medidata

WHITE PAPER

Electronic Informed Consent in Clinical Research

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Executive Summary

Medidata is conducting a study to understand the regulatory positions, adoption and the variability regarding electronic informed consent (eConsent) around the world. This exercise has come about due to the extensive number of regulatory relevant inquiries Medidata gets from sponsors and organizations managing trials in research. The life science industry is keen to have the option to leverage electronic means for consenting trial participants but are uncertain of the regulatory positions on the topic. The only way to seek clarity on this topic was to directly engage with relevant authorities.

The study initially focused on the countries in the European geographic region but has evolved to other regions including Asia Pacific and the Americas. The study prioritized countries where there was an aspiration to utilize electronic informed consent by organizations running clinical trials.

Throughout the study, Medidata has directly engaged with regulators, health authorities and ethics groups to assess the eConsent landscape. Overall, the Medidata study team has collected meaningful feedback and engaged in positive and encouraging dialogues with these organizations. However, almost half of the bodies Medidata contacted have not responded or did not fully respond to the question being asked. We deduce this may be due to a lack time to consider the topic and/or a lack of general position.

The patient-centric benefits of electronic informed consent technologies have been well documented.[1,2] The US Food and Drug Administration (FDA) provide non-binding recommendations[4] on the topic, and the US has seen accelerated adoption of eConsent solutions.

Subsequently, UK regulator, MHRA (Medicines and Healthcare Regulatory Agency) has also been exemplary in the thought leadership and guidance in terms of the interplay of eConsent and the consideration of the multiple EU regulations and UK laws[2].

The EU has seen variable eConsent adoption, mostly due to a lack of regulatory clarity and operational reasons. It is good to note that new EU eSystems/eSource guidance is being written to include electronic informed consent. In addition, the recent Regulatory Science Strategy issued by the EMA indicates an aspiration for oversight of decentralized trials, of which electronic consenting should be a key consideration.

This white paper is the first in a series to provide an overview of findings from the Medidata eConsent study as it progresses and as we gain further feedback from relevant bodies. This paper highlights the key themes that various bodies have so far communicated.

Introduction

INFORMED CONSENT GOVERNANCE

Informed consent is one of the most important and fundamental ethical aspects of biomedical clinical research, as it supports the right of participants to make their own decision whether to participate in clinical research.

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 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 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[5] and more fully developed through international standards such as ICH GCP E6 (R2)[6], US 21 CFR[7], US 45 CFR[8], HIPPAA[9], eIDAS[10] GDPR[11], EU Clinical Trial Directive[12] and its replacement, the new EU Clinical Regulation [13].

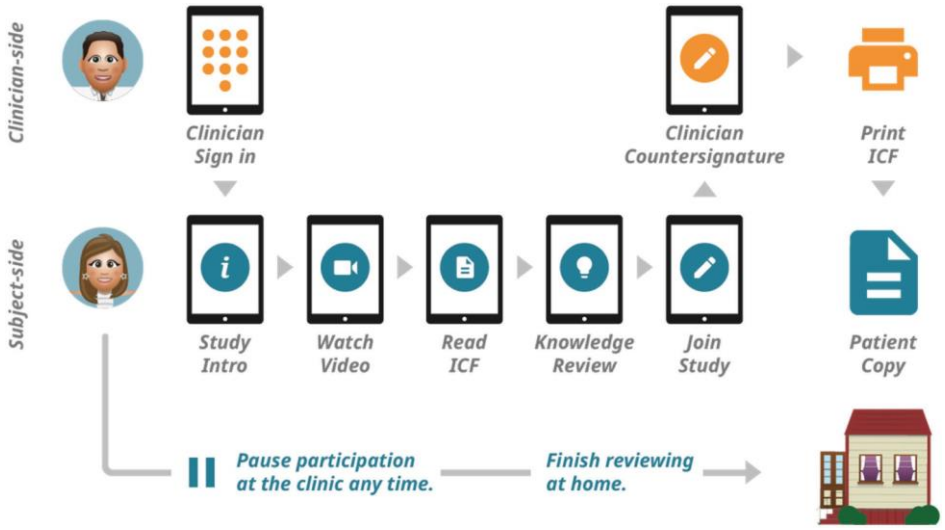
This study looks into the various interplay of regulations and laws to be considered at a regional and local level when implementing eConsent.

THE INFORMED CONSENT PROCESS

ICH 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. Informed consent is documented by means of a written, signed, and dated informed consent form."* [6]

Informed consent is not a single event related to a form that requires a signature. It entails an educational process that starts by informing a potential study participant and continues throughout the study. It requires disclosure of sufficient information to allow the participant to adequately comprehend the study and make a voluntary decision to take part.

Traditionally, the disclosure is made via a paper-based process. Information sheets are presented to the participant by an investigator face-to-face. Once the participant has been informed and educated on the trial, the participant agrees to take part in the study by signing a paper form.



BENEFITS OF ELECTRONIC INFORMED CONSENT

The MHRA defines the electronic informed consent process[2] as *"consisting of two distinct phases of educating and giving consent via a signature:*

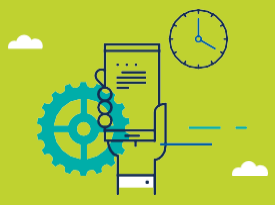
1. *'Electronic methods for seeking informed consent' and 'eConsent' refer to the use of any electronic media (such as text, graphics, audio, video, podcasts, or websites) to convey information related to the study.*

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

Electronic consent is gradually being adopted by sponsors and researchers, and some regulatory authorities are actively engaging and provisioning guidance on the topic. The electronic process can be used to augment or substitute traditional paper-based methods.

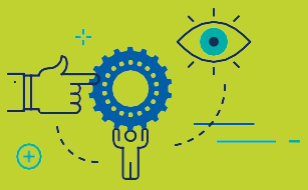
It is thought that information relayed via multimedia formats are preferred by participants[2] and that overall comprehension is greater in aiding the decision to become involved or not. The sponsor and investigator can use additional means to confirm the participant's comprehension, such as an assessment provided in the same electronic format. The assessment can highlight areas of uncertainty for the participant and information that should be repeated.

Using eConsent offers a number of potential benefits:



Reduces trips to the research site and allowing for remote interactions for the patient.

Reduces the pressure and anxiety of decision making at a site, as the documentation can be reviewed online at a participant's convenience and together with family members.



Augments the study participant's understanding of the clinical trial, allowing them to make more informed decisions.

Provides the opportunityto assess comprehension and reinforce participant understanding.

Provides an easy mechanism for feedback on the informed consent process and how consent materials could beimproved

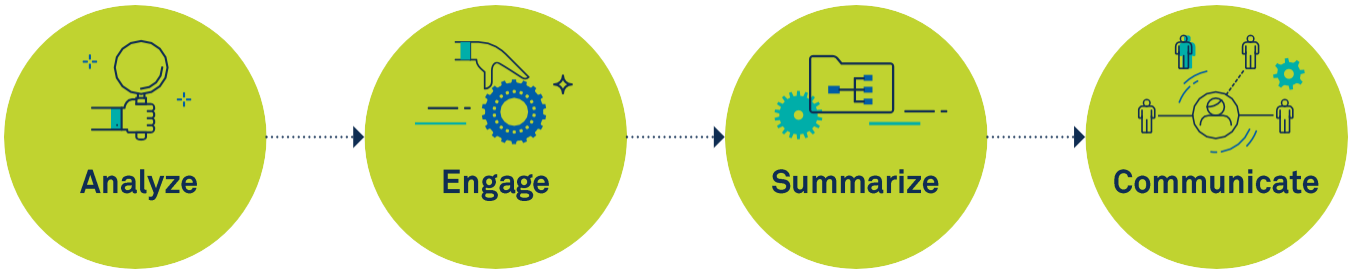
Improves the patient recruitment process and has the potential to reduce dropout rates. For research sites, there could be benefits for higher enrollments and engagement, as shown by various trials, including the US-Government-sponsored ADAPTABLE Trial Medidata is supporting

(see appendix 1).

Electronic Consent Study Methodology

MEDIDATA eCONSENT STUDY

Medidata initiated this study within Europe as a priority. To develop a robust understanding of the electronic consent landscape and common themes, Medidata adopted a four-stage methodology:



Analyze

Understand the current status and position ofeConsent adoption, countries, clients, partners, prioritization and review regulatory authority positions.

Engage

Engage Stakeholders Regulators and Ethics/IRB groups, starting with EU and expanding based on business needs.

Summarize

Define position of each market area. Where there is no position — collaborate on how to progress.

Communicate

Communicate findings to various interested stakeholders.

When there wasn't a conclusive formal statement about electronic consent on the relevant authority websites, Medidata engaged directly with various regulatory agencies, authorities and ethical committees. The question asked specifically focused on their position on:
(see appendix 2).

1. Using electronic methods to educate the trial participant.

2. Capturing an electronic signature.

It was clearly stated that this would be performed face to face with the investigator and trial participant instead of a virtual trial.

EU Regional eConsent Landscape

The first step was to contact the European Medicines Agency to confirm the regional European position. EMA provided very comprehensive information on the concerns with the use of electronic informed consent and confirmed there was no common position or harmonized guidance in the EU. They recommended to directly reach out to the relevant national health authorities and local privacy data protection authorities.

> **"Sponsors must seek input from Health Authorities and data privacy bodies when implementing eConsent in a country. Sponsors should therefore consider notification of Heath Authorities with regards to the use of eConsent, in addition to just gaining Ethics Committee approval, as they may bring different perspectives that otherwise may not come up until inspections."**
>
> European Medicines Agency

This approach was pursued, and in general the European region shows a degree of variability with regard to electronic consent, despite the harmonizing nature of key European regulations. Gradually over several months, a mix of responses were obtained and a picture of the landscape started to form. In many cases, the request for information was not always read accurately or it was assumed the participant was remotely signing. In addition, many answers were not definitive or conclusive.

> **"Consent must be given in writing."**
>
> EU Regulatory Body

Many answers came back referencing eIDAS[10], which notes if a electronic signature is used, it must be a qualified signature to ensure the verification of the trial participant. If the trial participant is face to face with the investigator then a qualified signature is not necessary, suggesting the respondents assumed the trials were virtual or remote.

> **"The informed consent document may be signed by an electronic signature as long as it meets the requirements for a qualified electronic signature set out in Article 3 (12) of Regulation (EU) No. 910/2014 of the European Parliament and of the Council."**
>
> EU Regulatory Body

High Level Findings

Along the way, Medidata has shared findings internally, with interested external parties and industry trade associations. The data coming back to us from the authorities indicated five common scenarios.

1

Full eConsent is permitted. So far, the only example is the UK.

2

The use of electronic methods for informing a trial participant is permitted, but the signature, if electronic, has to be a qualified signature. Poland is an example.

3

The use of electronic methods for informing a trial participant is permitted, but the signature has to be a handwritten wet signature on paper only. Austria is an example.

4

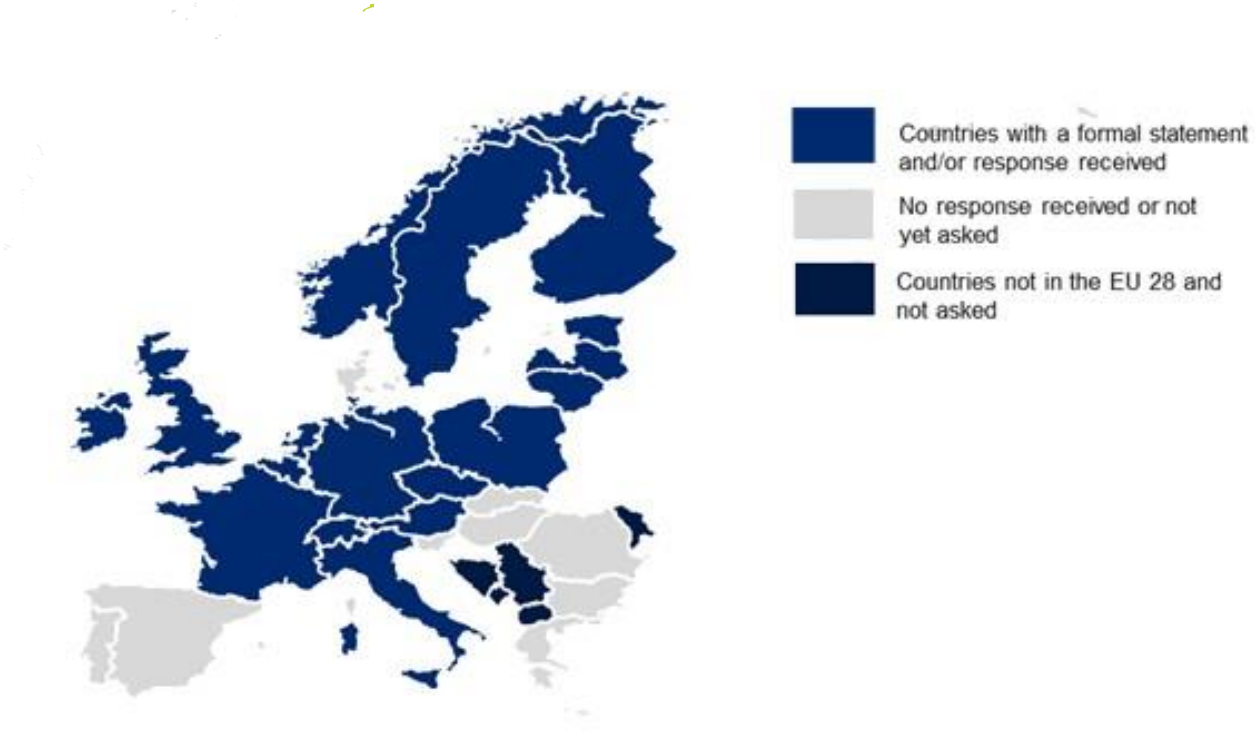
There was either no position and/or the position was pending EMA and inspector's working group guidance.

5

Pending a response or acknowledgement .

There was also a country scenario where the regulatory authority and the national ethics group were not aligned and the answers received differed.

The graphic below indicates the progress of the dialogues with the various local country authorities. The majority of countries have been contacted and around half have not responded or not responded in full to gain a definitive conclusion. With others, an active dialogue on topic is being progressed. Surprisingly, very few have formal written statements on the topic. UK and Switzerland were the only countries so far that we are aware of providing a comprehensive statement.



COMMON AUTHORITY CONCERNS

The common themes and concerns provided by the EU regulatory authorities fall into six main categories:

1. **Protection of patient data.** This is the responsibility of the investigator and should not go beyond the site. If such patient data does go beyond the site, is this under the management/oversight of the investigator or the sponsor?

2. **Sharing electronic consent data.** Only anonymized data should be shared with the sponsor.

3. **Regional and local data privacy laws.** Is the hosting of the patients' signature by a third party meeting European data privacy rules?

4. **Study participant verification.** How can it be ensured that the person electronically signing the ICF is the actual person participating in the clinical trial?

5. **Responsibilities and the investigator as process owner for the informed consent process.** How should the investigator qualify and supervise the third parties' personnel and computer system(s) used for the e-patient information according to the ICH E6 sections 4.2.5 and 4.2.6?

6. **Site burden.** eConsent may introduce site burden, which may limit the investigator's appetite for such technologies as they need to use multiple systems per trial.

The following section goes through each point in detail.

1. PROTECTION OF PATIENT DATA

"This is the responsibility of the investigator and should not go beyond the site. If such patient date goes go beyond the site, is this under the management/oversight of the investigator or the sponsor?"

PERSONALLY IDENTIFIABLE INFORMATION

Within the informed consent process, personally identifiable information (PII) collected from the participant is similar whether the process is paper or electronic-based. PII is any data that could potentially identify a specific individual. The data fields being considered as PII in the context of eConsent are first name, last name, signature, date of birth (dd.mm.yyyy or dd.mm), and age. Acknowledgment checkboxes or initials can be used to indicate that content has been read and understood. Within electronic informed consent solutions, metrics are also tracked relating to the subject's interaction with the application.

WHAT DOES ICH GCP SAY?

According to ICH GCP E6 (R2)[6], the investigator is obligated to:

- Maintain a confidential list of the names of all subjects participating in a trial

- Share only pseudonymized data with the sponsor

The investigator accomplishes patient confidentiality by assigning a unique identifier (also called a key-coded value), to each trial subject, which is used in lieu of the subject's name or any other directly identifying personal data when the investigator provides the sponsor with access to subject data.

Per ICH GCP E6 (R2)[6], the list of unique identifiers is never shared with the sponsor and remains under the control of the investigator. Personally identifiable fields are not shared with the sponsors, and access to a system is controlled based on user login. Only the investigator can directly re-identify a patient, and, if permissible by regulation and policy, the monitors may have this access.

Sponsors are blinded to patient name, signature and other identifying information. Only de-identified, pseudonymized data is shared with the sponsor.

Within the context of the European Clinical Trial Regulations, even though protection of patient data is part of the investigator's responsibilities, it is also a sponsor responsibility.[13]

HOW IT WORKS IN PRACTICE

Within the context of the Medidata eConsent solution, the sponsor never has login access to electronic consent data. Additionally, PII is never transferred from the electronic consent solution to the electronic data capture tool. Only de-identified or pseudonymized data is transferred.

In the typical scenario where a sponsor contracts with a third-party vendor to provide electronic consent technology, the appropriate procedural and data governance arrangements, with access and retention controls, are in place to ensure that participant confidentiality is protected. Where the sponsor is responsible for routine auditing, compliance checking and maintaining access controls oversight to the electronic consent system, the third-party vendor will be able to provide the appropriate certifications and documentation to the sponsor and site.

2. SHARING ELECTRONIC CONSENT DATA

"Only anonymized data should be shared with the sponsor."

In the context of eConsent, pseudonymized data is shared with the sponsor rather than anonymized data. What do we mean by pseudonymization? Under GDPR11 pseudonymous data refers to data from which identifiers in a set of information are replaced with artificial identifiers, or pseudonyms, that are held separately and subject to technical and organizational measures to ensure that the personal data are not attributed to an identifiable person.

As in the first point, the PII data is the responsibility of the investigator and should not go beyond the site. The investigating site maintains control and management of a confidential list of names of all subjects allocated to trial numbers upon enrolling in a trial. The investigator assigns a unique identifier to each trial subject to protect the subject's identity. It is used in stead of the subject's name when the investigator reports adverse events and other trial-related data. Only the investigator can re- identify the individual upon regulatory, scientific or ethical governance

3. REGIONAL AND LOCAL DATA PRIVACY LAWS

"Is the hosting of the patients' signature by a third party meeting European data privacy rules?"

Europe has a complex plethora of regulations, directives and national laws around data privacy. There is ongoing apprehension around the hosting of the patient's signature by a third party in accordance with European data privacy rules. The GDPR11 helps to harmonize and clarify the position around data protection and privacy requirements. GDPR11 has been incorporated into the local laws and implemented within each member state. In addition to GDPR11 requirements, there are also national laws that may supersede and impose additional restrictions at a sovereign level.

The hosting of the patient's signature by a third party meets EU data privacy requirements where:

- The third party is appointed by the investigator and is bound by a data processing agreement with the investigator that meets the requirements pursuant to Art. 28 GDPR11
- The third party also complies with the requirements of the eIDAS[10] regulation on electronic identification and trust services for electronic transactions in the internal market which may be applicable, i.e., based on the nature of the electronic signature used

The eIDAS Regulation allows for three different types of electronic signatures: basic, advanced and qualified. In the case of qualified electronic signatures, eIDAS requires the appointment of a trust service provider to create, verify, validate and preserve electronic signatures (Article 3 [16] and [19] eIDAS Regulation).[10]

An electronic consent technology provider complies with GDPR when it either enters into a direct data protection agreement with the investigator or where its contract with the sponsor is for the benefit of the investigator (in either case the technology provider's data protection agreements are as set forth in the GDPR).

HOW IT WORKS IN PRACTICE

At Medidata, direct data access is restricted to staff who are specifically trained to handle PII and protected health information (PHI). Log-monitoring and intrusion detection system appliances along with firewalls, are installed on the production network.

Controls for physical access at the hosting facility are well documented, audited and have multiple fail-safes. These controls are appropriate in their specific circumstances, and implement a reasonable and appropriate equivalent measure of intrusion detection and access logs. Electronic records and signatures have audit trails, as required by 21 CFR Part 117 and ICH GCP6 and all data in the database is audit trailed in compliance with FDA and ICH guidelines. All data provided through the sponsor web portal is pseudonymised and does not contain PII.

4. TRIAL PARTICIPANTVERIFICATION

"How can it be ensured that the person electronically signing the ICF is the actual person participating in the clinical trial?"

Many of the comments and questions received from EU regulators in the Medidata study pertain to the actual participant signing the form. Our request for information included a clarification that we are not referring to a virtual or remote participant but a scenario where the participant is face to face with the investigator staff so you could verify that the participant is who they say they are.

Regulatory Authority concerns include:

- How can it be ensured that the person electronically signing the ICF is the actual person participating in the clinical trial?
- Can the consent form be altered and compared?
- Can it be verified when the signature was applied?

HOW CAN IT BE ENSURED THAT THE PERSON ELECTRONICALLY SIGNING THE INFORMED CONSENT FORM IS THE ACTUAL PERSON PARTICIPATING IN THE CLINICAL TRIAL?

There are a number of common scenarios to consider when answering this question, and the response depends on the nature of the trial and the demographics. An electronic consent solution does not necessarily have to replace the paper-based methods of seeking informed consent but can supplement the existing process.

Electronic consent with the participant and investigator F2F. Typically and traditionally when using electronic consent, participants are provided information onsite via a face-to-face interview with someone on the site team. The entire eConsent process can be conducted at the study site, and the electronic consent technology assists the investigator in explaining the consent information to the subject. The study site is responsible for ensuring study personnel is available through the entire consent process to explain the material to the subject, provide clarification and answer questions. It is the responsibility of the investigator to confirm that all of the subject's questions have been answered, obtain the subject's signature and countersign the electronic consent. The site team verifies the electronic signature and the subject's identity.

- **Electronic consent via audio-visual methods.** When the informed consent is performed via real time audio or audio-visual methods, the interactive communication should allow for confirmation of the participant's identity, especially where the interview and the documentation of consent are carried out by electronic means.

- **Virtual electronic consent.** When it is not possible to verify that the participant is who they say they are through an official photo ID or other interactive mechanism, regulators in some EU countries may permit the use of an advanced or qualified electronic signature. An advanced electronic signature is uniquely linked to the signatory and capable of identifying the signatory. It allows the signatory to retain control and is linked to data within the signature that can detect any changes made. A qualified electronic signature is uniquely linked to the signatory and created by a qualified electronic signature device, which is based on a qualified certificate for electronic signatures.

In the UK, the MHRA/HRA Joint statement on Seeking Consent by Electronic Methods states:

"Whilst any type of electronic signature is admissible as court evidence by virtue of the 'eIDAS' Regulation, some are more reliable and carry greater evidential weight and assurance than others. For example, 'qualified' electronic signatures are automatically granted the legal effect of a handwritten signature with mutual recognition in EU member states (Art. 24 [2]) but may place a disproportionate burden on both the researcher and the participant and will not always be appropriate."[5]

CAN THE CONSENT FORM BE ALTERED AND COMPARED?

The signature should not be alterable and signatures can be compared. For example, the Medidata eConsent technology electronically captures the physical manifestation of the patient's handwritten signature for each form or document where a signature is required. The method used to capture and store the signature ensures that the captured signature cannot be altered, copied or reused in any fashion within the application. The signature is uniquely associated with a specific form, and each form can be printed out with the signature exactly as it was signed on the iPad. The signatures on the forms may also be viewed on a computer screen by site personnel. Each version of the documents may be viewed to compare signatures from one version to the next. The investigator is able to print a signed copy of each subject's consent form to be stored in their local files.

5. RESPONSIBILITIES: THE INVESTIGATOR AS PROCESS OWNER OF THE INFORMED CONSENT PROCESS

"How should the investigator qualify and supervise the third parties' personnel and computer system(s) used for the e-patient information according to the ICH E6 sections 4.2.5 and 4.2.6?"

Based on inspection metrics [14,15], there have been many findings around the division and delegation of tasks and responsibilities between the sponsor, investigator and third parties. As a result, ICH has added two new items to the guideline pertaining to the delegation of authority and training:

- 4.2.5. The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

- 4.2.6. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

These added provisions assist the investigator in understanding that delegation of tasks in a clinical trial goes hand-in-hand with ensuring adequate qualification to conduct delegated tasks as well as supervising the delegated individuals. Item 4.2.6. specifically requires the implementation of procedures to ensure the integrity of the trial-related duties and of any data that are generated during the trial. Investigators and their institutions should create appropriate (written) procedures to be followed by site personnel during the trial.

It is the sponsor who typically contracts with a third-party vendor for consent technology. If a solution is proposed to an investigator, it is the sponsor and third party who need to provide assurance that the process and technology are in line with ICH GCP and computer system validation compliance. They should also assure that the appropriate procedural and data governance arrangements are in place to ensure participant confidentiality is protected with appropriate access and retention controls to the technology.

Where the sponsor is responsible for routine auditing, compliance checking and maintaining access controls oversight to the eConsent system, the third-party vendor can provide the appropriate certifications and documentation to the sponsor and site.

After electronic signatures are captured, the investigator is able to print a signed and dated copy of the consent form to store locally in the investigator's files at the site. It would, therefore, be expected that the investigator would follow local record-keeping procedures to maintain copies of each subject's signed informed consent form.

6. SITE BURDEN

"eConsent may introduce site burden, which may limit the investigator's appetite for such technologies as they need to use multiple systems per trial."

The simultaneous adoption of multiple technologies to support operational site activities is a common topic in clinical research. Site burden needs to be analyzed in the context of the patient. Sponsors and CROs should review their technology footprint to help reduce the apparent burden. Discussions around site burden can often reveal an organization's ability or willingness to adapt to change and traditional ways of doing things and its awareness of future innovations.

A NEW ERA OF COLLABORATION AND INTEGRATION

Medidata believes that as an industry, we need to collaborate to develop a common set of requirements and standards on this topic. The relevant bodies should also align on a common standard of what is acceptable or where local laws add specificity then develop a statement similar to the MHRA[2] and Swiss Ethics Committee[19].

There needs to be developed more streamlined, simplified, integrated processes with an end-to-end unification of technologies moving away from siloed point solutions that are not interoperable. This approach will assist sites in reducing the amount of technology across their clinical trial process and allow them to focus on optimizing interactions with patients and increase patient engagement, patient retention and quality of clinical trials overall. Ultimately, this approach will result in an accelerated and more effective delivery of life-saving medicines to those in need.

Conclusion

The use of new technology solutions to conduct clinical trials will only continue to accelerate as researchers and sponsors seek to offer trial participants a better patient experience and to harness greater efficiencies in the drug development process. It has been well documented that existing technology solutions offer significant benefits.[5] eConsent enables potential research participants to make an informed decision via the convenience of a tablet, smartphone or other digital multimedia, and it enables their informed consent to be documented using electronic signatures. Electronic consent can supplement the traditional paper-based approach or, where appropriate, replace it.

This is a first in series of white papers looking at the topic of eConsenting in clinical trials focused on the European region. The full picture in Europe is still not totally clear, and this is attributable to responses still pending and/or that the clarity of position by a good proportion of the local authorities is outstanding.

It is very clear to see the countries that are more open to reviewing new advancements in new technologies. Respectfully, it is a complex topic, and one that needs to consider multiple regional and national clinical and data laws and the type of clinical trial. In general, among the responses we received, there were more concerns highlighted than a definitive position given.

Appendix 1: ADAPTABLE Virtualized Trial

The US-government sponsored Patient Centered Outcomes Research Institute (PCORI) is using a virtual trial platform to screen, consent, enroll and randomize 15,000 patients through an interactive web portal. A remote clinical team is following patients throughout the 30-month study, using the centralized platform for investigators and clinical staff to interact with patients and collect patient-reported outcomes, adverse events and demographic data.

Patients engage through BYOD technology using smart phones, tablets, laptops or computers.

https://www.adaptablepatient.com/en/auth/code
https://theaspirinstudy.org/

Table 1: ADAPTABLE Results

Clinical Trial Engagement	Industry Average	ADAPTABLE (as of Feb 2019)
Interested Parties	100%	27,441
Consenting Parties	**13%**	**13,246 (48.3%)**
Randomized Patients	9%	13,214 (48.2%)
Completed Studies	7%	Estimated >~35%

Appendix 2: Email communication to authorities

Dear X, please can you provide some advice and clarity on the use of electronic informed consent within Clinical Trials in X country?

For further context, I am referring to the use of electronic methods for seeking informal consent meaning:

1. The use of electronic media such as graphics, audio, video via an iPad to convey information related to the study.

2. Subsequently to then document the informed consent by an electronic signature via an electronic device such as a smartphone, tablet or computer.

Please note this would be all done face to face between investigator and volunteer within this context we don't refer to a virtual trial or participant that is remote.

Please could you provide your position and advice on parts 1 and 2. Please could you advise if I should consult with another authority/ethics committee in x country.

Thank you very much in advance for your acknowledgement and advice.

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