Achieving the multiple aims of informed consent to research

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Disclosures

- I have no relevant financial relationships to disclose
- I will not be discussing unapproved uses of medical products
- Although I might trespass into legal territory, I am not a lawyer
1. Define the multiple purposes of informed consent to research
2. Describe ways in which those purposes can come into conflict
3. Identify strategies for achieving key purposes
My core message

- Different studies implicate different goals of informed consent
- Clarity about which functional goals of consent are most important in a particular study should drive the consent process
Reframing Consent for Clinical Research: A Function-Based Approach

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Sara F. Goldkind, Research and Clinical Bioethics Consultant
Christine Grady, National Institutes of Health
Steven Joffe, University of Pennsylvania
Bernard Lo, Greenwall Foundation
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Rebecca D. Pentz, Emory University School of Medicine
Robert Silbergleit, University of Michigan
Kevin P. Weinfurt, Duke Clinical Research Institute
David Wendler, National Institutes of Health
Scott Y. H. Kim, National Institutes of Health
Philosophical goals of the act of informed consent to research
1. Consent as *autonomous authorization*

- **Autonomous**: self-directed, free from coercion/deception, based on sufficient understanding
- **Authorization**: permission-giving
2. Consent as **agreement to co-voyage**

Participant adopts the investigator’s ends as his/her own

“authentic identification with the cause that it is the subject’s as well as the researcher’s cause – whereby his (sic) role in its service is not just permitted by him, but willed. That sovereign will of his which embraces the end as his own restores his personhood to the otherwise depersonalizing context.”

Jonas H, Daedalus 98(2):219, 1969

3. Consent as *moral transformation*

Participant’s consent transforms an impermissible action into a permissible one

- Sometimes consent is the *only* pathway to moral transformation (e.g., sex)
- Sometimes alternate pathways are available (e.g., authorization to share confidential information)

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Functional goals of the *process* of informed consent to research
Participant-centered functions

1. Share information – *How comprehensive?*
2. Achieve participant understanding – *Comprehensive v. gist?*
3. Obtain authorization for actions
4. Promote concordance with values
5. Prepare for what to expect
6. Protect & promote welfare interests
Table 1. Consent Form Template in English

What is the purpose of this study?
We are asking you to be a part of a phase I research study. We are doing this study
in order to evaluate the safety of a new agent called a...... that would be used in humans. Future studies phase I trials will evaluate the agent's safety against cancer.

What are the procedures of this study?
Different doses of the agent will be given to different patients. The first several doses may be done. If the agent does not cause any side effects, it will be given to other patients in order to increase the dose (for every new group of......) until several patients are on the study. About...... people will take part in the study. You may be chosen as one of the patients. You are less likely to have side effects, or benefit.

We will give you the research agent...... every week (every 1-2 weeks) for...... as long as your cancer is responding to the study. We will do some tests and procedures to monitor both your cancer and any treatment that you and your doctor agree will benefit you.

What are the risks that I have if I enroll in this trial?
We do not know all the possible side effects of the research agent because it is being studied in a small number of patients. We have listed below possible side effects that you might experience and any treatment that may help prevent or treat these side effects. The research agent used in this study and

Expected Tests and Procedures (example inclusion criteria)

<table>
<thead>
<tr>
<th>Days Before Starting Treatment</th>
<th>Expected Tests and Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7 Days</td>
<td>Blood test, physical exam, chest x-ray, baseline labs</td>
</tr>
<tr>
<td>14 Days</td>
<td>Blood test, physical exam, x-ray, baseline labs, additional tests</td>
</tr>
</tbody>
</table>

Sample Outline of Possible Side Effects

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Feeling sick or having to throw up</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Feeling sick or having to throw up</td>
</tr>
<tr>
<td>Mild allergic reaction</td>
<td>Feeling sick or having to throw up</td>
</tr>
</tbody>
</table>

Immediate side effects include:
- Nausea
- Vomiting
- Mild allergic reaction

Possible side effects:
- Fatigue
- Low blood count
- Diarrhea
- Mouth sores
- Mild infection

Delayed side effects include:
- Weakness
- Fatigue
- Rash

Other side effects include:
- Infertility
- Fertility damage

What happens if I have side effects?
We will monitor you closely during the trial and treat any side effect that you have. If side effects are severe, we may decide to either lower your dose or stop you in the study.

How can I benefit from being in this trial?
The main goal of this study is to test the safety of the research agent. It is not to treat your cancer. However, you may benefit from the study by getting new treatments earlier and possibly extending your life.

What are my options if I decide not to enroll?
It is your choice whether or not to be a part of this research study. If you decide not to

Consent

I have read and understand the information provided in this consent form and the details of this study, and I agree to participate in the study.

[Signature]
[Date]

IRB 31(4):1, 2009

Please print your name

Please print your signature

Date

Please print your name

Please print your signature

Date

Please print your name

Please print your signature

Date

Please print your name

Please print your signature

Date
Share information

Longer Consent Forms for Clinical Trials Compromise Patient Understanding: So Why Are They Lengthening?

Fig 1. Page numbers of consent forms during a 5-year period.

Promote understanding

“Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research.”

45CFR46.116(a)(5)(i), finalized January 2017, pending implementation
Promote understanding

“Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.”
Obtain authorization for actions

Default: require autonomous authorization

- But we accept permissibility of waivers in certain circumstances
  - Minimal risk + impracticability
  - Emergency research

- Proxy permission (children, other incompetents)
  - ≠ autonomous authorization
Obtain authorization for actions

What token of consent is needed for valid authorization?
- Written vs. verbal vs. other?
- Opting in vs. not opting out?
Concordance matters more for some studies than for others

- Studies that implicate participants’ ends with respect to their own lives
  - E.g., choice between participation in early-phase cancer trial vs. enrolling in hospice

- Studies pursuing aims that prospective participant does not share
  - E.g., studies that seek to improve in vitro fertilization techniques, for (some) individuals who believe life begins at conception
Promote welfare interests

More complicated than it seems at first blush

- Investigators, IRBs share responsibility for protecting welfare interests
- Many studies involve minimal risk
  - therefore do not substantially implicate welfare interests
- Pediatric studies should (virtually) never threaten welfare interests

We should generally not depend on participants to protect their own welfare
Non-participant-centered functions

1. Adhere to legal & regulatory requirements
2. Establish legal defense if participant suffers expected adverse event
3. Obtain waiver of certain rights*
4. Advance professional integrity
5. Promote public trust

*stay tuned
Legal defense

Assume consent form/process clearly discloses a material fact

- Potential toxicity
- Study arrangement (e.g., sharing of data with third party)

Absent negligent performance or substantial deviation, consent should immunize investigator/institution from legal liability

No different from clinical scenario
Waiver of rights

What are you talking about, Joffe?
Waiver of rights

Participant waives right to fiduciary patient-doctor relationship

- Protocol constrains investigator’s ability to exercise discretion on behalf of patient-participant
- Investigator’s primary (co-primary?) loyalty is to answering the study question, and to the future patients who will benefit
- Closely related to concern underlying therapeutic misconception

Fried C. Medical experimentation: personal integrity and social policy, 1974
J Law Med Ethics.33:586, 2005
Participant waives right to receive standard of medical care (or, consents to deviation there from)

“researchers...do have a duty to protect the well-being of subjects, but it is a different sort of duty than a doctor usually has to a patient. ...it is a weaker duty, in the sense that while a doctor has to do what is best for a patient, a researcher has a much less demanding obligation... This change in legal status is acceptable... only because subjects have agreed to be under the weakened legal protections that apply to the relationship between subject and researcher.”

Menikoff J. What the Doctor Didn’t Say. 2006
Professional integrity

Promotes virtues of investigator
- Honesty with self & others
- Transparency
- Accountability to participant

Requirement to tell participant what you propose to do → unlikely you will do something you couldn’t defend in public
- In theory, peer review fulfills same function
What can we do to improve the process and outcome of informed consent to research?
Key challenges

Evidence base (esp. intervention studies conducted in real-world settings) is limited

What to measure is unclear

- Understanding?
- Perceptions of voluntariness vs. coercions?
- Discrepancies between actual vs. anticipated experience of study participation?
- Subsequent regret?
Interventions to Improve Research Participants’ Understanding in Informed Consent for Research
A Systematic Review

James Flory, BA
Ezekiel Emanuel, MD, PhD

Context Available data suggest that prospective research participants may frequently not understand information disclosed to them in the informed consent process. Little is known about how understanding can be improved.

Conclusions Efforts to improve understanding through the use of multimedia and enhanced consent forms have had only limited success. Having a study team member or a neutral educator spend more time talking one-on-one to study participants appears to be the most effective available way of improving research participants’ understanding; however, further research is needed.
Are shorter consent forms beneficial?

A randomized trial comparing concise and standard consent forms in the START trial

Christine Grady¹*, Giota Touloumi², A. Sarah Walker³, Mary Smolskis⁴, Shweta Sharma⁵, Abdel G. Babiker³, Nikos Pantazis⁶, Jorge Tavel⁷, Eric Florence⁷, Adriana Sanchez⁸, Fleur Hudson⁹, Antonios Papadopoulos⁹, Ezekiel Emanuel¹⁰, Megan Clewett¹¹, David Munroe¹², Eileen Denning⁵, the INSIGHT START Informed Consent Substudy Group¹¹

Background
Improving the effectiveness and efficiency of research informed consent is a high priority. Some express concern about longer, more complex, written consent forms creating barriers to participant understanding. A recent meta-analysis concluded that randomized comparisons were needed.
Are shorter consent forms beneficial?

Hypotheses

- Shorter form non-inferior
- Participant satisfaction with shorter form greater

<table>
<thead>
<tr>
<th>Table 3. Primary and secondary outcomes by consent group.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td># (%) correctly answered randomization question</td>
</tr>
<tr>
<td>Median (IQR) Comprehension Score</td>
</tr>
<tr>
<td>Median (IQR) Satisfaction score</td>
</tr>
<tr>
<td>Median (IQR) Voluntariness score</td>
</tr>
</tbody>
</table>
What about higher-touch consent process?

**Telephone-Based Nursing Intervention Improves the Effectiveness of the Informed Consent Process in Cancer Clinical Trials**

By Neil K. Aaronson, Elly Visser-Pol, Gerleen H.M.W. Leenhouts, Martin J. Muller, Astrid C.M. van der Schot, Frits S.A.M. van Dam, Ronald B. Keus, Caro C.E. Koning, Willem W. ten Bokkel Huinink, Joop A. van Dongen, and Ria Dubbelman

**Purpose:** Here we report the results of a randomized study undertaken to test the efficacy of a supplementary, telephone-based nursing intervention in increasing patients’ awareness and understanding of the clinical trials in which they are asked to participate.
What about higher-touch consent process?

Aaronson randomized 180 cancer patients considering a phase II or III trial to receive (or not) a supplemental phone call from an oncology nurse.

- Underwent blinded interviews 1 week later to assess knowledge, decisionmaking, anxiety.
- Highly significant effect on overall awareness ratings (66.3 vs. 83.1, p<0.001).
- Associated with greater knowledge of risks, objectives, randomization, voluntary participation/right to withdraw, alternatives.

J Clin Oncol 14:984, 1996
Given limited evidence base, what should investigators, sponsors, and IRBs do?
1. Decide which goals of informed consent are most important for the particular study

Emphasize participant-centered goals

My vote, for the typical greater-than-minimal-risk study:

- Emphasize gist understanding of purpose, major risks and potential benefits, alternatives
- Prepare for what to expect
- Support values-concordant decision making
2. Present information hierarchically, with core information front & center

Put core information on the metaphorical home page

- Consent form: executive summary
- Verbally: “here are the most important things I’d like you to be aware of”

Additional information (e.g., that’s nice-to-know, or that’s disclosed to protect investigator.) can be 1-2 levels down
3. Place study information in context

- Understand disease & clinical status
- Understand current treatment
- Understand clinical trial
4. Use best practices to facilitate considered, values-concordant decisions

Reviewed 139 consent forms for trials registered in clinicaltrials.gov
Evaluated them for concordance with 32 International Patient Decision Aids Standards (IPDAS) criteria
4. Use best practices to facilitate considered, values-concordant decisions

| Clarifying & Expressing Preferred Outcomes (2 items) |
| Describes adv/sadv, with enough detail to help imagine impact on life |
| Asks PPs to think about which adv and/or adv matter most to them |

| Structured Guidance in Deliberation & Communication (2 items) |
| Includes a tool designed to facilitate further discussion |
| Provides a step-by-step way to decide whether or not to participate |

| Describes disadvantages of NOS-participation in a consistent order |
| Describes disadvantages of NOT participating |
| Comparison of adv & adv, for participation & non-participation |

| Presenting Probabilities (8 items) |
| Provides information on probabilities for all advant |
| Provides information about levels of certainty around probabilities |
| Specifies probabilities in natural frequencies |
| Provides more than one way of viewing probabilities |
| Specifies population(s) that yielded the probabilities |
| Specifies time period over which probabilities apply |

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J Clin Epi 65:708, 2012
Summary

- When we seek informed consent, we have multiple goals in mind
- If we try to achieve all goals at once—or don’t distinguish between goals—we will fail
- Therefore we must
  - Prioritize goals
  - Design consent processes and materials to achieve highest-priority goals
Thank you!

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