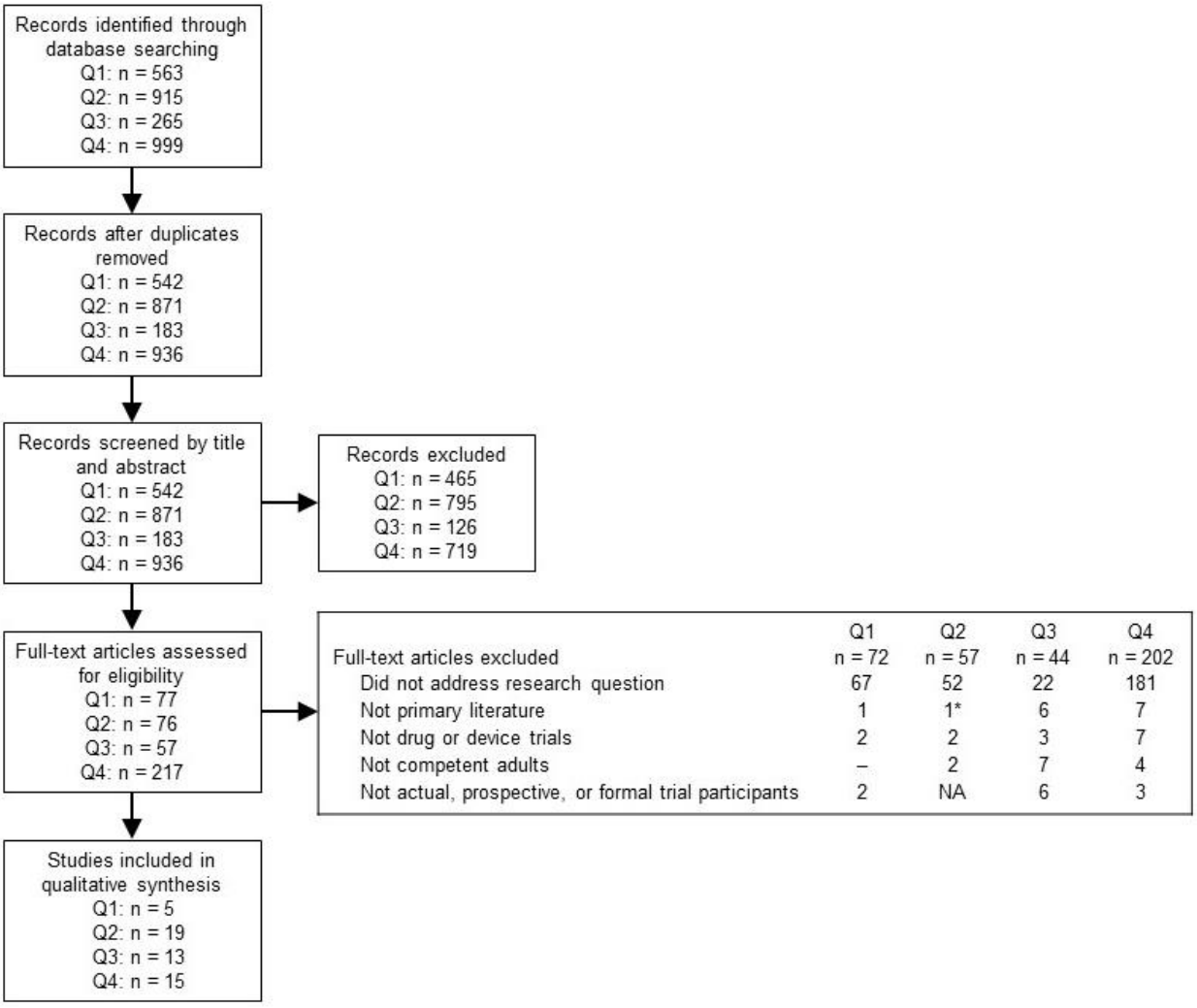
Figure 1.
Literature Review Flow Diagram

Question 1 (Q1): What formal assessments have been done of tools and methods for measuring or evaluating informed consent in clinical trials? Question 2 (Q2): What operational-level policies and procedures within clinical research sponsors, IRBs, and/or investigative sites pose a barrier to implementing better informed consent processes? Question 3 (Q3): What factors are associated with greater or lower patient satisfaction with the informed consent process? Question 4 (Q4): In what ways does informed consent increase or reduce enrollment, retention, or protocol adherence of participants or prospective participants in clinical trials?



Full-text articles excluded	Q1 n = 72	Q2 n = 57	Q3 n = 44	Q4 n = 202
Did not address research question	67	52	22	181
Not primary literature	1	1*	6	7
Not drug or device trials	2	2	3	7
Not competent adults	–	2	7	4
Not actual, prospective, or formal trial participants	2	NA	6	3

*For Q2, opinion and editorial publications were retained, but literature reviews were excluded.

Table 2.

Formal Assessments of Instruments for Evaluating Informed Consent (Question 1)[8]

Reference	*Instrument*	*Description*	*Administration*	*Study population*[a]	*Therapeutic area*[a]	*Content validity*	*Construct validity*	*Internal consistency*[b]	*Test-retest*[c]
Appelbaum (2012)	Therapeutic Misconception (TM) Questionnaire	10-item scale measuring misunderstanding of the degree of individualization of the intervention, the likelihood of benefit, and the purpose of research as intended to benefit future patients	Verbally, in person, or by telephone after consent was obtained	N = 189 45% female, ages ranged from < 30 to > 70 years, 81% completed at least some postsecondary education, 100% enrolled in trial	Psychiatry, oncology, neurology (phase I-III drug* trials)	Yes	Factor analysis, criterion	0.90	–
Chou and O'Rourke (2012)	Therapeutic Misunderstanding Scale (TMU)[d]	20-item scale measuring therapeutic misconception, therapeutic misestimation (of risks and benefits), and undue therapeutic optimism	Online	N = 37 for actual and prospective participants	NS	Yes	Factor analysis, criterion	0.92	0.49
Hutchison (2007)	Questionnaire—Patient Understanding of Research	12-item scale measuring knowledge and understanding of RCTs	At the clinic or taken home and returned by mail	N = 26 62% female, ages 38 to 76 years	Oncology	Yes	Discriminative	0.77	–
Joffe (2001)	Quality of Informed Consent (QuIC)	34-item scale measuring objective and subjective understanding attained during informed consent process	By mail or delivered in hospital 3 to 14 days after ICD was signed	N = 207 55% female, mean age 55 years, 53% had a college education, 100% enrolled in trial	Oncology (phase I-III drug trials)	Yes	–	–	0.66-0.77

Reference	*Instrument*	*Description*	*Administration*	*Study population*[a]	*Therapeutic area*[a]	*Content validity*	*Construct validity*	*Internal consistency*[b]	*Test-retest*[c]
Sugarman (2005)	Brief Informed Consent Evaluation Protocol (BICEP)	12 open-ended probes for telephone administration, measuring therapeutic misconception and general understanding of informed consent elements	By telephone immediately after informed consent process	N = 632 26% female, mean age 67 years, 72% had some college education, 100% enrolled in trial	Various (most not drug or device trials)	Yes	–	–	–

See note 8 in the article for the full citations for all references in Table 2.
ICD = informed consent document; NS = not specified; RCT = randomized controlled trial.
*Denotes data interpreted or estimated by reviewer when not fully specified in publication.
[a]Population information extracted: sex, age (mean, range), ethnicity, postsecondary education, proportion enrolled in trial, phase of trial. If not present in table, information was not specified in the publication.
[b]Standard is 0.7-0.9.
[c]Standard is 0.7-0.8.
[d]Factor analysis conducted with general population; psychometric data for trial participants presented but highly limited.

Table 3.

Publications Describing Operational Barriers to Better Informed Consent (Question 2)[17]

Reference	*Article focus*	*Objective*	*Design*	*Methods*
ASCO (2003)	IRB	Enhance public trust in the cancer clinical trials process	Opinion/editorial	–
Brody and Miller (2003)	Site	Discuss possible role conflict between the investigator and treating physician	Opinion/editorial	–
Cook et al. (2008)	IRB	Discuss challenges associated with randomized clinical trials in vulnerable populations	Opinion/editorial	–
De Ville et al. (2007)	IRB	Discuss experience reorganizing an IRB	Opinion/editorial	–
DeBruin et al. (2011)	Sponsor, site	Describe ethical and professional concerns encountered by clinical research nurses	Observational research	7 focus groups among 37 nurses
Denzen et al. (2012)	IRB	Recommendations for the development and formatting of easy-to-read ICDs	Opinion/editorial	–
Ferguson et al. (2003)	Sponsor	Medical researchers' views on the level of information given to participants and participant understanding	Observational research	Interviews among 78 principal investigators
Frank et al. (2008)	IRB	Discuss challenges encountered while running a multinational trial at two institutions	Opinion/editorial	–
Glickman et al. (2011)	IRB	Describe variability in policies for a population with limited English proficiency	Opinion/editorial	–
Gogtay et al. (2011)	Site	Medical researchers' views on the level of information given to participants and participant understanding	Observational research	Interviews among 78 principal investigators
Iltis et al. (2013)	IRB	Discuss risk communication in mental health research	Opinion/editorial	–
Kao et al. (2003)	IRB	Description of challenges that a single institution encountered while participating in a multicenter study	Opinion/editorial	–
Klitzman et al. (2008)	IRB	Examine differences in perceptions of the informed consent process among U.S. IRBs and IRBs in South Africa	Observational research	Survey of IRB/REC members (n = 113 respondents)
Kotecha et al. (2011)	IRB	Description of challenges encountered by CPCSSN when seeking approvals for multisite trial across IRBs	Opinion/editorial	–

Reference	*Article focus*	*Objective*	*Design*	*Methods*
Koyfman et al. (2013)	IRB	Determine the relative readability and length of IRB-approved ICDs used at seven academic institutions with their corresponding cooperative group ICDs. Also assess the variability of these metrics across institutions.	Observational research	Analysis of 197 ICDs from 56 cooperative group trials
Mackin et al. (2009)	Site	Discuss recruitment barriers for older adults for clinical trials in the hospice setting	Opinion/editorial	–
McNay et al. (2002)	IRB	Compare experiences across countries regarding ethical issues for a single protocol; study impact of U.S. regulatory processes	Opinion/editorial	–
Pogorzelska et al. (2010)	IRB	Describe changes in IRB submission practices and implications	Observational research	Comparison of IRB experiences in 2 studies conducted in 2002 and 2008
Silverman et al. (2001)	IRB, sponsor	Determine variability among IRBs on approved research practices and ICDs for a multisite trial	Observational research	Survey of approved research practices among IRBs, review of IRB forms for readability and content, review by a separate IRB

See note 17 in the article for the full citations for all references in Table 3.
ASCO = American Society of Clinical Oncology; CPCSSN = Canadian Primary Care Sentinel Surveillance Network; ICD = informed consent document; IRB = institutional review board; REC = research ethics committee.

Table 4.

Studies on Patient Satisfaction with the Informed Consent Process (Question 3)[29]

Reference	*Description*	*Study population*[a]	*Therapeutic area*[a]	*Satisfaction metrics*	*Factors increasing satisfaction*[b]	*Factors decreasing satisfaction*[b]	*Factors with no effect*[b]
Quantitative							
Coyne et al. (2003)	RCT of easy-to-read vs. standard ICD; assessment via telephone survey 1 to 2 weeks after signing consent but before treatment began	N = 207 91% female, mean age 53 years, 52% completed at least some postsecondary education, 85% enrolled in trial	Oncology (phase III drug trials)	4-item consent anxiety scale; 4-item scale of patient satisfaction with ease of reading and understanding consent statement	Intervention: easy-to-read ICD (lower consent anxiety, satisfaction with ease of reading and understanding)	NA	–
Hietanen et al. (2007)	Investigated whether a short course in communication skills for physicians would improve the quality of informed consent; survey administered by mail 3.5 months after randomization	N = 288 100%* female, mean age 50 years, 50%* completed at least some postsecondary education, 100% enrolled in trial	Oncology (drug trials)	Satisfaction with consent discussion and adequacy of information for making enrollment decision via distinct single-item responses	Intervention: investigator communication training (satisfaction with consent discussion)	NA	Intervention: investigator communication training (adequate information for making decision)
Jefford et al. (2011)	Survey administered approximately 5 to 10 days after signing of consent	N = 102 33% female, age 29 to 85 years, 51% completed at least some postsecondary education, 100% enrolled in trial	Oncology (phase I-III drug trials)	Satisfaction with decision to participate via previously published Satisfaction With Decision scale	Subjective understanding	NA	Objective understanding, depression, anxiety, age, desire for participation in decision-making, perceived level of actual participation in decision-making, global quality of life

Reference	*Description*	*Study population*[a]	*Therapeutic area*[a]	*Satisfaction metrics*	*Factors increasing satisfaction*[b]	*Factors decreasing satisfaction*[b]	*Factors with no effect*[b]
Pope et al. (2003)	Survey administered by mail 2 months to 5 years after signing of consent	N = 190 56% female, age 22 to 84 years, 36% completed at least some postsecondary education, 100% enrolled in trial	Rheumatol-ogy, ophthalmol-ogy cardiology (primarily phase III drug trials)	Satisfaction with informed consent process via single item	–	NA	Objective understanding
Sørensen et al. (2004)	Survey administered at clinic immediately following the informed consent review (second discussion)	N = 68 31% female, age 37 to 79 years	Oncology (phase II and III drug trials)	Adequacy of treatment information, adequacy of information for making enrollment decision, satisfaction with consultation via distinct single-item responses	Informed consent for randomized trial (treatment information adequate, patients felt able to decide)	NA	Physician experience (satisfaction with consultation)
Stryker et al. (2006)	Two-part survey administered by mail shortly after patients identified for trial and again 6 weeks after	N = 50 78% female, 72% younger than 56 years, 75%* completed at least some postsecondary education, 100% enrolled in trial	Oncology (phase I-III drug trials)	Satisfaction with decision-making via previously published Satisfaction With Decision scale; decisional regret via 10-item scale	Subjective understanding	NA	Waiting to sign consent
Wray et al. (2007)	RCT of trial-specific vs. general brochure; assessment via survey administered by mail 2 to 8 weeks after initial appointment in which patient was identified as trial candidate	N = 92 75%* female, mean age in the "46-55-year-old range," 75%* completed at least some postsecondary education	Oncology (drug* trials)	Satisfaction with decision-making via previously published Satisfaction With Decision scale	–	NA	Intervention: trial-specific supplemental written information

Reference	*Description*	*Study population*[a]	*Therapeutic area*[a]	*Satisfaction metrics*	*Factors increasing satisfaction*[b]	*Factors decreasing satisfaction*[b]	*Factors with no effect*[b]
Qualitative							
Ågård et al. (2001)	Semistructured interviews administered at the clinic after signing ICD for trials of treatment in the very early phase of acute myocardial infarction	N = 31 29% female, age 46 to 85 years, 23% had an education level higher than compulsory schooling, 100% enrolled in trial	Cardiology or vascular diseases (drug and device trials)	NA	–	Too little time to deliberate, being asked to give written informed consent to participate in the study, feeling involuntarily responsible for the choice of treatment	–
Behrendt et al. (2011)	Combined unstructured and semistructured interviews administered at the clinic within 6 months of patients' being informed about trial	N = 10 40% female, age 18 to 69 years, 80% enrolled in trial	Oncology (phase III drug* trials)	NA	Trial physician described as friendly and dedicated; physician encouraged questions; presence of "significant others," relatives, and nurses	Physician's language and structure of consultation, pressured by the trial physician ("It all went so fast.")	–
Cox (2002)	Semistructured interviews administered in patient homes or clinic at the point of trial recruitment	N = 55 60% female, age 37 to 74 years, 100% enrolled in trial	Oncology (phase I and II drug trials)	NA	Information about trial presented to patients in positive language	Where patients acknowledged that the choice of trial participation rested with them (~20%), making a decision was anxiety provoking, ICD could have been more detailed, ICD an additional burden in relation to the amount of information patients were already given, inability to ask questions due to being so shocked by all that was happening	–

Reference	*Description*	*Study population*[a]	*Therapeutic area*[a]	*Satisfaction metrics*	*Factors increasing satisfaction*[b]	*Factors decreasing satisfaction*[b]	*Factors with no effect*[b]
Knifed et al. (2008)	Semistructured interviews administered at the clinic* within 1 month of ICD signing; patients were presumed to be under significant stress due to their grave diagnoses	N = 21 33% female, ages 26 to 65 years, 57% completed at least some postsecondary education, 100% enrolled in trial	Neuro-oncology (phase I-III drug* trials)	NA	Having time to think their decisions over	A few patients felt that the whole process was too rushed but also realized the urgency of their situation, so they were more satisfied than upset; two patients who expressed some dissatisfaction with the process wished there had been more information available regarding the study and indicated that taking the informed consent papers home to read was not enough.	–
Locock and Smith (2011)	Combined unstructured and semistructured interviews administered at the patient's home or preferred location an unspecified period of time after accepting or declining participation	N = 42 64% female, age 38 to 84 years, most* enrolled in trial	Wide variety of trials	NA	–	Long leaflets, being left alone reading a leaflet without the immediate opportunity to ask questions	–

Reference	*Description*	*Study population*[a]	*Therapeutic area*[a]	*Satisfaction metrics*	*Factors increasing satisfaction*[b]	*Factors decreasing satisfaction*[b]	*Factors with no effect*[b]
Sand et al. (2008)	RCT of original vs. shortened ICD; assessment via semistructured interviews administered 90 minutes to 30 hours after receipt of ICD	N = 21 43% female, age 44 to 84 years, 52% completed at least some postsecondary education	Oncology (phase III drug trials)	NA	–	Desire for additional information (medication or treatment and side effects, study results, who to contact, general or unspecified desire), redundant information (detailed explanations unnecessary or some elements could be removed from the text, depending on each patient's degree of illness)	Intervention to minimize text in ICD on "formalities" (publishing, financing, insurance, approving authorities, etc.); this information not brought up or perceived as insignificant

See note 29 in the article for the full citations for all references in Table 4.
ICD = informed consent document; NA = not applicable; RCT = randomized controlled trial.
*Denotes data interpreted or estimated by reviewer when not fully specified in publication.
[a]Population information extracted: sex, age (mean, range), ethnicity, postsecondary education, proportion enrolled in trial, phase of trial. If not present in table, information was not specified in the publication.
[b]For quantitative studies, two types of information were collected: factors that increased satisfaction (with those that decreased satisfaction implied) or factors that had no effect. For qualitative studies, information was collected on factors that increased satisfaction, decreased satisfaction, or had no effect.

Table 5.

Studies Examining the Relationship between Informed Consent and Trial Enrollment or Adherence (Question 4)[39]

Reference	*Description*	*Study population*[a]	*Therapeutic area*[a]	*Factors assessed*	*Enrollment or adherence metric*	*Key findings*
Enrollment						
Cox (2002)	Semistructured interviews conducted before, during, and after trial participation; results focus on interviews at point of trial recruitment	N = 55 60% female, mean age 59 years (range 37 to 74), 100% enrolled in trial	Oncology	Contribution of informed consent discussion and standard ICD on decision to participate	Patient self-report	Positive language was used in the informed consent discussion, which may have influenced decision to enroll. Standard ICD was perceived as a useful reference but not as a replacement for the verbal discussion. The majority of patients wanted their doctor to make a decision for them.
Coyne et al. (2003)	RCT of easy-to-read vs. standard ICD; assessment via telephone survey 1 to 2 weeks after signing consent but before treatment began	N = 207 91% female, mean age 53 years, 93% Caucasian, 52% completed at least some postsecondary education, 85% enrolled in trial	Oncology (phase III drug trials)	Intervention: easy-to-read ICD	Trial accrual data	Accrual rates between the intervention group and the control group did not differ significantly.
Gotay (2001)	Mailed questionnaires about trial experience in participants' second year of trial participation	N = 69 100% male, mean age 68 years (range 50 to 83 years), 39% Caucasian, 74% with at least some college education, 100% enrolled in trial	Oncology	Contribution of standard ICD on decision to participate	Patient self-report	Most had no remembrance of the consent process, and only a minority (not significant) reported that the ICD had helped in decision-making about study participation. Twenty-seven of 40 reported that the consent process did not help them in deciding to participate.
Grant et al. (2000)	Telephone interview of patients who were eligible for a clinical trial and who had recently discussed participation with	N = 130 51% female, mean age 60 years, 71% enrolled in trial	Oncology	Patients' perceptions of their physicians' communicative behavior during informed consent	Patient self-report	Patients who agreed to participate perceived their physician to be friendlier, having a better communicator image, and being less attentive vs. patients that declined to participate.

Reference	*Description*	*Study population*[a]	*Therapeutic area*[a]	*Factors assessed*	*Enrollment or adherence metric*	*Key findings*
	their physician			discussion and decision to participate		
Hutchison et al. (2007)	RCT of audiovisual patient information plus standard ICD vs. standard ICD alone	N = 173 77% female, 29% with degree-level or higher education, 74% enrolled in trial	Oncology	Intervention: audiovisual patient information	Consent rates	There was no difference in recruitment rates between the two groups. Audiovisual patient information was shown to be useful in improving patient knowledge and reducing patient anxiety.
Kenyon et al. (2006)	Qualitative interviews conducted post trial and after participants received a summary of study results	N = 20 100% female, 95% Caucasian, 0% educated to university level, 100% enrolled in trial	Obstetrics (RCT of antibiotics in preterm labor)	Contribution of consent discussion and standard ICD on decision to participate	Patient self-report	Most made the decision to enroll based on the socioemotional aspects of the informed consent discussion rather than informational content. Close to half of the participants recalled being provided the ICD, but the form did not appear to affect their decision to participate.
Kernan et al. (2009)	Comparison of a multi-institutional recruitment strategy, including the use of an in-home consent visit by a nurse vs. conventional recruitment strategies	N = 763 37% enrolled in trial. Enrolled population: 38% female, mean age 67 years	Cardio-vascular	In-home consent visit by a nurse (as part of a comprehensive recruitment strategy)	Average monthly randomization rate	The comprehensive recruitment strategy sites experienced higher enrollment rates than conventional sites. The high enrollment rate was the result of surveillance at multiple institutions and greater average productivity. In-home consent visit not directly tied to higher enrollment; however, implied to remove a barrier to participation.

Reference	*Description*	*Study population*[a]	*Therapeutic area*[a]	*Factors assessed*	*Enrollment or adherence metric*	*Key findings*
Locock and Smith (2011)	At-home semistructured interviews conducted with former trial participants and patients who declined to participate, did not meet eligibility criteria, or withdrew early from a trial	N = 42 64% female, ages 38 to 84), 90% Caucasian	Various	Contribution of informed consent discussion and standard ICD on decision to participate	Patient self-report	The length and complexity of the ICD led one participant to decline enrollment. Highlights importance of informed consent discussion, tailoring information presented, and ensuring enough time is allocated to address patient questions/concerns.
Patel et al. (2004)	Patients offered a variety of perioperative RCTs were asked to complete a questionnaire 1 to 2 days after surgery	N = 52 (31 had consented, and 21 refused to participate) 57% female; mean age 55 years (consenters), 44 years (nonconsenters) (range 36 to 68 years); Caucasian: 47% (consenters), 54% (nonconsenters); completed at least some college: 70% (consenters), 54% (nonconsenters)	Surgery	Contribution of standard ICD, discussion with doctor/staff, and trustworthiness on decision to participate; decision to enroll made in advance of informed consent discussion	Patient self-report	Patients who read the ICD concurred that it helped them understand the study. However, 100% of those patients agreed that they would have made the same decision to participate without the ICD. Perceptions of the study staff requesting participation was determined to be more of a predictor of consent (i.e., trusting the staff).
Pentz et al. (2002)	Patients referred by their doctor to a phase I trial were interviewed in person, by telephone, or by mail; classified as pre- or post-informed consent	N = 100 (79 were pre-informed consent) mean age 56 years (range 25 to 79 years), 86% Caucasian, 69% had at least some college education,	Oncology	Contribution of standard ICD and discussion with staff on decision to participate; decision to enroll made in advance of discussion	Patient self-report	The pre- and post-informed consent groups did not differ In terms of their decision to enroll if they were offered a place in the trial, suggesting that they had made their decision to participate in advance of the consent discussion and/or a lack of effect of the informed consent process

Reference	*Description*	*Study population*[a]	*Therapeutic area*[a]	*Factors assessed*	*Enrollment or adherence metric*	*Key findings*
	depending on whether they had met with investigators to discuss the trial	96% enrolled in trial				on their decision.
Shannon-Dorcy and Drevdahl (2011)	Semistructured interviews conducted before trial, and approximately 80 and 365 days after trial	N = 25 patients and 20 caregivers 44% female, mean age 54 years (range 22 to 69 years), 80% Caucasian, 100% enrolled in trial	Oncology (early-stage phase II trials)	Decision to enroll already made in advance of informed consent discussion, contribution of standard ICD on decision to participate	Patient self-report	Almost all patients had already decided to participate well in advance of consent discussions. Most did not reread the ICD (with some not reading it at all), and some deliberately chose to ignore some of the information presented because it was too overwhelming.
Stevens and Ahmedzai (2004)	Qualitative interviews of patients with breast cancer who declined participation in adjuvant therapy trials; interviews scheduled postdiagnosis, with follow-up interviews 6 and 12 months later	N = 22 100% female, ages 42 to 70 years, 100% Caucasian, 100% *not* enrolled in trial	Oncology (breast cancer)	Effect of consent discussion, lack of prior clinical research knowledge on decision not to participate	Patient self-report	Presentation of complex information in limited amount of time can lead to information overload and decision not to enroll. Interactions with research personnel may also influence decision to participate.
Wallace et al. (2006)	Multidisciplinary educational session as part of informed consent vs. conventional process	N = 218 0% female, 16% enrolled in trial	Oncology	Intervention: educational session, video, presentations by former trial participant and doctors	Consent rates	The intervention group achieved a 1 in 6 consent rate among eligible patients. The control group accrued 0 patients.
Wray et al. (2007)	RCT of tailored informational materials vs. standard materials; mailed surveys 2 and 8 weeks after	N = 92 75% female, ages 46 to 55 years, 90% Caucasian, 70% completed at least some college, 100%	Oncology	Intervention: tailored informational materials	Patient self-report	No significant differences were identified between the intervention group and the control group on satisfaction with materials and decision-making elements.

Reference	*Description*	*Study population*[a]	*Therapeutic area*[a]	*Factors assessed*	*Enrollment or adherence metric*	*Key findings*
	consent discussion and receipt of materials	enrolled in trial				
Adherence						
Ravina et al. (2010)	Questionnaire at final visit of 12-month Parkinson's disease trial	N = 149 34% female, mean age 61 years, 96% Caucasian, average 15-year education, 100% enrolled in trial	Neurology	Long-term comprehension of key study information, how comprehension was related to cognitive function, and if comprehension was related to compliance and satisfaction with study procedures	Tablet count	No correlation between comprehension and compliance was identified.

See note 39 in the article for citations for the references in Table 5; for a few of the publications, note 39 directs readers to note 29 for the full citation.
ICD = informed consent document; NA = not applicable; NS = not specified; RCT = randomized controlled trial.
[a]Population information extracted: sex, age (mean, range), postsecondary education, proportion enrolled in trial, phase of trial. If not present in table, information was not specified in the publication.