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 basis

Respect for autonomy – respect for 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 to benefit others and not necessarily 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? Adequate, accessible, relevant information?

How should information be presented so that it is understandable, considering circumstances, setting, population?
Informed consent

§116 (a)(3) The information given to the subject or LAR shall be \textit{in language understandable to the subject or LAR}.

§116 (a)(4) …. \textit{that a reasonable person would want to have in order to make an informed decision}. 
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 that does not merely provide lists of isolated facts, but rather facilitates the prospective subject’s or LAR’s understanding
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**—often 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, and 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).

**Required or relevant elements are often missing**

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; Tam et al. 2015; Pietrzykowski et al. 2021)

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; Ponzio et al. 2018)

- Of research risks (28%-100%) Bergler 1980; Joffe et al. 2001; Leach et al, 1999; Dougherty et al 2000; Schumacher et al. 2017)

- Of randomization (10%-42%) Harrison et al 1995; Hietanen 2000; Pace et al. 2005; Chu et al. 2012; Bertoli et al. 2007)
Fig. 2. Participants’ understanding of components of informed consent in clinical trials, by meta-analysis*

Component of informed consent

<table>
<thead>
<tr>
<th>Component</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>
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<td>Knowing that treatments were being compared</td>
<td>62.9</td>
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<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>
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* 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: motivations, trust in providers, cultural views, therapeutic misconception and related misunderstandings

Process related factors: what is disclosed and how and by whom, 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>Assume&lt;sup&gt;b&lt;/sup&gt;</th>
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<th>Consider formal assessment</th>
</tr>
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<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

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
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

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- 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
- Telehealth
Typical clinical research
Typical clinical research
Research with Data and Biospecimens
### Acceptable consent?

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<tr>
<td>No consent</td>
<td>No consent needed</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>

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Grady et el. *AJOB* 2015
Pragmatic trials
Research with big data
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 comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed under “Written/Paper Submissions” and “Instructions”.

Written/Paper Submissions
Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5600 Fishers Lane, Rm. 1016, Rockville, MD 20852.

- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, 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 8 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, you should 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 that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.11. Applicable disclosure will be made available to the public.

FURTHER INFORMATION: Cheryl Grandiuzzi, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Avenue, Bldg. 51, Rm. 3343, Silver Spring, MD 20993–6002, 301–766–5266; Nora Wolanski, Office of Good Clinical Practice, Office of Medical Products, Office of Medical Products and Tobacco, Food and Drug Administration, 10903 New Hampshire Avenue, Bldg. 32, Rm. 5230, Silver Spring, MD 20993, 301–766–6970; Stephanie Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Avenue, Bldg. 71, Rm. 7044, Silver Spring, MD 20993–6002, 301–766–9421; Irfan Khan, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Avenue, Bldg. 66, Rm. 3459, Silver Spring, MD 20993, 1–800–638–2041 or 301–766–7100; or Irene Still-Coleman, Office for Human Research Protections, 1101 Wootton Pkwy., suite 200, Rockville, MD 20852, 240–453–6800.
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.
# 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>
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