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Paving the way to a more effective informed consent process: Recommendations from the Clinical Trials Transformation Initiative

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ABSTRACT

Ethically sound clinical research requires that prospective study participants provide voluntary informed consent before any study procedures begin. The original intent was to provide the participant with clear, accurate information about study specifics (e.g., risks/benefits) to aid in the decision to participate. Broad consensus among sponsors, research staff, study participants, and advocates indicate that the current process could be improved to enhance participants' understanding of study-related information and meet the needs of individuals.

The Clinical Trials Transformation Initiative (CTTI) convened a project to identify problems in the current process and to formulate recommendations for improvement. A literature review, expert interviews, and multi-stakeholder meeting were conducted to identify barriers and develop solutions for a more effective informed consent process.

Four key topics were the foundation of the recommendations: 1) defining an effective informed consent process, 2) training research staff, 3) improving the informed consent document, and 4) exploring the use of electronic consent. The ideal informed consent process involves an ongoing, interactive conversation between the participant and knowledgeable, responsive research staff who were trained in best practices. The informed consent process should be supported by a tiered informed consent document that provides critically relevant information to aid in the decision to participate in a study.

Adoption of the CTTI informed consent recommendations should lead to a more participant-centric informed consent process. Participant involvement better meets the needs of participants and benefits the clinical trial enterprise by promoting a research culture that encourages informed participation in clinical studies.

1. Introduction

In accordance with medical ethics research on human subjects and federal regulatory requirements, it is necessary to obtain informed consent (IC) from prospective clinical study participants [1–3]. It is intended that through the IC process (ICP) the study participant will be provided with information on the study elements, including risks and benefits of participation, and that the participant's decision to engage in research is made autonomously. While the intention of the ICP is to provide participants with clear, study-specific information, evidence indicates that the current ICP revolves around cumbersome and ineffective IC documents (ICDs) that often do not meet the needs of study participants [4–6].

To help address the widely recognized need for improvement in the ICP, the Clinical Trials Transformation Initiative (CTTI; www.ctti-clinicaltrials.org) launched a multi-stakeholder Informed Consent Project, guided by the following objectives:

- Understand previous and current efforts to improve the ICP and ICDs, including alternatives to the traditional paper ICD.
- Recognize barriers and identify potential remedies to concisely communicating the required elements of IC.
- Propose a more effective process, including IC documentation, to ensure study participants' understanding of critical IC elements.

Using evidence gathered through a comprehensive literature review [7], expert interviews [8], and a multi-stakeholder meeting [9], the CTTI Project Team, composed of a diverse group of stakeholders from across

Abbreviations: CTTI, Clinical Trials Transformation Initiative; e-consent, electronic consent; IC, informed consent; ICD, informed consent document; ICP, informed consent process; IRB, institutional review board.

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the clinical study enterprise, developed recommendations around four key topics: 1) conducting the ICP, 2) training research staff, 3) improving the ICD, and 4) using electronic consent (e-consent). This manuscript describes the methods employed to delineate the current issues with IC and the solutions proposed via the CTTI Informed Consent Project Recommendations for a successful ICP.

2. Methods

2.1. Approach

The Informed Consent Project Team included individuals representing a wide range of stakeholders, including industry, academic institution, institutional review board (IRB), regulatory, patient advocate, and other important perspectives, following a multi-stakeholder approach that considers all groups equal partners. The team employed three main research strategies to address stated objectives: a literature review, a series of expert interviews, and an expert meeting. A high-level overview of these methods is described herein; detailed methods and results of the literature review and expert interview activities are described in two sister publications [7,8]. A summary of the major findings of the literature review and interviews is provided in Fig. 1.

The recommendations described in this manuscript represent consensus opinions from a diverse group of 60 experts who evaluated the findings of the evidence-gathering activities. The recommendations are intended to be viewed as describing a path forward for improving the ICP.

2.2. Literature review

For the literature review [7], initial project information-gathering activities included reviewing existing IC literature reviews to provide a high-level guide to the extent work on IC and to identify knowledge gaps. Forty-five review articles were assessed. The project team used these findings to guide development of a set of four parallel systematic reviews of the primary literature conducted between May and June of 2014 using iteratively developed search terms and restricted to publications in English during or after the year 2000. The systematic reviews focused on the following: 1) validated methods for evaluating the ICP, including consent forms; 2) operational barriers to change in IC; 3) factors associated with patient satisfaction with IC; and 4) the effect of IC on participation in clinical trials.

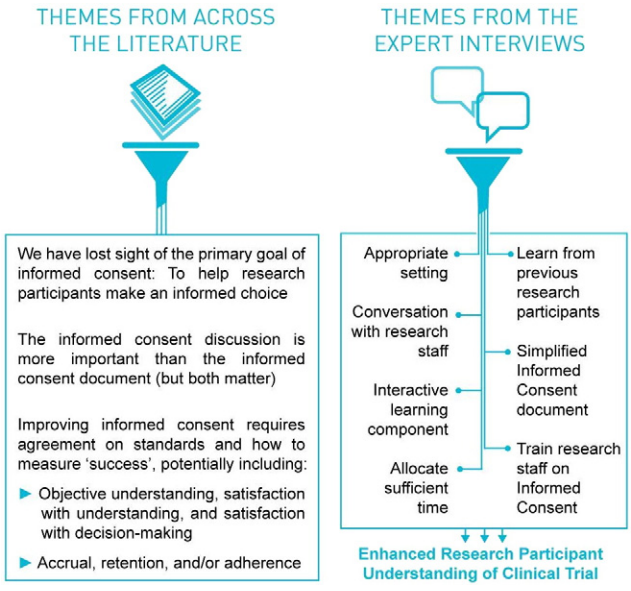

Fig. 1. Themes from the literature review and expert interviews.

2.3. Expert interviews

One-hour telephone interviews were conducted individually with twenty-five participants who were identified by the Project Team for their extensive knowledge of and experience with IC in the United States. A diverse set of stakeholders was included, including IRB chairs, ethicists, medical device and pharmaceutical senior executives, the United States Food and Drug Administration (FDA) and National Institutes of Health (NIH) medical officers/directors, patients and patient advocates, senior clinical-research coordinators, academic medical center professionals, an electronic consent (e-consent) company executive, and a nonprofit organization executive. The findings of these interviews are described elsewhere [8].

2.4. Expert meeting

The Informed Consent Project convened a two-day meeting [9] among approximately 60 stakeholders who represented academia, nonprofit organizations, government agencies, IRBs, industry, independent consulting companies, health systems, patient representatives, law firms, site representatives, and professional societies. Findings and key themes from the literature review and expert interviews were presented. Following these sessions, attendees formed discussion groups and brainstormed strategies to overcome barriers by proposing recommendations to transform the ICP, and methods to facilitate adoption of the recommendations. Discussion from throughout the meeting was used by the CTTI Project Team to later refine and finalize the IC recommendations through iterative, consensus-driven discussion.

3. Results & discussion

Based on the evidence-gathering activities, the CTTI Informed Consent Project Team agreed that the overall process of obtaining IC is paramount; therefore, any recommendations should begin by defining elements of an ideal ICP, with the goal of ensuring that study participants can make an informed choice regarding research participation.

3.1. Defining and conducting the informed consent process

It is well established that the ICP should ideally be an ongoing, interactive conversation between study participants and research staff that extends from the initial consideration of study participation through to completion [4,6,10]. In addition, the CTTI Project Team believed that the conversation should be customized to meet the particular needs of each study participant (Appendix A1). This requires that research staff be sensitive to participants' emotional disposition, culture, level of education, and inquiries, and be willing and able to explain key points of the ICD. Those staff obtaining consent should be skilled in communicating study-specific information and responsive to the needs and concerns of individuals considering participation.

To facilitate adoption of these ideals, CTTI developed a discussion tool for the ICP (Table 1). Although not intended to be a regulatory compliance document, this tool can help ensure 1) the specific needs of each study participant are considered, 2) critical elements of the study are reviewed and addressed, and 3) interactive techniques are used to facilitate study participants' understanding. It can also be used to document the ICP.

CTTI agrees with the general practice that IC should take place in a private, nonthreatening environment when the study participant is able to focus, and should include family or friends if the participant so desires. Resources should be provided to study participants to enhance their understanding of clinical studies, including sample questions to help participants better engage with the investigator in a dialogue

Table 1
CTTI's Informed Consent Discussion Tool.

I have considered:
A private, nonthreatening place to hold the informed consent discussion
Inclusion of family/friends in the informed consent discussion, as desired by the study participant
The study participant's individual needs and geared my discussion to match his/her

- Learning style
- Language facility
- Education level
- Health literacy
- Interest in learning as much as possible
- Comfort with numbers/probabilities
- Disabilities that may hinder the ICP

Providing the study participant with ample time to review the informed consent document and ask questions as needed
I have described, when appropriate, the following items to the study participant using plain language:

- Purpose of the research
  - Research procedures, including those that are experimental, relative to visits required for standard care
  - Duration of participation, compared to standard of care
  - Reasonably foreseeable risks/discomforts, compared to standard of care
  - Benefits to participants and others
  - Compensation for research-related injury
  - Additional costs to the study participant for participation, compared to standard of care
  - Voluntary nature of participation
  - Confidentiality of records
  - Available alternative treatments
  - Whom to contact with questions/concerns
  - Whom to contact in the event of a research-related injury
  - Availability of trial information on clinicaltrials.gov
  - Number of trial participants (if required)
  - Reasons for terminating participation by research team
  - Options for and consequences of research participant withdrawal
  - Statement that participants will be updated throughout the process and informed of significant new findings

I have:
Answered all of the study participant's questions before the document was signed, and proactively asked participants about their questions
Evaluated the study participant's understanding of the information discussed
Provided the study participant with a signed copy of the current version of informed consent document, and a copy of the detailed reference section

Following stakeholder and expert discussions, CTTI developed this tool to facilitate an improved informed consent process. This is one part of the official "CTTI Recommendations: Informed Consent;" the full recommendations and associated appendices are presented in Appendix A1.

about benefits and risks of participation [11,12]. Use of IRB-approved multimedia approaches (e.g., diagrams of procedures, study calendars) can also be considered to increase understanding. To evaluate a study participant's understanding, using the "teach-to-goal" method is recommended [13–15]. To gauge participants' accuracy and depth of knowledge, those obtaining consent can ask study participants to explain key points in their own words and pose open-ended questions.

Although study participants must sign the ICD, the document itself should be viewed as supportive to the overall ICP rather than the primary focus [10,16]. The IRB-approved ICD can be used as an outline for the ICP, but an interactive discussion is more conducive to study participants' understanding [4,6,17,18]. Once the ICD is signed, follow-up conversations should occur periodically to correct any misconceptions; remind participants of anticipated side effects, upcoming procedures, and the voluntary nature of their participation; and provide information about study progress. Tools, such as an Informed Consent Discussion Tool (Table 1), can be used to ensure that important messages are delivered. These recommendations may increase interaction between study participants and the staff obtaining consent, and help ensure study participants have the information they need to make an informed decision.

3.2. Research staff training

To deliver the most accurate information in an efficient and responsive manner, the research staff should be educated on the ICP and the specific study they will be discussing. Proper training of those participating in the ICP is likely to benefit staff, study participants, and sponsors alike [7]. With training, research staff may become more confident in the accuracy of their knowledge, improve their interaction skills, and maintain the highest ethical standards. Other benefits include a more streamlined ICP, increased assurance that study participants receive appropriate information and have the best experience possible, and compliance with regulations.

CTTI recommends that research staff designated to obtain consent attend training programs designed to improve their knowledge and communication skills, including best practices to impart study-specific information while remaining sensitive to study participants' needs. Training programs should be determined by individual research sites and tailored to local and organizational needs. Programs need not be required, nationally driven, or sponsor-specific. However, it may be helpful for professional organizations and/or the NIH to develop comprehensive programs that research sites can choose to use fully or partially as their organizational ICP training program.

Learning styles vary among people, which can pose a challenge for developing a training program to meet the needs of numerous individuals. The Informed Consent Project Team used learning theory resources [19–21] to develop the framework for the ideal training program, which includes 1) didactic information, 2) interactive opportunities, and 3) continuing education as needed. Didactic training imparts facts and information that the learner should understand about the ICP and establishes a foundation and framework for additional training; it may be part of general research training. Interactive training provides learners an opportunity to apply information from didactic training, including practicing or observing ICP best practices and communication techniques. Continuing education provides an opportunity for learners to reflect or receive feedback on their experience managing the ICP and consider ways to improve the process in future situations. Suggestions for each component of the training program to facilitate a more successful ICP are presented in Table S1.

Study participants should be included in the development and/or implementation of training programs, using currently available resources for meaningful patient engagement [22,23]. Training programs should be evaluated periodically, and processes should be adjusted as needed to ensure the needs of trainees are met [24]. Furthermore, the benefits and effectiveness of training should be assessed.

3.3. Improving the informed consent document

An ICD is an essential element of the ICP; however, often the ICD seems to place greater emphasis on satisfying a variety of legal and institutional needs than on facilitating study participants' understanding [16]. The literature review and expert interviews suggest that ICDs often use overly complex language and are too lengthy and confusing for many participants [7,8].

At the same time, information needs may vary widely: some study participants want access to all the information available, whereas others might benefit from and prefer a brief summary of the information that is most relevant to the decision-making process [7]. Education, cultural differences, and health literacy also may affect study participants' ability to fully understand information in an ICD. As a result, many research participants may sign the ICD without adequately understanding the content.

CTTI recommends the use of a tiered approach in developing the ICD. The first tier of the document should contain only the basic elements of IC required by federal regulation. Those developing the ICD must critically assess whether information in this tier is truly required. The second tier of the ICD should contain additional information, in chapter

format, on a range of study-related issues for each study participant to review as he or she deems necessary. As some participants may elect to bypass this section, information that is critical to the decision-making process should not be introduced for the first time in the second tier. An optional introductory tier consisting of a 1- to 2-page summary of the study may be valuable for complex studies.

Draft ICDs should be evaluated using health literacy/plain language assessments, reading level assessments, and usability testing with patients similar to those who would be eligible for the study [25,26]. Simplifying language, limiting the amount of information presented, and incorporating pictograms or lists have been shown to increase patients' comprehension of the information in the ICD [6,27]. It may also be worthwhile to develop and reach consensus on a standard language library for text that is not specific to the study, and is universally accessible and widely acceptable to IRBs, study sponsors, investigators, and others involved in preparation of the ICD.

3.4. Use of e-consent

Electronic consent ("e-consent") [28,29] may offer another way to facilitate the ICP. E-consent is IC that is interactive, delivered via electronic media, and may contain multi-media functions. In agreement with previous findings [30–32], CTTI Project Team findings suggest that the unique attributes of e-consent systems may support an improved ICP [33], and provide a good framework for implementation of the Tiered Consent model. Advantages plus detailed examples of opportunities provided by e-consent are described in Table S2.

Although barriers still remain in the adoption of e-consent (e.g., concerns about security/confidentiality, lack of well-established processes, initial development costs, and global acceptance of e-signatures), the advantages seem to outweigh the concerns. CTTI encourages sponsors and research sites to continue exploring the use of e-consent and share best practices and lessons learned [6,32,34]. Achieving widespread adoption may be accelerated by demonstrating, via interventional studies, that e-consent is superior to traditional consent processes using metrics such as 1) study participants' comprehension of information presented in the ICP/ICD, 2) study participants' satisfaction with decision making and the ICP, 3) retention of study participants, and 4) protocol compliance by study participants [6,32].

4. Conclusions

The Informed Consent Project Team focused their efforts on achieving consensus across a wide range of stakeholders on which aspects of the ICP need improvement and to provide general recommendations for best practices. The ideal ICP should facilitate interactive conversations between the study participant or prospective participant and a well-trained, responsive research staff supported by a clear, tiered ICD that incorporates plain language principles and flexibility with IC approaches. This helps to ensure that study participants adequately understand the content, enhancing the effectiveness of the ICP. The recommendations in this manuscript serve to place the study participant at the forefront of considerations related to the ICP, and to promote a research culture that facilitates health-literate IC. CTTI recognizes that implementation of new processes in clinical research is often challenging and will work to drive adoption of these recommendations across the clinical trial enterprise.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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