Informed Consent: History, COVID-19 Vaccine Trials and Future Directions

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History of Informed Consent

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- **1897:** Sanarelli announced he discovered the bacillus of yellow fever and produced yellow fever in 5 patients.

- **1898:** Osler condemns Sanarelli:

"To deliberately inject a poison of known high degree of virulency into a human being, unless you obtain that man's sanction, is not ridiculous, it is criminal."

History of Informed Consent

- Early research was frequently unethical and frequently failed to fully inform patients of the risks of a study or ask permission for participation.
- In 1966, Harvard professor Henry Beecher wrote:

“The statement that consent has been obtained has little meaning unless the subject or his guardian is capable of understanding what is to be undertaken and unless all hazards are made clear. If these are not known this, too, should be stated.”

Informed Consent

Informed consent consists of **4 elements**

1. Competence of the subject
2. Disclosure of information to the subject
3. Understanding or comprehension by the subject
4. Voluntariness of the decision

But in some ways, current informed consent documents are failing to live up to these ideals -- especially comprehension

Informed Consent

- Informed consent is a process, not a document or a discrete event
- But a clear and complete informed consent document is essential in research ethics

Current Issues In Informed Consent

Length
Readability
Comprehension

Issues in Informed Consent: Length

- From 1978-2002, the length of the consent form increased roughly linearly by an average of 1.5 pages per decade.

- Over these 25 years, there was no year in which consent forms had a mean length that was shorter than the forms from three years earlier.

Malik, L., Kuo, J., Yip, D., & Mejia, A. (2014). *Clinical Trials*,

Issues in Informed Consent: Length

- A 2014 study of 112 medical oncology informed consent forms for Phase 1-3 studies found a median length of 20 pages (range 8-28)

Malik, L., Kuo, J., Yip, D., & Mejia, A. (2014). *Clinical Trials*,

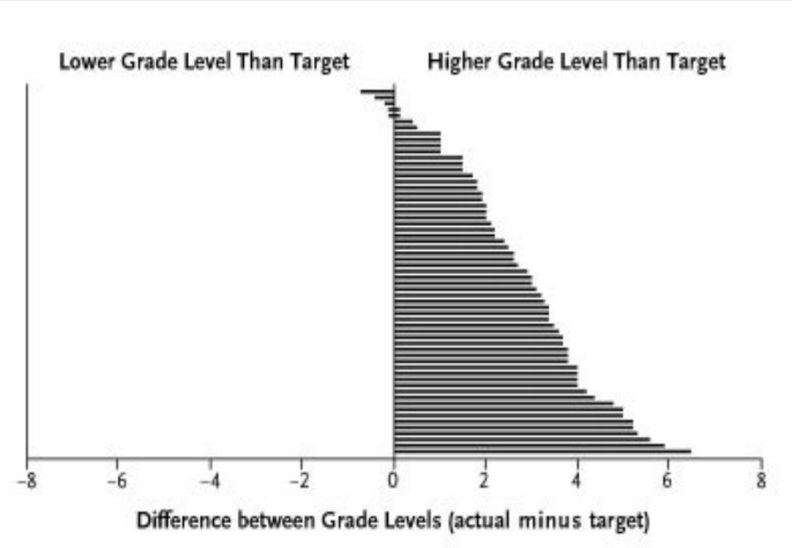
Issues in Informed Consent: Readability

- One study examined the informed consent templates of US medical schools and compared it to the IRB standard listed for the same school.

- The mean Flesch–Kincaid grade level for sample text supplied by IRBs was 10.6. Recommended grade level is 6.

Paasche-Orlow, M. K., Taylor, H. A., & Brancati, F. L. (2003). NEJM

Issues in Informed Consent: Readability



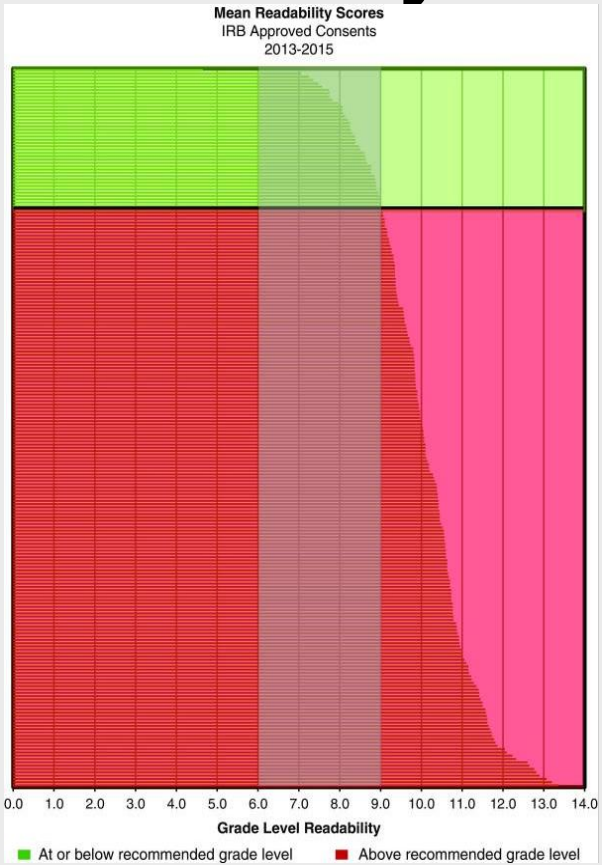
- Among the 61 schools with specific grade-level standards, only 8% met their own standards. The mean score for readability exceeded the standard by 2.8 grade levels.

Paasche-Orlow, M. K., Taylor, H. A., & Brancati, F. L. (2003). NEJM

Issues in Informed Consent: Readability

- Analysis of 217 IRB-approved informed consents from 2013 to 2015 revealed a mean readability of 10th grade.

- The vast majority of informed consent documents did not fall below the recommended grade level.



Hadden, K. B., et al (2017). *Journal of clinical and translational science*,

Issues in Informed Consent: Comprehension

- In 2001, Joffe et al surveyed 207 cancer clinical trial patients. Most of the patients considered themselves to be well informed.

- Many did not recognize non-standard treatment, the potential for incremental risk from participation, the unproven nature of the treatment, the uncertainty of benefits, or that trials are done mainly to benefit future patients.

Joffe, S., Cook, E. F., Cleary, P. D., Clark, J. W., & Weeks, J. C. (2001).. *The Lancet*,

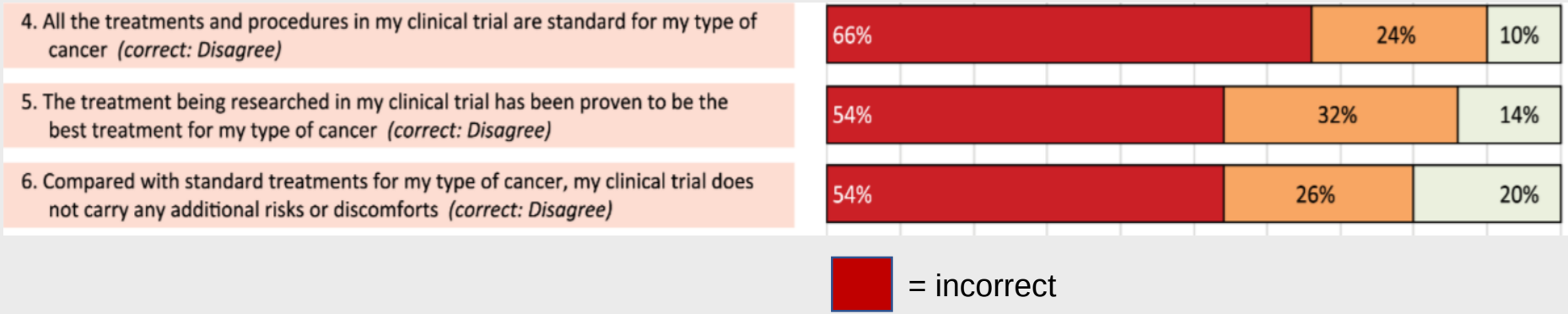
Issues in Informed Consent: Comprehension

Percent of respondents who answered comprehension questions incorrectly	
The main reason cancer clinical trials are done is to improve the treatment of future cancer patients	25%
All the treatments and procedures in my clinical trial are standard for my type of cancer	74%
The treatment being researched in my clinical trial has been proven to be the best treatment for my type of cancer	70%
Compared with standard treatments for my type of cancer, my clinical trial does not carry any additional risks or discomforts	63%
There may not be direct medical benefit to me from my participation in this clinical trial	29%

Joffe, S., Cook, E. F., Cleary, P. D., Clark, J. W., & Weeks, J. C. (2001).. *The Lancet*,

Issues in Informed Consent: Comprehension

- 10 years later, a study using the same questionnaire found similar results: Over 50% of participants answered incorrectly on comprehension questions



Schumacher, et al. (2017). *PLoS One*

Issues in Informed Consent: Comprehension

- A 2019 study tested the recall of 266 volunteers in Phase I clinical trials with 7 questions, awarding a point for each correct answer
- The mean total score for all volunteers was 4.5 points out of 7
- Only 7% were able to state the aims of the study correctly

Tadros, R., Caughey, G. E., Johns, S., & Shakib, S. (2019). *Clinical Trials*,

Informed Consent and COVID-19 Vaccine Trials

How well do informed consent documents from COVID-19 vaccine trials achieve the ideal of being succinct and readable?

Background

- Informed consent documents should be brief, readable and prioritize participants' understanding. However, over time, these documents have become longer and more complex.
- COVID-19 vaccine clinical trials have been the most visible clinical trials in more than 30 years that collectively enrolled well over 150,000 participants a multiple global trial sites.

Selection of Phase III Randomized Trials

We systematically evaluated the informed consent documents from 4 COVID-19 phase III vaccine randomized clinical trials:

- AstraZeneca
- Johnson & Johnson
- Moderna
- Pfizer

Evaluation Criteria

The forms were evaluated based on 4 criteria:

Criteria	Metrics
Length	Word Count; Time-to-Read
Language Complexity	Flesch-Kincaid Grade Level Assessment
Readability	Flesch Reading Ease Score
Placebo	Clarity on how the placebo group could access the vaccine if proven safe and effective

Characteristics of Phase III COVID-19 Vaccine Informed Consent Documents

Metric	Pfizer	J&J	Moderna	AstraZeneca	Mean
Page Count	25	25	20	17	***21.8***
Reading Time (min) at 240 wpm	32.6	34.8	38.9	32.6	***34.7***
Word Count	7828	8341	9340	7821	***8333***
Reading Grade Level	9.8	8.8	9.6	11.3	***9.9***
Reading Ease*	52.2	56.8	51.1	49.6	***52.4***

*Range, 0 to 100, with 100 indicating easiest to read and scores less than 60 considered “difficult” by the U.S. HHS

Issue #1: Length

- At 240 words per minute, a participant would need a **mean of 34.7 minutes** to read the document.
  - *These calculations do not account for rereading, which would add additional time.*

Issue #2: Readability

- It is recommended that informed consent forms are written at a grade 6 reading level.

- That was not the case for any document. The language complexity in all four documents **exceeded a grade 9 reading level**.

- All documents had scores of less than 60 in the reading ease metric, categorizing them as “difficult”.

Issue #3: Clarity for Placebo Arm

- Only one document informed participants in the placebo group what would happen if the the vaccine proved safe and effective.

- Even then, the reference was oblique, and failed to specify the timeline or other details.

Proposed Alternative Document

- It is possible to create a shorter, more readable informed consent document for these trials.

- We formulated a substitute informed consent document covering the same topics:
    - < 3,000 words,
    - a reading time of 12.3 minutes, and
    - a reading level under grade 8.

Proposed Alternative Document

Metric	Mean	Proposed Alternative
Page Count	21.8	10
Reading Time (min) @ 240 wpm	34.7	12.3
Word Count	8333	2960
Reading Grade Level	9.9	7.6
Reading Ease	52.4	61.8

Reworking Informed Consent Documents

Document section	Original				Potential simplification			
	Text	Length, words, No.	Grade level	Readability score[a]	Text	Length, words, No.	Grade level	Readability score[a]
Purpose	Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe disease, such as Middle eastern respiratory syndrome and SARS-CoV. Coronaviruses are zoonotic, meaning they are transmitted between animals and people. An outbreak of COVID-19 caused by the 2019 novel coronavirus SAFr-CoV-2 began in Wuhan, Hubei Province China in December 2019 and has spread throughout China and to over 200 other countries and territories, including the United States. There is currently no vaccine that has been shown to be effective against SARS-CoV-2. Therefore there is an urgent public health need for rapid development of novel interventions to prevent the spread of this disease. This study is testing mRNA-1273 study vaccine at a dose of 100 µg. The main purpose of this study is to understand if MrNA-1273 can prevent COVID-19 and to understand the safety of the mRNA study vaccine	146	12.4	43.1	This study will test a vaccine against the virus that causes COVID-19.	12	6.8	67.8

Reworking Informed Consent Documents

Document section	Original				Potential simplification			
	Text	Length, words, No.	Grade level	Readability score[a]	Text	Length, words, No.	Grade level	Readability score[a]
Risk	As in all research studies, the COVID-19 vaccines may involve risks that might be expected based on results from studies of similar vaccines, as well as risks that are currently unknown	31	14.4	47.1	This vaccine may cause currently unknown risks.	7	5.7	66.8
Pregnancy protections	The study doctor will discuss with you the methods of birth control that you should use while you are in this research study and will help you select the method(s) that is appropriate for you. The study doctor will also check that you understand how to use the birth control method and may review this with you at each of your research study visits	65	13.1	59.3	The study doctor will help you choose and implement an effective method(s) of birth control.	16	8.4	61.9

It was possible to develop a measurably better informed consent document that uses less complex language.

Takeaways

- The 4 informed consent documents are:
  - **Too long**, presenting an unreasonable time burden for participants that may impede comprehension and create pressure to skim.
  - **Too difficult to read**, posing a potential comprehension challenge for participants with lower education levels.

Overall Conclusions

- The results of this study suggest that the practice of informed consent has been compromised by lengthy, complex documents.

- Organizations involved in clinical trials should explore hiring an editor rather than leaving the creation of informed consent documents to researchers and legal teams without expertise in careful, succinct writing.

Contributing Factors

- Ethics reviewers may not insist on shorter, more readable documents or may even require additional material that they think will improve information transfer.

- Informed consent documents may be created by copying sections from previous documents.

- Legal teams may prioritize exhaustive details or preventing lawsuits over participants' comprehension.

Future Directions

- **Phase 1:** A randomized control trial to evaluate shorter, more readable documents on time of consent, enrollment, comprehension, and participant satisfaction.

- **Phase 2:** A randomized control trial to evaluate non-document informed consent on time of consent, enrollment, comprehension, and participant satisfaction.