



Vilnius
University

VILNIUS UNIVERSITY
FACULTY OF MEDICINE

Centre for Health Ethics, Law and History
Institute of Health Sciences

Elizabeth Thoppil, 2019, group 10

INTEGRATED STUDY MASTER'S THESIS
***Informedness of Patients Participating in Clinical Research. Analysis of Tools
Used to Evaluate the Understanding of Clinical Trials Information***

Supervisor

Dr. Asist. Asta Čekanauskaitė

Head of the department

Prof. Dr. Eugenijus Gefenas

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elizabeth.thoppil@mf.stud.vu.lt

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1. ABBREVIATIONS

Abbreviations	Full Term
AI	Artificial intelligence
FDA	Food and Drug Administration Governing body of drug safety in the United States of America
FK	Flesh-Kincaid reading grade level A readability by grade level formula
FRES	Flesch reading ease score A readability formula
GPT	Generative Pre-trained Transformer How an artificial intelligence comes to its conclusions
GF	Gunning Fog A readability formula
IBM	International Business Machines
ICH	International Council for Harmonization
LLM	Language Learning Model
SMOG	Simple Measure of Gobbledygo A readability formula
SD	Standard Deviation
WHO	World Health Organization

Keywords: Clinical Trials, Reading Comprehension, Informed Consent, Research Ethics

2. SUMMARY

Informed consent is an important part of human research. It is important participants fully understand what they are getting into before joining a trial. Additionally, they should also know what rights they are entitled to.

In this thesis multimedia tools, artificial intelligence, leaflets and other paper aids were compared to see how well they inform patients on the topic of informed consent in clinical research. Analyzing and identifying the need to improve of traditional informed consent forms. Complications that can complicate informed consent. How clinical trial recruitment faces similar challenges that relate to informed consent forms.

Multiple articles related to the topic of informed consent forms in human subjects were analyzed to see if the traditional informed consent form is lacking and if there are viable alternatives. Articles covered many regions but were all published in the English language. The artificial intelligence ChatGPT 4 was used solely to define its function. The results found that the use of artificial intelligence chatbots in improving informedness of patients understanding of clinical trials appears to be the most promising. AI search engines also helped streamline the recruitment process. Examining multimedia tools found them to be a promising second place. Leaflets and other paper aids proved to not differ significantly compared to the traditional informed consent forms. A lack of understanding of informed consent can hamper patient enrollment. Minors require special considerations depending on their age, but they should receive at least some method of providing informed consent. Research in emergency situations tended to operate under an 'act now ask questions later' environment as everything is too time sensitive to put proper informed consent into action.

3. INTRODUCTION

There are many attempts at universal guidelines that safeguard human research. For example, the Helsinki declaration, International Ethical Guidelines for Health-related Research Involving Humans and the International Council for Harmonization's Guidelines for Good Clinical Practice. They all advocate for the process of informed consent and offer advice for delicate situations where the informed consent process is hampered. (1-3)

However, it all comes at odds with how patients are able to understand them. Their uniformity of informed consent forms comes at the risk of lacking relevance to the researcher being undertaken. (4) There is also a trend of informed consent forms increasing in reading levels. The recommended reading level of informed consent forms is that of the 8th grade, but research shows that the average

is at 11th grade. (5) As a result, supplemental tools are now more important than ever to help fill in the gap of knowledge.

The aim of this thesis is to evaluate different types of tools that researchers use to improve informedness of patients who participate in clinical research. It will also analyze the traditional informed consent form against them. The three methods chosen were multimedia tools, artificial intelligence (AI), leaflets and other paper aids. They were chosen due to their prevalence or novelty in the field. AI in this context refers mainly to the use of chatbots and search engines in the way the average person understands them. In practice, they are technically the same thing as modern chatbot can be used to search for information, though they can be less precise as an algorithm deliberately designed for the task.

The research focuses on the following objectives:

1. To compare different types of tools that researchers use to improve informedness of patients who participate in clinical research (multimedia tools, AI, leaflets and other paper aids).
2. To indicate issues that can complicate the informed consent form and recruitment process.

The strengths and weaknesses of each tool will be based on the experiences of researchers and patients who have used them. Additionally, their use in dealing with informed consent of minors will also be covered in its own overarching section. The main goal of evaluation is to see how they can improve the readability and ultimately informedness of patients. Other factors such as ease of implementation and cost will also be considered, but it is not the main goal of this thesis. Claiming that one is objectively better than the others will ignore the nuances involved in providing informedness.

The perspectives of researchers, patients and other parties interested in joining the clinical trials will be looked at. The reason for this is because these events have shared problems and similar needs.

Possible improvements will also be provided from either discussions that the relevant parties have had or based off of points that were found during research.

4. LITERATURE SEARCH STRATEGY

When checking a patient's informedness it is important to have a baseline of their basic language comprehension. Unfortunately, there is no universal baseline of how to measure such a thing. Even something as simple as trying to see how reading levels are measured can give a wide list of results in just America alone. Add other English-speaking countries to the mix and suddenly trying to determine what is the best way to measure English comprehension will become a thesis topic in

itself. Not to mention the fact that some of the papers used in this thesis are English translations making direct comparisons on even more difficult to determine since every language is unique.

As a result, the thesis will use each researchers' discretion on how they came to the conclusion of whether or not the patient was adequately informed. Most of whom measured this by use of questionnaires or interviews with the patients sometime after the consent form was signed. It will mean that this thesis is more susceptible to bias, but the aim of this thesis is more related to the patients' final understanding of what they are getting into. Checking if a patient understands a specific topic thoroughly enough to give informed consent is far easier than checking their language comprehension abilities as a whole.

Articles used also discussed at least one aspect of a clinical trial in relation to informed consent, including the requirement process. Articles used include systemic reviews, prospective studies, qualitative study, and mixed methodology study. The full article must be accessible in English and published after 2014. Three main databases were used Connected Papers, PubMed, and Google Scholar. Connect Papers was used first, resulting in many duplicates noticed on the other databases. The duplicates were omitted. The phrases "Tools Used Evaluate Understanding of Clinical Trials Information", "Reading Comprehension Patients Participating in Clinical Research", "What is a informed consent form", "AI improving informed consent forms for clinical trials", "Videos used for informed consent in clinical trials" and "Informed consent for clinical research in emergency situations" were used to search through them. Additional papers were found on PubMed by the 'Similar articles' feature and references, and on Connected Papers' graph feature.

Some information was searched for on Google to provide explanations of terms which needed a more in-depth explanation from a non-medical angle. Chat GPT 4, an AI, was used to define what an AI chatbot is. No further use of AI was used in this paper.

5. READABILITY OF INFORMED CONSENT FORM

An informed consent form in the context of clinical research is a legal document meant to protect patient autonomy in a clinical trial. (5) It is important to acknowledge that each country's requirement about regulating this varies. That said, they adhere to this core idea of protecting patient autonomy.

Some countries, such as the United States of America, have laws requiring to informed consent forms to provide clear and concise information in a way to promote comprehension. Yet, the guidelines themselves fail to provide any information on how to achieve this. (5) In comparison, the ICH gives the example of using simple language, avoiding unnecessary volume and complexity. (4)

And lastly there are countries like the Republic of Korea (South Korea) which makes no comment on the simplicity of the form itself, only what absolutely needs to be included. (6)

The readability of informed consent forms is important for the concept of informed consent. Informed consent is made up of three basic principles; that the patient is adequately informed, competent and is not acting under coercion. Researchers have both an ethical and legal obligation to provide informed consent. (7) Informed consent forms provide an easy way for researchers to fulfil their duty. (4)

A well written informed consent form is able to cover all the basis of informed consent. First, researchers must make sure the patient is adequately informed about the clinical trial. This means the patient is able to understand that clinical trials are not the same as treatment. Secondly, it can act as a filter to determine a patient's clinical competency. Patients must be able to express their capacity to choose to participate in clinical trials. (5)

Last but not least, it can show if a patient is being coerced. For example, a healthy patient may be pressured by their family to take part in a clinical drug trial in order to bring in more money for the household. Alternatively, a patient with a rare disease might be pressured to join a research study since it is hard to find individuals with their condition. (8)

Patients, especially those from collectivist societies, could also be coerced into staying involved by the researchers. That is why informed consent forms must make it very clear that patients have the right to withdraw at any point of the trial and should encourage them to speak up if something is making it difficult for them to leave. If not, then the patient will not be able to practice full bodily autonomy. (8)

On the other hand, a recent multinational trial studying the timing of starting antiretroviral therapy in HIV+ adults consisting of nearly 4300 patients compared concise and standard informed consent forms against each other. The groups did not differ significantly in independent factors such as education, gender and age. The end result suggested that altering language did not improve comprehension or patient satisfaction. (9)

In an analysis of how informed consent forms present the risks and benefits of clinical trials by experts, researchers found that they were more in favor of using supplemental material to enhance the experience for patients. They did not find much value in 'take-it-home' material, however. They also noted that patients reading aloud the form to patients may have benefited those whose reading level's they were unsure of. Though, they noted that by doing so the patient may disengage. They found that discussions and summaries of each section were other common strategies. (10)

5.1 TRENDS OF INCREASING READING LEVELS AND LENGTH

Over the years the reading levels of informed consent forms have increased. The ideal reading level is between 6th to 8th grade. However, in a survey of over one hundred consent forms, the mean reading level was Grade 11.6. A common failure of informed consent in clinical trials is that it makes the patient believe that they have signed up for treatment rather than treatment. (8)

A review of 26 informed consent forms, representing nine disease groups taken from large tertiary academic cancer center found that none reviewed were under an 8th grade level. Similar to the first paper, using the Flesh-Kincaid reading grade was 11.2. The average Flesh reading ease was rated as “fairly difficult”, at 50.7. It was calculated that the average words used per sentence was 18-20. They came to the conclusion that the overall reading level was still high at a 10th grade level. (11)

In another study conducted in Center for Research and Training in Skin Diseases and Leprosy, Tehran, Iran, on informed consent forms found that the mean \pm SD Flesch reading ease score (FRES) was 31.96 ± 5.62 . This would place them firmly in the difficult range. (5) They were also measured using the FK formula with the mean \pm SD grade level was calculated as 10.71 ± 1.8 (8.23–14.09). Using the Gunning fog index it was 14.64 ± 1.22 (12.67–18.27). These results indicate that they are at the 11th grade reading level. Granted this study was conducted on Persian material, which is a language that does not have a formula to measure its readability, something the researchers themselves noted. (5)

A different study evaluating informed consent forms in British Columbia, Canada, regarding breast and gastrointestinal cancer research the median length and word count of main and optional informed consent forms were 16 and 6 pages and 6183 and 1862 words. According to them, main informed consent forms increased at a rate of 1 page and 364 words per year over a 15-year period ($p < 0.001$). It was also found that the more recent of the trial were more likely to have optional informed consent forms ($p < 0.001$) and that those with industry funding were also longer ($p = 0.006$). (11)

Ironically, optional informed consent forms, which are made to provide supplemental information to the main informed consent form, were generally more difficult to read. Comparing FRES, optional were at 48.3 with the main at 50.0 ($p = 0.024$). FK was similar, optional at 11.8 and main at 11.1 ($p < 0.001$). (12)

In terms of length, one systemic review found that they have increased 10-fold between 1987 to 2010. They ironically concluded that patient understanding was inverted to the number of pages used. They also noted the effects of other variables on informed consent. (13)

In general, short forms are just as effective as long forms at informing potential participants about their involvement in a study. (14)

One explanation for the trend is that researchers are worried about litigation. As unfortunate as that is, the fear of being sued is a common one. (8,10) Researchers expressed that they recognized the need to simplify language but expressed concerns about not meeting the legal requirements. (10)

There is also pressure to protect the institutions and other stakeholders. The result is that the informed consent forms taken on a more contractual legalese rather than normal everyday language. (8) Additionally, the content matter of informed consent forms can be broken down into 29% study methods, 20% risks, and 11% confidentiality occupied, making it 60% of the paper in total. (12) These features generally cover the most important aspects of informed consent so it makes sense why they would be the most intensive.

What is interesting is that another paper found that researchers reported formatting 42% as key information and 63% in plain language in their key information sections for patients with Alzheimer's disease. Formatting to clarify, is a synonym of structure. The way the paper was designed, such the amount of white space between words, is what it ultimately refers to here. (15) There is also disagreement about what does and does not make good formatting. Some researchers insisted on adding precise numbers and statistics to informed consent forms. Others thought it was better to use it as supplemental material and a verbal descriptor should be added to explain them. On the other hand, other researchers believe that numbers should not be used during the consent encounter. (10)

5.2 SIMPLIFICATION OF LANGUAGE

It is consistently advised that researchers use simplified language when designing informed consent forms. Some basic strategies are to avoid legal/medical jargon and focus more on simplistic alternative word choices when possible. Using shorter sentences and simplified writing structures will also improve reading comprehension. (2,11,13)

Despite that developing an adequate informed consent form at 8th grade reading levels may not be feasible. Since the nature of an informed consent form is both an ethical and legal requirement in many areas, some terms cannot be altered. For example, the recreational drug marijuana has many names that can vary across regions. These include hash, weed, kush, Mary Jane, etc. If the informed consent form needs to be reviewed for whatever reason, using only a street name can appear nonsensical to the reviewer and can lead to confusion as to what substance the researchers were investigating. Thus, it would be important for the researchers to write the widely accepted name written into their country's legal framework in most places where the drug is being discussed in the

paper. That said, they should also have a section that lists the many street names for the drug to prevent confusion amongst the patients. Additionally, it is unclear what exact methods should be used to raise comprehension in order to compensate for such language. (8,16)

AI tools, such as ChatGPT 4, have showed promising results in lowering the reading levels of informed consent forms for oncological research down to 6th to 9th grade reading levels, but more research is needed. (17) As informed consent is such a complex concept any changes implemented need to show consistent objective success. Every failed attempt can mean more money spent during research, less patients enrolling and more time wasted by researchers in vain.

Additionally, many researchers strongly emphasize the importance of oral discussions in the informed consenting process. The discussions can improve patient's active decision making. The background of the patients themselves also plays an important role in how effective these methods can be.

Improving health literacy of patients has also shown to improve comprehension, but that is not the main topic of this thesis. (2,16) Efforts are made to better accommodate these special population groups, like children. (16)

5.3 LACK OF UNIVERSAL STANDARDS

Lack of universal standards was directly sighted by researchers as an issue in the informed consent process. For example, when discussing risks, it is unclear which rare risks are relevant or not. (10) In medicine there is a general rule of thumb to not add unnecessary stress to patients. This clashes with the world of contract law, that is hyper fixated on preventing lawsuits. Informing a patient that even something as begin as getting their blood drawn can kill them is often considered over doing it. However, in the event that the patient does die because of getting their blood drawn the patient's estate can use that lack of disclosure as a means to seek compensation. Granted, if such a hypothetical occurs it is most likely medical malpractice, but it only strengthens the estate's claim against the doctor, nurse or institution.

Each country also has their own standards of what non-medical information is or is not needed to be disclosed in an informed consent form. For example, South Korea lists the contents of the informed consent document that must be included according to the Korean Good Clinical Practice, Article 7. It lists twenty pieces of information that must be made clear to patients. (6) Conversely, Ireland's Health Service Executive has only very recently called for the creation of a national guideline for human research.(18) Of course, being a member of the European Union, the current standards would have defaulted to decisions of the European Commission which does have a standard of disclosure. (19)

These closely match the information needed in the World Health Organization's 'Informed Consent Form Template for Clinical Studies'. As well as the Institutional Review Board's versions.

However, the Korean Good Clinical Practice requires the disclosure of the number of patients prior to

starting, while in the EU this data must be disclosed afterwards. The World Health Organization and the Institutional Review Board make no comment on this topic. (6,19-21)

These minor differences, such as the number of patients may, seem trivial but can have interesting cultural or personal implications when expounded on the topic of enrollment. If patients know prior that a breast cancer study of only has ten patients, they may feel less confident in what they are doing. However, if they know that a study of Hutchinson-Gilford Progeria Syndrome has ten patients they may feel more inclined to join as it is a rare disease.

Lack of universal standards also influences what kind of human research can be conducted in the first place. For example, human cloning is a well-known topic of contention amongst ethics boards. The practice is outright banned in Ireland but in the United Kingdom it can be done provided it is not for reproduction. (22) Medical researchers are navigating a legal midfield of what they can or cannot do. Thus, if they are foreign to the country they may accidentally follow the standards of their homeland over the host country leading to a clash of ethical and legal ideals. Which if not caught, violates the informed consent of the patients because they are taking part in a study that is illegal in their country.

Global Oncology Patient Insight Panels, a patient advocacy group, was given the opportunity to work with researchers review, edit and advise informed consent forms for company clinical trials to improve understanding. They reviewed draft informed consent forms and then completed a questionnaire regarding its readability, content, and formatting, or provided open-ended feedback. (23)

They found 5 main themes. First, make the documents easy to read. Simplify the word choice and use visuals. Second, be sociable. Clearly communicate the executive summary or table of logistical, financial, and patient reported outcomes requirements. Third, be transparent. Provide the background of the treatment, list the personnel involved, explain the privacy policies, and what should happen if the patient is no longer eligible for the trial. Fourth, use supplemental material to improve understanding. Finally, give instructions to the investigator/trial team presenting the informed consent form. The points they raised provide an interesting perspective to informed consent forms, but they also align with changes FDA proposed. (23)

Another issue is that not every language has means to calculate readability, such as Persian.² Unless someone makes a universal formula, researchers will have to rely on their own digression to make the informed consent forms easily readable. Adopting preexisting scales from other languages comes at its own risks.

Culture can also play apart, as even if the readability can be calculated if there is a culture of poor literacy, under the 6th grade reading level, then simplifying them will be in vain. It was very

revealed that 54% of American adults have literacy below the 6th grade reading level, with 20% under the 5th grade reading level. Not to mention, 21% of American adults were deemed illiterate.²⁴ It is also estimated that 7.1 million people (16% of adults) living in England have very poor literacy according to the National Literacy Trust. (25) That means even if the informed consent form was able to meet current guidelines, there will still be quite a lot of adults who are unable to understand them.

It is also important to ensure that the language used in the informed consent form is one the patient is familiar with. For example, some countries have multiple official languages, such as Wales. Researchers might write the informed consent form perfectly in English but could be seeking patients in a Welsh speaking region. Translating the form into Welsh may drastically alter the readability of it, making it harder for patients to comprehend it. Though when conducting the translation process, it is better to not do so literally and instead focus on comprehension from the participants' perspective. (26)

There is also the question of whether or not literacy level truly influences a patient's understanding of research details. According to a study conducted in sub-Saharan Africa, literacy had little effect. According to the participants, the more personable aspects of discussing informed consent provided the most information. For example, they held group sessions with the patients before then holding one-on-one meetings. They deemed that a detailed questions and answers format was agreed to be the best method to facilitate comprehension. (27)

Another study proposed that excluding individuals from low to mid-income countries from controlled human infection studies in the name of informed consent is also baseless. They called for the changes of the informed consent process to be less reliant on literacy. Like the pervious study, human sociability was the key point they highlighted. (28) Working with local communities can also help with this process. (26,28)

Afterall, literacy is not the be all end all of intelligence or competency. One should never assume that the inability to read makes a person an idiot. The very concept of written language has only recently become a widespread phenomenon, with some languages today still not having a writing system. For example, the Pirahã Language not only lacks a writing system, but also numbers and most colors. Yet they are able to work with researchers who wish to study their culture just fine. As this is technically human research, they would have to undergone the informed consent process. (29)

That said, for those who can read it is still important not to make everything overly complex for them. Even if they do have the understanding of a twelfth grader, it is a well-known phenomenon

that when faced with a wall of text, people tend to not read things thoroughly. Think about the terms and conditions when buying something online. It is estimated that only one-two out of every thousand users even bother to access the end-user license agreement, and those who do read very little. (30)

6.1 THE INFORMEDNESS OF TRADITIONAL INFORMED CONSENT FORMS

Of the studies found that evaluated alternative means all of them drew comparison against the traditional informed consent form. For good reason. As they are the oldest method of providing informed consent. As a result, there is an expectation that most studies conducted will have implemented them at some point. Especially in the modern era where they have become both a legal and ethical requirement for research to be conducted on human subjects.

That said, they are only a means of presenting this information. As long as the information is adequately given, and the participant fully understands the requirements of informed consent, then they do not necessarily need to exist as they are. Additionally, many have attempted to simplify or have called for simplification of the informed consent form as there are concerns that they are inadequate at fulfilling their role. (13,16)

Definition

Traditional informed consent forms in this context are text-based documents that cover the topics needed to provide informed consent. It must cover all the legal requirements outlined by the country and institution the clinical trial is a part of. Optionally, they can include figures or tables, but this is not the norm.

There are many possible templates of clinical consent forms. Some are especially tailored to deal with certain types of research. Regardless, the contents must relate to clinical trial being conducted. The form itself can be presented digital or physically printed out.

Strengths

The wide variety of templates can make it easier for researchers to write one. It ensures that they do not forget any points they are required to cover. The use of templates also reduces the costs to make them. Accessing an appropriate template online is also quite easy. Multiple respected medical bodies have templates available to download for free. (20,21)

If researchers feel daring enough to write one themselves. All they need is access to some type of word processing software. While templates are useful, by doing it themselves researchers may be more inclined to better format them. Some may even go as far as supplementing their form by

adding tables and figures. Though it is important to note that while formatting is not the main topic of this thesis, it is still important to acknowledge.

One can also argue that they are effective because they have been around for a long time. It is also easier to compare different informed consent forms against each other since it is required for a clinical trial to be conducted. As there is a constant call to reform the informed consent form instead of outright replacing it shows that the concept itself is not the problem, but the execution of the informed consent form is.

As for the other obvious strengths, an informed consent form can be considered as a type of legally binding contract. Typically, these forms also have a section where participants or their representatives are also required to sign/stamp the form as proof of consent alongside the researchers or institutions. As they need to be signed by both the patient and authorizer tracking down who participated and who approved of the participation is made clear. (20,21)

Ergo, in the event that something goes wrong, the compensation process, or in the worst-case scenario the litigation process, can go smoothly. The IRB even makes an additional note that these papers should be stored for at least five years after the study by researchers. (21)

Weaknesses

The weaknesses are heavily dependent on the way the content itself is presented and less so on the informed consent form. That includes word choice, formatting and font. As emphasized across this thesis, informed consent forms consistently fail to meet the established standards of being between a 6th and 8th grade reading level.

Despite the many calls to make them shorter, it is still important to remember that they have a role to cover all aspects of informed consent in detail. When it comes to the more technical aspects of what exactly is going on in the trial, simplification can lose the nuance.

For example, a speaking book can get away with not using a generic drug name that can be given during the trial and may instead opt to use the drug class throughout it to help prevent confusion for the patient. Due to the legal aspects of informed consent forms, they cannot get away with never listing technical jargon.

Consider the phrase ‘painkillers’. It might not be very precise, but it is certainly used more colloquially than the word ‘paracetamol’. Even if the patient does regularly say the word in conversation ‘paracetamol’ one must admit that it is harder to read and spell, which can increase complexity.

Caution should also be taken to avoid the time sunk fallacy. While it is true that they are the oldest means of providing informed consent, that does not necessarily mean that they are the best. Traditional informed consent forms have lower satisfaction amongst patients compared to other supplemental means. Multimedia methods in particular were shown to consistently have a higher satisfaction amongst patients.

While not discussed in detail here, patients also tend to prefer more social interaction with the researchers when going through the informed consent process. (27) Complexity of informed consent forms can stop doctors from even bothering to discuss clinical trials in detail. If they even bother to scout for one, they might be tempted to leave the patient with an informed consent form to read and not do anything to facilitate open conversation. This is especially something to look for if the doctor is a clinician instead of a researcher, which means they are less invested in the trial. (14)

6.2 THE INFORMEDNESS OF MULTIMEDIA TOOLS

In theory, multimedia tools might improve the informed consent process. As informed consent forms often contain technical language, it can be difficult for the layperson to understand. (31) For the sake of consistency, audiovisual websites, interactive videos even in person events with activities would be considered as multimedia tools.

Definition

A presentation or series of presentations that actively engage the viewer while they are watching or immediately after. For example, a website that prevents patients from progressing through the presentation unless they perform a short task related to it. (32) Alternatively, it can be conducted in person so the patient can watch a live presentation and are engaged throughout. Though such a method is rather rudimentary and difficult to organize.

Strengths

In a study the informed consent process of multiple different studies, found that patients who watched videos had statistically significant better understanding scores compared to those that went through the standard consent form process, 4.4% difference between; $p = 0.02$. Due to the way the study was conducted, patients had time for open ended questions after the video/ form. Patients who watched the video scored significantly higher in this section (difference 6.3%, 95% CI: 1.6 to 10.9%, $p = 0.008$). Patients had higher satisfaction for video over the standard form (difference -6.9, 95% CI: -10.8 to -2.1, $p < 0.01$; lower scaled scores represent greater satisfaction). (33)

Caregivers who completed an interactive multimedia web-based video consent and those who filled conventional informed consent forms did not show a difference. However, it was found to be superior at 20 weeks after the study (mean -2.20, 95% CI -3.9 to -0.5). (34)

In a study to determine if video-assisted informed consent improved recruitment into a clinical trial about resuscitation of extremely preterm infants, it was found that 95% of women asked felt that the study was explained to them well or extremely well. They were also able to answer five knowledge questions about the study correctly 63 to 98%. 56% of the women offered the video chose to watch it. (35)

Another benefit is that patients can rewatch the presentation at any time. Patients and researchers also do not need to be in the same area to conduct it. To ensure cyber security, the video can be on a website that requires an account to access. There is also the possibility to easily test understanding by integrating questions directly into it. (36)

A different study on sexually active homosexual men on the topic of their risk and preventive behaviors for HIV, found that professional video consent and staff video consent increased comprehension compared to those who did standard consent. There was a score increase=1.79; 95% CI 1.02-2.55 for professional video consent and a score increase=1.79; 95% CI 0.99-2.59 for staff video consent. It was theorized that the reason for the increase in comprehension was because the patients spent more time engaging with the subject matter when watching the videos. Median time for professional video was 115 seconds, staff video was 117 and standard consent was 37 seconds. (37)

In a study of Swiss prisoners comparing audiovisual and standard paper-based material for informed consent in prison research also suggests that audiovisual tools improve understanding. Understanding was significantly higher for adults who engaged in audiovisual material. 4.61 for traditional and 5.09 for audiovisual means. However, it seems in the juvenile age group there is no significant difference. 6.02 and 6.31 for traditional and audiovisual respectively. (38)

Interestingly, juvenile detainees were more likely to sign the consent form after engaging with the audiovisual material, whereas the likelihood of an adult signing didn't change with what he was presented. It was advised that audiovisual material be given to adolescents as a result. (38)

Another study compared an interactive digital program to traditional paper format for a childhood cancer trial. The digital presentation was made for an iPad. It was a series of slides that were read through automatically. The presentation only progressed once the slide was finished. Patients were required to complete five interactive exercises to advance. Each exercise used corrective feedback

to inform the patients of their mistakes. The paper method did not include any exercises, but was written to a 7th-8th grade reading level according to the Flesch-Kincaid reading formula. (32)

148 parents and 135 children were given a pretest to check their familiarity on the topics of clinical trials, participation, protocol, randomization, placebo, blinding, double-blinding, effectiveness, and informed consent. They were then randomly split into groups to determine if they would do a paper or digital multimedia presentation. Unlike the Swiss study, there was no significant difference between the adult participants, but there was between the children. (32)

The pre and post-test understanding of parents using traditional paper bases methods saw a jump from 7.67 to 12.71. Those that used the presentation had results jump from 7.90 to 13.34. Children that used the paper method pre-test was 3.97 and post-test was 8.85. The children who used the presentation saw a jump from 3.76 to 11.65. (32)

They also noted that children in the 8th grade (12-13-year-olds) or higher had a better understanding than those in lower grades, but it was only significant for those who used the interactive digital program (10.3 (4.2) vs 6.96 (3.3), 0–18 scale, $p < 0.01$). (32) Participants also noted that they were more in favor of using multimedia methods compared to traditional paper-based ones. (16,32)

In terms of live presentations, the in-person aspect of it did significantly improve understanding. However, adding supplemental slideshows or theater performance did not. It is important to note that this is an understudied technique, and it was deployed in Tanzania. (39) However, it supports other findings that patients do benefit from the more sociable aspects of the informed consent process that other African studies noted. (26,28)

Weaknesses

As patients can do it at home, there is a chance that they can disengage from the program without anyone noticing causing them to provide consent without fully understanding what they are getting into. Doing at home can also increase the risk of fraud if the website does not have a means to ensure proper identification of the participant. (9)

Another issue with web-based multimedia is that someone can use it as a ‘Trojan Horse’ to install malware or gain sensitivity patient data. Even the more cautious of patients might not be as vigilant when dealing with a website like this since they would naturally be more trusting of it. Thus, if the website suddenly asks them to install software they might do so without question. Especially if the malicious actors prompt the participant to do so for the sake of ensuring smooth operation or claim that it is required to proceed.

One must also consider what to do with all of these digital records. Data security must be extra vigilant as these groups are often amongst some of the most vulnerable of the general population. (9,13)

For example, in India, it is a legal requirement that the faces and voices of patients and investigators or designees are clearly recorded. While there is an emphasis on confidentiality, the recordings are to be archived for a minimum of 5 years. Being recorded can also make patients more hesitant to enroll if they learn it is part of the informed consent process. (9)

While this would reduce the chance of fraud, making the records loses the convenience of doing this in the first place (remote connection). This can make it more expensive than making a webpage. These methods can be referred to as 'dummy'. The term 'dummy' in this context is often used to refer to devices or methods that do not require a connection to work. It is the opposite of 'smart' which typically refers to devices that can wirelessly connect to other devices. A DVD player for example can be called a 'dummy' device since it connects to a television using a cable. Casting a video onto a television requires two 'smart' devices as the television must be able to accept the wireless connection and the device that is casting must also be able to wirelessly connect to the television.

The main issue with using 'dummy' devices is that they are becoming obsolete. What is the use of making a CD or DVD and mailing it out to prospective participants if most the participants do not have access to a disk drive? It does not make sense in this day and age when most people in general have a means of accessing a smart device such as a computer or smartphone.

On the other hand, even if the tools themselves at the event are digital, there is significantly less security risk to the patients as they are not using their own devices. Researchers can also make sure that they are adequately engaged throughout the entire process and can provide live feedback.

Another angle to consider is techno-illiteracy. While techno-illiteracy is decreasing, if researchers rely too heavily on technology to ensure informed consent it can alienate those who are not techno-literate. Someone with little to no understanding of how to use a computer or smart phone might not know how to proceed in giving informed consent when they would have otherwise if it was done traditionally on paper. (16)

Multimedia tools also require more financial commitment compared to traditional informed consent forms. (16) For example, if researchers wish to make a dedicated website, they will need to consider the cost to maintain the web pages and to host its servers. If they do not have programming skills, they will also need to hire a dedicated web designer which can be another cost and avenue of security risks since they are bringing in non-medical personnel into the project. Of course, the web

designer will be under as much scrutiny as medical staff but typically they lack the knowledge on how to handle this data, requiring more money to train them on that.

Additionally, these methods are inconsistent when it comes to demonstrating a significant difference amongst the adult and children's populations. (16) One possible explanation for the dramatic differences between the studies is how varied the patients' groups are and the dramatically different circumstances they are going through. The healthy prison population in Switzerland is not the same as parents and their children who have cancer in Michigan, nor are they the same as homosexual men being survived on their behaviors in regard to their risk of developing HIV. It is also important to note that children are required to understand less of the process than adults, which can also help explain the discrepancy amongst ages. (32,38)

However, an additional study in India found that video-supplemented consent was not superior to traditional methods. Though they sighted that patients with limited education, mental health or substance use problems, would still require more research to be sure in those groups. (40)

Thus, the use of multimedia is extremely dependent of patient groups. Those who value data security and older participants may want to stick to other methods of supplementing informed consent. Meanwhile, those who value satisfaction and younger patient groups may want to focus on using some form of multimedia tool. These rules are not set in stone, as shown by the Swiss study, but can help lead researchers in the right direction.

6.3 THE INFORMEDNESS OF ARTIFICIAL INTELLIGENCE

The use of AI in writing informed consent forms is limited. Unfortunately, researching this topic has only yielded very minimal results. That said, the inclusion of AI was left in as it is still a new technology. Like Pandora's Box of Legend, the flood gates of AI technology on a consumer level have opened. It would be naïve to assume that researchers would not take advantage of it too, especially when the convenience aspect of it makes it very appealing.

Definition

As this technology is still emerging, it would be fitting to allow an AI to explain what it is. When asked the phrase: "Please describe what you are and your function as an AI Chat Bot.", ChatGPT 4 (41) responded as followed: "I'm an AI chatbot built on OpenAI's GPT-4 technology, designed to engage in natural and informative conversations. My function is to assist with a wide range of tasks, from answering questions to providing advice, generating creative content, or helping with problem-solving. Here are a few things I can do: 1. Answering Questions: I can provide information on a variety of topics, from science and technology to history, culture, and more. 2. Assisting with

Writing: Whether it's writing essays, stories, emails, or brainstorming ideas, I can help with creative or formal writing. 3. Providing Recommendations: I can suggest books, movies, restaurants, or even travel destinations based on your preferences. 4. Helping with Learning: I can explain complex concepts in simpler terms, tutor on different subjects, and provide learning resources. 5.

Collaborating on Projects: If you're working on a project, I can assist in brainstorming, offering feedback, or generating code if needed. In short, my main role is to make your experience smoother, whether you need information, assistance, or even just a friendly conversation! How can I assist you today?"

How ChatGPT 4 described itself matches the common colloquialism of what an AI chatbot is amongst most technology enthusiasts. That said, it failed to provide additional context that AI chatbots are a subsection of Large Language Models (LLM). To quote computer giant IBM (42) "LLMs are designed to understand and generate text like a human, in addition to other forms of content, based on the vast amount of data used to train them. They have the ability to infer from context, generate coherent and contextually relevant responses, translate to languages other than English, summarize text, answer questions (general conversation and FAQs) and even assist in creative writing or code generation tasks."

Strengths

In the paper, "Improving clinical trial consent form readability through artificial intelligence" Kazunaru et al. (17) used ChatGPT 4 to simplify seventy informed consent forms of past oncological clinical trials. ChatGPT 4 was able to analyze sixty-six of them. The results of its work provided mean reading levels of 6.2, 8.6, and 9.2 based on FK, Gunning Fog (GF) and Simple Measure of Gobbledygook (SMOG) indices respectively. Fifty-four of the initial clinical forms that were as able to be analyzed by FK, GF and SMOG. The respective mean text reading levels were 7.9, 9.3, and 10.5. These shows that ChatGPT 4 was able to significantly lower readability.

ChatGPT 4's more intensive cousin, GPT-4, a LLM, was able to use information provided by ClinicalTrials.gov to create direct summarizations and sequential summarizations of informed consent forms. The researchers were even able to have GPT-4 create a multiple-choice test to gauge patient understanding. The results found the AI-generated summary improved readability, with sequential summarization yielding higher accuracy and completeness. The multiple-choice tests were harmonious with human-annotated responses. More than 80% of surveyed patients reported enhanced understanding of broadband trials. (43)

Another study using a different LLM, Mistral 8x22B, was able to generate informed content forms comparable to human made ones. No significant differences in accuracy and completeness were

noted ($P>.10$). However, in readability ($P=0.26$), understanding ($P=0.02$) and actionability ($P=0.01$) of key information superiority of AI. (45)

It is particularly interesting to note that when asked about its function, ChatGPT 4 made a point that it was able to assist in the writing process. It also states that it can provide information on science and facilitate brainstorming. (41) Thus, in theory, ChatGPT 4 has all capabilities needed to write an informed consent form from scratch.

Weaknesses

The lack of research into the use of AI chatbots leaves in an ethical grey area in terms of appropriateness for use. Additionally, one must consider the overwhelming number of potential biases that could have occurred considering only one paper was found to have used it to simplify the language used in researched based informed consent forms. While the researchers were not sponsored, that does not mean they might not have had other motives. (17)

Shi et al. (45) also only evaluated four papers, yet determined that LLM was perfect at actionability, but humans were not. The limited nature of this study makes it too small to make any wide-reaching assumptions but it shows that there is potential.

Simplification of language, which is something AI has done for years, might not even be worth it in the end. A randomized trial of concise and standard informed consent forms found no significant difference between comprehension. (9) Considering the environmental impact of running an AI, justifying that waste of power only to speed up the process can weigh heavy on those with eco conscious minds. Though, one can argue that the time saved can be spent elsewhere in the research process.

One scary thought, that is well known amongst AI enthusiasts is the so called ‘AI Hallucination’. (43) This is when AI derails and creates completely false information. Typically, this is a result of an AI learning off an AI generated data to create a response. Poisoning the data set with misinformation will also produce similar results. While there are instances where users deliberately want the AI to hallucinate for comedic or artistic purposes, in the context of human research the danger cannot be understated. If a human does not catch these errors, it can cause serious harm to patients.

Even if the AI is fed correct information, the results might not be accurate. An infamous case of this happened very recently in the United Kingdom. Apple’s AI-generated news summaries were absurd as best and blatantly misleading at worst. (44)

One example of Apple's AI failure summarized a quote from Gisele Pelicot, a victim of a mass rape trial, so badly that it called her the UK's youngest knife murder who defends her conviction when her sentence increased. Pelicot not a knife murder nor is she British. Her quote was "for my children and grandchildren" in the context as to why she came to court in the first place.

The failure to summarize properly Pelicot, is a perfect example of an AI hallucination in action. Knife crime is a hot button topic in Britain, and she appeared in court talking about children. As a result, the AI used these topics to imagine a situation where she is a young knife murderer. Since AI works in this context by skimming over the text, it did not properly read the full article, hence the offensive results. It is safe to say that the feature was so bad that Apple had to roll it back. (44)

Additionally, comparisons of LLM and human output mean score informed consent forms did not show a significant difference when it comes to conveying the study purpose (LLM 2.88, Human 2.63), duration and procedures (LLM 2.5, Human 2.38), risks and discomforts (LLM 2.63, Human 2.38), benefits (LLM 3.0, Human 2.57), alternatives (LLM & Human 2.75) and overall impressions (LLM 2.63, Human 2.31). (45)

One can then infer that using this technology is ultimately pointless. While it can be convenient to use AI, we are not at the point where it can completely replace humans. Additionally, due to the limited research in this topic there is still a long way to go before its worth is conclusively determined.

6.4 THE INFORMEDNESS OF LEAFLETS AND OTHER PAPER AIDS

Leaflets, brochures, and pamphlets are very popular tools used to give basic summary of informed consent. Other paper-based aids are Speaking Books, which are similar to leaflets by come with an attached speaker that reads the content of each page aloud. Frequently asked questions (FAQ) take a similar approach but focus more on feedback from others. Ideally, these aids are short.

In theory these tools are able to aid the patients by informing them of the content of the full informed consent form in a concise manner. As the long length of clinical consent forms can be intimidating to perspective participants it could potentially stop them enrolling. Additionally, doctors are not found of the length either. (14) Alternatively, the length promotes laziness, meaning the patient signs the form without properly reading the content.

Definition

Patient information leaflets are designed to give a basic overview of the contents of an informed consent form in this context. Other tools supplementary that summarize informed consent forms to improve patient's understanding are Speaking Books.

A Speaking Book is an illustrated book designed to improve a patient's knowledge of what a clinical trial is, how they are conducted, and the patient's rights and responsibilities in the trial. The Speaking Book had 16 pages, each with a button corresponding on a sound device allowing the text to be read aloud in English. Each monologue lasts less than a minute describing one topic in regard to participation in a clinical trial. (46)

Frequently asked questions in this context are a collection of questions that researchers gathered that related to informed consent. They are used to predictively answer questions patients have about the topic.

Strengths

Patient information leaflets are meant to give a basic overview of informed consent. As they have a long history in clinical research it can be argued that they are used for a reason. A good pamphlet is also short, well formatted, uses concise language and makes use of images and figures. It is also advised that health care professionals have good communication with the perspective participants prior to giving these materials. Ultimately the strengths of patient information leaflets are similar to those of a good, informed consent form. (25,47)

Comparing the knowledge test scores of speaking books against traditional methods showed significant differences. The means of knowledge traditional methods was 76.5%, but the Speaking Book was 71.7%. However, they did a second trial where the traditional was at 79.2% and the Speaking Book was at 83.3%. The only variable between trials was the initial allocation of the groups. There was no association between knowledge change and other variables such as demographic characteristics, educational level, or previous exposure to clinical trials. (46)

FAQs showed no perceived benefit compared to the traditional informed consent form. (37) However, research of FAQs is quite scarce. Additionally, given the amount of data available evaluating informed consent forms, creating more improved and robust FAQs can become easier for researchers to put together. They can also work closely with patient advocacy groups to gather feedback directly for research that focuses on specific diseases. This is particularly relevant as patients value how the clinical trials relate their conditions. (48)

Weaknesses

Contrary to using speaking books, the use of leaflets as they exist now do not seem to improve patient understanding. They have similar weaknesses of traditional informed consent forms. For example, an evaluation of COVID-19 vaccine trials found the mean word count of s was 8333

words (average reading time of 35–48 min) and that the language complexity was high. (25) For context, that is almost as many words as this paper.

An additional study of 154 patient information leaflets and their accompanying informed consent form, found that not a single one was at the mean reading age of <12 years old. Only 7.1% were deemed to be in ‘Plain English’, but the majority at 51.3% were ‘Difficult. 40.3% were ‘Fairly Difficult’, and the remaining 1.3% were ‘Very Difficult’. (47)

Considering that these leaflets are typically small booklets, it is rather impressive that this can happen. Regardless, they have ironically missed the point as to why such material is supposed to exist in the first place. Instead of giving a basic overview of informed consent forms, these pamphlets are seemingly trying to replace them. One possible explanation could once again boil down to fear of litigation. However patient information leaflets are not designed to be legally binding contracts. Patients and researchers do not sign them or seal them with stamps of approval, making them even more null and void in the court of law.

Things like leaflets and speaking books also qualify more as ‘take-it-home’ material than something a patient would go through with a doctor. Considering that some researchers already have reservations about giving copies of the actual informed consent form home, there might not be much value in having these materials to begin with. Some have compared it to giving the patient homework. (10) At the very least, the leaflet certainly has a lot of work to do in order to prove its worth the paper it is printed on.

That said, it was found that patients with speaking books shared them with an average of 8 other members of their household. This can help inform the general population about clinical trials. However, they are still very novel and were tested on population that didn’t not have English as their first language. Additionally, they require two visits to properly make use of them. This raises costs and patients can be lost to follow up. (46)

Another unique issue with speaking books is that they are partly electronic. Thus, it is more expensive to produce than an informed consent form. Electronic components can also become faulty, making the resulting audio difficult to understand. This can be exacerbated if the recorded reader has a strong accent. For example, certain accents can make the word ‘ask’ sound like the word ‘axe’. Since speaking books are designed for individuals with low literacy, it cannot be expected that the reader would be able to double check the words spoken against the words written.

Mean comprehension of FAQs did not differ significantly against traditional informed consent forms. It was significantly lower than those who watched professional videos and staff made videos. About half of the FAQ participants spent less than 20.5 seconds on the consent page. This suggests

that either the participants read through it very quickly or did not read every question. Compared to video, it held participant's attention less as half of the video group spent less than 2 minutes on the consent page despite the videos taking 3.5 minutes. (37)

7. ADDITIONAL REMARKS OF INFORMED CONSENT FOR MINORS

Given the rarity of many pediatric diseases and the fact that researchers are dealing with a very vulnerable population groups who assist in legal limbo in regard to what they can and cannot do, proper informed consent becomes even more difficult to administer. (13,49) Another major issue with dealing with minors is the justification of using minors in the first place. (49)

For example, in the United States the opinion of child capable of assent must be considered equal to their parents. (50) This is similar to suggestions made by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and amongst other ethics boards. Not only that, but these other guidelines call for the minor also needing to have an informed assent agreement that is appropriate for their mental capacity. (3,4,49)

As a result, the US stands as a rather interesting place for children's research. Though each individual state has their own guidelines. Look at the State of Florida, for example. It appears to lack any legislation on providing this information to children who are under someone's guardianship despite having a section to clarify which children can join research without parental consent. Those being adolescents who are married, emancipated or unwed and pregnant with the caveat that is only relates to the pregnancy. (51)

Now, how exactly one can determine assent of is an entirely different. There is a large selection of tests available to check a child's cognitive abilities. Maturity on the other hand is a lot harder to judge. This is important as depending on the nature of the study it is possible for younger children to demonstrate that they have the maturity and intelligence to give assent when others of similar ages may have the intelligence but lack that maturity. (16)

The reason maturity and intelligence are separate is because of how they influence the processing of information. Some children display excellent feats of intelligence from a young age, such as by reading several grades level higher than their peers or doing university level mathematics. However, they can still struggle to understand more complex medical or social issues like 'side-effects' or 'compensation'. Do not assume that because a child that can read four syllable words fully understand intricacies of the word. 'Death' is only five letters in comparison. It is not unreasonable for a five-year-old to be able to read the word, but it is unreasonable to expect them to fully comprehend it.

While ultimately researchers should defer to the local regulation. It is not necessarily harmful at the very least to give an older child access to an adult informed form to read over in addition to a specially designed form for children. Even if the child does not fully understand the informed consent form their parents received, it can make them feel more like they are a part of the process. Which when it comes to dealing with children, can certainly help make them more cooperative in the long run.

Neonates also come with their own set of challenges in research. As are a very vulnerable population group with strict timing criteria of what does and does not qualify as one. Patients in this group might find themselves more often in situations where deferred or waived consent is carried out because of the rarity and time sensitivity researchers have to work with. Of course, individuals of all ages can be effected by this, but because of the fragility of neonates it poses more risks to them especially since these exceptions are only granted in emergency situations. (52)

7.1 INVOLVEMENT OF PARENTS

It is important that informed consent forms clearly explain the researcher's role and what they can and cannot do to the child for the parents. As parents will have the final say for children who cannot assent and still play an important role for children who can, they need to be aware that they are the biggest advocate for their child's rights during the trial. That includes that they properly understand their child's right to withdraw but also understand in some circumstances, depending on the law, they may have to supersede the child's wishes for the sake of the child's health. (49)

Parents of children who are suffering from complex diseases, like childhood cancer, are also under immense stress. They might feel pressured to sign up for things without giving it proper thought out of desperation for their child. While it can be slightly easier if the child can assent, when the child cannot assent the parents may find it even more difficult to decide what is or is not best for them.

On a lighter note, it's not uncommon for parents to enroll healthy children into clinical trials as well. Some of these studies are designed to track lifetime outcomes while others are designed to research normal human development in particular age groups. The role of maintaining the best interest remains the same. While the children in lifetime studies are not beholden to the study once they are able to assent, it is important that they do go through age-appropriate informed consent process once they can.

Other considerations should be noted for trials that follow both the parent and child. Not only are the parents now advocating for their children's best interest during the trial, but they must also focus on themselves.

Researchers are also mandatory reporters. They need to be alert of parents, guardians, and even fellow staff members who may pose harm to the child patient. We do not live in an ideal world and parents do not act always in the best interest of their children. Considering the nature of children's clinical trials, there is an increased chance of researchers stumbling across cases of Munchausen Syndrome by Proxy. Dishearteningly, most abusive parents cannot fall back on that excuse.

Even if the parents have lost both rights and legal access to the child, they can still be an issue. Now when these rights are willingly terminated, like in the case of closed adoption, the parent typically never comes back. However, when these rights are terminated by court order it can create a lot of resentment. Despite court orders, the reality for many children of abusive individuals is that they are still in contact with them.

Another issue with mandatory reporting is that it takes time to carry out. Not only does a social worker need to get involved, but it takes time to build a case. If the belligerent parent(s) comes to the research facility directly, not only is the patient at risk but everyone at the facility is as well.

Inversely, there is even the possibility of false reporting by researchers which can increase stress in the parents and children. Thankfully, false reporting can stem from simple misunderstands which can quickly be addressed, but there is always the possibility of malice from the research staff. Considering the track record of various child protective agencies around the world, one should not sigh in relief and assume that they are any good at spotting false reports. They can barely spot true reports as it. Fighting a legal battle while your child is fighting for their life is not something most parents wish to endure.

It is also important to note that in some cases, the biological parent has lost parental rights but retains legal access to the child. For example, children who are adopted by other family members. Teenage parents giving up their children to their parents or older siblings to raise is a classic example of this. Typically, when that happens the biological parent gives up the parental rights on good terms and does not interfere or care for much the parenting of the child.

7.2 QUIRKS OF DEALING WITH ADOLESCENCE

Depending on the country, adolescents may have more rights in regard to managing their health care compared to young children or equal rights. These rights can include the right to give informed consent to participants in clinical trials without parental approval.

Conflict can occur if the parents do not want the adolescent to join a clinical trial, but the adolescent thinks otherwise or vice versa if they live in a country that gives more autonomy to the teenager. If

the law states that adolescents do not have the right to give informed consent, then that only becomes an ethical issue since researchers are beholden to the law at the end of the day.

For example, the State of Florida has legislation that allows married/divorced, or emancipated teenagers to participate in research without parental consent. It even expanded that right to include unwed pregnant adolescents, but only in relation to research in regard to her pregnancy.

Unfortunately, in Florida there is a lack of proper legislation that concerns those in foster care whose parents have not lost their parental rights. (51)

Regardless of that, adolescents are in a bit of gray zone when it comes to what they can and cannot fully comprehend. As many countries believe it is important for children regardless of age to understand why they are taking part in a clinical trial, the information they are legally required to know is less than what an adult does. (32,49)

Despite that, one should take into consideration that a 17-teen-year-old is only a year away from the age of majority in most countries. Treating them like a young child could not only make them less cooperative but begs the question as to why they are not deserving of the same level of detail that their parents received in regard to their own health. Additionally, if they age up during the trial they have to go through the informed consent process again. Even if the researchers are in a situation where they have no legal obligations to be completely transparent with them, it is still suggested that they are treated more like adults than children. (3,49)

Dealing with emancipated adolescents by contrast seems significantly easier on the surface because they have the same legal rights as adults. However, they too can come with their own set of legal issues as some jurisdictions might not recognize the individual as emancipated. As for ethical issues, they are still adolescents and in the event that they lose their ability to consent during the trial it can be a nightmare trying to find someone who can give consent on their behalf. One might think that it should differ to the parents but depending on the unique circumstance that led to the emancipation, the parents might not have the right to do so. Of course, such details should be discussed prior to the patient's enrollment, but sometimes despite the approval of the regulatory body the legal system's many loopholes can lead to unforeseen complications.

Additionally, some teenagers are emancipated because they are married. Having to deal with the spouse of an adolescent patient can bring about its own set of challenges. For example, how should researchers proceed if the spouse is also an adolescent? As the spouse, they would gain the right to advocate for the patient by default, but an institutional practice might forbid them from doing so despite approval from both the courts and the ethics boards.

Another thing to consider about married adolescents is the age gap between them and a significantly older adult partner. While it is one thing for a cultural practice of child brides to exist, it is another matter entirely when the legal system allows it. The correct answer to the question of ‘what researchers should do in the scenario where a 40-year-old man claims husband of a 15-year-old girl patient whose parent cannot be contacted’ changes far too drastically to give a final ruling.

8. SHARED PROBLEMS WITH RECRUITMENT TO CLINICAL TRIALS

Informed consent often serves as one of the final parts in the selection process for clinical trials. If a patient cannot fill out the informed consent form, then naturally they cannot participate. Given the key the informed consent process provides, prospective participants may read through the process and find that the trial was not the risk fit for them, causing them to enforce their right to withdraw.

For example, a patient may learn through the informed consent form that part of a study that is not therapeutic. While it is a shame for them to have gotten to that point without knowing, this information can cause them to withdraw. This can make the patient and researchers feel as if they have wasted each other’s time by getting to this point.

It is also important to consider why patients even wish to participate in a clinical trial in the first place. Of course, there is the sense of altruism that comes to advancing science, but there is also selfishness of wanting access to the latest therapies and possible misunderstanding of how therapeutic these studies are. (53)

8.1 COMPLEXITY CAN STOP PATIENTS FROM ENROLLING

If patients do not understand what a study is about upon first learning about them, they may be declining studies that they would have otherwise joined or be opting to join studies that they otherwise would have never signed up for. (48) Thankfully, an adequate informed consent form is designed to help the later patients identify their mistakes so that they can leave the trial before getting too involved.

During the research process, it is known that prospective participants try to relate their own experiences to the information they find about the trial. (48) An example of how a study can miss out or attract the wrong patient groups is that it has an overly generic name like ‘Cancer in transgender youth’. That name is both too vague and unclear as to what exactly the study is about. To be clear, the study being discussed as an example is fictitious to prove a point.

Now, of course there would be more information provided to explain in more detail about what that study means and what population groups would be a good fit for it. ‘This is a study of transgender youth under the age of 18-years-old to see the likelihood of developing childhood cancer’ requires

a different patient group from a study states, ‘This is a study of how cancer affects the overall health transgender youth between 12 to 18-years-old’. Other details that can be disclosed up front include financial reimbursement for patients.

However, in this example there are still many unlisted factors here that can continue to cause confusion. The researchers’ definition of transgender youth might require that the perspective participant has used puberty blockers and are currently on hormone replacement therapy. Naturally, this can invite the use of more complex scientific language, making it harder for the perspective participants to understand who the target of the study is. Even more common words such as ‘cancer’ can prove to be a barrier, especially amongst those with low literacy. (48) Additionally, since this example is also calling for children, one must consider their desires when it comes to whether or not they think they should join.

Recruitment for clinical trials themselves can also vary drastically depending on what is being studied. For example, a preliminary human drug trial requires healthy volunteers. Thus, those interested in it would likely not learn about it from a physician but rather from an advertising campaign or already have a history volunteering in these trials.

Compare that to say, ‘a study on breast cancer in women who have trisomy 13’. Such as trial most likely recruit patients who learned about the study from their oncologists. Regardless, perspective participants are found to focus on connections between their own health care experience and the trial descriptions. (48)

The real issues can occur when patients actively try to look for clinical trials without the aid of a medical professional. Their medical knowledge might not be adequate enough to properly identify trials that qualify for or would be comfortable with.

To help prevent this confusion, shared decision-making during clinical trial recruitment can act as a sort of preliminary informed consent form. Key information covered during the recruitment process closely matches the main points of what is required in an informed consent form but there are differences. These are assessing the health and literacy of the potential research, disclosing the physician interests in the study, discussing the patient’s motives for joining, simplifying and explaining technical language, comparing risks and benefits of the placebo and intervention, discussing how participation would affect the patient’s lifestyle, and allows the patient to decide if they want to become a human subject. (53)

The use of AI chatbots is also being developed in this sector to mimic the shared decision-making process. It is still too early to call, but participants who used an AI chatbot achieved better understanding about their eligibility than those who did not. AI interfaces were also rated as

significantly better in terms of perceived usability, interactivity, and dialogue. (54) Use of AI search engines also improve patient awareness of clinical trials that were recruiting, and they were eligible for. (55)

Interestingly, the length of the informed consent forms can also be an obstacle that deters clinicians from recruiting patients to trials. Even observational studies suffer to recruit as doctors may find discussing the forms a waste of time. One has to remember that most doctors are not focused on research to begin with. Knowing about the latest trials that are recruiting can be a low priority for clinicians. (14)

Additionally, building trust amongst researchers and perspective participants is an important first step in recruitment. (25) Not being recommended by a clinician can lower some of that trust.

Health literacy can also impact the values perspective participants care about the most when trying to make a selection. A study on the use of search engines for finding clinical trials noted that 33% of those with high health literacy endorsed the theme of invasiveness of the trial compared to 13% of those with low health literacy. However, 33% of those with low health literacy endorsed the theme of existing conditions (of) self when only 27% of the high health literate did. (48)

While it is a unique issue independent of informed consent forms, perspective participant needs to be aware that a clinical trial is recruiting. Otherwise, it begs the question as to why someone would even bother to look in the first place. While patients might learn about the concept of clinical trials from their doctors, if doctors do not direct them to a trial they can be left searching in the dark for one. There is some headway that is being made for these patients using AI, though the technology is still underdeveloped. (55)

Even then, if the perspective participant does not know how to make the most out of those tools, then those tools become pointless. High health literacy is beneficial, but if the person has low techno-literacy it would be silly to assume that they can adequately navigate a search engine in the first place. Literacy in general is also important for keyword-based search engines as they become unusable for those who struggle with reading, writing and spelling. Misspellings in general are noted to be an extremely common user error for these style of search engines in general. Additionally, they can struggle with reforming queries to get narrower or boarder results which is important to consider when most people do not go beyond the first page of responses. (48)

Think of it as every problem looking like a nail to a hammer so to speak. A loose screw requires a screw driver to put it back into place, but that does not necessarily mean that hammer cannot do the job. The hammer would instead be rather inefficient and have a high chance of breaking the screw.

Kind of like how this awkward metaphor was hammered in to demonstrate this phenomenon in action.

Recruitment of children poses its own set of challenges. A novel website “DigiKnowItNews”, was created to help inform on children what exactly a clinical trial is. It uses different multimedia techniques like videos, activities and comic books to do so. Patients reported high satisfaction with the website which is similar the impression they had to the use of multimedia in informed consent. (56)

In situations where the patient group large and easily identified deploying an ‘opt-out’ system recruitment could be to use. Most importantly, these should be deployed in low-risk situations where possible harm to patients is at a minimum. (14)

8.2 ISSUES WITH RESEARCH THAT CONCERNS EMERGENCY SITUATIONS

The major issue with gathering informed consent in these situations is that they are not only extremely time sensitive but also emotionally sensitive. Additionally, the researchers lack an established relationship with patients which can make it harder to recruit them. Doctors that conduct research in the emergency room are also put at odds with their duty to provide lifesaving care and gathering data. (14)

Having a research assistant around can mitigate some of the problems of conducting research in the emergency department in the first place. However, this is not feasible in all institutions as that requires bringing in an extra member of staff. Said members not only need to be paid, but they might require additional training that can incur more costs. (14)

One could argue that these patients are unable to give proper informed consent because they are in a situation that causes duress. For example, a woman who is at risk for a preterm delivery can be on a lot of medications and emotional distress that can impair her judgement. Thus, deferred consent may have to be employed instead. (35)

Guidelines in place that consent can be waived for clinical research in emergency circumstances provided that the situation is life threatening, there is no proven better treatment option that exists, and the data is needed to show safety and effectiveness. (52)

The Helsinki Guidelines specifically called for research into those who are unable to physically or mentally give informed consent to only be carried out if it is a *necessity* of the research group. Naturally, consent must be given by a legally authorized representative instead. Research can only proceed without a representative if it is a time sensitive situation where the representative cannot be

contacted, and it is a part of research protocol and previously approved by a research ethics committee. As soon as possible free, and informed consent must be given. (1)

In situations involving children, parents provided deferred consent at a higher rate than those were electively admitted. Additionally, parents tended to have positive or neutral reactions upon learning that they waived consent for their very recently born neonate to be enrolled in a clinical trial when asked specifically about the quality of care their child received. Some parents also did even remember enrolling their neonates into a study but still remained positive. Though for neonatal studies they noted that they would have preferred to have been consulted by researchers before birth or at the very least outside of the labor ward. (52)

9. OVERALL COMPARISON OF EACH TOOL ANALYZED

After analyzing the tools researchers use to provide informed consent, it is important to also compare them. As direct comparisons of all of these methods against each have not been found during research, it is unwise to conclude that one is truly better than another. Instead, listing their strengths and weaknesses plainly can help one draw their own conclusion.

Table 1 Overall comparison of each tool analyzed

Method of Informed Consent	Strengths	Weaknesses
Informed Consent Form	Wide range of templates available	Consistently too advanced language
	Cheap	*Technical jargon
	Can be used as legal protection for both participants and researchers	*High reading level
	Very in depth	Minium considerations for translations
		Performed worst at patient understanding
Multimedia Tools		Length demotivates both patients from joining and doctors from recruiting
		Patients prefer direct communication with doctors during the informed consent process which can take a lot of time
	Consistently high user satisfaction	Expensive and time consuming to make
	Good long-term retention	Unclear to what extent each age group
	Improved recruitment	benefits from using it
	Can be rewatched	Dependant on patient's technoliteracy
	Can be done remotely	Older technology reduces cyber security
	Testing of understanding can be implemented while the patient is doing it	risk, but reduces accessibility
	In-person approach can prevent fraud and allow researchers to ensure engagement	Remotivity increases risk of disengagement
		Patients might not want to be filmed during the consenting process
		Adding slideshows or theater to inperson meetings did not improve understanding

(continued)

Artificial Intelligence	Can simplify preexisting informed consent form to improve understanding	Experimental technology
	Can write a consent form on its own	Ethical grey area of appropriateness for use
	*Accuracy on par with human work	*Exacerbates biases in data sets
	Improved, understanding and actionability	*AI hallucinations
Leaflets and other paper aids		Well written human made consent forms showed no difference in comprehension
	Patient information leaflets are not the issue when done properly they can provide a basic overview of informed consent	FAQs showed no perceived benefit compared to traditional consent forms
	*Long history in informed consent	*Lack of research into use in relation to clinical trials
	Speaking books showed improved knowledge test scores	*Patients maybe incentivized to skip over questions and not read it thoroughly
	*Patients were likely to share the books with others, increasing trial awareness	Not enough research into speaking books
	As FAQs rely on patient feedback, the more questions that are asked the more useful they can become	*Electronic components can break
	Can be created alongside patient advocacy groups for select disease to improve feedback as patients value their own existing conditions when looking for trials	*Poor audio quality can lead to confusion
		*Costly to manufacture
		Inherently 'take-it-home' material
		*Creates impression that it is homework
		*Patient might not bother reading it
		Requires meeting with the patient twice
		*Loss of patient from follow up

Starting with the only method everything supplemental tool has been tested against, the traditional informed consent form. When it comes to traditional informed consent forms, it seems researchers are bogged down by the use of technical language resulting in high reading levels. By doing this, it makes them unapproachable to the average patient. It becomes even more egregious, when guidelines often state the need to use less technical language and to aim for low reading levels. They have also increased in length, which reduces doctors' motivation to recruit. That it is likely the result of pressure from institutions' legal departments as they instill the fear of lawsuits into researchers.

Now, despite AI being an emerging technology it seems that it is almost ready to replace humans. Of course, AI always needs to have a human overseer to double check its work, but completing monotonous tasks is the very reason why AI is being so heavily invested in it. Not to mention the large data pool of examples that an AI can learn from. Perhaps it can even make improvements that humans have failed to notice.

That said, the danger of AI hallucinates is ever present. Hence why the need for human oversight must never be understated. While some mistakes can be obvious, such as AI getting the name of a drug wrong, others can promote blatant misinformation.

The most surprising results were how closely the patient information leaflets followed the trends of the informed consent form. One would imagine that this would not be the case considering how leaflets are used outside of medicine. A possible explanation is that because they are summaries of

the informed consent form, they used the same language and word choices. If the informed consent form thus uses complex language that requires a high reading level, its leaflet in turn would also be the same.

The frequently asked questions and speaking books are too niche to make a wide sweeping judgement on. While the speaking books do hold promise it is not the same as AI which has widespread appeal amongst all researchers. They also increased awareness of clinical trials amongst the general population as patients were likely to share them amongst their family and friends. The electronic component makes is more expensive to produce and easier to damage. The nature of FAQs certainly needs more research into it as it's common for people not to read them even in a non-medical context. It is possible that the more refined FAQs become the better they can be. To be honest, it seems as though people use them as a means to trouble shoot a new device not to find information about their health. Thus, they could ultimately be a waste of resources.

The biggest issue with these tools is that they can be considered 'take-it-home' material. This can create the impression that they are homework for patients. There is also no reason to assume the patient will read it, or at the very least read it thoroughly. The final nail in the coffin is that it requires meeting with the patient twice, which can lose them between the follow up.

Multimedia tools are the most controversial. Some studies suggest that they are amazing for the recruitment of young people, another counters that it is better for adults. One thing that was consistent was the high patient satisfaction. As for how it relates to the usefulness in improving patient understanding, it leans towards yes. Interestingly, differences between what kinds of multimedia techniques were deployed are not very evident. The biggest influencing factor here appears to be the patient groups involved.

It does come with the risk of injecting malware or fraud if done in an at home setting. Patients can also disengage and mindlessly consent without properly thinking it through. Conversely, the ability to do it at home can expand the potential patient groups. The use of testing after each section can improve engagement and check understanding every step of the way. This can improve long-term understanding of informed consent, which is important since clinical trials can last years.

While not thoroughly analyzed, it is interesting to note the importance that conversing with the patients has on improving their understanding. Properly explaining everything and going through the informed consent form maybe time consuming, but patients seemed to enjoy it. No comment can be made on whether or not it improves understanding in this thesis.

10. CONCLUSIONS

The informed consent process is the moral backbone of human research. The informed consent form exists to inform patients of informed consent. By ensuring patient understanding of informed consent researchers can ensure ethical research is being conducted, hence why it is important the research into improving patient informedness is conducted.

The conclusions of the research are as followed:

1. When comparing multimedia tools, artificial intelligence, leaflets and other paper-based aids against each other; artificial intelligence can hesitantly be viewed as the best. That said, when compared to informed consent forms alone all performed better except leaflets and frequently asked questions. The use of speaking books did show to improve informedness. Multimedia was a mixed bag of success and failure that varied greatly amongst age groups and cultures. Artificial intelligence was the only one that showed consistency, but it is too understudied to say for sure.
2. The biggest obstacle to the traditional informed consent form is the technical language, length and high reading levels. Problems with children's research arise as child's autonomy can clash with the wishes of the parent. Emergency situations come with the added pressure of time sensitivity, focus on saving lives and the fact that the patient is under duress. Recruitment can be hampered by form length which deters doctors from discussing them. Shared decision making between doctors and patients can help the patients find the trial that is the best fit for them as they often struggle to do it alone. In place of a doctor, artificial intelligence is being researched to see if they can make proper alternatives.

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