Electronic Informed Consent Implementation Guide

Practical Considerations

Version 1.0 | March 2021

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About EUCROF

The European Contract Research Organisation Federation, EUCROF (www.eucrof.eu), consists of members from most European countries and partner members from nearby countries with the aim of promoting clinical research of high quality in Europe in general and in the European Union in particular. EUCROFs objectives include promoting discussions on selected topics with representatives of the pharmaceutical industry to enhance business relations and identify common concerns, supporting more productive discussions with European bodies (EMA/EU Commission), and endeavouring to develop transcontinental relationships with other associations e.g., with ACRO (Association of Clinical Research Organisations) in the USA and JCROA (Japanese Clinical Research Organization) in Japan.

About the eClinical Forum

The eClinical Forum, eCF (www.eclinicalforum.org) is a global, technology independent group representing members of industries engaged in clinical research. The eClinical Forum's mission is to serve these industries by focusing on those systems, processes and roles relevant to electronic capture, handling, and submission of clinical trial data. For further information visit the website at www.eclinicalforum.org . The eClinical Forum has sought out opportunities to promote electronic Clinical Trials since its inception in 2000. The cross-industry forum has a broad view of research with members - Sponsors, Contract Research Organizations (CROs), Technology vendors (both clinical research and healthcare), Academia, and Investigators - and with invited outreach opportunities with global Regulatory representatives.

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The information presented in these works draws upon the combined current understanding and knowledge of EUCROF and the eClinical Forum on this topic and is provided as an aid to understanding the environment for electronic clinical research. The opinions of the author(s), EUCROF and the eClinical Forum do not necessarily reflect the position of individual companies. Users should assess the content and opinions in the light of their own knowledge, needs and experience as well as interpretation of relevant guidance and regulations.
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Glossary of Terms

BYOD – "Bring Your Own Device", the use of a participant's personal electronic device

eCOA - electronic Clinical Outcomes Assessment

eConsent – refers to the overall process of informed consent performed using electronic means

EDC – electronic data capture

eICF – electronic Informed Consent Form (with the interactive participant education component)

ePRO – electronic patient-reported outcome

GCP – Good Clinical Practice

ICF – Paper Informed Consent Form

ICH - International Conference on Harmonization

IEC – Independent Ethics Committee

IRB – Institutional Review Board

PII – personally identifiable information, including PHI – protected health information

For expanded definitions of the terminology, please refer to [1].

Executive Summary

The aim of this document is to serve as an implementation guide when transitioning to electronic informed consent (eConsent) in clinical trials. The main purpose of the implementation guide is to provide a background of the benefits, processes and nuances of eConsent and offer practical advice to facilitate implementation. Other eConsent papers are available, although the following guide is providing the most up-to-date overview and is not meant to be a detailed in-depth analysis, but instead serves as a document to guide organisations through a brief overview of considerations required prior to implementing eConsent. Each organisation's processes are different, hence detailed scenarios would be subject to change dependant on the organisation and are not specified in this guide. It is important to address the regulatory feasibility of implementing eConsent first, hence local regulations should be considered as a first step in the decision-making process of potential eConsent implementation.

The focus of the guidance will be of particular relevance to sponsors and regulators. The guide offers a combination of practical considerations from stakeholders, an updated landscape overview of eConsent in today's world, with an outlook on the current regulations and the impact of COVID-19 on demand for eConsent. It is important to stress the significance of ensuring that local regulations, which are often subject to dynamic changes, are followed prior to implementation. The document was created by the joint task force from EUCROF and eClinical Forum, consisting of eConsent experts from the industry. Stakeholders with experience of eConsent from other organisations were also involved in providing their personal accounts of eConsent.

The following implementation guide outlines the sequence of activities necessary for eConsent implementation, starting with an introduction to the process, where the reader will learn about the possibilities and opportunities that eConsent presents. Then, once it is decided that eConsent implementation is to be considered, it is possible to learn more about the process of the eConsent procedure for the sponsor, site and participant. Afterwards refer to the implementation section for a detailed implementation guide. Lastly, this document presents other stakeholders' experience, which was gathered from representative stakeholder participation from patient, site, monitor, sponsor and ethics committee in the stakeholder perspectives section and provides a view of the generic global perspective.

Introduction to eConsent

Informed consent is a pivotal part of clinical trials and is a paramount characteristic of ethical clinical trial conduct. The GCP ICH R2 defines informed consent as "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" [2]. As the healthcare sector and clinical trial conduct evolves at an accelerated pace beyond the use of paper-based systems into electronic alternatives, eConsent is one of the components of clinical trial virtualisation that the healthcare industry is heading towards [3].

The Medicines and Healthcare products Regulatory Agency (MHRA) and Health Research Authority (HRA) in the UK define the electronic informed consent process as "consisting of two distinct phases of educating and giving consent via a signature" [4]. Both of these phases, the interactive participant education tool and the electronic signature are addressed in detail in the next section.

Electronic consenting is not a new phenomenon but already established and proven and has been in use for around 15 years. As per a survey conducted in 2017, it was indicated that the main drivers for implementation were improved participant satisfaction, reduced regulatory risk, increased participant comprehension and accelerated study and site start-up [5]. Whilst eConsent has been in use for over a decade and there are clear benefits to participants and efficiency gains to be harnessed, there has been slow adoption due to various aspects, such as regulatory barriers, hesitation to change and cultural resistance, to name a few.

"1. Electronic methods for seeking informed consent' and 'eConsent' refer to the use of any electronic media (such as text, graphics, audio, video, podcasts, or websites) to convey information related to the study."

"2. To seek and/or document informed consent via an electronic device such as a smartphone, tablet, or computer."

MHRA eConsent Definition
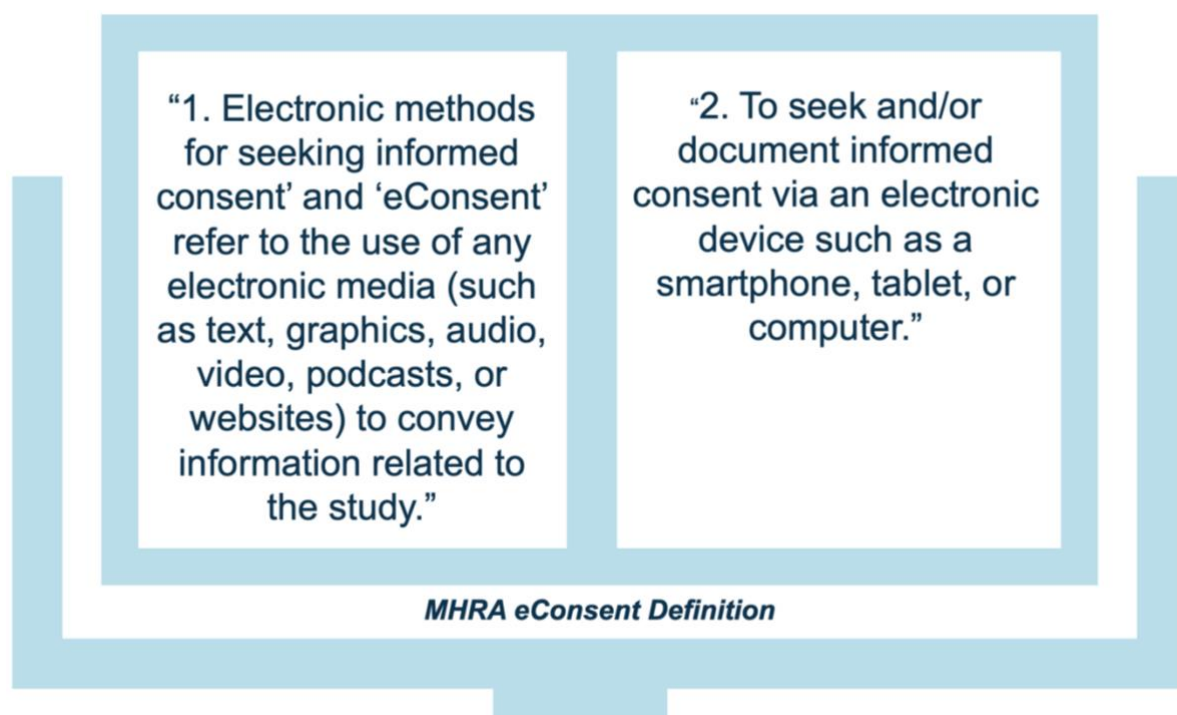
Improve Participant Experience

The motivation to switch to eConsent does not merely stem from process efficiency and convenience of an electronic procedure over a paper alternative. eConsent provides participants the opportunity to understand and learn information using a variety of more interactive methods. This in turn increases participant comprehension. This was positively demonstrated in a study that compared paper ICF to eICF directly [6].

Better participant comprehension reduces the risk of participant drop out due to a lack of understanding of what they had consented to. This was demonstrated in a study where eConsent was shown to increase participant adherence to the study requirements and retention [7]. Reduced drop-out rates and increased protocol adherence ultimately aid the participants, who are able to continue benefiting from the trial treatment, which may be potentially lifesaving. Notably, eConsent preserves the valuable participant- study team interaction, much like the paper consent process.

A pilot study that was conducted demonstrated that eConsent improves long-term recall of the informed consent elements [8]. This is valuable, as data suggests high rates of participant loss can be traced back to a lack of understanding of paper ICFs, which either leads to less participants enrolling, or increases participant drop-out rates as participants are unaware that they consent to all the aspects and requirements of the clinical trial due to a lack of understanding. The participant still receives a copy of the eICF for their own record.

In a survey [9] 35% of prospective participants said that they did not enrol onto a clinical trial due to a lack of understanding of the long paper ICF, clearly indicating that the informed consent process format needs to be improved. Accessibility of ICF content is improved in eICF, due to the ability to adjust screen readers, magnification, font size, contrast and brightness. eConsent eliminates many of the roadblocks for participants considering participation in a clinical trial and engages them by optimising and clarifying the informed consent content and allowing them to make a more informed and ethical decision.
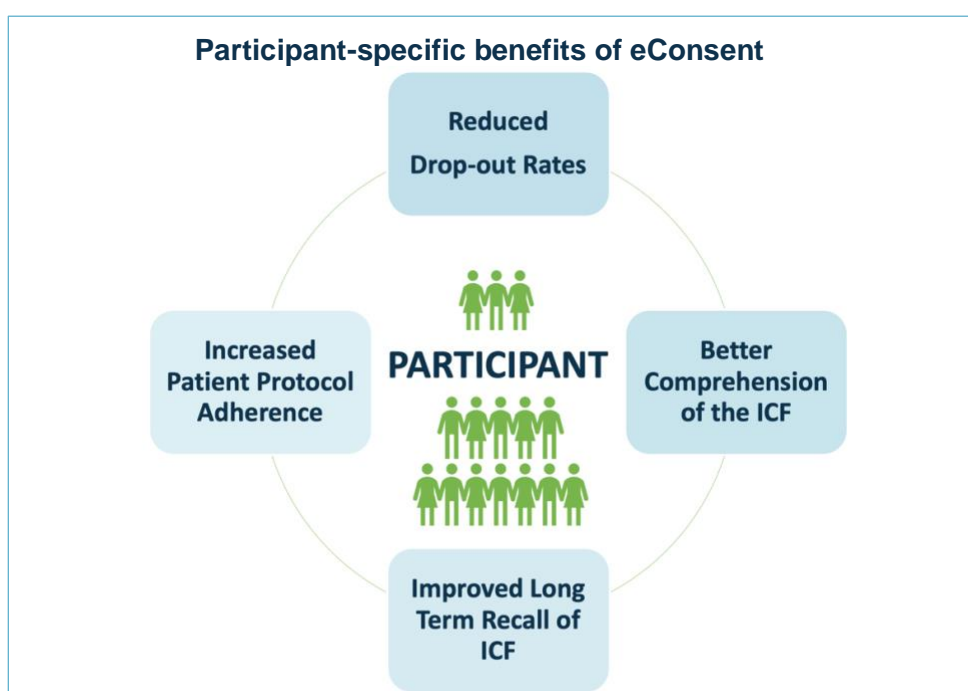

Figure 1: *Participant-specific benefits of eConsent that facilitate trial understanding, helping participation according to the protocol, maximising potential benefits to participant's health.*

The 'Electronic' in Electronic Informed Consent

What exactly does the word 'electronic' refer to in eConsent? The electronic aspects of eConsent are highly configurable, with the option to opt in or out of using an electronic interactive participant education component and an electronic signature. Both of these elements of eConsent can serve as substitutes or an addition to the existing paper informed consent processes.

Interactive Participant Education Component

The interactive participant education component could include video, infographics, audio components, along with a function for looking up definitions and flagging up areas of uncertainty. Comment boxes can be used to note down any important areas and clarifications.

This interactive participant education component can be used to augment or substitute traditional paper-based methods of informing the participant. Research has demonstrated that information relayed via multimedia formats is preferred by participants and that overall comprehension is greater [10]. It is important to design any clinical trial with the participant's interests as a priority, and it is recommended to involve patient engagement groups in assessing the appropriateness of the proposed e-consent solution to the patient population.

The sponsor and investigator can use additional means to confirm the participant's comprehension through an eConsent knowledge review, which can be configured into the interactive participant education component to highlight areas of uncertainty for the participant and information that should be further emphasised in the participant- site discussions.
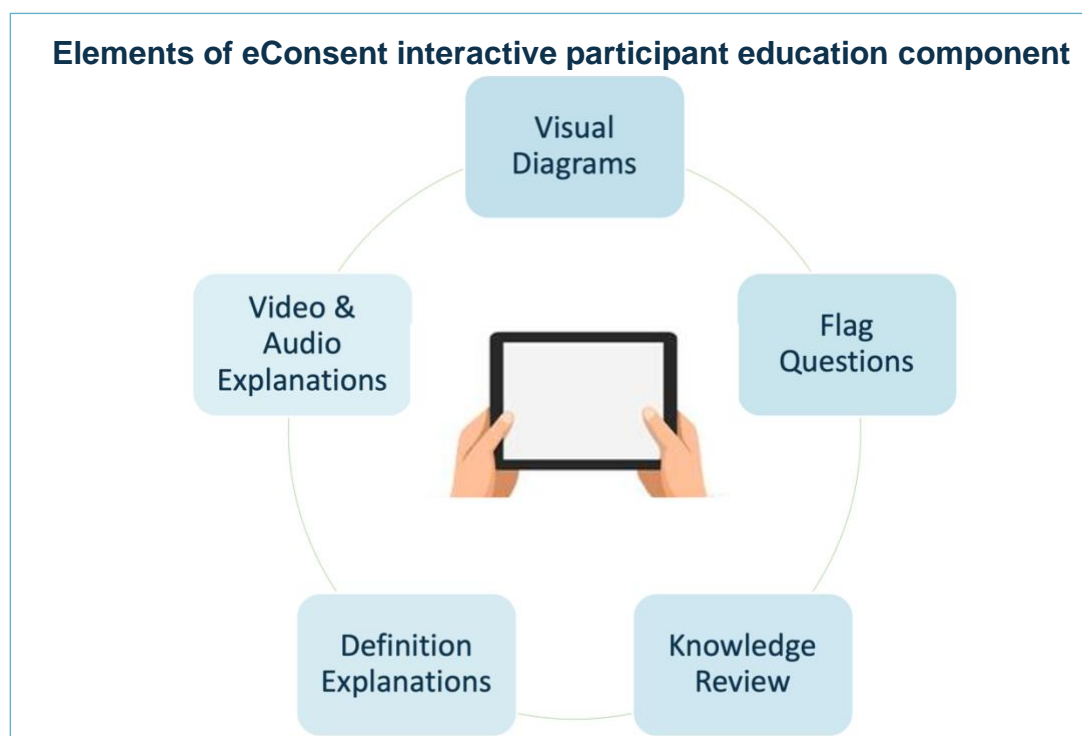

Figure 2: *Examples of elements of eConsent interactive participant education component that elevate the traditional experience of reading a paper ICF.*

Multimedia integration into written text can have a significant impact on information processing in older participants. The interactive participant education component of eConsent provides elderly participants with better support to make a truly informed decision to participate in a clinical trial. Senior participants over 60 have shown to easily adapt to eConsent in a study [11] as they claim it is easy to use, which may also be explained by the intuitive nature of device interaction.

eSignature

An eConsent platform can be configured to accommodate different signature types, which can be paper or electronic options compliant and in line with the country-specific regulations.

Within Europe, electronic identification and trust services (eIDAS) EU Regulation 910 [12] addresses electronic identification and trust services for electronic transactions specific to the EU region. eIDAS highlights three electronic signature types:

- ✓ **Simple electronic signature** is defined as data in electronic form that serves a role of authentication. Some examples of simple signatures may include stylus, finger drawn, typed signatures.

- ✓ **Advanced electronic signature**, which is linked to the signatory in a unique and non-transferable manner as it has verification steps embedded, confirming that the person signing is indeed who he claims to be. An advanced signature is also linked to the document, preventing further modifications post the signing process.

- ✓ **Qualified signature** is an advanced signature created by an electronic signature device and qualified certification process.

The FDA also recognises electronic signatures and the criteria under which an electronic signature is considered trustworthy and reliable are outlined in 21 CFR § 11 [13]. All the criteria of 21 CFR § 11 must be fulfilled in order for the electronic signature to be considered equivalent to a wet ink paper signature. A variety of electronic signature methods are recognised by the FDA, however no particular method is mandated.

It is crucial that the country-specific signature requirements are followed, for more information refer to the 'Acceptance in Countries' section. eConsent tools currently support the use of simple and advanced signatures. The laws around electronic signatures vary across the world and some countries do not yet accept electronic signatures or require a qualified signature for informed consent purposes. If that is the case, then eConsent can still be implemented with a print-to-sign signature. This print-to-sign option would involve printing the ICF, obtaining a wet ink paper signature from the participant and a wet-ink countersignature from the study team captured. The signed forms can be stored on site like the traditional paper consent process, or alternatively can be scanned and uploaded into an electronic system for record keeping. However, it is important to consider both the country-specific requirements, as well as site-specific SOPs (standard operating procedures), which will specify the requirements for storing consent documents, whether that be in an electronic system or as a physically printed copy on site.

Remote and On-Site Options

eConsent is at times viewed as an exclusively remote process. eConsent scenarios may vary as it may be any combination of the remote or on-site interactive participant education component and remote or onsite signature, as is demonstrated in Figure 3. Currently a good proportion of eConsent is performed on site.

eConsent can be configured to be a hybrid combination of paper and electronic consent elements
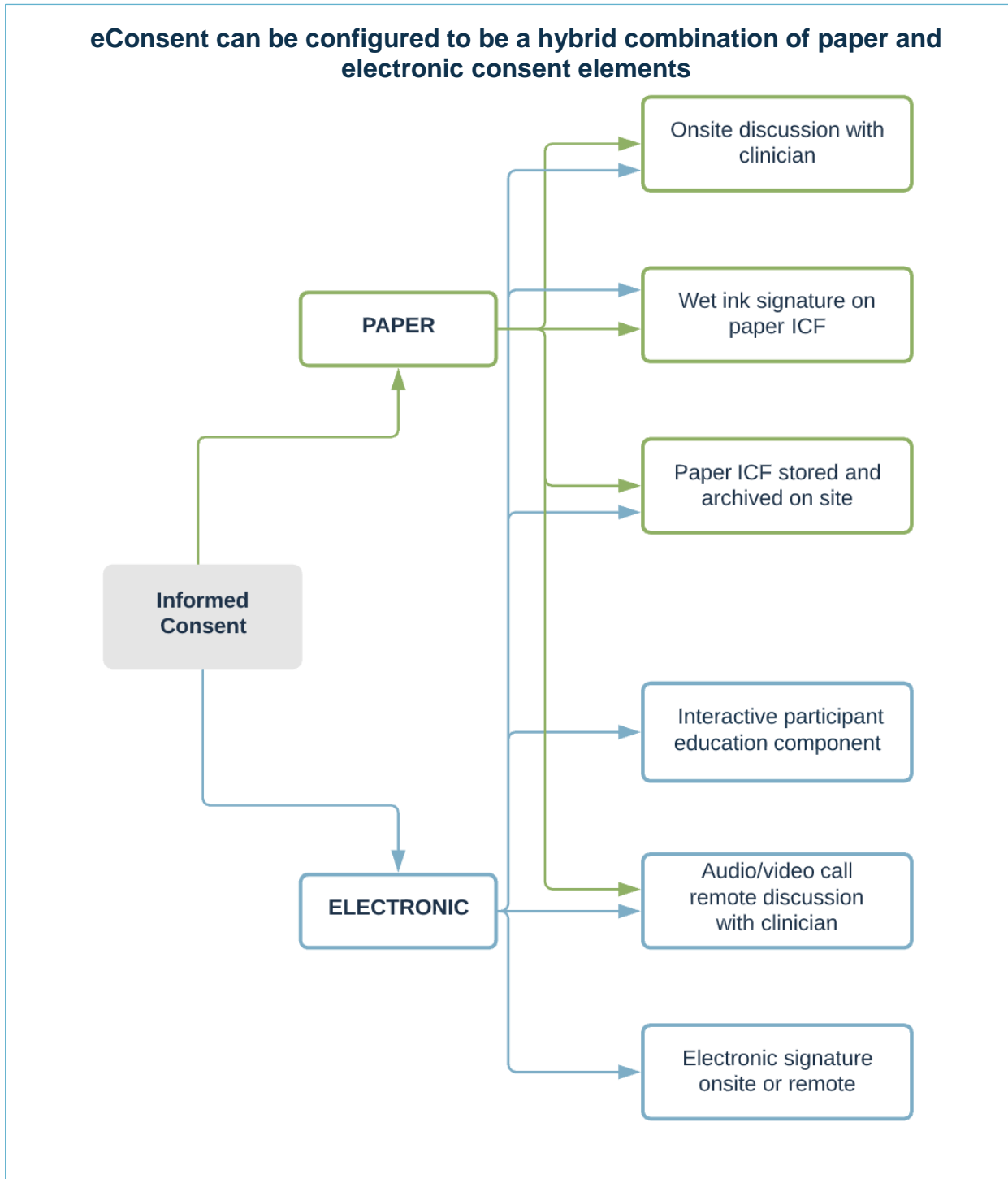

Figure 3: *eConsent can be configured to be a hybrid combination of paper and electronic consent elements. The arrows demonstrate how paper consent is enhanced by adding electronic consent elements. This is a non-exhaustive view of the possible combinations of paper consent and eConsent aspects of informed consent. Adapted from [14].*

In traditional paper-based trials the informed consent process is typically fully performed on site, where the participant reads the ICF, has a discussion with the study team, and finally, signs the ICF, which is later stored on site. Nonetheless, it is also possible to implement paper consent remotely using post to send consent forms to and from the participant whilst conducting online discussions between the site and participant. Meanwhile eConsent offers the chance to substitute or add some electronic alternatives to the existing paper process. These include an electronic interactive participant education component instead of the paper ICF, as well as an electronic signature that can be captured on site or remotely and an electronic database for documentation storage. When considering remote informed consent, particular attention is required to participant ID verification and data privacy considerations for both paper and eConsent. Implementing eConsent does not necessarily have to involve adopting all the electronic elements of eConsent at once, as any combination could also be value driven. For further details on remote eConsent, including other decentralised clinical trial components, such as remote monitoring, please refer to the ACRO DCT working party [15].

COVID-19: The eConsent Catalyst

The current COVID-19 pandemic, although a humanitarian crisis, has served as an exceptional catalyst, allowing nations to shift to more remote strategies for the continuation of current trials and start of new trials during this pandemic.

eConsent opens a new opportunity of remote access, which is a critical advantage particularly during the current COVID-19 pandemic, as clinical trials worldwide are experiencing enrolment and re-consent issues due to travel restrictions and quarantines.

Some countries have released COVID-19 specific clinical trials guidelines, with a general trend towards virtualisation of trials to allow for the continuation and start-up of clinical trials. The FDA have responded to the challenge of obtaining informed consent during the pandemic faced by investigators by rolling out the COVID MyStudies application which provides a platform for participants to consent electronically when face-to-face informed consent is impossible or impractical [16].

While the value of eConsent is significantly heightened during a crisis like this, eConsent is not an innovation that would only last as long as the global pandemic. It transforms the traditional paper consent by bringing additional value to the sponsor and investigator, as well as exceptional benefits to the participants. It also supports the ethical mandates of clinical research to have respect for persons, provide beneficence, and meets the standards of justice [17].

Support Other Opt-in/out Consent Options

The value of participant understanding of the consent forms extends even beyond the trial itself. Biosamples that are collected during the trial have the potential to be incredibly useful for research purposes. It is not uncommon for these valuable biological samples obtained from participants to be disposed of due to a lack of a centralised electronic record keeping system. Some companies have disposed of hundreds of thousands of participant biosamples that could have been used for research purposes. eConsent addresses this

issue, as the consent documents are stored in the electronic system, easily obtainable with minimal risk of data loss and in general a more efficient access to the historical ICFs.

Benefits for Ethics Committees/ Regulatory Agencies

eConsent can provide a unified platform from which the individual aspects of informed consent compliance can be managed remotely and effectively. eConsent has an electronic audit trail, which introduces new data analytics opportunities, as all amendments to the consent documents are recorded on the system, including the precise date and timing, the person performing the amendment, and the reason behind the amendment. This allows sites to easily demonstrate real-time compliance. Additional datapoints can be available to the sponsor about the time participants spend reviewing the eICF sections, which is an excellent way of determining that the participant was given sufficient time to review the information.

Paper-based solutions are more error prone than electronic alternatives when it comes to filling of consent documents. In comparison to hand-written surgical consent forms, a study showed that 44% of paper forms were not completed, signed or dated properly, while the electronic forms indicated no errors [18]. This could be explained by the fact that electronic solutions have multiple additional compliance control elements and are validated, and the users have such warnings about missing fields in the form, which prevent mistakes which can be a frequent occurrence with paper-based processes [19]. eConsent facilitates regulatory compliance by offering additional visibility into confirming that all parties have signed all required study type consent forms through the ability to set auto reminders and system supporting the reconsenting capability through easy configuration.

EMA inspection report of ethically relevant issues in clinical trials over 4 years of 2008-2012 outlines that informed consent alone was a source of 11% of the inspection findings during the course of the four years [20]. A quarter of all the informed consent violation findings were caused by signature and ICF date issues. The likelihood of these errors occurring with eConsent is reduced as the missing field or error would be flagged up as a missing or incorrect field, and be rectified at the time, unlike in paper ICF [20].

eConsent Implementation Guidance

This section will provide an account of all the points to consider when implementing eConsent, whilst offering some practical advice on how to best approach the transition and make sure that it is smooth and thorough. The eConsent implementation roadmap can guide through the sequence of events that will occur during implementation, providing an excellent overview of all the necessary points to remember to ensure the best prepared position to kick-start the process.

The implementation of eConsent is in some ways similar to paper informed consent start-up. As the industry is slowly becoming comfortable with the idea and the transition to eConsent is rapidly expanding, there needs to be a comprehensive guide of all the implementation steps to remember.

The implementation guidance is outlined in the next section, consisting of a roadmap and a detailed implementation table. The length of implementation timelines depends on the specific stakeholders and varies depending on the organisations involved. The individual steps outlined in the following section could be performed sequentially or in parallel with different groups, depending on the organisational procedures.
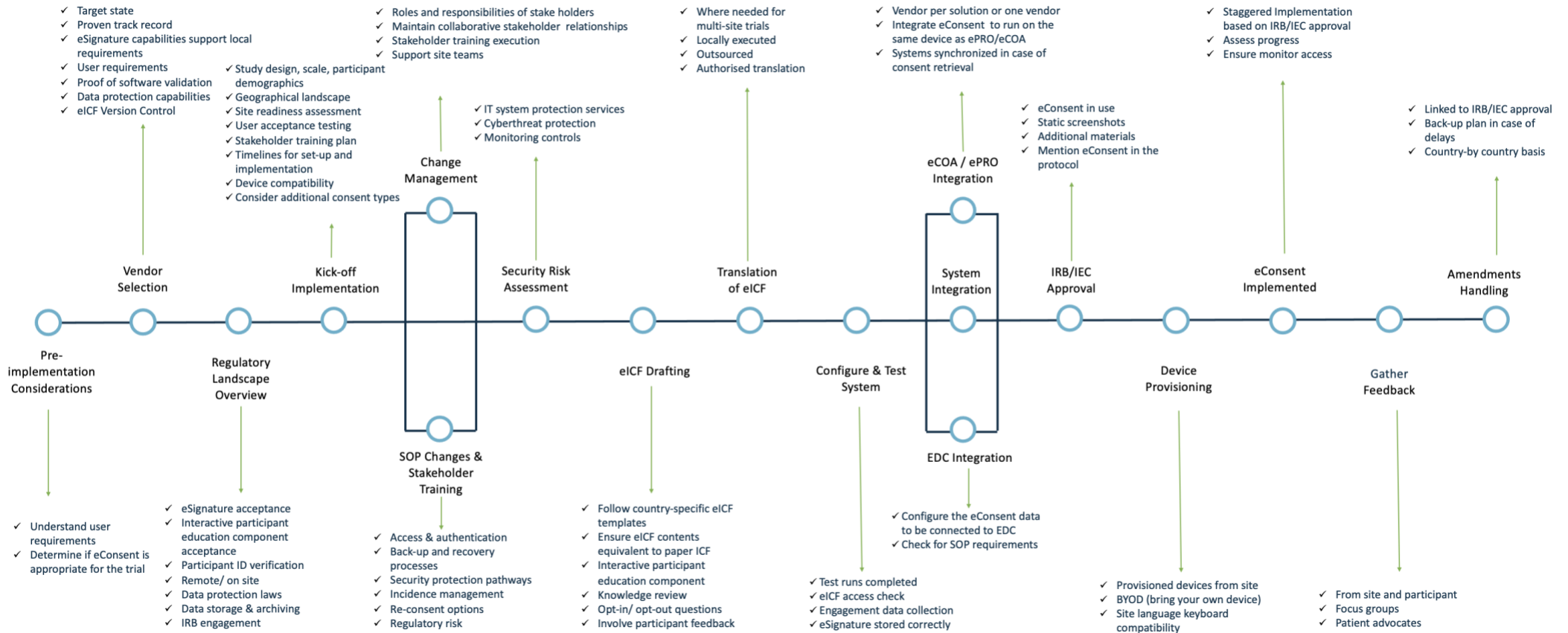
eConsent Implementation Roadmap

Figure 4: **eConsent Implementation Roadmap** - showcases the major steps of eConsent implementation, all of which need to be taken into account prior to eConsent implementation [21,22].

Detailed Practical Implementation Guidance

The points below address and expand upon the steps mentioned in the Implementation Roadmap (Figure 4).

Pre-implementation Considerations	✓ Understand user requirements which will form the basis of the eConsent system requirements for the trial and help in the vendor selection process ✓ Determine if eConsent is appropriate for the trial based on the user requirements
Vendor Selection	✓ Consider the target state of the eConsent use and select a vendor that can support organisational business processes, data storage and document archiving requirements and respond to market demands the best ✓ Consider systems that allow development and control of eConsent as a self-service if there are existing systems, tools and/or teams already handling consent processes in-house, even if this is a longer-term target state ✓ Consider a simple solution if the need is only to collect signatures electronically and just convert the paper ICF documents into digital format ✓ Check for a proven track record of eConsent regulations, security, eSignature and data privacy requirements as well as compliance with regional TMF requirements, such as the EMA TMF guidance [23] ✓ Make sure that the selected vendor offers an eConsent system with eSignature capabilities that support local electronic signature type requirements where electronic signatures are used in the eConsent process ✓ Compare user and protocol requirements to the software capabilities, for example for paediatric studies ✓ Confirm software validation, including performance qualification ✓ Ensure robust due diligence practices are performed and system validation documentation is available ✓ Select a flexible solution, as multiple Institutional Review Boards (IRB) and Independent Ethics Committees (IECs) involved may have differences in approval requirements ✓ Consider data storage, access rights levels and protection, access to PII (personally identifiable information, including PHI, protected health information), archiving process decided upon by the sponsor and vendor according to the local laws ✓ Ensure the vendor has the capabilities to store all the eICF versions, including re-consent and consent withdrawal information ✓ Ensure system capabilities for an electronic audit trail that captures all amendments made to the consent documents, including the nature of the change, the person executing it and the date and time of execution ✓ Assess vendor mechanisms to pseudo anonymise PII (to block sponsor from accessing PII) and securely storing identifiable information on site only ✓ Vendor and site should agree on a role-based access plan for PII depending on how crucial it is for the specific staff member

Regulatory Landscape Overview	Understand the country-specific regulations on the use of eConsent, in particular requirements for: ✓ Interactive participant education component ✓ Electronic signature type or a print-to-sign alternative ✓ Participant identity verification ✓ Participant- study team discussion ✓ Remote and on-site use acceptance ✓ Remote monitoring and study team access to source data containing PII ✓ Data storage and document archiving requirements, for more details refer to [24] ✓ Compliance with applicable data protection laws, including GDPR [25], HIPAA [26], CFR [27], and any local laws Engage with IRBs as soon as possible with a gap analysis to identify that the IRB's SOPs can support the electronic process review and approval
Kick-off Implementation	✓ Initiated once the contract has been obtained ✓ Consider study design, scale and demographics of the participants ✓ Consider geographical landscape, when selecting countries pay attention to regulatory and cultural environment, as well as the infrastructure to assess eConsent suitability ✓ Consider additional consent types, for example in a paediatric study requirement for both parental consent and paediatric age-related assent form and the use of sub-study additional consents in some trials ✓ Stakeholders change management and training plan should be discussed, aiming to train all stakeholders in eConsent use and engaging with through the process ✓ Plan for user acceptance testing (UAT) where it is needed: on global, country and/or site level ✓ Collaborate with your vendor on the desired participant and site workflow for enrolment/eConsent ✓ At the kick-off meeting discuss set-up timelines, timelines for UAT, compatibility for relevant device types (desktop, tablet, mobile), operating systems, web browsers and/or other native applications to be implemented
Change Management	Change management is not to be underestimated and should be planned out from the very beginning to make sure all stakeholders relevant to the process are considered and involved. ✓ Plan and agree on roles and responsibilities between stakeholders early on in the process ✓ Manage and maintain collaborative relationships with all stakeholders involved ✓ Stakeholders change management and training execution ✓ Arrange a training version of the eConsent to allow study team to test the eConsent in practice ✓ Engage with the site teams to ensure a smooth transition from the paper-based consent process to eConsent ✓ Support sites throughout eConsent implementation through training and additional helpdesks
SOP Changes and Stakeholder Training	✓ Consider regulatory risk, security protection pathways, operational changes to system management, including access and authentication ✓ Back-up and recovery processes, security testing and incident management

	✓ Device management if provisional devices are used instead of BYOD options ✓ Plan out re-consent options, align them with the country specific regulations Outline and update roles and responsibility as needed if any changes are expected, such as data protection responsibility of investigator, sponsor and the vendor
Security Risk Assessment	✓ Consider the security systems in place that are provided by the vendor, including their IT system protection services, such as cyberthreat protection. Consider using paper consent in the emergency case of inability to use the system ✓ Pay attention to remote monitoring controls being in place
eICF Drafting	✓ The eICF drafting process should follow the same steps as a paper ICF drafting for quality control of the information for local regulation compliance with the content requirements and protocol alignment ✓ Ensure the eICF and the paper ICF are equivalent and contain identical information, this guarantees that the participant is fully informed of the clinical trial and avoid later issues with monitoring and inspections ✓ Refer to relevant country-specific templates of the eICF that can be accessed from the health authorities ✓ Consider where to use multimedia, how to structure and create layers for the information and making some parts of the content optional to read, thus implementing a tiered consent system, more details on which can be found here [28]. Be aware of the reusability of eICF templates and materials from a central sponsor or site library ✓ Plan the knowledge review to check that the participant is truly informed prior to signing the form ✓ Identify if there are opt-in/out questions (e.g., on future use of samples) that need to be included ✓ Involve participant feedback in the review and amendment process through performing test runs with potential participants
Translation of eICF	If multiple languages are needed for different sites, the eICF should be translated. Any other site-specific configurations should also be configured. ✓ Determine if translations will be executed locally or outsourced through a third-party provider and if any translation process automation is available ✓ Preferable method is an authorised translation that some vendors provide
Configure & Test the System	✓ Complete test runs to check that the eICF can be accessed via the chosen mechanism, such as a web page or app, the flag feature is functioning properly Check that all data points about participant engagement are collected, data and eSignatures are stored securely on the system with an immutable and transparent audit trail. Test technical support for participants in remote eConsent.

System Integration	eConsent provides the most value as part of the eClinical data flow when it is possible to integrate the consent information with other systems (IVR (interactive voice response), EDC, eCOA (electronic Clinical Outcomes Assessment), Site Monitoring Systems, DataWarehouse or lab sample management system, screening surveys and conferencing tools or inbuilt teleconference features in the eConsent tool). The benefits include reduced manual labour, reduced manual errors and real time availability of the data. Nonetheless, system integration is an additional feature, and is not a requirement for initial implementation of eConsent. ✓ Understand early on what data to integrate and to what systems, data storage and document archiving expectation and requirements ✓ Often it is needed to involve vendors for both eConsent and the target system to agree the details of the integration, especially for first integrations ✓ Check that sufficient firewalls are in place to ensure PII is not transmitted into other systems ✓ Data flow diagrams would be useful to summarise the data exchange between the integrated systems
eCOA/ePRO Integration	✓ Select either a vendor per solution, or only one vendor for all solutions ✓ Configure the systems to integrate both services to run on a single device, allowing for efficiency gains of integrated systems with reduced challenge of multiple logins and system differences ✓ Select multiple vendors if looking for the best of each product, with an inherent efficiency trade-off. If the participant retrieves their consent, ensure that updates are synchronised with other systems.
EDC Integration	EDC (electronic data capture) is often the central location for collecting the participant data and historically also for consent status. ✓ Check for SOP requirements for all parties involved ✓ Make sure it is possible to configure the eConsent data to be connected to the clinical trial EDC ✓ Ensure maintenance of data privacy requirements
Obtain IRB/IEC approval of the eConsent	✓ The MHRA/FDA GCP Symposium 2020 suggests that the trial protocol should outline the following information: how the eICF is administered; how subjects access the eICF; what methods are used to obtain the subject's signature; how copies of eICF are provided to the subject; how amendments to the eICF are communicated to the subject; how the investigator/sub-investigator plans to assess the subject's understanding of the eICF ✓ Ideally the IRB/IEC would be able to review the eConsent in action but will often accept static screenshots for review, providing a portal link and video scripts may also be required ✓ Both a paper and eConsent should be submitted, as this also allows the paper version to be used if there is an issue with eConsent ✓ Some IRBs require paper printouts for archival purposes, check whether this is the case for sites ✓ Consider all information that is participant facing, such as privacy statements, user instructions for provisioned devices etc.

	Additional materials or formats may be required by specific IRB/IEC, so it is worth enquiring prior to submissions where possible
Device Provisioning	The devices used for the eConsent process can be either provisional devices from the site, or a BYOD (bring your own device) option may also be implemented, where the participant uses their own personal electronic device to review and sign the eICF. When deciding on the method consider the following points: ✓ BYOD allows the participant to easily integrate the informed consent process into their life, without the need to familiarise themselves with a new device ✓ For the site, implementing BYOD eConsent prevents some costs and storage burden that may be associated with managing and storing many devices on site ✓ BYOD avoids shipping delays and allows the trial to commence efficiently ✓ If the participant is utilising BYOD remotely, ensure the eConsent tool is adequately supported ✓ Some participants may require provisional devices if their personal device does not support eConsent ✓ Provisional devices can be recycled, but data privacy requirements must be carefully fulfilled. ✓ eConsent and other eClinical applications, such as ePRO, should ideally be run on the same device to allow the participant to control all the clinical trial elements with ease whether a provisional device or BYOD is used ✓ Ensure devices can be configured for study team with a local language keyboard
eConsent Implemented	✓ Consider following a staggered implementation based on IRB/IEC approvals ✓ Participants begin the informed consent process and subsequent enrolment ✓ Assess the progress through dashboards and reports ✓ Make sure monitors can access the informed consent data ✓ Remote monitoring will generate many benefits as problems can be identified quickly and accurately
Gather Feedback	From the site and the participant on the eConsent process, adapt the eICF according to the participant requirements based on the time spent per section data, the number of flagged items and the knowledge reviews to improve the informed consent process. Consider including focus groups or working with patient advocates to improve health literacy.
Amendments Handling	✓ Plan a mechanism to ensure amendment implementation is linked to IRB/IEC approval ✓ Create a back-up approach in case of any delays ✓ Ensure ability to trigger amendment handling on a country-by-country basis

eConsent Advances the Informed Consent Process

This section will outline what a typical informed consent process involves from the point of view of the sponsor, site study team and participant when using eConsent.
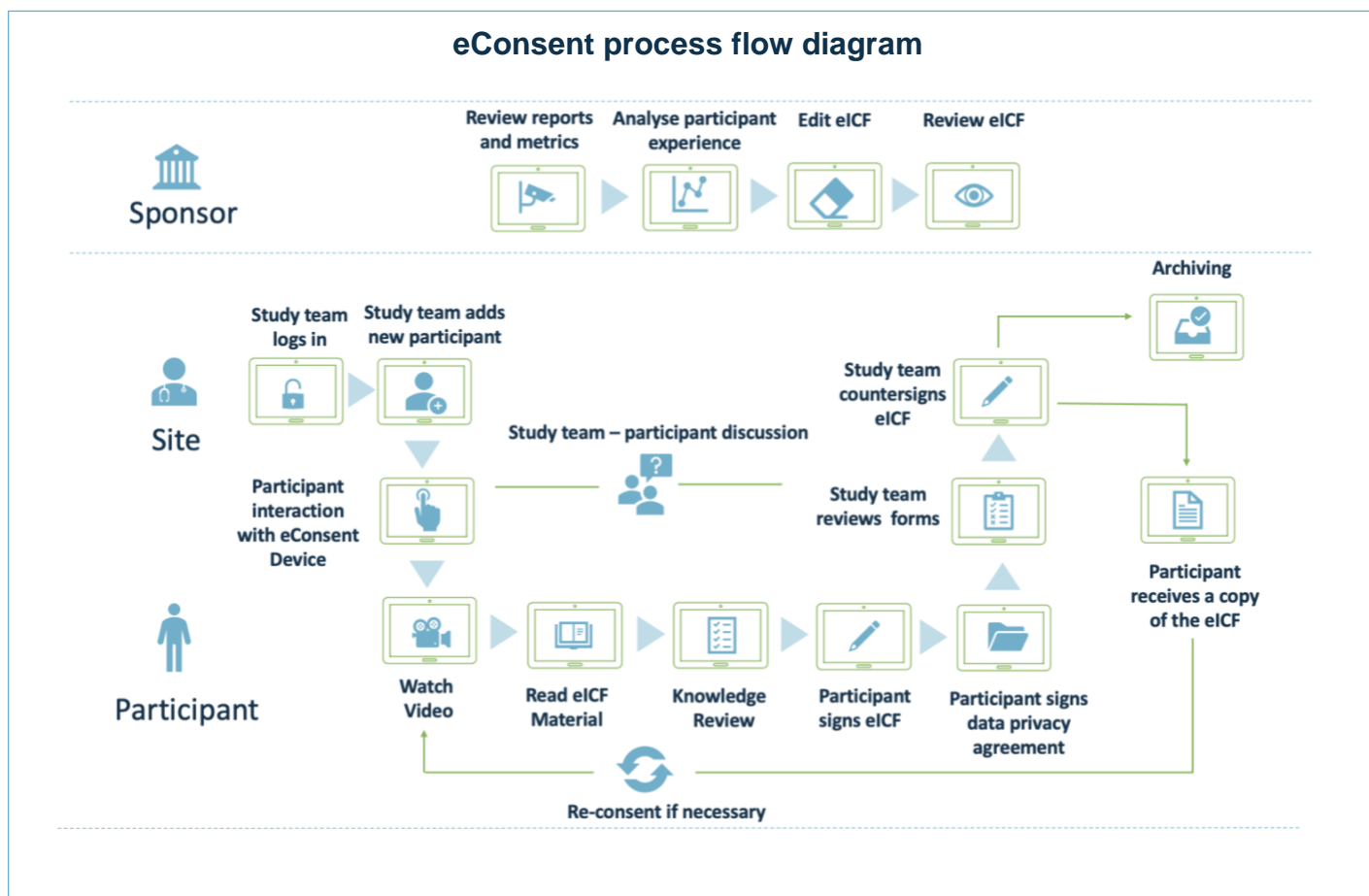

Figure 5: Typical eConsent Process Flow Diagram – summarises what the typical eConsent process may look like to the participant, site and sponsor, including the specific roles and activities within the eConsent process.

The Sponsor:

As per Figure 5, the sponsor is involved in implementing the eConsent solution, but in the process of carrying out the informed consent, the sponsor's main function is reviewing reports and metrics available and data gathering of how well the eConsent is working for the participant and site. eConsent allows for the collection and analysis of data points that were not previously available to sponsors, such as information about the way participants interact with the eICF, how much time they spend reviewing each section, identifying particular sections that may be leading to more questions and require additional clarification. These data points allow the sponsor to improve the eICF based on participant experience, which is a novel opportunity exclusive to eConsent. A further data capability unique to eConsent is real time reporting on enrolment numbers to enable the sponsor to gather early indication of recruitment issues.

The Site and Participant:

The study team logs in to the eConsent platform and adds a new participant to the system. The participant starts interacting with the eConsent device under the study team's guidance through the process. As the participant is progressing through the eICF video, multimedia and text components, any areas of uncertainty can be flagged up and addressed during the active discussion with the study team. eConsent preserves and facilitates the vital site team – participant interaction element, bringing the focus on any remaining questions that need to be clarified and ensuring the participant is well-informed of the trial requirements, main principles and risks. It is possible to remotely imitate the site process with a simple Q&A discussion, or with system enabled tools such as inline commenting, comments sections or other features of eConsent. Participant's understanding may be additionally confirmed by a knowledge review. After the participant decides to sign the eICF and the relevant data privacy agreements, the study team reviews all the documents and provides a countersignature. The participant receives copy of the signed eICF for their record. Regardless of the tool used, paper or electronic, the responsibility of storing participant consent information in a secure manner and safely securing any participant identifiable information is still the site's responsibility. The site archives the data and securely stores it in the system according to the relevant data archiving requirements. For specific details, refer to [24].

Re-consent

Re-consent may be required in certain cases, where the original informed consent provided by the participant is no longer valid due to changes in the protocol or the participant's condition. Some examples of such scenarios include changes in procedures, risks, potential benefits, or the worsening of the participant's condition. Re-consent aims to ensure that the trial participation remains consistent with the participant's interests. Re-consent principles and requirements are not dependent on the consent format, paper or electronic, thus standard procedures may be followed. An updated version of the eICF containing all the amendments is sent to the participant again, and the consent process is repeated (Figure 5) in an identical manner with the updated information. If the participant chooses to consent to and sign the updated eICF, the site countersigns and the trial participation continues.

Stakeholder Perspectives

This page showcases some of the thoughts on eConsent that other stakeholders have expressed following their personal experience with the implementation and use of eConsent. Please note that this is not an exhaustive list of all stakeholders involved in the informed consent process.

INSPECTOR & AUDITOR

Inspectors might observe improved compliance as a result of the document management and integrity controls, and easy system access for inspection purposes. eConsent offers an immutable audit trail, facilitating the auditing process.

PARTICIPANT	SPONSOR	SITE	MONITOR	ETHICS COMMITTEE
Technology has become the norm, and participants expect to be able to benefit from a similar level of convenience in the clinical trial informed consent process with a life-like and easily digestible information presentation.	Participants enrolled are more informed and qualified to participate in the trial, increasing participant retention rates and participant compliance, and hence data quality. The ability to access real time data analytics and incorporate amendments make for a dynamic system, empowering the sponsor to improve its processes and better adapt them to the participant's needs.	eConsent creates transparency, the ability to track consent and systematically update eICF versions, which results in reduced site burden and improved participant retention. eConsent supports the site in inspection readiness and a consequent reduction in the risk of non-compliance and increased quality overall.	The electronic audit trail of eConsent facilitates the process of compliance monitoring of the informed consent process, allowing for more time to be spent on valuable monitor work, such as engaging with the site staff to understand how the informed consent process is performed and perceived.	Motivation to publish a position statement was the fact that the tools and possibilities for electronic informed consent already exist, but the use is limited due to a lack of clear regulatory guidance. A bioethics professor says that there is no ethical opposition to eConsent and authorities should be finding ways to enable technology to move clinical trials forward.
✓ Technology expectations ✓ Life-like format ✓ Easy comprehension	✓ Improved data quality ✓ Access real time data ✓ Adapt to participant needs	✓ Transparency ✓ Reduced burden ✓ Inspection readiness ✓ Reduced risk of non-compliance	✓ Electronic audit trail facilitates process ✓ Allows to spend more time with site staff	✓ Technology exists with a lack of regulatory guidance ✓ Participant-site interaction preserved

Regulatory Acceptance

Data Security and Laws

The ICH E6 R2 Guideline for GCP provides the expectations and requirements for a computer system validation, data access control, as well as metadata and audit trails in clinical trials [2]. Consent forms contain personally identifiable information (PII), such as name, date of birth, signature and age. Europe has a complex plethora of regulations, directives and national laws around data privacy. For more details on the specific data security regulations to be aware of when implementing eConsent, refer to GDPR [25], HIPAA [26] and CFR [27]. GDPR applies to European countries and it addresses rights of the data subject, general obligations of controller and processor, and transfers of personal data internationally. In the context of consent within the GDPR regulation, it is emphasised that consent must be freely given, specific, informed, unambiguous and can be revoked [25].

Verifying participant identity using eConsent does not have to differ from the traditional paper consent process, as the face-to-face verification can be carried out on site as normal. eConsent can simply be used to facilitate the explanation of the clinical trial aspects to the prospective participant using the interactive participant education component. The electronic signature of the eICF, or the wet ink signature of the print-to-sign option can be obtained on site. In the case of remote eConsent, participants can be identified using real time audio and visual methods, such as an audio or video call with the study team. An advanced signature might be used where acceptable by the regulatory authorities. eConsent platforms will have a security system in place that ensures that signed documents cannot be altered. An electronic audit trail keeps a bulletproof record of all activities related to the informed consent process performed by the participant or on their behalf, as required by 21 CFR § 11 and ICH/GCP. These activities will include the date and time when the participant accessed the eICF, the record of the eSignature if applicable, as well as any record of further viewing, printing and email of the ICF documents. The informed consent records are only stored transiently on the eConsent device and are transmitted to a secure remote server and all the data is subsequently removed from the device.

To ensure data security, the design of eConsent should follow relevant laws and the study team should take a proactive approach to data protection, such as for example ensuring that updated anti-virus and anti-malware software is in place, and sponsors should prefer the use of eConsent platforms with embedded end-to-end encryption security. Location of the database and IT administrators should also follow any applicable regulations on data protection, such as the EU data protection 2016/679 regulations [30]. Importantly for international trials, data transfer across countries needs to be treated with due respect to all the applicable data privacy requirements.

Acceptance in Countries

Before clinical research is initiated, it is the responsibility of relevant competent institutional review boards or independent ethics committees to review the research protocol and informed consent documentation to ensure adequate electronic or paper informed consent procedures are established and implemented in an ethical way without endangering the rights, safety and well-being of the participants. Informed consent is governed by clear global and local regulations and guidelines, beginning with the Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects adopted by the World Medical Association as amended in 2013 and more fully developed through international and regional standards [31].

It is very typical for pharmaceutical companies to conduct multi-site and multi-country clinical trials. Markets can have their own in country laws which can add inefficiencies and delays to the drug development process. International Council for Harmonization, ICH, acts to standardise and harmonise guidelines for international use, allowing for clinical trial reporting and marketing applications to be submitted to regulatory agencies around the world in a consistent manner, avoiding duplicative processing and testing.

eConsent regulations still remain country-specific due to a lack of a unified position. Certain countries have published official position statements on the use of eConsent. If no specific guidance or position is formally available, seek guidance from engaging with the regulatory authority. Unless there is an official position or a response from a health authority confirming the acceptance of eConsent use in the specific country, implement paper consent instead.

In 2018, the UK MHRA and HRA published a joint statement [32] that sets out the legal and ethical requirements for seeking and documenting consent using electronic methods. This was the first official statement and position by a European country. Belgium has since also released an official regulatory guidance [33] on the use of eConsent in interventional clinical trials, outlining regulatory acceptance of eConsent. The FDA allows the use of eConsent and further details can be found in their guidance [34]. Singapore's HSA has recently released an updated guidance [35] on clinical trial conduct in response to the COVID-19 pandemic, where eConsent has been mentioned as an acceptable procedure. More countries are following this example, and official regulations are becoming clearer, allowing for eConsent implementation. It is vital to follow the country-specific regulations, which are subject to change. For the latest updates on the regulatory positions, contact info@eucrof.eu.

In light of the COVID-19 pandemic, the EMA has released guidance [36] on the management of clinical trials, where informed consent is addressed. The EMA outlines that in the case where a participant is unable to consent in person when in isolation, an alternative method of obtaining informed consent should be considered, such as oral consent in the presence of an impartial witness, who can sign the ICF on behalf of the participant. For re-consent purposes, the EMA proposes an oral re-consent with a supplemented confirmation via email. Importantly, the EMA confirms that any valid electronic methods of obtaining informed consent can still be used throughout the pandemic as long as they are permitted by the individual country legislation. eConsent brings the unique advantage of audit ability and immutability that alternatives do not provide.

In Summary

Overall, the above eConsent implementation guide has introduced the process of electronic informed consent and provided an outline of consideration points to guide through eConsent implementation planning. The participant-centric benefits of eConsent have been explained, as well as viewpoints from some other stakeholders. A breakdown of the most up-to date regulatory guidance was provided to facilitate the implementation to prepare for eConsent implementation.

In order to ensure that eConsent is able to make a change in the compliance monitoring activities, it is vital to ensure that regulatory authorities around the world set out clear guidance on the regulations surrounding the use of eConsent in clinical trials performed in their respective countries. This aim needs to become a priority of regulatory bodies to ensure that trials running in their nations can implement eConsent, and hence eliminate many inspection findings that arise due to the informed consent process non-compliance. ICH (E6) R3 is set out to address eConsent as "patient involvement, openness to eConsent, decentralised trials and the need for consent to be informative" should be incorporated into the new revision, which will be a great step forward towards global eConsent adoption [37]. eConsent provides an unprecedented opportunity to adapt to the changing times in an effective manner, without compromise to the trial process and efficiency. A unified approach to addressing novel technologies will allow nations to implement value-driving improvements to clinical trials, and ultimately improve the participant experience and facilitate healthcare progress.

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