INFORMED CONSENT

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Disclaimer

- The views expressed are mine and do not necessarily represent the policies of the Department of Bioethics, National Institutes of Health, or the Department of Health and Human Services.

- I have no conflicts of interest to disclose

Informed consent

- What is informed consent?
- Why is it important to clinical research?
- What are some of the enduring and emerging challenges?

Consent

- A moral and legal protection from unauthorized invasions of one's body and property
- A facilitative moral power- making certain interpersonal conduct permissible that otherwise would be prohibited as wrong
- Well entrenched in societal values, jurisprudence, and health care

Informed consent

- Authorization of an activity based on understanding what the activity entails.
- A legal, regulatory, and ethical requirement in most health care and most research with human subjects
- A process of reasoned decision making (not a form or an episode)
- Autonomous authorization (Faden and Beauchamp 1986)

Ethical requirement

- Respect for autonomy - an individual's capacity and right to define his/her own goals and make choices consistent with those goals.

- "Informed consent is rooted in the fundamental recognition…that adults are entitled to accept or reject health care interventions on the basis of their own personal values and in furtherance of their own personal goals" Presidents Commission for the study of ethical problems…1982

- Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided…[when] informed consent are satisfied. Belmont Report

Informed consent in clinical research

- Unlike clinical care in which the goal is to improve the patient's medical condition, the goal of research is to produce knowledge.

- Special importance to the ethical injunction against using people for the benefit of others without their valid consent.

- One aspect of conducting ethical clinical research

Informed consent in clinical research

- Codes of research ethics, regulations, and laws (limited exceptions) require informed consent from the research participant or her legally authorized representative (and documentation):
  - ICH-GCP
  - Declaration of Helsinki
  - US Federal Regulations (Common Rule (45CFR46) and FDA (21CFR50))
  - National, state, institutional requirements

Research Informed consent: Regulatory requirements

- …no investigator may involve a human being as a subject in research ..unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative…(45CFR.46.116, 21CFR.50.20) (limited exceptions)

- Informed consent must be sought prospectively, and documented to the extent required under 45 CFR 46.117 and 21CFR50.27.

Informed consent

- "Informed consent involves providing a potential subject with adequate information to allow for an informed decision about participation in the clinical investigation, facilitating the potential subject's comprehension of the information, providing adequate opportunity for the potential subject to ask questions and to consider whether to participate, obtaining the potential subject's voluntary agreement to participate, and continuing to provide information as the clinical investigation progresses or as the subject or situation requires."

- US FDA Informed Consent Guidance Sheet, July 2014

Elements of informed consent

- (Capacity to consent)
- Disclosure of information
- Comprehension
- Voluntariness
- (Consent authorization)

Prototypical research informed consent

- Discussion of study information
- Written consent form
- Signatures

MEDICAL RECORD

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY
• Adult Patient or • Parent, for Minor Patient

INSTITUTE:

STUDY NUMBER: PRINCIPAL INVESTIGATOR:

STUDY TITLE:

Initial Review Approved by the IRB on Date Posted to Web:
Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

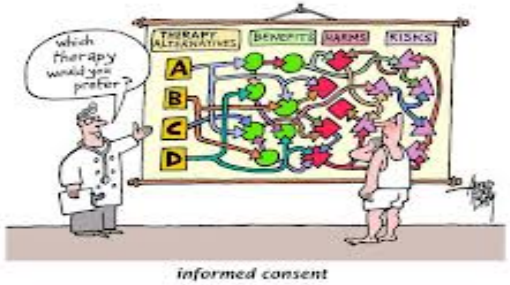
First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

Disclosure of information: Issues and challenges

- What information should be disclosed?
- How should the information be presented?
- Circumstances and setting?



Disclosure of information

- Written consent form
  - A summary of study information–explanation of what the study is about, the procedures, related risks and possible benefits, alternatives, rights;
  - Elements required by regulations
- Advertisements, fliers, brochures
- (Reviewed and approved by IRB)

Writing and using a consent form

- Writing consent forms that are readable and understandable and explain the study
- Consideration of length, format, reading level, complexity
- How to use consent forms in discussion

Studies of consent form readability

- **Reading level is high**
  - Consent forms and templates usually written at about the 11th grade level or higher LoVerde et al, 1989; Grossman et al 1994; Paasche-Orlow et al., 2003; Sharp 2004
- **Consent forms are long**
  - Consent documents have increased in length over time Baker and Taub, 1983; LoVerde et al 1989; Tarnowski et al 1990; Beardsley et al 2007, Albala et al. 2010
- **Missing required or relevant elements**
  - Silverman et al. *Critical Care Medicine* 2001; Horng et al, *NEJM* 2002; Beardsley et al. *JCO* 2007; Abeysena C et al *Ind J Med Ethics* 2012

"Hey, no problem!"

Informed consent

- §___.116 (a)(5)(i) Informed consent *must begin with a concise and focused presentation of the key information* that is most likely to assist a prospective subject or LAR in understanding the reasons why one might or might not want to participate
- …organized in a way that facilitates comprehension.

Challenges

- What is key information?
- How to make it “concise and focused”
- What happens to the rest?

Challenges

- It is difficult to write concise and clear consent forms

  "Easy reading is damn hard writing."

  Nathaniel Hawthorne ~1840, Maya Angelou ~2000

- Written informed consent protects the institution or sponsor

- IRBs often make consent forms longer and more complex

Readable/understandable

- "The purpose of this study is to test the safety of XXX at different dose levels in patients with cancer who have different degrees of normal and abnormal liver function. XXX is an experimental drug that has not been approved by the FDA for use in patients with cancer. XXX was designed to enter cancer cells and block the activity of proteins that are important for cancer cell growth and survival. This is the first study in which XXX will be given to people with different degrees of liver function. We already know the safe dose for people with normal liver function…"

- We want to find a dose of XXX that is safe in patients with cancer whose livers are not working normally. XXX is an experimental drug that aims to block cancer cells from growing. It is not approved by the FDA for patients with cancer. We know the safe dose in patients with normal liver tests. This is the first time we will give XXX to people who have abnormal liver tests

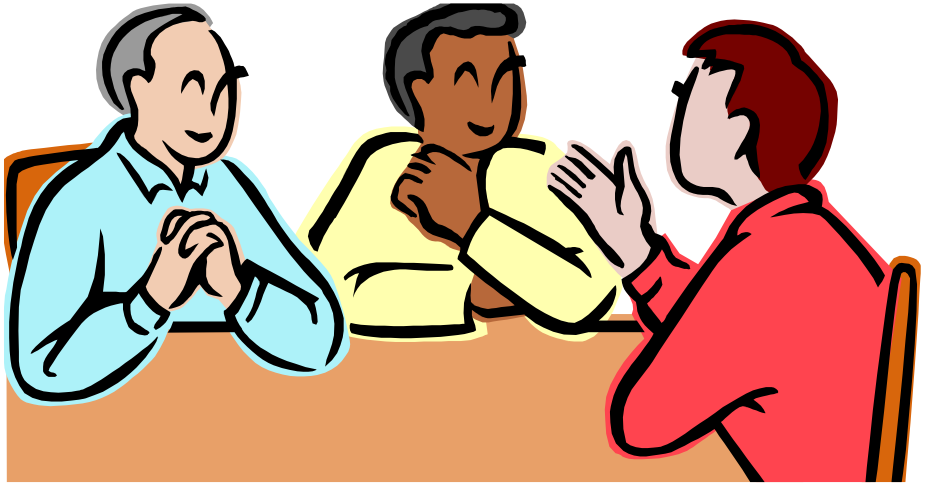
Informed consent

- §___.116 (a)(5)(ii) Informed consent as a whole must present information *in sufficient detail*…and be organized and presented in a way that does *not merely provide lists of isolated facts,* but rather *facilitates the prospective subject's or LAR's understanding of the reasons* why one might or might want to participate

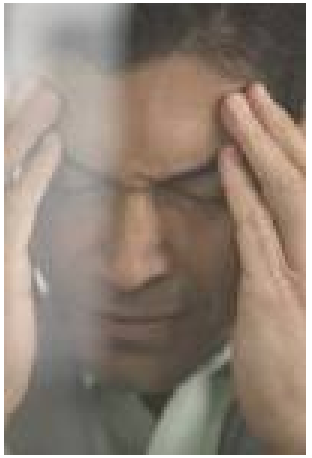
Easy-to-read informed consent documents

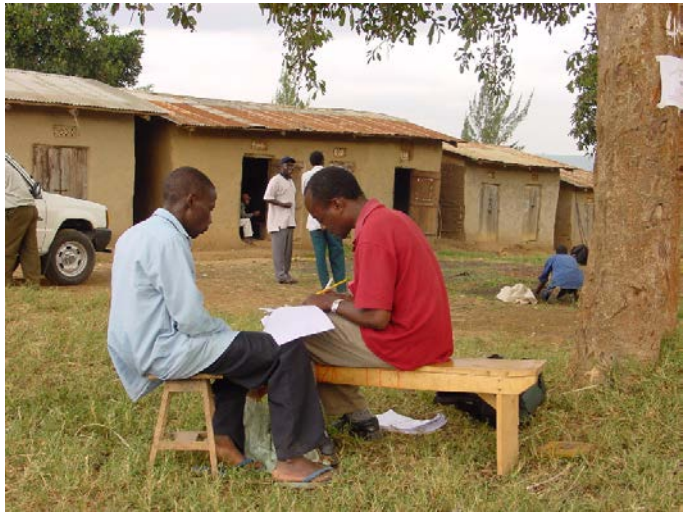
- Familiar, consistent words, Active voice and personal pronouns
- Short, simple, and direct sentences with limited line length
- Short paragraphs, one idea per paragraph.
- Clear and logically sequenced ideas
- Highlight Important points
- Avoid acronyms and abbreviations
- Format:
  - Titles, subtitles, simple headers
  - Balance white space with words and graphics
  - Font, style, spacing,
  - Underline, bold, or boxes (rather than all caps or italics) give emphasis.
- **From NCI Simplification of Informed Consent Documents, Appendix 3**. <http://www.cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/page1

Presentation



SETTING





Summary- disclosure

- What, where, who, when, and how matter
- Consent documents
  - usually include relevant information,
  - not always compliant with regulations,
  - are long, complex and written at a high level
- Disclosure by investigators variable- very few studies *
- Limited training for investigators

Changes affecting decisions about disclosure and informed consent

- Research methodologies
- Information technologies
- Understanding of informed consent
- Regulations and guidance

Research methodologies- research with data and biospecimens

- When is informed consent needed for research with data or biospecimens?
- What and how should research information be disclosed?

Consent for research with data and biospecimens

1. Shows respect, allows donors to control whether their samples and data are used for research.
2. Allows them to decide whether
   - research risks and burdens are acceptable.
   - to contribute to the goals of research, thus protecting and possibly promoting their non-welfare interests.
3. Promotes public trust and the ongoing viability of research

1. No (low) risk, further mitigated in other ways (de-identification, data security, etc.)
2. Consent bias can jeopardize science.
3. Tracking consent is logistically complex and expensive
4. In busy clinical environments-naïve to think meaningful consent is possible.
5. Public generally supports research with stored samples/data because of its value to society.

No consensus on acceptable consent

	TYPE OF CONSENT	DESCRIPTION
Less Control, Less burden	No consent	Do not obtain donor consent
	Blanket	Consent to future research with no limitations
	Broad*	Consent to future research with specified limitations
More control, more burden	Checklist	Donors choose which types of future studies are allowed
	Study specific	Consent for each specific future study

Grady et el. *AJOB* 2015

Information technologies

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2015–D–0390]

Use of Electronic Informed Consent—Questions and Answers; Guidance for Institutional Review Boards, Investigators, and Sponsors; Availability

AGENCY: Food and Drug Administration and Office for Human Research Protections, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP), Department of Health and Human Services (HHS), are announcing the availability of a guidance entitled ''Use of Electronic Informed Consent—Questions and Answers.'' The guidance is intended for institutional review boards (IRBs), investigators, and sponsors engaged in or responsible for oversight of human subject research under HHS and/or FDA regulations. The guidance provides recommendations on the use of electronic systems and processes that may employ multiple electronic media to obtain informed consent for both HHS-regulated human subject research and FDA-regulated clinical investigations of medical products, including human drug and biological products, medical devices, and combinations thereof. This guidance finalizes the draft guidance entitled ''Use of Electronic Informed Consent in Clinical Investigations—Questions and Answers'' issued in March 2015.

DATES: Submit either electronic or written comments on Agency guidances at any time.

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically,

as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *http://www.regulations.gov*

- If you want to submit a comme with confidential information th do not wish to be made availab public, submit the comment written/paper submission a manner detailed (see ''Writ Submissions'' and ''Instru

Written/Paper Submissio

Submit written/paper follows:

- *Mail/Hand delivery written/paper submissio* Dockets Management (H and Drug Administration Lane, Rm. 1061, Rockville
- For written/paper com submitted to the Division o Management, FDA will post comment, as well as any attach except for information submitte marked and identified, as confiden if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2015–D–0390 for ''Use of Electronic Informed Consent—Questions and Answers; Guidance for Institutional Review Boards, Investigators, and Sponsors; Availability.'' Received comments will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *http://www.regulations.gov* or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- *Confidential Submissions*—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The

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Products and Tobacco, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, Rm. 5108, Silver Spring, MD 20993, 301 796–6570; Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993–0002, 240–402–7911; Irfan Khan, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3459, Silver Spring, MD 20993, 1–800–638–2041 or 301–796–7100; or Irene Stith-Coleman, Office for Human Research Protections, 1101 Wootton Pkwy., suite 200, Rockville, MD 20852, 240–453–6900.

SUPPLEMENTARY INFORMATION:

I. Background

"…electronic consent refers to the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive and interactive Web sites, biological recognition devices, and card readers, to *convey information* related to the study and to obtain and document informed consent."

Table 1. Components and Challenges of Informed Consent with Traditional Paper Forms and Electronic Methods.

Component	Traditional Paper Informed Consent	Electronic and Digital Informed Consent	Challenges and Areas for Research
Disclosure	Information is written, usually on paper Discussion with investigator takes place, usually face to face	Consent can involve electronic information, multimedia information, video graphics, and interactive computer interfaces Investigator can be remote in time or place from participant	All types of disclosure require determining the appropriate content (amount and complexity of information) for disclosure User-friendly disclosure is needed Amount and style of information tailored to electronic platforms need to be determined
Understanding	Investigator and participant discuss information Participant asks questions Investigator assesses understanding, in some cases using questions, structured quizzes, other methods	Interaction can take place during disclosure Questions and assessment of understanding are easily built in Ongoing engagement is enabled Links to additional information can be included	Evidence indicates that people do not read click-through agreements on computers and mobile devices Information should be engaging and user-friendly to promote reading and understanding It may be difficult to assess capacity and understanding Empirical evidence to date indicates that video and multimedia consent strategies have not resulted in consistent advantages or disadvantages with regard to participant understanding[47]
Voluntariness	Investigator asks participant to make a choice in a setting free from coercion and undue influence Research team observes participant's body language and any hesitation	Some electronic systems facilitate participant control Participant can easily sign off or disengage Participant can decline	It may be difficult to assess voluntary choice without the clues of body language and tone It may be difficult to verify the identity of the person consenting Some data collection is passive In some cases, contributing data is a required part of the arrangement
Authorization	Paper consent document is signed Copies of document are kept in records	Options might include clicking agreement or an electronic signature Records of agreement are kept electronically	It may be difficult to verify the identity of the authorizing person

Grady C et al. N Engl J Med 2017;376:856-867.

Elements of informed consent

- Disclosure of information
- *Understanding / comprehension*
- Voluntariness
- Consent authorization

Understanding is variable

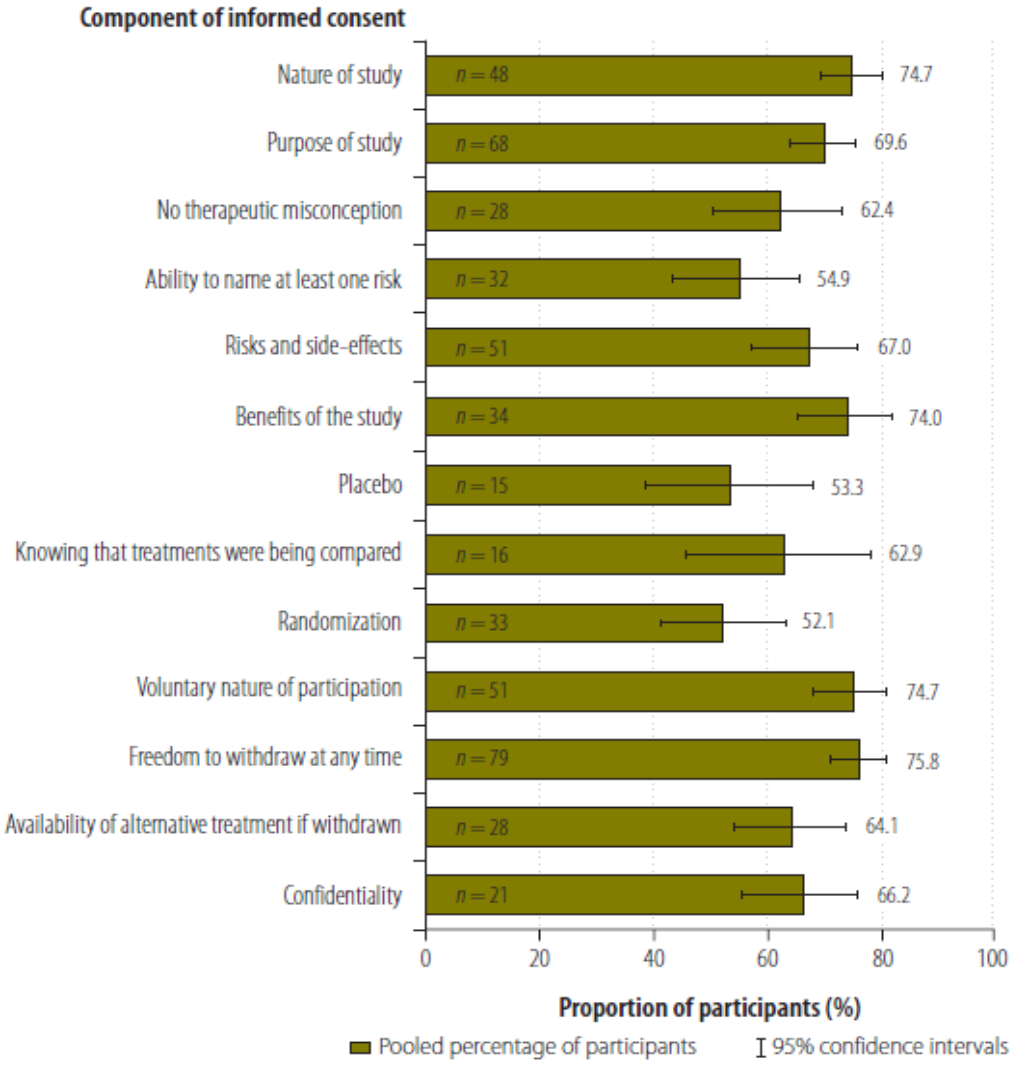
- Studies continue to show that research participants often have limited understanding of study information

e.g. Mandava A et al *J Med Ethics* 2012

Participant Understanding: Research Purpose/ Nature, Risks, and Randomization

- Range of understanding about the purpose and nature of research (27% -100%) Krosin et al 2006; Joffe et al 2001; Pace et al. 2005; Criscione et al. 2003
- Range of understanding about research risks (28%-100%) Bergler 1980; Joffe et al. 2001; Leach et al, 1999; Dougherty et al 2000
- Range of understanding about randomization (21%-42%) Harrison et al 1995; Hietanen 2000; Pace et al. 2005; Howard 1981

Fig. 2. **Participants' understanding of components of informed consent in clinical trials, by meta-analysis[a]**



[a] The number of studies included in the evaluation of each component is given.

Tam T et al. Bull of WHO 2015

Understanding: issues and challenges

- Factors that might affect understanding
- How is/should understanding be assessed?
- How much should participants understand?
- What happens (or should happen) when they don't understand?

What affects understanding?

- "Host" factors- Age*, education*, pain, cognitive capacity,* literacy

- Expectations and familiarity with research
  - Trust in providers, deference
  - Therapeutic misconception and related misunderstandings

- Process related factors
  - What is disclosed and how
  - How does participant listens to/reads the information?

Once you've estimated how long it takes to read the consent form you can time how long subjects take to read the consent form during the consent process, or ask them how long it took them to read the consent form at home. Unfortunately, I suspect you'll find most subjects not taking adequate time to read the consent form, but are scanning it fairly quickly.

Summary

Even though typical consent forms require subjects to sign that "I have read and understood this consent form…" that signature does not guarantee that subjects took enough time to read the consent form. Subjects may want to believe that they have read and understood the consent form; researchers may want to believe that their subjects have read and understood the consent form. If so, both are engaging in self-deception. Unless more direct evidence shows that subjects actually have read the consent form, it's probably wise to assume that they have not. If so, future research needs to focus on what--if anything--can be done to encourage subjects to take the time needed to read the consent form.

Table #2: Minutes to read a consent form

Consent Form Length (Words)	Very Slow Reading Speed (100 words/min)	Average Reading Speed (200 - 250 words/ min)	Fast Reading Speed (300 words/ min)
2,000	20 minutes	8 - 10 minutes	7 minutes
3,000	30	12 - 15	10
4,000	40	16 - 20	13
5,000	50	20 - 25	17
6,000	60	24 - 30	20
7,000	70	28 - 35	23
8,000	80	32 - 40	27
9,000	90	36 - 45	30
10,000	100	40 - 50	33
11,000	110	44 - 55	37
12,000	120	48 - 60	40

References

1. Davis, T.C., Holcombe, R.F., Berkel, H.J., et al. (1998) Informed Consent for Clinical Trials: a Comparative Study of Standard Versus Simplified Forms. *Journal National Cancer Institute*, 90, 668-674.
2. McNutt, L., Waltermaurer, E., Bednarcyk, R.A., et al (2008) Are We Misjudging How Well Informed Consent Forms Are Read? *Journal of Empirical Research on Human Research Ethics*, 3(1), 89-97.
3. Davis, T.C., Bocchini, J.A., Fredrickson, D., et al (1996) Parent comprehension of polio vaccine information pamphlets. *Pediatrics*, 97(6), 804-810.
4. Davis, T.C., Fredrickson, D.D., Arnold, C., et al (1998) A polio immunization pamphlet with increased appeal and simplified language does not improve comprehension to an acceptable level. *Patient Education and Counseling*, 33, 25-37.

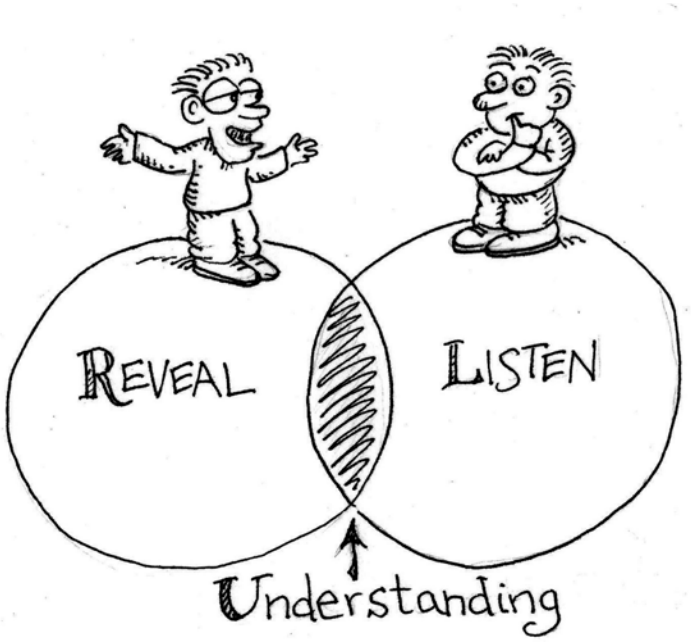
Challenges

- Complex Science
- Health literacy and capacity
- Measuring understanding
- Different kinds of "mis-understanding"
  - Misconception
  - Mis-estimation
  - Optimism

    Horng & Grady *IRB* 2003
- Knowledge v. appreciation

Understanding

- Knowledge of relevant information
- Appreciation of how it applies
- Therapeutic misconception



Therapeutic Misconception

- When a research participant fails to recognize how individualized medical care (i.e. physician obligation to make medical decisions in the patient's best medical interests) may be compromised by research procedures Appelbaum et al. IRB 2004

- Failure to recognize the differences between research and ordinary care negate the ability to provide meaningful informed consent. Appelbaum et al. KIE 2006

Strategies to improve understanding

- Multimedia (e.g. audiotapes, videotapes, interactive computers)
- Enhanced consent form (e.g. modified style, format or length)
- Extended discussion (with team member or neutral educator)
- Test/feedback (e.g. quizzes and review)
- Mixed and miscellaneous (e.g. online presentations, supplementary vignettes, etc)

Flory and Emanuel JAMA 2004; Nishimura A et al. *BMC Medical Ethics* 2013

Strategies to improve understanding

- Significant increase in understanding with enhanced consent form compared to controls (meta-analysis).

- "The question of whether "shorter forms are better (or no worse than) longer" for participant understanding is still an open question…need for direct comparison in randomized studies…"

Nishimura A et al. *BMC Medical Ethics* 2013

Strategies to improve understanding

- Randomized participants to either a concise or standard consent form.
- Does a simpler, more concise consent form affect study understanding or satisfaction with consent?
  - Healthy volunteers: Flu vaccine studies, Phase 1 drug development. Stunkel et al *IRB* 2010; Enama et al *Cont Clin Trial* 2012
  - Patient volunteers: Multinational HIV study. Grady et al *PloS One* 2017


IRB
ETHICS & HUMAN RESEARCH

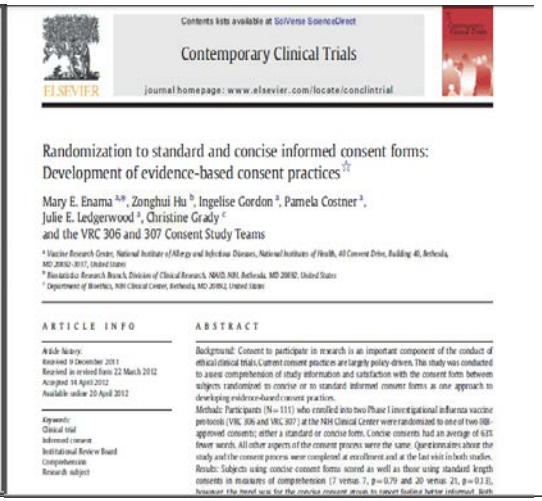
Comprehension and Informed Consent: Assessing the Effect of a Short Consent Form

IN THE FIELD

Assessing the Readability of Non-English-Language Consent Forms: The Case of Kiswahili for Research Conducted in Kenya

Comprehension and Informed Consent:
Assessing the Effect of a Short Consent Form

BY LEANNE STUNKEL, MEREDITH BENSON, LOUISE MCLELLAN, NINET SINAI, GABRIELLA BEDARIDA, EZEKIEL EMANUEL, AND CHRISTINE GRADY


Contents lists available at SciVerse ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Randomization to standard and concise informed consent forms: Development of evidence-based consent practices

Mary E. Enama, Zonghui Hu, Ingelise Gordon, Pamela Costner, Julie E. Ledgerwood, Christine Grady and the VRC 306 and 307 Consent Study Teams


PLOS ONE

RESEARCH ARTICLE

A randomized trial comparing concise and standard consent forms in the START trial

Abstract

Background

Methods

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Grady C et al. N Engl J Med 2017;376:856-867.

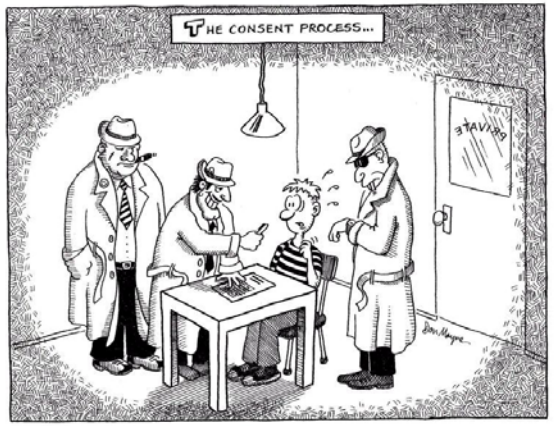
Improving informed consent

- More is not always better
- Timing matters
- Technology can help

Schenker Y and Meisel A, *JAMA 2011*

Voluntariness

- Able to make a voluntary choice?
- No deception, coercion, undue influence



Possible influences on voluntariness

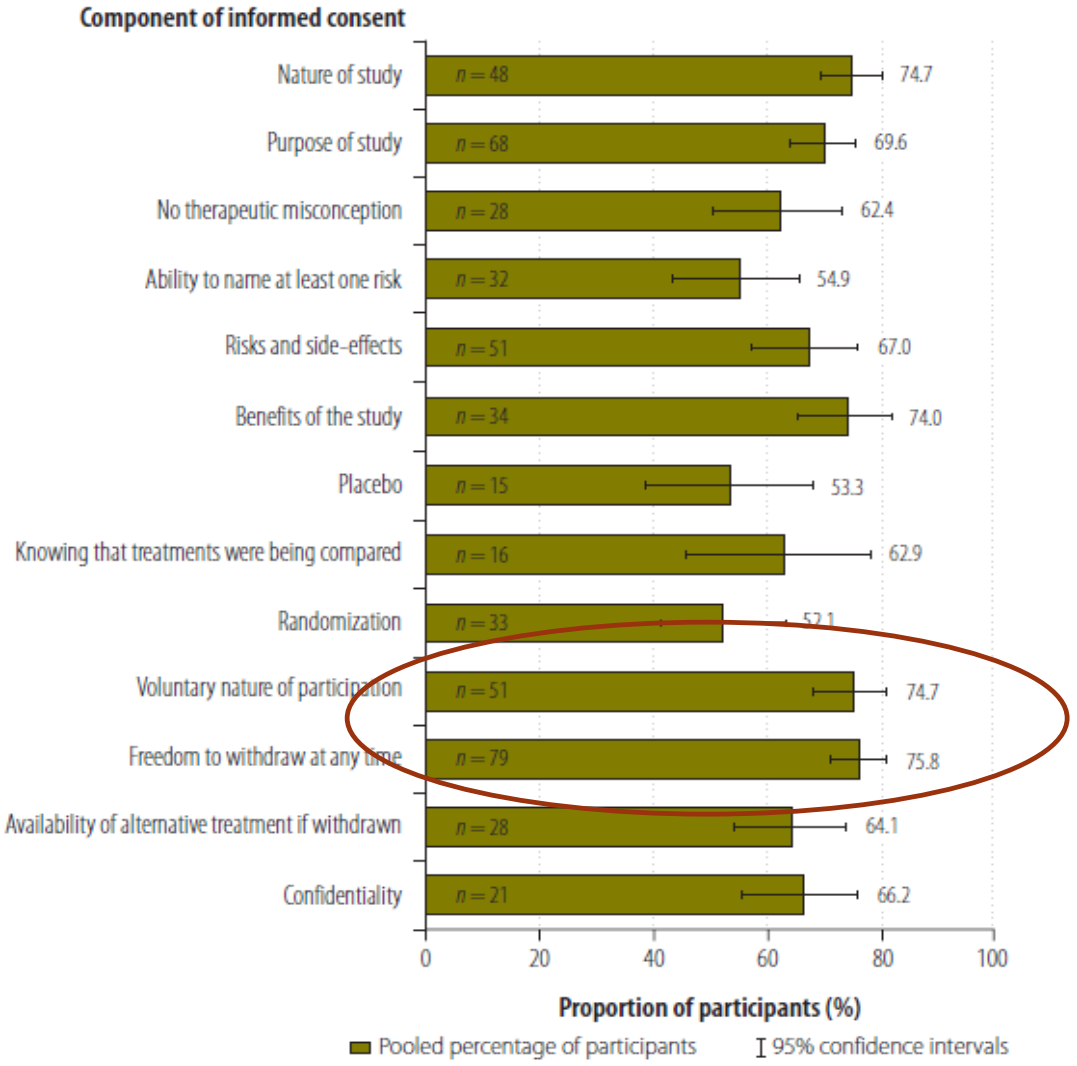
- Dependent position
- Power relationship
- Pressure from others (family, friends)
- Trust in health care provider
- Restricted choices?
- Illness?
- Incentives?

Voluntariness

- Pressure from others
  - 2%- 25% (ACHRE 1996, van Stuvensten et al 1998, Pace et al 2005)
  - 58% from child's disease (Pace et al 2005)

- Knew they could quit
  - 44% Swedish women in gyn trial, 88% Thai HIV vaccine participants, 90% US Cancer patients (Lynoe et al 1991 and 2001, Pitisuttithum et al 1997, Joffe et al 2001)

Fig. 2. **Participants' understanding of components of informed consent in clinical trials, by meta-analysis[a]**



[a] The number of studies included in the evaluation of each component is given.

Tam T et al. Bull of WHO 2015

Voluntariness: Data on refusal

Study	Refusal rate
Cardiac intervention studies	7% (range 1-21%)
Breast conserving treatment trial	9%
NHANES interviews and samples	18.9 %, 14.7%
Intensive diabetes therapy- adolescents	43%
Genetics study Guarani Indians	58%

Summary: voluntariness

- Limited Data
- Measurement of voluntariness difficult
- Few feel pressure from others
- Many (too many?) say they cannot quit or could not say no
- Individuals refuse participation at variable rates

Table. Steps for Validating Potential Research Participants' Consent to Research

	Risk/Benefit Profile for Participants[a]		
	Low Risk	Moderate Risk and High Risk/ Potential Benefit	High Risk/ Little or No Potential Benefit
Example	Buccal sampling; few blood draws; standardized surveys	Phase 2 study; research biopsy	Treatment withdrawal for serious condition; challenge studies with high risk
Domains of valid consent			
Competence	Assume[b]	Assume[b]	Consider formal assessment
Understanding	Assume (following explanation of study)[b]	Informal or brief formal assessment	Formal assessment by team or independent party
Voluntariness	Assume[b]	Informal assessment	Formal assessment by team or independent party

[a] As determined by the institutional review board.
[b] Unless there is reason for concern.

Wendler D How to enroll participants in research ethically. *JAMA* 2011

Informed consent-conclusions

- Informed consent in research is ethically important, but imperfectly realized

- Data suggest:
  - Consent forms are long and complex,
  - Understanding is variable
  - Many participants do not know/feel they can quit or refuse
  - Spending more time may enhance understanding

- More (and rigorous) data are needed
  - to improve our understanding of informed consent
  - Improve the process in a variety of settings
  - Enhance participants' experience, understanding, and decision making

Informed consent

- As research and technology evolve, maintain clarity about the purpose(s) of informed consent

- Quality training of researchers, research teams, clinicians, and IRB members

- Creativity and evidence