The informed consent process for clinical research is one that includes personal interactions, the informed consent document, and an individual’s decision about whether to participate in research. The intent is to enable an individual to make a decision about participation on the basis of a clear understanding of the research, its risks and benefits, and the commitments associated with enrolling in the study. While there is no ideal standard for the informed consent process, we looked at informed consent with the assumption that the consent process should be understandable, that participant satisfaction with the consent process matters, and that a good consent process will improve retention and adherence within a study. An effectively communicative informed consent process may aid recruitment, but the goal should be for potential research participants to make an informed decision, not simply to opt in to a research study.

The informed consent process as it currently exists often fails to accomplish these objectives. Long and complex informed consent documents and informed consent processes may obscure the information most relevant to the potential research participant and appear to be designed primarily to serve the role of protecting institutions and meeting regulatory needs rather than to inform the potential participant. The proposed revisions to the Common Rule announced in September 2015 suggest that a shorter informed consent document is preferable, but a key question is whether such a change will accomplish the objectives described above.

Based on the idea that there are opportunities to improve the consent process, the Clinical Trials Transformation Initiative (CTTI) initiated the Informed Consent Project, with objectives to identify and understand existing informed consent improvement efforts, identify barriers to communication of informed consent elements, and develop recommendations for improving the informed consent process that will enhance understanding by potential participants about the study for which they...
### Table 1.
**Search Strategy for MEDLINE and PubMed**

<table>
<thead>
<tr>
<th>Question</th>
<th>Concept</th>
<th>Medical subject headings terms</th>
<th>Text word searches</th>
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</thead>
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<tr>
<td><strong>All questions</strong></td>
<td>Informed consent</td>
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</tr>
<tr>
<td></td>
<td>AND Clinical trials</td>
<td>“Clinical Trials as Topic”</td>
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</tr>
<tr>
<td></td>
<td>AND Measurement of informed consent</td>
<td>“Quality Assurance, Health Care” OR “Health Care Surveys” OR “Health Impact Assessment” OR “Interviews as Topic” OR “Questionnaires” OR “Outcome and Process Assessment (Health Care)” OR “Quality Control” OR “Comprehension”</td>
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</tr>
<tr>
<td></td>
<td>AND Validation of the measurement instrument</td>
<td>“Evaluation Studies” [publication type] OR “Validation Studies” [publication type] OR “Validation Studies as Topic” OR “Randomized Controlled Trial” [publication type]</td>
<td>OR tested OR testing OR evaluate OR evaluates OR surveyed OR evaluating OR evaluation OR assesses OR assessed OR assessment OR assessing</td>
</tr>
<tr>
<td><strong>Question 2</strong></td>
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<td></td>
<td>OR Site</td>
<td>“Research Personnel” OR “Nursing Staff” OR “Medical Staff” OR “Nurses”</td>
<td>OR investigator OR investigators OR researcher OR researchers OR ((research OR study OR clinical) AND (nurse OR nurses OR coordinator OR coordinators OR site OR sites OR staff OR personnel))</td>
</tr>
<tr>
<td></td>
<td>OR Sponsor</td>
<td>“Drug Industry” OR “Support of Research” [Publication Type] OR “Research Support as Topic”</td>
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</tr>
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<td></td>
<td>AND Policies and procedures</td>
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<td>OR policy OR policies OR procedure OR procedures OR guideline OR guidelines OR rules OR practice OR regulation OR regulations OR standards</td>
</tr>
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<td>AND Barriers</td>
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<td>OR challenge OR challenges OR barrier OR barriers OR quality OR effectiveness OR understanding OR satisfaction</td>
</tr>
</tbody>
</table>
are being recruited. The project developed recommendations\(^3\) based on evidence gathered via the literature review discussed in this paper, a concurrently conducted series of qualitative interviews,\(^4\) and feedback from a diverse group of experts in attendance at a multi-stakeholder meeting.

Initial project information-gathering activities included reviewing existing informed consent literature reviews to provide a high-level guide to the extant work on informed consent and to identify knowledge gaps. Forty-five review articles were assessed and covered a range of topics, including but not limited to comprehension, decision-making, information disclosure, risk assessment, and communication. Among other important findings, these articles suggest that many patients may be enrolling in clinical trials without adequate understanding of fundamental concepts such as voluntariness and risk of participation;\(^5\) that empirical evidence is lacking with respect to what potential participants want to know before deciding to enroll and how information needs vary between individuals;\(^6\) and that no single intervention is most effective in improving participant understanding, but enhanced consent documents (e.g., with simplified language or a revised layout) and extended one-on-one discussion both appear helpful.\(^7\) The project team used these findings to identify four research questions for which a review of primary literature would help fill knowledge gaps, rather than duplicate previously conducted literature reviews. The primary literature review, described herein, was designed to gather information on the following areas of interest: 1) validated methods for evaluating the informed consent process, including consent forms; 2) operational barriers to change in informed consent; 3) factors associated with patient satisfaction with informed consent; and 4) the effect of informed consent on participation in clinical trials. This information may help direct meaningful changes for the informed consent process and documents used, including understanding the potential effects of proposed revisions to the Common Rule regarding consent requirements, consent forms, and the informed consent process.

### Literature Review Methods

Separate but parallel systematic searches were conducted between May and June 2014 to address each of the four areas of interest for the literature review. The following electronic databases were searched: PubMed and MEDLINE, EMBASE, the Cochrane Library, CINAHL, and ScienceDirect. Search terms were identified by iterative consultation with the project’s literature review team (see Acknowledgments) and through review of identified literature for potential additional terms. Table 1 shows the search strategies as they were implemented within PubMed and MEDLINE. Searches were restricted to publications in English during or after the year 2000.

Reference libraries were maintained and any duplications of a given publication eliminated within EndNote reference management software. Each library of potentially relevant literature was screened twice and in each case by two independent reviewers: first by title and abstract, with disagreement between reviewers resolved by adjudication. Identification of multiple publications describing the same study was addressed during the subsequent data extraction and analysis. Identifying literature was assessed for relevance to the research question of interest as well as adherence to the following inclusion criteria: 1) primary literature describing empirical research (except for Questions 3 and 4).

<table>
<thead>
<tr>
<th>Question 3</th>
<th>AND Patient satisfaction</th>
<th>“Quality of Life” OR “Personal Satisfaction” OR “Patient Satisfaction” OR “Consumer Satisfaction” OR “Patient Preference” OR “Happiness” OR satisfaction OR satisfied OR satisfy OR dissatisfaction OR dissatisfied OR “decision quality” OR (decision AND quality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question 4</td>
<td>AND Recruitment, retention, adherence</td>
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</tr>
</tbody>
</table>
tion 2, where opinion and editorial publications were also retained); 2) addresses informed consent for clinical trials of drugs, biologics, or devices; 3) focus is nonspecific to patient population or else includes an examination of informed consent for competent adults; 4) focus is nonspecific to country or else includes an examination of informed consent for the United States or other developed nations; 5) describes research conducted among actual prospective, active, or former clinical trial participants (except for Question 2). For Questions 3 and 4, satisfaction and adherence, respectively, were accepted as self-defined in each publication (i.e., reviewers did not impose a definition). We were not attempting to assess studies that addressed individuals' competence or capacity to consent to research.

Data characterizing the methods, findings, and author conclusions or recommendations of included publications were extracted via standardized data extraction forms, assessed for a minimum inter-rater reliability level of .80, and reviewed by a senior member of the research team for accuracy. Author conclusions or recommendations were extracted as a point of reference for the CTTI project team in preparing recommendations to improve the informed consent process, one of the primary goals of this work. Although the widely varying research methodologies of included primary literature did not allow data pooling and reanalysis with respect to research findings, it proved possible to identify a number of important themes via summary statistics and qualitative synthesis.

Results of Literature Review

Supplementary Figure 1 (available, along with Tables 2, 3, 4, and 5, via the IRB: Ethics & Human Research web page) shows the numbers of abstracts and full-text articles that were screened for each research question. The literature we finally included encompassed a range of in-person and telephone interviews, ethnographic analyses, quantitative instruments, and other methodologies. In some cases, data were collected from single clinical trials, and in others it was collected from multiple trials, populations within a particular area of interest, or patients at one or more research sites.

Question 1: What formal assessments have been done of tools and methods for measuring or evaluating informed consent in clinical trials? In order to evaluate the success of the informed consent process, having standardized measures is important. Formal assessments of five evaluative instruments for informed consent were described in the identified literature. Four of the instruments are quantitative in design (Table 2). Three assessments were primarily conducted in the U.S. and one in the United Kingdom (U.K.); for the other one, country was not fully specified. In each case, the goal was to develop an instrument that would measure important information that patients would be expected to understand before deciding to enroll in a clinical trial, focusing on types of information that would be important across a range of trials. Two of the instruments focus primarily on therapeutic misconception: the Therapeutic Misconception Questionnaire and the Therapeutic Misunderstanding Scale. The one qualitative instrument, the Brief Informed Consent Evaluation Protocol, assesses both therapeutic misconception and a general understanding of the elements of consent. The Quality of Informed Consent Questionnaire is intended for oncology trials following a traditional phasing (phase I, II, III, and IV) approach, and the Questionnaire—Patient Understanding of Research is intended for randomized trials.

To determine the rate of use of these instruments after the validation studies, we also reviewed the abstracts of publications citing the original article and searched PubMed for the name of the instruments and any variants. The instrument with the most subsequent use was the Quality of Informed Consent Questionnaire. It has been used in at least seven subsequent publications. All of the uses have been in oncology, so the instrument's utility in other domains requires further validation. The Questionnaire—Patient Understanding of Research was the only other instrument that has been used in a subsequent publication, in one other study.

For three of the identified instruments (Quality of Informed Consent Questionnaire, Brief Informed Consent Evaluation Protocol, and Questionnaire—Patient Understanding of Research), the authors measured average questionnaire-completion times and reported values of less than 10 minutes in each case, suggesting the burden on patients would be low. The most singular message from our review of tools for the assessment of consent was that there is little consensus on what makes an ideal consent process, but understanding was a core element of all of these instruments. The tools for assessment focused only on aspects of the consent process, like understanding or therapeutic misconception, and reflected a diverse set of views on what matters in obtaining consent. It is reasonable to conclude that if our research group wants to explore the effect of changing elements in the consent process, there is no one validated tool to which we can turn as a gold standard.

Question 2: What operational-level policies and procedures within clinical research sponsors, institutional review boards (IRBs), and/or investigative sites pose a barrier to implementing better informed consent processes? Because there has been longstanding discontent-
ment with the consent process, we wanted to understand why attempts to further improve the consent process have not been successful in changing the current standard. Nineteen publications were identified that characterized operational barriers to changing standard informed consent processes (Table 3). Of these, seven described new empirical research, and twelve described a research-based perspective or recommendations, but not new research. Most publications (14 of 19) were focused on perspectives in the U.S., though two presented Canadian perspectives, one focused on the U.K., and three examined perspectives in both the U.S. and one or more additional countries.

Barriers identified by these publications include the introduction into the consent document of challenging and ambiguous legal language by IRBs and sponsors in order to reduce liability. It was also reported that investigative site staff feel a substantial disconnect between what they are asked to discuss with research participants and the realities of what they are able to communicate during an actual informed consent discussion. Related concerns include the observation that site staff members may be asked to convey more information about potential side effects than participants find helpful and that time-pressure from aggressive enrollment targets may lead to staff behaviors that place the needs of the trial before the needs or protection of potential research participants.

Of all the operational barriers that were identified included lack of accepted readability standards or methods for assessing readability of consent documents, varying interpretation of regulations, and IRB staffs’ not having received adequate training in plain-language practices.

As identified by the publications, potential consequences of the failure to address these barriers could range from delays in study start-up and completion to patients’ feeling overwhelmed or frightened and making decisions about study participation too quickly and with too little understanding. Authors overwhelmingly suggested both that IRBs, research sites, and sponsors may have lost sight of the need to help research participants make an informed choice as the primary purpose of the informed consent process and that improving the process must start with a collective effort by the research enterprise to ensure that patients’ needs are put first. Specifically, authors recommended more effective collaboration among IRBs, research sites, and sponsors to achieve the following: educate IRBs on the risks of the protocol so that only relevant risks are included in the consent document, collaborate with IRBs before meetings to agree on a template and layout of the consent document, have IRBs stress key elements of the consent process to site staff members and then follow up with the site to ensure implementation of these elements, and better understand and integrate the realities of the consent process into the prospective IRB review of the research study.

Additional recommendations targeted at IRB-related barriers included maintaining a core group of IRB attendees to reduce inconsistency and arbitrary comments, as well as solidifying decisions into boilerplate language. Some authors believed that to reduce variability in IRB interpretations, more guidance is needed from regulators on unclear aspects of the federal regulations. Authors generally agreed that centralized IRB review would be most effective for multicenter studies, though some advocated for structured options for sites about whether to accept central review approval, modify central review to account for local factors, or use local review entirely, especially for situations in which there are important cultural or other local considerations to account for. Authors also called for consistency across IRBs in terms of the level of review and regulatory compliance decisions that would fall under the central review process.

Suggestions for sponsors were related to improving processes for drafting the informed consent document. These included providing accepted reading-level recommendations, developing a robust glossary of lay language, avoiding words that confuse research with treatment, and training staff responsible for drafting and reviewing consent documents on using simplified language and doing a readability analysis for each paragraph.

Site-related recommendations were aimed at avoiding therapeutic misconception. These included assisting investigators in resolving role conflicts as physicians versus researchers and ensuring that consent practices for research are distinct from those used in the clinical practice setting.
**Question 3: What factors are associated with greater or lower patient satisfaction with the informed consent process?** We identified 12 studies (as reported across 13 publications) that evaluated satisfaction with the informed consent process (Table 4). Most of these studies (9 of 12) were in the oncology setting, and almost all of the patients evaluated had opted to enroll in the study for which consent was being requested, as opposed to being part of the population who declined to participate. Studies were evenly distributed between those that used qualitative interview-based methodologies and those that were quantitative and used survey instruments. Four of the published studies evaluated a consent-related intervention, while 8 observed the standard consent process. The publications came from nine different countries in Europe and North America, so the consent process was not constrained by the regulations of any one country.

Considering the qualitative studies first, there were several factors associated with satisfaction or dissatisfaction with the consent process. In general, providing sufficient time to consider consent was well-supported as a positive factor. Three studies reported that feeling rushed or having limited time to deliberate was a problem. One study specifically noted patient satisfaction with having time to think things over. Being asked to sign the consent document and feeling involuntarily responsible for the choice of treatment were two other negative factors cited, though it is notable that one of these studies examined informed consent for an interventional trial in patients with myocardial infarction, and the other examined informed consent in phase I and phase II cancer trials. Both too much detail and not enough detail in the informed consent document and associated materials were cited as issues. Finally, a friendly physician who encouraged questions and used positive language in the consent process was cited as a positive factor for satisfaction.

Quantitative evaluation of satisfaction with the informed consent process used a range of metrics. Two of the six survey studies (as reported across three publications) used the same instrument, the six-item Satisfaction with Health Care Decisions scale, which was developed for and tested in the context of health care decisions and does not appear to have been explicitly validated with patients making decisions about participation in clinical trials. While trends were hard to find, the clearest lesson was that patients' belief that they understood the proposed research, or subjective understanding, was more important to their satisfaction than objective understanding (i.e., knowledge demonstrated via assessments).

The most consistent recommendations from the authors who evaluated satisfaction were that the training of the informed consent presenter matters and that sufficient time should be allowed for potential research participants to consider the consent decision. Further, authors noted the critical importance of understanding and meeting the sometimes widely varying needs of different patients enrolling in the same trial. In part for this reason, the informed consent discussion may be more important for potential research participants than the documents, because a well-conducted consent discussion can be more readily tailored to the types and depth of information each patient needs in order to make what they perceive to be a good decision about whether to participate.

**Question 4: In what ways does informed consent increase or reduce enrollment, retention, or protocol adherence of participants or prospective participants in clinical trials?** Fifteen publications were identified that examined the effect of the informed consent process or document and participant enrollment, retention, and/or adherence in clinical trials (Table 5). Twelve of the studies used a quantitative, survey-based methodology that examined different aspects of the consent process (as defined by each study and summarized below and in Table 5), and three used a qualitative, interview-based methodology. Studies were conducted across the following countries: Canada (1 study), the U.K. (5 studies), and the U.S. (9 studies).

None of the identified publications examined the relationship between retention of study participants and informed consent. A single publication examined the potential relationship between comprehension during the informed consent process and research protocol adherence. In this study, participants in a 12-month Parkinson’s disease trial completed a questionnaire at their last trial visit that evaluated understanding of study information explained during the informed consent process. Scores were analyzed against treatment adherence as measured by tablet counts. No statistically significant correlation between the two was identified.

The main focus of the majority of the identified publications was the effect of the informed consent discussion or document on participant enrollment in a clinical trial. Factors of the consent discussion that were associated with a higher likelihood of participant enrollment included a friendly physician who was easy to maintain a conversation with, trust in clinical research personnel, an in-home consent visit by a nurse (as part of a comprehensive recruitment approach), and the use of positive language or positive framing of information. Factors of the consent discussion that were associated with a decreased likelihood of enrollment included a less-friend-
ly physician who was a poor communicator and the presentation of complex information in a limited amount of time. Three of the identified studies found evidence that individuals may be deciding whether to participate in a clinical trial before the informed consent discussion takes place.

There was less evidence that the informed consent document or supporting materials positively or negatively affected participant enrollment. Six studies suggested that the standard informed consent document was essentially a nonfactor in the enrollment decision. In one of these studies, for example, patients who read the consent document agreed that it was helpful for understanding the study but indicated that they would have made the same decision without having read it. One study described a potential research participant who decided against enrollment because of the length and complexity of the consent document. Three tests of enhanced consent documents (a document easier to read, supplemental brochures containing study-specific versus general clinical trial information, use of audiovisual materials) also found no effect on enrollment, though one intervention that included a video as well as an educational session and presentations by doctors and former trial participants was found to increase enrollment of eligible patients.

Author recommendations for improving the informed consent process included focusing on the importance of the informed consent discussion, as opposed to the document, and ensuring that those conducting the consent process are fully aware of factors or conditions (such as those summarized above) that may affect the decision to participate in a study. Also proposed was the use of independent personnel (i.e., not someone directly involved in the trial) to present trial information so that prospective participants receive an unbiased view of the study. Continuous communication of key study information to research participants throughout the study, not just at the beginning, was noted as important to enhance compliance. Finally, the publications recognized that future research is needed on the decision-making process between patients and their physicians, especially involving patients who choose not to enroll, to better understand their motivations for not participating in clinical trials.

Discussion

Although the Belmont Report has long established informed consent as fundamental to the ethical conduct of clinical research, as an application of the principle of respect for persons, the current implementation of the informed consent process in the U.S. may often prioritize the needs of institutions over the needs of prospective clinical trial participants. In attempting to determine why problems with informed consent persist despite recognition of the need for continuous improvement, this systematic review of the informed consent literature focused on better understanding barriers to change within the research enterprise. We identified not only operational challenges, such as inconsistent review by IRBs and confusion about regulations, but also incomplete understanding of what patients want and expect from the informed consent process. Perhaps the greatest challenge in addressing this situation is that the research enterprise lacks accepted, proven tools for measuring the quality of informed consent or even agreement as to how “quality” should be defined to best meet the needs of all stakeholders, patients as well as researchers. We even see evidence, although limited, that the current state of affairs, and the research enterprise’s failure to achieve meaningful change, may have hindered the ability to conduct ethical clinical trials.

Summary findings related to operational barriers to improving informed consent suggest that improvements to the informed consent process may not be delivered promptly due to system fragmentation, with IRBs, sponsors, and sites working in isolation and focused on their individual needs rather than those of the research participant. Greater use of central IRBs may resolve several important barriers to improving the standard informed consent process. As central IRBs have been widely recognized as potentially useful for a more focused review process, the greatest challenge may come in implementation. Potential solutions are being actively explored, including proposed revisions to the Common Rule that would require use of a single IRB of record for multisite research with few exceptions (e.g., FDA-regulated device trials).

While there is no “gold-standard” metric for evaluating adequacy of informed consent from the research participant perspective, studies found that research participant satisfaction with consent is varied, potential research participants have widely differing information and communication needs, and it is hard for a single document to meet those requirements. The reviewed publications suggest that many issues seem to be best addressed through the informed consent discussion, moderated by a well-trained member of the research team. Therefore, we may see substantial improvements to the informed consent process with a focus on process and conversation over document, and with a better-trained community of researchers and staff members. There may also be potential for electronic consent to support an improved and more flexible consent process in the future, and it should also be feasible to develop printed consent documents that better cater to the widely
varying informational needs of different participants in order for each individual to make an informed decision about participation in clinical research. A challenge in shortening consent documents, as proposed in revisions to the Common Rule, is determining what information is essential to include. As noted in this and other systematic reviews, there is a lack of empirical evidence for determining what information and what levels of detail belong in the informed consent process. Thus, an important step will be defining gold-standard metrics for evaluating the quality of informed consent.

Findings from the literature review also suggest that prospective participants’ interactions with investigative-site staff members can both positively and negatively affect the enrollment decision. The effect of the informed consent discussion raises ethical concerns, with some evidence indicating that enrollment can be increased when site personnel frame trial information positively, even unintentionally. It can be asked, “Is it good to sell a study to potential participants?” In addition, while we have some information about how the informed consent process can affect enrollment, there are less data available regarding how informed consent acts as a driver of patient behaviors during the trial, if at all. There is a logical argument to be made, however, that a better consent process (as measured, for example, by patient understanding and satisfaction) would lead to greater retention rates and adherence.

Two points were clear from the review of the literature on formal assessments of tools and methods for evaluating informed consent in clinical trials. First, there is no single instrument that has been agreed upon as a tool to evaluate strategies to improve the consent process. Second, while “understanding” is the goal most often being assessed by the current instruments, there is no consensus as to what needs to be understood. Therapeutic misconception is an obvious focus, for example, but the narrow focus of the therapeutic misconception evaluation tools misses many important elements of the consent process. Until more widely accepted instruments to assess the outcome of the consent process are developed, it will be difficult to compare novel strategies that aim to improve the informed consent process.

There are limitations to the literature available for review. The studies revealed strong weighting toward oncology, as well as toward middle-age, middle-class Caucasians. While the latter skew may be supportable as representing the typical clinical trial participant in developed nations (as several of the reviewed papers claimed), the bias toward one therapeutic area substantially limits the extent to which findings can be reasonably extrapolated. The additional bias toward conducting research among patients who decided to enroll in a trial leaves us blind to important differences that may exist among patients who decided not to enroll. These limitations are important to consider when designing further research.

This literature review identified and confirmed important gaps in knowledge related to informed consent, thereby informing subsequent stages of the CTTI Informed Consent Project. Further project activities included the development of specific recommendations for improving informed consent, which have been posted on the CTTI website. The data gathered in this literature review will also serve as a resource for other professionals and organizations seeking to improve the informed consent process.

Figure and Tables
Supplementary Figure 1 and Tables 2, 3, 4, and 5 are available via the IRB: Ethics & Human Research web page, part of The Hastings Center website.

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10. See ref. 8, Chou and O’Rourke 2012.

11. See ref. 8, Appelbaum et al. 2012.

12. See ref. 8, Chou and O’Rourke 2012.


15. See ref. 8, Hutchinson et al. 2007.


17. See ref. 17, Ferguson 2003.


22. See ref. 17, Gogtay et al. 2011.


