

# Engagement Shift: Informed Consent in the Digital Era

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Prior to a patient’s enrollment in a clinical trial, the prospective participant is often handed a document that is 15 to 25 pages long. Known as the informed consent form (ICF), the document is largely comprised of a combination of medical terminology and “legalese” that even members of the pharmaceutical community would have difficulty

comprehending in full. To further complicate matters, important information on the benefits, and risks of the clinical trial experience that patients are about to undergo is often only a small part of the document. This practice is outdated and is not consistent with current calls for increased patient engagement in the clinical trial process.

For many clinicians, informed consent is thought of as a signature on a document, but it should be a process that leads to greater understanding of what lies ahead for patients participating in a clinical trial. Though it took our industry 20 years to embrace electronic data capture (EDC), and at least 10 years to embrace electronic reported outcomes/electronic clinical outcome assessments (ePRO/eCOA), both now play an increasingly crucial role in new drug development. Electronic trial master files (eTMF) are also making significant gains. Still, even though “patient centricity” has become the new buzzword, our industry has not yet implemented an electronic informed consent (eIC) process that would benefit our patient partners in clinical trials.

The FDA published guidance on informed consent in 2014.<sup>1</sup> and followed up with guidance on eIC in 2015.<sup>2</sup> The guidance document defines eIC as using electronic systems and processes that may employ multiple electronic media to convey information related to the study and to obtain and document

informed consent. The general principles of each are similar to the following recommendations for obtaining patient agreement:

- Description of the clinical investigation
- Risks and discomforts of treatment
- Benefits of treatments
- Alternative procedures or treatments
- Confidentiality
- Compensation and medical treatment in the event of injury
- Contact information for questions
- Patient understanding that participation is voluntary
- The total number of patients in the study

In addition to the above, the patient should understand what will happen if the study, or their participation in the study, is terminated either involuntarily or voluntarily, and the patient must be made aware that new, unanticipated adverse events may occur during the course of the trial. Importantly, proof of comprehension is not a requirement. Consequently, information about whether the patient truly understands what they have signed can be sparse. This should be of great concern as informed consent is, by its intent, established to ensure that the patient is both freely participating in a process and making an informed decision based on a complete understanding of the benefits, risks and alternatives.

### **How effective is the current paper process?**

Although the current adoption rate for eIC has been slow both in clinical trials and in hospitals, there have been several studies conducted in medical centers proving the value of computer-assisted learning and consent that date back over 20 years.

Many studies have shown that most patients are unable to recall or do not understand most of the information that is presented to them in the informed consent process. In 2009, Finch et al. presented 100 patients scheduled for transurethral prostatectomies. When the patients were interviewed three hours after consent was obtained, less than 50% of them could accurately recall the risks or potential complications.<sup>3</sup> In another study, only 18% of guardians who provided consent for surgery in pediatric patients could recall the specifics of the procedure two to four weeks after the surgery.<sup>4</sup> Krupp et al. showed that 65% of patients who consented for neurosurgery were unable to remember more than two of six major risks associated with their surgery only two hours after informed consent was obtained.<sup>5</sup>

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In 2007, an article published in the American Heart Journal revealed that among 633 patients who were to undergo coronary artery bypass grafting or percutaneous coronary interventions, there was poor agreement between what patients expected as symptom benefits versus what they were told by their physicians. On the important outcome of mortality, there was no correlation between what physicians and patients expected because patients believed there would be an improvement in survival even when physicians did not describe this as a benefit.<sup>6</sup>

Cassileth et al.<sup>7</sup> had 200 cancer patients complete a test of their recall within one day of signing consent forms for chemotherapy, radiation therapy, or surgery. Only 60% understood the purpose and nature of the procedure, and only 55% correctly listed even one major risk or complication. Further, a mere 40% of the patients stated that they had read the form “carefully.” Although most thought that consent forms were necessary, comprehensible, and contained worthwhile information, the legalistic connotations of the forms appeared to lead to cursory reading and inadequate recall. In general, most believed that consent forms were primarily meant to “protect the physician’s rights.”<sup>7</sup>

Although these studies were conducted in a healthcare instead of a pharmaceutical clinical trial environment, it is reasonable to assume that the patients in each environment would be similar. Of greater concern is that a typical informed consent for a hospital procedure is generally one to three pages, but many clinical trial ICFs are 20 or more pages. Naturally, this significantly increases the problem of comprehension and retention.

In 2013, The Center for Information and Study on Clinical Research Participation (CISCRP) conducted a Perception and Insights Study that included 724 patients who had participated in clinical trials. Those that participated in North America were at least somewhat satisfied that their questions were answered with the current process—85% of the time.

However, approximately 33% of patients outside North America were dissatisfied in regard to the answering of their questions. Importantly, as an indicator of what is to come in the future, 28% of respondents ages 18 to 34 were not satisfied that their questions were answered. Younger generations are used to receiving a lot more information than their elders. As they continue to age, we can expect that the level of dissatisfaction with the current process will grow exponentially.

The same CISCRP study also measured the impact of dissatisfaction with the informed consent process on patient retention. The results of the study (see Table 1 below; click to enlarge) showed that patients who were not satisfied with or did not understand the informed consent process were much more likely to drop out of a trial than those that were satisfied with the process. As patient recruitment becomes more difficult and costly, it is essential to retain those patients that have entered a clinical trial. There is a substantial cost when a patient is lost after passing through the screening process, and the cost is even greater if they have also started treatment and undergone a significant amount of testing. Additionally, there is no potential benefit in regard to proving the primary endpoints needed for drug approval. Time is also lost as new patients now need to be recruited to fill the void.

Informed Consent Process: Retention Impact			
	OVERALL	DROPPED OUT, N=260	COMPLETED, N=1,326
It was "Somewhat/Very Difficult" to understand the ICF	19%	35%	16%
After reading the ICF, the purpose of the study was "Not Very/Not at all Clear"*	5%	14%	2%
"Not Very/Not at all Satisfied" questions were answered during IC review*	4%	12%	1%
I did not understand parts of the study after ICF review*	12%	21%	11%

\*Dropped Out vs. Completed significantly different at P<0.05

**Table 1.** The results of a CISCRP study measuring the effects of dissatisfaction with the informed consent process on patient retention.

## **What is the impact of the patient's native language?**

The importance of language on patient understanding of informed consent is often overlooked, especially if English is not the patient's native language and he or she is in an English speaking country. Patients who have a poor understanding of English are less likely to receive adequate informed consent. For example, when the charts of 74 Spanish- and Chinese-speaking patients who underwent thoracentesis, paracentesis, or lumbar puncture at a hospital with well-trained interpreters in Spanish and Chinese were compared with those of 74 English speakers, only 28% of foreign language-speaking patients had well documented informed consent, versus 53% of the English speakers.<sup>8</sup>

## **The value of video educational tools**

Trials of video educational tools have shown greater patient understanding. For example, a randomized controlled trial of an informational video for women considering laparoscopic tubal ligation showed that women who watched the video, in addition to standard consent procedures, demonstrated 56% higher knowledge scores than women who were engaged in standard consent procedures alone ( $p < 0.001$ ).<sup>8</sup>

In another example, English- and Spanish-speaking patients receiving intravenous contrast for computed tomography who viewed a video in their preferred language showed 20% higher knowledge and 10% higher satisfaction scores than those who did not watch the video. This result was consistent for Spanish and English speakers. Importantly, Spanish and English speakers in the video group had similar post-consent knowledge scores while Spanish speakers in the non-video group had significantly lower scores than English-speaking controls.

In 2013, Rowbotham et al.<sup>9</sup> completed a research study with a presentation of the same information using paper versus an iPad device. Among patients (n = 55), iPad subjects had significantly higher test scores than standard paper consent subjects (mean correct = 75% vs 58%,  $p < .001$ ). The total time spent reviewing the paper consent was 13.2 minutes, significantly less than the average of 22.7 minutes total on the three components to be reviewed using the iPad (introductory video, interactive quiz, consent form). Overall, the study demonstrated that combining multimedia videos, interactive assessment questions, and standard consent language on a tablet-based system improved comprehension of research study procedures and risks.

### **What is the electronic informed consent process?**

Electronic informed consent can be obtained at clinical sites via a computer or tablet (preferred) or can be obtained over the web as long as the user provides sufficient information that the person signing the document is actually the patient. If the information for consent is obtained via the web and the patient still has questions, the site clinician needs to have a procedure in place to ensure that the patient's questions are answered before the form is signed. The process should begin with a secure login by the site staff or by the patient if consent will be obtained remotely. User groups should be defined, by role, to determine their access to information. The patient can then watch videos that will explain the clinical trial process and contain the elements described earlier that should be required of the informed consent process. During or after the video segment, patients may be asked questions to assess their retention of the information imparted. To reinforce the learning process, any incorrect answers a patient may provide should be visually corrected on screen, showing them the correct answer. Once the video and assessment questions are complete, the patient will then have access to a digital screen copy of the ICF for review.

Tablets provide an additional opportunity to use built-in dictionary functionality on the device to allow patients to look up definitions of terms used within the ICF. Patients can note and record any questions they have to discuss with the investigator. The patient or site should be able to print the consent form at any time. Upon completion of the process, a digital signature can be obtained for the patient and/or guardian, the investigator, and a witness. The entire process will be entered and recorded in an audit trail.

## **Why use electronic informed consent versus paper?**

The eICF process allows for improved patient engagement and understanding from the outset of the clinical trial process. The interaction with the site is enhanced by using a system that enables patients to self-educate in their native language and prompts them to ask questions. At the same time, institutional review board (IRB) and independent ethics committee (IEC) review is enhanced by allowing them to review the script of the patient video alongside the ICF via a web-based portal. They can also possess a greater certainty that all sites will communicate the needed information in a consistent manner.

Sponsors can monitor regulatory issues by viewing a complete audit trail, which will show precisely when patients viewed the information, how long they took to review the video and the ICF, what additional questions they had, and their degree of retention of the information given. This process also allows for adjustments to the videos and/or ICF if a large number of patients are unable to answer certain assessment questions correctly. Importantly, it is currently difficult to monitor what version of an ICF a patient has signed if the study has protocol amendments containing adverse events that were not previously noted.

eICF systems can be used to notify both the clinical sites and the patients for follow-up in these situations. Finally, from a site monitoring standpoint, digitally stored documents are easily stored and easy to review via a web portal. The benefits just mentioned are outlined in Table 2 below (click to enlarge).

<b>Paper vs. Electronic Informed Consent</b>		
	<b>PAPER INFORMED CONSENT</b>	<b>ELECTRONIC INFORMED CONSENT</b>
<b>Patient-site interaction</b>	Patient is given a form to sign and site personnel are responsible for ensuring that patient understands the ICF and answers all questions	Patient engages in an interactive process with videos, retention questions, and dictionary definitions. Site personnel answer questions that are prompted by the patient within the software application. Patient's retention of information is documented
<b>Patient comprehension</b>	Limited due to extent of documents and medical and legal terminology	Enhanced due to video assistance in native language and layman's terms
<b>Multiple languages</b>	Studies show that many paper translations are not up to par	Video augmentation of the process with high quality translations
<b>Fraud protection</b>	Complete reliance on the paper document	Complete audit trail showing when all parties signed the document
<b>IRB and EC review</b>	Multiple circulating paper copies varying by IRB/EC and by country	Standardized process with web portal for review
<b>Site consistency</b>	Process varies considerably from site to site	Standardized process at all sites
<b>Storage, access, and site monitoring</b>	Cumbersome review of charts and paper	All forms and data are easily accessible via a secure web portal
<b>Version control and new signatures for protocol amendments</b>	Poorly done with paper, with a significant number of patients not receiving updated safety information	Strict version control with notifications to sites and patients when a form is updated and requires a signature
<b>Source:</b> Litwin		
<b>Table 2.</b> Comparing the advantages of electronic informed consent approaches over paper across several categories.		

## Challenges to the adoption of eIC

As has been the case with most new technology, the greatest challenges to adoption are inertia and cost. As paper has served the purpose of obtaining consent, and it is viewed as easy and inexpensive, the challenge is convincing sponsors that there is a significant enough benefit to outweigh the additional expense and learning curve of adopting a new technology. This can be difficult as the costs of paper processes are often not well quantified. Studies with few patients and multiple languages can result in considerable additional cost primarily due to the fees for translation and voice-over of the videos produced. Larger studies with fewer languages can be much more cost efficient.

Several pharmaceutical sponsors view the eIC as part of their patient recruitment process, especially for rare diseases where a consistent well-

scripted message can lead to increased enrollment as well as retention. In these cases, cost justification is easier with the value proposition becoming part of the decision-making process of the clinical team.

Finally, there is still concern about IRB and, particularly, EC adoption of both the educational videos and the eICF forms. There are certainly individual reviewers who are still not completely comfortable with this process but, in general, we have found most IRBs and ECs to be very receptive, as they recognize that this method is well controlled and that the message received by patients is standardized.

## **Conclusions**

Patient engagement in clinical trials should start at the beginning and continue throughout. The best way to start a process that is patient-centric is to ensure that the patient is fully aware of what her or she is signing up for. Many studies conducted in the healthcare and clinical trial setting have shown that we are currently falling short when it comes to providing our patients with the information they need to truly give informed consent. Providing patients with video educational tools and retention aids that explain information in layman's terms and in their native language improves both patient recall and comprehension.

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eICF has been used worldwide and is accepted by IRBs and ECs, but the overall adoption rate has been slow. The regulatory safeguards for documentation and re-consenting, the ease of use for ICF approval on a local level, and the benefits to the patient will hopefully move the ICF from being one of the last remaining bastions of the paper process into the modern digital era.

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