INFORMED CONSENT

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Disclaimer

The views expressed are mine and do not necessarily represent the policies of the CC, Department of Bioethics, NIH, or DHHS.

I have no conflicts of interest to disclose
Informed consent

BASICS

CHALLENGES

CHANGES
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 [is] 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
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
Informed consent

(Capacity to consent)

Disclosure of information

Understanding

Voluntariness

(Consent authorization)
Disclosure

What information should be disclosed? So that it is accessible and relevant information?

How should information be presented so that it is understandable, considering circumstances, setting, population?
§116 (a)(3) The information given to the subject or LAR shall be *in language understandable to the subject or LAR*.

§116 (a)(4) .... *Information that a reasonable person would want to have in order to make an informed decision* about whether to participate, and an opportunity to discuss that information.
Informed consent

§ 116 (a)(5)(i) ... 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.

§ 116 (a)(5)(ii) ... 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.
Consent forms

Readable, understandable *forms* that explain the study. Including ads, pamphlets, fliers (approved by the IRB)

Length, format, reading level, complexity, are all important

Using written or visual material in discussion
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
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.
<http://www.cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/page1>
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

**Missing required or relevant elements**
Presentation and setting
Challenges

“Easy reading is damn hard writing.”
Nathaniel Hawthorne ~1840

Written informed consent protects the institution, sponsor, investigator

IRBs often want more information—making forms longer and more complex
Participant Understanding Data

Research participants have variable understanding e.g. Mandava A et al. *J Med Ethics* 2012

Range of understanding

- Of research purpose and nature (27% -100%) Krosin et al 2006; Joffe et al 2001; Pace et al. 2005; Criscione et al. 2003

- Of research risks (28%-100%) Bergler 1980; Joffe et al. 2001; Leach et al, 1999; Dougherty et al 2000

- Of 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**

<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.
What affects understanding?

“Host” factors - Age, education, pain, cognitive impairment, capacity, literacy

Expectations and familiarity
- Trust in providers
- Therapeutic misconception and related misunderstandings

Process related factors
- What is disclosed and how
- How (and how well) the participant listens to/reads the information?
Understanding

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>
</tbody>
</table>

### Domains of valid consent

<table>
<thead>
<tr>
<th>Competence</th>
<th>Assumed&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Assumed&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Consider formal assessment</th>
</tr>
</thead>
<tbody>
<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>Assumed&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.
Understanding

Different kinds of “mis-understanding”
- Misconception
- Mis-estimation
- Optimism (Horng & Grady IRB 2003)

Distinction between knowledge of relevant information and appreciation of how it applies
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: 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
Research: improving understanding

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

- Randomize actual participants
- 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

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

By Limin Stunkel, Meredith Benson, Louise McLeish, New Soo Chia, Gabrielle Bowden, Edith Emery, and Christine Grady

IRB Ethics and Human Research

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

Mary E. Enama, Zonglu Hu, Jiyin Gorton, Patrick Cooper, Julie E. Legdenwood, Ursula Grady

Stunkel et al IRB 2010; Enama et al Cont Clin Trial 2012

Grady et al PloS One 2017
Voluntariness

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

**Deception** - concealing or distorting the truth in order to mislead

**Coercion** - compelling another party to act by force or by threatening to make them worse off

**Undue inducement/influence** - 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?
Data on 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*

Component of informed consent

- Nature of study: 74.7%
- Purpose of study: 69.6%
- No therapeutic misconception: 62.4%
- Ability to name at least one risk: 54.9%
- Risks and side-effects: 67.0%
- Benefits of the study: 74.0%
- Placebo: 53.3%
- Knowing that treatments were being compared: 62.9%
- Randomization: 51.1%
- Voluntary nature of participation: 74.7%
- Freedom to withdraw at any time: 75.8%
- Availability of alternative treatment if withdrawn: 64.1%
- Confidentiality: 66.2%

Proportion of participants (%)

* The number of studies included in the evaluation of each component is given.
Informed Consent- complex and imperfect

- Enduring challenges in disclosure, understanding, voluntary choice

- Informed consent affected by (and by differences in):
  - Motivations and expectations
  - Capacity
  - Experience of and tolerance for inconvenience, burden
  - Differential responses to incentives
Informed consent
Changes

Types of research
- Biobanks and Data Repositories
- Big Data
- Pragmatic trials

Types of information exchange
- Electronic consent
- Devices and apps
- Web interfaces

COVID and telehealth
Typical clinical research
Typical clinical research
Research with Data and Biospecimens
## Acceptable consent?

<table>
<thead>
<tr>
<th>Less Control, Less burden</th>
<th>TYPE OF CONSENT</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No consent</td>
<td>No consent needed</td>
</tr>
<tr>
<td></td>
<td>Blanket</td>
<td>Consent to future research with no limitations</td>
</tr>
<tr>
<td></td>
<td>Broad*</td>
<td>Consent to future research with specified limitations</td>
</tr>
<tr>
<td></td>
<td>Checklist</td>
<td>Donors choose which types of future studies are allowed</td>
</tr>
<tr>
<td></td>
<td>Study specific</td>
<td>Consent for each specific future study</td>
</tr>
</tbody>
</table>

Grady et al. *AJOB* 2015
Pragmatic trials
Research with big data
…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.”
## Informed Consent

### Table 1. 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</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>
COVID Changes

Decentralized trials

Consent (at site)
Paper or digital consent at one physical location
Requires:
Travel, Time, Repeat Visits

Remote eConsent
Increases patient access. Patients can be anywhere when the time works for them and consult their caregivers and physician for deeper comprehension.
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.
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