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

- The BASICS
- CHANGES
- 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.

- 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

- The goal of research is to produce knowledge, not always benefit to the participant.

- 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

- Required by virtually all codes of research ethics, regulations, and laws (limited exceptions):
  - US Federal Regulations (Common Rule (45CFR46) and FDA (21CFR50))
  - ICH-GCP
  - Declaration of Helsinki, CIOMS
  - National, state, institutional 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
- Understanding
- Voluntariness
- (Consent authorization)
Decisions about Disclosure of information

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

- Written consent form
  - Study summary—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)
Consent forms

- Writing readable, understandable consent forms that explain the study
- Consider length, format, reading level, complexity
- Using consent forms in discussion
Easy-to-read informed consent documents

- Familiar, consistent words, Active voice and personal pronouns
- Short, simple, direct sentences with limited line length
- Short paragraphs, one idea per paragraph.
- Clear, logically sequenced ideas
- Highlight Important points
- Avoid acronyms and abbreviations
- Format (headers, white space, graphics, font, bold)

*From NCI Simplification of Informed Consent Documents, Appendix 3. [Link](http://www.cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/page1)*
Health literacy

- “In ensuring that information is understandable, it should be noted that
  - more than one-third of U.S. adults, 77 million people, have basic or below basic health literacy,
  - Limited health literacy affects adults in all racial and ethnic groups,
  - More than one-half of U.S. adults have basic or below basic quantitative literacy and are challenged by numerical presentations of health, risk, and benefit data.

FDA Informed Consent Guidance Sheet, July 2014
Length and readability

- **Reading level is high**
  - Consent forms and templates usually written at or above the 11th grade level. 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**
§116.116 (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

- 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, sponsor, investigator

- IRBs often make consent forms longer and more complex
Prototypical research informed consent

► Discussion of study information
► Written consent form
► Signatures

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:

Talking 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.
Setting
Elements of informed consent

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

- Studies continue to show that research participants have variable understanding e.g. Mandava A et al. J Med Ethics 2012

- Range of understanding about research purpose and nature (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

Component of informed consent

<table>
<thead>
<tr>
<th>Component of informed consent</th>
<th>Number (n)</th>
<th>Proportion of participants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature of study</td>
<td>48</td>
<td>74.7</td>
</tr>
<tr>
<td>Purpose of study</td>
<td>68</td>
<td>69.6</td>
</tr>
<tr>
<td>No therapeutic misconception</td>
<td>28</td>
<td>62.4</td>
</tr>
<tr>
<td>Ability to name at least one risk</td>
<td>32</td>
<td>54.9</td>
</tr>
<tr>
<td>Risks and side-effects</td>
<td>51</td>
<td>67.0</td>
</tr>
<tr>
<td>Benefits of the study</td>
<td>34</td>
<td>74.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>15</td>
<td>53.3</td>
</tr>
<tr>
<td>Knowing that treatments were being compared</td>
<td>16</td>
<td>62.9</td>
</tr>
<tr>
<td>Randomization</td>
<td>33</td>
<td>52.1</td>
</tr>
<tr>
<td>Voluntary nature of participation</td>
<td>51</td>
<td>74.7</td>
</tr>
<tr>
<td>Freedom to withdraw at any time</td>
<td>79</td>
<td>75.8</td>
</tr>
<tr>
<td>Availability of alternative treatment if withdrawn</td>
<td>28</td>
<td>64.1</td>
</tr>
<tr>
<td>Confidentiality</td>
<td>21</td>
<td>66.2</td>
</tr>
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Proportion of participants (%)

- Pooled percentage of participants
- 95% confidence intervals

^a The number of studies included in the evaluation of each component is given.
Understanding: issues and challenges

- What affects understanding? age, education, expectations, disclosure
- How is/should understanding be assessed?
- How much should participants understand?
- What happens (or should happen) when participants don’t understand?
Table. Steps for Validating Potential Research Participants’ Consent to Research

<table>
<thead>
<tr>
<th>Risk/Benefit Profile for Participants&lt;sup&gt;a&lt;/sup&gt;</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>Example</td>
<td>Buccal sampling; few blood draws; standardized surveys</td>
<td>Phase 2 study; research biopsy</td>
<td>Treatment withdrawal for serious condition; challenge studies with high risk</td>
</tr>
<tr>
<td>Domains of valid consent</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
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<sup>a</sup>As determined by the institutional review board.

<sup>b</sup>Unless there is reason for concern.
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 negates the ability to provide meaningful informed consent. Appelbaum et al. KIE 2006
Research on improving 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

- Does a simpler, more concise consent form affect study understanding or satisfaction with consent?

- RCT

- 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
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
Voluntariness

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

- Deception- concealment or distortion of the truth in order to mislead
- Coercion- compelling another party to act by force or by threatening to make them worse off
- Undue inducement- an offer that distorts judgement or entices someone to participate in research that is contrary to their interests.
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**
  - 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)

- **Decline participation**
  - Range of actual decliners
**Fig. 2.** Participants' understanding of components of informed consent in clinical trials, by meta-analysis

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Informed consent

- The BASICS
- CHANGES
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Paradigmatic clinical research
Paradigmatic clinical research
Research with Data and Biospecimens
Research with Data and Biospecimens
## No consensus on acceptable consent

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<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 el. *AJOB* 2015
Pragmatic trials
Pragmatic trials
Research with big data
Information technologies
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.
# Components and Challenges of Informed Consent with Traditional Paper Forms and Electronic Methods.

<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. Investigator can be remote in time or place from participant.</td>
<td>Consent can involve electronic information, multimedia information, video graphics, and interactive computer interfaces.</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. 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>
<td></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. 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>
<td></td>
</tr>
<tr>
<td>Authorization</td>
<td>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.</td>
<td>It may be difficult to verify the identity of the authorizing person.</td>
<td></td>
</tr>
</tbody>
</table>

Dynamic consent

Interactive technology based platform. Not “… locked in time to the beginning of the research process. Depending upon the nature of the research enterprise, participants could consent to a broad range of uses of their samples and data, or opt to be approached on a case-by-case basis, or set different preferences for different types of research. These preferences can be ‘opt ins’ or ‘opt outs’: participants can tailor their profiles to receive no information for specified periods of time or to give a broad consent if they so wish.”

Kaye et al 2015
App based consent

Interactive consent

https://www.youtube.com/watch?v=dM7lnKSzW7g
Improving informed consent

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

Schenker Y and Meisel A, JAMA 2011
Informed consent

- No consent
- Waiver

- Notification
- Simplified disclosure

- Full informed consent
- Full in person informed consent
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
Conclusions

Informed consent is a process based on respect for persons, that also promotes participant welfare, respects values, offers control, promotes trust, complies with regulations, and helps to ensure integrity.

Changes in research methodologies, information technologies, participant engagement, regulations, and our understanding of informed consent offer opportunities for innovative evidence-based strategies for informed consent.