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

- 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
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
- Understanding
- Voluntariness
- (Consent authorization)
Decisions about Disclosure of information

- What information should be disclosed?
- How should 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

- Readable, understandable consent forms that explain the study

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

- Using consent forms 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)

Previous clinical trials have evaluated the xxx vaccine, subcutaneously administered (applied under skin as an injection), in people with advanced cancers. In these trials, there were no side effects considered life threatening or severe due to the administration of the vaccine. Xxxx has not been previously given into the vein (intravenously) to humans. This trial represents a new way of activating different segments of your immune system that may induce additional anticancer effects. This way of administering vaccine is used in other clinical trials using different viral vaccines.
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**

- **Missing required or relevant elements**
Informed consent (revised Common Rule)

§ 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

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

- 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
Presentation
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*

- **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**: 52.1%
- **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%

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

- 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>
<thead>
<tr>
<th>Example</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>

<table>
<thead>
<tr>
<th>Domains of valid consent</th>
<th>Competence</th>
<th>Understanding</th>
<th>Voluntariness</th>
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<tbody>
<tr>
<td>Competence</td>
<td>Assume&lt;sup&gt;b&lt;/sup&gt;</td>
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</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>Informal assessment</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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</table>

<sup>a</sup>As determined by the institutional review board.

<sup>b</sup>Unless there is reason for concern.

Wendler D How to enroll participants in research ethically. *JAMA* 2011
Understanding

- Knowledge of relevant information
- 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 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
Research to improve 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
Understanding 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/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?
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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<th>Component of informed consent</th>
<th>Proportion of participants (%)</th>
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<td>Purpose of study</td>
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<td>66.2</td>
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* The number of studies included in the evaluation of each component is given.
Informed consent

- The BASICS
- CHANGES
- ENDURING AND EMERGING CHALLENGES
Paradigmatic clinical research
Paradigmatic clinical research
Research with Data and Biospecimens
Research with Data and Biospecimens
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
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><strong>Disclosure</strong></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><strong>Understanding</strong></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><strong>Voluntariness</strong></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><strong>Authorization</strong></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>

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
Informed consent

- No consent
- Waiver
- Notification
- Simplified disclosure
- Full informed consent
- Full in person informed consent
Waiver or alteration of informed consent

(1) **Waiver.** An IRB may waive the requirement to obtain informed consent for research under paragraphs (a) through (c) (general, basic and additional requirements), provided the IRB satisfies the criteria (paragraph (e))

An IRB cannot waive consent for the storage, maintenance, or secondary research use of the identifiable private information or identifiable biospecimens if a person was asked for broad consent and refused (par d).

(2) **Alteration.** An IRB may approve a consent procedure that omits some, or alters some or all, of the elements of informed consent set forth in paragraphs (b) and (c) of this section provided the IRB satisfies the requirements of paragraph (e)(3) of this section. An IRB may not omit or alter any of the requirements described in paragraph (a) of this section. If a broad consent procedure is used, an IRB may not omit or alter any of the elements required under paragraph (d) of this section.
The IRB must find and document that:

- (i) The research involves no more than **minimal risk** to the subjects;
- (ii) The research could not **practically** be carried out without the requested waiver or alteration;
- (iii) If the research involves using **identifiable** private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
- (iv) The waiver or alteration will not adversely affect the **rights and welfare** of the subjects; and
- (v) Whenever appropriate, the subjects or legally authorized representatives will be provided with **additional pertinent information** after participation.
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