

Compliance vs. Communication in Clinical Trial Registries

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Abstract

The 1997 FDA Modernization Act called for a clinical trial registry "...in a form that can be readily understood by members of the public." Unfortunately, most consumers will likely find current clinical trial registries – even the study titles and purposes – hard to read and understand. A selection of nine clinical trial registry web sites average a grade 16 (4th-year college) reading level. That makes them "very difficult" to understand on the Flesch Reading Ease Score. Too many unfamiliar and complicated words and complex sentences contribute to a "poor" writing style. Consumers are more likely to understand registries written in plain English. However, unfamiliarity with complex medical, legal, privacy and research concepts means that even plainly-written materials will still be incomprehensible by many consumers.

How Readable are Clinical Trial Registry Web Sites?

In developing a national clinical trials registry, McCray and Ide noted that the 1997 FDA Modernization Act requires that the registry "shall be in a form that can be readily understood by members of the public." Their usability studies found some complaints about language in titles and summaries being too technical, but they didn't analyze other components of the registry system.

Based on the 2000 US Census, the average grade-16 reading level of the registries is suitable for only about 25% of the US adult population. But even that 25% may be an overestimate. Because college students can choose majors from Art History to Zoology, a four-year degree – or even an advanced degree – does not guarantee familiarity with the language of clinical trials.

Clinical research is so complicated that scientifically naïve consumers cannot become clinical trial experts merely by reading a clinical trial registry Study Introduction and Glossary. Consumers without a science or healthcare background may not know basic clinical research concepts.

If clinical trial registries are to accomplish their goal of providing consumers and their physicians with information about ongoing clinical trials, they must be comprehensible. To be comprehensible, they first must be readable. The author selected nine registries from a Google search on the term "clinical trial registry." The readability of study introductions, legal notices, and glossaries (if present) were analyzed with three readability software programs: Pro-Scribe, Grammatik 6.0 and WStyle 1.6. The Flesch-Kincaid readability tool in Microsoft Word was not used because it does not report scores above grade 12 – a serious flaw for this analysis.

Readability analysis of clinical trial descriptions is not possible because the information is presented in outline form and therefore not analyzable using readability algorithms.

As shown in Table 1, registries are written at a college to post-graduate reading level. The numerous unfamiliar and complicated words and complex sentences create a "poor" writing style, making them "very difficult" for consumers to understand. Consumers can identify possibly relevant trials even if they can't make much sense of the information provided.

However, they may compile a very long list because they can't narrow their selection to those most likely to meet their needs.

Table 1. Readability of Registry Introductions, Legal Notices and Glossaries

	Reading Grade Level^a	Flesch Reading Ease^b	Sentence Complexity^c	Vocabulary Complexity^d	Writing Style^e
Readability Recommendations^f	8	60-70 (Standard)	<25	<25	60% (Good)
Introduction^g	14-17	11-43 (Very Difficult to Difficult)	32-62	57-76	20%-43% (Poor-Weak)
Legal Notice^h	15-16	31-37 (Difficult)	56-82	43-68	34%-40% (Poor-Weak)
Glossaryⁱ	16-19	11-31 (Very Difficult to Difficult)	36-73	54-70	23%-38% (Poor-Weak)

- a. Reading Grade Level is based Pro-Scribe software.
- b. The Flesch Reading Ease Score ranks writing from 0 (very difficult) to 100 (very easy).
- c. Grammatik 6.0 calculates sentence complexity (100 = most complex) based on the number of words and clauses in a document.
- d. Grammatik 6.0 calculates vocabulary complexity (100 = most complex) based on the number of syllables in a document and compared words to a list of unusual or difficult words.
- e. WStyle 1.6 calculates writing style based on four variables: active voice, word economy, readability and word choice.
- f. Typical readability scores that software developers and literacy researchers recommend for materials written for the general public
- g. Sample: clinicaltrials.gov, GlaxoSmithKline, Millennium Pharmaceuticals, and Organon
- h. Sample: Forest Labs GlaxoSmithKline, Merck and Roche
- i. Sample: clinicaltrials.gov, Forest Labs, Eli Lilly and Bayer

Can Consumers Understand the Glossaries?

To help consumers understand the study information, some registries include 1,000- to 3,000-word glossaries of basic clinical trial terms. Some glossary entries are more enlightening than others. For example:

Adverse Reaction (Adverse Event): An unwanted effect caused by the administration of drugs. Onset may be sudden or develop over time (See side effects).

Adverse Events (AEs): Any untoward medical occurrence in a consumer or clinical investigation subject administered a pharmaceutical product. While AEs may be

associated with the temporal use of the drug, there may not be a causal relationship.

Adverse Event (AE): An unfavorable or unintended sign, symptom, reaction, or disease that is associated in time with the use of an investigational drug, whether or not the event is related to the investigational drug, or expected.

Adverse Event (AE): Any untoward medical occurrence in a consumer or clinical investigation subject administered a pharmaceutical produce and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use for a medicinal (investigational) produce, whether or not related to the medicinal (investigational) produce (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Can Consumers Understand the Study Introductions?

Study protocols include titles and statements of purpose designed for scientific exactitude. The resulting language does not necessarily meet the needs of consumers who are not medical scientists:

KLEAN Study: Kaletra or Lexiva with Ritonavir Combined with Epivir and Abacavir in Naïve Subjects over 48 Weeks

Purpose: This study will compare the ability of fosamprenavir 700 mg with ritonavir 100 mg twice a day or lopinavir 400 mg with ritonavir 100 mg twice a day both combined with a fixed dose combination tablet of abacavir 600 mg and lamivudine 300 mg once a day to suppress virus levels of HIV to less than 400 copies/mL of blood. In addition we will study the safety and tolerability of these compounds over the 48 week study period in consumers naive to anti-HIV therapy.

Phase III Study of Irinotecan and Cetuximab Vs Irinotecan as Second-Line Treatment in Consumers with Metastatic, EGFR-Positive Colorectal Cancer

Purpose: The purpose of this study is to determine whether overall survival is prolonged in subjects with metastatic, EGFR-positive colorectal cancer treated with cetuximab in combination with irinotecan compared with irinotecan alone as second-line therapy following treatment with a fluoropyrimidine and oxaliplatin based, non-irinotecan- containing regimen.

PEG-Intron Plus Rebetol Treatment of Chronic Hepatitis C Subjects Who Failed Response to Alpha-Interferon Plus Ribavirin

Purpose: The objective of this study is to determine the effectiveness of PEG-Intron 1.5 ug/kg/wk plus REBETOL 800-1400 mg/day in adults with chronic hepatitis C with moderate to severe liver fibrosis or cirrhosis who failed to respond to previous treatment with an a interferon in combination with ribavirin. Consumers who do not respond to PEG-Intron plus Rebetol will be enrolled in a long-term maintenance study to evaluate the effectiveness of PEG-intron therapy monotherapy versus no treatment for the prevention of disease progression (Protocols P02569 and P02570).

What Can Be Done?

Over the past few years, the pharmaceutical industry rewrote its unreadable and microscopic "Brief Summaries" in direct-to-consumer drug ads to more readable and legible "Consumer Summaries." Readability improved from the post-graduate to the high school level, as shown in Table 2.^{1,2}

Table 2. Readability of Direct-to-Consumer Drug Summaries

Document	Flesch Reading Ease	Reading Grade Level	Sentence Complexity	Vocabulary Complexity
Recommended	60-70 (Standard)	8	<25	<25
Brief Summaries (n=6)	18 (Very Difficult)	17	80	70
Consumer Summaries (n=4)	54 (Fairly Difficult)	11-12	31	40

Unfortunately, this "Plain English" approach may not be practical for clinical trial registry materials. To start with, what is the relationship between patient registries and clinical trial registries? The concepts of "common" and "rare" are undefined for side effects. The meaning of standard clinical research concepts such as "enrollment" vs. "randomization" are unfamiliar even to some clinical research investigators. The industry has largely failed to make informed consent forms readable. Registries face a greater challenge because study personnel are not standing by to answer questions. Fortunately, there is some good news. Registries do not have to obtain informed consent; they just have to help consumers narrow their search to a relatively short and accurate list of trials for further investigation.

Web-based registries invite the application of computerized methods to increase comprehension. Consumers can pop-up helpful information at the pause of a mouse. Statistical analysis of website usage patterns can identify problem areas for improvement. Human factors engineers can improve the user experience with standard techniques and by studying how consumers actually use registry websites. (Consumer behavior differs from consumer self-reports of behavior, so usability studies are more accurate than surveys or focus groups.)

Many consumers may find a step-by-step wizard process more effective than an unstructured search. Expert systems can detect confusion by individual users and volunteer personalized guidance. If worse comes to worse, registries can make human assistance available through online chat or telephone.

Most pharmaceutical companies have resisted the creation of government-mandated clinical trial registries because of concerns about proprietary information. However, most have readily adopted more-or-less the same technology for online subject recruiting purposes. By adapting these sites to the combined purpose, sponsors can accomplish both objectives.

References

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