BRIEF REPORT

Initial Steps in Creating a Patient-Centric Addendum to Clinical Trial Informed Consent Forms

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ABSTRACT

Introduction: The purpose of the informed consent form (ICF) is to outline the risks and benefits of an interventional clinical trial to potential participants. The aim of this study was to explore the feasibility of a short addendum to the ICF, summarizing key points most relevant to potential participants.

Methods: A sample of 20 ICFs was reviewed against the requirements of the U.S. federal regulation documents and assessed for readability. Alongside the ICF review, we conducted focus groups and one-on-one interviews with people with lung cancer (n = 9) to learn what information was most important when considering participation in a clinical trial using a hypothetical phase 3 ICF.

Results: The 20 ICFs reviewed were from phases 1 to 3, expanded-access, and single-patient trials covering predominantly NSCLC; 60% were global. The mean length of the ICFs was 21 (range: 15–34) pages. The average reading level was tenth grade whereas the average U.S. reading level was eighth grade. Readability varied by section, the "purpose of the study" section had the highest reading level. In the qualitative research component, participants were "overwhelmed" by the hypothetical ICF. Participants were also asked to list information for the addendum; their suggestions broadly map to federal regulations. An addendum with reference to sections in the ICF for additional details was well received.

Conclusions: The variations in ICF architecture and readability make it difficult for patients to make an informed decision to participate in a clinical trial. Implications extend beyond lung cancer, highlighting key areas for ICF improvements and providing a roadmap for developing a patient-centric addendum.

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Introduction

Clinical trials have become complex operations.[1] However, when a patient and their family sit down to weigh the risks and benefits of participation, they should be armed with clear and straightforward information. Yet the prevailing characteristic of trial informed consent forms (ICFs) is that they are lengthy and riddled with scientific jargon. This phenomenon continues despite the U.S. Food and Drug Administration (FDA) recommendation that ICFs provide "adequate information to allow for an informed decision" and avoid features (e.g., length, reading grade) that "may inhibit reading of the full document and understanding of the relevant information."[2]

Decades of previous work have explored how to improve the ICF[3–7]; however, these efforts have not had an appreciable impact. Using lung cancer as a case study, in this article, we describe our initial work to determine the feasibility of a 1- to 2-page patient-centric ICF addendum—an approach that may achieve the FDA goal of optimizing patient understanding while still adhering to practice standards and legal requirements.

Materials and Methods

We collected and analyzed a sample of 20 ICFs across lung cancer subtypes and phases of drug development. ICFs were convenient samples provided by a mix of drug companies, academic centers, and patients. The ICFs were reviewed using the requirements outlined in 45 Code of Federal Regulations, 46 Health and Human Services regulations for the Protection of Human Subjects in Research,[8] and FDA's informed consent information sheet including guidance for institutional review boards (IRBs), clinical investigators, and sponsors.[2] The Health and Human Services regulations include nine basic elements and nine additional elements; for this review, we included 17 elements (e.g., "purpose of the research" and "which procedures are experimental"). These were reviewed in terms of the presence of information, location of information (i.e., page number), total number of pages, and use of section title and headings. Assessing the readability of the entire ICF was not feasible because of the ICF structure. Therefore, we focused on the readability of five key elements using Flesch-Kincaid Grade Level scoring (FKGL), namely: (1) study purpose; (2) study expectations and procedures; (3) potential benefits; (4) potential risks; and (5) patient financial responsibilities. The FKGL tool is the most typically used readability assessment for documents written in English.[9] The ICFs were edited to make them suitable for readability assessment. For example, study drug names and procedures for which there is no plain language term (e.g., chemotherapy a six-syllable word) were changed to simple, single-syllable words, and formatting amendments (e.g., removal of headings).[10] This was because the FKGL algorithm relies on average sentence and syllable length.[11] The score generated is a reading grade level ranging from grade 5 to college.

We then invited patients with lung cancer to focus groups (FGs) and one-on-one interviews to discuss a hypothetical ICF (developed on the basis of our ICF review) for a phase 3 lung cancer trial, which we provided 1 week before the discussion. We created a discussion guide to learn about the challenges participants faced in trying to read through the hypothetical ICF and to specifically discuss the information they preferred to see included in a brief ICF plain language executive summary that is meant to complement the full ICF. The study was determined to be exempt (Advarra IRB; IRB #Pro00050819), and all participants consented to participate.

Results

A total of 20 ICFs were reviewed, of which 45% were for advanced trials, five (25%) were for phase 3 trials, and 12 (60%) were for global trials (see Supplementary Table 1 and Supplementary Fig. 1 for additional ICF characteristics and readability). We attempted to cover a range of ICFs across different trial phases and types of therapies. The mean page length was 21 pages (range: 15–34), with a mean FKGL of 10.4 (range across sections and sponsors: 4.4–15.5). Sections that were generally included in the first half of the ICF included purpose, duration, what will happen, and experimental procedures, whereas the sections covering foreseeable risks, voluntary, benefits, alternative treatments, costs, study termination, and general contact information were more likely to be presented in the second half of the ICF.

In total, nine patients participated in either a FG ($n = 5$) or a one-on-one interview ($n = 4$), of whom five had previously participated in a clinical trial (Supplementary Table 2). All participants endorsed the idea of an addendum to the ICF.

"That's why an index might be nice. Something will catch your eye. Oh, I want to see this first, or then the patient can determine right from the start their first question, they could find the answer to whatever they're concerned about," stated a participant with no trial experience.

Table 1 summarizes participant feedback. Although participants generally agreed on content and formatting (including suggestions to incorporate bullet points,

Table 1. Categories Participants Listed as Important to Include in an ICF Addendum to Aid Comprehension and Make an Informed Decision Regarding Trial Participation

Content	Exemplary Quote
Specific about study • Which drug is being tested and what is the other drug (e.g., What is experimental? What is control?) • Study is optional	*"…at least actually label which drug is the experimental one and which one is not the experimental one in case people aren't sure"* FG with no trial experience
Specifics about the study protocol • How the drug will be administered and how frequently • Length of study and brief statement about what comes next (continue drug if effective, provided until commercially available, etc.) • Explanation (bullet points) of criteria to qualify for the study • If tests and further screening is required, which tests	*"…the steps the patients have to take: what tests they have to, do they have to have a biopsy or not, all the tests they have to do, getting a blood test and CT scan-stuff like that"* Interviewee trial experience *"… something about how long the study will take … and what would be done afterward"* FG with trial experience
Risks • Most common adverse effects snapshot	*"Quick snapshot of the of the common side effects. I think the most common ones are the ones … to watch out for…"* FG with trial experience
Travel logistics and cost • Where is the trial happening? • Where treatment will take place, where tests will take place (e.g., Is travel involved? Will it be the same place for treatment and tests?) • What expenses are reimbursable?	*"… any guidance about how to interact with our insurance company or if there is an advocate … or social worker affiliated with the trial, you know, to help us with the … insurance and with travel plans"* FG with no trial experience
Privacy and confidentiality • Brief privacy statement: Patient assigned an ID number, info is confidential when third parties are involved—they only get patient ID	*"… third parties only get your patient number, no personal information"* FG with trial experience
Contact information clearly stated • All contact information in one place (study doctor, advocate and navigator, IRB)	*"I think a small list of all the important people would be helpful with where they're located, their phone number, or something like that..."* Interviewee with no trial experience

CT, computed tomography; FG, focus group; ICF, informed consent form; ID, identification; info, information; IRB, institutional review board.

tables, and a calendar), we observed differences in the preferred ordering of information according to trial experience. Patients who had previously participated in clinical trials suggested that trial eligibility be presented initially, as they would not continue with the consenting process if they knew they were ineligible for the study. Conversely, trial-naive patients prioritized having a clear explanation of treatment arms and common adverse effects, and a clear explanation of the trial phase.

"Somehow, start with letting them know there's a drug A and a drug B and you'll be put in one of the categories. … So, I would start with that and then definitely the side effects somewhere up on top…" stated a participant with no trial experience.

Discussion

Because efforts to simplify clinical trial ICFs have made relatively little headway, we instead investigated the possibility of providing patients with a brief ICF addendum, thereby enhancing understanding while still adhering to regulatory and site requirements. As reported previously, we found that most clinical trial ICFs were very lengthy[12] and written at a reading level well beyond the U.S. adult average of eighth grade.[13] Perhaps for these reasons, patients unanimously expressed interest in a brief summary of key points.

Although we presumed that patients would prioritize the inclusion of information routinely found in trial ICFs, for example, risks and benefits and privacy information, patients with previous trial experience suggested that trial eligibility criteria also be included. This unexpected recommendation may reflect the delay and disappointment associated with not qualifying for a trial. Over time, trial inclusion and exclusion criteria have increased in both number and stringency,[14] which may both increase the screening interval and decrease the likelihood of being eligible. The notion of expanding patients' role in this process may enhance both transparency and efficiency, as a patient may recognize an exclusionary concomitant medication or comorbidity far more quickly than a research coordinator or investigator combing through health records. There are also system improvements; for example, the IRB, which holds the authority to approve (or disapprove) the ICF, could require trial sponsors to uphold the requirement that ICFs be written in "language understandable to the subject."[2] In turn, this could lead to improving trial recruitment. Overall, we recognize that there needs to be a multipronged approach to engage more patients in clinical trials.[15]

There are some caveats to our findings. First, we recognize that informed consent represents a process encompassing detailed discussion with investigators and study staff, albeit unstandardized, unregulated, and guided by the ICF, and personal reading of the ICF. However, the ICF is the formal contract research participants enter into and is a document that, once signed, should leave the person feeling that it was nothing but a well-informed decision. Regarding readability and comprehension, readability is a proxy assessment that will penalize any efforts to simultaneously include technical terms and educate the reader. Moving forward in assessing the health literacy of these types of documents, a more comprehensive assessment of readability may be required. We also did not assess participant comprehension in the group of patients who reviewed the hypothetical ICF for our FGs and interviews. In addition, the present report included feedback from a small sample size limited to U.S. patients. Education was not collected, however, as participants were recruited by means of patient advocacy groups whose communities tend to be highly educated and not be representative of the larger lung cancer community—we recognize this as an important limitation. Whereas our study focuses on lung cancer trials and the people it affects, the principles explored are applicable across cancer types.

In conclusion, clinical trial ICFs remain lengthy and complicated. Patients seem enthusiastic about the concept of an ICF addendum that might be imagined as a trial pamphlet for patients. This would be intended as a straightforward reference on key trial features, potentially including eligibility criteria, and not to replace the ICF. Moving forward, it will be important to gain the perspectives of a broader patient population, and input from other stakeholders such as study sponsors, IRBs, compliance experts, regulatory authorities, and investigators on the feasibility of an ICF addendum.

CRediT Authorship Contribution Statement

Bellinda King-Kallimanis: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing.

Andrea Ferris: Conceptualization, Methodology, Writing - review & editing.

Lisa Dropkin: Data curation, Formal analysis, Writing - review & editing.

Mariel Molina: Data curation, Formal analysis, Writing - review & editing.

Lydia Redway: Data curation, Formal analysis, Writing - review & editing.

David Gerber: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing.

Tracey Grant: Resources, Writing - review & editing.

Upal Basu Roy: Conceptualization, Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100575.

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