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

- What is informed consent?
- Why is it important to clinical research?
- What are some of the challenges and how can we approach them?

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 health care and in most research with human subjects
- A process of reasoned decision making (not a form or an episode)
- One aspect of conducting ethical clinical research

Ethical requirement

- Respect for autonomy - an individual's capacity and right to define his/her own goals and make choices consistent with those goals.

- "Informed consent is rooted in the fundamental recognition…that adults are entitled to accept or reject health care interventions on the basis of their own personal values and in furtherance of their own personal goals" Presidents Commission for the study of ethical problems…1982

Informed consent in medical practice

Informed consent in medical practice

- …frequently inadequate…
- Physicians receive little training… and misunderstand requirements and legal standards…
- Time pressures and competing demands…
- Patient comprehension is often poor…
- Recent studies have demonstrated that teaching communication skills to physicians can improve patient understanding of risks
- Schenker et al 2010; Matiasek et al. 2008; McClean et al. 2004, and others

Informed consent in clinical research

- Codes of research ethics, regulations, and laws (limited exceptions) require informed consent from the research participant or her legally authorized representative (and documentation):
  - ICH-GCP
  - Declaration of Helsinki
  - US Federal Regulations (Common Rule (45CFR46) and FDA (21CFR50))
  - 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.

Two senses of informed consent

(Faden & Beauchamp)

- An autonomous authorization:
  - "the intentional authorization of an activity based on substantial understanding and in the absence of control by others"
- Social rules of consent
  - An institutionally or legally effective authorization, as determined by prevailing rules

Elements of informed consent

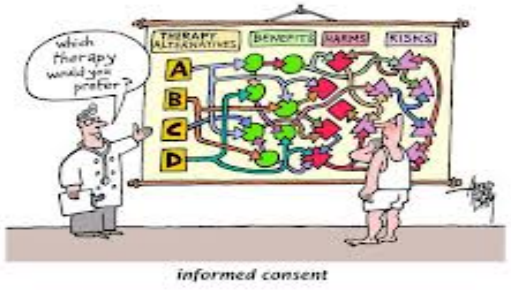
- Capacity to consent
- Disclosure of information
- Understanding
- Voluntariness
- Consent authorization

Elements of informed consent

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

Disclosure of information: Issues and challenges

- How much and what information should be disclosed?
- How should the information be presented?
- Circumstances and setting?



Disclosure of information

- Written consent form
  - A summary of study information–explanation of what the study is about, the procedures, related risks and possible benefits, alternatives, rights;
- Advertisements, fliers, brochures
- (Reviewed and approved by IRB)

- Discussion with research team, other providers, other participants, etc.

Disclosure- required elements

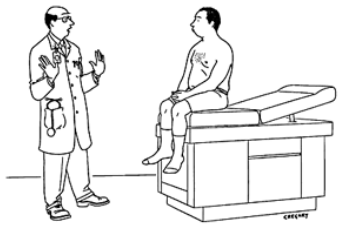
(from 45CFR46.116 and 21CFR50.25)

- Statement of research
- Purpose and procedures
- Foreseeable risks and discomforts
- Any benefits to subjects or others
- Appropriate alternatives
- Extent of confidentiality
- Treatment or compensation for injury
- Who to contact for answers to questions
- Participation is voluntary

- Additional elements

Writing a consent form

- What information to include
- Making it readable and understandable
- Format
- Consideration of length and complexity



"Whoa—way too much information!"

Readable/understandable

- "The purpose of this study is to test the safety of XXX at different dose levels in patients with cancer who have different degrees of normal and abnormal liver function. XXX is an experimental drug that has not been approved by the FDA for use in patients with cancer. XXX was designed to enter cancer cells and block the activity of proteins that are important for cancer cell growth and survival. This is the first study in which XXX will be given to people with different degrees of liver function. We already know the safe dose for people with normal liver function…"

- We want to find a dose of XXX that is safe in patients with cancer whose livers are not working normally. XXX is an experimental drug that aims to block the growth of cancer cells. It is not approved by the FDA for patients with cancer. We know the safe dose in patients with normal liver tests. This is the first time we will give XXX to people who have abnormal liver tests

Studies of consent form readability

- **Reading level is high**
  - Consent forms and templates usually written at about the 11th grade level or higher 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**
  - Silverman et al. *Critical Care Medicine* 2001; Horng et al, *NEJM* 2002; Beardsley et al. *JCO* 2007; Abeysena C et al *Ind J Med Ethics* 2012

"Hey, no problem!"

Once you've estimated how long it takes to read the consent form you can time how long subjects take to read the consent form during the consent process, or ask them how long it took them to read the consent form at home. Unfortunately, I suspect you'll find most subjects not taking adequate time to read the consent form, but are scanning it fairly quickly.

Summary

Even though typical consent forms require subjects to sign that "I have read and understood this consent form…" that signature does not guarantee that subjects took enough time to read the consent form. Subjects may want to believe that they have read and understood the consent form; researchers may want to believe that their subjects have read and understood the consent form. If so, both are engaging in self-deception. Unless more direct evidence shows that subjects actually have read the consent form, it's probably wise to assume that they have not. If so, future research needs to focus on what--if anything--can be done to encourage subjects to take the time needed to read the consent form.

Table #2: Minutes to read a consent form

Consent Form Length (Words)	Very Slow Reading Speed (100 words/min)	Average Reading Speed (200 - 250 words/ min)	Fast Reading Speed (300 words/ min)
2,000	20 minutes	8 - 10 minutes	7 minutes
3,000	30	12 - 15	10
4,000	40	16 - 20	13
5,000	50	20 - 25	17
6,000	60	24 - 30	20
7,000	70	28 - 35	23
8,000	80	32 - 40	27
9,000	90	36 - 45	30
10,000	100	40 - 50	33
11,000	110	44 - 55	37
12,000	120	48 - 60	40

References

1. Davis, T.C., Holcombe, R.F., Berkel, H.J., et al. (1998) Informed Consent for Clinical Trials: a Comparative Study of Standard Versus Simplified Forms. *Journal National Cancer Institute*, 90, 668-674.
2. McNutt, L., Waltermaurer, E., Bednarcyk, R.A., et al (2008) Are We Misjudging How Well Informed Consent Forms Are Read? *Journal of Empirical Research on Human Research Ethics*, 3(1), 89-97.
3. Davis, T.C., Bocchini, J.A., Fredrickson, D., et al (1996) Parent comprehension of polio vaccine information pamphlets. *Pediatrics*, 97(6), 804-810.
4. Davis, T.C., Fredrickson, D.D., Arnold, C., et al (1998) A polio immunization pamphlet with increased appeal and simplified language does not improve comprehension to an acceptable level. *Patient Education and Counseling*, 33, 25-37.

Challenges

- Research informed consent usually requires a written form
- It is hard to communicate clearly

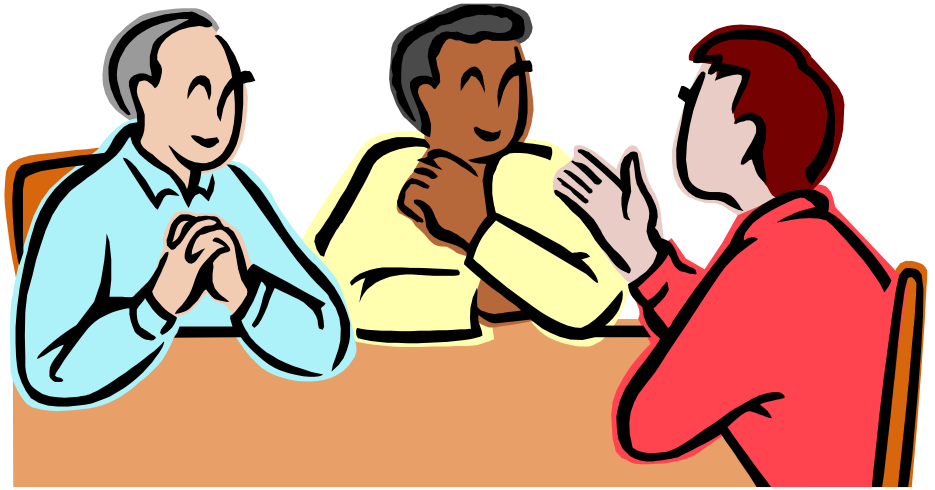
  "Easy reading is damn hard writing."

  Nathaniel Hawthorne ~1840 Maya Angelou ~2000
- Written informed consent protects the institution, sponsor, investigator
- IRBs make consent forms longer and more complex

Easy-to-read informed consent documents

- Familiar, consistent words, Active voice and personal pronouns
- Short, simple, and direct sentences with limited line length
- Short paragraphs, one idea per paragraph.
- Clear and logically sequenced ideas
- Highlight Important points
- Avoid acronyms and abbreviations
- Format:
  - Titles, subtitles, simple headers
  - Balance white space with words and graphics
  - Font, style, spacing,
  - Underline, bold, or boxes (rather than all caps or italics) give emphasis.
- **From NCI Simplification of Informed Consent Documents, Appendix 3**. <http://www.cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/page1

Presentation



Data on investigator practices regarding consent

- Investigators (n=117) of a multinational HIV trial surveyed about consent practices
  - Provided a copy to read (99%)
  - Gave subjects opportunity to read before clinic (97%)
  - Provided a great deal of information about risks and purpose (>75%)
  - Emphasized randomization (<56%)
  - Formal assessment of understanding (8.6%)

Sabik et al. *IRB* 2005

SETTING

Summary- disclosure

- What, where, who, when, and how matter
- Consent documents
  - usually include relevant information,
  - not always compliant with regulations,
  - are long, complex and written at a high level
- Disclosure by investigators variable- very few studies *
- Limited training for investigators

Elements of informed consent

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

Understanding is variable

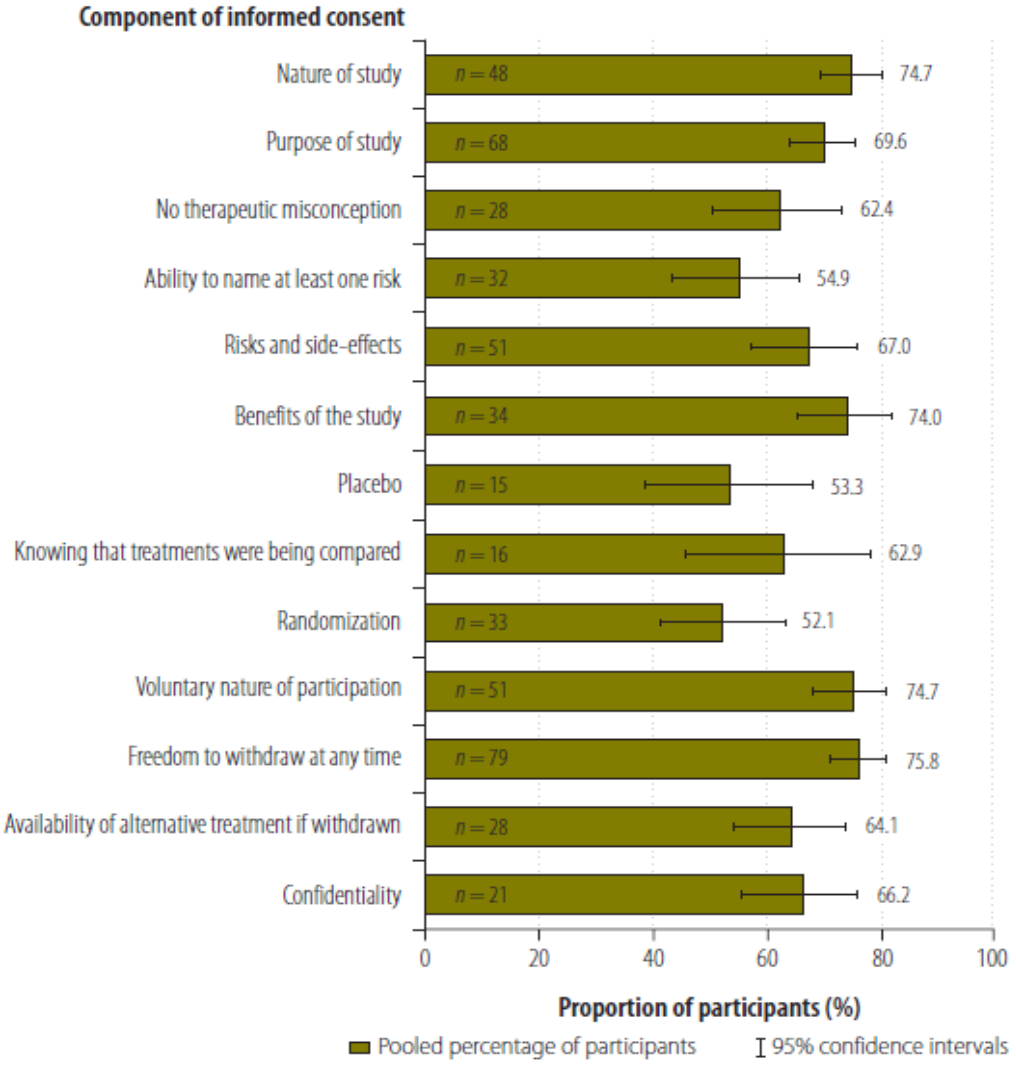
- Studies continue to show that research participants often have limited understanding of study information

e.g. Mandava A et al *J Med Ethics* 2012

Participant Understanding: Research Purpose/ Nature, Risks, and Randomization

- Range of understanding about the purpose and nature of research (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]**



[a] The number of studies included in the evaluation of each component is given.

Tam T et al. Bull of WHO 2015

Understanding: issues and challenges

- Factors that might affect understanding
- How is/should understanding be assessed?
- How much should participants understand?
- What happens (or should happen) when they don't understand?

What affects understanding?

- "Host" factors- Age*, education*, pain, cognitive capacity,* literacy

- Expectations and familiarity with research
  - Trust in providers, deference
  - Therapeutic misconception and related misunderstandings

- Process related factors
  - What is disclosed and how
  - How does participant listens to/reads the information?

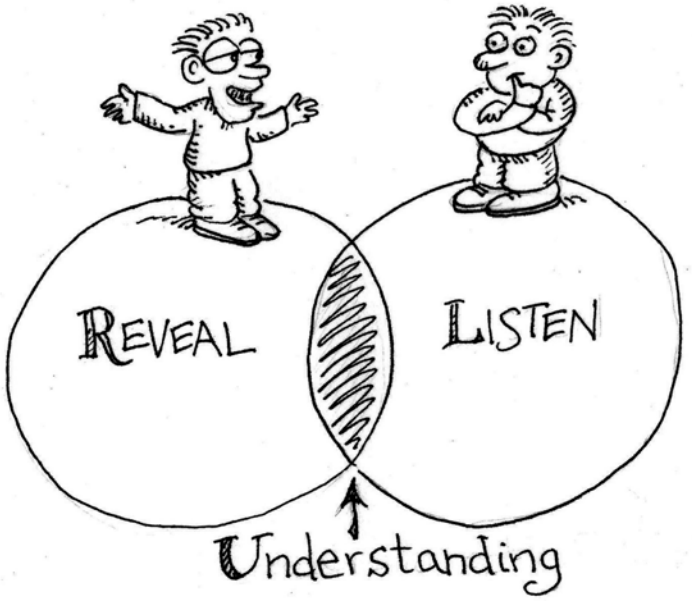
Challenges

- Complex Science
- Health literacy and capacity
- Measuring understanding
- Different kinds of "mis-understanding"
  - Misconception
  - Mis-estimation
  - Optimism

    Horng & Grady *IRB* 2003
- Knowledge v. appreciation

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 negate the ability to provide meaningful informed consent. Appelbaum et al. KIE 2006

Studies of strategies to improve 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)
  - Flory and Emanuel *JAMA* 2004

Strategies to improve understanding

- No significant improvement in understanding using multimedia strategies (1/12- computerized presentation in mental health study)
- 6 of 15 enhance consent forms showed significant improvement in understanding
- Limited data suggest that more person-to-person contact (through extended discussions (3/5) , test/feedback strategies (5/5) may help improve understanding

Flory and Emanuel JAMA 2004

Strategies to improve 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)

Nishimura A et al. *BMC Medical Ethics* 2013

Strategies to improve understanding

- Significant increase in understanding with enhanced consent form compared to controls (meta-analysis).

- "The question of whether "shorter forms are better (or no worse than) longer" for participant understanding is still an open question…need for direct comparison in randomized studies…"

Nishimura A et al. *BMC Medical Ethics* 2013

Strategies to improve understanding

- Randomized participants to either a concise or standard consent form.
- Does a simpler, more concise consent form affect study understanding or satisfaction with consent?
  - 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


IRB
ETHICS & HUMAN RESEARCH

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

IN THE FIELD

Assessing the Readability of Non-English-Language Consent Forms: The Case of Kiswahili for Research Conducted in Kenya

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

BY LEANNE STUNKEL, MEREDITH BENSON, LOUISE MCLELLAN, NINET SINAII, GABRIELLA BEDARIDA, EZEKIEL EMANUEL, AND CHRISTINE GRADY


Contents lists available at SciVerse ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

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

Mary E. Enama, Zonghui Hu, Ingelise Gordon, Pamela Costner, Julie E. Ledgerwood, Christine Grady, and the VRC 306 and 307 Consent Study Teams

ARTICLE INFO

ABSTRACT

Improving informed consent

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

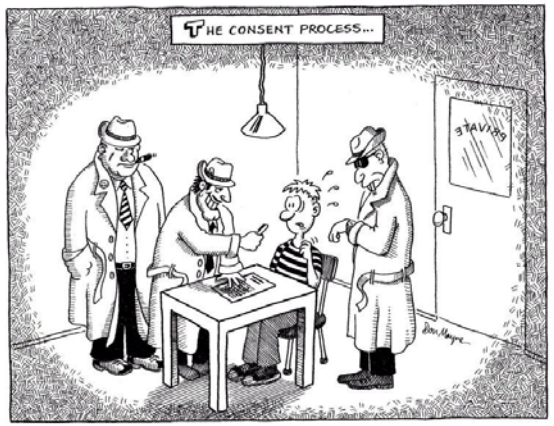
Schenker Y and Meisel A, *JAMA 2011*

Elements of informed consent

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

Voluntariness

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



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
  - 2%- 25% (ACHRE 1996, van Stuvensten et al 1998, Pace et al 2005)
  - 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)

Voluntariness: Data on refusal

Study	Refusal rate
Cardiac intervention studies	7% (range 1-21%)
Breast conserving treatment trial	9%
NHANES interviews and samples	18.9 %, 14.7%
Intensive diabetes therapy- adolescents	43%
Genetics study Guarani Indians	58%

Summary: voluntariness

- Limited Data
- Measurement of voluntariness difficult
- Few feel pressure from others
- Many say they cannot quit or could not say no
- Individuals refuse participation at variable rates

Table. Steps for Validating Potential Research Participants' Consent to Research

	Risk/Benefit Profile for Participants[a]		
	Low Risk	Moderate Risk and High Risk/ Potential Benefit	High Risk/ Little or No Potential Benefit
Example	Buccal sampling; few blood draws; standardized surveys	Phase 2 study; research biopsy	Treatment withdrawal for serious condition; challenge studies with high risk
Domains of valid consent			
Competence	Assume[b]	Assume[b]	Consider formal assessment
Understanding	Assume (following explanation of study)[b]	Informal or brief formal assessment	Formal assessment by team or independent party
Voluntariness	Assume[b]	Informal assessment	Formal assessment by team or independent party

[a] As determined by the institutional review board.
[b] Unless there is reason for concern.

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

Informed consent-conclusions

- Informed consent in research is ethically important, but imperfectly realized

- Data suggest:
  - Consent forms are long and complex,
  - Understanding is variable, and especially low in certain areas
  - Many participants do not know/feel they can quit or refuse
  - Spending more time may enhance understanding

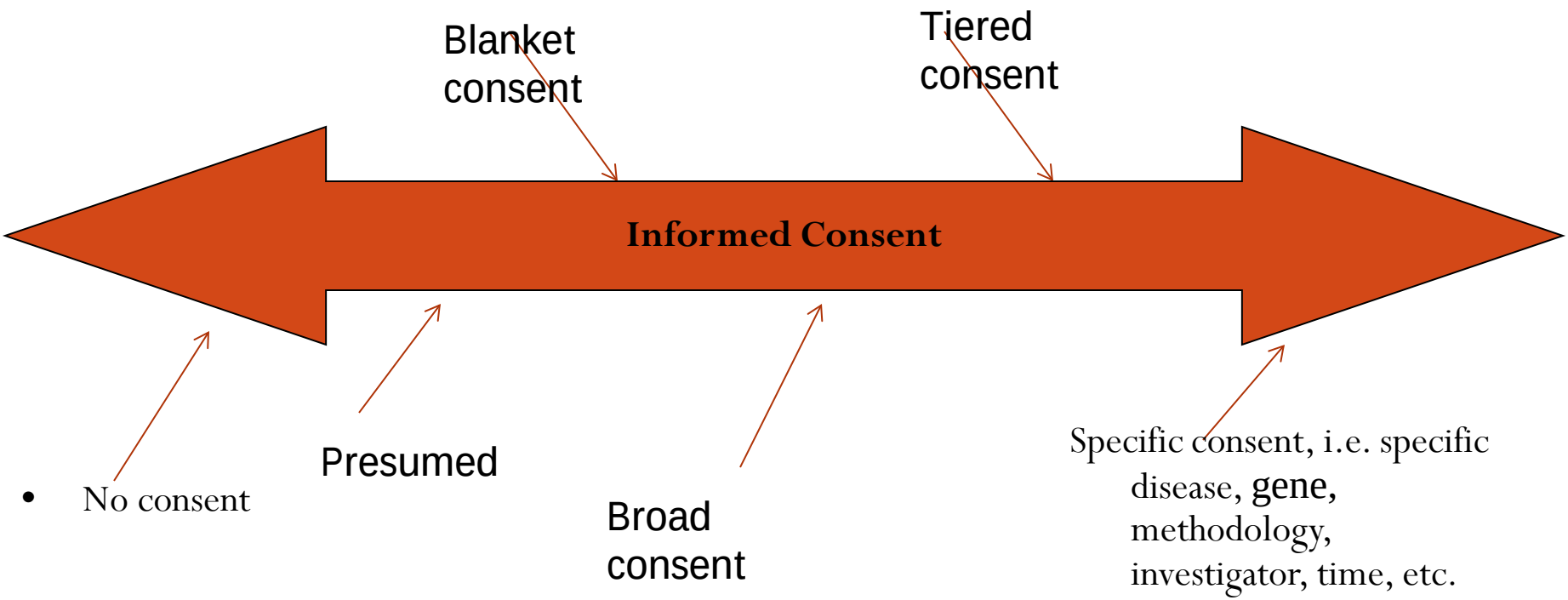
- More (and rigorous) data are needed
  - to improve our understanding of informed consent
  - Improve the process in a variety of settings
  - Enhance participants' experience, understanding, and decision making

Contemporary challenges

- Consent for research with biological specimens and data

- What and how should information be disclosed? What level of understanding? Voluntary choice?
- Should consent be required for research use of de-identified data or biospecimens?

The spectrum of consent



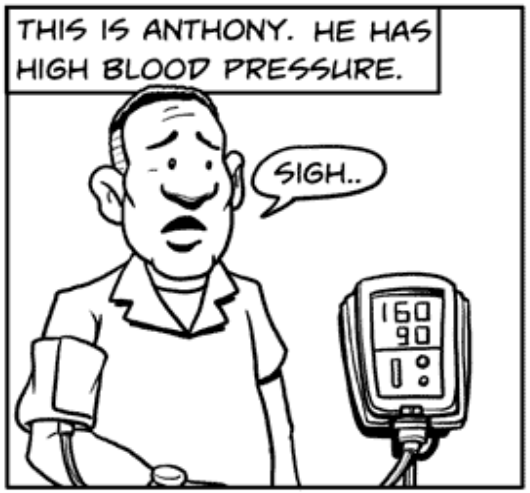
Contemporary challenges

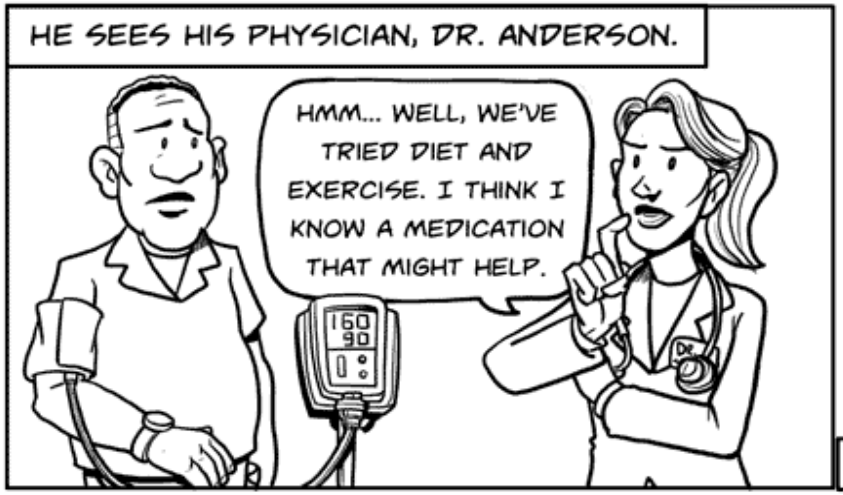
- Consent for comparative effectiveness research, research on medical practice, pragmatic trials, learning health care systems.

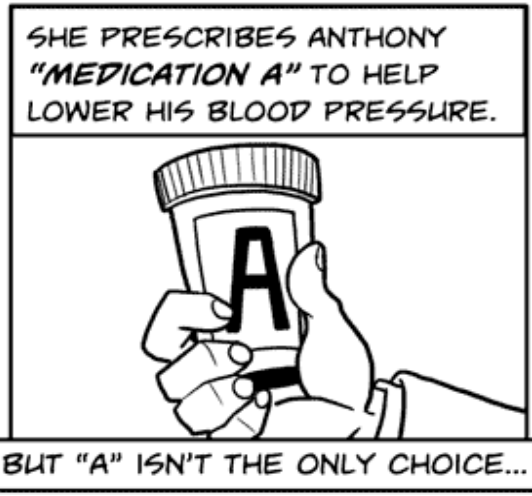
- What and how should information be disclosed? What level of understanding? Voluntary choice?
- What kind of consent is appropriate for research on medical practice?

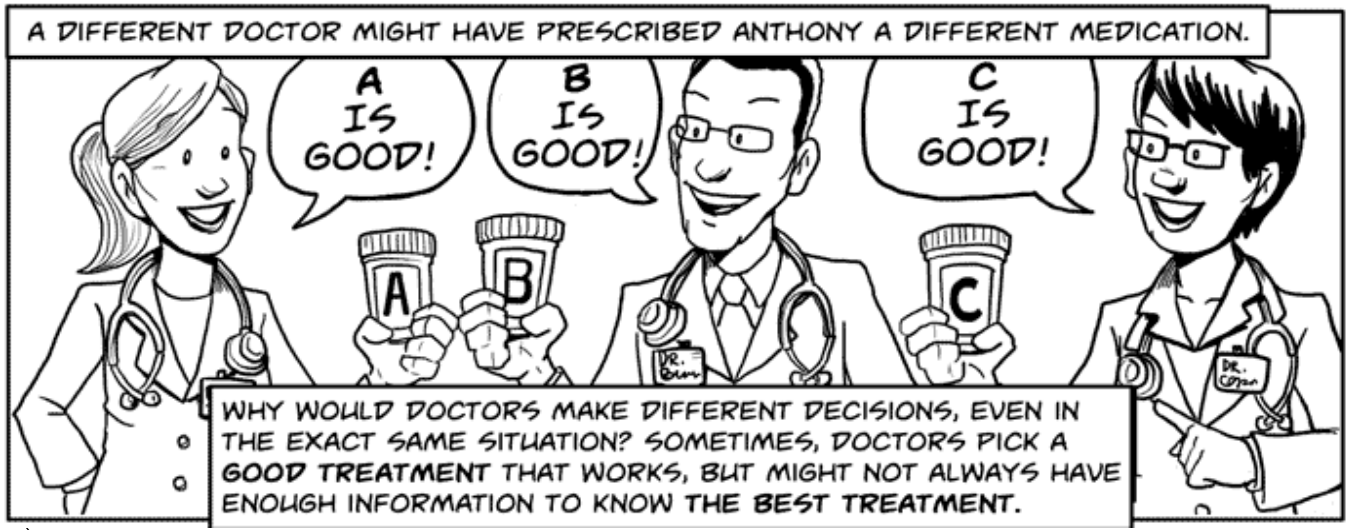
The ROMP Ethics Study

Exploring the ethical issues in Research on Medical Practices (ROMP)









ORIGINAL RESEARCH IMPROVING PATIENT CARE

Attitudes Toward Risk and Informed Consent for Research on Medical Practices

A Cross-sectional Survey

Mildred K. Cho, PhD; David Magnus, PhD; Melissa Constantine, PhD, MPAff; Sandra Soo-Jin Lee, PhD; Maureen Kelley, PhD; Stephanie Alessi, JD; Diane Korngiebel, DPhil; Cyan James, PhD; Ellen Kuwana, MS; Thomas H. Gallagher, MD; Douglas Diekema, MD, MPH; Alexander M. Capron, LLB; Steven Joffe, MD, MPH; and Benjamin S. Wilfond, MD

Background: The U.S. Office for Human Research Protections has proposed that end points of randomized trials comparing the effectiveness of standard medical practices are risks of research that would require disclosure and written informed consent, but data are lacking on the views of potential participants.

Objective: To assess attitudes of U.S. adults about risks and preferences for notification and consent for research on medical practices.

Design: Cross-sectional survey conducted in August 2014.

Setting: Web-based questionnaire.

Patients: 1095 U.S. adults sampled from an online panel (n = 805) and an online convenience river sample (n = 290).

Measurements: Attitudes toward risk, informed consent, and willingness to participate in 3 research scenarios involving medical record review and randomization of usual medical practices.

Results: 97% of respondents agreed that health systems should evaluate standard treatments. Most wanted to be asked for permission to participate in each of 3 scenarios (range, 75.2% to 80.4%), even if it involved only medical record review, but most would accept nonwritten (oral) permission or general notification if obtaining written permission would make the research too difficult to conduct (range, 70.2% to 82.7%). Most perceived additional risk from each scenario (range, 64.0% to 81.6%).

Limitation: Use of hypothetical scenarios and a nonprobability sample that was not fully representative of the U.S. population.

Conclusion: Most respondents preferred to be asked for permission to participate in observational and randomized research evaluating usual medical practices, but they are willing to accept less elaborate approaches than written consent if research would otherwise be impracticable. These attitudes are not aligned with proposed regulatory guidance.

Primary Funding Source: National Center for Advancing Translational Sciences at the National Institutes of Health.

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For author affiliations, see end of text.

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Table 3. Notification and Permission Preferences for Research on Medical Practices

Response	Research Scenario (n = 1095), n (%)		
	Medical Record Review	Randomization (Hypertension)	Randomization (Serious Condition)
"If you were newly diagnosed with high blood pressure and this research were happening in your health system, how would you prefer to be notified about this research?"			
No notification	109 (10.0)	71 (6.5)	61 (5.6)
General information	162 (14.8)	212 (19.4)	153 (14.0)
Discussion plus verbal permission	266 (24.2)	295 (26.9)	307 (28.0)
Discussion plus written permission	558 (51.0)	517 (47.2)	574 (52.4)

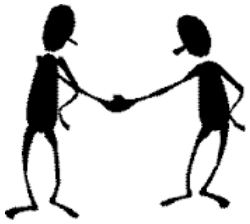
Contemporary challenges

- Consent for research collected through social media and other digital platforms

- What kind of consent is appropriate for digital research?
- What and how should information be disclosed? What level of understanding? Voluntary choice?

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