Policy and Practice

DIGITAL HEALTH

DIGITAL HEALTH
Volume 9: 1–8

DOI: 10.1177/20552076231222361
journals.sagepub.com/home/dhj

Sage

Personalized and longitudinal electronic informed consent in clinical trials: How to move the needle?

Evelien De Sutter[1,2,*], Liese Barbier[1,2,*], Pascal Borry[3], David Geerts[4], John P.A. Ioannidis[2,5,6,+] and Isabelle Huys[1,+]

Abstract

Changes in the clinical trials landscape have been driven by advancements in digital technology. The use of electronic informed consent to inform research participants and to obtain their consent electronically has the potential to improve participant–researcher interactions over time, facilitate clinical trial participation, and increase efficiency in clinical trial conduct. A personalized electronic informed consent platform that enables long-term interactions with the research team could function as a tool to empower participant engagement in clinical trials. However, significant challenges persist impeding successful and widespread implementation. This Perspective provides insights into the opportunities and challenges for the implementation of electronic informed consent in clinical trials. It sets out key recommendations to promote the implementation of this innovative approach to the informed consent process, including the creation of uniform electronic informed consent platforms at regional and national level.

Keywords

Technology, clinical research, informed consent, trial, implementation, regulatory

Submission date: 8 May 2023; Acceptance date: 5 December 2023

Current status and potential

Historically, clinical trials have been designed using the traditional paradigm of bringing research participants to the trial site.[1] However, a constellation of evolving digital technologies as well as the COVID-19 pandemic have accelerated the digital transformation of clinical trials, also enabling participation from locations away from the site.[2,3] In the digitalization of clinical trials, electronic informed consent offers the opportunity to solve many challenges related to the static paper-based informed consent process that still remains the default today.[4,5] According to the U.S. Food and Drug Administration (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.*"[6] A largely comparable definition is offered by

[1]Clinical Pharmacology and Pharmacotherapy, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium
[2]Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, California, USA
[3]Centre for Biomedical Ethics and Law, Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium
[4]KU Leuven Digital Society Institute, KU Leuven, Leuven, Belgium
[5]Stanford Prevention Research Center, Department of Medicine, Stanford University School of Medicine, Stanford, California, USA
[6]Department of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, California, USA

[*]These authors share first authorship
[+]These authors share last authorship

Corresponding author:
Liese Barbier, O&N II – Herestraat 49 – Box 521, 3000 Leuven (Belgium), Clinical Pharmacology and Pharmacotherapy, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium.
Email: liese.barbier@kuleuven.be

the European Medicines Agency (EMA).[4] In other words, an informed consent process is considered to be an electronic informed consent (eConsent in short) process if one or multiple elements of the process are set up in a digital way. These elements may include (i) conveying information (e.g. information delivery via digital platforms to facilitate tailoring to the individual's needs), and (ii) obtaining and documenting informed consent (e.g. electronic documentation contributing to efficiency of trial sites).

Electronic informed consent, while making use of digital means, does not deviate from the long-established ground principles of informed consent. It provides similar information as a paper-based informed consent form but does so through digital technology and this offers several advantages to trial participants, but also the sites and sponsors/different stakeholders involved in the consent process.[4] First, the electronic information delivery can be tailored to the research participants' individual preferences and needs and offers the opportunity to incorporate learning principles.[7,8] Empirical studies comparing electronic informed consent with paper-based informed consent forms have shown that the former can translate into participants having a better understanding of the information presented.[9–11] For example, multiple layers of information can be presented, allowing participants to dig deeper into certain topics as desired, or multimedia tools can increase the interaction of participants with the information.[7,12] A randomized trial comparing electronic informed consent models with varying degrees of customizable information found that, after 6-month follow-up, participants who used the interactive electronic informed consent module with the option of making use of hyperlinks to access additional content had a higher understanding of information compared with the standard, non-customizable electronic informed consent model.[13] An interactive, multimedia-enabled format, tailored to participants' needs, may have advantages over a static electronic document. Participants are ultimately better positioned to envision what the clinical trial truly entails and what the implications are from their participation.

Second, electronic informed consent may facilitate the relationship between the participant and the research team during a clinical trial by enabling longitudinal and dynamic interaction; for example, by offering in an understandable way new informed consent versions upon study amendments or a lay summary of any interim or final study results. In this way, electronic informed consent offers the opportunity to improve participant engagement by providing participants with the possibility to indicate their preferences; for example, related to receiving the trial results through a digital platform.[7,14] This may be even more important in adaptive trials, where interventions and participant allocations may change over time. Electronic informed consent, when done in a longitudinal and personalized manner with opportunity for participant reciprocity and engagement, has shown to enhance the participant-centeredness of the research, satisfaction of participants and trust-building.[15,16] Third, electronic informed consent enables decentralized trial activities and thus facilitates clinical trial participation for patients, especially so for those who are geographically remote from the trial site or have physical, financial, or emotional circumstances that hamper (multiple) on-site visits.[3,12,17] As such electronic informed consent supports the fundamental principle of providing equitable opportunity to access information about a trial for informed consent decision-making.

Finally, electronic informed consent offers advantages from an efficiency point of view; for example, by automatically recording an audit trail which eases the administrative burden.[18,19] As such, electronic approaches can support not only participants but also trial sites, inspectors, and sponsors through more efficient documenting, and oversight.

While the advantages of electronic informed consent are clear, its application in clinical trial research so far has been scattered.[3,20,21] Available literature reporting the use of electronic informed consent in clinical trials is sparse.[18,22,23] Despite some case examples of eConsent in practice (see Table 1), widespread implementation of personalized, interactive platforms going beyond the use of electronic signatures and static electronic documents is lagging. For example, a recent survey conducted by the TransCelerate's Modernizing Clinical Trial Conduct initiative, involving global pharmaceutical developers, shows that most have no or limited experience with electronic informed consent in clinical trials.[20] Conversely, in the context of biobanking, dynamic consent platforms make already standard use of an interactive interface which enables participants to control how their personal data is used over time.[14,15,24]

Challenges to implementation

While electronic informed consent may bring significant opportunities, multiple barriers impede the broader roll-out and implementation of electronic informed consent in clinical trials. First, because of the high configurability of electronic informed consent systems, misconceptions appear to exist among stakeholders about what electronic informed consent exactly entails.[26] While electronic informed consent is a container term to describe digital practices, ranging from simply embedding an electronic signature in a scanned version of the paper-based informed consent form to using an interactive electronic platform (see Figure 1), electronic informed consent appears at times to be mistakenly understood as an exclusively remote process.[4,6,26] However, electronic informed consent can be used either on-site or remote (some elements can be digital and others not). This broad context of use and the sometimes misaligned understanding among stakeholders complicate the discussion on challenges and benefits of electronic informed consent. The challenges may

Table 1. Examples (non-exhaustive overview) of the use of electronic informed consent in clinical trials published in the scientific literature.

Context of the trial	Location	Reason for using electronic informed consent	Characteristics of the electronic informed consent process
A thrombectomy trial involving legally authorized representatives (LARs)[18]	United States	To investigate the advantages and drawbacks when using electronic informed consent	• The investigator discussed the trial with the LARs via phone • The LARs received the trial-related information via a REDCap-based electronic informed consent system and provided their consent electronically • The interfaces displayed a static, text-based electronic document without making use of multimedia elements
A clinical trial conducted in pediatric trauma centers involving teens and their parents[22]	United States	COVID-19 pandemic	• The research staff discussed the trial with the parents in-person or via phone • Parents received the trial-related information via a REDCap-based electronic informed consent system and provided their consent electronically • The research staff connected with the parents and teens to review the electronic informed consent • The interfaces displayed a static, text-based electronic document without making use of multimedia elements
A clinical trial involving pregnant women[23]	United States	Previous successful experience	• The investigator discussed the trial with the pregnant women via phone • The pregnant women were provided with a REDCap-based electronic informed consent system to review the trial-related information and to provide their consent • The investigator offered to remain on the phone while the women completed the REDCap-based electronic informed consent • The interfaces displayed an online version of a standard, paper-based consent form
A clinical trial involving women with overactive bladder[25]	United States	To investigate the advantages and drawbacks when using electronic informed consent	• The women were provided with the electronic informed consent to review the trial-related information and to provide their consent • The interfaces displayed a slide presentation in which the investigator explained the trial, followed by the full informed consent form. Hereafter, the women completed a multiple-choice test to assess their understanding • After signing the informed consent document, participants received a phone call from the study personnel who read and discussed the informed consent document with them, and answered questions they might have. If the participant remained interested in participating, the study investigator countersigned the informed consent document.

be directly linked to the level of electronic informed consent that is applied. For example, barriers for the implementation of electronic signatures may be less difficult to overcome than those that arise with the use of a fully developed platform, allowing personalization and a dynamic interaction between the participants and research team. Similarly, the

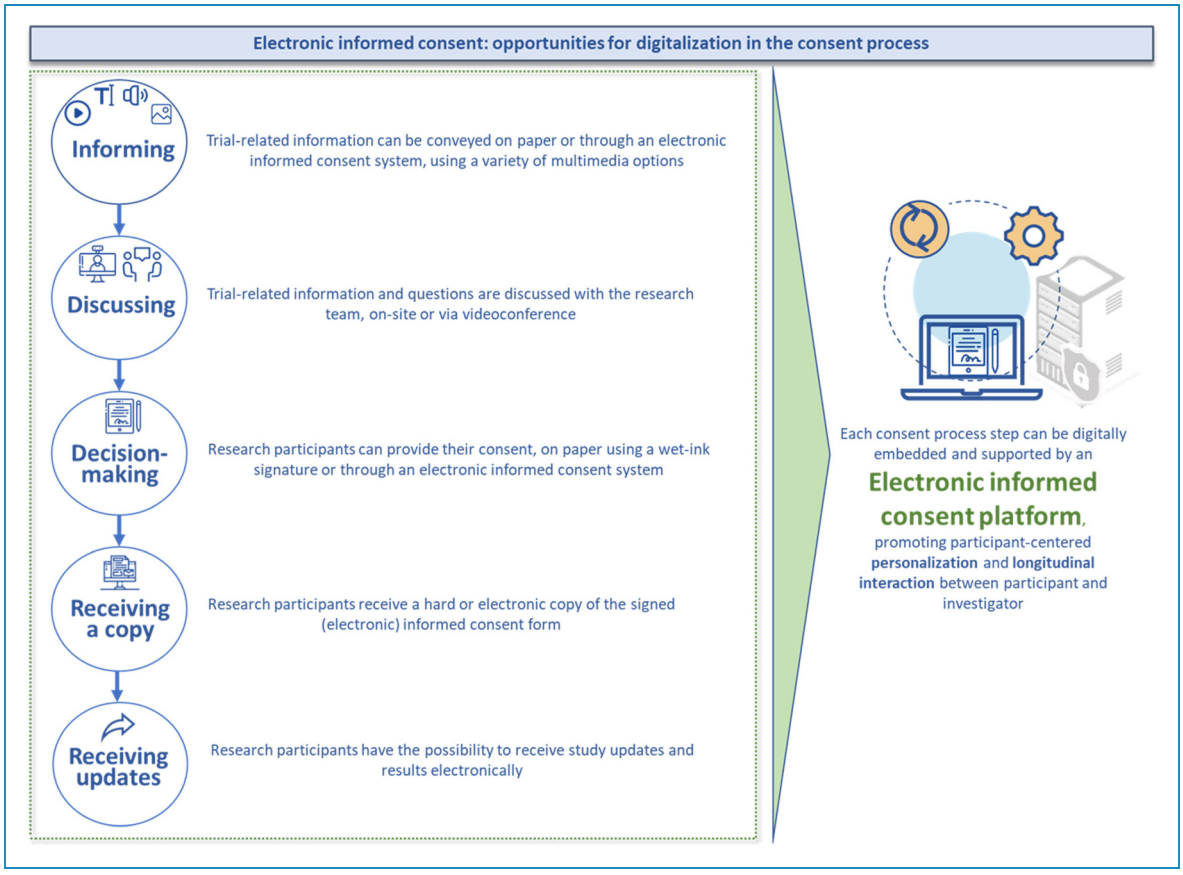

Figure 1. The opportunities for digital interaction in the informed consent process.

advantages for participants and sites are arguably higher with the use of a personalized and longitudinal platform compared to those of a static consent process with focus on electronic signature.

Another often voiced concern about electronic informed consent is that it may skew participant inclusion to those who are digitally literate, excluding older, vulnerable, and disadvantaged participants. To overcome this, a hybrid consent approach with both electronic and paper-based consent can be pursued. This way, participants themselves have the choice to opt in or out of digital platforms based on their personal preferences and accessibility. It should be noted that electronic means in informed consent are meant to support, rather than replace, interaction between the research participants and the research team. Interaction, either online or in-person, is crucial for any informed consent process.[6,27] In the context of fully decentralized trials, a video consultation can facilitate interaction between participant and research team to discuss the trial and any concerns or questions the participants might have. Ethics committees have an important role in assessing if a fully remote approach is suitable for the specific trial at hand.[28,29] For conceptual clarity, we use here the term electronic informed consent process to refer to both consent processes that make solely use of electronic informed consent and processes that make use of a

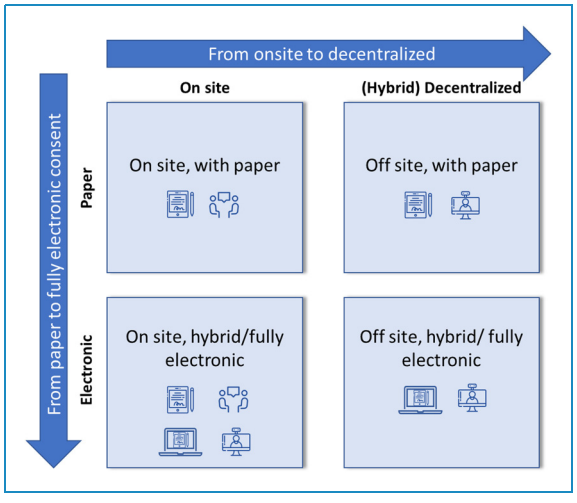

Figure 2. Electronic informed consent: not only for remote use.

combination of electronic and paper consent. Electronic informed consent can take place fully off-site, fully on-site, or can entail a combination of on- and off-site interaction (see Figure 2). There are relatively few trials that have been conducted fully remotely (i.e. where participants do not visit the site at all during the trial, also called fully decentralized clinical trials).[25,30] However, guidance development and

industry interest to increase the use of decentralized clinical trials may go hand in hand and drive forward the implementation of electronic informed consent as well.[3]

Hybrid: approach which combines elements of traditional face-to-face clinical trials and virtual or remote elements delivered digitally.

On the other hand, hybrid consent approaches may decrease process efficiency and be less cost proportionate, especially if only a small percentage of trial participants would choose electronic consent (high-cost system versus low adoption). A recent survey conducted among pharmaceutical industry identified the heavy resource demand to support development, approval, and maintenance of electronic informed consent as a key factor impeding its adoption.[20,22] Because sponsors across trials and regions may use different platforms, implementation burdens are also put on trial sites when onboarding these platforms. To avoid duplication of efforts and decrease the resource demand on individual sponsor/investigator team level, there is a need to harmonize and invest in the development of uniform and broadly applicable electronic consent platforms.

Furthermore, while the COVID-19 pandemic compelled regulators to formulate guidance about the use of digital technologies in clinical trials,[31–33] regulatory and legal guidance for electronic informed consent is scattered between US and Europe, and also within European Member States.[34] Given the multicentric nature of many clinical trials, there is a need for convergence of regulations and regulatory guidelines. Among stakeholders active in European Union Member States, such as investigators and data protection officers/legal experts, there is currently a perceived low degree of regulatory acceptance and the heterogeneity in guidelines among regulatory authorities further clouds the application potential of electronic informed consent.[21]

Together, these barriers and fragmented guidance at operational, resource, stakeholder understanding, legal, and regulatory level explain the low and scattered use of electronic informed consent. Harmonized guidance and the development of centrally endorsed platforms for electronic consent will be key. Furthermore, empirical research in the perspective and preference of trial participants regarding the use of electronic informed consent is warranted. Table 2 provides an overview of the key advantages and challenges for electronic informed consent in clinical trials.

Table 2. Key advantages and challenges for electronic informed consent.

Advantages	Challenges
• Tailored information delivery based on the research participant's needs and preferences • Longitudinal and dynamic relationship between participants and the research team • Broader access to clinical trials • Process efficiency for the research team	• Diverse understanding and misunderstanding of the term and context of use of electronic informed consent • Diverse legal and regulatory landscape • Heavy resource demand • Cost-efficiency not always optimal

How to facilitate broad implementation of a participant-centric electronic informed consent system?

Uniformity and standardization both in terms of guideline development and platform development may help electronic informed consent adoption. Having an electronic informed consent platform that is reviewed and endorsed at central regulatory level would be useful. For example, in Europe, the EMA could perform the role of hosting party, enabling research sites to make use of one single system. Through such a streamlined approach, the need for Institutional Review Boards (IRBs) and Ethics Committees (ECs) to evaluate the technical aspects of platforms on a case-by-case level, each time when a clinical trial with electronic informed consent is submitted for review, would be circumvented. IRBs and ECs in turn can focus on the evaluation of the trial content and information that will be presented through the digital platform itself. Such standardized, interoperable platform(s) will not only help to overcome the heavy resource burden for sponsors and trial sites, but also offer an integrated approach for participants who may take part in several trials over time. In addition, a centrally regulatory endorsed platform could provide sponsors and researchers with a template to develop personalized electronic informed consent forms enabling the establishment of long-term interactions with the participants. Templates may be built upon a repository of necessary elements to streamline the process of setting up electronic informed consent. 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 European Union as required by the Clinical Trials Regulation, EMA could be hosting party for a central electronic informed consent platform in Europe.[35] Although the CTIS was originally planned to enter into application in December 2015, technical difficulties pushed the go-live date back to January 2022.[36] Therefore, the feasibility of having an electronic informed consent platform endorsed at European level in the short term can be questioned. Alternatively, a stepwise approach could be applied to the hosting of an electronic informed consent platform, starting at local level. First, a local body could perform the role of hosting party, allowing stakeholders to gain practical experience with the platform.

If the platform shows to deliver on its benefits 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 issues.[37,38] A similar approach could be taken to foster the successful implementation of a central electronic informed consent platform. Alternatively, emphasis could be placed on setting out minimum standards and specifications that a participant-centric electronic informed consent platform should fulfill. It could be considered to apply for the EMA qualification process to establish regulatory acceptability of these standards and specifications, which could already be an important step forward.[39]

Compatibility and integration of digital systems with other information systems is one of the key determinants for success, as outlined by the World Health Organization (WHO) in their "Mobile Health Assessment and Planning for Scale (MAPS)" toolkit to scale mobile health innovations and maximize their impact.[40] Flexibility, interoperability, and scalability should become fundamental elements of electronic informed consent platforms to be successfully integrated within the digital health ecosystem. An electronic informed consent platform that allows for seamless integration into the trial site's workflow will ease the burden for the research staff. Before starting a particular trial, it is key to consider all the different technologies deployed in the trial environment and how these can integrate with each other. Choosing one electronic informed consent platform removes the need for trial sites to use multiple electronic consenting methods in trials, set up by different sponsors, and thus, results in greater trial site efficiency. In addition, electronic informed consent should make use of an interactive, multimedia-enabled format rather than sticking to a static electronic document, to deliver on its advantages for participants and research teams. Furthermore, the platform would benefit from a user-centered design approach, putting participants at the center of the design and development of a system that meets their needs.[41]

There are several initiatives that can be built upon to leverage and scale up the implementation of electronic informed consent in clinical trials. On a global level, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6(R2) guideline, entitled Good Clinical Practice (GCP), is being revised to address the rapidly evolving clinical trial landscape. The updated GCP guideline aims to support efficient clinical trial design and conduct, in which emerging technologies can play an important role.[42,43] Furthermore, the WHO published their Regional digital health action plan for the WHO European Region 2023–2030 in which four strategic priorities are put forward to leverage digital transformation in the health sector. 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.[44] In Europe, in the context of the Accelerating Clinical Trials in the European Union (ACT EU) program, a recommendation paper on the use of decentralized elements in clinical trials, such as electronic informed consent, has been issued.[28,45] In addition, the EMA published a guideline on computerized systems and electronic data in clinical trials, setting out various principles that apply to the use of electronic informed consent.[4] Furthermore, the new EU Clinical Trials Regulation aims to harmonize the submission, assessment, and supervision of processes for clinical trials throughout the European Union. The CTIS may offer an opportunity for the integration of electronic approaches for informed consent.[46] In the United States, a collaboration between the FDA and the Office for Human Research Protections resulted in guidance on the use of electronic informed consent in clinical investigations.[6] In this guidance, reference is made to the relevant regulatory requirements that should be complied with when using electronic informed consent.[6] 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.[47]

Conclusions

Electronic informed consent, when done in a personalized and longitudinal manner, may benefit clinical trial participants, trial sites, and sponsors by improving participant–researcher interaction, enabling clinical trial access, and increasing efficiency in clinical trial conduct. However, electronic informed consent faces at present several barriers at the conceptualization, regulatory, legal, and incentive level, impeding its widespread adoption and success. Many challenges stem from misconceptions rooted in a lack of knowledge of and experience with electronic informed consent. As the digital literacy of trial participants may differ, electronic informed consent should be set up in a hybrid manner where participants have the choice to opt in or out of digital features in the consent process. To advance the adoption of electronic informed consent, for the benefit of participants and clinical trial research as a whole, a collaborative effort involving relevant stakeholders, including regulators and policy makers, and continuous guidance development will be essential.

Acknowledgements: We are thankful to Prof. Hank Greely (Stanford Law School), Prof. Andrew Auerbach (UCSF School of Medicine), Allison Marie Gerger (Stanford Department of Research Compliance), Prof. Mark Musen (Stanford Center for Biomedical Informatics Research), and Prof. David Magnus (Stanford Center for Biomedical Informatics Research) for sharing their insights with us on this topic. We also thank Prof.

Stefania Boccia (Coordinator of ExACT) from the Preventive Medicine and Public Health at UCSC, Rome.

Contributorship: EDS and LB conceptualized and wrote the original draft, which was critically reviewed and edited by PB, DG, JPAI, and IH. All authors approved the final manuscript.

Declaration of conflicting interests: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the KU Leuven C2 Project C24M/19/071 – ePIC, the European Network Staff Exchange for Integrating Precision Health in the Health Care Systems (ExACT) project, which receives funding from the European Union's Horizon 2020 research and innovation programme MSCA-RISE-2017 Marie Skłodowska-Curie Research and Innovation Staff Exchange (RISE) under the grant agreement No. 823995, and the Research Foundation Flanders (FWO) under the grant No. K229122N.

Guarantor: IH

ORCID iD: Liese Barbier https://orcid.org/0000-0003-1786-2080
Evelien De Sutter https://orcid.org/0000-0001-6575-2033

References

1. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf (2016).
2. Van Norman GA. Decentralized clinical trials: the future of medical product development?. *JACC Basic Transl Sci* 2021; 6: 384–387.
3. de Jong AJ, Grupstra RJ, Santa-Ana-Tellez Y, et al. Which decentralised trial activities are reported in clinical trial protocols of drug trials initiated in 2019–2020? A cross-sectional study in ClinicalTrials.gov. *BMJ Open* 2022; 12: e063236.
4. European Medicines Agency. Good Clinical Practice Inspectors Working Group (GCP IWG). Guideline on computerised systems and electronic data in clinical trials. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-computerised-systems-and-electronic-data-clinical-trials_en.pdf (2023).
5. Rogers A, De Paoli G, Subbarayan S, et al. A systematic review of methods used to conduct decentralised clinical trials. *Br J Clin Pharmacol* 2022; 88: 2843–2862.
6. U.S. Department of Health and Human Services Office for Human Research Protections (OHRP), U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), et al. Use of Electronic Informed Consent Questions and Answers. Guidance for Institutional Review Boards, Investigators and Sponsors, https://www.fda.gov/media/116850/download (2016).
7. De Sutter E, Borry P, Geerts D, et al. Personalized and long-term electronic informed consent in clinical research: stakeholder views. *BMC Med Ethics* 2021; 22: 108.
8. Antal H, Bunnell HT, McCahan SM, et al. A cognitive approach for design of a multimedia informed consent video and website in pediatric research. *J Biomed Inform* 2017; 66: 248–258.
9. Rowbotham MC, Astin J, Greene K, et al. Interactive informed consent: randomized comparison with paper consents. *PLoS One* 2013; 8: e58603.
10. Warriner AH, Foster PJ, Mudano A, et al. A pragmatic randomized trial comparing tablet computer informed consent to traditional paper-based methods for an osteoporosis study. *Contemp Clin Trials Commun* 2016; 3: 32–38.
11. Simon CM, Klein DW and Schartz HA. Interactive multimedia consent for biobanking: a randomized trial. *Genet Med* 2016; 18: 57–64.
12. De Sutter E, Zaçe D, Boccia S, et al. Implementation of electronic informed consent in biomedical research and Stakeholders' perspectives: systematic review. *J Med Internet Res* 2020; 22: e19129.
13. Golembiewski EH, Mainous A3, Rahmanian KP, et al. An electronic tool to support patient-centered broad consent: a multi-arm randomized clinical trial in family medicine. *Ann Fam Med* 2021; 19: 16–23.
14. Kaye J, Whitley EA, Lund D, et al. Dynamic consent: a patient interface for twenty-first century research networks. *Eur J Hum Genet* 2015; 23: 141–146.
15. Mascalzoni D, Melotti R, Pattaro C, et al. Ten years of dynamic consent in the CHRIS study: informed consent as a dynamic process. *Eur J Hum Genet* 2022; 30: 1391–1397.
16. Teare HJ, Morrison M, Whitley EA, et al. Towards 'engagement 2.0': insights from a study of dynamic consent with biobank participants. *Digital Health* 2015; 1: 2055207615605644.
17. Almeida-Magana R, Maroof H, Grierson J, et al. E-Consent—a guide to maintain recruitment in clinical trials during the COVID-19 pandemic. *Trials* 2022; 23: 88.
18. Haussen DC, Doppelheuer S, Schindler K, et al. Utilization of a smartphone platform for electronic informed consent in acute stroke trials. *Stroke* 2017; 48: 3156–3160.
19. TransCelerate Biopharma Inc. eConsent: Implementation guidance, https://www.transceleratebiopharmainc.com/wp-content/uploads/2021/02/eConsent-Implementation-Guidance_February-2021.pdf (2017).
20. TransCelerate Biopharma Inc. TransCelerate's Modernizing Clinical Trial Conduct (MCTC) Initiative. Modern Solution Adoption. Maturity Survey Results., https://www.transceleratebiopharmainc.com/wp-content/uploads/2021/12/MCTC-Maturity-Survey-Detailed-Report-2021.pdf (2021, accessed 22 June 2022).
21. De Sutter E, Lalova-Spinks T, Borry P, et al. Rethinking informed consent in the time of COVID-19: An exploratory survey. *Front Med (Lausanne)* 2022; 9: 995688. Original Research.
22. Bromberg JR, Nimaja E, Kiragu AW, et al. Developing and implementing electronic consent procedures in response to COVID-19 restrictions. *Ethics Hum Res* 2022; 44: 39–44.
23. Phillippi JC, Doersam JK, Neal JL, et al. Electronic informed consent to facilitate recruitment of pregnant women into research. *J Obstet Gynecol Neonatal Nurs* 2018; 47: 529–534.

24. Teare HJA, Prictor M and Kaye J. Reflections on dynamic consent in biomedical research: the story so far. *Eur J Hum Genet* 2021; 29: 649–656.
25. Orri M, Lipset CH, Jacobs BP, et al. Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial. *Contemp Clin Trials* 2014; 38: 190–197.
26. European Contract Research Organisations Federation and eClinical Forum. Electronic informed consent imlementation guide: practical considerations, https://www.eucrof.eu/images/Electronic_Informed_Consent_Implementation_Guide_Practical_Considerations_Version_1.0___March_2021_2.pdf (2021, accessed 14 July 2022).
27. World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; 310: 2191–2194.
28. Heads of Medicines Agencies, European Commission and European Medicines Agency. Recommendation paper on decentralised elements in clinical trials., https://health.ec.europa.eu/system/files/2022-12/mp_decentralised-elements_clinical-trials_rec_en.pdf (2022, accessed 15 October 2023).
29. van Rijssel TI, de Jong AJ, Santa-Ana-Tellez Y, et al. Ethics review of decentralized clinical trials (DCTs): results of a mock ethics review. *Drug Discov Today* 2022; 27: 103326.
30. de Jong AJ, van Rijssel TI, Zuidgeest MGP, et al. Opportunities and challenges for decentralized clinical trials: European Regulators' perspective. *Clin Pharmacol Ther* 2022; 112: 344–352.
31. Federal Agency for Medicines and Health Products. Guidance on the Management of Clinical Investigations During the COVID-19 (Coronavirus) Pandemic. Version 1., https://www.fagg.be/sites/default/files/content/guidance_during_covid19_pandemic_for_ci.pdf (2020, accessed 14 May 2021).
32. European Medicines Agency. Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic., https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf (2021).
33. U.S. Food and Drug Administration. Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency. Guidance for Industry, Investigators, and Institutional Review Boards., https://www.fda.gov/media/136238/download (2021, accessed 14 May 2021).
34. De Sutter E, Meszaros J, Borry P, et al. Digitizing the informed consent process: a review of the regulatory landscape in the European union. *Front Med (Lausanne)* 2022; 9: 906448.
35. European Medicines Agency. Clinical Trials Information System, https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system. (accessed December 2022).
36. European Medicines Agency. Development of the Clinical Trials Information System, https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system/development-clinical-trials-information-system (accessed 21 February 2023).
37. European Medicines Agency. Clinical Trials Information System (CTIS) webinar: Six months of CTIS and looking forward, https://www.ema.europa.eu/en/documents/presentation/presentation_en-0.pdf (2022, accessed 21 February 2023).
38. European Medicines Agency. Regulatory harmonisation of clinical trials in the EU: Clinical Trials Regulation to enter into application and new Clinical Trials Information System to be launched., https://www.ema.europa.eu/en/news/regulatory-harmonisation-clinical-trials-eu-clinical-trials-regulation-enter-application-new (2022, accessed 21 February 2023).
39. European Medicines Agency. Qualification of novel methodologies for medicine development., https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development-0 (accessed 21 February 2023).
40. World Health Organization, United Nations Foundation, UNDP/UNFPA/WHO/World Bank Special Programme of Research, et al. The MAPS toolkit: mHealth assessment and planning for scale, https://apps.who.int/iris/handle/10665/185238 (2015).
41. Sanders EBN and Stappers PJ. Co-creation and the new landscapes of design. *CoDes* 2008; 4: 5–18.
42. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Final Business Plan. ICH E6(R3): Guideline for Good Clinical Practice., https://database.ich.org/sites/default/files/E6-R3_FinalBusinessPlan_2019_1117.pdf (2019, accessed 18 October 2022).
43. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6(R3) Expert Working Group. ICH-E6 Good Clinical Practice (GCP) - Explanatory note, https://database.ich.org/sites/default/files/ICH_E6-R3_GCP-Principles_Draft_2021_0419.pdf (2021, accessed 14 July 2022).
44. Regional Committee for Europe. Seventy-second Regional Committee for Europe: Tel Aviv, 12–14 September 2022: Regional digital health action plan for the WHO European Region 2023–2030. World Health Organization. Regional Office for Europe., https://apps.who.int/iris/handle/10665/360950 (2022).
45. European Medicines Agency, European Commission and Heads of Medicines Agencies. ACT EU Multi-stakeholder meeting on decentralized clinical trials, https://www.ema.europa.eu/en/documents/presentation/presentations-act-eu-multi-stakeholder-meeting-decentralised-clinical-trials_en.pdf (2022).
46. European Medicines Agency. Six-month countdown to go-live for the Clinical Trials Information System (CTIS), https://www.ema.europa.eu/en/news/six-month-countdown-go-live-clinical-trials-information-system-ctis (2021, accessed December 2022).
47. U.S. Food and Drug Administration. Digital Health Center of Excellence, https://www.fda.gov/medical-devices/digital-health-center-excellence (2022, accessed December 2022).