

INFORMED CONSENT

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Disclaimer

- The views expressed are mine and do not 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

- Well entrenched in American values, jurisprudence, medical practice, and clinical research.
- Informed consent is the bedrock principle on which most of modern research ethics rest...This was at the heart of the crucial ethical provision stated in the first words of the Nuremberg Code, and it remains equally compelling a half century later. *Menikoff J, Camb Quarterly 2004 p 342*

Informed consent

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

Legal requirement

- *“Every human being of adult years and sound mind has a right to determine what will be done with his body...”*
 - Justice Cardozo, 1914

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

Informed consent in medical practice



Informed consent in medical practice

- ...informed consent in clinical practice is frequently inadequate...
- Physicians receive little training...
- Misunderstand requirements and legal standards...
- Time pressures and competing demands...
- Patient comprehension is often poor...
- Recent studies have demonstrated improvement in patient understanding of risks after communication interventions
- Schenker et al 2010; Matiasek et al. 2008; McClean et al. 2004, and others

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.

Two senses of informed consent

(Faden & Beauchamp)

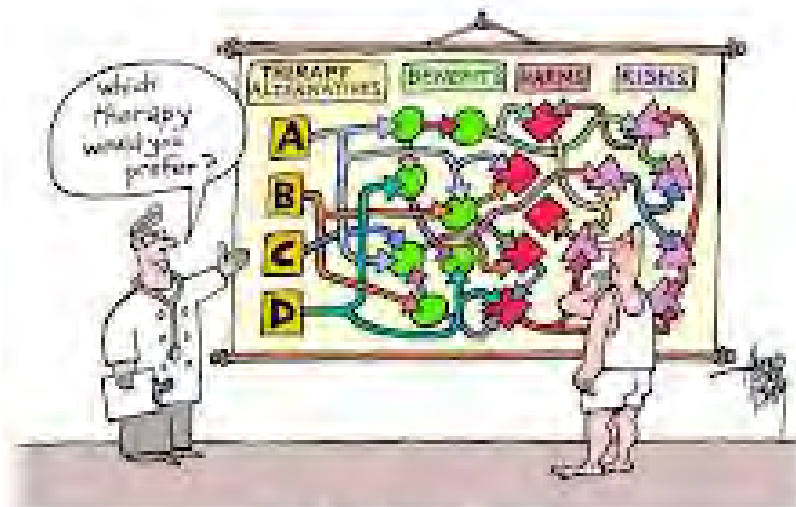
- An autonomous authorization:
 - “the intentional authorization of an activity based on substantial understanding and in the absence of control by others”
- Social rules of consent
 - An institutionally or legally effective authorization, as determined by prevailing rules

Elements of informed consent

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

Disclosure of information: Issues and challenges

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



informed consent

Writing a consent form

- A summary of study information—explanation of what the study is about, the procedures, related risks and possible benefits, alternatives, rights.
- Goal- informed decision making
- Reviewed and approved by IRB
- Advertisements, fliers, brochures are considered part of the process

Writing a consent form

- What information to include
- How to make it readable and understandable
- Format
- Consideration of length and complexity



Disclosure- required elements

(from 45CFR46.116 and 21CFR50.25)

- Statement of research
- Purpose and procedures
- Foreseeable risks and discomforts
- Any benefits to subjects or others
- Appropriate alternatives
- Extent of confidentiality
- Treatment or compensation for injury
- Who to contact for answers to questions
- Participation is voluntary

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 out what dose of XXX is safe in patients with cancer whose livers are not working normally. XXX is an experimental drug that blocks the growth of cells related to cancer. 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

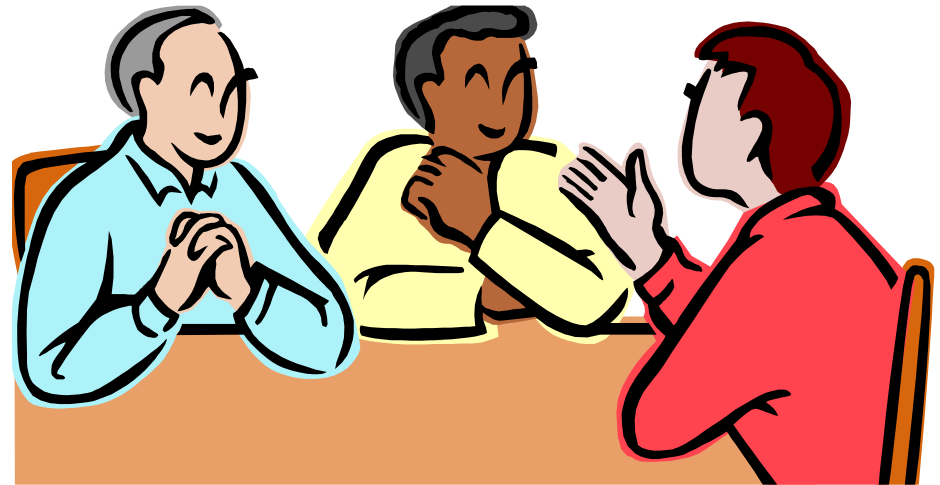
Checklist for easy-to-read informed consent documents

- Familiar words, consistent words
 - Short, simple, and direct sentences.
 - Limited line length
 - Short paragraphs, one idea per paragraph.
 - Verbs in active voice
 - Personal pronouns
 - Clear and logically sequenced ideas
 - Highlight Important points
 - Present study purpose early in the text.
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- **From NCI Simplification of Informed Consent Documents, Appendix 3.**
<<http://www.cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/page1>

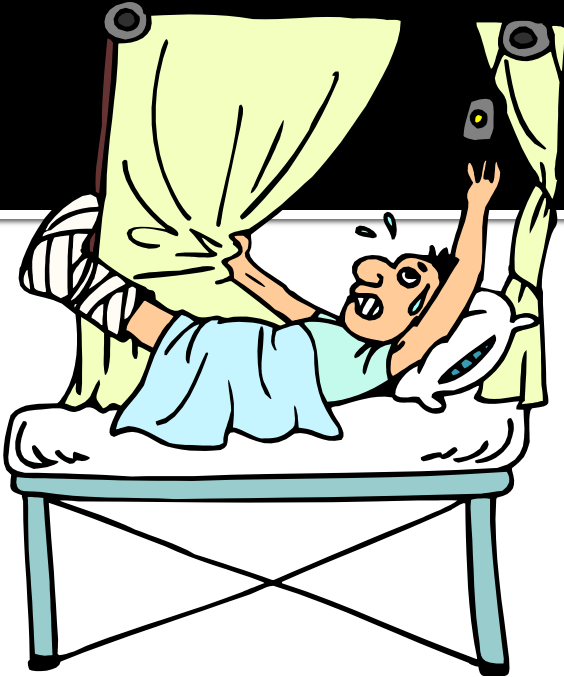
Easy to read consent forms- format

- Titles, subtitles, and other headers help to clarify organization of text.
 - Headers are simple and close to text.
 - Underline, bold, or boxes (rather than all caps or italics) give emphasis.
 - Layout balances white space with words and graphics.
 - Left margins are justified. Right margins are ragged.
 - Upper and lower case letters are used.
 - Style of print is easy to read.
 - Type size is at least 12 point.
 - Readability analysis is done to determine reading level (should be \leq 8th grade).
 - Avoid abbreviations and acronyms.
- From NCI Simplification of Informed Consent Documents, Appendix 3.
<<http://www.cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/page1>

How should information be presented?



Context-setting and timing



Data on disclosure

- Consent documents
 - Readability
 - Content
- Discussion
 - Content
 - Interaction

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](#)



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.

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.

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

Data on consent form content

- Only 3 of 16 consent forms (multicenter trial common protocol) contained all elements required in 45CFR.46 *Silverman et al. Critical Care Medicine 2001*
- Most Phase I oncology consent forms (n=267) described research (99%), purpose (92%), right to withdraw (99%) ; risk of death (67%), unknown risks (84%); cure as a possible benefit (5%) *Hornig et al, NEJM 2002*
- Review of 27 trials across 4 hospitals found significant information missing from consent forms *Beardsley et al. JCO 2007*

Data on investigator practices regarding consent

- Investigators (n=117) of a multinational HIV trial surveyed about consent practices
 - Provided a copy to read (99%)
 - Gave subjects opportunity to read before clinic (97%)
 - Provided a great deal of information about risks and purpose (>75%)
 - Emphasized randomization (<56%)
 - Formal assessment of understanding (8.6%)

Sabik et al. *IRB* 2005

Summary- data on disclosure

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

Elements of informed consent

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

Understanding: issues and challenges

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

Factors that might affect understanding

- Age*
- Severity of illness and need
- Educational level*
- Cognitive capacity*
- Familiarity with research
- Language and customs
- Literacy

Participant Understanding: Research Purpose/ Nature

- 27% Malian parents that study involved unproven malaria vaccine. [Krosin et al 2006](#)
- 30% U.S. Phase I, II, III oncology trial participants that treatments were unproven [Joffe et al 2001](#)
- 88% Thai HIV treatment participants knew study purpose [Pace et al. 2005](#)
- 100% rheumatoid arthritis RCT participants knew they were in a medical experiment [Criscione et al. 2003](#)

Participant Understanding: risks/side effects

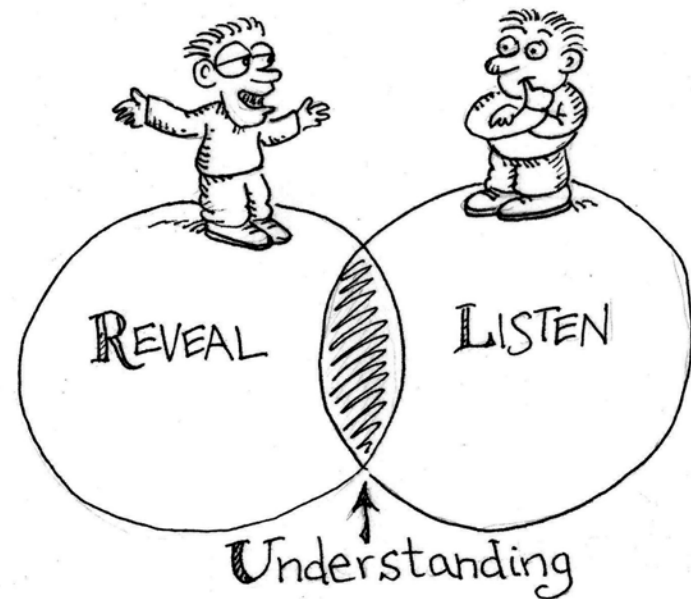
- 28% of subjects in a Hypertension trial remembered 2 side effects [Bergler 1980](#)
- 37% of US Cancer patients were aware of research risks [Joffe et al. 2001](#)
- 56% of Gambian mothers could name ≥ 1 side effect of HIB vaccine [Leach et al, 1999](#)
- 100% of US cancer patients could name ≥ 1 side effect of their Phase I trial [Dougherty et al 2000](#)

Participant Understanding: Randomization

- 21% of US IDUs knew that not everyone would get the same HIV vaccine [Harrison et al 1995](#)
- 23% of Finnish women remembered that breast cancer treatment was chosen randomly. [Hietanen 2000](#)
- 31% of Thai participants knew that only half would get the experimental HIV treatment [Pace et al. 2005](#)
- 42% of US men in heart attack trial were aware that there was a control group and that beta blocker assignment was based on chance [Howard 1981](#)

Understanding

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



Therapeutic Misconception



- When a research participant fails to recognize how personal care (i.e. the obligation of the physician to make medical decisions solely with the patients interests in mind) 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](#)

Summary: data on understanding

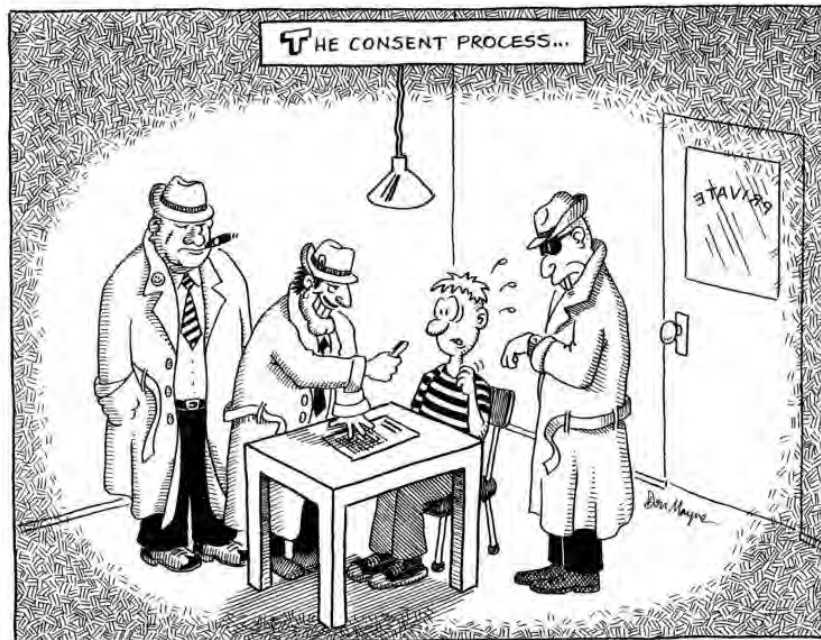
- Data are limited
- Understanding is variable
- Most subjects seem to know they are in research
- Research methodologies (e.g. randomization) are poorly understood
- Understanding = knowledge + appreciation

Elements of informed consent

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

Voluntariness

- Able to make a (free) choice
- No coercion or 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: Data on pressure to join

- 2% of 570 U.S. participants in cardiology and oncology studies [ACHRE 1996](#)
- Ugandan parents enrolling their children in a malaria treatment trial: 15% from others, 58% because of their child's illness. [Pace et al. AJPH 2005](#)
- 25% Dutch parents "felt obliged" to enroll their children in an anticonvulsant study [Van Stuijvenberg 1998](#)

Voluntariness: Data –knew they could quit

- 44% Swedish women in a gyn trial [Lynoe et al 1991](#)
- 48% of Bangladeshi pregnant women in an iron supplement trial [Lynoe 2001](#)
- 88% of Thai HIV vaccine trial participants [Pitisuttithum 1997](#)
- 90% of US Cancer Patients [Joffe et al 2001](#)

Voluntariness: Data on refusal

STUDY

- Cardiac intervention studies
- Breast conserving treatment trial
- NHANES interviews and samples
- Intensive diabetes therapy-adolescents
- Genetics study Guarani Indians

REFUSAL RATE

- 7% (range 1-21%)
- 9%
- 18.9 %, 14.7%
- 43%
- 58%

Summary: data on voluntariness

- Data are limited
- Measurement of voluntariness difficult
- Small numbers feel pressure from others to participate
- Many say they cannot quit or could not say no
- Individuals do refuse to participate in certain studies

Research on informed consent

- Studies of the quality of informed consent
- Studies of interventions to improve consent

Studies of strategies to improve consent

- 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)
 - Flory and Emanuel *JAMA* 2004

Strategies to improve consent: multimedia

- Only 1 of 12 studies of multimedia strategies, showed significant improvement in understanding (computerized presentation in mental health study)
- Others – no significant difference.
- May be as good as usual process, and
- May be
 - more appropriate for certain populations
 - useful in standardizing disclosure

Flory et al 2004

Strategies to improve consent: Audio visual interventions

- 4 trials (3 RCT) involving data from 511 people, conducted in USA and Canada.
- Audio-visual interventions
 - No consistent increase in understanding
 - 1 study showed better retention of knowledge
 - Transient increase in willingness to participate in trials, not sustained at 2-4 weeks
- Ryan RE, Prictor MJ, McLaughlin KJ, Hill SJ. *Cochrane Database of Systematic Reviews* 2008.

Strategies to improve consent: consent form

- Enhanced consent form (e.g. modified style, format or length)
 - 6 of 15 showed significant increase in understanding [Flory et al 2004](#)
 - Variable interventions, measurements, and populations studied

Strategies to improve consent

- Limited data suggest that more person-to-person contact (through extended discussions (3/5) , test/feedback strategies (5/5) may help improve understanding

Flory and Emanuel *JAMA* 2004

Studies of strategies to improve consent

- Haiti: Case-control study of HIV transmission
 - To enroll, prospective participants had to pass a T/F quiz on study purpose, voluntary participation, risks, benefits and HIV prevention.
 - 20% passed when attended single consent meeting; 80% passed when attended 3 information sessions and a consent meeting

Fitzgerald et. al. Lancet 2002; 360: 1301-2

Informed consent-conclusions

- Informed consent in research is ethically important, but imperfectly realized
- Data suggest:
 - Consent forms are long and complex,
 - Understanding is variable, and lacking in certain areas (e.g. randomization)
 - Many participants do not know/feel they can quit
 - 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-conclusions

- Clarity about the purpose(s) of informed consent in research
- Quality training of researchers, research teams, and IRBs
- Creativity

