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
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

“Wow—way too much information!”
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  

- **Missing required or relevant elements**
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
“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>
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

<table>
<thead>
<tr>
<th>TYPE OF CONSENT</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>No consent</td>
<td>Do not obtain donor consent</td>
</tr>
<tr>
<td>Blanket</td>
<td>Consent to future research with no limitations</td>
</tr>
<tr>
<td>Broad*</td>
<td>Consent to future research with specified limitations</td>
</tr>
<tr>
<td>Checklist</td>
<td>Donors choose which types of future studies are allowed</td>
</tr>
<tr>
<td>Study specific</td>
<td>Consent for each specific future study</td>
</tr>
</tbody>
</table>

Grady et al. *AJOB* 2015
Information technologies
For the purposes of guidance, electronic informed 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>
<thead>
<tr>
<th>Component</th>
<th>Traditional Paper Informed Consent</th>
<th>Electronic and Digital Informed Consent</th>
<th>Challenges and Areas for Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disclosure</td>
<td>Information is written, usually on paper. Discussion with investigator takes place, usually face to face.</td>
<td>Consent can involve electronic information, multimedia information, video graphics, and interactive computer interfaces. Investigator can be remote in time or place from participant.</td>
<td>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.</td>
</tr>
<tr>
<td>Understanding</td>
<td>Investigator and participant discuss information. Participant asks questions. Investigator assesses understanding, in some cases using questions, structured quizzes, other methods.</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Voluntariness</td>
<td>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.</td>
<td>Some electronic systems facilitate participant control. Participant can easily sign off or disengage. Participant can decline.</td>
<td>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.</td>
</tr>
<tr>
<td>Authorization</td>
<td>Paper consent document is signed. Copies of document are kept in records.</td>
<td>Options might include clicking agreement or an electronic signature. Records of agreement are kept electronically.</td>
<td>It may be difficult to verify the identity of the authorizing person.</td>
</tr>
</tbody>
</table>
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%)**  
Fig. 2. **Participants’ understanding of components of informed consent in clinical trials, by meta-analysis**

<table>
<thead>
<tr>
<th>Component of informed consent</th>
<th>Proportion of participants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature of study</td>
<td>74.7</td>
</tr>
<tr>
<td>Purpose of study</td>
<td>69.6</td>
</tr>
<tr>
<td>No therapeutic misconception</td>
<td>62.4</td>
</tr>
<tr>
<td>Ability to name at least one risk</td>
<td>54.9</td>
</tr>
<tr>
<td>Risks and side-effects</td>
<td>67.0</td>
</tr>
<tr>
<td>Benefits of the study</td>
<td>74.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>53.3</td>
</tr>
<tr>
<td>Knowing that treatments were being compared</td>
<td>62.9</td>
</tr>
<tr>
<td>Randomization</td>
<td>52.1</td>
</tr>
<tr>
<td>Voluntary nature of participation</td>
<td>74.7</td>
</tr>
<tr>
<td>Freedom to withdraw at any time</td>
<td>75.8</td>
</tr>
<tr>
<td>Availability of alternative treatment if withdrawn</td>
<td>64.1</td>
</tr>
<tr>
<td>Confidentiality</td>
<td>66.2</td>
</tr>
</tbody>
</table>

*The number of studies included in the evaluation of each component is given.*
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

<table>
<thead>
<tr>
<th>Consent Form Length (Words)</th>
<th>Very Slow Reading Speed (100 words/min)</th>
<th>Average Reading Speed (200 - 250 words/min)</th>
<th>Fast Reading Speed (300 words/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,000</td>
<td>20 minutes</td>
<td>8 - 10 minutes</td>
<td>7 minutes</td>
</tr>
<tr>
<td>3,000</td>
<td>30</td>
<td>12 - 15</td>
<td>10</td>
</tr>
<tr>
<td>4,000</td>
<td>40</td>
<td>16 - 20</td>
<td>13</td>
</tr>
<tr>
<td>5,000</td>
<td>50</td>
<td>20 - 25</td>
<td>17</td>
</tr>
<tr>
<td>6,000</td>
<td>60</td>
<td>24 - 30</td>
<td>20</td>
</tr>
<tr>
<td>7,000</td>
<td>70</td>
<td>28 - 35</td>
<td>23</td>
</tr>
<tr>
<td>8,000</td>
<td>80</td>
<td>32 - 40</td>
<td>27</td>
</tr>
<tr>
<td>9,000</td>
<td>90</td>
<td>36 - 45</td>
<td>30</td>
</tr>
<tr>
<td>10,000</td>
<td>100</td>
<td>40 - 50</td>
<td>33</td>
</tr>
<tr>
<td>11,000</td>
<td>110</td>
<td>44 - 55</td>
<td>37</td>
</tr>
<tr>
<td>12,000</td>
<td>120</td>
<td>48 - 60</td>
<td>40</td>
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References
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
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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
  - 58% from child’s disease (Pace et al 2005)

- Knew they could quit
Fig. 2. Participants' understanding of components of informed consent in clinical trials, by meta-analysis

Component of informed consent

- Nature of study: n = 48, 74.7%
- Purpose of study: n = 68, 69.6%
- No therapeutic misconception: n = 28, 62.4%
- Ability to name at least one risk: n = 32, 54.9%
- Risks and side-effects: n = 51, 67.0%
- Benefits of the study: n = 34, 74.0%
- Placebo: n = 15, 53.3%
- Knowing that treatments were being compared: n = 16, 62.9%
- Randomization: n = 33, 52.1%
- Voluntary nature of participation: n = 51, 74.7%
- Freedom to withdraw at any time: n = 79, 75.8%
- Availability of alternative treatment if withdrawn: n = 28, 64.1%
- Confidentiality: n = 21, 66.2%

Proportion of participants (%)

- Pooled percentage of participants
- 95% confidence intervals

*The number of studies included in the evaluation of each component is given.
### Voluntariness: Data on refusal

<table>
<thead>
<tr>
<th>Study</th>
<th>Refusal rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac intervention studies</td>
<td>7% (range 1-21%)</td>
</tr>
<tr>
<td>Breast conserving treatment trial</td>
<td>9%</td>
</tr>
<tr>
<td>NHANES interviews and samples</td>
<td>18.9 %, 14.7%</td>
</tr>
<tr>
<td>Intensive diabetes therapy- adolescents</td>
<td>43%</td>
</tr>
<tr>
<td>Genetics study Guarani Indians</td>
<td>58%</td>
</tr>
</tbody>
</table>
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>
<thead>
<tr>
<th>Domain of Valid Consent</th>
<th>Low Risk</th>
<th>Moderate Risk and High Risk/ Potential Benefit</th>
<th>High Risk/ Little or No Potential Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Competence</td>
<td>Assume&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Assume&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Consider formal assessment</td>
</tr>
<tr>
<td>Understanding</td>
<td>Assume (following explanation of study)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Informal or brief formal assessment</td>
<td>Formal assessment by team or independent party</td>
</tr>
<tr>
<td>Voluntariness</td>
<td>Assume&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Informal assessment</td>
<td>Formal assessment by team or independent party</td>
</tr>
</tbody>
</table>

<sup>a</sup> As determined by the institutional review board.
<sup>b</sup> Unless there is reason for concern.
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