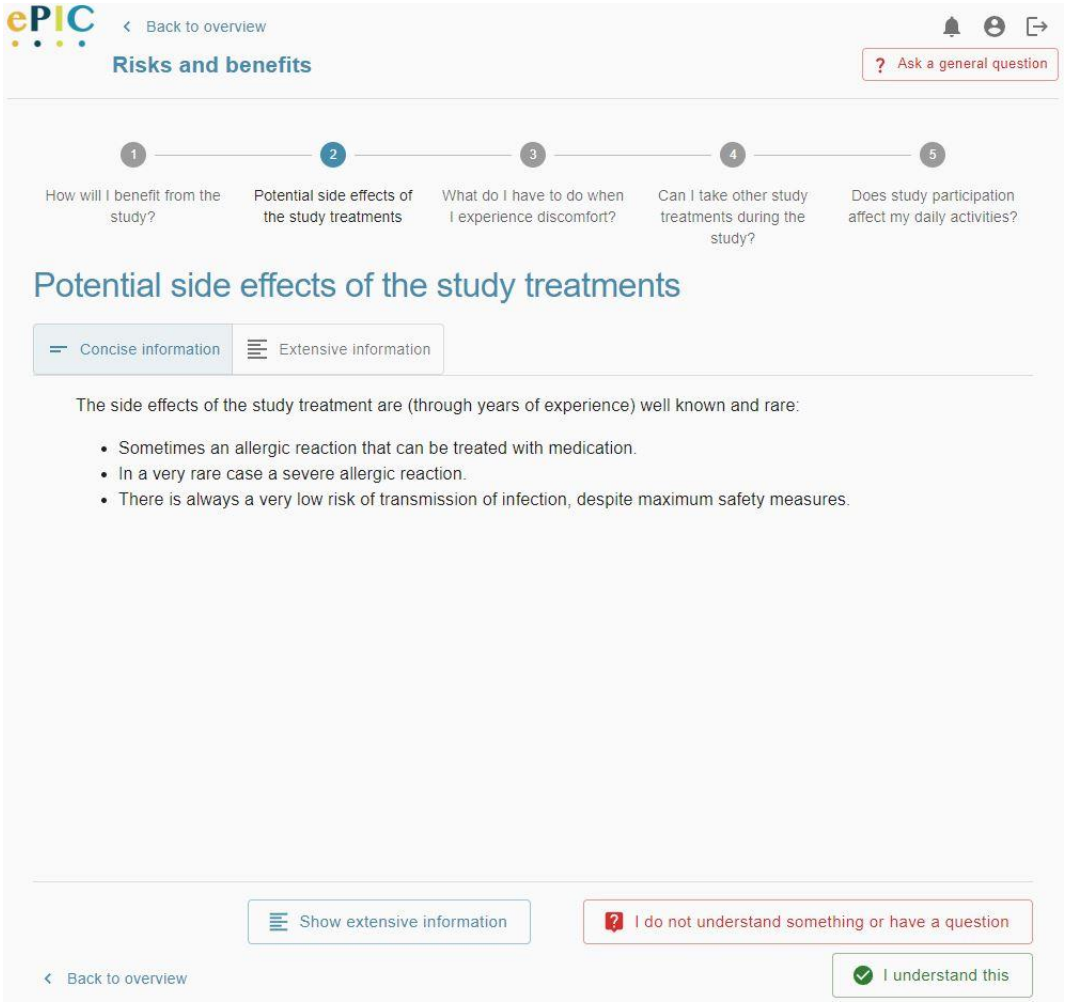

Figure 8. *Screenshot of the eIC prototype in the third iteration: offering information in layers*

b) Adding questions and indicating unclear information

The eIC prototype allowed participants to mark information that is not clear to them and to add a general question to the investigator in case this question does not belong to a particular piece of information included in the consent form. Some difficulties with usability were noted for both functions. The main issues observed during the first iteration were that (i) participants did not indicate which paragraph contains unclear information (although the system expects this) and (ii) participants did not link the button label 'I have a question' to the phrasing '[…] indicate that you do not understand particular information', mentioned in the task. After completion of the first iteration, the following adjustments were made to the eIC prototype: (i) changing the text label of the button 'I have a question' into 'I do not understand something or have a question' and (ii) adding the following instructions when the button 'I do not understand something or have a question' is clicked: 'You can select multiple paragraphs. Please click the button 'Continue' to continue with the other information sections. By clicking the button 'Cancel', your designations on this page will be removed.'.

By making these changes, a positive evolution was noticed in the second iteration. However, there were still some participants who did not indicate the paragraph containing unclear information. In the second iteration, we also asked participants to add a general question, which was perceived difficult by the majority of participants: "*I am looking in all information sections but I cannot find how to add this question.*" (P13).

After completion of the second iteration, we clarified in the task that this question was not related to any of the information sections. In addition, the eIC prototype was adjusted as follows: the abovementioned message, appearing when clicking the button 'I do not understand something or have a question', was highlighted in red and specified that a general question can be added by pressing the button on the top right of the interface (Figure 9). However, in the third iteration, we still observed multiple participants who had difficulty with indicating and saving the paragraphs containing unclear information. Specifically, these participants did not know that the question mark icon, displayed next to each paragraph, needed to be clicked or made use of the button 'Cancel' instead of 'Continue'.

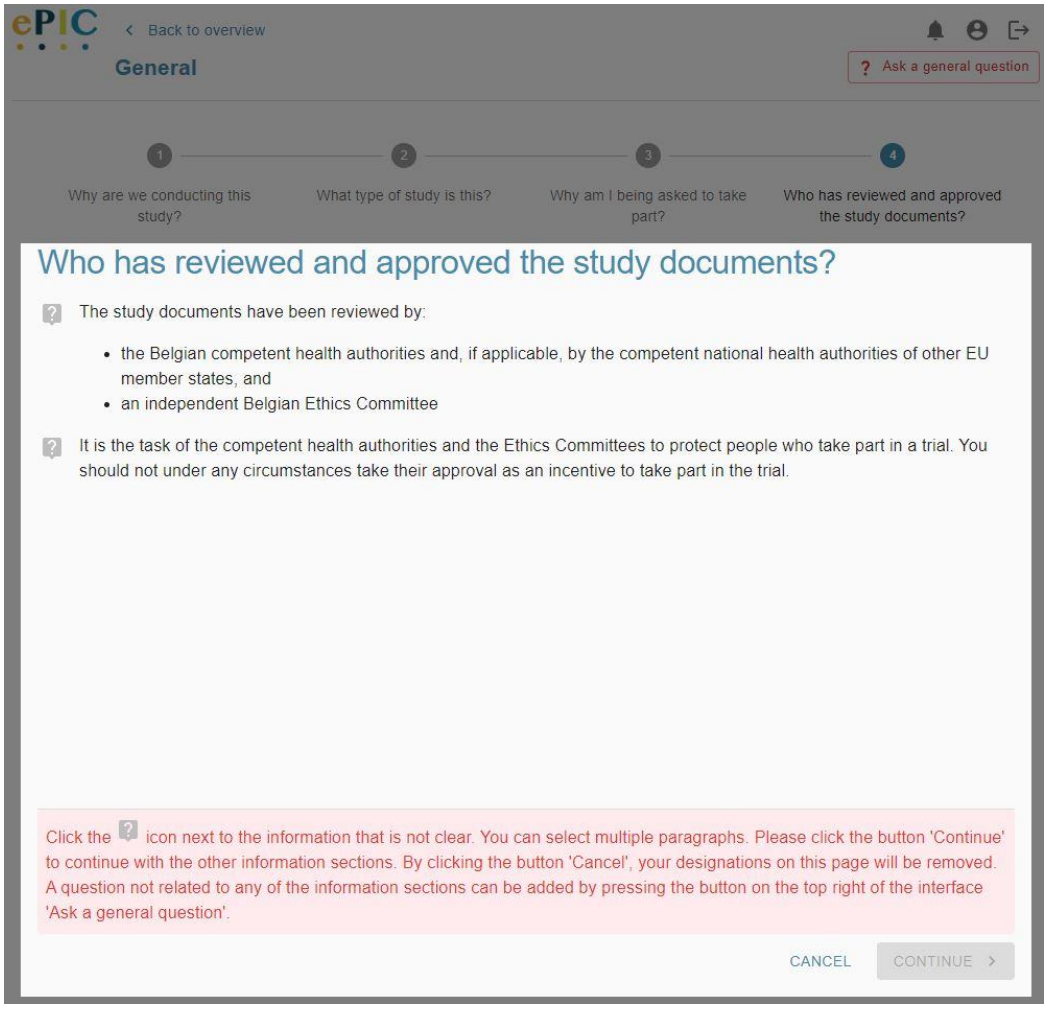

Figure 9. *Screenshot of the eIC prototype in the third iteration: indicating unclear information*

c) Providing informed consent

Participants were asked to provide their IC. The eIC prototype enforces that all general questions and unclarities are explicitly marked as resolved before consent can be given. Therefore, the participants had to imagine that their general question and unclear study-related information were discussed with the research team. The major usability problems revealed in the first iteration concerned shortcomings in indicating that all questions were answered. Following this iteration, the text button 'Marked as solved' was put next to the question or unclarity. Nevertheless, the second iteration revealed that the indication 'Marked as solved' was confusing for various participants: "*I already clicked 'Marked as solved' but it seems that it is not indicated as solved*" (P19). This error was corrected by implementing a slider, resulting in all but three participants who successfully completed this task in the third iteration, mainly because these participants did not know how to use this slider (Figure 10).

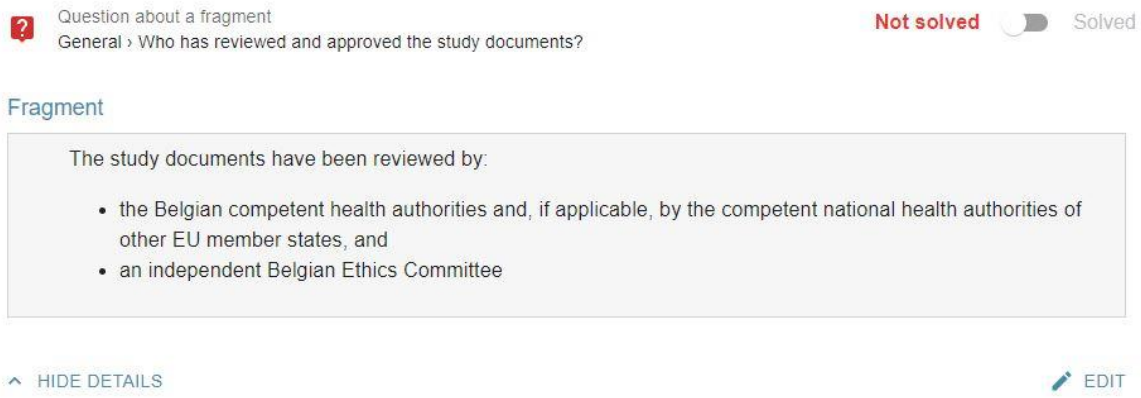

Figure 10. *Screenshot of the eIC prototype in the third iteration: indicating questions as solved*

4.2.2 SEMI-STRUCTURED INTERVIEWS

a) Offering information in layers

Several interviewees had reservations about this feature. Some pharmaceutical industry representatives raised that it could be burdensome for a clinical trial sponsor to provide extensive information. Therefore, they advised that a library be established, containing detailed information on specific health conditions or clinical trial designs. It was also raised that an (electronic) IC should, among others, facilitate the dialogue with the research team and should not be conceived as a document to educate research participants. In addition, pharmaceutical industry representatives were doubtful about the ECs' and inspectors' views on the tiered approach.

"*There is a high chance that inspectors have comments on this functionality, in particular because participants are not obliged to access the extensive information before providing consent*." (13, pharmaceutical industry representative)

Almost all EC members were of the opinion that offering information in layers would not be an issue in their assessment process. They highlighted that research participants who would prefer a paper-based ICF rather than eIC should be provided with all the information. EC members considered it important to inform the participants, using eIC, of the possibility to access additional information, if preferred. They also believed that the first information layer should contain all crucial information for participation in the trial whereas the second layer could further lay down background information. However, one EC member raised the point that it would be challenging to decide which information should be made available in the first and second information layers.

"*All pertinent aspects of a study should be conveyed to the participants. In case background information is provided, this information can be mentioned under 'Extensive information'. However, I think it will be difficult to make a distinction between important information, mentioned in the first layer, and background information.*" (5, EC member)

b) Discussing and indicating unclear information

The interviewees mainly reported that the participants should indicate in the eIC application that their questions have been discussed and answered. However, some HCPs raised that they should also be able to do so in name of and upon demand of the participant.

"If it concerns a person with limited digital literacy, we can go through the electronic informed consent system together. In that case, it would be useful that I can also indicate that questions have been answered using my account." (4, health care professional)

In addition, it was unclear how and when these questions should be discussed. It was raised that this could result in an additional burden for the research team, in particular when questions would be discussed remotely.

"*If participants read the informed consent form on site, we can immediately discuss any questions. But if the participants would like to discuss questions via a video consultation, does that mean that someone of the research team should always be available?*" (6, health care professional)

c) A personalized interface for ethics committees

One feature that was discussed specifically with the EC members was the possibility of using the eIC platform itself to manage the comments and decisions of the EC, rather than an out-of-band mechanism (e.g., custom platforms or documents sent via e-mail). The majority of EC members raised several challenges related to this feature. First, it was argued that there are numerous eIC applications that do not offer the same functionalities, negatively impacting a broadly consistent and workable approach. Second, all comments on the trial protocol should be returned in a comprehensive document. To this end, an eIC application should be interoperable with the other systems already in place. Third, it was considered to be burdensome for the patient representatives involved in the EC, who may be elderly, to provide their comments in an eIC application.

d) Additional functionalities

When interviewees were asked which additional functionalities, related to personalization, would be needed to add value over paper-based ICFs, several suggestions were raised. HCPs believed that it would be useful to gain insights into metrics related to a participant's interaction with the eIC application (e.g., the total time interacting with the application). In addition, some pharmaceutical industry representatives raised that it would be valuable to know which sections result the most in questions.

> "*It would be interesting to gain insights into which information sections most often raise questions. I would not say this is a must, but it could help to improve informed consent forms.*" (14, pharmaceutical industry representative)

4.3 LONG-TERM INTERACTION

The long-term interaction features of the eIC prototype concern the ability for participants to autonomously change earlier choices (i.e., related to sharing their personal data for other research or receiving results of the study), review and sign an updated version of a consent form, and withdraw their consent to participate in the study.

4.3.1 USABILITY TESTING

a) Personal data re-use preferences

Participants were asked to indicate that they no longer consented to the use of their personal data in other research and development activities. In the first iteration, changing choices and withdrawing from the study could be done on the same page (Appendix M). Almost half of participants withdrew

their consent for study participation instead of changing their preferences on data sharing. One participant (P5) raised the following: "*I noticed the button 'Withdraw' so I thought that I had to click this button*". Following this iteration, some adjustments were made to the eIC prototype: 'Withdraw' buttons were also introduced to undo earlier choices as well as a confirmation dialog to verify whether participants want to continue or cancel the requested action when the IC for study participation would be withdrawn. Nevertheless, similar results were observed in the second iteration. For the third iteration, it was therefore decided to present the actions of changing preferences on data sharing and withdrawing consent for study participation on two distinct interfaces (Figure 11), which positively impacted the results. However, there was still one participant who withdrew his consent for study participation.

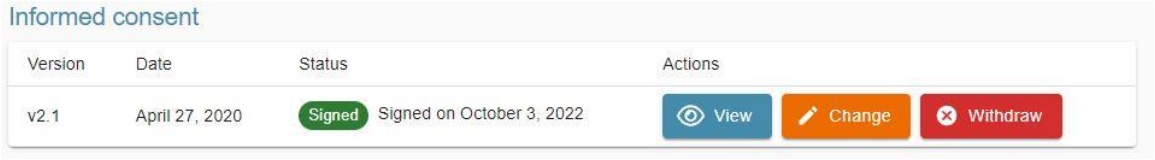

Figure 11. *Screenshot of the eIC prototype in the third iteration: presentation of the actions of changing preferences and withdrawing on different interfaces*

b) Changing preferences regarding study results

The participants were requested to change their preferences regarding receiving the study results via email. This could be done in the prototype by clicking the 'Manage' button under the section 'Study preferences'. The main issue observed in the first iteration related to some participants who instead consulted the information section 'Findings and results' of the consent form to change their preferences: "*In this section it is mentioned that the results will be made available on specific websites. I believe I have to click these hyperlinks to indicate that I wish to receive the results.*" (P8). To support end users in changing their preferences regarding study results, we changed the title 'Study preferences' to 'Study results' and the text label of the button 'Manage' to 'Manage your preferences'. As a result, all but one participant in the second iteration and all participants in the third iteration were able to successfully change their preferences.

c) New informed consent version

Participants received a notification that a new IC version had been made available. When viewing the new ICF, the eIC prototype indicates which sections have changed, and provides a side-by-side view to compare the changes to the text. In the first iteration, unchanged information sections (i.e., those identical to the previously signed consent form) were highlighted in green while changed sections had

a white background with an icon that indicated they were changed (Appendix M). Some participants thought that the unchanged information sections, highlighted in green, were those that included changes. In addition, almost half of participants were confused about how the concrete changes to the text were displayed. It was raised that "*the logic was hard to find*" (P1) and that "*it would be better to put the new version on the right side of the interface*" (P3). In response, for the second iteration, we highlighted the information sections containing changes in orange, and put the integral text of the previous consent version on the left of the interface while only showing modifications on the right (Figure 12). Nevertheless, one participant (P22) involved in the second iteration raised that "*it was unclear which sections included changes*". To this end, efforts were made to further emphasize the changed information sections by explicitly adding a 'CHANGED' label (Figure 13), resulting in all participants successfully completing this task in the third iteration.

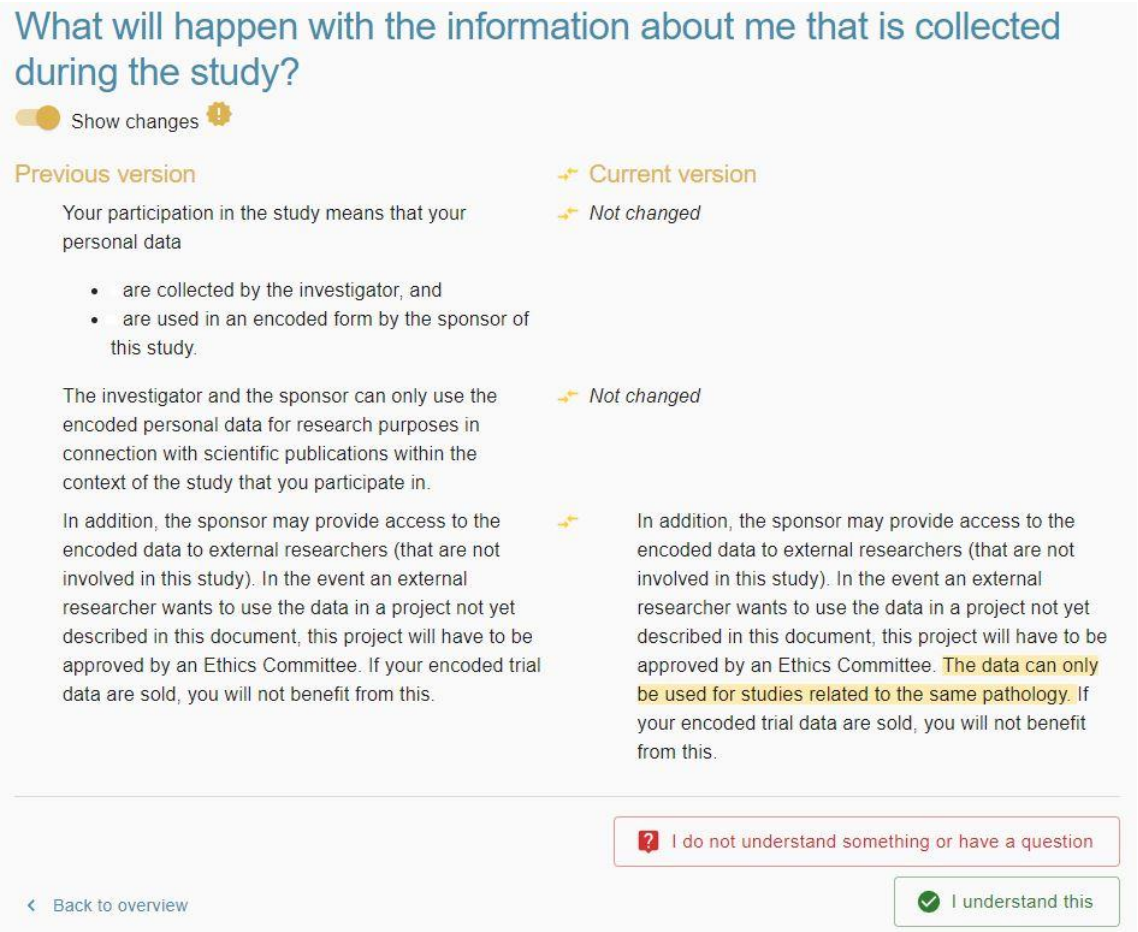

Figure 12. *Screenshot of the eIC prototype in the third iteration: presentation of the concrete changes of a new IC version*

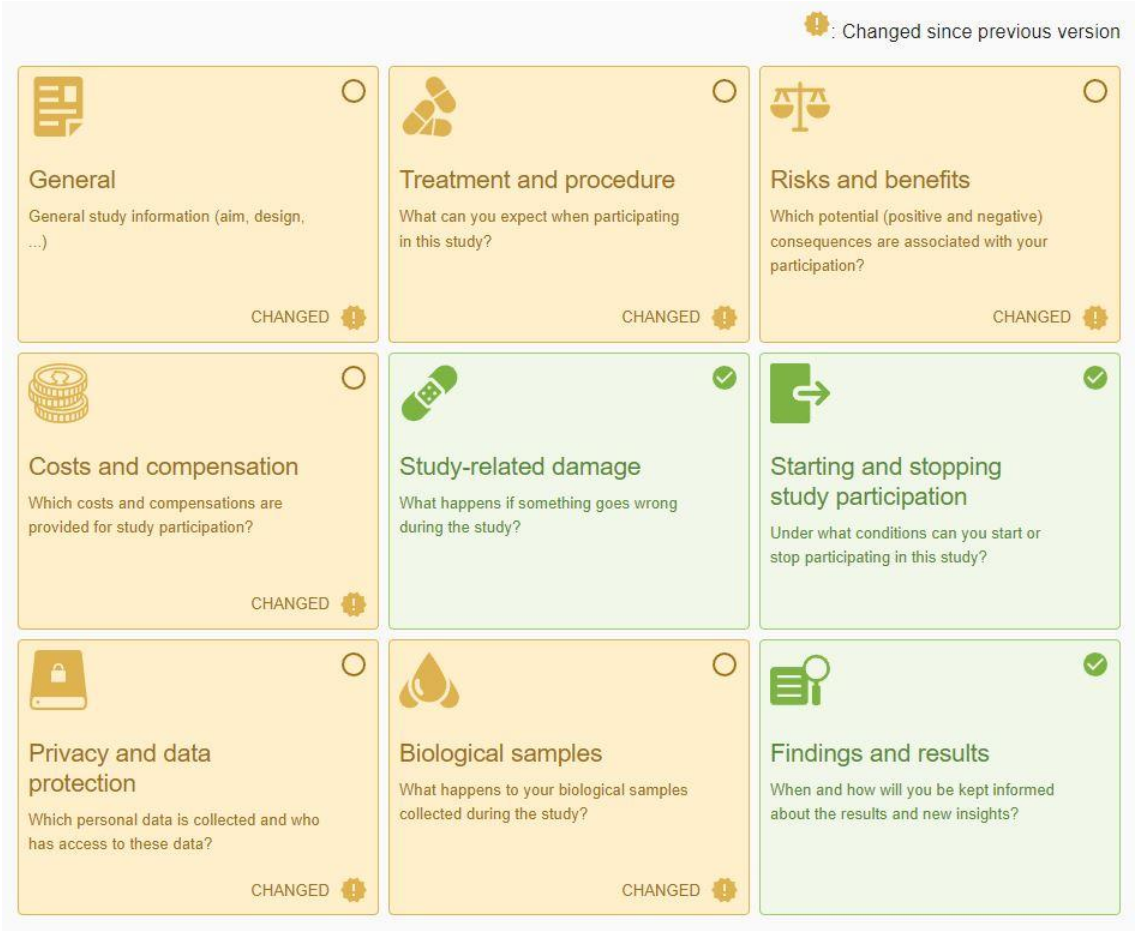

Figure 13. *Screenshot of the eIC prototype in the third iteration: presentation of the information sections of a new IC version*

4.3.2 SEMI-STRUCTURED INTERVIEWS

a) Withdrawing trial participation and changing preferences

Some EC members and pharmaceutical industry representatives argued that withdrawing consent should be as easy as giving it, and therefore, agreed that participants should be able to withdraw their consent electronically. In addition, a few pharmaceutical industry representatives voiced that this functionality is in line with the Good Clinical Practice standard and would ensure consent process efficiency by providing an audit trial, which is a reliable record of all consent-related activities. Many interviewees across stakeholder groups raised that it is of utmost importance that the participants' further medical care is discussed with the research team after withdrawing. To this end, it was suggested to organize a conversation with the research team, once the button 'Withdrawing consent' is clicked, to give the participants a variety of instructions for ending their participation in the trial. For instance, additional visits may be required to monitor the participant for any future adverse events. Some interviewees were reluctant to enable participants to withdraw their consent electronically, in

particular because participants may have unwarranted concerns about the study. Therefore, it was raised that the eIC interface should enable participants to provide their reason(s) for withdrawing prematurely from the trial and that clicking the button 'Withdrawing consent' should not immediately result in permanent withdrawal from the study.

> "*It should be avoided that participants have unwarranted concerns and are therefore withdrawing from the study. I would also not activate the withdrawal immediately but first organize a consultation with the research team to discuss any issues.*" (2, health care professional)

In addition, several HCPs stated that they should receive an alert when a participant would like to withdraw from a trial, preferably via the participant's electronic health record.

> "*I am already overloaded with emails. In case of paper-based informed consent forms, the participant informs the investigator or the study nurse orally about withdrawing from the trial. If the participant withdraws his or her consent electronically, I would prefer to be informed via the participant's electronic health record rather than via email.*" (4, health care professional)

Similarly, questions arose regarding how the research team would be informed of changed preferences (e.g., about data sharing) and whether these preferences would be linked to a particular database. Some interviewees also stated that it is key to inform participants about this feature and the potential implications.

> "*There are studies in which the participants should explicitly consent to additional investigations on their samples. These investigations are key to advance scientific research. Therefore, I think it is important to inform participants about the implications of changing their preferences*." (16, pharmaceutical industry representative)

b) Receiving information about new studies

An additional functionality discussed with the interviewees was a feature to inform participants of new studies they could consider participating in. This was not deemed valuable by the interviewees. Some pharmaceutical industry representatives raised that this feature is not useful because it is already part of established eSource systems. In addition, some interviewees across stakeholder groups stated that this feature does not belong in an eIC application.

"*Receiving information about new studies via an electronic informed consent system goes too far. I am not in favor of it.*" (10, EC member)

Moreover, questions arose regarding the type of studies that participants would be informed about and whether this functionality would not result in revealing the identity of participants who have taken part in a particular trial.

c) Providing results

Several interviewees raised the point that an eIC application can be used to inform the research participants about the final study results. However, it was mentioned that preliminary results are often not shared for various reasons, such as to avoid creating false expectations or the potential to have increased drop-out rates in the control and experimental arms. Therefore, it was not considered useful to have the option to share preliminary results in an eIC application. Some interviewees indicated that the return of a clinical trial summary in lay language is a mandatory requirement of the Clinical Trials Regulation and therefore questioned the need to explicitly ask participants whether they would like to receive this summary via an eIC application.

"*Offering the participants the choice will result in logistic issues. Either we do it by default or we inform the participants that they can access the results on the Clinical Trials Information System website.*" (15, pharmaceutical industry representative)

In addition, a pharmaceutical industry representative advised to clearly specify the duration until when participants can change their preferences regarding study results to enable this functionality from an organizational perspective.

4.3.3 Set-up and interoperability of a personalized and long-term electronic informed consent application

Some interviewees believed that interoperability, for example with electronic health records or with eSource systems, is a key enabler for successful implementation of eIC. An EC member also voiced the opinion that interoperability between the eIC application and the Clinical Trials Information System would be valuable.

"*It would be useful if the electronic informed consent system could communicate with the Clinical Trials Information System. However, I doubt the feasibility because it concerns a European system.*" (5, EC member)

According to some pharmaceutical industry representatives, it would be challenging to develop a personalized and long-term eIC application. Therefore, they advised that a template, which already offers the building blocks, be developed. Similarly, an HCP, mainly involved in phase 1 trials, raised that there are often changes in the ICF due to study amendments. To this end, the ability to quickly set up and modify the eIC application was deemed paramount.

5 Discussion

This study aimed to identify insights for the design and implementation of a user-friendly personalized and long-term eIC application in clinical research, based on a usability study with (potential) research participants and semi-structured interviews with various stakeholder groups (i.e., EC members, HCPs, and pharmaceutical industry representatives). The eIC prototype, evaluated in the third iteration of usability testing, scored 69.5 (SD=8.35) and 71.3 (SD=16.1) out of 100 on the SUS for personalization and long-term interaction, respectively, rating the overall usability as above-average (278). Overall, stakeholders reported divergent views with regard to the eIC prototype; for example, related to the functionality of withdrawing consent for taking part in a study through an eIC system. Furthermore, they emphasized the importance of an eIC system that can be easily set up and implemented in practice.

5.1 Improving the participant's understanding

In designing the eIC prototype, we aimed to include (i) a tailored approach based on the individual's information needs and (ii) the potential to establish a longitudinal interaction with the research team. Our eIC prototype included similar information as included in a paper-based ICF of a trial conducted in Belgian research sites. However, this information was presented in another format; for example, by using expandable sections and a layered approach, allowing distillation of information to meet the individual participant needs. In this study, emphasis was mainly put on functionalities related to personalization and long-term interaction rather than on enhancing the participants' understanding. A systematic literature review conducted by Pietrzykowski et al. indicates that study participants' deficiencies in understanding are primarily related to not grasping the concept of randomization and placebo as well as the risk(s) associated with study participation (36). By using interactivity and multimedia, eIC may contribute to a better understanding of study-related information (57, 58). To

this end, efforts should be made to present specialized medical and legal terminology in a way it meets the unique learning needs of patient populations, and thus, facilitate informed decision-making.

5.2 Leveraging a personalized and flexible electronic informed consent system

A few participants in the third iteration of usability testing had difficulty completing the tasks related to the personalization features of the eIC prototype; for example, to access information presented in the second layer of the interface, potentially compromising a valid consenting process. However, EC members highlighted that all the crucial information should be part of the first information layer, thus overcoming the ethical issue of research participants not being fully informed about what it means for them to take part in a clinical study. Furthermore, if research participants would like to learn more about a particular topic, a consultation with the research team could be set up.

Next to usability testing, the likelihood that an eIC system will be accepted by stakeholders in the field is a prerequisite for successful adoption (279). Several comments from stakeholders indicate a hesitant attitude toward our proposed eIC format. For example, during the semi-structured interviews it was mentioned that an ICF should not be conceived as a document to educate research participants, thereby eliminating the need for providing background information in the second layer of the interface. While there is no one definition of IC, it usually includes that participants agree to take part in a study "*based on an understanding of (usually disclosed) relevant information*", which can only be possible if they are sufficiently educated (280). Other issues observed during usability testing relate to indicating paragraphs that contain unclear information and marking questions and unclarities as resolved, which prevents participants from providing their consent. However, for the latter, HCPs raised that they should also be able to indicate that these questions have been answered in name of the participant, thus mitigating the impact of this usability issue.

To minimize the aforementioned usability issues in practice, we propose the design and use of a personalized and long-term eIC system to be centered on the following recommendations: (i) pay careful attention to making the existence of additional information readily apparent on the eIC interface, (ii) inform research participants about the opportunity to access additional study-related information, (iii) prefer interfaces that lead participants to record superfluous questions, rather than accidentally removing questions, and (iv) inform research participants that (general) questions can be added, clarify how to do so, and how these can be resolved after discussing with the research team.

In addition to personalization features for research participants, an eIC system could also provide ECs with a personalized interface to manage their comments and decisions. However, one of the challenges raised by EC members regarding this feature concerns interoperability with already established systems. It should be avoided that an eIC application would be isolated from existing infrastructure, resulting in an additional workload for stakeholders (254). To this end, it is key that an eIC application can be integrated into existing IT systems to enable seamless communication across these systems (190). In the context of the ethical review, software could be leveraged to automatically generate comprehensive documents (potentially in multiple formats), including all comments on the IC and the trial protocol provided electronically by the EC members, thereby increasing interoperability without increasing EC members' workload.

5.3 Design considerations for driving long-term interaction features

The developed eIC prototype includes various long-term interaction features: research participants are able to change their preferences with regard to sharing personal data and receiving study results, to re-consent upon study amendments, and to withdraw their consent to take part in the clinical study. In the third iteration of usability testing, we identified participants who accidentally withdrew from the study, which can seriously hinder research (39). Although one might question whether the introduction of additional hurdles is ethically and legally acceptable, stakeholders' proposal to organize a consultation with the research team when a participant wishes to withdraw from the study may act as a safeguard in this regard. Generally, to minimize usability issues with longitudinal features in real-life clinical situations, the following recommendations can be derived from our study: (i) provide alternatives that prevent participants from accidentally withdrawing their consent. For example, at the beginning of the interface to withdraw consent, first refer to the possibility of changing preferences (e.g., regarding data sharing), or use an interactive decision aid that ensures the correct choice is made, (ii) inform research participants that they can change preferences with regard to receiving study results, and (iii) ensure that the changes in a new IC version are clearly visible. However, even when taking into account the abovementioned recommendations for personalization and long-term interaction features, additional considerations may be necessary to ensure inclusion of participants who are unaccustomed to digital interactions in their personal lives. For example, support of the research team may be needed to guide participants through the eIC interfaces or participants can be given the choice between eIC and a paper-based IC.

5.4 STRENGTHS AND LIMITATIONS

Participants with varying digital skills were involved in all iterations of usability testing, which can be considered a major strength. However, the usability results should be viewed in the context of its limitations. The eIC prototype was evaluated in a simulation-based setting and its usability in real-life clinical situations, where patients may be overwhelmed, may be different. To this end, in-situ testing, meaning that end users are observed in live contexts when interacting with the application, may result in additional usability-related barriers (281). In addition, some usability issues may be due to the fact that participants did not completely review the study-related information and therefore, did not fully grasp the process of providing IC (i.e., reviewing information, discussing questions with the research team, and providing consent). With regard to the semi-structured interviews conducted with stakeholders involved in clinical research, it should be noted that the participating stakeholders were mainly active in Belgium. To this end, firm generalizations should not be made from this qualitative study.

6 CONCLUSIONS

This study aimed to identify barriers and enablers for the use of a personalized and long-term eIC prototype as well as to gather multi-stakeholder insights regarding the practical integration of such a prototype in their daily practice. During iterative usability testing, participants were presented with several tasks that trial participants would typically perform with an eIC application. In summary, our study shows that usability testing is a critical step in the development of eIC to learn about the gaps in functionality. In addition, a key step toward achieving successful eIC implementation is to understand how stakeholders' daily practice would be influenced. Overall, the stakeholders involved in the semi-structured interviews emphasized the importance of establishing an accessible library and template to enable an efficient set-up of a personalized and long-term eIC prototype. In addition, divergent views were identified with regard to withdrawing consent for study participation electronically. The various findings that emerged from this study are useful in the design and implementation of a personalized and long-term eIC system in clinical research.

PART 4:
INFORMING THE CREATION OF A EUROPEAN REGULATORY FRAMEWORK ON ELECTRONIC INFORMED CONSENT

CHAPTER 7:
RETHINKING INFORMED CONSENT IN THE TIME OF COVID-19:
AN EXPLORATORY SURVEY

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Rethinking informed consent in the time of COVID-19: an exploratory survey

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1 ABSTRACT

Background: Owing to the infectious nature of COVID-19, alternative solutions, such as electronic informed consent (eIC), needed to be implemented to inform research participants about study-related information and to obtain their consent. This study aimed to investigate stakeholders' experiences with alternative consenting methods as well as their views on any regulatory or legal guidelines for eIC implementation in clinical research. Results may serve as the cornerstone to rethink the informed consent process in clinical research.

Materials and methods: This study consisted of an online survey among three stakeholder groups across European Union (EU) Member States and the United Kingdom. The stakeholder groups included (i) investigators, (ii) data protection officers or legal experts working in the pharmaceutical industry, academia, and academic biobanks, and (iii) ethics committee members. Data collection occurred between April and December 2021. The data collected were analyzed using descriptive and inferential statistics.

Results: The online survey was completed by 191 respondents, of whom 52% were investigators. Respondents were active in 24 out of the 27 EU Member States and the United Kingdom. The majority of each stakeholder group considered validated electronic methods moderately or extremely useful to reconsent previously enrolled research participants upon study amendments or to obtain consent from COVID-19 patients. Nevertheless, this exploratory survey identified that only 13% of data protection officers/legal experts, 26% of investigators, and 41% of ethics committee members had experience with eIC. In addition, results suggest that the legal acceptance of eIC across EU Member States and the United Kingdom is variable and that a definition of eIC, issued by national law or policy, is rarely available. The results also showed that the COVID-19 pandemic brought additional challenges to inform participants and to obtain their consent; for example, related to travel restrictions.

Conclusion: A number of alternative consenting methods were recommended, for example by the European Medicines Agency, to ensure clinical study continuation during the COVID-19 pandemic. Although stakeholders support the use of eIC in clinical research, it seems that the experience with eIC is low. To harmonize eIC practices as much as possible, further investments in multi-stakeholder, multi-national guidance are needed.

2 INTRODUCTION

The COVID-19 pandemic heavily affected the conduct of clinical research (282, 283). Ongoing clinical studies required protocol modifications to safeguard the wellbeing, safety, and rights of the research participants (284). For example, participants were not allowed to visit the research site to receive the investigational medicinal product (IMP). As a result, the distribution of the IMP shifted from the delivery at the research site to shipment to the participants' home (202). In addition, to minimize physical contact between the research team and the research participants, alternative informed consent (IC) procedures were required. Next to the clinical studies that started during the pre-pandemic period, various new studies have been initiated; for example, to evaluate the efficacy of therapeutic medicines and vaccines against the 'Severe acute respiratory syndrome coronavirus 2' (282). These clinical studies also faced challenges to embody ethical principles such as informing participants and obtaining their IC for participation in the study. According to the Declaration of Helsinki, voluntary consent of participants, having the capacity of providing IC, must be obtained prior to their inclusion in medical research (3). Nevertheless, the decision-making capacity of COVID-19 patients may be impaired; for example, when experiencing respiratory distress and requiring ventilation (285).

To promote the safety of the research participants and the research team while maintaining the clinical research integrity, several guidance documents were issued (286). These documents, issued by the European Medicines Agency (EMA) and several national regulatory bodies, provided recommendations on the conduct of clinical studies during the COVID-19 pandemic (143). The guidance document of the EMA sets out alternative consent procedures to inform COVID-19 patients and to obtain their IC. For example, it could be considered to obtain these patients' oral consent in the presence of an impartial witness (202). Due to urgent protocol modifications, mainly in clinical studies that started during the pre-pandemic period, there was a need to obtain reconsent of already included participants. Therefore, alternative means to reconsent were suggested. For example, the EMA states that "*any validated and secure electronic system already used in the trial in the particular member state for obtaining informed consent can be used as per usual practice and if in compliance with national legislation"* (202).

Electronic informed consent (eIC) is one of the digital alternatives that has been used during the COVID-19 pandemic to ensure clinical study continuation (287). According to the EMA, eIC refers to "*the use of any digital media (e.g. text, graphics, audio, video, podcasts or websites) to firstly convey information related to the clinical trial to the trial participant and secondly document informed consent*

via an electronic device (e.g. mobile phones, tablets or computers)" (48). It establishes the opportunity for research participants to access the study-related information via a variety of interactive methods and to provide their eIC (151). Moreover, eIC may tailor the information based upon the participants' needs and may engage them in a longitudinal relationship with the research team; for example, to receive study results (207). Despite the (potential) benefits of eIC, its adoption is slow due to various reasons, such as legal constraints or concerns about security and protection of personal data (60, 151, 288).

The effect of the COVID-19 pandemic on the conduct of clinical research has been immense and may result in new insights to improve the IC process (289, 290). However, the perspectives of stakeholders involved in clinical research on the use of alternative consenting methods during the COVID-19 pandemic is not yet investigated. In addition, empirical results related to stakeholders' experience with eIC in clinical research are scarce. In an effort to address these gaps, this exploratory study provides an understanding into stakeholders' views on obtaining IC before and during the COVID-19 pandemic as well as on how they experience the European or country-specific support, from a regulatory and legal point of view, for the implementation of eIC in clinical research. More concretely, the views of the following stakeholders were collected: (i) investigators, (ii) data protection officers (DPOs) or legal experts working in the pharmaceutical industry, academia, and academic biobanks, and (iii) members of ethics committees (ECs). The insights provided by these multiple stakeholder groups may be fundamental to capitalize on the evolving IC process in the context of future clinical research.

3 METHODS

3.1 STUDY DESIGN AND DATA COLLECTION

This study consisted of an online survey that was disseminated to various stakeholder groups, involved in clinical research, across European Union (EU) Member States and the United Kingdom (see details below). This survey, made available in English via the Qualtrics platform, consisted of two main parts: (i) compliance with the General Data Protection Regulation (GDPR) for clinical studies and (ii) general aspects related to obtaining (electronic) IC. The results of the first part are described elsewhere (291). The second part of the survey consisted of (i) a general question aiming to investigate the best practices in IC communication, (ii) questions related to eIC to assess stakeholders' experiences with and views on eIC, and more specifically, the regulatory and legal support related to its implementation, and (iii) questions to investigate stakeholders' views on the alternative IC methods, recommended by for example the EMA, and the challenges in IC communication they may have experienced during the

COVID-19 pandemic (Appendix R). The survey included multiple choice questions, Likert scale questions, and open-ended questions to allow the collection of in-depth qualitative data. More concretely, a set of questions relevant across stakeholder groups as well as more tailored questions were included in the survey. The survey was pilot tested with a representative from each stakeholder group. During pilot testing, the representatives were asked to think aloud to facilitate the collection of spontaneous comments while filling out the survey (276). Based on their feedback, the survey was adapted to increase the understanding of questions. An online invitation to fill out the survey was distributed to stakeholders between April and December 2021.

3.2 Participants and recruitment

The survey targeted the following stakeholder groups: (i) investigators (more specifically, we recruited physicians-investigators only), (ii) DPOs or legal experts working in the pharmaceutical industry, academia, and academic biobanks, and (iii) EC members. Stakeholders needed to be fluent in English, active in an EU Member State or the United Kingdom, and needed to be involved in clinical research. The survey was broadly disseminated to stakeholders. More concretely, dissemination occurred via social media (e.g., LinkedIn, Twitter), via the professional networks of the research team, and via international consortia and networks, such as the Innovative Medicines Initiative (IMI) Consortium Corona Accelerated Research & Development (CARE), the European Organization for Research and Treatment of Cancer (EORTC), the European Network of Research Ethics Committees (EUREC), the European Association of Health Law (EAHL), and the European Forum for Good Clinical Practice (EFGCP). The study was approved by the EC Research UZ/KU Leuven (S65106).

3.3 Analysis

The results obtained were analyzed descriptively via Microsoft Excel. Percentages were calculated based on the number of respondents for each question. Due to the logic applied in the survey questions and respondent drop-out, the sample size varied throughout the survey. Additional inferential statistics to test for differences between stakeholder groups were performed using IBM® SPSS® Statistics 28.0. For these stakeholder analyses, the Fisher-Freeman-Halton Exact test was used to analyze categorical variables. A p-value of less than 0.05 was considered statistically significant.

4 RESULTS

4.1 STAKEHOLDER CHARACTERISTICS

Among 191 survey respondents, most were investigators (52%, n=100/191), followed by EC members (24%, n=46/191), and DPOs/legal experts (24%, n=45/191). Respondents' organizations were based in 24 out of the 27 EU Member States and the United Kingdom. A detailed overview of the country representation for each stakeholder group can be found in Table 16.

Table 16. *Country representation for each stakeholder group*

Country	**Investigators (n=82) n (%)**	**DPOs/legal experts (n=31) n (%)**	**EC members (n=39) n (%)**
Austria	2 (2%)	/	3 (8%)
Belgium	13 (16%)	8 (26%)	5 (13%)
Bulgaria	/	5 (16%)	/
Croatia	3 (4%)	/	1 (3%)
Czechia	2 (2%)	1 (3%)	/
Denmark	/	2 (7%)	/
Estonia	/	/	1 (3%)
Finland	/	/	2 (5%)
France	7 (9%)	2 (7%)	/
Germany	6 (7%)	3 (10%)	3 (8%)
Greece	/	/	3 (8%)
Ireland	1 (1%)	/	1 (3%)
Italy	14 (17%)	1 (3%)	/
Latvia	/	/	2 (5%)
Lithuania	3 (4%)	/	2 (5%)
Luxembourg	1 (1%)	/	1 (3%)
Malta	1 (1%)	/	/
The Netherlands	8 (10%)	1 (3%)	2 (5%)
Poland	1 (1%)	2 (7%)	2 (5%)
Portugal	5 (6%)	/	4 (10%)
Slovakia	1 (1%)	/	1 (3%)
Slovenia	2 (2%)	/	/
Spain	4 (5%)	/	2 (5%)
Sweden	1 (1%)	1 (3%)	/
United Kingdom	7 (9%)	5 (16%)	4 (10%)

The majority of EC members were physicians (33%, n=13/39) and lawyers (26%, n=10/39), and were involved in a local or regional EC (56%, n=22/39). Over one-third of EC members reported to have another occupation, such as pharmacist or bioethicist. DPOs/legal experts were mainly working at a pharmaceutical company (19%, n=6/31), a research institute (19%, n=6/31), or other institutions/organizations (42%, n=13/31) such as universities, consultancy companies, or law firms (Table 17). In addition, the majority of DPOs/legal experts (71%, n=22/31) was involved in multi-country clinical studies whereas investigators were mainly involved in national studies (71%, n=58/82), more specifically in the country where they are based. Almost all EC members (90%, n=35/39) had experience with assessing clinical studies conducted in several EU countries.

Table 17. *Characteristics of EC members and DPOs/legal experts*

Characteristics	**EC members (n=39)** **n (%)**
Occupation	
Physician	13 (33%)
Lawyer	10 (26%)
Patient representative	2 (5%)
Statistician	1 (3%)
Other (e.g., bioethicist, pharmacist)	13 (33%)
Type of EC involved in	
National EC	17 (44%)
Local or regional EC	22 (56%)
Characteristics	**DPOs/legal experts (n=31)** **n (%)**
Working environment	
Academic sponsor of clinical trials	2 (7%)
Pharmaceutical company	6 (19%)
Clinical research organization	3 (10%)
Research institute	6 (19%)
Hospital	1 (3%)
Other	13 (42%)

All stakeholder groups were mainly involved in interventional and non-interventional clinical trials (Figure 14). Moreover, the majority of DPOs/legal experts (55%, n=17/31) and investigators (61%, n=50/82) were involved in the conduct of a registry-based trial.

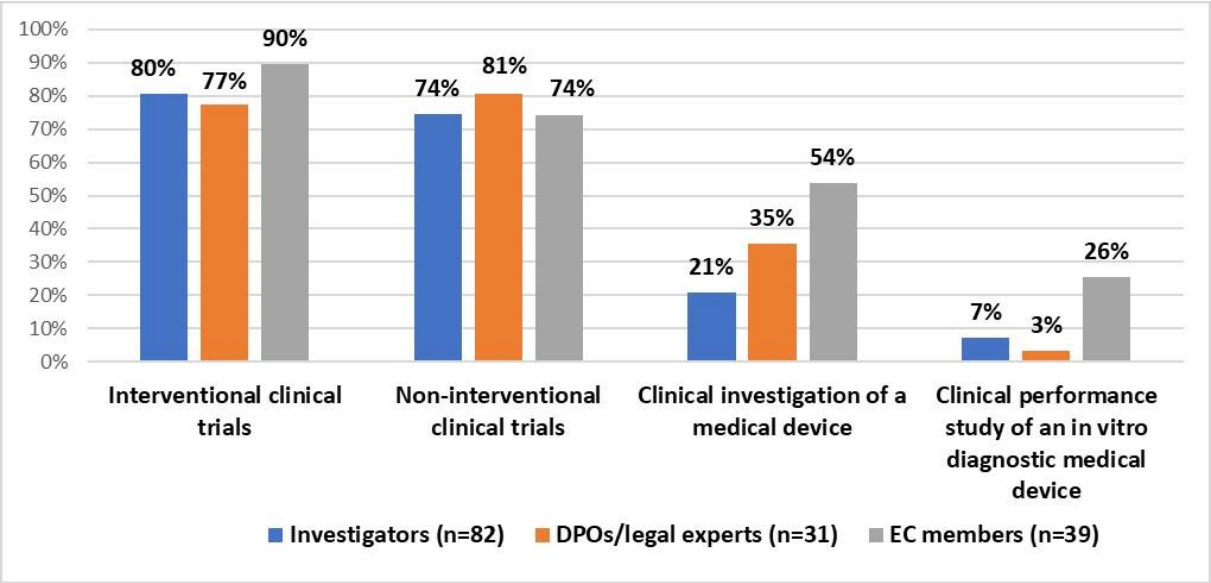

Figure 14. *Stakeholders' experiences with clinical studies*

In addition, investigators (99%, n=81/82) and DPOs/legal experts (87%, n=27/31) were primarily involved in non-COVID-19 studies (i.e., clinical studies that investigate a medicine, diagnostic product or device, and/or vaccine for other medical conditions than COVID-19). In addition, some investigators (29%, n=24/82) and the majority of DPOs/legal experts (58%, n=18/31) had experience with COVID-19 studies (Figure 15).

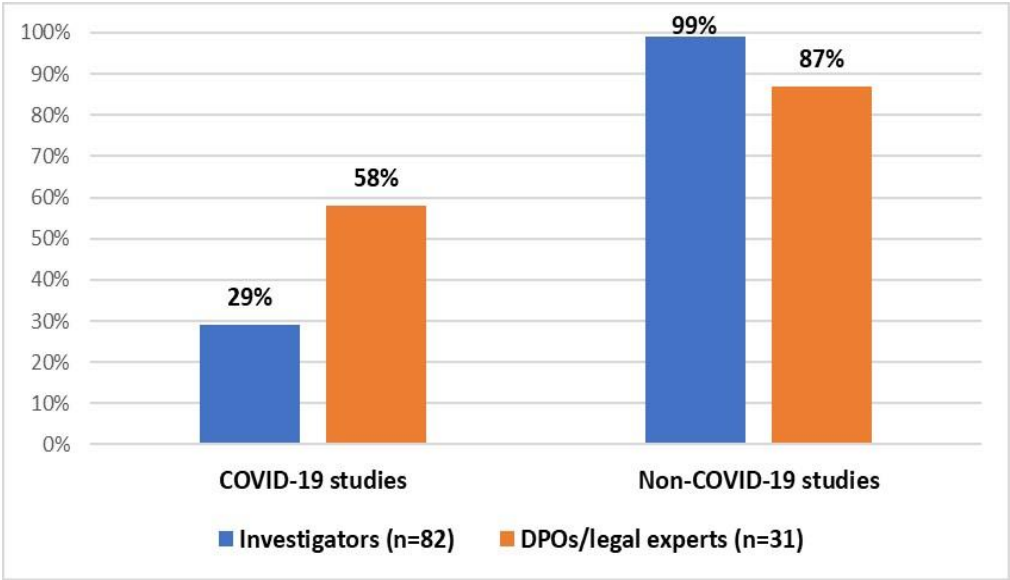

Figure 15. *Stakeholders' experiences with COVID-19 and non-COVID-19 studies*

4.2 BEST PRACTICES IN INFORMED CONSENT COMMUNICATION

All stakeholders were asked what the ideal means of communication would be, regardless of the COVID-19 pandemic, to inform research participants about study-related information (e.g., the study objectives, study conduct, and risks and benefits). The 62 stakeholders who answered this open-ended question included 31 investigators, 12 DPOs/legal experts, and 19 EC members. All stakeholder groups emphasized the importance of in-person or virtual interactions between the research participants and the research team. It was raised that these personal interactions could support the provision of study-related information in an understandable and tailored manner. In addition, the majority of respondents across the stakeholder groups mentioned that this personal contact should be supported by written information, presented on paper-based forms or via electronic media. It was reported that research participants' understanding may be facilitated by using flowcharts, illustrations, or a video providing visual cues to point out important information. In addition, according to a limited number of EC members, a chat feature could be integrated in an eIC system that allows the research participants to ask questions to the research team or information could be offered in layers, enabling participants to access general and detailed information based on their preferences.

4.3 ELECTRONIC INFORMED CONSENT

4.3.1 EXPERIENCE

Only 13% (n=2/15) of DPOs/legal experts and 26% (n=11/43) of investigators had experience with informing research participants and obtaining their IC via electronic means. These two DPOs/legal experts indicated that their organizations used electronic means in interventional clinical trials, whereas only one organization had experience with the use of eIC in non-interventional clinical trials and in clinical investigations of a medical device. More specifically, both organizations made use of a tablet-enabled eIC while one organization conveyed information to participants and obtained their IC via a mobile phone. The majority of investigators had experience with eIC, in the format of a computer, in non-interventional clinical trials (Table 18). About 41% (n=9/22) of EC members responded that their EC reviewed eIC in the past. The majority of them (75%, n=6/8) considered the review process of eIC more complex than of paper-based IC forms (ICFs). For example, it was considered essential to investigate whether the research participants' personal data would be adequately protected when their IC is obtained electronically.

Table 18. *Experience of investigators with eIC*

Types of clinical studies	Investigators (n=11) n (%)
Interventional clinical trials	5 (46%)
Non-interventional clinical trials	10 (91%)
Clinical investigation of a medical device	1 (9%)
Types of electronic means	
Computer	9 (82%)
Tablet	4 (36%)
Phone	5 (46%)

4.3.2 DEFINITION AND FUNCTIONALITIES

Stakeholders were asked whether they were aware of a definition of eIC, issued by national law or policy, in at least one of the countries where their organizations operate. Only three investigators (7%, n=3/43), three DPOs/legal experts (20%, n=3/15), and one EC member (5%, n=1/22), all of their organizations operating in the United Kingdom, indicated that national law or policy provide a definition of eIC. In addition, an EC member active in Latvia mentioned that a new law on biobanks will be issued that will provide a definition of eIC. Finally, 67% (n=29/43) of investigators, 40% (n=6/15) of DPOs/legal experts, and 9% (n=2/22) of EC members did not exactly know.

Survey respondents who indicated that they were not aware of a definition were asked what they understand by eIC. Based on the responses of all three stakeholder groups (i.e., 27 investigators, 9 DPOs/legal experts, and 17 EC members), three main viewpoints arose. The first viewpoint was that eIC refers to electronic means to convey information only whereas the second viewpoint consisted of electronic means to obtain and record the research participants' consent only. The third viewpoint was that eIC enables research participants to review study-related information and to provide their consent electronically.

When asked for the type of functionalities that should be ideally part of an eIC system, almost all stakeholders indicated that it should enable the provision of study-related information in an interactive and dynamic way, followed by obtaining and documenting the participants' signature, and the possibility to reconsent participants upon study amendments (Table 19). Only for the latter functionality, a significant difference was found between stakeholder groups (p=0.029) (Appendix S). In addition, approximately half of investigators (52%, n=22/42) and DPOs/legal experts (47%, n=7/15),

and a small majority of EC members (60%, n=13/22) preferred to integrate the return of research results to the research participants in an eIC system. Other functionalities described by some stakeholders (11%, n=9/79) related to the integration of a functionality that enables face-to-face contact between the research team and the participant, the possibility for the participants to withdraw their IC, the implementation of a quiz to test the participants' understanding, and the possibility for the research team to invite research participants to participate in surveys.

Table 19. *Type of functionalities of an eIC system*

Type of functionalities	**Investigators (n=42) n (%)**	**DPOs/legal experts (n=15) n (%)**	**EC members (n=22) n (%)**
Providing research study information in an interactive and dynamic way to (potential) research participants	39 (93%)	14 (93%)	22 (100%)
Obtaining and documenting the signature of the research participants	36 (86%)	14 (93%)	18 (82%)
The possibility to reconsent research participants	29 (69%)	15 (100%)	18 (82%)
The return of research results to the research participants	22 (52%)	7 (47%)	13 (60%)
Other	1 (2%)	2 (13%)	6 (27%)

4.3.3 LEGAL ACCEPTANCE

Stakeholders were asked whether it is legally allowed in at least one of the countries where their organization operates to provide study-related information to research participants via electronic means, before obtaining their IC. In total, 47% of investigators (n=20/43), 40% of DPOs/legal experts (n=6/15), and 59% of EC members (n=13/22) stated that providing study-related information electronically is legally allowed. These stakeholders' organizations were mainly operating in Belgium (10%, n=4/39), Germany (10%, n=4/39), Italy (10%, n=4/39), Poland (10%, n=4/39), and the United Kingdom (18%, n=7/39). Nevertheless, some of the respondents (investigators: 5%, n=2/43; DPOs/legal experts: 7%, n=1/15; and EC members: 41%, n=9/22) explicitly reported that providing information electronically can only take place under certain conditions. For example, there must be confirmation that the participant will also receive oral explanation about the clinical study or the participant must have the possibility to ask questions, if any. Additionally, 42% of investigators (n=18/43), 53% of DPOs/legal experts (n=8/15), and 23% of EC members (n=5/22) did not know.

In a subsequent question, stakeholders were asked whether it is legally allowed in at least one of the countries where their organization operates to obtain research participants' IC via electronic means. One-third of investigators (33%, n=14/43) and the majority of DPOs/legal experts (60%, n=9/15) and EC members (71%, n=15/21) indicated that it is legally allowed whereas 56% of investigators (n=24/43), 33% of DPOs/legal experts (n=5/15), and 10% of EC members (n=2/21) did not exactly know. The majority of stakeholders who stated that it is legally allowed were operating in Belgium (16%, n=6/38), Germany (11%, n=4/38), Poland (11%, n=4/38), and the United Kingdom (26%, n=10/38). Nevertheless, a few EC members (14%, n=3/21) noted that the legal acceptance depends on the type of the clinical study. Stakeholders who indicated that it is legally allowed to obtain the research participants' IC electronically were further asked to specify the type of signature(s) that are allowed to use. Generally, the majority of DPOs/legal experts (56%, n=5/9) indicated that a simple or basic electronic signature as well as a qualified advanced electronic signature can be used (Table 20). It was mentioned that the type of suitable signature may depend on the risk level of the clinical study. Some DPOs/legal experts (22%, n=2/9) and EC members (27%, n=4/15) mentioned that other signatures are legally allowed to use, such as a tick box in combination with a check of the participants' identity documents. Additionally, 50% of investigators (n=7/14), 22% of DPOs/legal experts (n=2/9), and 13% of EC members (n=2/15) indicated that they did not know.

Table 20. *Stakeholders' views on the type of signatures that are legally allowed to obtain the research participants' IC*

Type of signatures	**Investigators (n=14) n (%)**	**DPOs/legal experts (n=9) n (%)**	**EC members (n=15) n (%)**
Simple or basic electronic signature	6 (43%)	5 (56%)	5 (33%)
Advanced electronic signature	4 (29%)	4 (44%)	3 (20%)
Qualified advanced electronic signature	1 (7%)	5 (56%)	6 (40%)
I do not know	7 (50%)	2 (22%)	2 (13%)
Other	0 (0%)	2 (22%)	4 (27%)

When asked which laws or regulations regulate (i.e., allow or prohibit) the use of eIC, respondents across stakeholder groups referred to EU regulations such as the Regulation on electronic identification and trust services for electronic transactions in the internal market (eIDAS Regulation) (145), the GDPR (28), and the Clinical Trials Regulation (CTR) (6). Other answers related to national legislation such as the Slovak Act No. 362/2011 on medicines and medical devices (292). Moreover, other respondents stated that there are no laws or regulations in place that specify the use of eIC in clinical research.

4.4 INFORMED CONSENT DURING THE COVID-19 PANDEMIC

4.4.1 RE-CONSENTING ALREADY INCLUDED RESEARCH PARTICIPANTS

Investigators and DPOs/legal experts were asked whether they used the following alternative methods to reconsent already included research participants during the COVID-19 pandemic, as recommended by for example the EMA: (i) obtaining oral consent (e.g., via phone or video-calls) supplemented with email confirmation, (ii) obtaining oral consent (e.g., via phone or video-calls) followed by an appropriately signed and dated IC as soon as possible, and (iii) using validated electronic systems (e.g., eIC). Most of investigators (41%, n=17/42) and DPOs/legal experts (60%, n=9/15) obtained the participant's oral consent, followed by an appropriately signed and dated IC as soon as possible. Moreover, 19% of investigators (n=8/42) and 33% of DPOs/legal experts (n=5/15) made use of oral consent supplemented with email confirmation, and 17% of investigators (n=7/42) and 13% of DPOs/legal experts (n=2/15) used validated electronic systems (e.g., eIC) to reconsent for already included participants. Other methods used by 7% of investigators (n=3/42) related to obtaining written IC in person. All stakeholders were asked about the usefulness of these alternative method(s) to reconsent for already included research participants. The majority of investigators considered all alternative methods moderately or extremely useful (Figure 16A). On the contrary, the majority of DPOs/legal experts considered the second method slightly useful or not useful at all (Figure 16B). EC members mainly considered the second and third method moderately or extremely useful (Figure 16C).

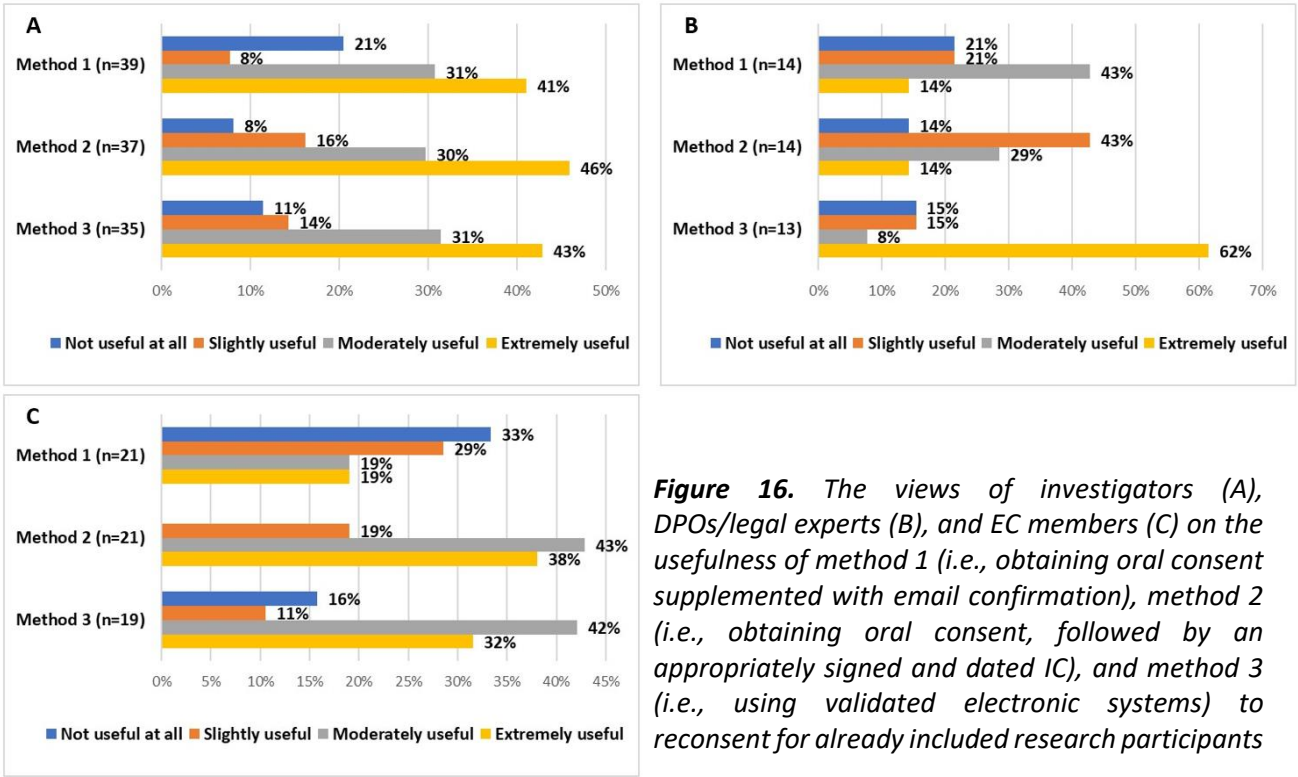

Figure 16. *The views of investigators (A), DPOs/legal experts (B), and EC members (C) on the usefulness of method 1 (i.e., obtaining oral consent supplemented with email confirmation), method 2 (i.e., obtaining oral consent, followed by an appropriately signed and dated IC), and method 3 (i.e., using validated electronic systems) to reconsent for already included research participants*

Potential advantages and challenges, raised by stakeholders, of these alternative methods can be found in Table 21.

Table 21. *Potential advantages and challenges of alternative methods to reconsent for already included research participants*

Obtaining oral consent, supplemented with email confirmation	
(Potential) advantages	**(Potential) challenges**
• Saves participants to visit the research site • No pressure to provide research information during a medical consultation • Manageable	• Legality • Adequate email encryption to avoid a data breach • Identity check of participants • Traceability in case of audits and inspections
Obtaining oral consent, followed by an appropriately signed and dated IC as soon as possible	
(Potential) advantages	**(Potential) challenges**
• Saves participants to visit the research site • No pressure to provide research information during a medical consultation • Appropriate security and attributability	• Legality • Identity check of participants • Susceptible to documentation issues because of the risk of forgetting to obtain the participants' written IC later on
Using validated electronic systems	
(Potential) advantages	**(Potential) challenges**
• Saves participants to visit the research site • No pressure to provide research information during a medical consultation • Unequivocal documentation and storage of signed consent forms • Information can be provided via multiple media	• Legality • Complex for participants who lack digital literacy • Access to electronic means • Numerous eIC systems are confusing • The setup may place time and logistical demands on the sponsor/study team

4.4.2 Obtaining informed consent from COVID-19 patients

Investigators and DPOs/legal experts were questioned which method(s) they used, if applicable, to obtain IC of COVID-19 patients. It should be noted that the responses were recorded between April and December 2021, when the COVID-19 pandemic continued its worldwide spread. In total, 41% of investigators (n=16/39) and 64% of DPOs/legal experts (n=9/14) did not have experience with obtaining IC of COVID-19 patients. Nevertheless, 31% of investigators (n=12/39) and 29% of DPOs/legal experts (n=4/14) indicated that the patients and the principal investigator signed and dated separate paper-based ICFs and that an appropriately signed and dated ICF was obtained later on. In addition, validated electronic methods were used by 26% of investigators (n=10/39) and 7% of DPOs/legal experts (n=1/14). A minority of investigators (10%, n=4/39) and DPOs/legal experts (7%, n=1/14) had

experience with obtaining the patients' oral IC in the presence of an impartial witness, who signed and dated the ICF. In addition, 8% of investigators (n=3/39) indicated that they made use of other methods.

All stakeholders were asked about the usefulness of these methods. Investigators and DPOs/legal experts mainly considered using validated electronic methods moderately or extremely useful (Figures 17A, B). In addition, a vast majority of EC members considered signing and dating separate ICFs, followed by obtaining an appropriately signed and dated ICF later on, moderately or extremely useful, as well as using validated electronic systems (Figure 17C).

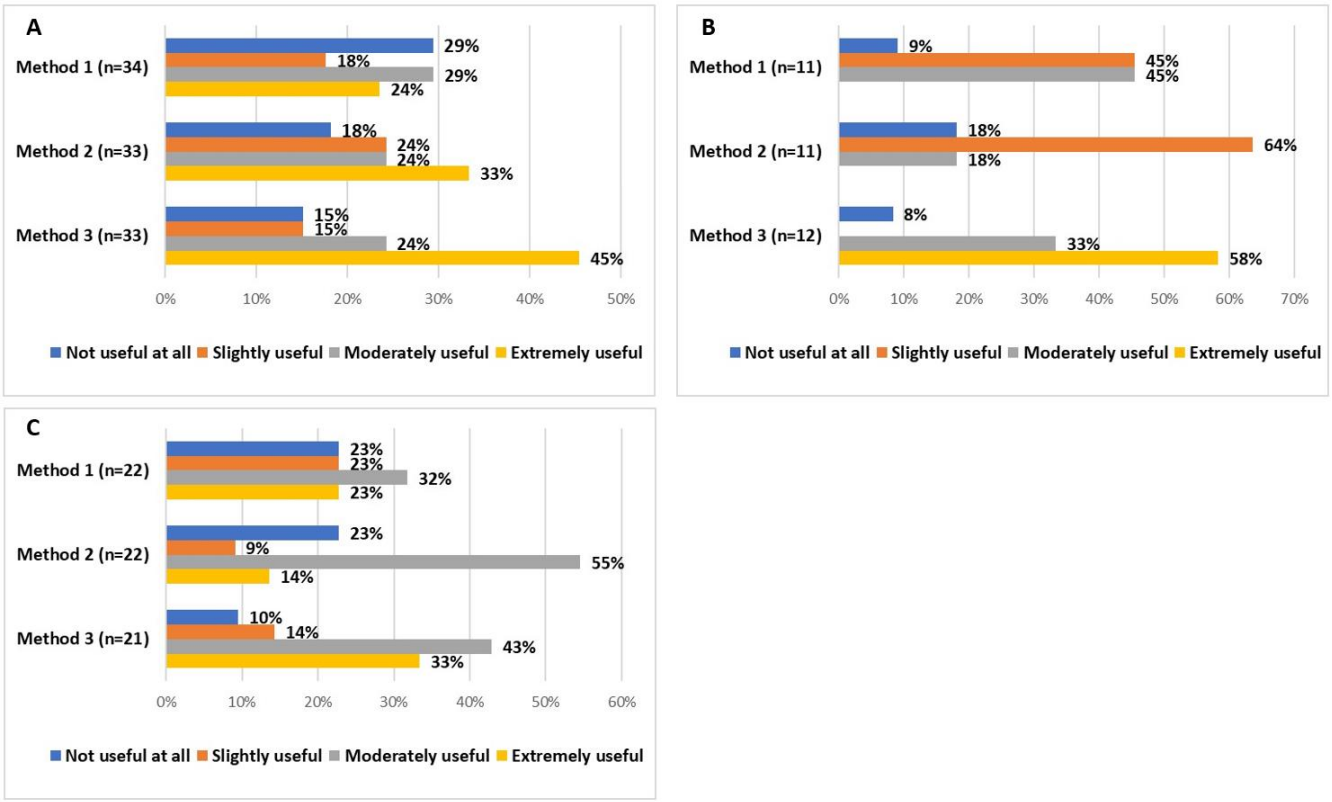

Figure 17. *The views of investigators (A), DPOs/legal experts (B), and EC members (C) on the usefulness of method 1 (i.e., if written consent by the research participant is not possible, IC could be given orally by the research participant in the presence of an impartial witness, who is required to sign and date the ICF), method 2 (i.e., the research participant and the person obtaining consent sign and date separate ICFs and an appropriately signed and dated IC should be obtained from the participant as soon as possible), and method 3 (i.e., using validated electronic systems) to obtain IC from COVID-19 patients*

The advantages and challenges of these methods, described by stakeholders, are displayed in Table 22.

***Table 22**. Potential advantages and challenges of alternative methods to obtain informed consent from COVID-19 patients*

Obtaining oral consent in the presence of an impartial witness, who signs and dates the IC	
(Potential) advantages	**(Potential) challenges**
• Trustworthy • Ensures impartiality	• Legality • Susceptible to documentation issues • Burdensome
Signing and dating separate ICFs, followed by an appropriately signed and dated IC as soon as possible	
(Potential) advantages	**(Potential) challenges**
• Pragmatic solution	• Legality • Susceptible to documentation issues • Burdensome
Using validated electronic systems	
(Potential) advantages	**(Potential) challenges**
• Saves patients to visit the research site • Unequivocal documentation and storage of signed consent forms • Information can be provided via multiple media	• Legality • Complex for participants who lack digital literacy • Access to electronic means • Numerous eIC systems are confusing • The setup may place time and logistical demands on the sponsor/study team

4.5 Challenges in informed consent communication prior to and during the pandemic

To evaluate the challenges in IC communication, investigators and DPOs/legal experts were asked about the challenges they experienced, prior to the COVID-19 pandemic, when providing study-related information to research participants and obtaining their IC. A common topic that arose from the responses of 12 investigators and 7 DPOs/legal experts was the provision of study-related information in understandable language and avoiding lengthy ICFs. Moreover, having enough time to convey detailed information about the study and the need to physically obtain IC were considered challenging by a few investigators. In addition, correct documentation of paper-based ICFs and deciding which type of consent (e.g., broad consent) is needed, were mentioned as other challenges by a limited number of DPOs/legal experts. The majority of investigators (74%, n=26/35) and DPOs/legal experts (75%, n=9/12) reported that they experienced the same challenges during the COVID-19 pandemic. A new challenge experienced, due to the COVID-19 pandemic, related to making sure that surfaces are

disinfected to avoid COVID-19 transmission. In addition, the organization of face-to-face consultations was considered challenging. At particular moments during the pandemic, restrictions were in place to organize such consultations or study participants were not allowed to cross the border. When oral consent was obtained from the participant, it was raised that this consenting method impaired the ability to perceive the readability of emotions; for example, to check whether participants understood the study-related information. Also having proof of oral consent was considered challenging.

5 Discussion

The arrival of COVID-19 has plummeted the clinical research activity in many countries. Multiple challenges were posed to ensure study continuation while minimizing the risk of infection for the participants as well as the research team; for example, related to informing research participants about study-related information and obtaining their IC (286). Because some alternative IC practices may be incorporated into common clinical practices in the future, it is key to understand stakeholders' experiences and to investigate their opinions on the acceptance of eIC in the clinical research process.

5.1 A need for guidance and harmonization of electronic informed consent

According to Mitchell et al., the use of eIC is increasing but is still relatively uncommon, which is in line with the results of our pilot survey (293). In addition, our survey found varying answers to some survey questions; for example, about the legal acceptance of eIC or about how stakeholders understand eIC. Given the complexity such divergence brings for the conduct of (especially multi-state) clinical trials, it may be argued that there is a substantial demand for more guidance about eIC in clinical research. Only a limited number of national regulatory bodies or ECs have issued public statements on eIC, such as Austria, Belgium, Denmark, and the United Kingdom (147, 148, 150, 294). The European Commission, the Heads of Medicines Agencies, and the EMA have launched the initiative 'Accelerating Clinical Trials in the EU (ACT EU)' in 2022, which puts forward ten key priorities to facilitate the initiation, design, and conduct of clinical trials. In this ACT EU, the EU bodies state that "*disharmony of regulatory requirements between Member States complicates the submission of multi-state trial applications*" (295). In addition, the EMA's 'Regulatory Science to 2025' strategy indicates that the Good Clinical Practice (GCP) regulatory oversight can be modernized to enable the conduct of decentralized clinical trials, in which eIC can play an important role. The EMA's strategy indicates that "*improving guidance on the design, conduct and analysis of clinical trials through broad stakeholder engagement, including patients and researchers can build a sound basis for advancing international consensus and its harmonisation via organisations such as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)*" (296). The ICH E6 GCP guideline

is a cornerstone of clinical trial design, conduct, recording, and reporting (5). In March 2021, the ICH E6(R3) Expert Working Group published a draft of the updated ICH E6 principles. These updated principles are intended to support more efficient approaches to trial design, considering emerging technologies (22). Besides these initiatives, the EMA has already taken the necessary steps forward to set out unified requirements. In 2021, they issued a draft guideline on the use of computerized systems in clinical trials (48). Similarly, the U.S. Food and Drug Administration issued a guidance specifically targeting eIC in clinical research in 2016 (49). Furthermore, one shall also keep in mind that reproducing evidence that patients have been duly informed and have provided a valid (electronic) consent is subject to national patient rights protection and evidence rules. Therefore, all these initiatives may contribute to clarifying the elements of valid consent and to harmonizing requirements related to the use of eIC in clinical research.

5.2 Informed consent during the COVID-19 pandemic

During the COVID-19 pandemic, national and European regulatory bodies responded with guidance about the conduct of clinical trials during the outbreak. According to de Jong et al., 24 out of the 27 regulatory bodies of EU Member States issued such guidance, supplementary to the EMA guideline. More specifically, 16 guidances specifically addressed obtaining IC during the COVID-19 pandemic (297). Some included the use of electronic systems to obtain the participants' IC, such as the guidances issued by the EMA and by the Belgian Federal Agency for Medicines and Health Products (203, 298). At the same time, in the Hungarian guidance it is stated that "*electronic patient information sheets and informed consent forms are not permitted, according to the law that must be followed in the current extraordinary situation as well*" (162). The group of the 27 national data protection authorities, known as the European Data Protection Board (EDPB), has also issued guidelines in which requirements for a valid consent under data protection law were discussed. The EDPB further stressed the need for a 'freely given' consent in the context of the CTR (299, 300). Already before the COVID-19 pandemic, stakeholders supported the use of eIC as it offers opportunities compared to paper-based ICFs, such as using multimedia to convey information or enabling online storage of signed ICFs (151). Based on the survey data, it cannot be concluded whether the support for eIC has increased during the COVID-19 pandemic. Nevertheless, existing literature shows that the use of eIC in research centres located in the United States has increased during the pandemic, mainly for minimal-risk studies (301). Nevertheless, institutions without previous experience with eIC considered it challenging to educate a sufficient number of researchers to use eIC systems. Moreover, challenges were reported related to the accessibility of eIC for potential study participants, which is in line with the concerns raised by survey respondents (302).

Informing research participants about all the pertinent aspects of a clinical trial and obtaining their consent is a foundational ethical requirement (3). According to the available literature, the paper-based IC process may be ineffectual in truly informing research participants about the trial (97, 207, 303-305). The changes in clinical practice, forced by the COVID-19 pandemic, offer an opportunity to reconsider the IC process in clinical research. As reported by survey respondents, eIC could offer particular advantages compared to the other recommended consenting methods. Similarly, Knoppers et al. stated that eIC can be used, including informational videos, to inform COVID-19 patients and to obtain their consent for the processing of their samples (306). Nevertheless, attention must be paid to the accessibility of this technology to participants as well as to a potential power imbalance (151, 300, 307). To this end, it could be advised to make use of an adaptive approach to the consent process, considering research participants' needs and relationships, in order to maximize participant benefit.

5.3 Study strengths and limitations

This study presents the views of key stakeholder groups involved in the set-up, review process, or conduct of clinical studies, allowing us to gain a broad understanding of their experiences and views on informing research participants and obtaining their IC, before and during the COVID-19 pandemic. Moreover, these stakeholders represented 24 out of the 27 targeted EU Member States and the United Kingdom. This study aimed to equally represent these countries and the stakeholder groups involved. Nevertheless, it is important to recognize that investigators were the most responsive stakeholder group and that the majority of stakeholders were based in Belgium, Germany, Italy, the Netherlands, and the United Kingdom. The survey was widely disseminated via the network of research consortia and social media. Nevertheless, a small sample size and a high drop-out rate were observed. Potential reasons for this limitation may relate to survey fatigue, a lack of interest in the topic, or a high workload due to the COVID-19 pandemic. Due to a small sample size, the generalization of survey results should be done with caution. Nevertheless, this exploratory nature of this survey provides valuable insights into stakeholders' views on and experiences with alternative consenting methods, including eIC, as well as the main challenges they experience to inform participants and to obtain their consent, prior to and during the COVID-19 pandemic. Moreover, some questions remained theoretical to some survey respondents, for example, related to the usefulness of alternative consenting methods. Their views may change if they would gain practical experience with these methods.

6 CONCLUSIONS

Our survey indicates that all stakeholder groups support the use of eIC during the COVID-19 pandemic and beyond. The survey data showed that the IC process, regardless of the COVID-19 pandemic, should ideally consist of personal interactions and written information. eIC offers the opportunity to convey information interactively, by making use of multimedia or by offering information in a layered approach. Nevertheless, stakeholders had little practical experience with eIC and reported some challenges that hinder the deployment of eIC in clinical research. In addition, it appears that there is a varying understanding of the term 'eIC' as well as limited European or country-specific support, from a regulatory and legal point of view, to facilitate implementation. Therefore, multi-stakeholder, multi-national guidance could contribute to a more harmonized eIC approach in clinical research. Finally, the survey results showed that the COVID-19 pandemic resulted in some additional challenges to convey study-related information to participants and to obtain their consent.

CHAPTER 8:
DIGITIZING THE INFORMED CONSENT PROCESS: A REVIEW OF THE REGULATORY LANDSCAPE IN THE EUROPEAN UNION

This chapter is based on:

De Sutter E.*, Meszaros J.*, Borry P., Huys I.

Digitizing the informed consent process:

a review of the regulatory landscape in the European Union

Frontiers in Medicine. 2022;9:906448

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1 ABSTRACT

Background: Rapid technological advancements are reshaping the conduct of clinical research. Electronic informed consent (eIC) is one of these novel advancements, allowing to interactively convey research-related information to participants and obtain their consent. The COVID-19 pandemic highlighted the importance of establishing a digital, long-distance relationship between research participants and researchers. However, the regulatory landscape in the European Union (EU) is diverse, posing a legal challenge to implement eIC in clinical research. Therefore, this study takes the necessary steps forward by providing an overview of the current regulatory framework in the EU, relevant to eIC.

Methods: We reviewed and analyzed the key EU regulations, such as the EU General Data Protection Regulation (GDPR) and the Clinical Trials Regulation (CTR). We investigated the legality of eIC in several EU Member States, Switzerland, and the United Kingdom. To this end, we contacted the medicines agencies of various countries to clarify the national requirements related to the implementation and use of eIC in clinical research. Our research was complemented by comparing the legal acceptance of eIC between the EU and the United States.

Results: In the EU, a distinction must be made between eIC for participation in clinical research and eIC for processing the participants' personal data, complying respectively with requirements laid down by the CTR and the GDPR. On a national level, countries were classified into three groups: (i) countries accepting and regulating the use of eIC, (ii) countries accepting the use of eIC without explicitly regulating it, and (iii) countries not accepting the use of eIC. As a result, the regulation of eIC through laws and guidelines shows a large variety among EU Member States, while in the United States, it is harmonized through the Code of Federal Regulations.

Conclusion: Various requirements must be considered when implementing eIC in clinical research. Nevertheless, requirements across the EU Member States may differ significantly, whereas, in the United States, efforts have already been made to achieve a harmonized approach.

2 INTRODUCTION

The principle of obtaining informed consent (IC) from participants as a prerequisite to participate in clinical research has initially been embedded in the Nuremberg Code and Helsinki Declaration (1-3). The practice of IC is also enshrined in guidelines for Good Clinical Practice (GCP). The GCP guideline of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use describes ethical and scientific requirements when designing, conducting, recording, and reporting clinical trials involving human subjects. According to this guideline, IC is "*a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate*" (5). IC may also serve as a legal ground for processing research participants' personal data, according to the basic principles embedded in the European Union (EU) General Data Protection Regulation (GDPR) (27, 28). In the GDPR, IC is one of the legal bases for processing personal data[1].

The IC process has historically always been documented on paper forms. However, digital technologies are reshaping this process, since electronic informed consent (eIC) could offer various advantages compared to paper-based IC forms (47). For instance, eIC could include multimedia components such as audio and video to present information in an interactive and engaging way (151). Moreover, eIC could include a personalized communication interface and facilitate ongoing communication with research participants. Nevertheless, face-to-face contact between the participants and the research team remains crucial to establishing a relationship of trust, and it is necessary for individuals who do not have access to technology or lack digital literacy (151, 207). Various initiatives have already implemented innovative types of consent and reported on the use of dynamic consent, a type of eIC, in biobanking and epidemiological research (52, 64). Dynamic consent is primarily developed to provide participants with more control over the future use of their data and samples (64). It enables participants to interact with the interface to manage their decisions on the use of their personal data or samples in research studies over time and thus, to have more control over their involvement in research (52, 308). Additionally, dynamic consent may increase transparency by providing an overview of participants' data usage or by feeding back study results (61).

In 2021, the European Medicines Agency (EMA) published a draft 'Guideline on computerised systems and electronic data in clinical trials'. As described in this guideline, eIC refers to "*the use of any digital media (e.g. text, graphics, audio, video, podcasts, or websites) to firstly convey information related to*

[1] GDPR Article 6(1)(a).

the clinical trial to the trial participant and secondly document informed consent via an electronic device (e.g. mobile phones, tablets, or computers)". As the EMA highlighted, investigators need to pay attention when using electronic methods since it might discriminate against people who are not comfortable using this kind of technology, potentially leading to bias in clinical research. Therefore, alternative methods for providing information and documenting IC should be available for those unable or unwilling to use electronic procedures. The EMA emphasized that any sole use of eIC should be justified and described in the protocol (48). Despite the increasing interest in eIC, its adoption has been hampered due to various reasons. The most critical issue is the legal acceptance of eIC in clinical research (50, 151, 207). Concerns have been raised regarding whether eIC would comply with local regulations (50, 151). Moreover, it was reported that legal requirements, related to eIC, may differ across countries. For example, some countries require participants' wet-ink signature and do not accept the use of electronic signatures to provide IC for study participation (207). To this end, this manuscript aims to analyze the current regulatory framework relevant to (electronic) IC, examining how this framework could be further developed to facilitate eIC implementation in clinical research.

3 METHODS

We reviewed and analyzed the key EU regulations, such as the GDPR, Clinical Trials Regulation (CTR), and the Regulation on electronic identification and trust services for electronic transactions in the internal market (eIDAS Regulation). Moreover, we complemented our analysis showcasing national requirements related to the implementation and use of eIC in clinical research. For this purpose, we contacted the medicines agencies of several countries and described the various approaches currently used. This research was complemented by comparing the legal acceptance of eIC in the United States (US). Furthermore, recommendations were suggested to promote the implementation of eIC in clinical research.

4 RESULTS

4.1 ELECTRONIC INFORMED CONSENT IN EUROPEAN REGULATIONS

4.1.1 INFORMED CONSENT FOR PARTICIPATION IN CLINICAL RESEARCH

The CTR, an EU-level binding legislative act, aims to harmonize the conduct of clinical trials throughout the EU and increase transparency in this field (6, 23). IC, which has a central relevance within the CTR, is defined as "*a subject's free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to*

the subject's decision to participate or, in case of minors and of incapacitated subjects, an authorization or agreement from their legally designated representative to include them in the clinical trial". Pursuant to Article 29 of the CTR, requirements are defined to obtain valid IC. IC must be written, dated, and signed by the research participant and a member of the investigating team performing the interview, in which the necessary study-related information is conveyed to the participant (6). As a result, the CTR does not offer specific guidance for the use of eIC for participation in clinical trials.

4.1.2 INFORMED CONSENT AS A LEGAL GROUND FOR PROCESSING PERSONAL DATA

The GDPR defines personal data as any information that can be directly or indirectly linked to an individual[2]. Special categories of personal data refer to sensitive information, such as health data, and it is restricted to process this type of data. According to the GDPR, data processing must be based on one of the legal grounds described in Article 6 and one of the conditions in Article 9 in the case of sensitive data. IC is one of these legal bases for the lawful processing of personal data. The consent of the data subject is specified as "*any freely given, specific, informed and unambiguous indication of the data subject's wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her*" (28). The GDPR clarifies that consent may be given by an oral or a written statement, including by electronic means[3]. The human subjects' IC related to data processing can be obtained together with their IC for research participation. However, the request for IC related to data processing should be clearly distinguished from IC for research participation (28, 35).

The GDPR aims to foster transparency regarding the way human subjects' data are processed (28, 309). Therefore, clear and plain language must be used when informing human subjects about the purpose and legal basis for data processing, the categories of recipients, the contact details of the controller and the data protection officer and if applicable, the transfer of personal data to a third country or international organization. Additionally, information must be conveyed about other aspects, such as the period of data storage and the data subjects' rights (e.g., the right to be forgotten) (28).

[2] GDPR Article 4(1).
[3] GDPR Recital 32.

4.1.3 *The interaction between the General Data Protection Regulation and the Clinical Trials Regulation*

The CTR provides that EU Member States shall apply the GDPR to the processing of personal data carried out in the framework of the CTR[4]. Therefore, protecting the participants' privacy is one of the conditions to conduct a clinical trial[5]. The GDPR also refers to the relevant legislation applicable to clinical trials[6]. Therefore, both regulations apply simultaneously, and the CTR constitutes a sectoral law containing specific provisions relevant to data protection. Regarding the legal basis for the processing of personal data during the lifecycle of a clinical trial, the European Data Protection Board (EDPB) considers distinguishing between two main categories of processing activities (299):

(i) Processing operations related to reliability and safety purposes: these processing activities do not necessarily have to rely on consent. Processing for reliability and safety can be covered by the legal grounds of 'legal obligation'[7] or 'public interest' in the case of sensitive data[8]. As noted by the EDPB, several activities envisaged under the CTR satisfy the conditions for the applicability of this legal basis. For instance, archiving of the clinical master file[9] or disclosure of clinical trial data to the competent authorities for an inspection[10].

(ii) Processing operations purely related to research activities in the context of a clinical trial cannot be based on a 'legal obligation'. Depending on the trial and the concrete data processing, they may either fall under the data subject's explicit consent[11], a task carried out in the public interest[12], or the legitimate interest of the controller[13].

[4] CTR Article 93.
[5] CTR Article 28(1)(d).
[6] GDPR Recital 161.
[7] GDPR Article 6(1)(c).
[8] GDPR Article 9(2)(i) allows the processing of personal data when this is "*necessary for reasons of public interest in the area of public health, such as [. . .] ensuring high standards of quality and safety of healthcare and of medicinal products or medical devices, on the basis of Union or member State law, which provides for suitable and specific measures to safeguard the rights and freedoms of the data subject, in particular professional secrecy*".
[9] CTR Article 58.
[10] CTR Articles 77–79.
[11] GDPR Article 6(1)(a) in conjunction with Article 9(2)(a).
[12] GDPR Article 6(1)(e).
[13] GDPR Article 6(1)(f) in conjunction with Article 9(2)(i) or (j).

4.1.4 *Informed consent in the Clinical Trials Regulation and General Data Protection Regulation: not the same*

As the EU Commission's Directorate-General for Health and Food Safety highlighted, the IC under the CTR must not be confused with the notion of consent as a legal ground for the processing of personal data under the GDPR (310). Under the CTR, IC serves as an ethical standard and procedural obligation[14], addressing the ethical requirements of research involving humans derived from the Helsinki Declaration. The IC under the CTR functions as a measure to protect the right of human dignity and integrity of individuals under the Charter of Fundamental Rights of the EU (311). Therefore, IC under the CTR is not conceived as an instrument to comply with data protection requirements. As the Directorate-General pointed out, IC in the context of the CTR is a safeguard for the participants, and not a legal basis for data processing (310).

Under the GDPR, consent must be specific, informed, unambiguous, and freely given. Moreover, the consent must be explicit when special categories of data, such as health data, are processed[15]. From these requirements, the 'freely given' may be the most challenging one in the GDPR, since it implies real choice and control for the data subjects (34). Therefore, IC cannot be a valid legal ground for data processing where there is a clear imbalance between the data controller and the data subject[16]. The EDPB clarified that imbalance of power might exist wherever there is "*a risk of deception, intimidation, coercion or significant negative consequences (e.g. substantial extra costs) if the data subject does not consent. Consent will not be free in cases where there is any element of compulsion, pressure, or inability to exercise free will*". The primary examples for these situations are when the employer, public authority, or doctor ask for consent from the employee, citizen, or patient to process personal data (34). In the case of clinical trials, the imbalance between the investigator and the participant might occur. Therefore, IC may not always be the proper legal ground for processing personal data in clinical trials (Table 23). Thus, for processing personal data, other legal bases may be necessary, such as 'public interest' or 'legitimate interest' (35). The CTR also addresses the issue of imbalance, highlighting "*[…] whether the potential subject belongs to an economically or socially disadvantaged group or is in a situation of institutional or hierarchical dependency that could inappropriately influence her or his decision to participate*"[17]. Additionally, the EDPB considers that this will be the case when a participant is not in good health condition (35). However, ethics committees (ECs) can allow consent in these imbalanced situations, with specific safeguards, such as supporting the patients' decision-making by

[14] CTR Article 28.
[15] GDPR Article 9(2)(a).
[16] GDPR Recital 43.
[17] CTR Recital 31.

discussing their choice with a trusted adult or relative, especially when potentially vulnerable groups are involved (312).

Table 23. *Processing health data in imbalanced/dependent cases*

Imbalanced/dependent situations (e.g., employer-employee, physician-patient, public authority-citizen)	
Clinical Trials Regulation	**General Data Protection Regulation**
Consent might be possible (e.g., with EC review and specific safeguards)	Consent may not be the proper legal ground, since not freely given. Another legal ground is necessary for processing personal data (e.g., public interest)

The withdrawal of IC under the CTR and the GDPR should also not be confused. The CTR clarifies that participants may withdraw from a clinical trial at any time by revoking their consent. This withdrawal shall not affect the activities already carried out[18] before the withdrawal[19]. Under the GDPR, there is also a possibility for data subjects to withdraw their consent at any time[20], and there is no exception from this rule in the case of scientific research (32). The GDPR requires that consent can be withdrawn by the data subject as easily as giving consent; thus, eIC is a convenient method to fulfill this requirement[21]. The GDPR does not imply that giving and withdrawing consent must always be done through the same action. As a result, it is possible to withdraw a paper-based IC electronically. However, when the participant's IC was acquired electronically, he or she should be able to withdraw it as easily as giving it (34). In this case, similarly to the CTR, the withdrawal of consent shall not affect the lawfulness of processing the data based on consent before the withdrawal. Once the consent has been withdrawn, the data controller must stop data processing and ensure that the data are deleted or anonymized, unless the data can be processed on another legal ground (6, 28).

4.1.5 SIGNING INFORMED CONSENT ELECTRONICALLY

Next to providing study-related information to research participants electronically, eIC also refers to documenting their IC via an electronic device (48). To this end, various types of electronic signatures may be used. The eIDAS Regulation establishes a legal framework for electronic services, including electronic signatures, across the EU Member States. The main objective of this Regulation is to "*remove existing barriers to the cross-border use of electronic identification means used in the Member*

[18] CTR Recital 76.
[19] CTR Article 28(3).
[20] GDPR Article 7(3).
[21] GDPR Article 7(3).

States to authenticate, for at least public services". Therefore, the Regulation does not create a general obligation to use electronic signatures. EU Member States "*remain free to use or to introduce means for the purposes of electronic identification for accessing online services*", in particular in the private sector[22]. The Regulation only provides a legal framework for electronic services and encourages the use of them. According to Article 3 of the eIDAS Regulation, an electronic signature is defined as "*data in electronic form which is attached to or logically associated with other data in electronic form and which is used by the signatory to sign*" (145). Another signature type defined in this Regulation is an advanced electronic signature. More specifically, an advanced electronic signature is an electronic signature that is "*(a) uniquely linked to the signatory, (b) capable of identifying the signatory, (c) created using electronic signature creation data that the signatory can, with a high level of confidence, use under his sole control, and (d) is linked to the data signed therewith in such a way that any subsequent change in the data is detectable*"[23]. In addition, the eIDAS Regulation sets the standard and criteria for a qualified electronic signature. A qualified electronic signature is defined as "*an advanced electronic signature that is created by a qualified electronic signature creation device, and which is based on a qualified certificate for electronic signatures*", and is the legal equivalent of a handwritten signature (145). One of these three different types of signatures could be used to document IC via an electronic device, considering the requirements set out by this Regulation.

4.2 THE ACCEPTANCE OF ELECTRONIC INFORMED CONSENT

Aside from the requirements of the European legislation that need to be complied with, requirements at the national level need to be considered when implementing eIC in clinical research. Therefore, we shed light on the legal acceptance of eIC in several EU Member States, Switzerland, and the United Kingdom. Generally, three groups of countries were identified. The first and second groups refer to countries that accept the use of eIC (including electronic signatures), with or without explicitly regulating it. The third group includes countries that do not accept the use of eIC (including electronic signatures). We provided examples for each of these groups. In addition, we compared the legal acceptance of eIC in the EU and the US (Table 24).

Table 24. *The acceptance of eIC in the EU and US*

EU Member States			**United States**
eIC is allowed		**eIC is not allowed**	**eIC is allowed**
Group 1: Explicitly regulated (e.g., Belgium)	Group 2: Not regulated (e.g., Finland)	Group 3: Explicitly regulated (e.g., Switzerland)	Regulated and clarified by a regulatory body

[22] eIDAS Regulation Recitals 13, 17, and 21.
[23] eIDAS Regulation Article 26.

4.2.1 Across European Union Member States, Switzerland, and the United Kingdom

Group 1: Countries that regulate and accept the use of electronic informed consent (including electronic signatures) in clinical research

Austria. According to the Austrian Medicines Act Article 39(2), participants must provide IC in written form to participate in a clinical trial (313). Nevertheless, Article 4(1) of the Federal Act on Electronic Signatures and Trust Services for Electronic Transactions (Signature and Trust Services Act) describes that "*a qualified electronic signature satisfies the legal requirement of written form as defined in §886 of the General Civil Code*", meaning that a qualified electronic signature is allowed to document the participants' eIC (314). Moreover, the Austrian Federal Office for Safety in Health Care specifies that electronic information, such as audio and video, can be used to inform participants on the condition that it is approved by an EC (147).

Belgium. In Belgium, the conduct of clinical trials is regulated by the Law of May 7, 2004 on experiments on human beings. Pursuant to Article 6(1) of this Law, the participants' consent must be given in writing (174). In addition, the use of electronic signatures is governed by the Law of July 21, 2016 on eIDAS and electronic archiving, which further implements the EU eIDAS Regulation (315). The Clinical Trial College, an independent body within the Federal Public Service Health, Food Chain Safety, and Environment issued a guidance on the use of eIC in interventional clinical trials in Belgium. This guidance summarizes the following requirements: informing participants, signing consent forms, access to eIC after signing, the dossier to be submitted to the EC, and the application of the GDPR. For example, this guidance specifies that the electronic method of signing the IC must be adapted to the clinical trial, the context of the IC process as well as the participants' needs. If it concerns a phase 1 trial that requires the participants to show their official identity card at each visit, electronic signatures can be used that "*involve participant's handwritten signature using a finger or a stylus under the condition that there is a table trail which makes it possible to demonstrate that the person making the electronic signature was indeed the participant (e.g. the check of the ID document of the person)*". In addition, this guidance sets out that if the participants' identity is not verified, an advanced or a qualified electronic signature must be used (148).

United Kingdom. The United Kingdom Health Research Authority (HRA) and Medicines and Healthcare products Regulatory Agency (MHRA) issued a joint statement, setting out the ethical and legal requirements when using eIC. In this statement, reference is made to the Medicines for Human Use (Clinical Trials) Regulations 2004 which lay down the requirements on informing and documenting

consent in clinical trials. In addition, this statement clarified that electronic methods may be used for seeking, confirming, and documenting IC in research studies (150).

With regard to electronic signatures, the EU eIDAS Regulation is supplemented by the United Kingdom eIDAS Regulations (Statutory Instrument 2016/696) (316). Electronic signatures can be classified as 'simple', 'advanced', or 'qualified'. The type of electronic signature that should be used depends on the specific study. In the case of clinical trials of investigational medicinal products involving risks no higher than that of standard medical care, also referred to as type A trials, any simple electronic signature may be used (including typewritten or scanned eSignatures). In the case of type B and C trials involving a somewhat higher or a markedly higher risk compared to standard medical care, respectively, simple electronic signatures "*that involve the participant tracing their handwritten signature using a finger or a stylus or biometric eSignatures should normally be used as these allow for direct comparison with eSignatures and/or wet-ink signatures previously used by the participant for the purpose of audit or where the consent is contested*". However, the HRA and MHRA advise against the use of typewritten or scanned images of handwritten signatures. When clinical trials are conducted remotely, it may not always be possible to verify the participants' identity face-to-face. In these cases, the authorities prefer the use of advanced or qualified electronic signatures. In other types of research, any form of simple electronic signature should be sufficient to document consent. However, the HRA and MHRA emphasized that signatures traced with a finger or a stylus or biometric electronic signatures may be preferable for studies involving more than minimal risk, burden, or intrusion (150).

The Netherlands. Medical scientific research, involving participants who are subject to procedures or are required to follow rules of behavior, is subject to the Medical Research Involving Human Subjects Act (WMO) (188, 317). In 2020, a legislative procedure was initiated aiming to include the use of electronic signatures for obtaining the participants' IC in the WMO (149). This amendment will enter into force at a time to be determined by Royal Decree. Article 6 of the WMO will be modified and will include that the participants' IC "*can be obtained by electronic means, on the condition that such means are sufficiently reliable and confidential, appropriate to the research, and are set forth in the research protocol*". In addition, Article 6 will lay down that the research participants shall be informed in the same manner, if possible and preferred by the participants, as in which consent can be given. In any case, information must be conveyed in writing and, if desired, in an interview with the research team (318).

Group 2: Countries that accept the use of electronic informed consent (including electronic signatures) in clinical research without explicitly regulating it

Finland. Although eIC is not mentioned in the national legislation, the use of eIC in clinical research is possible. Cases are assessed individually by the Finnish Medicines Agency (FIMEA), which is the competent national authority for regulating pharmaceuticals (319). According to FIMEA, researchers must describe in their application how they would organize the eIC process. Based on that, applicants may have permission to use eIC. The National Committee on Medical Research Ethics (TUKIJA) in Finland, an expert group on research ethics, advises regional ECs on ethical principles related to medical research (320). The TUKIJA has issued guidance and templates on IC for participation in clinical trials. In these documents, the Committee has clarified that eIC is also accepted: "*Written consent can also be provided electronically. If you intend to use an online system for obtaining consent, please provide a description of the method and your reasons for opting for this alternative in your application to the committee.*" (321).

Furthermore, the Finnish National Health Information system KANTA allows Finnish citizens to access their electronic prescriptions and medical records and manage their consent online for several purposes (322, 323). These purposes might include secondary use of data for medical research. The Act on the Secondary Use of Health and Social Data (552/2019) allows the further use of health data for medical research through the Social and Health Data Permit Authority (FINDATA) (324, 325). The Authority's jurisdiction on data permits and requests is based on section 44 of the Act on the Secondary Use of Health and Social Data (552/2019) (324). However, this Act applies to registry-based research, not to clinical trials. Register-based research "*utilizes health and social data for other purposes than for which the data was originally saved in the customer register or utilizes national registries*" (326). Although FINDATA and KANTA are not supporting clinical trials yet, the regulation and establishment of complex online health data management systems may help to foster the acceptance and trust in health cloud systems and eIC in the case of clinical trials.

Group 3: Countries that do not accept the use of electronic informed consent (including electronic signatures) in clinical research

Switzerland. The Swiss Ethics Committees on research involving humans issued a guideline on the use of eIC in clinical trials. According to this guideline, information can be conveyed by using electronic media, such as video or podcasts. The Swiss Ethics Committees recommend that "*the investigator, project leader, or the sponsor of the research project discuss plans for using an eIC with the Ethics Committee prior to finalizing the development of the eIC to ensure that the Ethics Committee agrees that the format may be used to convey the information the subjects*". Nevertheless, a hand-written

signature of the trial participants is necessary to document their consent. At the time of writing, the legal validity of electronic and/or digital signatures is under review. In addition, other requirements are set out in this guidance that must be taken into account when developing and using eIC. For example, it is required that "*a validated system is in place to ensure subject's privacy, when electronic communication tools are used as part of the eIC interview process*" (327).

4.2.2 IN THE UNITED STATES

In the US, there is no comprehensive, national data protection law. However, there are several sector-specific privacy and data security laws at federal, state, and local levels (328). At the federal level, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) Privacy Rule aims to strike a balance between limiting the disclosure of personal health information and allowing researchers to access health data to support medical research. The disclosure of protected health information for research is allowed when: (i) the individual provides written consent or (ii) the Privacy Rule requires or permits it in other ways, such as approved by an institutional review board (329, 330). In the US, eIC is allowed and thoroughly regulated. The requirements for eIC are set forth by the U.S. Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS). More concretely, the relevant FDA and HHS regulations are outlined in the Code of Federal Regulations (CFR), under titles 21 and 45 (49, 331). Requirements related to IC, including the elements the participants need to be informed about, are presented in 21 CFR part 50 (332). Similarly, requirements related to documentation of IC are described in 45 CFR part 46. This part also addresses the elements that need to be included when broad consent is sought for the storage, maintenance, and secondary research use of identifiable information or samples (333). The use of electronic signatures is subject to 21 CFR part 11. This part sets out the criteria under which electronic signatures are considered equivalent to paper-based signatures. An electronic signature is defined as "*a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature*". The CFR clarifies the criteria of electronic signatures by detailing rules on the components, controls, integrity, and safety of electronic signatures, which are also applicable to clinical trials and biobanking (Table 25) (332).

***Table 25**. The regulation of eIC in the US and the EU*

	US	**EU**
Presentation of study-related information	HIPAA 21 CFR part 50 45 CFR part 46	CTR/GDPR
Electronic signatures	21 CFR part 11	eIDAS Regulation

Moreover, in 2016, the FDA and HHS issued a guidance on eIC, intended for institutional review boards, investigators, and sponsors engaged in or responsible for oversight of human subject research under HHS. The guidance clarifies eIC as "*the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent*" (49). This clarification and further guidance on eIC are crucial for the unified application of rules on electronic signatures and IC. Overall, the requirements of electronic signatures and the IC process are regulated on the federal level in the US, resulting in a harmonized legal environment for acquiring eIC in the fields of healthcare and medical research.

5 Discussion and recommendations

Our manuscript provided an overview of the most important regulatory instruments relevant to eIC in clinical research. Although in the EU several regulations are regulating (parts of) eIC in clinical research, Member States still have room for introducing diverse requirements. The CTR, laying down the principles for IC for trial participation, does not set out requirements specifically related to eIC (6). The GDPR has strict rules on data protection, and allows the use of eIC, but does not require it (28). In addition, the eIDAS Regulation is not necessarily targeting the use of electronic signatures in clinical research (145). Some countries, accepting the use of electronic signatures, refer in their statements to the eIDAS Regulation while others, such as Switzerland, still require a wet-ink signature to document the participants' consent. On the contrary, in the US, the CFR lays down the requirements for eIC, and the FDA considers electronic signatures equivalent to handwritten, paper-based signatures. Overall, the regulations in the EU on data protection, clinical trials, and electronic signatures result in a complex, partially harmonized legal environment, which poses a significant challenge for researchers implementing eIC.

Official position statements on the regulatory acceptance of eIC across EU Member States are highly variable. Some countries such as Austria and the United Kingdom published comprehensive guidance, allowing the use of eIC (including electronic signatures) in clinical research, whereas others such as Switzerland forbid it (147, 150, 327). Since drug development has been globalized to make treatments available to patients around the world, it may be crucial to harmonize the legal requirements across the EU Member States (143, 334, 335). Moreover, the EMA published a statement to urge the conduct of large multi-center, multi-arm clinical trials to investigate COVID-19 treatments. This statement stressed the importance of involving all EU Member States in these trials (336). When multi-country clinical trials are conducted, it needs to be ensured that the regulatory requirements in these countries

are met. Due to the lack of harmonized eIC requirements, significant costs and additional delays may be added to the process of clinical research (337). Therefore, efforts are required to ensure that requirements have a high level of consistency to facilitate the conduct of multi-country clinical trials. Over the years, progress has been made in drafting guidance documents for eIC. In 2016, the FDA issued a guidance document in the US (49). In the EU, the EMA has taken the necessary steps to foster the adoption of eIC in clinical research by publishing a draft 'Guideline on computerised systems and electronic data in clinical trials' (48). These guidelines may contribute to increasing the regulatory convergence at a global level.

Requirements stemming from various regulations need to be considered during the implementation and use of eIC. When participants' eIC is sought for research participation, the rules laid down by the CTR must be met. For instance, the eIC interface must inform participants about the aspects of the research study that are relevant to their decision on participation (6). An eIC system could make use of telemedicine technology to interactively guide participants through the information (151). In addition, the CTR specifies that obtaining participants' written, dated, and signed IC is a condition for a valid IC (6). If IC is documented via an electronic device, several electronic signature types could be used, as outlined by the eIDAS Regulation. However, a qualified electronic signature is the only type that has an equivalent value as a wet-ink signature (145). Next to IC for participation in research as an ethical requirement, it can also serve as one of the legal grounds for the processing of personal data. In this case, the eIC system must comply with the multiple obligations imposed by the GDPR. For example, similar to the CTR, the eIC interface must offer participants the possibility to withdraw their consent related to data processing (28).

6 CONCLUSIONS

The application of eIC is increasingly becoming part of the clinical trial landscape, due to the COVID-19 outbreak and technological advancements. Therefore, our research outlined the regulatory framework relevant to eIC in clinical research, focusing on the EU. Although eIC has the potential to provide a safe, fast, and reliable tool to expedite research, the regulation of it is lagging behind, pulling back its potential. In the EU, despite the efforts to harmonize the rules on data protection and clinical trials, the legal acceptance of eIC significantly differs among the Member States. As our research highlighted, some Member States allow eIC (including electronic signatures), with or without explicitly regulating it, while other States simply do not allow the application of eIC, resulting in an unharmonized and confusing legal environment for researchers. In the US, the acceptance and regulation of eIC on the federal level enable researchers to use the full potential of this technological application to enroll

participants and have an interactive relationship with them during the research study. However, the sectorial approach and less strict rules on data protection rules are less efficient and result in an unharmonized protection in the US. Alignment of the regulatory requirements on eIC and data protection rules across countries may successfully advance the adoption of eIC, which would be crucial to enhance clinical research and successfully fight against present and future pandemics.

CHAPTER 9:
INFORMING A EUROPEAN GUIDANCE FRAMEWORK ON ELECTRONIC INFORMED CONSENT IN CLINICAL RESEARCH: A QUALITATIVE STUDY

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Informing a European guidance framework on electronic informed consent in clinical research: a qualitative study

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1 ABSTRACT

Background: Electronic informed consent (eIC) may offer various advantages compared to paper-based informed consent. However, the regulatory and legal landscape related to eIC provides a diffuse image. By drawing from the perspectives of key stakeholders in the field, this study aims to inform the creation of a European guidance framework on eIC in clinical research.

Methods: Focus group discussions and semi-structured interviews were conducted with 20 participants from six stakeholder groups. The stakeholder groups included representatives of ethics committees, data infrastructure organizations, patient organizations, and the pharmaceutical industry as well as investigators and regulators. All were involved in or knowledgeable about clinical research and were active in one of the European Union Member States or at a pan-European or global level. The framework method was used for data analysis.

Results: Stakeholders underwrote the need for a multi-stakeholder guidance framework addressing practical elements related to eIC. According to the stakeholders, a European guidance framework should describe consistent requirements and procedures for implementing eIC on a pan-European level. Generally, stakeholders agreed with the definitions of eIC issued by the European Medicines Agency and the United States Food and Drug Administration. Nevertheless, it was raised that, in a European guidance framework, it should be emphasized that eIC aims to support rather than replace the personal interaction between research participants and the research team. In addition, it was believed that a European guidance framework should include details on the legality of eIC across European Union Member States and the responsibilities of an ethics committee in the eIC assessment process. Although stakeholders supported the idea to include detailed information on the type of eIC-related materials to be submitted to an ethics committee, opinions varied on this regard.

Conclusions: The creation of a European guidance framework is a much needed factor to advance eIC implementation in clinical research. By collecting the views of multiple stakeholder groups, this study advances recommendations that may facilitate the development of such a framework. Particular consideration should go to harmonizing requirements and providing practical details related to eIC implementation on a European Union-wide level.

2 INTRODUCTION

Clinical trials, an essential part of the drug lifecycle, intend to add knowledge to health-related biomedical or behavioral outcomes of a medical intervention (338, 339). While generally essential in the drug lifecycle, shortcomings of traditional clinical trials have been described, for example, related to the required number of participants to achieve the study objectives or the risk of failure, which may hamper the development of medical interventions (340, 341). As a result, focus has been put on novel approaches to design clinical trials, such as making use of master protocols (341, 342). In addition, technological advancements are catalyzing the conduct of clinical trials from a traditional clinical site to a remote setting (343, 344) .

Electronic informed consent (eIC), one of these technological advancements, refers to providing trial-related information to research participants and obtaining their consent electronically [8]. Benefits of eIC, complementing the verbal elucidation provided by the research team, have been argued to be manifold (151, 207, 270). First, eIC may empower participants to make an informed decision on taking part in a trial through a personalized approach. For instance, trial-related information can be conveyed through multimedia elements, tailored to the research participants' needs (151, 270). Next to this personalized approach, eIC may facilitate ongoing interaction between the participants and the research team, for example, for providing the trial results (207). In addition, eIC may support quality assurance by automatically generating date/time stamps and ensuring correct versioning (51, 207).

Whilst eIC may offer various advantages compared to paper-based informed consent forms (ICFs), there are questions about practical elements related to the implementation of eIC in clinical research, such as the legality of eIC throughout European Union (EU) Member States and its impact on the ethical review process (151). Although the Clinical Trials Regulation (CTR) facilitates harmonization of the conduct of clinical trials throughout EU Member States, it does not specifically address eIC (6, 345). The Regulation on electronic identification and trust services for electronic transactions in the internal market lays down the requirements for electronic signatures. According to this Regulation, a qualified electronic signature is the legal equivalent of a handwritten signature (145). However, this Regulation does not specifically target the use of electronic signatures in clinical research and thus, the legality of obtaining the participants' consent via electronic means may vary across EU Member States (345).

Over the past years, guidance documents addressing the implementation of eIC in clinical research have been issued by regulatory bodies. In 2016, the U.S. Food and Drug Administration (FDA) published a guideline setting out the requirements for seeking and documenting eIC in clinical investigations (49).

In the light of the COVID-19 pandemic, the European Medicines Agency (EMA) issued guidance to support the continuation of clinical trials. This guidance states that "*any validated and secure electronic system already used in the trial in the particular member state for obtaining informed consent can be used as per usual practice and if in compliance with national legislation*" (202). In addition, a draft 'Guideline on computerised systems and electronic data in clinical trials' was released by the EMA in 2021, aiming to support stakeholders in complying with the relevant regulatory and legal requirements. This guideline, which was opened for public consultation, further specifies the use of eIC in clinical trials; for example, related to conveying trial-related information to research participants and access to the informed consent (IC) documentation prior and after obtaining their consent (48).

The latter guideline may be a stepping stone towards wider adoption of eIC across EU Member States (48). However, a number of important issues remain. It remains unclear what kind of European guidance framework would ideally be needed to facilitate harmonization and how national guidance should relate to such a European framework. In addition, practical elements that could be addressed in a European guidance framework demand further attention, for example, related to the legality of eIC and the ethical review process. Given the multi-stakeholder nature of (electronic) IC, input on these issues should be gathered from all actors involved (i.e., investigators, regulators, and representatives of ethics committees (ECs), data infrastructure organizations, patient organizations, and the pharmaceutical industry). The insights provided by these stakeholder groups may inform the creation of a European guidance framework related to the implementation of eIC in clinical research.

3 METHODS

This qualitative study adheres to the Consolidated Criteria for Reporting Qualitative Research (COREQ) recommendations (Appendix T) (152).

3.1 DESIGN

A qualitative study was designed, involving focus group discussions and semi-structured interviews, to investigate the perspectives of various stakeholder groups active in EU Member States or at a pan-European or global level. A focus group discussion was chosen to facilitate interaction and information exchange between stakeholders (346, 347). In addition, semi-structured interviews were conducted to tap further into the expert knowledge of stakeholders, who could express themselves individually without constriction. The topic guide used during the focus group discussions and semi-structured interviews was informed by previous research and the research aims. Based on a systematic literature review and semi-structured interviews with various stakeholder groups involved in clinical research,

uncertainties related to eIC were identified that need further discussion (151, 207). These uncertainties were related to (i) the legality of eIC, (ii) the eIC materials that need to be submitted to the EC, (iii) the responsibilities ECs have when assessing eIC, and (iv) the conduct of the eIC process (e.g., whether it can take place via telephone calls). Hereafter, it was investigated whether and how these uncertainties were addressed in the guidance documents of the EMA (draft 'Guideline on computerised systems and electronic data in clinical trials') and the FDA ('Use of electronic informed consent in clinical investigations – Questions and answers') (48, 49). This investigation further informed the design of the topic guide. The topic guide followed a semi-structured format and consisted of questions around (i) the definition of eIC, (ii) the type of European guidance framework required, and (iii) the abovementioned uncertainties (Appendix U).

3.2 PARTICIPANTS

A purposeful sampling approach was used to select the following key stakeholders involved in clinical research: investigators, regulators, and representatives of ECs, data infrastructure organizations, patient organizations, and the pharmaceutical industry. A purposive sample was gathered by searching stakeholder websites and via the research group's network. In addition, we asked the enrolled stakeholders to disseminate our study invitation to other participants of interest and refer us to eligible contacts (i.e., snowballing). Eligible participants needed to be (i) active in an EU Member State or at a pan-European or global level, (ii) involved in or knowledgeable about clinical research, and (iii) fluent in English. An invitation containing the IC for study participation and data processing was mailed to suitable participants. Recruitment continued until no new themes emerged, indicating that data saturation was achieved (217).

3.3 DATA COLLECTION

Focus group discussions and semi-structured interviews were conducted via Microsoft Teams between November 2021 and August 2022. In addition, focus group discussions and interviews were audio-recorded, conducted in English or Dutch, and were 1–2 h and 30–50 min long, respectively. Prior to participation in the focus group discussion or semi-structured interview, participants were provided with the topic guide and, for the sake of completeness, with the guidance documents issued by the EMA and the FDA (48, 49). At the beginning of each interaction, the moderator (JD or EDS) introduced him- or herself and explained the purpose and procedures. Next to a moderator, one or two observers (LB and JD or EDS) were present in the focus group discussions and were responsible for time keeping and for taking notes. A Microsoft PowerPoint presentation was used to guide participants through the focus group discussion or semi-structured interview.

3.4 DATA ANALYSIS

The audio-recordings were transcribed verbatim by the researchers (EDS, JD, and LB) and by a third-party. The data obtained were analyzed deductively (i.e., based upon the research aims and the topic guide) and inductively (i.e., based upon observed patterns) utilizing thematic analysis, through a process of data familiarization and generating codes using NVivo software (153). JD coded the first transcript and discussed regularly with the other researchers (EDS and LB) to refine and agree on the defined codes. Hereafter, a working analytical framework, also known as a coding tree, was created which was then applied to the other transcripts by one researcher (EDS) (Appendix V). Finally, the coded data were charted into a matrix using Microsoft Excel and were then interpreted.

4 RESULTS

4.1 PARTICIPANT CHARACTERISTICS

In total, two focus group discussions were conducted: (i) a multi-stakeholder focus group discussion (n=5) involving one EC representative, one investigator (who was also an EC representative), one representative of a data infrastructure organization, and two patient organization representatives, and (ii) a focus group discussion with EC representatives only (n=6). In addition, eight semi-structured interviews were held with regulators (n=5) and pharmaceutical industry representatives (n=4, of whom two interviewees were present at a single interview). Participants across the stakeholder groups were working in Austria, Belgium, Denmark, Finland, Italy, Lithuania, and the Netherlands; or were active at a pan-European or global level (Table 26).

Table 26. *Characteristics of participants in the focus group discussions and semi-structured interviews (n participants=20, n interviews=19)*

	Participant details
Focus group discussion 1 (n participants=5)	One representative of a data infrastructure organization active on a global level, one EC representative active in Belgium, one investigator (who was also an EC representative) involved in a pan-European organization, and two patient organization representatives active at a pan-European level.
Focus group discussion 2 (n participants=6)	EC representatives were active in Belgium (n=3), Denmark (n=1), Lithuania (n=1), and the Netherlands (n=1). Two representatives were also active at a pan-European level or in a national umbrella organization.

Semi-structured interviews (n participants=9, n interviews=8)	Regulators were active in Austria (n=1), Finland (n=1), Italy (n=1), Lithuania (n=1), and the Netherlands (n=1). Two regulators were also involved in a pan-European organization. Representatives of the pharmaceutical industry were involved in clinical research on a Belgian (n=1), European (n=1), and global (n=2) level.

4.2 High-level considerations on the development of a European guidance framework

4.2.1 The need and value of a European guidance framework

Almost all participants across stakeholder groups perceived the EMA draft 'Guideline on computerised systems and electronic data in clinical trials' as a core document in the field. Several pharmaceutical industry representatives and the data infrastructure organization representative asserted that this guideline will help to alleviate ambiguity and uncertainty about eIC implementation. Some EC representatives and regulators raised that the EMA guideline could function as a reference document during the assessment of eIC.

> "*The assessment process [by regulatory bodies] will be facilitated if the study protocol would state that certain guidelines were met. In that case, we have more certainty about the electronic informed consent system used in a clinical trial.*" (13, regulator)

However, multiple EC representatives argued that the EMA guideline is a rich source of information for sponsors rather than for ECs. They raised the point that the guideline is a relatively technical document that will have a limited place in their evaluation process.

> "*We were very optimistic when we first heard about a guideline issued by the European Medicines Agency. We had high expectations to find answers to very practical issues raised in daily practice, which was unfortunately not the case.*" (9, EC representative)

Similarly, some regulators and pharmaceutical industry representatives mentioned that it concerns a comprehensive guide on computerized systems and electronic data in clinical trials and that, for eIC implementation, additional, more specific issues have to be addressed. To this end, it was raised that a European guidance framework is needed, beyond an EMA guideline, that should include more practical details related to eIC (e.g., related to the ethical review process of eIC). In addition, the

majority of stakeholders agreed that a European guidance framework on eIC should have a high value to facilitate harmonization of eIC implementation in practice and thus, support an efficient conduct of multi-country clinical trials.

> "*We have electronic informed consent deployed in many clinical trials of which multiple involved more than 15 countries. The differences at national level are enormous and the burden to starting up studies and getting the ethics committee approvals is absolutely horrendous.*" (1, data infrastructure representative)

The investigator and a patient organization representative argued that a European guidance framework should be established by means of a regulation. On the other hand, many other participants across stakeholder groups reported that it would be more feasible to create and implement harmonized guidelines, for example, via good research practices or recommendations, that may ultimately result in legislation.

> "*We are in such an early stage with electronic informed consent. I think it would be difficult to have a framework that has a legislative and regulatory value. I believe that providing recommendations is the best we can do until the use of electronic informed consent is more mainstream.*" (18, pharmaceutical industry representative)

One regulator referred to the recommendations related to contraception and pregnancy testing in clinical trials, issued by the Clinical Trials Facilitation and Coordination Group (CTFG), and raised that a similar approach could be undertaken for eIC. In addition, this particular regulator as well as a pharmaceutical industry representative considered recommendations easier to amend in comparison to a legally binding act, which was deemed useful in the view of evolving technology.

4.2.2 TOWARDS A MULTI-STAKEHOLDER GUIDANCE FRAMEWORK

All stakeholders agreed that multi-stakeholder partnerships are needed, involving patient organizations, regulatory bodies, policy makers, health care professionals, sponsors, ECs, data protection authorities, and clinical research organizations to design a European guidance framework on eIC.

"*We really think that data protection authorities should be involved in the design of a European guidance framework in order to incorporate the relevant data protection requirements.*" (20, pharmaceutical industry representative)

Many participants across stakeholder groups referred to the Clinical Trials Expert Group (CTEG) of the European Commission or the EMA to take a leading role in designing such a framework. A particular EC representative emphasized that, when multiple stakeholder groups are involved, it is of utmost importance that they share similar objectives.

"*Before starting this joint effort, we have to be sure that all stakeholders share the same objectives behind developing a framework and implementing electronic informed consent.*" (7, EC representative)

4.2.3 A EUROPEAN VERSUS A NATIONAL GUIDANCE FRAMEWORK

When asked how national guidance should relate to a European guidance framework on eIC, it was raised that a European framework could be the guiding star to design national guidance. Therefore, many participants across stakeholder groups considered it important to not exhaustively describe all eIC-related aspects in a European guidance framework in order to enable the EU Member States to incorporate their jurisdictional requirements in national guidance.

"*In national guidance, the level of rolled out technologies should be considered, for example, related to electronic identity systems.*" (2, investigator)

However, many participants across stakeholder groups emphasized that harmonization at European level is the way forward. Therefore, it was argued that the information laid down in national guidance must not conflict with the requirements defined by a European guidance framework. In addition, a regulator and a pharmaceutical industry representative voiced the opinion that it is important to provide insights into the topics for which harmonization cannot be sought.

"*A European guidance framework should contain principles on which the Member States agree. Based on these principles, national initiatives may emerge. However, we need to investigate how we can harmonize as much as possible across Member States.*" (16, regulator)

4.3 Addressing particular aspects in a European guidance framework

4.3.1 Definition of electronic informed consent

Generally, all stakeholders agreed with the definition of eIC issued by the EMA as well as the FDA. A few regulators raised the point that, when reference is made to eIC, it may be unclear whether the eIC process occurs at the research site or remotely and whether it concerns a hybrid combination of paper and electronic consent elements. Therefore, it was suggested to further address these distinctions in an eIC definition. In addition, some participants mentioned that the definitions of eIC lack an explicit understanding that eIC applications are designed to support, rather than replace, the interaction between the research team and the research participants.

> "*The definitions are essentially very good. In my mind the one thing that both of these definitions [EMA and FDA definition] are missing is that electronic informed consent should not replace the physician-patient communication.*" (1, data infrastructure representative)

Moreover, one pharmaceutical industry representative was of the opinion that the definitions stick to a static rather than a longitudinal, interactive eIC process.

> "*Based on these definitions, a scanned paper-based informed consent form would also be considered an electronic informed consent."* (17, pharmaceutical industry representative)

4.3.2 Legality

Many stakeholders mentioned that the statement of the FDA, referring to the relevant regulatory requirements related to eIC, is the way forward. According to some EC representatives, regulators, and representatives of the pharmaceutical industry, the description of the EMA, stating that "*the sponsor should clarify legality and Good Clinical Practice (GCP) compliance with each country's ethics committees and national regulatory authorities*" is due to the structure and functioning of the EU.

> "*I think this is the only way that the European Medicines Agency can move forward. The European Medicines Agency's statement is due to the structure of the European Union and is a respectful approach with regard to the national regulatory authorities*." (12, regulator)

Nevertheless, participants pointed out that this description results in a complex and challenging environment to successfully adopt eIC in clinical research. A pharmaceutical industry representative

raised that the varying acceptability across EU Member States adds complexity and resource costs. Therefore, participants across stakeholder groups stressed that a European guidance framework should clearly specify the legal acceptance across EU Member States. However, providing up-to-date information was considered challenging by a few participants because the legality of eIC across EU Member States may change over time.

One particular regulator mentioned that when it is legally accepted to use eIC in clinical research, it may be unclear that other issues need to be taken care of, for example, related to identity verification in case of remote consenting. Therefore, it was suggested to list all elements that need to be considered when implementing eIC in a clinical trial.

4.3.3 DOCUMENTS TO BE SUBMITTED TO ETHICS COMMITTEES

Stakeholders reported differing opinions on the EMA and FDA statements. Most participants across stakeholder groups agreed with the FDA guidance, stating that all information materials the research participants will receive, including multimedia elements, must be submitted to the EC. According to the EMA, "*consideration should be given as to how the system would be presented documentarily to the ethics committee for approval such that it captures the functionality of the systems and the experience of the potential trial participant using it*". The data infrastructure organization representative and some regulators, EC representatives, and representatives of the pharmaceutical industry raised that this description is too vague and may lead to different interpretations.

> "*Most of the time it is better to be clear. A broad description leaves room for interpretation and can be a point of conflict or can result in misunderstandings.*" (12, regulator)

The fact that the EMA refers to the experience of the potential trial participant when using an eIC system was recognized as positive by various EC representatives, patient organization representatives, regulators, and the investigator. According to these stakeholders, it is important to pay attention to the user-friendliness of the system and its functionalities when assessing eIC. A few EC representatives raised that the eIC system can be presented by using screenshots. However, they pointed out that these screenshots, despite the valuable insights they provide, do not allow them to engage with the system in the same way a participant will.

> "*You can get a lot of information from the screenshots, except for the interaction*." (11, EC member)

The data infrastructure organization representative and a few representatives of the pharmaceutical industry argued that storyboards (i.e., visual roadmaps of multimedia elements) could be submitted to ECs. These storyboards could be supplemented with an attestation letter confirming that the content of eIC will be identical to the paper-based consent submitted for EC review. According to these representatives, this approach would support an efficient process since the digitization of the paper-based consent can already take place during EC review. On the other hand, some EC representatives argued that they would like to have access to the eIC application. One particular EC representative added that there was limited experience with assessing eIC, and therefore, it is key to take an in-depth look into the application.

> "*I believe that we should receive exactly what the patient receives and we should be able to assess how the patient will navigate through the electronic informed consent.*" (8, EC member)

4.3.4 RESPONSIBILITIES OF ETHICS COMMITTEES

The EMA guideline does not specifically address the responsibilities of ECs in the eIC assessment process whereas the FDA guidance mentions that the EC should look into aspects such as any optional questions to investigate the participants' understanding of study-related information, the usability of the eIC application to ensure that it is easy to navigate, and how the electronic signature is created. Several participants thought that the EC responsibilities are defined on national level and are therefore not included in the EMA guideline.

> "*I think the European Medicines Agency does not have a description of the responsibilities because it is already defined on national level.*" (6, EC representative)

Nevertheless, the majority of participants argued that, if possible, the responsibilities of an EC should be included in a European guidance framework to avoid inconsistent expectations amongst different ECs. Most of the participants agreed with the responsibilities listed in the FDA guidance. Nevertheless, one pharmaceutical industry representative raised that reviewing optional questions to gauge subject comprehension fits better with the investigator's responsibility. In addition, a few participants raised that it is important to keep in mind whether ECs will be able to fulfill the responsibilities if these would be listed.

4.3.5 CONDUCT OF THE ELECTRONIC INFORMED CONSENT PROCESS

Almost all participants across stakeholder groups agreed with the statement of the EMA on where and how the eIC process can take place. According to this statement, it can be "*conducted in person or, it could be done remotely where this can be justified and where allowed nationally and if approved by an ethics committee using electronic methods that allow for two-way communication in real time".* One pharmaceutical industry representative raised that this description is too vague and that further clarification is needed to know what is exactly allowed. The FDA describes that in-person discussions with the research team can be used to "*ask questions about the study before signing consent as well as at any time during the subject's involvement in the research*". In addition, the FDA also refers to electronic means such as video conferencing, electronic messaging, telephone calls, or a live chat to interact with the research team. Stakeholders' main views on the descriptions of the EMA and the FDA are presented in Table 27. According to many participants, a European guidance framework should emphasize the possibility to interact with the research team physically. However, participants should also be able to discuss study-related information or additional questions only electronically, based on their preferences.

> "*I think it depends on the study. Physical contact should always be offered but there must be the chance to contact the investigator electronically.*" (2, investigator)

Table 27. *Perspectives of stakeholders on the EMA and FDA descriptions*

The conduct of the eIC process	
EMA description	**FDA description**
Positive elements: • Emphasis on EC approval in case of a remote interview in which the investigator informs the participants about the pertinent aspects of a trial • Emphasis on electronic methods that allow real-time communication for conducting the interview • Reference to national legislation	**Positive elements:** • Emphasis on the eIC process (i.e., having the possibility to ask questions before and during the conduct of the trial) • Flexibility because the description refers to in-person discussions as well as multiple electronic options to discuss questions with the investigator
Negative elements: • No concrete options are provided for how the interview can be organized	**Negative elements:** • Reference is made to the use of electronic methods that do not necessarily allow real-time communication (e.g., electronic messaging)

5 DISCUSSION

A scattered regulatory and legal landscape poses challenges for the implementation of eIC in clinical research (91, 207, 345). The EMA draft 'Guideline on computerised systems and electronic data in clinical trials' may play a vital role in advancing the adoption of computerized systems, including eIC, in clinical research (48). However, further discussion and a more holistic guidance framework, specifically focused on eIC, is needed to advance its successful deployment in clinical research. To this end, semi-structured interviews and focus group discussions were conducted with key stakeholder groups to address identified issues and practical elements in order to support the development of a European guidance framework on eIC. Future activities could be centered around the recommendations outlined in Table 28.

Table 28. *Multi-stakeholder recommendations for the creation of a European guidance framework on eIC in clinical research*

Overarching recommendations regarding the development of European guidance framework
1. Involve a multi-stakeholder taskforce to guide the creation of a European guidance framework, with a neutral stakeholder preferably taking the lead
2. Develop a European guidance framework with a high legal value, starting from recommendations or good research practices that may ultimately result in legislation
3. Aim to harmonize as much as possible and to report transparently about the elements for which and the reasons why harmonization cannot be achieved
Recommendations regarding the content of a European guidance framework
4. Address specific types of eIC (e.g., a combination of paper and electronic consent elements may be used)
5. Report and update the legal acceptance of eIC across EU Member States
6. Include an overview of the responsibilities of ECs and preferably the documents to be submitted to ECs
7. Emphasize that eIC applications are designed to support the interaction between the research participants and the research team
8. Emphasize the interactive and flexible character of eIC applications

5.1 TOWARDS A UNIFIED UNDERSTANDING OF ELECTRONIC INFORMED CONSENT

A few regulators highlighted that it may be unclear what exactly eIC is referring to. eIC applications are often highly configurable. For example, they can be used in a fully remote setting or a combination of eIC elements and obtaining the participants' wet-ink signature can be employed (76, 80, 209, 348). To avoid misconceptions of what eIC could exactly entail, it is advisable to address these specific types of

eIC in a European guidance framework. In addition, as suggested by some stakeholders involved in this study, it should be mentioned that eIC is not meant to replace the personal interaction between the research participants and the research team. Previous research showed that this is one of stakeholders' main concerns with regard to eIC adoption (151, 207). This is likely influenced by their limited experience with eIC which, in turns, leads to a lack of awareness of its potential and functioning. Hence, clarification in issued guidance and the broader European guidance framework for eIC is essential.

5.2 The need for a coordinated multi-stakeholder collaboration

All stakeholders in this study highlighted the need for a multi-stakeholder approach when it comes to designing a European guidance framework on eIC, preferably coordinated by the EMA or the CTEG. In 2021, the CTEG, consisting of representatives of national competent authorities and ECs, reported their involvement in setting up a guidance on decentralized clinical trials (349, 350). As a result, together with the Clinical Trial Coordination Group of the Heads of Medicines Agencies (HMA) and the Good Clinical Practice Inspectors Working Group of the EMA, they issued a Recommendation paper on decentralized elements in clinical trials in December 2022 (351). In addition, other initiatives are ongoing to facilitate transformation of the design and conduct of clinical trials in view of the emerging technologies. For example, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6(R3) Expert Working Group, a multi-stakeholder collaboration, issued a draft version of updated ICH E6 principles in 2021 (22, 352). The revision of the E6(R2) GCP guideline aims to, among others, facilitate the use of digital health technologies in clinical trials (22). The availability of guidance documents, informed by key stakeholders in the field, may lay the foundation to successfully advance the conduct of clinical trials. However, it remains unclear to what extent these guidance documents will cover practical elements regarding eIC.

5.3 Further adoption of electronic informed consent in clinical research

Frameworks play an important role in clinical research and act as safeguards in regulating how stakeholders should undertake their responsibilities (5, 6). A European guidance framework on eIC may be the way forward to facilitate its implementation. However, even if such a framework would be in force, the adequacy of available infrastructure may affect the successful implementation of eIC in clinical research. A recent survey conducted by TransCelerate, a non-profit organization involving biopharmaceutical research and development organizations, found that one of the biggest challenges with implementing eIC is a heavy resource demand to support its development, approval, and maintenance (91). Due to the variation across eIC solutions on the market, additional complexity to

research operations may be added (67, 69, 77). Using an eIC solution in a clinical study requires training of research staff and the development of standard operating procedures, and thus may be considered burdensome (353). Another implementation challenge of eIC is related to achieving interoperability with other healthcare applications (288). To this end, a guidance framework could emphasize the importance of standards, such as Health Level 7 (HL7) Fast Healthcare Interoperability Resources (FHIR), to design eIC solutions that can connect to other systems in order to ease the burden for the site.

In the draft guideline issued by the EMA, it is stated that the legality of eIC should be clarified with the national regulatory authorities, which respects the sovereign rights of EU Member States (48). Nevertheless, when conducting multi-country clinical trials, the country-specific requirements should be understood, for example, related to the use of electronic signatures and the interaction between research participants and the research team (334). To this end, the abovementioned 2022 EMA/European Commission/HMA joint Recommendation paper on decentralized elements in clinical trials may be an important tool to increase transparency on the legality of eIC (351). Furthermore, based on consultations with regulatory bodies as well as available literature, an overview of the acceptance of electronic signatures for obtaining informed consent for participation in a study and for data processing could be compiled (345, 351, 354). However, to facilitate the conduct of these trials, an appropriate way forward would be to harmonize the eIC process as much as possible across EU Member States. Therefore, a fundamental debate is required about what principles should underpin harmonization and how it can be achieved. The topics for which it is not possible to achieve harmonization should be transparently described in a European guidance framework and may be further addressed in national guidance.

5.4 The assessment process by ethics committees

ECs are independent bodies in EU Member States that are empowered to give opinions for the purposes of the CTR (6). Their main responsibility is to protect the rights, safety, and wellbeing of research participants. Therefore, ECs have a key role in assessing the (electronic) ICF (5). Due to their independent nature, a uniform assessment of eIC is lacking. The CTR, applicable since 31 January 2022, aims to simplify and harmonize the application and evaluation procedures for clinical trials (6, 23). According to the CTR, the clinical trial application consists of two parts. Part I contains, among other things, the protocol and the investigator's brochure and will be reviewed by one reporting EU Member State taking into account considerations expressed by the other Member States involved. On the contrary, part II, consisting of other aspects such as the ICF and IC procedure, will be assessed by each

Member state concerned for its own territory (6, 355). Therefore, structured ethical evaluation of eIC may be a further matter of concern. To this end, a European guidance framework could consist of various elements. First, the draft guideline of the EMA on computerized systems and electronic data in clinical trials can lay down general requirements related to eIC. Second, there is a need for a detailed overview of the legality of eIC across EU Member States. This overview could be provided in view of the 'Accelerating Clinical Trials in the EU (ACT EU)' initiative which aims to, among others, support the conduct of multi-country clinical trials (295). Third, practical elements related to the ethical review process of eIC could be addressed, such as the type of materials an EC should have access to (i.e., printscreens or full access to the eIC application). For example, the European Network of Research Ethics Committees (EUREC) could promote the development of harmonized solutions for reviewing eIC (356).

5.5 Strengths and limitations

To the best of our knowledge, this is the first empirical study aiming to investigate and inform the creation of a European guidance framework related to the implementation of eIC in clinical research. Based on focus group discussions and semi-structured interviews with key stakeholder groups involved in clinical research, we were able to capture a diverse range of opinions. However, it should be noted that the results found in qualitative research are bound to the participant sample, and thus, may not allow for generalization. In addition, it is worth mentioning that we were not able to include stakeholders located in Eastern Europe, despite our sustained efforts to do so.

6 Conclusions

Whereas the conduct of clinical trials relies on a solid regulatory framework, the regulatory and legal landscape related to eIC in clinical research is scattered. Therefore, this study brought together key stakeholder groups in clinical research in order to investigate and inform the creation of a European guidance framework on eIC. Generally, the results show that there is a need for a European guidance framework, that both addresses practical elements on eIC and aims to harmonize eIC requirements as much as possible across EU Member States. In addition, stakeholders voiced several suggestions such as involving multi-stakeholder partnerships in the creation of a framework and providing overarching insights into the ethical evaluation process of eIC.

CONCLUDING DISCUSSION

Parts of this discussion are based on:

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Personalized and longitudinal electronic informed consent in clinical trials:

How to move the needle?

Manuscript in review

** Joint first authors*

The use of electronic informed consent (eIC) in clinical research could offer myriad benefits compared to a paper-based informed consent form (ICF) that still remains the default. However, challenges in the ethical, legal, regulatory, user interface, and technical domains impede successful and widespread implementation. This PhD thesis offers insights into different facets of eIC with the ultimate aim of formulating recommendations for developing and implementing a participant-centric eIC application in clinical research. It does so through a multidisciplinary approach, drawing from scientific advances and the integration of knowledge in the ethical, legal, regulatory, and user interface domains. These recommendations may serve as the foundation to unlock the full potential of eIC and may contribute to an advantageous future state of a participant-centric, personalized, and longitudinal eIC application which can improve the current IC process.

In this general discussion, I will first summarize the main findings of each research objective. Subsequently, I will discuss these findings and highlight recommendations to leverage the development and implementation of an eIC application, tailored to the end users' needs. Finally, I will dive into the future of eIC, the key strengths and limitations of this PhD project, and potential avenues for future research.

1 REVISITING RESEARCH OBJECTIVES

Research objective 1: To explore the ethical, legal, regulatory, and user interface perspectives of stakeholders on electronic informed consent

In **Chapter 1**, through a systematic literature review, the ethical, legal, regulatory, and user interface perspectives of stakeholders (i.e., research participants, researchers, ethics committee (EC) members, and health authorities) were investigated to assist responsible implementation of eIC in biomedical research. This systematic literature review identified that the possibility to convey information via a variety of interactive multimedia elements such as audio or video is considered a distinct benefit of eIC. Some empirical studies included in our review demonstrated that participants using eIC obtained a better understanding of study-related information compared to those using a paper-based ICF. However, other empirical studies did not identify differences in understanding, highlighting the need for more research to develop solutions for a more effective eIC process. In addition, this systematic literature review found that eIC could offer other advantages, such as enabling study access for participants who are geographically remote from the research site and providing an up-to-date record of participants' consent status. Major concerns of stakeholders centered on the impact of eIC on the ethical review process by ECs and its security and legal validity.

Based on this systematic literature review, we identified two major opportunities of eIC: (i) a personalized approach could be enforced, tailoring the information delivery to the research participants' preferences and needs, and (ii) a longitudinal relationship between the participants and the research team could be facilitated during and in the follow-up of a research study. However, the results of our review highlighted that research on the potential advantages and challenges of a personalized and long-term eIC for the current clinical research process was lacking. To this end, semi-structured interviews were conducted with various stakeholders involved in clinical research (i.e., representatives of the pharmaceutical industry, of patient organizations, and of regulators, physicians, and EC members) to further explore these features. During these interviews, described in **Chapter 2**, a series of opportunities, challenges, and functionalities of a personalized approach were identified. With regard to the latter, the idea was raised to present information in layers: a first layer offering essential information for participation in the research study, followed by a second layer allowing participants to access additional information if preferred. Furthermore, the qualitative insights revealed that the establishment of a longitudinal relationship between research participants and the research team via an eIC system could be valuable; for instance, to return study results or to inform participants of updates to the informed consent (IC). In line with Chapter 1, it was considered of utmost importance to adequately secure an eIC system to avoid confidentiality infringements. In the past few years, the healthcare sector has faced one of the most important data breaches among all sectors (357, 358). For example, in 2021, an Amsterdam-based hospital was fined by the Dutch Data Protection Authority for not adequately preventing unauthorized access to the patients' medical records (357). These data breaches may negatively impact the trustworthiness of digital systems such as eIC, which participants identified as a key factor (Chapter 1). Furthermore, potential hosting parties were elucidated through the multi-stakeholder interviews. In summary, a regulatory body preferably at a European level, the principal investigator (PI), or a trusted center controlled by a regulatory body could be responsible for hosting an eIC system. Finally, stakeholders highlighted that personal interaction with the research team is of utmost importance and that this cannot be replaced by an electronic application.

As derived from Chapter 1, it is key to focus on vulnerable populations who may have particular requirements. Therefore, in **Chapter 3**, drivers and barriers toward the use of eIC in clinical research involving neonates are described. Although similar results to those described in Chapter 2 were obtained, the semi-structured interviews conducted with health care professionals (HCPs) (i.e., physicians and study nurses) revealed some additional benefits of eIC in this particular setting, such as remotely obtaining both parents' consent which was considered practically challenging. However, these HCPs also raised that an unfavorable socioeconomic environment of the pregnant mother is a

risk factor found to be associated with premature birth. Therefore, concerns were raised that women admitted to the neonatal intensive care unit would lack digital literacy.

Research objective 2: To define electronic informed consent requirements with research participants

Technologies have traditionally been designed with little to no stakeholder input, and thus without considering user-centered design principles (243). Responsible Research and Innovation (RRI), a policy framework in the European Union and beyond, aims to align the research and innovation processes with the values, needs, and expectations of society. RRI entails engaging society through open and participatory forms of interaction in order to allow a proper embedding of scientific and technological advances in our society and to mitigate unintended consequences of future innovation (359, 360).

To meet the RRI standards in this PhD thesis, a 'research through design' approach was employed to investigate how an eIC application could meet the research participants' needs, reported in **Chapters 4 and 5**. In both chapters, research participants who had previously taken part in a clinical study were involved, as one of the key end user groups of eIC. Via co-creation workshops, semi-structured interviews, and a focus group discussion, as described in **Chapter 4**, we zoomed in on how research participants would personalize the ICF of the clinical study they had previously participated in, based on their needs, and how and for which reasons they would establish a longitudinal interaction with the research team. To facilitate intragroup dynamics in the co-creation workshops**,** we developed tools to stimulate reflection and structure the discussion more efficiently (212). Findings show that the extent of study-related information desired by participants varies, and thus it can be argued that there is no 'one-size-fits-all' approach to the (electronic) IC process in clinical research. Participants raised the suggestion to tailor the eIC form to their needs by presenting necessary and additional information in a first and second layer, respectively, which is in line with one of the suggestions raised in Chapter 2. Other recommendations for personalizing an (electronic) ICF were also identified through the provision of these qualitative methods. Furthermore, we found a broad willingness of participants to establish a longitudinal interaction with the research team to receive progress updates, study results, or invitations for new research studies.

In **Chapter 5**, through provocative interviews, the opinions of research participants about aspects related to trust, personalization, and the long-term interaction were sought. Based on Chapters 1 and 2, provocative prototypes were created to open up spaces of debate and discussion around the use and viability of a personalized and long-term eIC system (361). These prototypes brought particular situations into focus for reflection, inspiration, and provocation in order to collectively define a desirable future of such an eIC system. This qualitative study identified that participants mainly prefer

the hospital or the PI to host an eIC system. However, for the latter, the feasibility can be questioned. In line with the findings found in Chapter 4, participants reported different information needs, for example about the stakeholders who have access to their personal data, and different preferences about how to contact the PI in case of questions. Furthermore, in Chapter 2, stakeholders raised that not all research participants would be able to handle the responsibility of stating their preferences. However, Chapter 5 showed that the participants in this qualitative study did not feel personally responsible, but rather their involvement was encouraged. Finally, study results pointed to the need for research participants to decide the level of their engagement, for example, related to setting preferences for data sharing.

Research objective 3: To test and evaluate electronic informed consent modules, co-developed with DistriNet based on requirements

In **Chapter 6**, we identified insights for the implementation of a user-friendly personalized and long-term eIC application, based on usability testing with (potential) research participants and semi-structured interviews with EC members, HCPs, and pharmaceutical industry representatives. To facilitate the conduct of both methods, eIC modules were co-developed with DistriNet considering the requirements identified in Chapters 1 to 5. Chapter 6 highlights the importance of usability testing as an integral part of designing a user-friendly eIC system, which is an important milestone on the path to successful implementation. From the observations during iterative usability testing, we distilled a list of recommendations for developing a user-friendly personalized and long-term eIC system. Although the results obtained suggest that such a system is usable by a heterogeneous group of end users, additional support and alternatives to an eIC system should be foreseen when necessary or desired. Furthermore, Chapter 6 illustrates that some design ideas proposed by research participants during Chapter 4, such as receiving information about new clinical studies they could consider participating in, were not desirable in an eIC system according to other stakeholders. Finally, the need of an eIC system that can be easily set up and integrated with other systems was mentioned several times throughout this PhD project (Chapters 2, 4, 5, and 6).

Research objective 4: To inform the creation of a European regulatory framework on electronic informed consent

The survey conducted in **Chapter 7** explored the experiences of stakeholders (i.e., physicians, data protection officers or legal experts working in the pharmaceutical industry, academia, and academic biobanks, and EC members) with various consenting methods such as eIC, before and during the COVID-19 pandemic as well as their views on any regulatory or legal support for eIC implementation in clinical research. Although the use of eIC was considered moderately or extremely useful by all

stakeholder groups, the results of this exploratory survey indicate that the transformation from paper-based ICFs to eIC is a work-in-progress and results in hesitation and uncertainty. As such, the results argue for more guidance to assist implementation of eIC in clinical research.

Chapter 8 illustrates that the legal acceptance of eIC across European Union (EU) Member States, Switzerland, and the United Kingdom is highly variable. We identified countries that (i) accept and regulate the use of eIC, (ii) accept the use of eIC without explicitly regulating it, and (iii) not accept the use of eIC. In addition, this Chapter dives into the requirements set forth by the Clinical Trials Regulation (CTR), the General Data Protection Regulation (GDPR), and the Regulation on electronic identification and trust services for electronic transactions in the internal market (eIDAS Regulation) that must be considered when implementing (electronic) IC in clinical research. Since the CTR does not provide specific requirements with regard to eIC and the eIDAS Regulation does not necessarily focus on clinical research, it can be concluded that these Regulations are not sufficient in view of implementing eIC. However, to properly protect research participants' welfare and thus overcome the concerns identified in Chapters 1 and 2, it is of utmost importance that an eIC system is adequately governed.

Building further on the identified need for more guidance in Chapters 1, 2, 7, and 8, we organized focus group discussions and semi-structured interviews with various stakeholders involved in clinical research (i.e., representatives of data infrastructure organizations, patient organizations, regulators, and the pharmaceutical industry as well as EC members and investigators). Based on these qualitative expert insights described in **Chapter 9**, recommendations for a European guidance framework related to eIC were identified. The findings of this study argue for the development of a guidance framework with a high legal value to harmonize as much as possible throughout EU Member States, requiring close collaboration between the different actors involved. Furthermore, this study found that practical elements should be addressed in a guidance framework, such as the legal acceptance of eIC in EU Member States. Earlier research reported that it is unclear to researchers how eIC should be presented to ECs (Chapter 1). However, our study findings show that stakeholders did not have a uniform position on this regard, which may be due to the lack of experience with eIC (Chapter 7).

2 REFLECTIONS ON THE MAIN FINDINGS

2.1 WITHDRAWING INFORMED CONSENT ELECTRONICALLY

Although Chapters 1-3 highlight that eIC could offer various advantages, scientific evidence demonstrating that eIC is superior to the traditional paper-based IC process is limited. Chapter 4 found a high willingness of research participants to establish a longitudinal interaction with the research team. As raised in Chapter 2 and by various vendors of eIC applications, better comprehension of study-related information, frequent study updates, and the return of results are expected to increase participant retention in clinical research (362-365). However, as shown in Chapter 1, there is a lack of scientific literature reporting on the impact of consenting methods on participant retention. Stakeholders involved in Chapter 6 expressed reservations about the possibility of withdrawing IC through an eIC application. They would like to avoid participants clicking the button 'Withdrawing consent' due to unwarranted concerns about the study, which may negatively impact retention and thus introduce uncertainty about the validity of study results (366).

As mentioned in the Introduction of this thesis manuscript, voluntariness is an important pillar of the IC process which extends throughout the entire duration of a clinical study, meaning that participants should be able to withdraw at any time via an easy and accessible process (4). Furthermore, as specified in the GDPR, withdrawing consent for data processing should be as easy as giving it; for example, via an eIC application in case IC is the legal basis for data processing (28). In the draft 'Guideline on computerised systems and electronic data in clinical trials', issued by the European Medicines Agency (EMA), it is stated that "*there should be procedures and processes in place for a trial participant to be able to withdraw her/his consent*", leaving it up to the research site how this can be done (48). In the 'Recommendation paper on decentralized elements in clinical trials' of the Clinical Trial Coordination Group (CTCG), the Good Clinical Practice Inspectors Working Group (GCP IWG), and the Clinical Trial Expert Group (CTEG), released in December 2022, it is mentioned that "*procedures should be in place to handle follow-up steps after the consent has been withdrawn electronically*" (351). According to the abovementioned bodies, eIC could enable participants to withdraw from the study electronically. However, further attention should be given to the practical implementation of this feature.

2.2 COST-EFFECTIVENESS

As highlighted throughout this thesis manuscript, several foundational elements (e.g., security and interoperability) should be considered when implementing eIC in clinical research, which may add

costs for research sites. Furthermore, as outlined in Chapter 6 and in various guidance documents issued by regulatory bodies, alternatives for informing research participants and obtaining their consent should be available, such as a paper-based ICF, in case they are unwilling or unable to use eIC (48, 148, 351, 367). The IC process can also entail a combination of electronic and paper-based IC elements, such as conveying information electronically and obtaining the participants' consent via a wet-ink paper signature. A scoping review conducted by Gesualdo et al. found no evaluation of costs when it comes to digital interventions in the IC process (305). However, these hybrid paper and electronic consent approaches may be less cost proportionate, especially if it concerns a small study or if only a small percentage of participants in a clinical study choose eIC. According to available literature, stakeholders believe that the implementation of eIC is associated with a significant cost, which may impede broad implementation (137, 368). However, it should also be noted that digitizing the IC process may also offset the implementation costs, for example, by enhancing efficiency in documentation and storage of signed ICFs. Therefore, continuing implementation of eIC in clinical research may benefit from more clarity in this regard.

2.3 A MULTI-LAYERED ELECTRONIC INFORMED CONSENT MODEL

In addition to the primary purpose of the IC process of truly informing research participants about a clinical study, it must satisfy extensive legal and regulatory requirements (3, 6, 28). Therefore, the current paper-based IC process has been criticized for not focusing on the individual participant needs but rather on meeting these requirements, which was also raised by participants involved in Chapter 4 (36, 369, 370). eIC does not deviate from the long-established principles of IC. It provides similar information as a paper consent version, but does so through multimedia elements along with other features. For example, as raised in Chapters 2-4, multiple layers of information on a particular study could be presented, which is in line with the ongoing process of information exchange described by Mascalzoni et al. (371). Such a layered IC model has also been reported in literature in the context of genetic testing. Similar to the results obtained in Chapter 6, Bunnik et al. state that the first information layer should contain crucial information for taking an autonomous, well-informed decision on whether or not to take a genetic test, such as information about the purpose of the test, implications and risks, and data protection (372). Likewise, the Clinical Trials Transformation Initiative, co-founded by the United States Food and Drug Administration (FDA) and Duke University, recommends that information critical to participants' decision to take part in a clinical trial should be included in a first information layer (154, 373).

Literature suggests that the information retained after the IC process depends on various factors such as age, education, race, and the oral explanation given by the study team (374-376). Furthermore, a randomized trial comparing eIC models with varying degrees of customizable information found that, after 6-month follow-up, participants had a higher understanding of information with the interactive eIC module, making use of hyperlinks to access additional content (i.e., a second information layer), compared with the standard, least customizable eIC model (377). However, as raised by a stakeholder in Chapter 6, "*it will be difficult to make a distinction between important information, mentioned in the first layer, and background information"*. Therefore, it should be considered which information deserves priority and how it should be organized. This requires close collaboration between stakeholders involved in clinical research, in particular EC members, physicians, and research participants themselves.

2.4 Hosting party of an electronic informed consent application

Stakeholders throughout the Chapters reported differing opinions on who should ideally host an eIC application: a regulatory body, PI, hospital, or a trusted center controlled by a regulatory body. Having an eIC application that is reviewed and endorsed at central regulatory level would be useful. For example, the EMA could perform the role of hosting party, enabling research sites to make use of one single application. Through such a streamlined approach, the need for ECs to evaluate the technical aspects of eIC applications and the user experience on a case-by-case level, each time when a clinical study with eIC is submitted for review, would be circumvented. ECs in turn can focus on the evaluation of study-related information that will be presented through the digital platform itself. Furthermore, having a centrally regulatory endorsed application would require less training for researchers than when several applications would be used and thus, helps to overcome the heavy burden put on sites. Similarly to the new Clinical Trials Information System (CTIS) in Europe - which is the single electronic entry point platform for clinical trial application submission, authorization, and supervision in the EU as required by the CTR - EMA could be hosting party for a central eIC application in Europe (378). Although the CTIS was originally planned to enter into application in December 2015, technical difficulties pushed the go-live date back to January 2022 (379). Therefore, the feasibility of having an eIC application endorsed at European level in the short term can be questioned.

Alternatively, a stepwise approach could be applied to the hosting of an eIC application, starting at local level. First, a local body could perform the role of hosting party. For example, eIC could be integrated into Nexuzhealth's Clinical Workstation (CWS) in Belgium, allowing stakeholders involved in a particular hospital network to gain practical experience with the application (380, 381). If the

application is proven to be effective at local level, it can be endorsed at national or European regulatory level. Furthermore, during one year after the go-live date of the CTIS, sponsors were able to choose whether to submit their initial clinical trial applications via the CTIS or via previously established systems, thereby offering the EMA the opportunity to collect feedback on the CTIS, to improve its user-friendliness, and to resolve any issues (382, 383). A similar approach could be taken to promote the successful implementation of a central eIC application.

To gain competitive advantages, private parties could also host eIC applications. Competition among these parties could improve the quality of these applications and reduce their costs (271). Furthermore, the speed of eIC adoption may be related to market competition (384). However, to reduce the burden for the research team and to enable integration of these applications into the healthcare delivery system, emphasis could be placed on setting out minimum standards and specifications that a participant-centric eIC application should fulfill.

2.5 Adoption of participant-centric electronic informed consent: an ongoing process

The IC process in clinical research is experiencing a major paradigm shift, from traditional paper-based approaches to the implementation of eIC applications (63, 91). eIC is not a new technology in the strict sense of the word. Already a decade ago, eIC was used in a randomized clinical trial in the field of overactive bladder in the United States (385, 386). However, Chapter 7 indicates that experience with eIC in EU Member States is limited and that practice is therefore slow to change. Such a paradigm shift from paper-based IC to eIC does not happen overnight and is accompanied by new challenges and problems. Furthermore, it goes hand in hand with a change from the traditional mindset of paper-based approaches to the correct use of eIC. For example, in Chapters 1-3, stakeholders expressed ambiguity as they believed that eIC would interfere with personal contact between the research team and the participants. However, personal contact still has a place in the new paradigm, and is also required by guidance set out by national and European regulatory bodies (48, 148, 351). Moreover, available research highlights the importance of personal interactions for discussing study-related information (126, 387). For example, an empirical study conducted by Ramos et al. in which an eIC module was designed and evaluated, indicated that personal contact with the study team may be necessary to facilitate comprehension of information (126). Furthermore, eIC could offer opportunities for ECs. By using an eIC application, they could keep track of their comments in the application itself. However, in Chapter 6, concerns have been raised about the practical feasibility, highlighting the need for further collaboration in this regard.

3 RECOMMENDATIONS TO SUPPORT THE DEVELOPMENT AND IMPLEMENTATION OF A PARTICIPANT-CENTRIC ELECTRONIC INFORMED CONSENT APPLICATION IN CLINICAL RESEARCH

This section leverages the combined knowledge and insights of each chapter to set out recommendations for developing and implementing a participant-centric eIC application in clinical research. An overview of these recommendations can be found in Table 29.

Table 29. *An overview of recommendations supporting the development and implementation of a participant-centric eIC application in clinical research*

Build stakeholder understanding
1. Raise awareness to overcome misconceptions on eIC
Foster a participant-centric eIC process
2. Tailor the eIC process to research participants' needs
3. Reduce hurdles for successfully using a personalized and long-term eIC application
Support the set-up and practical implementation of a personalized and long-term eIC application
4. Facilitate the creation of eIC forms
5. Establish a flexible eIC architecture
Strengthen governance for eIC
6. Improve clarity on the legal acceptance of eIC at national level
7. Clarify and harmonize the ethical review process of eIC
8. Set out minimum requirements for an eIC system

3.1 BUILD STAKEHOLDER UNDERSTANDING

3.1.1 RAISE AWARENESS TO OVERCOME MISCONCEPTIONS ON ELECTRONIC INFORMED CONSENT

Because of the high configurability of eIC applications, misconceptions appear to exist about what eIC exactly entails (Chapters 7 and 9). While eIC is a container term to describe digital practices, ranging from simply embedding an electronic signature in a scanned version of the paper-based ICF to using an interactive electronic platform, the eIC process appears at times to be mistakenly understood as an exclusively remote process, negatively impacting personal contact with the research team (Chapters 2 and 3). Therefore, eIC seems to be viewed primarily as a stand-alone application rather than as a trigger for interaction between the participant and the research team. These misconceptions may be grounded in a lack of knowledge on and experience with eIC. Therefore, raising awareness among stakeholders could contribute to a better understanding of eIC.

3.2 FOSTER A PARTICIPANT-CENTRIC ELECTRONIC INFORMED CONSENT PROCESS

3.2.1 TAILOR THE ELECTRONIC INFORMED CONSENT PROCESS TO RESEARCH PARTICIPANTS' NEEDS

The use of eIC may result in new opportunities for extending user experiences and interactions. To achieve value-driven adoption of eIC, focus should be put on involving end users in its design process (Chapters 4, 5, and 6). The active participation of research participants in the design of eIC has illustrated that there is no 'one-size-fits-all' approach to the eIC process (Chapters 4 and 5). What works for one participant at a certain point in time will not necessarily work for someone else or in a different situation. Therefore, there is a need for tailoring the eIC process to research participants' preferences and needs. First, additional measures should be taken to engage participants who are unaccustomed to digital technologies in clinical research. It should be avoided that eIC would aggravate inequalities between different societal groups or across different regions. Therefore, sufficient resources should be dedicated to guide participants through the eIC application or they can be given the choice between eIC and a paper-based ICF. Second, information should be presented in a meaningful and tailored way, for example by using click-through systems to direct participants to more in-depth information about a study. Third, research participants should be offered the possibility to exercise control over the nature and extent of their involvement in the eIC process. For example, participants may prefer to not establish a longitudinal interaction with the research team or to set up a video consultation to discuss further questions rather than going to the research site.

3.2.2 REDUCE HURDLES FOR SUCCESSFULLY USING A PERSONALIZED AND LONG-TERM ELECTRONIC INFORMED CONSENT APPLICATION

Chapter 6 highlights the importance of usability testing to improve the quality of interaction between the end users and the eIC system, and thus to optimize the user experience which is one of the key drivers of adopting technological applications (388). Based on findings in Chapter 6, we conclude that it is of utmost importance to inform research participants about personalization and long-term features of an eIC system, such as the ability to change their preferences (e.g., with regard to receiving study results), to access multiple layers of information, and to indicate that they have questions. For the latter, the research team can clarify how these questions should be added and how these should be resolved using an eIC system. Furthermore, it is vital to design a user interface that is easy to use and helps prevent end users from making errors. Therefore, as derived from Chapter 6, we advise that (i) the existence of multiple layers of study-related information should be clearly visible, (ii) the design of interfaces should allow participants to recording their questions rather than accidentally deleting them, (iii) the user interface on which withdrawing is possible should prevent participants from

accidentally withdrawing from the study, and (iv) the changes in a new IC version should be clearly displayed.

3.3 Support the set-up and practical implementation of a personalized and long-term electronic informed consent application

3.3.1 Facilitate the creation of electronic informed consent forms

The initiation of a clinical study is a time-consuming process, influenced by a complex network of multiple oversight bodies (389, 390). To facilitate an efficient start-up of a study, sponsors and researchers could be provided with a template to develop personalized eIC forms enabling the establishment of long-term interactions with the participants (Chapters 2 and 6). Such a template may be built upon a repository of necessary elements and may include standard process flows, sections, images, etc. to streamline the process of setting up eIC forms.

3.3.2 Establish a flexible electronic informed consent architecture

The ability to integrate eIC into systems already used in practice is considered key to successfully advance eIC implementation in clinical research (Chapters 2-6). Similarly, as outlined by the World Health Organization (WHO) in collaboration with other organizations such as the Johns Hopkins University, in their 'Mobile Health Assessment and Planning for Scale' toolkit to scale mobile health innovations and maximize their impact, compatibility and integration of digital systems with other information systems is one of the key determinants for success (391). Therefore, flexibility, interoperability, and scalability should become fundamental elements of an eIC system to be successfully integrated within the digital health ecosystem. An eIC system that allows for seamless integration into the research site's workflow will ease the burden for the research staff, enabling them to deliver exceptional care to the participants.

3.4 Strengthen governance for electronic informed consent

Chapters 1, 2, 7, and 8 substantiate the need for a European guidance framework that addresses current gaps in the governance of eIC. Policy makers and regulators should ensure that innovation in clinical research is not stifled while protecting the welfare and rights of end users. They should join forces with other stakeholders in the field to establish a guidance framework, drawing from a triangulation of science, ethics, and society.

3.4.1 IMPROVE CLARITY ON THE LEGAL ACCEPTANCE OF ELECTRONIC INFORMED CONSENT AT NATIONAL LEVEL

Currently, the fragmented legal and regulatory landscape across EU Member States adds complexity to the conduct of clinical research in multiple regions (Chapters 7, 8). To this end, a harmonized position regarding the legal acceptance of eIC is believed needed, starting from harmonized guidelines that may ultimately result in legislation. Nevertheless, an important step forward would already be to clarify the legality of various eIC aspects (e.g., the use of multimedia to convey information or the use of electronic signatures) in order to provide clear guidance to stakeholders across EU Member States (Chapter 9). The abovementioned 'Recommendation paper on decentralized elements in clinical trials' provides an overview of the provisions of various EU Member States with regard to using electronic signatures and organizing a physical face-to-face meeting with the research team in view of the eIC process, and is thus an important step forward (351).

3.4.2 CLARIFY AND HARMONIZE THE ETHICAL REVIEW PROCESS OF ELECTRONIC INFORMED CONSENT

Based on the findings from Chapters 1-3, we conclude that researchers and sponsors face uncertainty with regard to the ethical review process of eIC. For example, it is unclear whether access to the eIC system, storyboards, or screenshots are required. Greater alignment between the ECs in EU Member States could promote the development of harmonized solutions for reviewing eIC. Closer collaboration between the European Network of Research Ethics Committees (EUREC) and national and local ECs, or national organizations such as the Belgian Association of Research Ethics Committees (BAREC), could be an important vehicle in this regard (356, 392).

3.4.3 SET OUT MINIMUM REQUIREMENTS FOR AN ELECTRONIC INFORMED CONSENT SYSTEM

It may be challenging for researchers and sponsors to find the appropriate eIC technology among the broad offer. Better uniformity in terms of platform development may help eIC adoption. To this end, a European guidance framework could provide a comprehensive set of requirements for an eIC system. It could be considered to apply for the EMA qualification process to establish regulatory acceptability of these requirements, which could be an important step forward (393). Based on Chapters 4 and 5, personalized and longitudinal features are vital to engage research participants in the eIC process, based on their preferences. Providing research participants with understandable information that can be consulted based on their needs; for example, via a variety of multimedia options, is of utmost importance to protect their autonomy and to facilitate decision-making. To this end, a guidance framework should emphasize that eIC should make use of an interactive, multimedia-enabled format rather than sticking to a static electronic document to deliver on its advantages for research participants. We also recommend that such a guidance framework should highlight the importance of

user-centered design, putting participants at the center of the design and development of an eIC system that meets their needs. Furthermore, a guidance framework could highlight the importance of developing an eIC system that can be easily integrated into established systems (see Recommendation 3.3.2). More uniform eIC platforms would require less training for researchers and participants and thus, help to overcome the heavy burden put on research sites.

4 THE FUTURE OF ELECTRONIC INFORMED CONSENT

In recent years, eIC has caught the attention from policy makers and regulators across the globe. In the United States, a collaboration between the FDA and the Department of Health and Human Services Office for Human Research Protections resulted in guidance on the use of eIC in clinical investigations. In this guidance, reference is made to the relevant regulatory requirements that should be complied with when using eIC (49). In addition, the Digital Health Center of Excellence, part of the FDA, provides centralized expertise and aims to accelerate high-quality digital health advancements and innovate regulatory approaches (394).

On a more global level, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6(R2) guideline, entitled Good Clinical Practice (GCP), is at the time of writing being revised to address the rapidly evolving clinical trial landscape. The updated GCP guideline aims to support efficient clinical trial design and conduct in view of emerging technologies, and may therefore address the use of eIC (21, 22). The digital transformation in the health sector also became part of the agenda of the WHO. In their 'Regional Digital Health Action Plan for the WHO European Region 2023-2030', four strategic priorities are put forward to leverage this digital transformation. One of these priorities relates to conducting horizon-scanning to identify patient-centered digital tools that can be scaled up at country or regional level (395).

In Europe, the European Commission, the Heads of Medicines Agencies, and the EMA launched the 'Accelerating Clinical Trials in the European Union (ACT-EU)' program to further develop the EU as a focal point for clinical research (295). To this end, the abovementioned 'Recommendation paper on decentralized elements in clinical trials' has been issued in the context of this program (351). In addition, the EMA published a draft 'Guideline on computerised systems and electronic data in clinical trials', setting out various principles that apply to the use of eIC (48). All these initiatives can be built upon to leverage and scale up the implementation of eIC in clinical research. Nevertheless, as outlined in the Recommendations section, further efforts should focus on providing more practical guidance with regard to eIC and on harmonizing requirements between different jurisdictions.

The future of eIC also depends on the willingness of research sites to bring the electronic transformation of the IC process to the grassroots level. The need for training of research sites and adaptation of existing clinical research infrastructure could be huge demotivating factors. Ultimately, the problem-solving capacities of eIC applications will determine whether eIC adoption will be promoted. Therefore, these applications should be easy to use, flexible, and should allow for interoperability to reduce professional burdens, as highlighted in the abovementioned Recommendations. Another barrier to achieve successful and widespread eIC implementation may be the digital divide, referring to citizens who do not have access to digital technology or are not able to use it (396). The 'EU survey on the use of Information and Communication Technologies (ICT) in households and by individuals' found that minimum 60% of the population between 16 and 74 years old made daily use of the internet in every region of the EU in 2021 (397). However, the European Commission's proposed program 'Path to the Digital Decade' aims to endow at least 80% of adults within the EU with basic digital skills in 2030, which may be a driver for widespread use of eIC (398).

Furthermore, multiple initiatives may have a positive impact on the future of eIC. For example, an ongoing multi-stakeholder initiative of the European Forum for Good Clinical Practice (EFGCP) aims to (i) establish practical guidance describing various eIC elements such as identity verification and (ii) create a database providing an overview of the legal acceptance of eIC across EU Member States and beyond (399). In addition, the abovementioned Clinical Trials Transformation Initiative paves the way for facilitating the use of digital technologies in clinical trials (400). These initiatives may further contribute to responsible and widespread implementation of eIC in clinical research.

5 STRENGTHS AND LIMITATIONS OF THE PROJECT

The strengths and limitations of each study are outlined within the individual chapters. However, some general considerations are worth further discussion. The interdisciplinary approach taken, supported by the Centre for IT & IP Law, the Centre for Biomedical Ethics and Law, the Meaningful Interactions Lab, and DistriNet is one of the key strengths of this PhD project. Furthermore, this project draws from both quantitative and qualitative research methodologies which enabled us to gain insights into a personalized and long-term eIC in clinical research, considering the ethical, legal, regulatory, and user interface domains. However, it should be noted that this PhD project has a strong qualitative component by employing methods such as semi-structured and provocative interviews, co-creation workshops, and focus group discussions. Although these methods allowed us to develop an in-depth understanding into experiences, needs, and concerns of stakeholders, these may suffer from bias and are bound to the participant sample, and may thus not be generalizable. Nevertheless, the use of topic

guides during the conduct of these qualitative methods and the framework method for analyzing the data ensured the trustworthiness of the data reported.

During the research studies, special focus was set on partnering with stakeholders involved in clinical research, such as research participants, investigators, EC members, the pharmaceutical industry, and regulators. The main emphasis was put on involving (potential) research participants, as a very important group of eIC end users, to learn about their needs, wishes, and concerns with regard to personalizing the eIC process and setting up the long-term interaction with the research team. However, because this PhD project mainly focused on personalization and long-term interaction features, a less in-depth examination on the level of each of the separate research domains was performed. Therefore, while this project provides a comprehensive view on a participant-centric eIC, multiple avenues for further investigation and additional research have emerged (see below).

Finally, despite the fact that multiple eIC systems are already on the market, identifying the characteristics of these systems is complicated by a lack of access to product details, which are often confidential or made available only when there is a particular interest in using such a system in practice. However, although it is challenging to provide full insight into the current state of the art, this PhD adds to the dearth of literature on a personalized and long-term eIC system, and contributes in this way valuable information to the scientific community.

6 AVENUES FOR FUTURE RESEARCH

Based on the results obtained in this PhD project, we would like to propose some avenues for future research in order to support the further development and implementation of a personalized and long-term eIC system in clinical research:

1. To assess the needs of particular population groups

To facilitate broad adoption of eIC in clinical research, we believe it would be interesting to investigate the needs of particular groups of research participants; for example, patients affected by mental health disorders. To this end, similar to Chapters 4 and 5, a user-centered design approach should be used.

2. To investigate and optimize the usability of a personalized and long-term electronic informed consent application in a real-life setting

In Chapter 6, we investigated the usability of eIC modules in a simulation-based setting. Therefore, extending the research to the clinical context may be a promising route. It would be worthwhile to

observe patients and healthy volunteers in more naturalistic settings when interacting with the eIC application to address specific factors that influence usability. Particular focus should go to investigating the usability of an eIC application by end users with different digital skills across disease areas.

3. To investigate how study-related information can be effectively communicated

While this PhD project focused on the user interface domain related to eIC, it did not specifically address the question of how study-related information can be conveyed to research participants while increasing their comprehension. Therefore, one could investigate how this information should be provided to meet the participants' informational and decision-making needs. Since research has already been conducted in this regard, we believe that the conduct of a literature review would be useful (47, 54, 401).

4. To investigate the impact of electronic informed consent on the participants' understanding

After conducting the abovementioned research (bullets 1-3), it may be of interest to study to what extent a personalized and long-term eIC system could enhance the understanding of participants taking part in clinical research. For this, a randomized study could be set up comparing participants' understanding when using eIC with a paper-based ICF.

5. To investigate the foreseen changes in the regulatory landscape

In this PhD thesis, the CTR, the GDPR, and the eIDAs Regulation were studied to distill the requirements relevant to (electronic) IC. However, other initiatives are underway that may change the legal and regulatory landscape for eIC implementation. For example, on 3 May 2022, the European Commission released its proposal for a Regulation on the European Health Data Space which could function as a milestone in the digital transformation in the EU (402). On 14 June 2022, the Council discussed the proposal for the first time, meaning that at the time of writing this dissertation, the legislative procedure is in its early stages (403). Further research could explore the impact of the changing legal and regulatory landscape on the use of eIC in clinical research.

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SUMMARY

The advent of electronic informed consent (eIC) offers the opportunity to solve many challenges related to the static paper-based informed consent (IC) process that still remains the default. According to the European Medicines Agency, eIC refers to "*the use of any digital media (e.g. text, graphics, audio, video, podcasts or websites) to firstly convey information related to the clinical trial to the trial participant and secondly document IC via an electronic device (e.g. mobile phones, tablets or computers)*". Despite the increasing interest in eIC to supplement or replace the traditional paper-based IC process, its application in clinical research so far has been scattered due to a number of barriers. To facilitate an advantageous future state of eIC, this PhD project aims to provide recommendations for developing and implementing a participant-centric eIC application in clinical research.

Part 1 of this dissertation describes the ethical, legal, regulatory, and user interface perspectives of stakeholders on eIC (Chapters 1-3). According to stakeholders, the possibility to implement multimedia is a distinct benefit of eIC as it may positively impact research participants' understanding of study-related information. Nevertheless, attention should be paid to participants with limited digital literacy, visual or auditory impairment, or participants who do not have access to computers or internet. Furthermore, stakeholders expected other advantages to an eIC application. For example, it could enforce a personalized approach, based on research participants' needs, and could establish a long-term interaction between participants and the research team. This interaction could be used to return study results or to inform participants of updates to the IC. Concerns shared by multiple stakeholder groups related to the ethical review process of eIC by ethics committees and the security and legal validity of an eIC application. In addition, it was highlighted that a personal interaction with the research team is of utmost importance and that this cannot be replaced by an electronic application.

To further inform the design of a participant-centric eIC application, patients and healthy volunteers who had taken part in a clinical study were involved in **Part 2** of this dissertation (Chapters 4-5). By undertaking this user-centered design process, various eIC requirements were defined. For example, the need for tailoring an eIC application to research participants' needs and preferences was demonstrated; such as with respect to the amount of information about stakeholders' access to an eIC application. Furthermore, a positive attitude of patients and healthy volunteers was identified to establish a long-term interaction via an eIC application, on the condition that they could indicate the type of study-related information they receive during and after the conduct of a clinical study.

Based on the perspectives and requirements identified in Part 1 and 2, an eIC prototype was co-developed with DistriNet and further refined through usability testing in **Part 3** (Chapter 6). The results obtained during usability testing with patients and healthy volunteers suggest that a personalized and long-term eIC prototype has the potential to be usable by a heterogenous group of research participants. However, additional participant support or alternatives to an eIC application should be foreseen. Furthermore, by discussing the eIC prototype with key stakeholders in the field, we identified other insights that could facilitate successful implementation of a user-friendly personalized and long-term eIC application, such as the need for an eIC system that can be easily set up.

To overcome one of the concerns raised in Part 1, **Part 4** of this dissertation focuses on informing the creation of a European regulatory framework on eIC (Chapters 7-9). While stakeholders involved in Part 4 appear to have limited experience with eIC, they support its use in clinical research during the COVID-19 pandemic and beyond. Nevertheless, the legality of eIC across European Union Member States, Switzerland, and the United Kingdom is highly variable. For example, there are countries that (i) accept and regulate the use of eIC, (ii) accept the use of eIC without explicitly regulating it, and (iii) not accept the use of eIC. To this end, stakeholders highlighted the need for a European guidance framework with a high legal value to support harmonization across countries. Moreover, according to stakeholders, such a guidance framework could provide clarification on the materials that should be submitted to ethics committees and their responsibilities in the eIC assessment process, and could emphasize that eIC aims to support rather than replace the personal interaction between research participants and the research team.

By combining the results of these four parts, this PhD dissertation points towards the need for (i) raising awareness to overcome misconceptions on eIC, (ii) tailoring the eIC process to research participants' needs, (iii) reducing hurdles for successfully using a personalized and long-term eIC application, (iv) facilitating the creation of eIC forms, (v) establishing a flexible eIC architecture, (vi) improving clarity on the legal acceptance of eIC at national level, (vii) clarifying and harmonizing the ethical review process of eIC, and (viii) setting out minimum requirements for an eIC system. The proposed recommendations may unlock the full potential of eIC and may contribute to an advantageous future state of a participant-centric, personalized, and longitudinal eIC application which can improve the current IC process.

SAMENVATTING

De komst van de elektronische geïnformeerde toestemming biedt de mogelijkheid om veel uitdagingen op te lossen met betrekking tot het statische, op papier gebaseerde proces van de geïnformeerde toestemming dat nog steeds de standaard is. Volgens het Europees Geneesmiddelenbureau verwijst de elektronische geïnformeerde toestemming naar "*het gebruik van digitale media (bijvoorbeeld tekst, afbeeldingen, audio, video, podcasts of websites) om eerst informatie met betrekking tot de klinische studie over te brengen aan de onderzoeksdeelnemer en vervolgens de geïnformeerde toestemming te documenteren via een elektronisch apparaat (bijvoorbeeld mobiele telefoons, tablets of computers)*". Ondanks de toenemende belangstelling voor de elektronische geïnformeerde toestemming om het traditionele, op papier gebaseerde proces van de geïnformeerde toestemming aan te vullen of te vervangen, is de toepassing ervan in klinisch onderzoek tot nu toe versnipperd vanwege een aantal belemmeringen. Om een gunstige toekomst van de elektronische geïnformeerde toestemming te faciliteren, heeft dit doctoraatsproject tot doel om aanbevelingen te formuleren voor het ontwikkelen en implementeren van een applicatie van de elektronische geïnformeerde toestemming in klinisch onderzoek waarin de deelnemer centraal staat.

Deel 1 van dit doctoraatsproject beschrijft de ethische, wettelijke, regelgevende en gebruikersinterface perspectieven van belanghebbenden in het kader van de elektronische geïnformeerde toestemming (Hoofdstukken 1-3). Volgens belanghebbenden is de mogelijkheid om multimedia te implementeren een belangrijk voordeel van de elektronische geïnformeerde toestemming. Dit kan namelijk een positief effect hebben op het begrip van onderzoeksdeelnemers wat betreft studiegerelateerde informatie. Niettemin dient aandacht te worden besteed aan deelnemers met een beperkte digitale geletterdheid, een visuele of auditieve beperking of deelnemers die geen toegang hebben tot computers of internet. Belanghebbenden verwachten bovendien andere voordelen van een applicatie van de elektronische geïnformeerde toestemming. Zo kan het bijvoorbeeld een gepersonaliseerde aanpak afdwingen, op basis van de noden van onderzoeksdeelnemers, en een lange termijn interactie tussen onderzoeksdeelnemers en het onderzoeksteam tot stand brengen. Deze interactie kan gebruikt worden om onderzoeksresultaten te bezorgen aan deelnemers of om hen te informeren over nieuwe versies van de geïnformeerde toestemming. Bezorgdheden die door meerdere groepen belanghebbenden werden gedeeld, hadden betrekking op het toetsingsproces van de elektronische geïnformeerde toestemming door ethische commissies en de veiligheid en rechtsgeldigheid van een systeem van de elektronische geïnformeerde

toestemming. Bovendien werd benadrukt dat persoonlijk contact met het onderzoeksteam heel belangrijk is en dat dit niet kan worden vervangen door een elektronische applicatie.

Om het ontwerp van een systeem van de elektronische geïnformeerde toestemming waarin de deelnemer centraal staat verder te informeren, werden patiënten en gezonde vrijwilligers betrokken die reeds deelnamen aan een klinische studie in **Deel 2** van dit doctoraatsproject (Hoofdstukken 4-5). Door het uitvoeren van dit gebruikersgericht ontwerpproces werden verscheidene vereisten van de elektronische geïnformeerde toestemming gedefinieerd. Zo werd aangetoond dat een systeem van de elektronische geïnformeerde toestemming idealiter moet worden afgestemd op de noden en voorkeuren van onderzoeksdeelnemers, bijvoorbeeld met betrekking tot de nodige hoeveelheid informatie over de toegang van belanghebbenden tot dergelijk systeem. Bovendien werd een positieve houding van patiënten en gezonde vrijwilligers geïdentificeerd om een lange termijn interactie uit te bouwen via een systeem van de elektronische geïnformeerde toestemming, op voorwaarde dat ze kunnen aangeven welke studiegerelateerde informatie ze willen ontvangen tijdens en na de uitvoering van een klinische studie.

Op basis van de inzichten en vereisten geïdentificeerd in Deel 1 en 2 werd, samen met DistriNet, een prototype van de elektronische geïnformeerde toestemming ontwikkeld en verder verfijnd door middel van gebruiksvriendelijkheidstesten in **Deel 3** (Hoofdstuk 6). De resultaten verkregen door middel van deze gebruiksvriendelijkheidstesten met patiënten en gezonde vrijwilligers suggereren dat een gepersonaliseerd en longitudinaal prototype van de elektronische geïnformeerde toestemming mogelijks door een heterogene groep van onderzoeksdeelnemers gebruikt kan worden. Niettemin dient er aanvullende ondersteuning van deelnemers of alternatieven voor een systeem van de elektronische geïnformeerde toestemming voorzien te worden. Bovendien werden, door het bespreken van dit prototype met de voornaamste belanghebbenden in het veld, andere inzichten geïdentificeerd die succesvolle implementatie van een gebruiksvriendelijk gepersonaliseerd en longitudinaal systeem van de elektronische geïnformeerde toestemming kunnen ondersteunen, zoals de behoefte aan een systeem dat eenvoudig kan worden opgezet.

Om tegemoet te komen aan één van de bezorgdheden beschreven in Deel 1, richt **Deel 4** van dit doctoraatsproject zich op het informeren van de creatie van een Europees regelgevend kader over de elektronische geïnformeerde toestemming (Hoofdstukken 7-9). Hoewel belanghebbenden weinig ervaring lijken te hebben met de elektronische geïnformeerde toestemming, achten ze het gebruik ervan in klinisch onderzoek tijdens de COVID-19 pandemie en daarbuiten nuttig. Echter is de legaliteit van de elektronische geïnformeerde toestemming in de lidstaten van de Europese Unie, Zwitserland

en het Verenigd Koninkrijk zeer variabel. Zo zijn er bijvoorbeeld landen die (i) het gebruik van de elektronische geïnformeerde toestemming accepteren en reguleren, (ii) het gebruik van de elektronische geïnformeerde toestemming accepteren zonder het expliciet te reguleren, en (iii) het gebruik van de elektronische geïnformeerde toestemming niet accepteren. Daarom benadrukten belanghebbenden dat er een nood is aan een Europees begeleidingskader met een hoge juridische waarde om harmonisatie tussen landen te ondersteunen. Bovendien zou dergelijk begeleidingskader verduidelijking kunnen verschaffen over de materialen die aan ethische commissies moeten worden voorgelegd en hun verantwoordelijkheden in het beoordelingsproces van de elektronische geïnformeerde toestemming, alsook dat de elektronische geïnformeerde toestemming eerder bedoeld is om de persoonlijke interacties tussen onderzoeksdeelnemers en het onderzoeksteam te ondersteunen dan te vervangen.

Door de resultaten van deze vier delen te combineren, wijst dit doctoraatsproject op de noodzaak van het (i) stimuleren van bewustwording om misvattingen over de elektronische geïnformeerde toestemming uit de wereld te helpen, (ii) afstemmen van het proces van de elektronische geïnformeerde toestemming op de noden van onderzoeksdeelnemers, (iii) verminderen van hindernissen om een gepersonaliseerd en longitudinaal systeem van de elektronische geïnformeerde toestemming succesvol te gebruiken, (iv) faciliteren van het maken van formulieren van de elektronische geïnformeerde toestemming, (v) ontwikkelen van een flexibele architectuur van de elektronische geïnformeerde toestemming, (vi) verduidelijken van de wettelijke aanvaarding van de elektronische geïnformeerde toestemming op nationaal niveau, (vii) verduidelijken en harmoniseren van het ethische beoordelingsproces van de elektronische geïnformeerde toestemming, en (viii) uiteen zetten van minimumvereisten voor een systeem van de elektronische geïnformeerde toestemming. De voorgestelde aanbevelingen kunnen bijdragen aan de implementatie en het gebruik van een gepersonaliseerd en longitudinaal systeem van de elektronische geïnformeerde toestemming dat het huidige proces van de geïnformeerde toestemming kan verbeteren.

APPENDICES

APPENDIX A. CHAPTER 1 – SEARCH STRATEGY

PubMed:

(online[tiab] AND informed-consent*[tiab]) OR “online consent”[tiab] OR “online consenting”[tiab] OR “electronic informed consent”[tiab] OR “electronic consent”[tiab] OR “electronic consenting”[tiab] OR “dynamic informed consent”[tiab] OR “dynamic consent”[tiab] OR “dynamic consenting”[tiab] OR e-consent*[tiab] OR econsent[tiab] OR econsenting[tiab] OR ((consent*[tiab]) AND (digital[tiab] OR interactive[tiab] OR multimedia[tiab] OR multimedia[MesH] OR video[tiab] OR telecommunications[MesH] OR telecommunication*[tiab] OR computer*[tiab] OR computers[MesH] OR “user-computer interface”[MesH] OR "online systems"[Mesh:NoExp] OR telemedicine[MesH] OR telemedicine[tiab])) OR ((“informed consent”[MesH]) AND (online[tiab] OR electronic[tiab] OR dynamic[tiab] OR digital[tiab] OR interactive[tiab] OR multimedia[tiab] OR multimedia[MesH] OR video[tiab] OR telecommunications[MesH] OR telecommunication*[tiab] OR computer*[tiab] OR computers[MesH] OR “user-computer interface”[MesH] OR "online Systems"[Mesh:NoExp] OR telemedicine[MesH] OR telemedicine[tiab])) AND ("2010/01/01"[Date - Publication] : "2019/11/14"[Date - Publication]) AND English[Language]

EMBASE:

'digital informed consent':ti,ab,kw OR 'digital consent*':ti,ab,kw OR 'online informed consent':ti,ab,kw OR 'online consent*':ti,ab,kw OR 'electronic informed consent':ti,ab,kw OR 'electronic consent*':ti,ab,kw OR 'dynamic informed consent':ti,ab,kw OR 'dynamic consent*':ti,ab,kw OR 'interactive informed consent':ti,ab,kw OR 'interactive consent*':ti,ab,kw OR 'e consent*':ti,ab,kw OR econsent*:ti,ab,kw OR ((consent*:ti,ab,kw) AND (multimedia:ti,ab,kw OR multimedia/exp OR video:ti,ab,kw OR telecommunication/exp OR telecommunication*:ti,ab,kw OR 'information technology device'/exp OR computer*:ti,ab,kw OR 'online system'/exp OR telemedicine/exp OR telemedicine:ti,ab,kw)) OR (('informed consent'/exp) AND (online:ti,ab,kw OR electronic:ti,ab,kw OR dynamic:ti,ab,kw OR digital:ti,ab,kw OR interactive:ti,ab,kw OR multimedia:ti,ab,kw OR multimedia/exp OR video:ti,ab,kw OR telecommunication/exp OR telecommunication*:ti,ab,kw OR 'information technology device'/exp OR computer*:ti,ab,kw OR 'online system'/exp OR telemedicine/exp OR telemedicine:ti,ab,kw)) NOT 'conference abstract':it AND [english]/lim AND [2010-2019]/py

Web of Science:

TS=("digital informed consent" OR "digital consent*" OR "online informed consent" OR "online consent*" OR "electronic informed consent" OR "electronic consent*" OR "dynamic informed consent" OR "dynamic consent*" OR "interactive informed consent" OR "interactive consent*" OR "e consent*" OR econsent* OR ((consent*) AND (multimedia OR video OR telecommunication* OR computer* OR telemedicine))) AND PY=(2010-2019)

ACM Digital Library:

recordAbstract:"digital informed consent" OR "digital consent*" OR "online informed consent" OR "online consent*" OR "electronic informed consent" OR "electronic consent*" OR "dynamic informed consent" OR "dynamic consent*" OR "interactive informed consent" OR "interactive consent*" OR e-consent* OR econsent* OR ((consent*) AND (multimedia OR video OR telecommunication* OR computer* OR telemedicine))

PsycARTICLES:

AB,TI("digital informed consent" OR "digital consent*" OR "online informed consent" OR "online consent*" OR "electronic informed consent" OR "electronic consent*" OR "dynamic informed consent" OR "dynamic consent*" OR "interactive informed consent" OR "interactive consent*" OR "e consent*" OR econsent*) OR ((AB,TI(consent*)) AND (MAINSUBJECT.EXACT.EXPLODE("telemedicine" OR "multimedia" OR "telecommunications media") OR AB,TI(multimedia OR video OR telecommunication* OR computer* OR telemedicine))) OR ((MAINSUBJECT.EXACT.EXPLODE("informed Consent")) AND (AB,TI(digital OR online OR electronic OR dynamic OR interactive OR multimedia OR video OR telecommunication* OR computer* OR telemedicine) OR MAINSUBJECT.EXACT.EXPLODE("telemedicine" OR "multimedia" OR "telecommunications Media"))) AND YR(>=2010)

APPENDIX B. CHAPTER 1 – MAIN CHARACTERISTICS OF THE 40 INCLUDED STUDIES

Author	Study design	Location	Target population	Age	Sex	Education level	Sample size
Abujarad et al. (121)	● Mixed methods	● United States	● Focus group: research participants (patients with asthma), researchers, EC member ● Usability evaluation: research participants (patients with asthma)	● Focus group: N/A ● Usability evaluation: age range (years): 21-74	● Focus group: N/A ● Usability evaluation: 55.6% women	● Focus group: N/A ● Usability evaluation: 11.1% high school graduate, 11.1% at least some college, 77.8% at least bachelor's degree	● Focus group: patients: n=2, researchers: n=2, EC member: n=1 ● Usability evaluation: n=9
Anderson et al. (93)	● Mixed methods	● United States	● Research participants (patients) with research experience ● Researchers	● Research participants: age range (years): 26-60 (63.6% of participants) and 36.4% of participants >60 years ● Researchers: age range (years): 26-60 (78.9% of researchers) and 21.1% of researchers >60 years	● Research participants: 77.3% women ● Researchers: 73.7% women	● Research participants: 27.3% less than high school diploma, 13.6% high school or GED, 4.5% technical college/trade school diploma, 31.8% some college, 9.1% bachelor's degree, 13.6% master's degree ● Researchers: 5.3% technical college/trade school diploma, 15.8% bachelor's degree, 31.6% master's degree, 37.4% doctoral degree or professional degree	● Patients: n=22 ● Researchers: n=19

Balestra et al. (108)	● RCT	● United States	● Research participants	● Mean age (years): 35.5 (SD=10.7)	● 58.8% women	● N/A	● n=259
Balestra et al. (109)	● RCT	● United States	● Research participants	● Mean age (years): 34.25 (SD=10.78)	● 48.3% women	● Some high-school education (n=1), high school diploma (n=12), some college education (n=58), bachelor's degree (n=59), master's degree (n=14), doctoral degree (n=3) and unknown (n=2)	● n=149
Bobb et al. (107)	● RCT	● United States	● Research participants (patients)	● Mean age (years): 54.4 (SD=16.9)	● 45% men	● N/A	● n=100
Budin-Ljøsne et al. (61)	● Qualitative	● European countries	● Researchers ● Research participants ● EC members	● N/A	● N/A	● N/A	● N/A
Bunnell et al. (134)	● Cross-sectional	● United States	● Researchers ● EC members	● N/A	● N/A	● N/A	● n=134
Chen et al. (118)	● Qualitative	● United States	● Research participants (patients)	● N/A	● N/A	● N/A	● n=434
Chhin et al. (130)	● Cross-sectional	● Canada	● Researchers	● N/A	● N/A	● N/A	● Feasibility study: n=86 ● User survey: n=71
Doerr et al. (123)	● Mixed methods	● United States	●Research participants (participants with and without Parkinson disease)	● Mean age (years): 35.9	● 21.55% women	● 57.53% ≥4-year college degree	● n=9846

Furberg et al. (124)	● Mixed methods	● United States	● Research participants (patients with a diagnosis of FXS) ● Researchers	● Research participants (interview): mean age (years): 22.3	● Research participants (interview): 100% men	● N/A	● Research participants: survey: n=104, interview: n=9 ● Researchers: n=3
Ham et al. (110)	● RCT	● Korea	● Research participants (patients with benign prostatic hyperplasia)	● Mean age (years): 66.9 (SD=6.4)	● 100% men	● 37.5% middle school or less, 32.5% high school, 30% university or more	● n=40
Harle et al. (117)	● Qualitative	● United States	● Research participants	● Mean age (years): 54.1 (SD=14.3)	● 87.5% women	● 31.3% high school or less, 25.0% some college, 43.8% master's degree or higher	● n=32
Harle et al. (106)	● RCT	● United States	● Research participants (patients)	● Mean age (years): 45.6 (SD=16.0)	● 68.4% women	● 9.8% less than high school, 33.9% high school graduate or GED, 31.9% some college, 14.4% bachelor's degree, 9.9% master's, professional, or doctorate degree	● n=734
Harmell et al. (111)	● RCT	● United States	● Research participants (outpatients with schizophrenia and normal comparison subjects)	● Normal comparison subjects: mean age (years): 50.6 (SD=14.0) ● Schizophrenia group: mean age (years): 57.5 (SD=9.42)	● Normal comparison subjects: 56.3% women ● Schizophrenia group: 26.3% women	● Normal comparison subjects: mean years education: 15.5 (SD=1.8) ● Schizophrenia group: mean years education: 12.1 (SD=1.4)	● Normal comparison subjects: n=16 ● Schizophrenia patients: n=19

Haussen et al. (136)	● Cross-sectional	● United States	● Legal authorized representatives	● Age range (years): 28-59	● 64% women	● 40% less than tertiary, 60% tertiary or more	● n=53
Iwaya et al. (120)	● Qualitative	● Australia	● Researchers	● N/A	● N/A	● N/A	● Usability evaluation: n=10 ● Interview: n=9
Jayasinghe et al. (122)	● Mixed methods	● United States	● Research participants	● Focus group: mean age (years): 77.47 (SD=7.54) ● Randomized pilot: mean age (years): 74.65 (SD=7.36)	● Focus group: 80% women ● Randomized pilot: 85% women	● Focus groups: 13% high school/GED, 20% some college, 47% college graduate, 20% postgraduate ● Randomized pilot: 5% elementary, 10% high school/GED, 15% some college, 20% college graduate, 50% postgraduate	● Focus group: n=15 ● Randomized pilot: n=20
Kane et al. (92)	● Cross-sectional	● United States	● EC chairpersons	● N/A	● N/A	● N/A	● n=114
Kim et al. (135)	● Cross-sectional	● United States	● Research participants (patients with chronic diseases)	● N/A	● 26% women, 2.4% not answered	● 19.8% graduate level, 18.3% 4-year college, 27.8% high school-some college, 10.3% <high school, 23.8% not answered	● n=126
Madathil et al. (128)	● Mixed methods	● United States	● Research participants (patients) ● Researchers	● Patients: age range (years): 18-77 ● Researchers: age range (years): 23-74	● N/A	● N/A	● Patients: n=40 ● Researchers: n=10

Mahnke et al. (127)	● Mixed methods	● United States	● Researchers ● Research participants	● Usability evaluation: age range (years): 48-78	● Usability evaluation: 67% women	● N/A	● Simulation of consents: research participants: n=6, researchers: n=5 ● Community advisory group focus groups: research participants: n=11 ● Hybrid focus groups: research participants: n=10 ● Usability evaluation: research participants: n=9
McGowan et al. (133)	● Cross-sectional	● United Kingdom ● Ireland	● Research participants	● N/A	● N/A	● N/A	● n=111
Moran-Sanchez et al. (129)	● Cohort	● Spain	● Research participants (patients with psychotic, mood and anxiety disorders)	● Mean age (years): 41.3 (SD=10.2)	● 47.7% women	● 59% primary, 32% secondary, 9% university degree	● n=88
Perrault et al. (132)	● Cross-sectional	● United States	● Research participants (students)	● Mean age (years): 19.89 (SD=1.54)	● 57.8% women	● University students	● n=429
Ramos et al. (126)	● Mixed methods	● United States	● Research participants (patients with HIV)	● Post-test design: mean age (years): 54.60 (SD=10.8)	● Post-test design: 25% women	● Post-test design: 20% some high school/no diploma, 10% high school diploma/GED, 15% some college/no degree, 5% trade/vocational school, 15% associate	● Icon selection: n=5 ● Post-test design: n=20

						degree, 30% bachelor degree, 5% graduate/ professional degree	
Rothwell et al. (112)	● RCT	● United States	● Research participants (women with full-term pregnancies who gave birth with normal birth outcomes)	● N/A	● 100% women	● 1.61% some high school, 8.06% high school diploma/GED, 17.74% some college, 9.68% associate's degree, 41.94% bachelor's degree, 20.97% graduate degree	● n=62
Rowan et al. (119)	● Qualitative	● Ireland	● Research participants (students)	● Age range (years): 25-34	● 25% women	● Graduate business students	● n=24
Rowbotham et al. (57)	● RCT	● United States	● EC members ● Researchers ● Research participants (patients)	● Research participants: age range (years): 18-80	● Research participants: 66% women	● Research participants: 43% college degree, 30% advanced degree, 4% high school	● EC members and researchers: n=14 ● Research participants: n=55
Schneiderheinze et al. (131)	● Cross-sectional	● Germany	● Research participants (patients)	● Mean age (years): 44.1	● N/A	● N/A	● n=47
Simon et al. (59)	● RCT	● United States	● Research participants (patients)	● Age range (years): 18-86	● 76% women	● 79% at least a college degree or higher	● n=200
Simon et al. (116)	● Qualitative	● United States	● Research participants (patients)	● Age range (years): 43-82	● 45% women	● 61% at least a college degree	● n=50
Simon et al. (137)	● Cross-sectional	● United States	● Researchers ● EC members	● N/A	● N/A	● N/A	● n=65

Spencer et al. (115)	● Qualitative	● United Kingdom	● Research participants (patients with chronic rheumatic disease)	● Mean age (years): 61 (SD=13)	● 58% women	● N/A	● n=40
Sundby et al. (138)	● Cross-sectional	● Denmark	● Research participants (patients with a mental disorder and healthy volunteers) ● Researchers	● Patients: mean age (years): 46.1 (SD=12.3) ● Healthy volunteers: mean age (years): 46.9 (SD=12.3) ● Researchers: mean age (years): 49.5 (SD=12.4)	● Patients: 74.7% women ● Healthy volunteers: 49.8% women ● Researchers: 65.4% women	● Patients: 5.0% none higher, 35.0% short higher, 30.0% medium higher, 24.2% long higher, 5.8% other ● Healthy volunteers: 1.7% none higher, 29.4% short higher, 32.0% medium higher, 32.7% long higher, 4.1% other ● Researchers: 100% long higher	● Patients: n=241 ● Healthy volunteers: n=2294 ● Researchers: n=102
Tait et al. (125)	● Mixed methods	● United States	● Research participants (parents and children)	● Parents: age range (years): 38-50 ● Children: age range (years): 8-14	● Parents: 40% women ● Children: 50% women	● Parents: 20% high school, 80% college graduates	● Parents: n=5 ● Children: n=4
Teare et al. (114)	● Qualitative	● United Kingdom	● Research participants (patients and healthy volunteers)	● N/A	● N/A	● N/A	● n=32
Vanaken et al. (50)	● Mixed methods	● Argentina ● Australia ● Canada ● China ● Denmark ● Germany ● Japan	● Research participants ● Health authorities ● EC members ● Researchers	● Research participants: survey: age range (years): 18-64 and 27% of participants ≥65 years; Participant	● Research participants: survey: 49% women; Participant advisory board: 60% women	● N/A	● Participant survey: n=3045 ● Participant advisory board: n=10

		● Sweden ● United Kingdom ● United States		advisory board: age range (years): 25-87			
Warriner et al. (58)	● RCT	● United States	● Research participants (patients with osteoporosis)	● Mean age (years): 70.4 (SD=8.0)	● 100% women	● 6.06% less than high school, 27.27% high school or GED, 36.36% some college, 30.30% 4-year college or higher	● n=33
Wood et al. (113)	● Qualitative	● United Kingdom	● Research participants	● Age range (years): 20-69	● 50% women	● N/A	● n=42

Abbreviations:
EC: Ethics committee
FXS: Fragile X syndrome
GED: General educational development
N/A: Not applicable
RCT: Randomized controlled trial

APPENDIX C. CHAPTER 1 – INTERVENTION, SCENARIO, AND TOOLS OF THE 40 INCLUDED STUDIES

Author	Intervention	Scenario	Tool
Abujarad et al. (121)	Patient centered virtual multimedia interactive IC tool: virtual coach, video clips, animations, audio, presentations, quiz, retrievable electronic record of IC	Hypothetical	Conceptual design, focus groups, usability evaluation (including SUS and computer efficacy scale)
Anderson et al. (93)	N/A	N/A	Focus groups, survey (including modified versions of the RTS, Research Attitude Questionnaire and SDHC scale)
Balestra et al. (108)	eIC without social annotations vs eIC with social annotations	Hypothetical	Survey based on Westin's privacy index, genomics tutorial comprising a quiz
Balestra et al. (109)	eIC with positive, negative or mixed-valence social annotations	Hypothetical	Survey based on Westin's privacy index, genomics tutorial comprising a quiz
Bobb et al. (107)	Telemedicine-enabled vs face-to-face consent	Real	Survey including the modified QuIC instrument
Budin-Ljøsne et al. (61)	N/A	N/A	Two-day workshop
Bunnell et al. (134)	N/A	N/A	Survey
Chen et al. (118)	REDCap-based eIC: possibility for changing consent elections and withdrawing consent	Real	REDCap
Chhin et al. (130)	eIC	Real	Survey
Doerr et al. (123)	eIC: 5-question summative evaluation	Real	Survey and question: “In what ways would you improve or change mPower?"
Furberg et al. (124)	eIC: multiple-choice quiz questions, interactive narratives	Hypothetical	Interview, survey (including MacCAT-CR)
Ham et al. (110)	Paper-based IC vs eIC: pictures, illustrations, animations, video clips	Real	Survey using a visual analogue scale
Harle et al. (117)	eIC application: 19 hyperlinks and 4 pages of information, bullet points	Hypothetical	Interview
Harle et al. (106)	Interactive trust-enhanced eIC: hyperlinks, trust-enhanced messages vs interactive-only eIC: hyperlinks vs standard eIC	Hypothetical	Survey (including SDHC, subscale of the QuIC instrument, Decision-Making Control Instrument and RTS)
Harmell et al. (111)	Paper-based IC vs web-media enhanced IC: video clips, static images/graphics, bullet pointed text	Hypothetical	Survey (including UBACC and MacCAT-CR)

Haussen et al. (136)	REDCap-based eIC	Real	Survey
Iwaya et al. (120)	eIC: icons, hyperlinks and quiz	Hypothetical	Interview
Jayasinghe et al. (122)	eIC: 39 separate screen views, large font size, audio narration of the text in a human voice, definitions, illustrations, multiple choice self-test, colored text vs paper-based IC: nine pages long	Hypothetical	Focus group, pilot study (including UBACC)
Kane et al. (92)	Case scenario with a multimedia consent module	Hypothetical	Survey
Kim et al. (135)	Tiered eIC: help texts, definitions	Hypothetical	Survey
Madathil et al. (128)	Paper-based IC vs Topaz-based eIC vs touchscreen-based eIC vs iPad-based eIC	Hypothetical	Survey (including IBM Computer Systems Usability Questionnaire), think-aloud session
Mahnke et al. (127)	eIC prototype	Hypothetical	Simulation of consents, readability analysis, survey (including SUS), (hybrid) focus group, usability evaluation
McGowan et al. (133)	eIC: progress bar	Real	Survey
Moran-Sanchez et al. (129)	eIC: slide show, bulleted much-simplified format, 1 key point per slide, staff member read aloud each presentation slide, large text size	Hypothetical	Survey (including Global Assessment Functional Scale and adapted version of MacCAT-CR), interview
Perrault et al. (132)	eIC with 71 words, four sentences vs eIC with 300 words	Hypothetical	Survey
Ramos et al. (126)	eIC: 16 screens, a five-icon home page, highlighted icons with simplified text, colored background and paper IC	Hypothetical	Icon selection (interview), post-test design (interview, survey)
Rothwell et al. (112)	eIC: video presentation, photographs, graphics and animations vs simplified paper-based consent	Real	Survey, interview
Rowan et al. (119)	eIC	Hypothetical	Observation, focus group
Rowbotham et al. (57)	Paper IC vs eIC: video, audio, interactive quiz	Hypothetical	Survey
Schneiderheinze et al. (131)	eIC: text and audio mode, animated pictograms, hyperlinks	Hypothetical	Survey (including SUS)
Simon et al. (59)	Standard interactivity paper IC vs enhanced interactivity paper IC: interactive questions vs standard interactivity eIC: graphics, audio vs enhanced interactivity eIC: graphics, audio, interactive questions	Real	Survey
Simon et al. (116)	Paper IC and eIC: web-based slideshow	Hypothetical	Focus group, survey
Simon et al. (137)	N/A	N/A	Survey

Spencer et al. (115)	eIC prototype: hyperlinks	Hypothetical	Interview, focus group
Sundby et al. (138)	Explanatory video films with subtitles and voice-over	N/A	Survey
Tait et al. (125)	Child version eIC: 3D modelled animated characters, clicking on icons to receive information about the trial and adult version eIC: live-action elements in an animated 3D office, clicking on icons to receive information about the trial	Hypothetical	Interview, survey
Teare et al. (114)	eIC mock-up: modifiable information options	Hypothetical	Focus group, interviews
Vanaken et al. (50)	N/A	N/A	Survey, focus group, interview, meeting
Warriner et al. (58)	eIC: audio, animated video, avatars, comprehension multiple choice questions vs paper IC	Hypothetical	Survey (including Health Information Technology Usability Evaluation Scale and QuIC instrument)
Wood et al. (113)	Web pages designed to achieve IC	Hypothetical	Interview

Abbreviations:
eIC: Electronic informed consent
IC: Informed consent
MacCAT-CR: MacArthur Competence Assessment Tool for Clinical Research
N/A: Not applicable
QuIC: Quality of Informed Consent
RTS: Researcher Trust scale
SDHC: Satisfaction with Decisions in Health Care
SUS: System Usability Scale
UBACC: University of California, San Diego Brief Assessment of Capacity to Consent

APPENDIX D. CHAPTER 2 – COREQ CHECKLIST

Item and guide questions	Response	Location in manuscript (Section)
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Interviewer/facilitator: Which author/s conducted the interview or focus group?	EDS	Methods
2. Credentials: What were the researcher's credentials? E.g., PhD, MD	PharmD	-
3. Occupation: What was their occupation at the time of the study?	At the time of the study, EDS working towards her PhD at KU Leuven	-
4. Gender: Was the researcher male or female?	Female	-
5. Experience and training: What experience or training did the researcher have?	EDS had previous experience in conducting interviews	-
Relationship with participants		
6. Relationship established: Was a relationship established prior to study commencement?	Prior to the interview, participants were briefed on the study and were provided with the informed consent	Methods
7. Participant knowledge of the interviewer: What did the participants know about the researcher?	The participants were informed that EDS was researching electronic informed consent as part of her PhD	Methods
8. Interviewer characteristics: What characteristics were reported about the interviewer/facilitator?	The background of EDS and that this interview study was part of her PhD	Methods
Domain 2: Study design		
Theoretical framework		
9. Methodological orientation and theory: What methodological orientation was stated to underpin the study?	Semi-structured interviews that were analyzed using a framework method	Methods
Participant selection		
10. Sampling: How were participants selected?	Through purposive and snowballing sampling	Methods
11. Method of approach: How were participants approached?	Via mail	Methods
12. Sample size: How many participants were in the study?	39 participants were interviewed	Methods
13. Non-participation: How many people refused to participate or dropped out? Reasons?	71% of invited individuals refused to participate. Reasons included unavailability, non-response to the invitation, or	-

	they had insufficient knowledge of the IC process in clinical research.	
Setting		
14. Setting of data collection: Where was the data collected?	Interviews took place remotely	Methods
15. Presence of non-participants: Was anyone else present besides the participants and researchers?	No	Methods
16. Description of sample: What are the important characteristics of the sample?	Participants belong to one of the five stakeholder groups. They were located across European Member States and the United Kingdom	Methods
Data collection		
17. Interview guide: Were questions, prompts, guides provided by the authors? Was it pilot tested?	Upon request, guides were provided to the interviewee. The interview questions were tested in three pilot interviews	Methods
18. Repeat interviews: Were repeat interviews carried out? If yes, how many?	No	-
19. Audio/visual recording: Did the research use audio or visual recording to collect the data?	Digital audio-recordings of all interviews were made	Methods
20. Field notes: Were field notes made during and/or after the interview or focus group?	Yes	Methods
21. Duration: What was the duration of the interviews or focus groups?	Interviews were 20 to 60 minutes long	Methods
22. Data saturation: Was data saturation discussed?	No	-
23. Transcripts returned: Were transcripts returned to participants for comment and/or correction?	No	-
Domain 3: Analysis and findings		
Data analysis		
24. Number of data coders: How many data coders coded the data?	The first two transcripts were coded by two researchers (EDS and FV or BC). The other transcripts were coded by one researcher (EDS).	Methods
25. Description of the coding tree: Did authors provide a description of the coding tree?	Coding was described in the methods section. Moreover, the coding tree is reported in the supplementary material.	Methods – Supplementary material
26. Derivation of themes: Were themes identified in advance or derived from the data?	Transcripts were coded by using a combination of an inductive and deductive approach	Methods

27. Software: What software, if applicable, was used to manage the data?	NVivo and Microsoft Excel	Methods
28. Participant checking: Did participants provide feedback on the findings?	No	-
Reporting		
29. Quotations presented: Where participant quotations presented to illustrate the themes/findings? Was each quotation identified?	Yes	Results
30. Data and findings consistent: Was there consistency between the data presented and the findings?	Yes	Results
31. Clarity of major themes: Were major teams clearly presented in the findings?	Results are presented per major theme	Results
32. Clarity of minor themes: Is there a description of diverse cases or discussion of minor themes?	Minor themes are discussed in the manuscript, for example by using quotations	Results

APPENDIX E. CHAPTER 2 – INTERVIEW GUIDE

I. Introductory question

1. To what extent do you have experience with clinical research?

II. Questions regarding the paper-based informed consent process

1. What is your experience with the paper-based informed consent process?
   a) What are the positive aspects?
   b) What are the negative aspects?
2. Does the ethics committee that you are a member of review the reading level of paper-based informed consent forms? *(for ethics committee members only)*

III. Questions regarding the electronic informed consent process

Definition (U.S. Food and Drug Administration) (49): *"Electronic informed consent refers to the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent."*

1. To what extent do you have experience with electronic informed consent?
2. How did/would electronic informed consent influence the evaluation process? *(for ethics committee members and regulator representatives only)*

The following questions (3-7) apply only to pharmaceutical industry representatives and physicians with practical electronic informed consent experience:

3. In which clinical research study (with regard to the design, population, therapeutic area) do you use electronic informed consent?
4. How does the use of electronic informed consent influence the clinical research process in comparison to a paper-based consent process?
5. How is the electronic informed consent platform designed?
   a) Do you have any recommendations? Which one(s)?
   b) Does the participant receive personalized information?
   c) What is your opinion regarding personalization?
   d) What are the advantages and disadvantages of personalization?
   e) If relevant, how would you personalize the platform?
   f) Who manages the platform?
6. What is your opinion regarding the return of relevant information of a clinical research study to a study participant using the electronic informed consent platform?
   a) Which information may be shared with the study participant via the electronic informed consent platform?

b) Who do you think should decide what kind of information may be shared via the electronic informed consent platform?

7. Did you experience any barriers in the implementation of electronic informed consent in this clinical research study/studies? Which one(s)?

<u>The following questions (3-8) apply only to pharmaceutical industry representatives and physicians who do not have experience with electronic informed consent, as well as to patient organization representatives, regulator representatives, and ethics committee members:</u>

3. For which clinical trials (with regard to the design, population, therapeutic area) would electronic informed consent be appropriate?
4. How would the use of an electronic informed consent platform influence the current practice of the clinical research process in comparison to a paper-based consent process?
5. About the design of an electronic informed consent platform:
   a) What is your opinion regarding personalization of the platform?
   b) What are the advantages and disadvantages of personalization?
   c) If relevant, how would you personalize the platform?
6. What is your opinion regarding the return of relevant information of a clinical research study to a study participant using the electronic informed consent platform?
   a) Which information may be shared with the study participant via the electronic informed consent platform?
   b) Who do you think should decide what kind of information may be shared via the electronic informed consent platform?
7. Which barriers or challenges may be experienced in the implementation of electronic informed consent in clinical research?
8. Who do you think is best placed to manage the platform?

<u>To end *(for all stakeholders)*</u>:

- Do you have any further comments or issues which you think may be relevant to the design, implementation, or use of an electronic informed consent platform?
- Do you have a suggestion for other interested interviewees?
- Do you have any questions?

APPENDIX F. CHAPTER 2 – CODING TREE

Code	Sub-code level 1	Sub-code level 2	Sub-code level 3	Description
Paper-based IC	Challenges			What are the disadvantages of the paper-based IC process?
		Cognitive burden		
		Static		
		Long-term interaction		
		Documentation and storage		
	Advantages			What are the advantages of the paper-based IC process?
		Traditional		
		Fixed		
		Face-to-face contact		
	Review reading level			Does the ethics committee review the reading level of IC?
eIC	Experience			Does the interviewee have experience with eIC?
	Managing the platform			Who is best placed to manage the eIC platform?
	Impact on review processes			What is the impact of using eIC on the review processes?
	Types of clinical trials			For which clinical trials may eIC be used?
		Population		
		Design		
		COVID-19		
	Personalization			- What is the opinion of the interviewee on personalization? - How can an eIC platform be personalized?
		Functionalities		
		Advantages		
		Challenges		
	Long-term interaction			How can eIC establish a long-term interaction?
		Recontacting		
		Communication of study results		- Which information may be shared via eIC? - Who should decide what kind of information may be shared via eIC?
			Decision-maker	
			Type of results	

	Impact on clinical research practice			How does eIC influence the current process of clinical research?
		Understanding		
		Recruitment and drop-out		
		Documentation and storage		
		Face-to-face contact		
	Framework			How can eIC adoption be facilitated?
		Harmonization		
		Legal and ethical measures		
	Design of the platform			Which elements related to the design of eIC are important?
		Integration with other systems		
		Security		

Abbreviations:
eIC: Electronic informed consent
IC: Informed consent

APPENDIX G. CHAPTER 3 – INTERVIEW GUIDE

I. Introductory questions

1. To what extent do you have experience with clinical research involving neonates?
2. What is your experience with parents' involvement in the informed consent process?
3. What was/is the impact of the COVID-19 pandemic on the informed consent process?

II. Questions regarding the paper-based informed consent process

1. What is your experience with the paper-based informed consent process?
    a) What are the positive aspects?
    b) What are the negative aspects?

III. Questions regarding the electronic informed consent process

1. To what extent do you have experience with electronic informed consent?

The following questions (2-5) apply only to health care professionals with practical electronic informed consent experience:

2. How does the use of electronic informed consent influence the clinical research process in comparison to a paper-based consent process?
3. How is the electronic informed consent system designed?
    a) Do you have any recommendations? Which one(s)?
    b) Do the parents receive personalized information?
    c) What is your opinion regarding personalization?
    d) What are the advantages and disadvantages of personalization?
    e) If relevant, how would you personalize the system?
    f) Who manages the system?
4. What is your opinion regarding the return of relevant information of a clinical research study to parents using the electronic informed consent system?
    a) Which information may be shared with the parents via the electronic informed consent system?
    b) Who do you think should decide what kind of information may be shared via the electronic informed consent system?
5. Did you experience any barriers in the implementation of electronic informed consent in this clinical research study/studies? Which one(s)?

The following questions (2-7) apply only to health care professionals who do not have experience with electronic informed consent:

2. What could be potential benefits or drawbacks when using an electronic informed consent system?

3. About the design of an electronic informed consent system:

   a) Which elements are needed to create an interactive electronic informed consent system?

   b) What is your opinion regarding personalization of the system?

   c) What are the advantages and disadvantages of personalization?

   d) If relevant, how would you personalize the system?

4. What is your opinion regarding the return of relevant information of a clinical research study to parents using the electronic informed consent system?

   a) Which information may be shared with the parents via the electronic informed consent system?

   b) Who do you think should decide what kind of information may be shared via the electronic informed consent system?

5. Which barriers or challenges may be experienced in the implementation of electronic informed consent in clinical research?

6. Who do you think is best placed to manage the system?

7. How long should the system be available to parents?

To end:

- Do you have any further comments or issues which you think may be relevant to the design, implementation, or use of an electronic informed consent system?
- Do you have a suggestion for other interviewees?
- Do you have any questions?

APPENDIX H. CHAPTER 3 – CODING TREE

Code	Sub-code level 1	Sub-code level 2	Description
Involvement of parents during the IC process	Obtaining parents' signatures		What is the opinion of the interviewee on the involvement of parents during the IC process?
	Conveying information to parents		
	Informed decision		
Current paper-based IC process	Challenges		What are the disadvantages of the paper-based IC process?
		Cognitive burden	
		Long-term interaction	
		Documentation and storage	
	Advantages		What are the advantages of the paper-based IC process?
		Detailed information	
		Face-to-face contact	
eIC process	Experience		Does the interviewee have experience with eIC?
	Advantages		What are the (potential) advantages of the eIC process?
	Challenges		What are the (potential) challenges of the eIC process?
	Managing the platform		Who is best placed to manage the eIC platform?
	Personalization		- What is the opinion of the interviewee on personalization? - How can an eIC system be personalized?
	Long-term interaction		How can eIC establish long-term interactions?
		Recontacting	
		Communication of study results	
	Accessibility		How long should the eIC system stay available to parents?
	Design of the platform		Which elements related to the design of eIC are important?
	COVID-19		- What is the impact of the COVID-19 pandemic on the IC process? - What is the potential of eIC during the COVID-19 pandemic?

Abbreviations:
eIC: Electronic informed consent
IC: Informed consent

APPENDIX I. CHAPTER 4 – CODING TREE

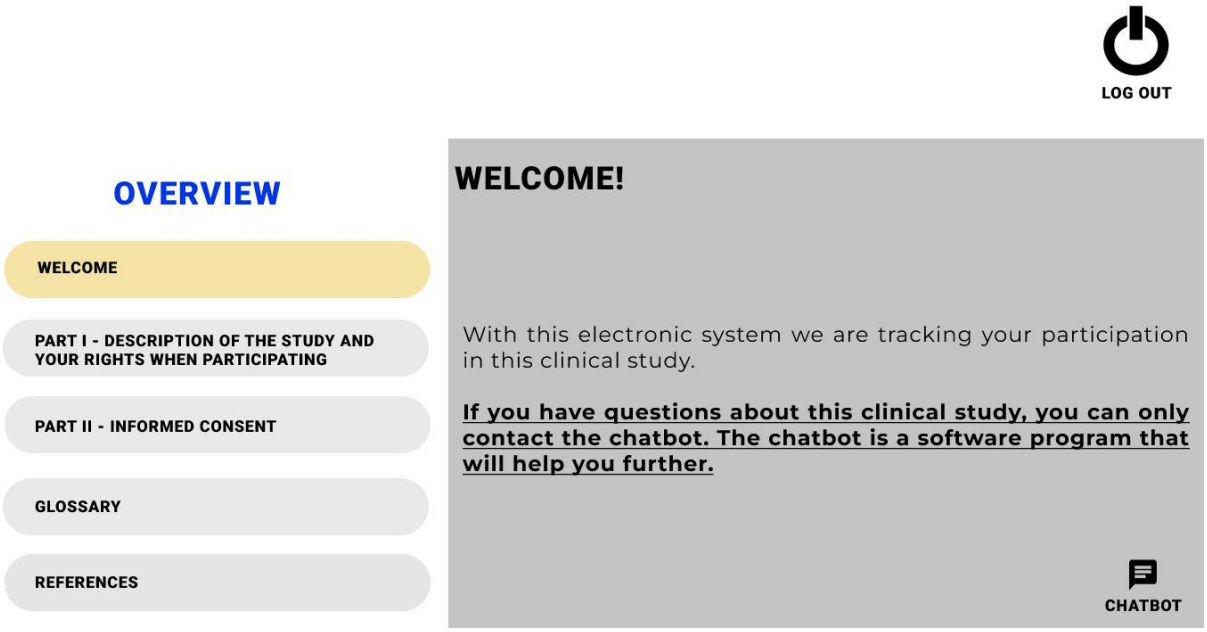
Code	Sub-code level 1	Sub-code level 2	Sub-code level 3	Description
Personalization				How can (electronic) IC be personalized?
	Structure			
	Signing			
	Type of information			
		Additional information required		
		Less information required		
	Understandability			
Long-term interaction				How and for which reasons can eIC establish long-term interactions?
	Aspects			
		Study results		
			Individual	
			General	
		Study status		
		Other research studies		
	Practical integration			
		Notification		
		Newsletter		

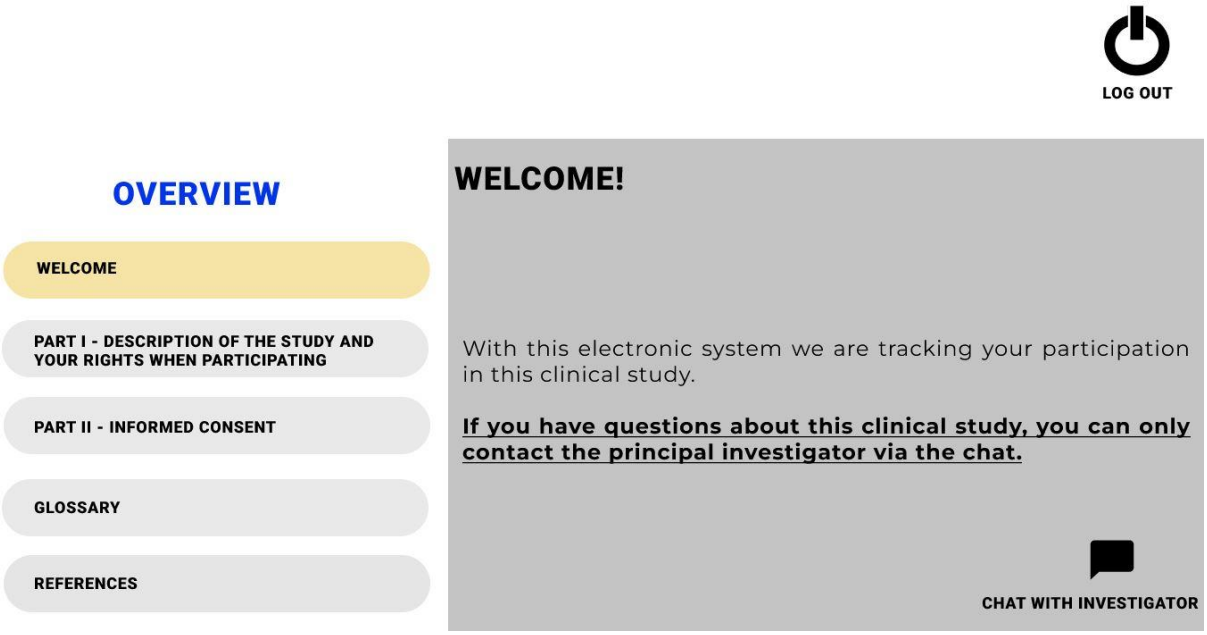
Abbreviations:
eIC: Electronic informed consent
IC: Informed consent

APPENDIX J. CHAPTER 5 – VISUALIZATION OF PROVOTYPE 5: CONTACTING THE PRINCIPAL INVESTIGATOR DURING THE COURSE OF THE STUDY






LOG OUT
OVERVIEW
WELCOME
PART I - DESCRIPTION OF THE STUDY AND YOUR RIGHTS WHEN PARTICIPATING
PART II - INFORMED CONSENT
GLOSSARY
REFERENCES
WELCOME!
With this electronic system we are tracking your participation in this clinical study.
If you have questions about this clinical study, you can only contact the chatbot. The chatbot is a software program that will help you further.
CHATBOT


LOG OUT
OVERVIEW
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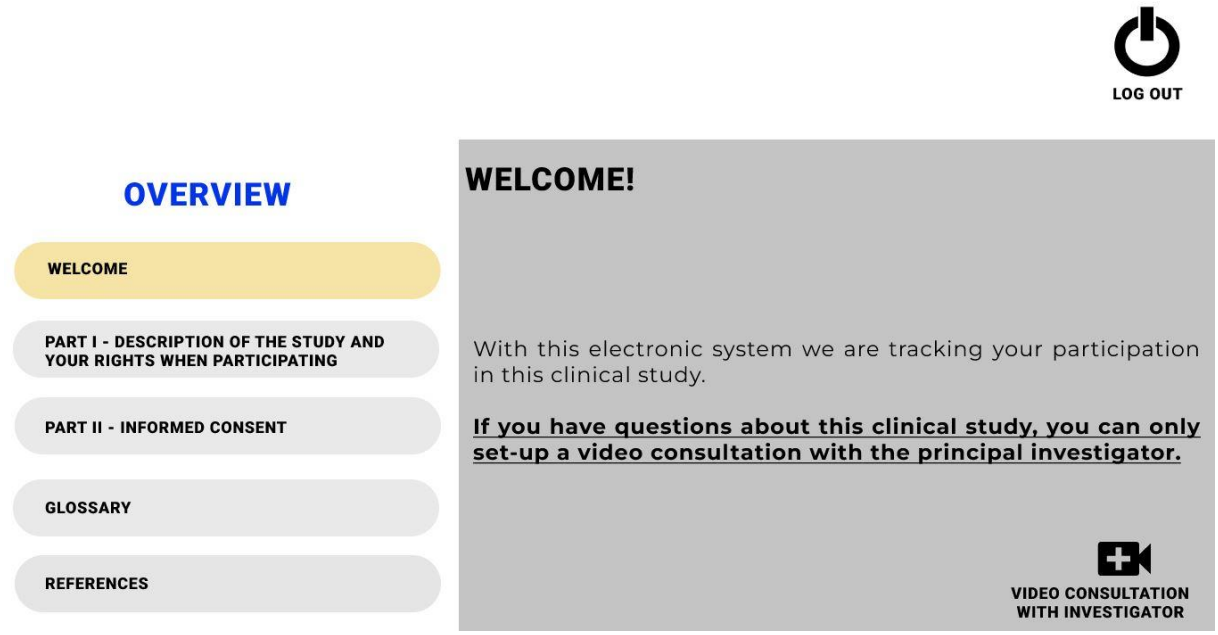
GLOSSARY
REFERENCES
WELCOME!
With this electronic system we are tracking your participation in this clinical study.
If you have questions about this clinical study, you can only contact the principal investigator via the chat.
CHAT WITH INVESTIGATOR


LOG OUT
OVERVIEW
WELCOME
PART I - DESCRIPTION OF THE STUDY AND YOUR RIGHTS WHEN PARTICIPATING
PART II - INFORMED CONSENT
GLOSSARY
REFERENCES
WELCOME!
With this electronic system we are tracking your participation in this clinical study.
If you have questions about this clinical study, you can only set-up a video consultation with the principal investigator.
VIDEO CONSULTATION WITH INVESTIGATOR


CLOSE
YOU ARE NOW LOGGED OUT

APPENDIX K. CHAPTER 5 – CODING TREE

Code	Sub-code level 1	Sub-code level 2	Description
Hosting	Pharmaceutical company		Who is best placed to manage an eIC system?
	Belgian government		
	Hospital		
	Principal investigator		
	Preferences		
	Advantages		
Level of detail on access information	Not possible to provide information		How much information must be provided about access of stakeholders to an eIC system?
	Legitimate rights		
	Detailed information		
	Minimal information		
Being searchable	Physicians all over the world		What are the participant's views on being searchable for future research studies?
	Pharmaceutical company		
	Hospital		
	Type of studies		
Being alerted about new information	Method of being alerted		How does the participant would like to be informed about new information?
	Opinion on being alerted		
Contact with the principal investigator	Chatbot		What is the opinion of the participant on methods to contact the principal investigator?
	Chatbox		
	Video consultation		
	Personal contact		
Reconsenting	Automatically agreeing		What are the most optimal conditions when asking the participant's reconsent?
	Highlighting changes		
	Additional information changes		
	Opinion on signature		
Responsibility	Opinion on responsibility		How does the participant experience the responsibility when indicating which types of information he or she would like to receive?
	Opinion on options	Status	
		Preliminary results	
		Final results	
		Additional investigations	

		New IC version	
Test	Single attempt		How can a test be effectively integrated in an eIC system?
	Multiple attempts		
	Additional explanation		
	Skipping questions - incorrect questions		
	Opinion on question and answer session		
Age			How old is the participant?
Education			What is the highest education level of the participant?

Abbreviations:
eIC: Electronic informed consent
IC: Informed consent

APPENDIX L. CHAPTER 6 – ELEMENTS RELATED TO PERSONALIZATION AND LONG-TERM INTERACTION, IDENTIFIED IN PREVIOUS RESEARCH

Elements related to personalization and the long-term interaction

1. Presentation of information *(personalization):*
Present a first layer of information that is essential for participation in the research study, followed by a second layer that offers more specific information to those who are interested (for example, by using hyperlinks or by hovering over a word). For example, the definitions of the terms 'randomization' or 'double-blinded' could be mentioned in the second layer.

2. Providing personalized information *(personalization):*
- Offer the ability for physicians to stratify groups and provide adapted information (e.g., only give information about pregnancies and breastfeeding to women with a childbearing age).
- Implement a decision tree for information related to pregnancy, contraception, and interaction with other drugs. By interacting with this decision tree, research participants are able to receive personalized information.

3. Lay-out *(personalization)***:**
Enable the research participants to change the layout (e.g., font size) and highlight information.

4. Accessing information *(personalization)***:**
Provide research participants with the option to choose between audio or video content (particularly in case of hearing or visual impairment).

5. Test *(personalization)***:**
When implementing a test to assess research participants' comprehension, automatically redirect them to the relevant information/specific topic when they have answered a question incorrectly. Moreover, provide them with the possibility to use the 'tell me more' button, before answering the question.

6. Metrics *(personalization)*
Provide the possibility to implement metrics that allow physicians to monitor various variables (e.g., how long did it take for research participants to read a certain topic).

7. Long-term contact *(personalization & long-term interaction):*
Enable the research participants to indicate if, how, for which duration, and for which reasons they would like to be recontacted (e.g., to receive final study results, results on additional investigations on the participants' samples, or to receive invitations for new research studies for which participants are being sought).

8. Notifications *(personalization & long-term interaction):*
If research participants would like to be recontacted, enable them to set preferences about the type (e.g., e-mail, text messages) and frequency of notifications.

9. Data sharing *(personalization & long-term interaction):*
Provide research participants with the option to tailor their preferences about whom they want to share their personal data with.

10. Contacting the research team *(personalization & long-term interaction):*
Research participants must have the opportunity to contact the research team if they have questions. Nevertheless, their preferences on how to contact the research team (e.g., via a chatbot, chat feature, or video consultation) may depend on the importance of their questions (e.g., non-urgent questions may be asked via the chat) and their familiarity with technology.

11. Presenting new versions of electronic informed consent *(personalization & long-term interaction):*
When presenting a new consent version, the changes can be indicated and additional information on the modifications can be presented. In this way, participants have the option on whether or not to access the additional information.

12. Overview of studies *(personalization & long-term interaction):*
Research participants could have the possibility to navigate throughout the electronic informed consent interface to have an overview of studies in which they have previously taken part, accompanied by their results.

APPENDIX M. CHAPTER 6 – DESCRIPTION OF THE INITIAL ELECTRONIC INFORMED CONSENT PROTOTYPE, AS USED IN THE FIRST ITERATION

Interface 1: Sign in to start

- Multiple options are provided to sign in (e.g., username and password).

Interface 2: Homepage

- This interface includes the headings 'My studies' and 'My preferences'.
- Under the heading 'My studies', an overview of clinical trials is displayed in which the participant had taken part (marked as 'Finished'), would like to participate (marked as 'Action required'), or is already participating. For each trial, the study details can be consulted by clicking the button 'Open' (in this case, the participant navigates to interface 3).
- Under the heading 'My preferences', a hyperlink is included to navigate to the participant's profile page (i.e., interface 8).
- The top of this interface contains a notification icon and a profile page icon. When clicking the latter, the participant has the choice to navigate to his/her profile page (i.e., interface 8) or to log out. These icons are also present on the following interfaces.

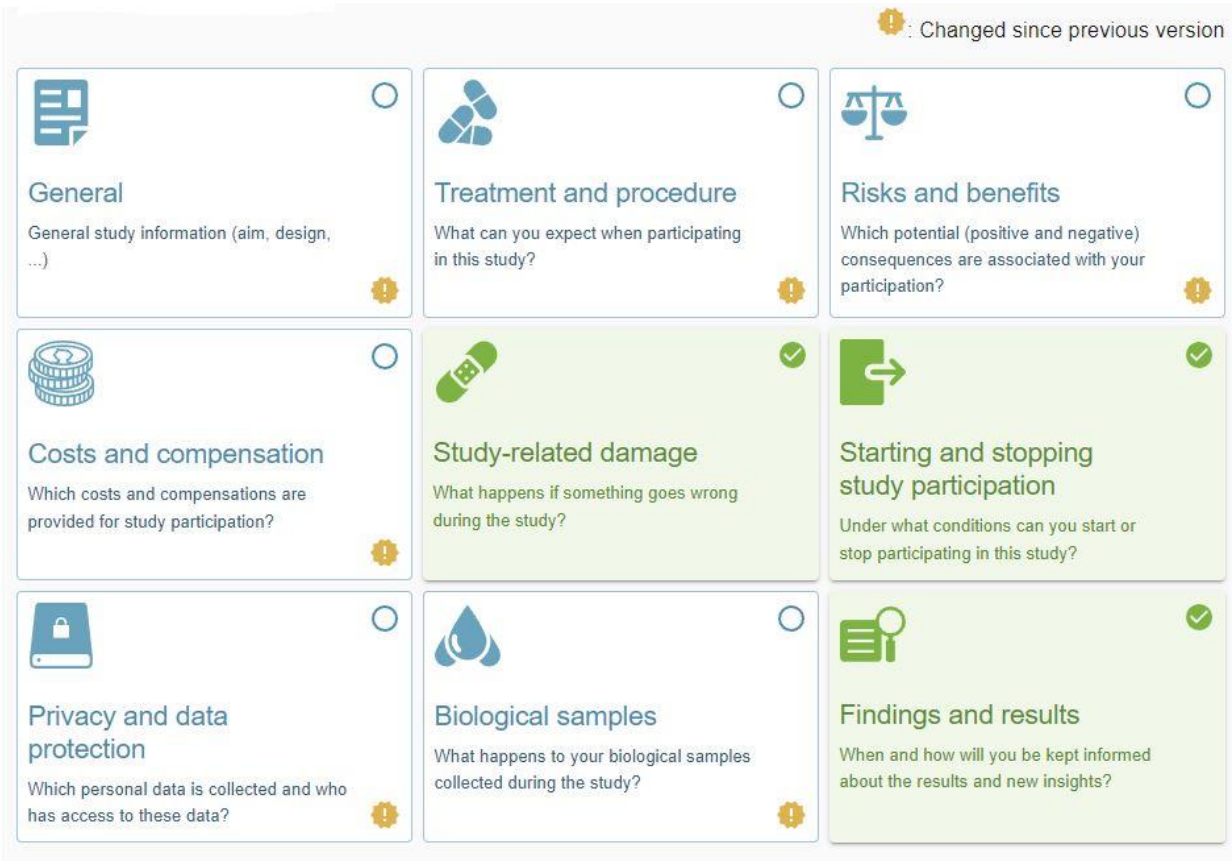
Interface 3: Study details of a specific clinical trial

- This interface includes the headings 'Contact information', 'Informed consent', 'My appointments', and 'Study preferences'.
- Under the heading 'Informed consent', the following is mentioned: version number, date, status (can be marked as 'To be signed', 'Signed' (accompanied by the date of signing), or 'Outdated'), and actions (can include the buttons 'View' and 'Change or withdraw' if the informed consent form has been signed or the button 'View and sign' if the informed consent form has yet to be signed). When clicking the buttons 'View' or 'View and sign', the participant navigates to interface 4. In case of clicking the button 'Change or withdraw', the participant is redirected to interface 10.
- The heading 'Study preferences' includes the button 'Manage' (when clicking this button, the participant navigates to interface 9).

Interface 4: Overview: signing the informed consent

- This interface includes the headings '1. View information', '2. Answering questions', and '3. Signing'.
- Under the heading '1. View information', clinical trial-related information is displayed in large information sections (i.e., 'General', 'Treatment and procedure', 'Risks and benefits', 'Costs and compensation', 'Study-related damage', 'Starting and stopping study participation', 'Privacy and data protection', 'Biological samples', and 'Findings and results'). This information can be accessed by clicking on a particular section or by clicking the button 'Start'.
- The section in which the participant marked unclarities/questions is highlighted in red. If the participant indicates that all information in a particular section is understood, this section is

highlighted in green. If it concerns a new informed consent version, the section that includes changes contains a yellow exclamation mark. Above the sections, the meaning of this exclamation mark is explained. The sections that do not contain changes are highlighted in green (see Figure below).

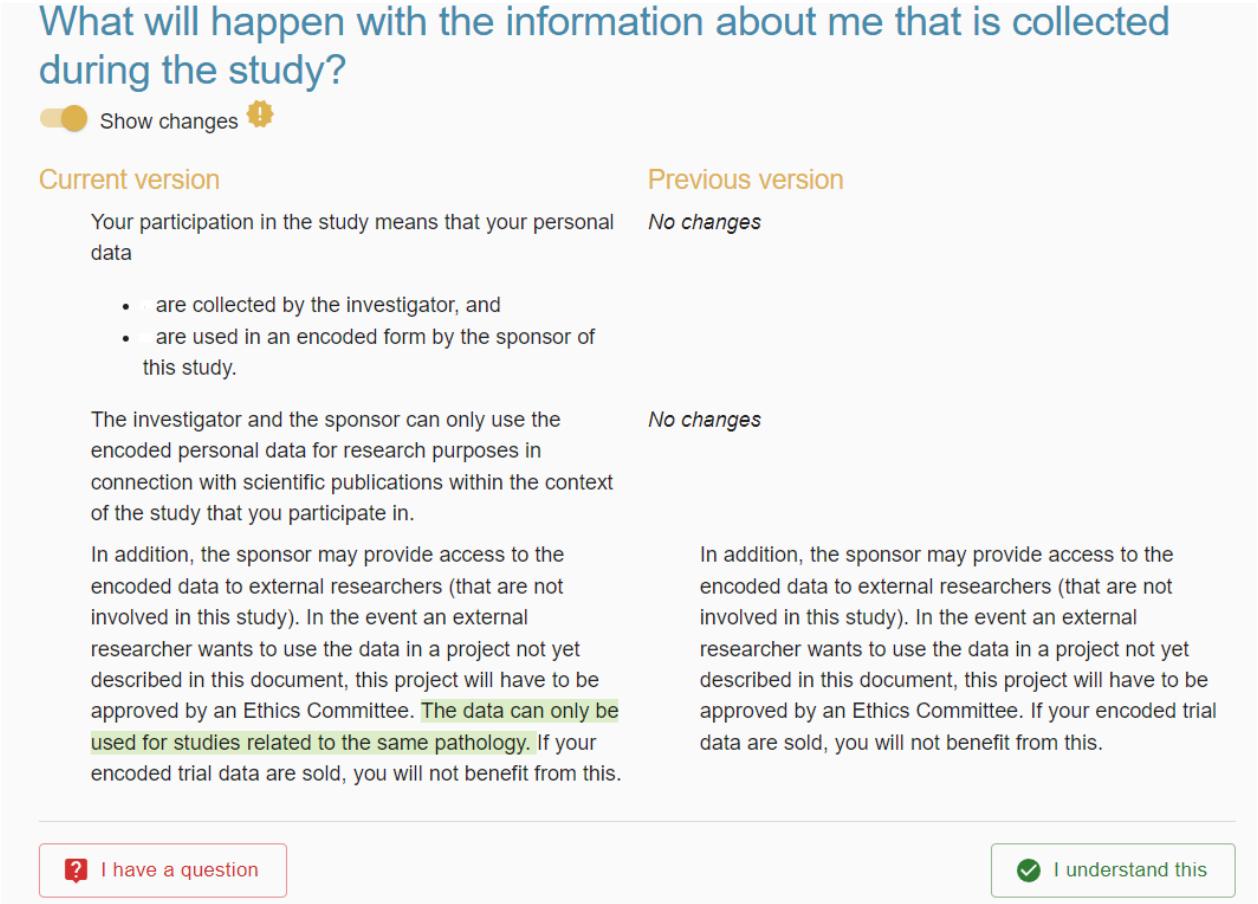


- Under the heading '2. Answering questions', the number of questions added by the participant is mentioned. In addition, the participant is informed that '*these questions can be solved via a conversation with one of the members of the study team*'. An overview of the questions can be displayed by clicking the button 'Open questions' (in this case, the participant navigates to interface 6).
- Under the heading '3. Signing', the participant is informed that the informed consent can be signed only if the participant has read all the study-related information and if all questions, if applicable, have been answered. The button 'Sign consent' is only clickable if these conditions are met (in case this button is clicked, the participant navigates to interface 7).

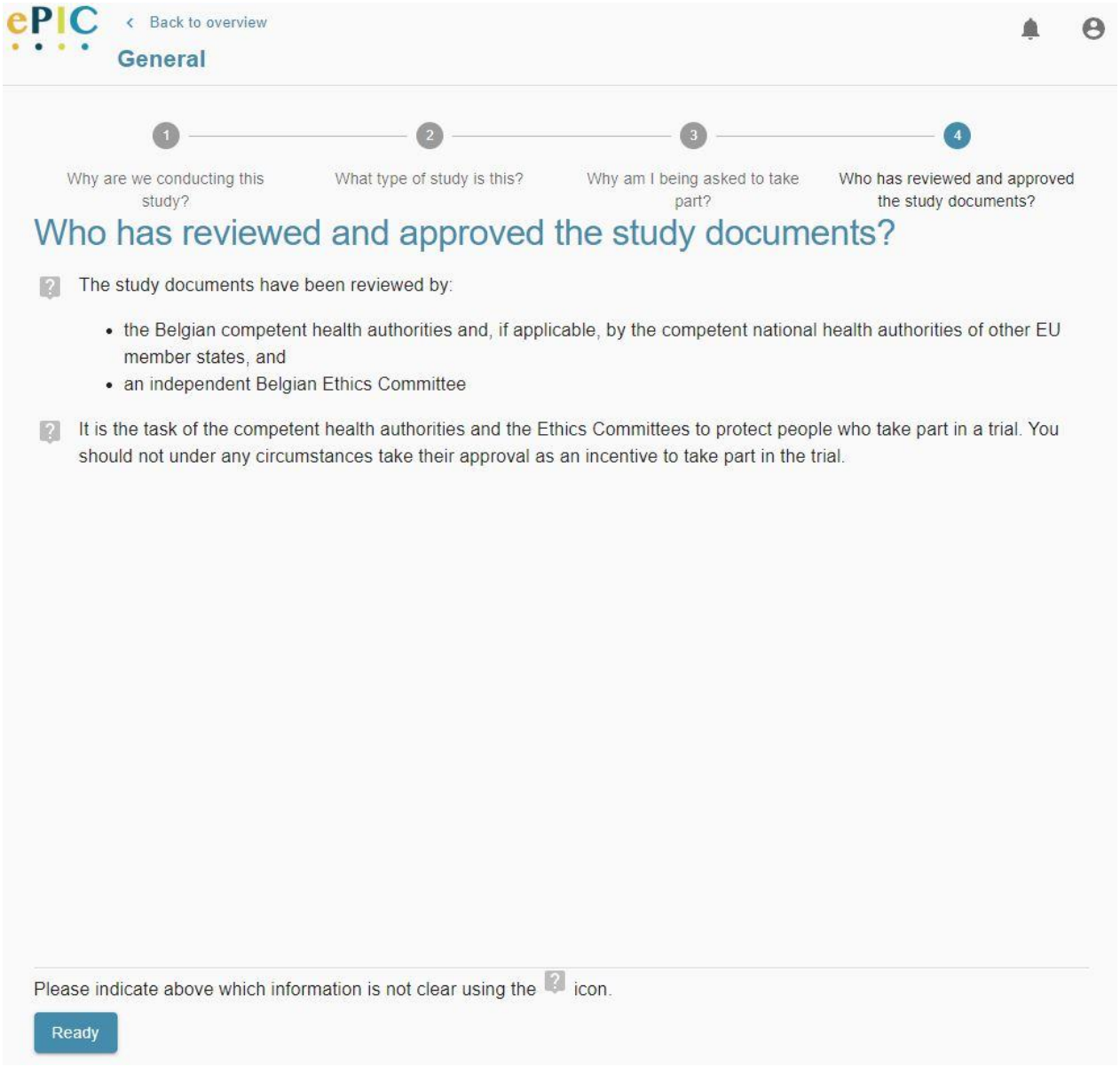
Interface 5: A particular information section

- The information included in a particular section is divided into multiple parts. These parts, visible at the top of the interface, are indicated with numbers and titles. When the participant clicks a particular information section, the first part is displayed. However, the participant has the possibility to view another part by clicking on the abovementioned numbers and titles.
- If it concerns a new informed consent version, the parts are preceded by an overview of the changes. In the parts containing changes, the updated study-related information is displayed on

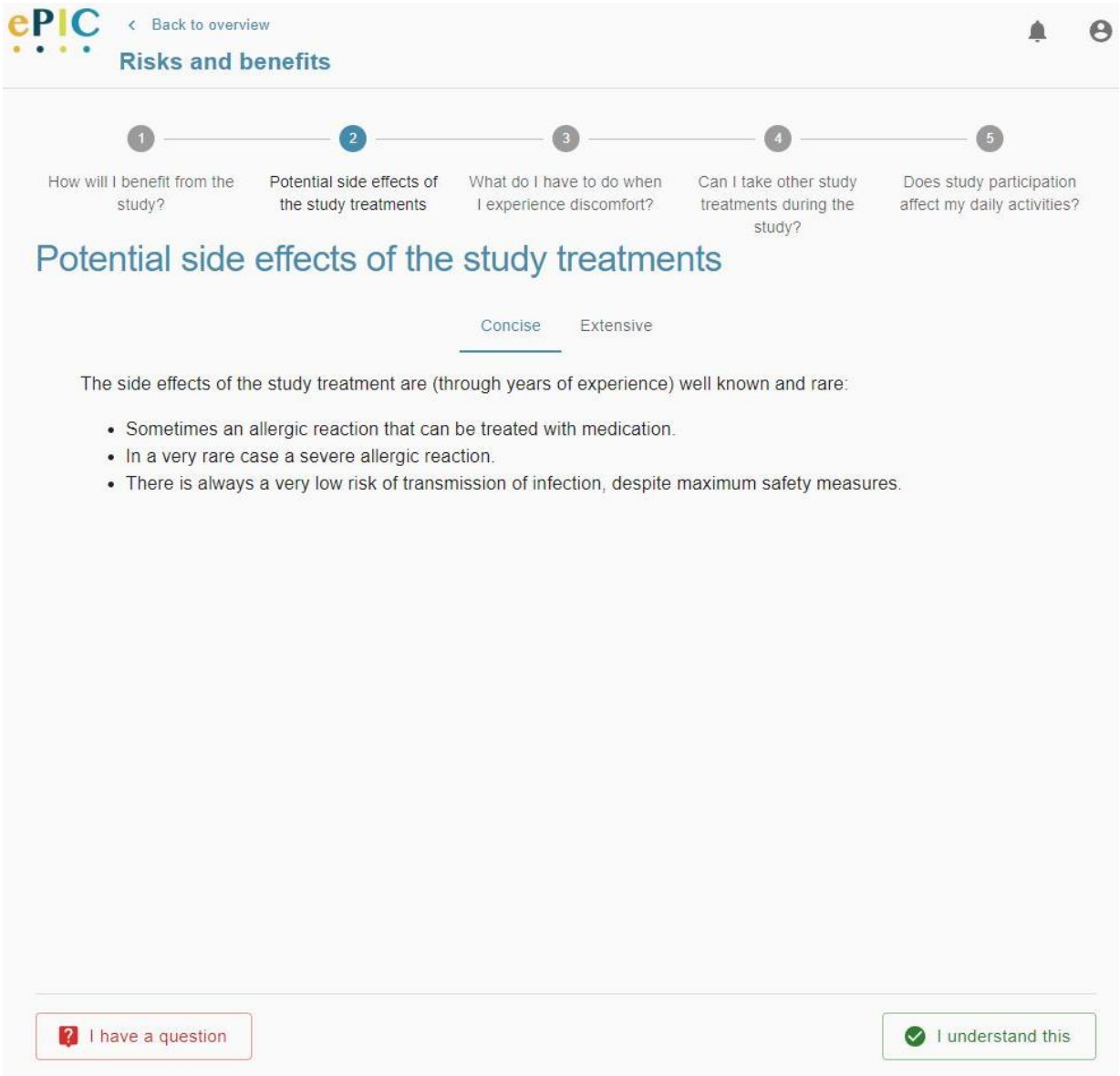
the left side of the interface in which the changes are highlighted in green. The right side of the interface contains the label 'No changes' or contains the information of the previous consent version for paragraphs in which changes have been made (see Figure below).



- The bottom of the interface contains the buttons 'I have a question' and 'I understand this information' on the left and right side of the interface, respectively. If the participant clicks the button 'I have a question', the following sentence is displayed '*Please indicate above which information is not clear using the question mark icon*'. By using this question mark icon, displayed next to each paragraph, the participant can indicate the paragraph containing unclear information (see Figure below). Hereafter, a pop-up screen appears in which the participant can take additional notes, if preferred. More specifically, the pop-up screen contains the following information '*We note that this information is not clear for you. You can discuss this with the investigator later on. If you wish, you can make notes. These notes are also visible for the investigator*'. The participant can use the buttons 'Remove question', 'Cancel', or 'Confirm'. If the button 'I understand this information' is clicked, the participant is redirected to the following part or the overview (i.e., interface 4) in case it concerns the last part.



- The 'i' symbol is added to some terms, marked in blue, such as 'adaptive' and 'randomized'. When hovering over these terms, a tooltip is shown (e.g., 'What is a randomized study?'). When clicking a particular term, a popover, containing more details, is displayed. In addition, some study-related information is offered in layers: a first layer offering concise information, followed by a second layer that includes more detailed information. At the top, in the middle of the interface, the text buttons 'Concise' and 'Extensive' are displayed, which allow the participants to navigate between the two layers (see Figure below). Further information is also offered in dropdown-boxes in particular sections.

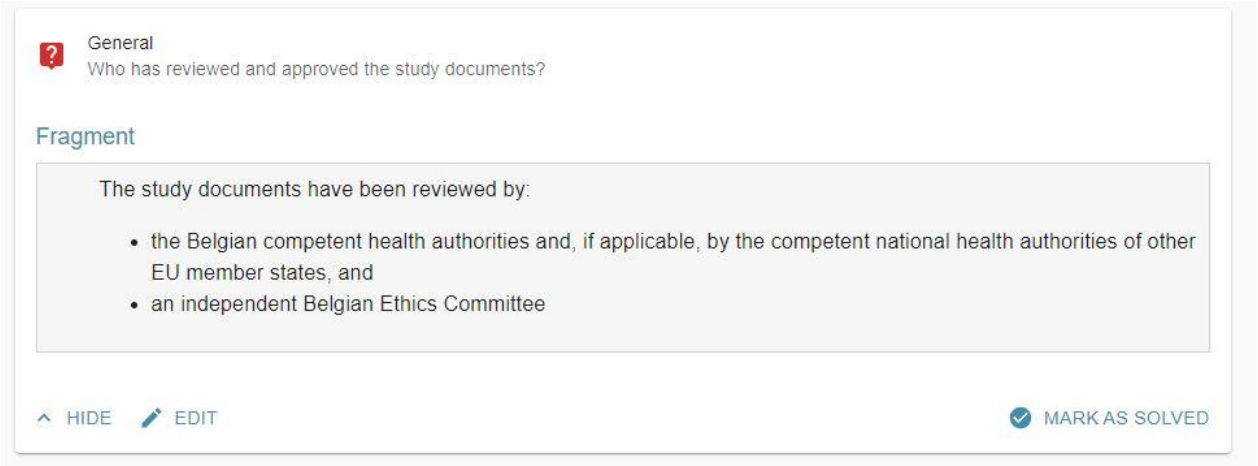


- The top of the interface includes the button 'Back to overview' (if this button is clicked, the participant navigates to interface 4).

Interface 6: Your questions

- This interface includes the headings 'Make an appointment' and 'Overview'.
- Under the heading 'Make an appointment', the participant is informed that a video consultation with a member of the study team can be scheduled to discuss unclarities about the trial by making use of the button 'Make an appointment for a video consultation'. Once scheduled, the video consultation can be started. In addition, the participant is informed that all unclarities must be solved to be able to sign the informed consent.
- Under the heading 'Overview', the sections and parts containing unclarities are listed with a red question mark icon. By clicking the button 'Show', the paragraph about which a participant has questions appears, accompanied by the participant's notes. Hereafter, the participant has the possibility to click on the text buttons 'Hide', 'Edit', or 'Mark as solved' (see Figure below). When

the questions or unclarities are marked as solved, the red question mark icon changes into a green checkmark.



Interface 7: Signing the consent

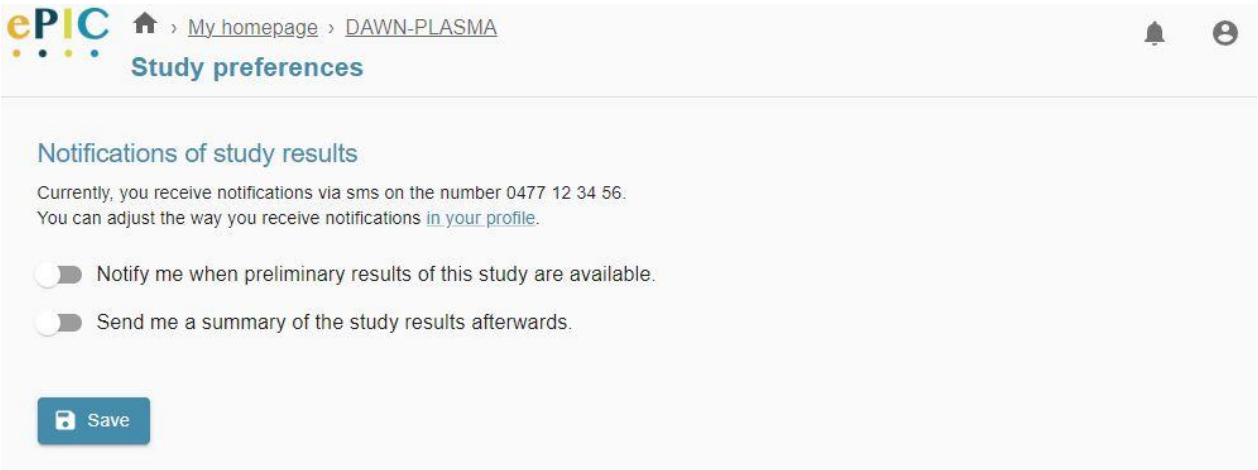
- This interface contains a summary of study-related information and multiple signing options to provide consent.

Interface 8: My profile

- This interface contains the headings 'Contact details' and 'Notifications'.
- Under the heading 'Contact details', the participant is able to enter or edit his/her email address and phone number.
- Under the heading 'Notifications', the participant can indicate, by making use of a slider, how he/she wishes to be informed about notifications of the platform or about new studies for which participants are being recruited.

Interface 9: Study preferences

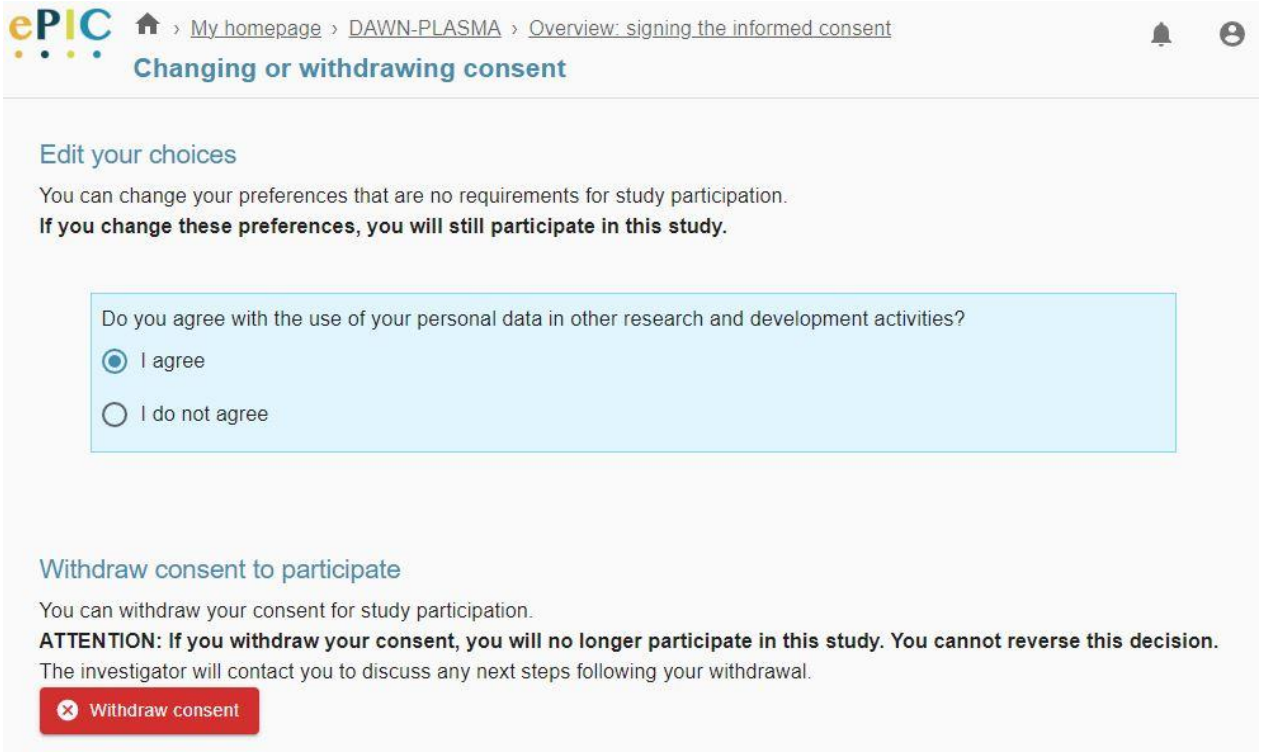
- The participant can use a slider to indicate if he/she would like to be informed when interim results or a summary of the final results are made available. In addition, a hyperlink to the participant's profile is included (i.e., interface 8).



Interface 10: Change or withdraw the consent

- This interface contains the headings 'Edit your choices' and 'Withdraw consent to participate'.
- Under the heading 'Edit your choices', the participant is able to change preferences (e.g., for data sharing) by selecting a radio button. The participant is informed that '*If you change these preferences, you will still participate in the study.*'.

Under the heading 'Withdraw consent to participate', the participant is able to withdraw his/her consent for study participation by clicking the red outlined button 'Withdraw consent'. The participant is informed that '*If you withdraw your consent, you will no longer participate in this study. You cannot reverse this decision.*' (see Figure below).



APPENDIX N. CHAPTER 6 – SURVEY INCLUDING DEMOGRAPHIC QUESTIONS AND QUESTIONS RELATED TO DIGITAL LITERACY

Part 1: Experiences with information and communication technologies

1. Do you have a computer or a tablet at home with internet access?

☐ Yes

☐ No → *Go to Part 2: Personal characteristics*

2. For which of the following activities do you use this computer or tablet?

☐ Internet banking

☐ Seeking information

☐ Sending / receiving emails

☐ Consulting social media

☐ Listening to music

☐ Other

3. How often on average did you use your computer or tablet in the last 3 months?

☐ Every day or almost every day, and even multiple times a day

☐ Every day or almost every day, but not multiple times a day

☐ At least once a week, but not (almost) every day

☐ At least once a month, but not every week

☐ Less than once a month

4. For which of the following activities did you use your computer or tablet in the last 12 months? *(tick all that apply)*

☐ Transferring files between computers, tablets, or other devices

☐ Installing software or applications (apps)

☐ Changing the settings of any software programs

☐ None of the above

5. Which of the following software activities did you carry out in the last 12 months? *(tick all that apply)*

☐ Copying or moving files or folders

☐ Using word processing software

☐ Creating presentations or documents integrating text, pictures, tables, or charts

☐ Using software to edit photos, video, or audio files

☐ Writing code in a programming language

☐ None of the above

Part 2: Personal characteristics

6. Wat is your first and last name?

7. Wat is your age?

8. Wat is your sex?

☐ Male
☐ Female
☐ Other
☐ I prefer not to answer

9. What is your highest level of education?

☐ I did not complete secondary school
☐ Secondary school or equivalent
☐ Bachelor's degree or equivalent
☐ Master's degree or equivalent
☐ PhD
☐ Other

10. What is your employment situation?

☐ Student
☐ Employed (full time, part time…)
☐ Unemployed and not looking for work
☐ Unemployed and looking for work
☐ Retired
☐ Other

APPENDIX O. CHAPTER 6 – INSTRUCTIONS FOR PARTICIPANTS TAKING PART IN A USABILITY TEST

Context for participants

- **The purpose of this research study:** to inform the design of a user-friendly electronic informed consent interface, tailored to your needs.
- **We ask you to imagine that:**
  - You had taken part in a clinical study on **skin blood perfusion in humans in the past.**
  - A few days ago, you were informed that you are infected with the **Coronavirus** and that there is currently a clinical trial "**DAWN-PLASMA**" investigating treatments for this virus.
  - You have already had an interview with the investigator of this "DAWN-PLASMA" study. Based on this interview, you are interested in participating in this study. In order to take part, the investigator asked you to read the **information** regarding this clinical study and to provide your **informed consent** for participation.

Instructions for participants

- While reading the information regarding the "DAWN-PLASMA" study and providing your informed consent, you will complete various **computer tasks**.
- We ask you **to think aloud** while performing these tasks.
- After tasks 5 and 8, you will complete a **questionnaire**. In addition, a **short interview** will be conducted after each task.
- You, as a participant, will not be evaluated. It is therefore no problem if you take wrong actions. By performing computer tasks, you help us to **evaluate our user interface**.

APPENDIX P. CHAPTER 6 – TASKS FOR PARTICIPANTS TAKING PART IN A USABILITY TEST

Task 1:

Consult the **symptoms** of an allergic reaction that may occur from the study treatment. You can find these symptoms in the section 'Risks and benefits'. Say these symptoms out loud.

Task 2:

Consult the definition of the term **'randomization'**. You can find this definition in the section 'General'. Say this definition out loud.

Task 3:

Consult the organizations/persons who review your **coded data** sent to other countries within and outside the European Union. You can find this information in the section 'Privacy and data protection'. Say one of these organizations/persons out loud.

Task 4:

a) Indicate that you do not understand this information, regarding **which organizations/persons review your coded data.**

b) Indicate that you have a question about **your preferences regarding the use of your data in other research and development activities.** *(for the first iteration only)*

c) Consult all information in the section 'Privacy and data protection'. Indicate, where necessary, that you agree to the use of your data in other research and development activities. *(for the second and third iterations only)*

d) You have another question that you would like to discuss with the researcher. Please add the following question: "Will I always be in contact with the principal investigator?". *(for the second iteration only)*

e) You have another question that you would like to discuss with the researcher. **This question does not belong to any of the sections.** Please add the following question: "Will I always be in contact with the principal investigator?". *(for the third iteration only)*

f) Make an appointment for a video consultation with the research team to discuss unclarities. Say the message that you receive after making this appointment oud loud.

Task 5:

Imagine that we are several days later and that your video consultation will take place today.

a) Start this video consultation.

b) Imagine that your questions were answered. By the explanation of the research team you consent to the use of your data in other research and development activities. Please provide your informed consent for participation in this clinical study. Say the message that you receive after providing your consent out loud. Please log out. *(for the first iteration only)*

c) Imagine that your questions were answered. Please provide your informed consent for participation in this clinical study. Say the message that you receive after providing your consent out loud. Please log out. *(for the second and third iterations only)*

Task 6:

Imagine that we are several months later. You **no longer consent** to the use of your data in other research and development activities. Please make the necessary changes. Say the message that you receive after changing your preferences out loud.

Task 7:

a) Indicate that you would like to be contacted to receive a summary of the results of the COVID-19 study.

b) In the past, you indicated that you would like to receive this summary via text message. Please change this to **email**. Say the email address this will be sent to out loud.

Task 8:

a) You have been notified that a new informed consent version is available. Please look into this version. Say the number of sections that contain changes out loud.

b) Please identify what has changed about **the use of your data**. Provide as much information as possible. Say this information out loud.

APPENDIX Q. CHAPTER 6 – INTERVIEW GUIDE

I. Introductory question

1. What is the practice of the ethics committee of which you are a member to assess a paper-based informed consent form? *(for ethics committee members only)*

2. What is your current practice to inform research participants and to obtain their consent? *(for health care professionals only)*

3. What are the sponsor's responsibilities with regard to the informed consent process? *(for pharmaceutical industry representatives only)*

II. Questions regarding electronic informed consent

- Providing the definition issued by the European Medicines Agency: *"An electronic informed consent refers to the use of any digital media (e.g. text, graphics, audio, video, podcasts or websites) to firstly convey information related to the clinical trial to the trial participant and secondly document informed consent via an electronic device (e.g. mobile phones, tablets or computers)."*
- Introducing the electronic informed consent prototype: showing all functionalities related to personalization and the long-term interaction

The following questions (4-12) apply to ethics committee members only:

4. What is your opinion on this prototype and on the integrated functionalities?

5. Which functionalities should be integrated in an electronic informed consent system to be an added value, compared to paper-based informed consent forms, for the ethics committee of which you are a member?

6. How would electronic informed consent influence the evaluation process for the ethics committee of which you are a member?

7. In what way would you like to assess the information presented in the electronic informed consent?

8. What is your opinion on keeping track of the ethics committee's comments and decisions in an electronic informed consent system?

9. When a new informed consent version should be assessed based upon study amendments, how could an electronic informed consent system facilitate the assessment of this new version?

10. Which barriers or challenges may be experienced in the evaluation process of electronic informed consent?

11. Who should have access to an electronic informed consent system (i.e., the system and not specifically the signed electronic informed consent)?

12. What other systems should an electronic informed consent system ideally interact with?

The following questions (13-18) apply to health care professionals only:

13. What is your opinion on this prototype and on the integrated functionalities? How would the use of this prototype influence your current practice?

14. In case you inform a digital literate participant and obtain this participant's consent, how would the use of electronic informed consent influence your workload?

15. Which functionalities should be integrated in an electronic informed consent system to be an added value, compared to paper-based informed consent forms, for you as a health care professional involved in clinical research?

16. Which barriers or challenges may you experience when using electronic informed consent?

17. Who should have access to an electronic informed consent system (i.e., the system and not specifically the signed electronic informed consent)?

18. What other systems should an electronic informed consent system ideally interact with?

The following questions (19-23) apply to pharmaceutical industry representatives only:

19. What is your opinion on this prototype and on the integrated functionalities? How would the use of this prototype influence your current practice?

20. Which functionalities should be integrated in an electronic informed consent system to be an added value, compared to paper-based informed consent forms, for a sponsor?

21. Which barriers or challenges may a sponsor experience when using electronic informed consent?

22. Who should have access to an electronic informed consent system (i.e., the system and not specifically the signed electronic informed consent)?

23. What other systems should an electronic informed consent system ideally interact with?

APPENDIX R. CHAPTER 7 – SURVEY QUESTIONNAIRE

TOPIC 1: Introductory questions

1 Which stakeholder group best characterizes you?

Note: this question applies to all stakeholder groups

☐ I am a data protection officer or a member of a legal team (and I am not a member of an ethics committee)

☐ I am a member of an ethics committee

☐ I am an investigator/physician (and I am NOT a member of an ethics committee)

☐ None of the listed stakeholder groups

2 Where do you work? (In case you work for more than one employer, please select the institution from the perspective of which you prefer to answer this survey)

Note: this question applies to data protection officers/legal experts only

☐ An academic sponsor of clinical trials

☐ A pharmaceutical company

☐ A biobank

☐ A clinical research organization (CRO)

☐ A research institute

☐ A hospital

☐ Other (please specify)

3 What is your profession?

Note: this question applies to ethics committee members only

☐ I am a physician

☐ I am a lawyer

☐ I am a patient representative

☐ I am a study nurse

☐ I am a statistician

☐ I am a philosopher/priest

☐ Other (please specify)

4 Where is your organization based? (Drop down list including European Union Member States and the United Kingdom)

Note: this question applies to all stakeholder groups

5 The ethics committee of which I am a member:

Note: this question applies to ethics committee members only

☐ Is a national ethics committee

☐ Is a local or regional ethics committee

6 What types of clinical studies does the ethics committee of which you are a member assess? (multiple answers possible)

Note: this question applies to ethics committee members only

☐ Clinical studies that are conducted only in the country where the ethics committee is based

☐ Clinical studies that are conducted in several EU countries

7 In which country is your organization involved/are you involved in clinical studies?

Note: this question applies to data protection officers/legal experts and investigators only

☐ Only in the country where it is/I am based (national studies)

☐ In several countries (international studies) (please specify in which countries)

8 Please select the answer that is applicable to you. My organization/I was/am involved in: (multiple answers possible)

Note: this question applies to data protection officers/legal experts and investigators only

☐ COVID-19 studies: clinical studies that investigate a COVID-19 medicine, diagnostic product or device, and/or vaccine

☐ Non-COVID-19 studies: clinical studies that investigate a medicine, diagnostic product or device, and/or vaccine for other medical conditions (e.g., cancer)

9 According to applicable legislation, there are different types of clinical studies. Below, we list several types of clinical studies. Please select the types of studies in which you are involved most often. (multiple answers possible)

Note: this question applies to all stakeholder groups

☐ Interventional clinical trials (Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more

investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy (Article 2(a) of Directive 2001/20/EC))

☐ Non-interventional clinical trials (A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data (Article 2(c) of Directive 2001/20/EC))

☐ Clinical investigation of a medical device (A study in one or more human subjects, which serves the purpose of verifying or testing the safety and/or performance of a medical device.)

☐ Clinical performance study of an in vitro diagnostic medical device (A study carried out to assess the clinical performance and safety of in vitro diagnostic medical devices.)

10 Has your organization/have you conducted a registry-based trial (i.e., an investigation of a research question which uses the infrastructure of a new or an existing registry for patient recruitment and/or data collection)?

Note: this question applies to data protection officers/legal experts and investigators only

☐ Yes

☐ No

TOPIC 2: General question related to informed consent

11 What would be the ideal means of communication, regardless of the COVID-19 pandemic, to inform research participants about the objectives and conduct of a clinical study (e.g., study procedures, risks, benefits...)? (Open question)

Note: this question applies to all stakeholder groups

TOPIC 3: Electronic informed consent

12 Does your organization/do you have experience with informing research participants and obtaining their informed consent via electronic means?

Note: this question applies to data protection officers/legal experts and investigators only. Moreover, only if the answer is "Yes", the respondent is redirected to questions 13 and 14.

☐ Yes

☐ No

☐ I do not know

13 For which clinical study(ies) does your organization/do you use electronic means to inform research participants and obtain their consent? (multiple answers possible)

Note: this question applies to data protection officers/legal experts and investigators only

☐ Interventional clinical trials (Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy (Article 2(a) of Directive 2001/20/EC))

☐ Non-interventional clinical trials (A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data (Article 2(c) of Directive 2001/20/EC))

☐ Clinical investigation of a medical device (A study in one or more human subjects, which serves the purpose of verifying or testing the safety and/or performance of a medical device.)

☐ Clinical performance study of an in vitro diagnostic medical device (A study carried out to assess the clinical performance and safety of in vitro diagnostic medical devices.)

14 Which electronic mean(s) does your organization/do you use to inform research participants and obtain their consent? (multiple answers possible)

Note: this question applies to data protection officers/legal experts and investigators only

☐ Phone

☐ Tablet

☐ Computer

☐ Other (please specify)

15 Does national law or policy of the country or at least one of the countries where your organization operates/your ethics committee operates/you operate, provide a definition of electronic informed consent?

Note: this question applies to all stakeholder groups. Moreover, only if the answer is "No" or "I do not know", the respondent is redirected to question 16.

☐ Yes (please specify)

☐ No

☐ I do not know

16 What do you understand by electronic informed consent? (open question)

Note: this question applies to all stakeholder groups

17 Which functionalities should be part of an electronic informed consent platform (which is a platform enabling research participants to give and manage their electronic informed consent)? (multiple answers possible)

Note: this question applies to all stakeholder groups

☐ Providing research study information in an interactive and dynamic way to (potential) research subjects

☐ Obtaining and documenting the signature of the research subjects

☐ The return of research results to the research subjects

☐ The possibility to reconsent research subjects

☐ Other (please specify)

18 Is it legally allowed in the country or in at least one of the countries where your organization operates/where your ethics committee is based/where you operate to provide study-related information to research participants via electronic means, before obtaining their informed consent?

Note: this question applies to all stakeholder groups

☐ Yes

☐ Only under certain conditions (please specify)

☐ No

☐ I do not know

19 Is it legally allowed in the country or in at least one of the countries where your organization operates/where your ethics committee is based/where you operate to obtain research participants' informed consent via electronic means?

Note: this question applies to all stakeholder groups. Moreover, only if the answer is "Yes" or "Only under certain conditions", the respondent is redirected to question 20.

☐ Yes

☐ Only under certain conditions (please specify)

☐ No

☐ I do not know

20 Which signature(s) is/are legally allowed to obtain the research participants' informed consent? (multiple answers possible)

Note: this question applies to all stakeholder groups.

☐ Simple or basic electronic signature (data in electronic form which is attached to or logically associated with other data in electronic form and which is used by the signatory to sign)

☐ Advanced electronic signature (an electronic signature which is (a) uniquely linked to the signatory, (b) is capable of identifying the signatory, (c) is created using electronic signature creation data that the signatory can, with a high level of confidence, use under his sole control and (d) is linked to the data signed therewith in such a way that any subsequent change is the data is detectable)

☐ Qualified advanced electronic signature (advanced electronic signature that is created by a qualified electronic signature creation device, and which is based on a qualified certificate for electronic signatures)

☐ I do not know

☐ Other (please specify)

21 Which laws or regulations regulate (i.e., allow or prohibit) the use of electronic informed consent? (open question)

Note: this question applies to all stakeholder groups

22 Did your ethics committee review electronic informed consent in the past?

Note: this question applies to ethics committee members only. Moreover, only if the answer is "Yes", the respondent is redirected to question 23.

☐ Yes

☐ No

☐ I do not know

23 In your experience, was the review process of electronic informed consent more complex, compared to the review process of paper-based informed consent?

Note: this question applies to ethics committee members only

☐ Yes (please specify)

☐ No

TOPIC 4: Informed consent during the COVID-19 pandemic

24 Alternative methods were recommended, for example by the European Medicines Agency, to reconsent for already included research participants (e.g., due to protocol changes). These methods include:

Method 1: Obtaining oral consent (e.g., via phone or video-calls), supplemented with e-mail confirmation.

Method 2: Obtaining oral consent (e.g., via phone or video-calls). An appropriately signed and dated informed consent form should be obtained from the research participant as soon as possible.

Method 3: Using validated electronic systems (e.g., electronic informed consent).

Which method(s) did your organization/did you employ during the COVID-19 pandemic? (multiple answers possible)

Note: this question applies to data protection officers/legal experts and investigators only

☐ Method 1

☐ Method 2

☐ Method 3

☐ Other method (please specify)

☐ Not applicable

25 How useful are the alternative methods to re-consent for already included research participants?

Note: this question applies to all stakeholder groups. Ethics committee members received more explanation on these alternative methods, as described in question 24. Moreover, if "Not useful at all" or "Slightly useful" is indicated, the respondent is redirected to question 26. If "Moderately useful" or "Extremely useful" is indicated, the respondent is directed to question 27.

	Not useful at all	Slightly useful	Moderately useful	Extremely useful
Method 1				
Method 2				
Method 3				

26 Please specify why the recommended method(s) is/are not useful at all or slightly useful. (open question)

Note: this question applies to all stakeholder groups.

27 Please specify why the recommended method(s) is/are moderately or extremely useful. (open question)

Note: this question applies to all stakeholder groups.

28 Specific methods were recommended, for example by the European Medicines Agency, when obtaining informed consent of COVID-19 patients. These methods include:

Method 1: If written consent by the research participant is not possible, consent could be given orally by the research participant in the presence of an impartial witness. In such cases, the witness is required to sign and date the informed consent form and the investigator is expected to record how the impartial witness was selected.

Method 2: The research participant and the person obtaining consent sign and date separate informed consent forms (i.e., one informed consent form signed and dated by the participant and another consent form signed and dated by the researcher). An appropriately signed and dated informed consent form should be obtained from the research participant later, as soon as possible.

Method 3: Using validated electronic systems (e.g., electronic informed consent).

Which method(s) did your organization/did you employ during the COVID-19 pandemic? (Multiple answers possible)

Note: this question applies to data protection officers/legal experts and investigators only

☐ Method 1

☐ Method 2

☐ Method 3

☐ Other method (please specify)

☐ Not applicable

29 How useful are the alternative methods for obtaining informed consent of COVID-19 patients?

Note: this question applies to all stakeholder groups. Ethics committee members received more explanation on these alternative methods, as described in question 28. Moreover, if "Not useful at all" or "Slightly useful" is indicated, the respondent is redirected to question 30. If "Moderately useful" or "Extremely useful" is indicated, the respondent is directed to question 31.

	Not useful at all	Slightly useful	Moderately useful	Extremely useful
Method 1				
Method 2				
Method 3				

30 Please specify why the recommended method(s) is/are not useful at all or slightly useful. (open question)

Note: this question applies to all stakeholder groups

31 Please specify why the recommended method(s) is/are moderately or extremely useful. (open question)

Note: this question applies to all stakeholder groups

32 Prior to the pandemic, what where the biggest challenges that you experienced when providing research information to participants and obtaining their consent? (open question)

Note: this question applies to data protection officers/legal experts and investigators only

33 During the pandemic, are these challenges the same, or different?

Note: this question applies to data protection officers/legal experts and investigators only

☐ The same

☐ Different (please specify)

TOPIC 5: Closing question

34 Do you want to mention an additional point of concern regarding electronic informed consent, not covered in this survey? (open question)

Note: this question applies to all stakeholder groups

APPENDIX S. CHAPTER 7 – ADDITIONAL STATISTICAL ANALYSIS TO ASSESS DIFFERENCES BETWEEN STAKEHOLDERS

Question 17: Which functionalities should be part of an electronic informed consent platform (which is a platform enabling research participants to give and manage their electronic informed consent)?

	Fisher-Freeman-Halton Exact test: p-value
Functionality 1: Providing research study information in an interactive and dynamic way to (potential) research participants	p=0.510
Functionality 2: Obtaining and documenting the signature of the research participants	p=0.627
Functionality 3: The return of research results to the research participants	p=0.756
Functionality 4: The possibility to reconsent research participants	p=0.029

APPENDIX T. CHAPTER 9 – COREQ CHECKLIST

Item and guide questions	Response	Location in manuscript (Section)
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Interviewer/facilitator: Which author/s conducted the interview or focus group?	Moderators: EDS or JD. Observers (in the focus group discussions only): LB and EDS or JD	Methods
2. Credentials: What were the researcher's credentials? E.g., PhD, MD	EDS: PharmD JD: Master's student in biomedical sciences LB: PharmD, PhD	-
3. Occupation: What was their occupation at the time of the study?	At the time of the study, EDS working towards her PhD and JD towards his Master dissertation at KU Leuven. LB held a postdoctoral position.	-
4. Gender: Was the researcher male or female?	Female (EDS and LB) and male (JD)	-
5. Experience and training: What experience or training did the researcher have?	EDS and LB had previous experience in conducting interviews, workshops, and focus group discussions	-
Relationship with participants		
6. Relationship established: Was a relationship established prior to study commencement?	Prior to the interview or focus group discussion, participants were briefed on the study and were provided with the informed consent.	Methods
7. Participant knowledge of the interviewer: What did the participants know about the researcher?	The participants were informed that EDS, LB, and JD were researching electronic informed consent at KU Leuven	Methods
8. Interviewer characteristics: What characteristics were reported about the interviewer/facilitator?	The background of the moderator and the observer(s), if applicable	Methods
Domain 2: Study design		
Theoretical framework		
9. Methodological orientation and theory: What methodological orientation was stated to underpin the study?	Semi-structured interviews and focus group discussions that were analyzed using a framework method	Methods
Participant selection		
10. Sampling: How were participants selected?	Through purposive and snowballing sampling	Methods
11. Method of approach: How were participants approached?	Via email	Methods

12. Sample size: How many participants were in the study?	In total, 20 participants had taken part in this study	Results
13. Non-participation: How many people refused to participate or dropped out? Reasons?	74% of invited individuals refused to participate. Reasons included unavailability and non-response to the invitation.	-
Setting		
14. Setting of data collection: Where was the data collected?	Interviews and focus group discussions took place remotely	Methods
15. Presence of non-participants: Was anyone else present besides the participants and researchers?	No	Methods
16. Description of sample: What are the important characteristics of the sample?	Participants belong to one of the six stakeholder groups. They were active across European Union Member States or at a pan-European or global level.	Results
Data collection		
17. Interview guide: Were questions, prompts, guides provided by the authors? Was it pilot tested?	The topic guide was provided to the participants. The questions were not pilot tested.	Methods
18. Repeat interviews: Were repeat interviews carried out? If yes, how many?	No	-
19. Audio/visual recording: Did the research use audio or visual recording to collect the data?	Digital audio-recordings of all interviews and focus group discussions were made.	Methods
20. Field notes: Were field notes made during and/or after the interview or focus group?	Yes	Methods
21. Duration: What was the duration of the interviews or focus groups?	Interviews: 30 - 50 min long Focus group discussions: 1 - 2 hours long	Methods
22. Data saturation: Was data saturation discussed?	No	-
23. Transcripts returned: Were transcripts returned to participants for comment and/or correction?	No	-
Domain 3: Analysis and findings		
Data analysis		
24. Number of data coders: How many data coders coded the data?	The first transcript was coded by one researcher (JD). However, the defined codes were discussed and approved by two other researchers (EDS and LB). The other transcripts were coded by one	Methods

	researcher (EDS).	
25. Description of the coding tree: Did authors provide a description of the coding tree?	Coding was described in the methods section. Moreover, the coding tree is reported in the supplementary material.	Methods – Supplementary material
26. Derivation of themes: Were themes identified in advance or derived from the data?	Transcripts were coded by using a combination of an inductive and deductive approach	Methods
27. Software: What software, if applicable, was used to manage the data?	NVivo and Microsoft Excel	Methods
28. Participant checking: Did participants provide feedback on the findings?	No	-
Reporting		
29. Quotations presented: Where participant quotations presented to illustrate the themes/findings? Was each quotation identified?	Yes	Results
30. Data and findings consistent: Was there consistency between the data presented and the findings?	Yes	Results
31. Clarity of major themes: Were major teams clearly presented in the findings?	Results are presented per major theme	Results
32. Clarity of minor themes: Is there a description of diverse cases or discussion of minor themes?	Minor themes are discussed in the manuscript, for example by using quotations	Results

APPENDIX U. CHAPTER 9 – TOPIC GUIDE

I. General introduction

- Welcoming the participant(s)
- Introducing the moderator(s), observers (if applicable), and the research study
- Explaining the general rules of the focus group discussion or semi-structured interview

II. Introduction to the topic of electronic informed consent

The U.S. Food and Drug Administration (FDA) as well as the European Medicines Agency (EMA) issued definitions of electronic informed consent.

- **Definition of the FDA**:
  "Electronic informed consent refers to the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to convey information related to the study and to obtain and document informed consent."
- **Definition of the EMA**:
  "*An electronic informed consent refers to the use of any digital media (e.g. text, graphics, audio, video, podcasts or websites) to firstly convey information related to the clinical trial to the trial participant and secondly document informed consent via an electronic device (e.g., mobile phones, tablets or computers)*."

Both definitions are more or less similar. What do you think of these definitions?

III. Type of European guidance framework

- When you first heard of a European guidance framework related to the implementation or use of electronic informed consent in clinical research, what was the first thing that came to your mind? What kind of European guidance framework would be needed?
- What type of value should this guidance framework ideally have?
- Who (which stakeholder(s)) should initiate the creation of this European guidance framework?
- The Good Clinical Practice Inspectors Working Group of the EMA issued a draft 'Guideline on computerized systems and electronic data in clinical trials'. What do you think of this guideline? What do you think the impact of this guideline could be on adoption of electronic informed consent in clinical research?
- How should national guidance relate to European guidance?

IV. A European guidance framework: detailed discussion of topics

A) Harmonization of electronic informed consent

The first topic that we would like to discuss is related to the legality of electronic informed consent. Participants in one of our research studies supported harmonization of electronic informed consent across European Union Member States and beyond. However, they indicated that establishing a harmonized approach would be challenging.

1) Legality

- **FDA guidance:** "*This guidance clarifies that when implementing an eIC, a variety of approaches may be used to fulfill HHS and FDA regulatory requirements for informed consent and IRB review (45 CFR part 46 and 21 CFR parts 50 and 56) and FDA regulations for electronic records and electronic signatures (21 CFR part 11).*"
- **EMA guideline:** "*Before implementation of an electronic consent procedure is considered, the sponsor should clarify legality and GCP compliance with each country's ethics committees and national regulatory authorities.*"

The FDA guidance refers to the relevant regulatory requirements to support compliant use of electronic informed consent. The EMA guideline indicates that legality must be clarified with national regulatory authorities. What is your opinion on this difference? What could be measures to facilitate the clarification of legality across European Union Member States?

B) Ethical review of electronic informed consent

2) Which materials need to be submitted to the relevant ethics committee?

- **FDA guidance**: "*The investigator should submit to the IRB copies of all forms (electronic and paper forms) and informational materials, including any videos and Web-based presentations, which the subject will receive and view during the eIC process*."
- **EMA guideline**: "*Consideration should be given as to how the system would be presented documentarily to the ethics committee for approval such that it captures the functionality of the systems and the experience of the potential trial participant using it.*"

The FDA guidance describes in a detailed way which materials need to be submitted to the ethics committee, whereas the guideline of EMA leaves some room for interpretation. Which description would you prefer? What would you have to change for a European framework?

3) What are the responsibilities of the relevant ethics committee in the evaluation process of electronic informed consent?

- **FDA guidance**: "*A critical part of this responsibility is for the IRB to ensure there is an adequate informed consent process that protects the rights and welfare of subjects participating in HHS-regulated research and FDA-regulated clinical investigations. Therefore, the IRB must review and approve the eIC and any amendments to the eIC that the subject will receive and view. The IRBs should also review any optional questions or methods used to gauge subject comprehension of key study elements. The IRB should also review the usability of the eIC materials to ensure that they are easy to navigate. If the program uses hyperlinks to convey study-related information, IRBs should review the contents to which subjects are referred in order to determine if the study-related information that has been supplied is accurate and appropriate. Because Web sites are often modified over time, IRBs must maintain the version of the Web site information that contains the study-related information that the IRB reviews and approves, either electronically or as a hard copy. IRBs, investigators, and sponsors should consider such issues as how the electronic signature is created and whether the informed consent or permission document can be produced in hard copy for review by the subject upon request. IRBs, investigators, and sponsors may rely on a statement from the vendor of the electronic system used for obtaining the electronic signature that describes how the signature is created and that the system meets the relevant requirements contained in 21 CFR part 11."*
- **EMA guideline:** /

Only the guidance of the FDA provides information on the responsibilities of the ethics committee when evaluating electronic informed consent. What is your opinion on incorporating the responsibilities of the ethics committee in a European guidance framework? Which responsibilities do you think that ethics committees should have?

C) Conduct of the electronic informed consent process

4) Where can the electronic informed consent process take place?

- **FDA guidance: "***The investigator should have methods in place to ensure that the eIC process allows subjects the opportunity to consider whether or not to participate and to ask questions about the study before signing consent as well as at any time during the subject's involvement in the research. This may be accomplished by in-person discussions with study personnel or through a combination of electronic messaging, telephone calls, video conferencing, or a live chat with a remotely located investigator or study personnel."*
- **EMA guideline:** "*The interview should be conducted in person or, it could be done remotely where this can be justified and where allowed nationally and if approved by an ethics committee using electronic methods that allow for two-way communication in real time*."

What do you think of the proposed options? What are the pros en cons?

V. Other considerations and closing

- We discussed several topics. Do you have any further comments or issues which you think may be relevant to a European guidance framework?
- Do you have any questions?

Abbreviations:
CFR: Code of Federal Regulations
EMA: European Medicines Agency
FDA: U.S. Food and Drug Administration
GCP: Good Clinical Practice
HHS: Department of Health and Human Services
IRB: Investigational review board

APPENDIX V. CHAPTER 9 – CODING TREE

Code	Sub-code level 1	Sub-code level 2
Definition		
	Suggestions/wishes	
Creation of a guidance framework	First thoughts	
	Why needed	
	Type and value	
	Stakeholders who should be involved in the creation	
	National framework vs European guidance framework	
	Impact of EMA guidance	
	Place of EMA draft guidance in a European guidance framework	
Discussion topics	Legality	
		EU structure
		Initiatives to clarify legality
		Other elements to be considered
	Ethical review	Ethics committee responsibilities
		Documents to be submitted
	Conduct of the electronic informed consent process	
		Positive elements
		Negative elements

Abbreviations:
EMA: European Medicines Agency
EU: European Union

PROFESSIONAL CAREER

EDUCATION

2019 – 2023	PhD in Pharmaceutical Sciences, KU Leuven
2017 – 2018	Master of Science in Industrial Pharmacy, Inter-university program (Ghent University, University of Antwerp, KU Leuven, Vrije Universiteit Brussel), Belgium
2015 – 2017	Master of Science in Drug Development, Ghent University
2012 – 2015	Bachelor of Science in Pharmaceutical Sciences, Ghent University
2006 – 2012	Latin-Sciences, Sint-Bernarduscollege, Oudenaarde

PROFESSIONAL EXPERIENCE

2019 – 2023	PhD researcher at the Clinical Pharmacology and Pharmacotherapy group of KU Leuven
2018 – 2019	Medical Information Architect, Healthdata.be, Sciensano, Brussels

PROFESSIONAL ENGAGEMENT

2020 - 2023	Board member, European Patients' Academy Belgium

PEER-REVIEWED PUBLICATIONS IN INTERNATIONAL JOURNALS

- **De Sutter E.**, Borry P., Huys I.*, Barbier L.*. Informing a European guidance framework on electronic informed consent in clinical research: a qualitative study. BMC Health Services Research, 23(1):181. Doi: 10.1186/s12913-023-09173-5 (*joint last authorship)
- **De Sutter E.**, Verreydt S., Yskout K., Geerts D., Borry P., Outtier A., Ferrante M., Vandermeulen C., Vanmechelen N., Van der Schueren B., Huys, I. (2022). Using provocative design to foster electronic informed consent innovation. BMC Medical Informatics and Decision Making, 22(1):296. Doi: 10.1186/s12911-022-02039-6
- Lalova-Spinks T., **De Sutter E.**, Valcke P., Kindt E., Lejeune S., Negrouk A., Verhenneman G., Derèze J-J., Storme R., Borry P., Meszaros J., Huys I. (2022). Challenges related to data protection in clinical research before and during the COVID-19 pandemic: an exploratory study. Frontiers in Medicine, 9:995689. Doi: 10.3389/fmed.2022.995689
- Simoens S., Abdallah K., Barbier L., Barcina Lacosta T., Blonda A., Car E., Claessens Z., Desmet T., **De Sutter E.**, Govaerts L., Janssens R., Lalova-Spinks T., Moorkens E., Saesen R., Schoefs E., Vandenplas Y., van Overbeeke E., Verbaanderd C., Huys, I. (2022). How to balance valuable

innovation with affordable access to medicines in Belgium? Frontiers in Pharmacology, 13:960701. Doi: 10.3389/fphar.2022.960701

- **De Sutter E.**, Geerts D., Borry P., Coteur K., Bamps D., Marynissen H., Ampe E., Geenens E., Depre M., Huys I. (2022). Co-creation with research participants to inform the design of electronic informed consent. SAGE Digital Health, 8. Doi: 10.1177/20552076221109068
- **De Sutter E.***, Meszaros J.*, Borry P., Huys I. (2022). Digitizing the informed consent process: a review of the regulatory landscape in the European Union. Frontiers in Medicine, 9:906448. Doi: 10.3389/fmed.2022.906448 (*joint first authorship)
- **De Sutter E.**, Lalova-Spinks T., Borry P., Valcke P., Kindt E., Negrouk A., Verhenneman G., Derèze J-J., Storme R., Huys I. (2022). Rethinking informed consent in the time of COVID-19: an exploratory survey. Frontiers in Medicine, 9:995688. Doi: 10.3389/fmed.2022.995688
- **De Sutter E.**, Coopmans B., Vanendert F., Dooms M., Allegaert K., Borry P., Huys I. (2021). Clinical research in neonates: redesigning the informed consent process in the digital era. Frontiers in Pediatrics, 9:724431. Doi: 10.3389/fped.2021.724431
- **De Sutter E.**, Borry P., Geerts D., Huys I. (2021). Personalized and long-term electronic informed consent in clinical research: stakeholder views. BMC Medical Ethics, 22(1):108. Doi: 10.1186/s12910-021-00675-7
- **De Sutter E.**, Zaçe D., Boccia S., Di Pietro M.L., Geerts D., Borry P., Huys I. (2020). Implementation of electronic informed consent in biomedical research and stakeholders' perspectives: systematic review. Journal of Medical Internet Research, 22 (10), e19129. Doi: 10.2196/19129
- Janvier S., **De Sutter E.**, Wynendaele E., De Spiegeleer B., Vanhee C., Deconinck E. (2017). Analysis of illegal peptide drugs via HILIC-DAD-MS. TALANTA, 174, 562-571. Doi: 10.1016/j.talanta.2017.06.034

PUBLICATIONS IN PEER-REVIEW

- **De Sutter E.**, Geerts D., Yskout K., Verreydt S., Borry P., Barbier L., Huys, I. Testing and practical implementation of a user-friendly personalized and long-term electronic informed consent in clinical research: mixed methods study. In review.
- **De Sutter E.*,** Barbier L.*, Borry P., Geerts D., Ioannidis J.P.A., Huys I. Personalized and longitudinal electronic informed consent in clinical trials: how to move the needle? In review. (*joint first authorship)

CONFERENCE/EVENT PARTICIPATION

Conference/event	Venue	Date	Title presentation	Oral/poster
World Congress of Bioethics	Basel	21-07-2022	Towards successful digital transformation: designing electronic informed consent with and for research participants	Oral
Knowledge for Growth	Ghent	19-05-2022	Rethinking informed consent in the time of COVID-19: the digital transformation	Poster
DIA Europe 2022	Brussels	30-03-2022	Tailoring the electronic informed consent process to patients' needs	Oral
Launch event KU Leuven Digital Society Institute	Leuven	26-10-2011	Personalized and long-term electronic informed consent in clinical research: stakeholder views	Poster
ISPOR Europe 2020	Virtual	16 to 19 November 2020	Electronic informed consent in biomedical research: a systematic review of stakeholders' perspectives	Poster

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CHAPTER 1: IMPLEMENTATION OF ELECTRONIC INFORMED CONSENT IN BIOMEDICAL RESEARCH AND STAKEHOLDERS' PERSPECTIVES: SYSTEMATIC REVIEW

The authors wish to thank Thomas Vandendriessche, Magdalena Jans, and Krizia Tuand, the biomedical reference librarians of the KU Leuven Libraries 2Bergen-learning Centre Désiré Collen, for their help in conducting the systematic literature search.

CHAPTER 2: PERSONALIZED AND LONG-TERM INFORMED ELECTRONIC INFORMED CONSENT IN CLINICAL RESEARCH: STAKEHOLDER VIEWS

The authors would like to thank the interviewees for participating in this study and for providing valuable insights. The authors also thank Birte Coopmans and Femke Vanendert for their help with the data analysis and Koen Yskout, Stef Verreydt, and Ilaria Buri for reviewing the study protocol.

CHAPTER 3: CLINICAL RESEARCH IN NEONATES: REDESIGNING THE INFORMED CONSENT PROCESS IN THE DIGITAL ERA

The authors would like to thank all the health care professionals who participated in our interviews.

CHAPTER 4: CO-CREATION WITH RESEARCH PARTICIPANTS TO INFORM THE DESIGN OF ELECTRONIC INFORMED CONSENT

The authors are extremely grateful to the participants who have taken part in our study, for sharing their perspectives, and valuable contributions. Moreover, the authors also thank Jan de Hoon for his support in recruiting participants.

CHAPTER 5: USING PROVOCATIVE DESIGN TO FOSTER ELECTRONIC INFORMED CONSENT INNOVATION

The authors would like to thank the participants for taking part in this study.

CHAPTER 6: TESTING AND PRACTICAL IMPLEMENTATION OF A USER-FRIENDLY PERSONALIZED AND LONG-TERM ELECTRONIC INFORMED CONSENT IN CLINICAL RESEARCH: MIXED METHODS STUDY

The authors are extremely grateful to all participants for taking part in a usability test or interview. The authors also thank T. Devos for his support in this study. In addition, we would like to acknowledge the following organizations for their support in recruiting participants for usability testing: 'Vlaams Patiëntenplatform' (VPP), 'Harpa', and the Seniors Council of Leuven, Belgium.

CHAPTER 7: RETHINKING INFORMED CONSENT IN THE TIME OF COVID-19: AN EXPLORATORY SURVEY

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CHAPTER 8: DIGITIZING THE INFORMED CONSENT PROCESS: A REVIEW OF THE REGULATORY LANDSCAPE IN THE EUROPEAN UNION

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CHAPTER 9: INFORMING A EUROPEAN GUIDANCE FRAMEWORK ON ELECTRONIC INFORMED CONSENT IN CLINICAL RESEARCH: A QUALITATIVE STUDY

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CONCLUDING DISCUSSION

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PERSONAL CONTRIBUTION

CHAPTER 1: IMPLEMENTATION OF ELECTRONIC INFORMED CONSENT IN BIOMEDICAL RESEARCH AND STAKEHOLDERS' PERSPECTIVES: SYSTEMATIC REVIEW

EDS, DG, PB, and IH designed the study. EDS and DZ conducted the search, selection, screening, and quality assessment of the studies. A first draft of the paper was written by EDS and DZ and was critically revised by DG, PB, SB, MLDP, and IH. All authors approved the final paper.

CHAPTER 2: PERSONALIZED AND LONG-TERM INFORMED ELECTRONIC INFORMED CONSENT IN CLINICAL RESEARCH: STAKEHOLDER VIEWS

All authors contributed to the design of the study protocol. EDS conducted the interviews, performed the data analysis, and wrote a first draft of the manuscript. PB, DG, and IH thoroughly reviewed the manuscript and were involved in the further refinement of it. All authors approved the final manuscript.

CHAPTER 3: CLINICAL RESEARCH IN NEONATES: REDESIGNING THE INFORMED CONSENT PROCESS IN THE DIGITAL ERA

EDS, FV, and BC designed the interview guides. The interview guides were reviewed by MD, KA, and IH. Interviews were conducted by FV and BC and supervised by EDS. Data analysis was conducted by FV, BC, and EDS. EDS wrote the first draft, which was revised and reviewed by FV, BC, MD, KA, PB, and IH. All authors approved the final manuscript.

CHAPTER 4: CO-CREATION WITH RESEARCH PARTICIPANTS TO INFORM THE DESIGN OF ELECTRONIC INFORMED CONSENT

EDS, DG, PB, and IH made a substantial contribution to the design of this study. Recruitment of participants was conducted via KC, DB, HM, EA, EG, and MD. EDS conducted the qualitative methods, transcribed the audio recordings, analyzed the data, and drafted the manuscript. All authors critically revised the manuscript. All authors read and approved the final manuscript.

Chapter 5: Using provocative design to foster electronic informed consent innovation

EDS designed the interfaces, which were informed by input of SV, KY, DG, PB, and IH. EDS, AO, MF, CV, NV, and BvDS coordinated the recruitment of participants. EDS conducted the interviews, performed the data analysis, and produced a first draft of the manuscript. This first draft was revised and finalized by all authors. All authors approved the final manuscript.

Chapter 6: Testing and practical implementation of a user-friendly personalized and long-term electronic informed consent in clinical research: mixed methods study

All authors were involved in the design of the study. KY created and refined the eIC prototype with the support of EDS, DG, and LB. EDS carried out the usability tests and interviews, performed data analysis, and drafted the manuscript. All authors critically revised the manuscript. The final manuscript was read and approved by all authors.

Chapter 7: Rethinking informed consent in the time of COVID-19: an exploratory survey

EDS, TL-S, and IH designed the study. The design of the study was further discussed with PV, EK, AN, GV, J-JD, and RS. EDS analyzed the data and drafted the manuscript. PB, PV, EK, AN, GV, J-JD, RS, and IH thoroughly reviewed the manuscript. All authors approved the final version of this manuscript.

Chapter 8: Digitizing the informed consent process: a review of the regulatory landscape in the European Union

ED and JM designed and conducted this study and produced the first draft. PB and IH was subsequently revised the manuscript. All authors approved the final manuscript.

Chapter 9: Informing a European guidance framework on electronic informed consent in clinical research: a qualitative study

All authors contributed to the design of this study. EDS and LB were involved in data collection and analysis. EDS wrote a first draft of the manuscript. All authors thoroughly reviewed this draft manuscript and were involved in the further refinement of it. All authors approved the final manuscript.

CONCLUDING DISCUSSION

EDS initiated the research and wrote the manuscript together with co-author LB. PB, DG, JPAI, and IH reviewed and edited the original draft. All authors approved the final manuscript.

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