INFORMED CONSENT

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DEPARTMENT OF BIOETHICS

NIH CLINICAL CENTER

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


ASSENT
VS
CONSENT

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

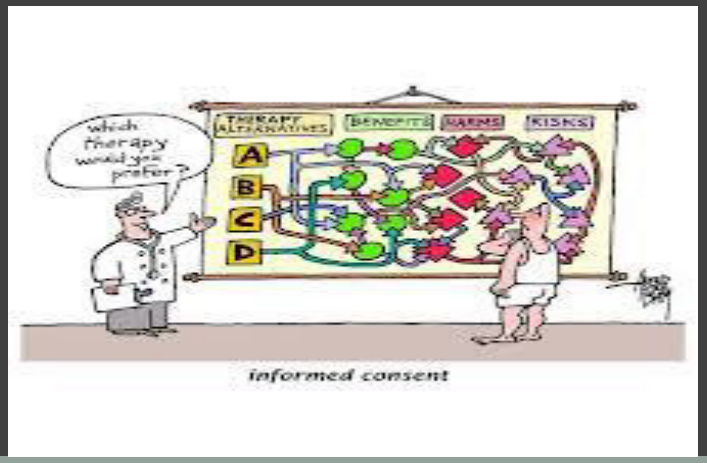
Voluntariness

(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 *in language understandable to the subject or LAR*.

§___.116 (a)(4) …. *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

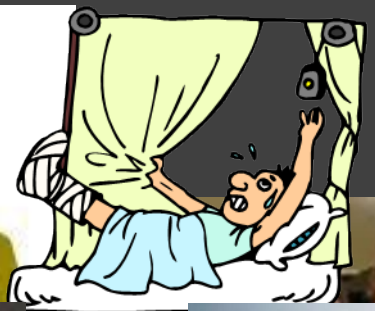
Reading level is high- often written at or above the 11th grade level LoVerde et al, 1989; Grossman et al 1994; Paasche-Orlow et al., 2003; Sharp 2004

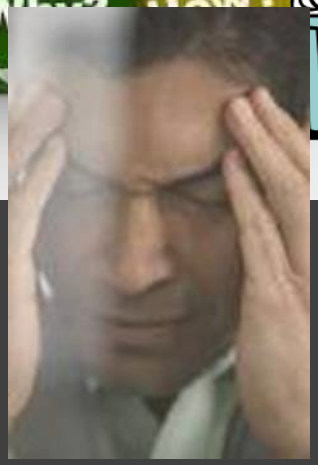
Consent forms are long, and have increased in length over time Baker and Taub, 1983; LoVerde et al 1989; Tarnowski et al 1990; Beardsley et al 2007, Albala et al. 2010

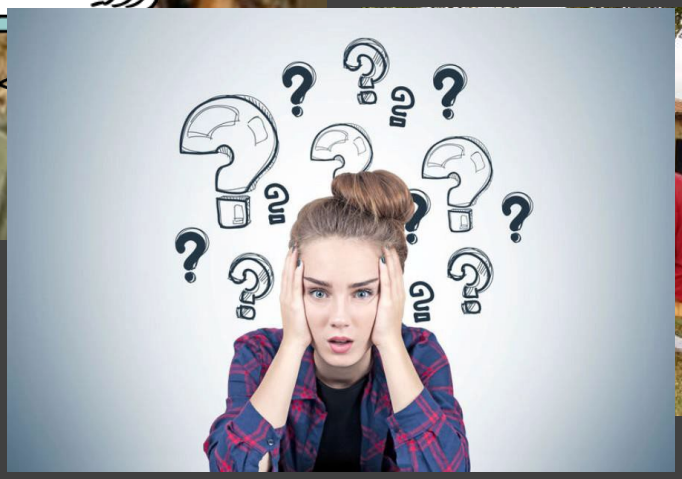
Required or relevant elements are often missing

- 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

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

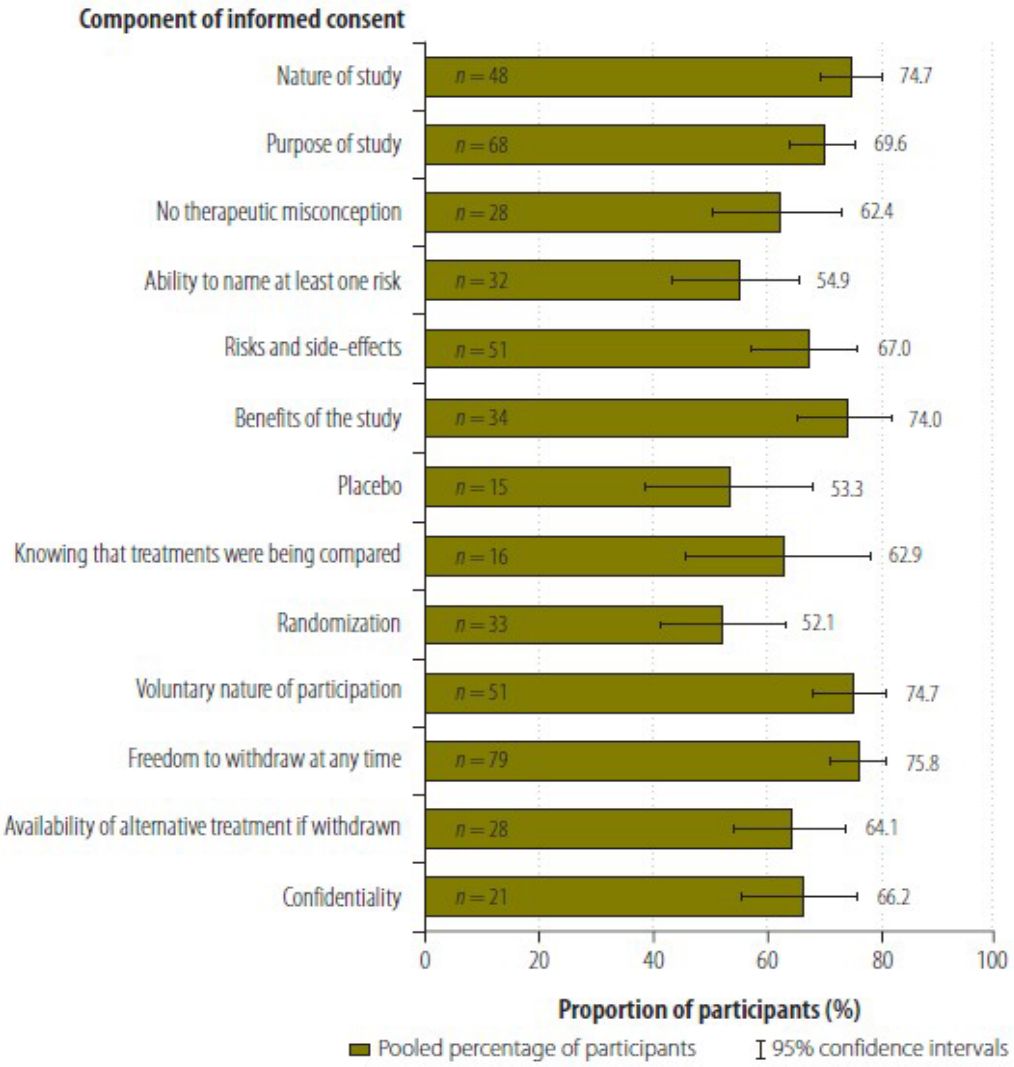
Participant Understanding Data

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[a]**



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

Tam T et al. Bull of WHO 2015

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

	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

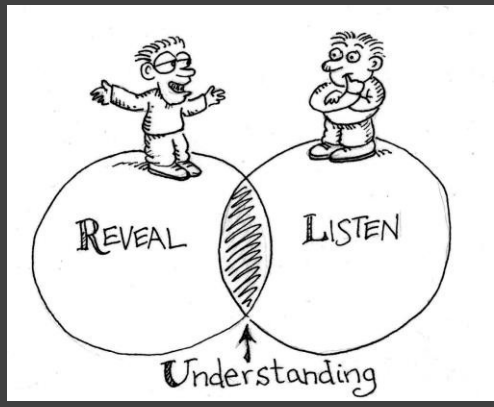
[a] As determined by the institutional review board.
[b] Unless there is reason for concern.

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

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


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

By Leanne Stunkel, Meredith Benson, Louise McLellan, Ninet Sinai, Gabriella Bedarida, Ezekiel Emanuel, and Christine Grady

Although informed consent is a fundamental ethical requirement for research with humans, many studies indicate that research volunteers often do not understand critical aspects of the research in which they are participating, suggesting that the "informed" part of consent to participate is imperfectly realized.[1] ing, satisfaction with the informed consent process, or both.[5] However, not all studies found improvement.[6] Moreover, these studies have important limitations. Many used consent documents in hypothetical situations rather than in actual research studies.[7] Also, most of the consent studies involved participants who were

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IN THE FIELD

Assessing the Readability of Non-English-Language Consent Forms: The Case of Kiswahili for Research Conducted in Kenya
Caroline Kithinji and Nancy E. Kass 10


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 ☆

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ABSTRACT

Background: Consent to participate in research is an important component of the conduct of ethical clinical trials. Current consent practices are largely policy-driven. This study was conducted to assess comprehension of study information and satisfaction with the consent form between subjects randomized to concise or to standard informed consent forms as one approach to developing evidence-based consent practices.
Methods: Participants (N = 111) who enrolled into two Phase I investigational influenza vaccine protocols (VRC 306 and VRC 307) at the NIH Clinical Center were randomized to one of two IRB-approved consents; either a standard or concise form. Concise consents had an average of 63% fewer words. All other aspects of the consent process were the same. Questionnaires about the study and the consent process were completed at enrollment and at the last visit in both studies.
Results: Subjects using concise consent forms scored as well as those using standard length consents in measures of comprehension (7 versus 7, p = 0.79 and 20 versus 21, p = 0.13), however the trend was for the concise consent group to report feeling better informed. Both


PLOS ONE

RESEARCH ARTICLE

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

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¶ For complete list of START investigators, please see S6 File.
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OPEN ACCESS

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Data Availability Statement: Participant level data are not provided as open access due to ethical and legal obligations to the participants in the clinical trials. Aggregate data will be available to all qualified researchers upon request to the INSIGHT

Abstract

Background

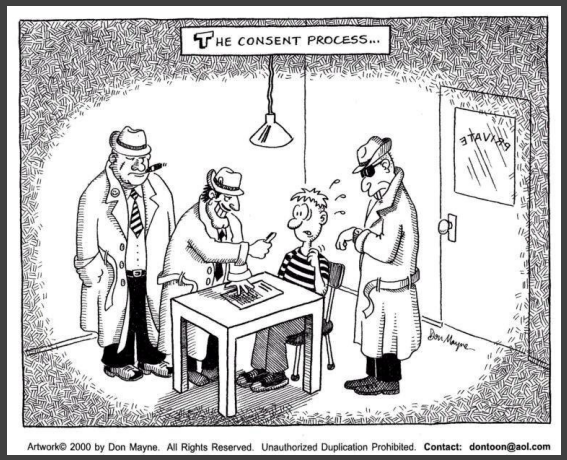
Improving the effectiveness and efficiency of research informed consent is a high priority. Some express concern about longer, more complex, written consent forms creating barriers to participant understanding. A recent meta-analysis concluded that randomized comparisons were needed.

Methods

We conducted a cluster-randomized non-inferiority comparison of a standard versus concise consent form within a multinational trial studying the timing of starting antiretroviral therapy in HIV+ adults (START). Interested sites were randomized to standard or concise consent forms for all individuals signing START consent. Participants completed a survey measuring comprehension of study information and satisfaction with the consent process. Site personnel reported usual site consent practices. The primary outcome was comprehen-

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

- 2%- 25% (ACHRE 1996, van Stuvensten et al 1998, Pace et al 2005)
- 58% from child's disease (Pace et al 2005)

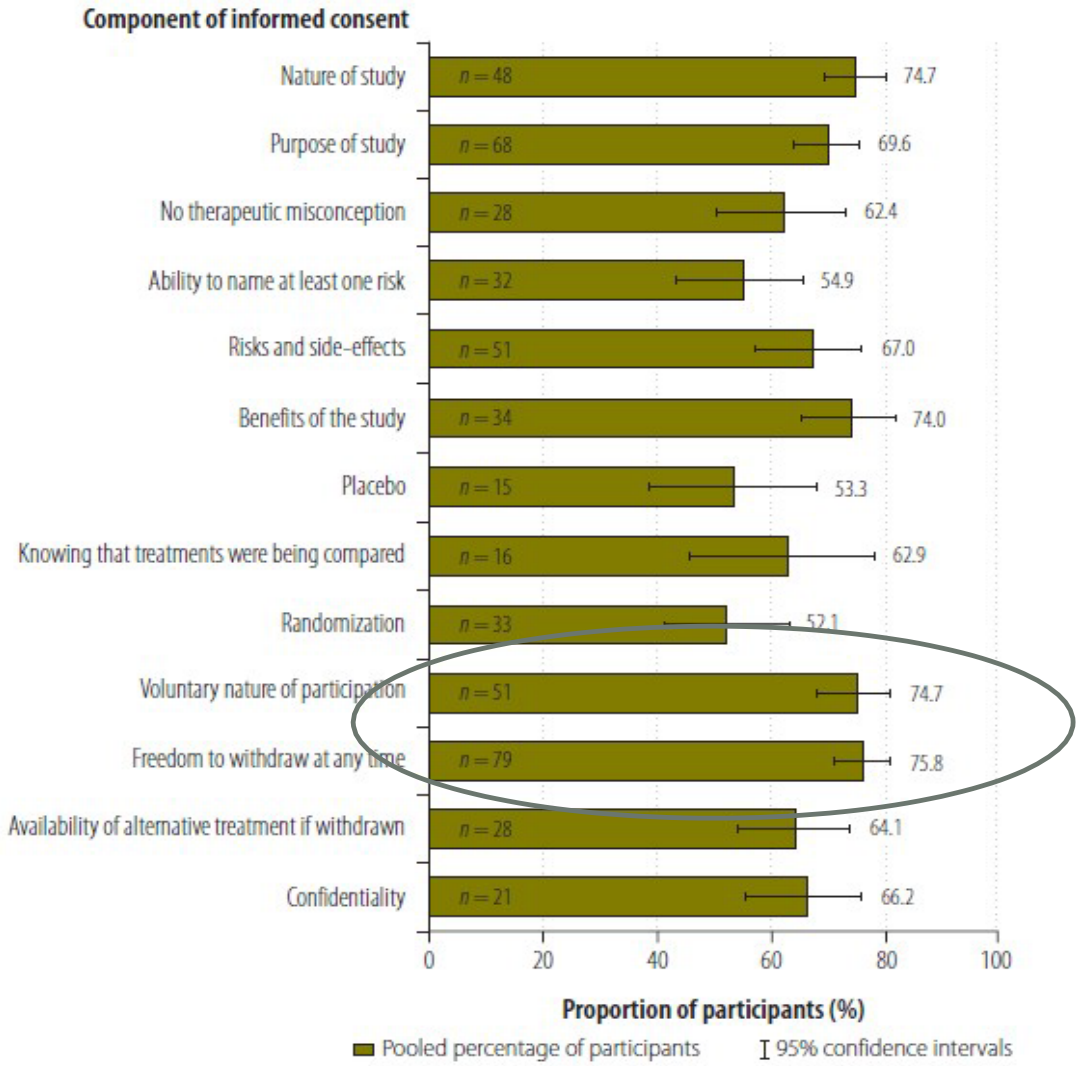
Knew they could quit

- 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, Schumacher et al. 2017)

Decline participation

- Range of actual decliners

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

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

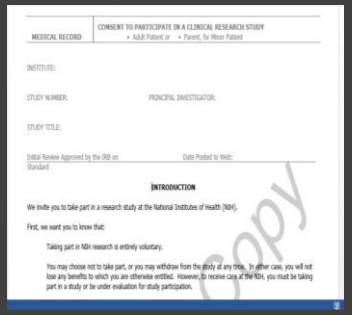
Types of research

- Biobanks and Data Repositories
- Big Data
- Pragmatic trials

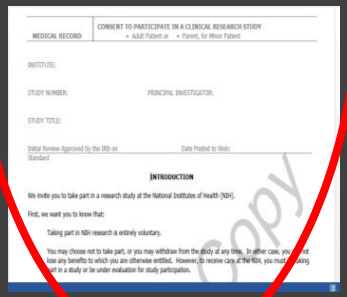
Types of information exchange

- Electronic consent
- Devices and apps
- Web interfaces
- Telehealth

Typical clinical research



Typical clinical research



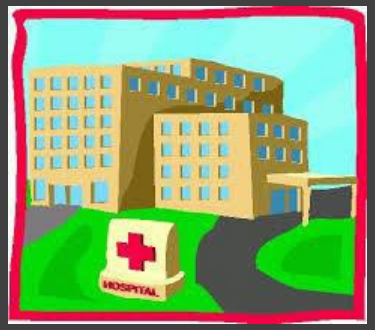
Research with Data and Biospecimens

Acceptable consent?

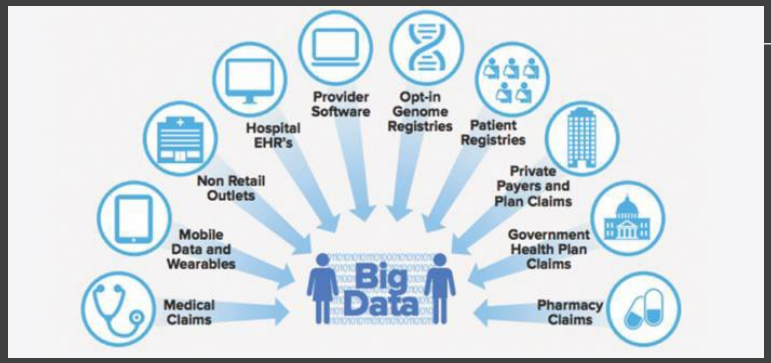
	TYPE OF CONSENT	DESCRIPTION
Less Control, Less burden  More control, more burden	No consent	No consent needed
	Blanket	Consent to future research with no limitations
	Broad*	Consent to future research with specified limitations
	Checklist	Donors choose which types of future studies are allowed
	Study specific	Consent for each specific future study

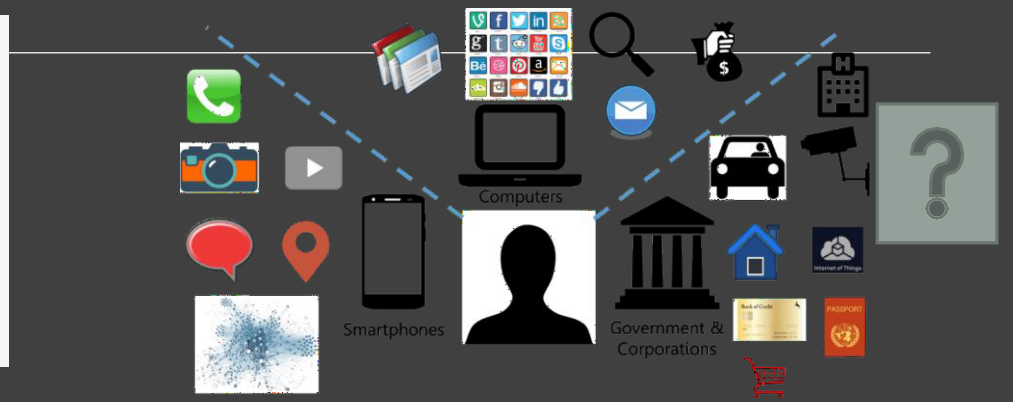
Grady et el. *AJOB* 2015

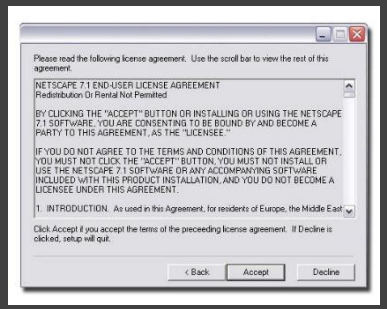
Pragmatic trials



Research with big data







DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2015–D–0390]

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 (see ''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, 5630 Fishers Lane, Rm. 1061, 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 9 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, 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 or cover note 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 ''confident will not be disclosed except i accordance with 21 CFR 1 applicable disclosure l information about E comments to publ 56469, Septemb the informatio *regulatoryin default.htm Docket:* read back electroni received *www.reg* docket n heading (''Search'' and/or go Manageme 1061, Rocky See section **INFORMATION** s written requests guidance and for e guidance document.

FOR FURTHER INFORMATIO Cheryl Grandinetti, Center Evaluation and Research, Food a Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 3348, Silver Spring, MD 20993–0002, 301–796–2500; Nicole Wolanski, Office of Good Clinical Practice, Office of Specia Medical Programs, Office of Medical Products and Tobacco, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, Rm. 5108, Silver Spring, MD 20993, 301 796–6570; Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993–0002, 240–402–7911; Irfan Khan, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3459, Silver Spring, MD 20993, 1–800–638–2041 or 301–796–7100; or Irene Stith-Coleman, Office for Human Research Protections, 1101 Wootton Pkwy., suite 200, Rockville, MD 20852, 240–453–6900.

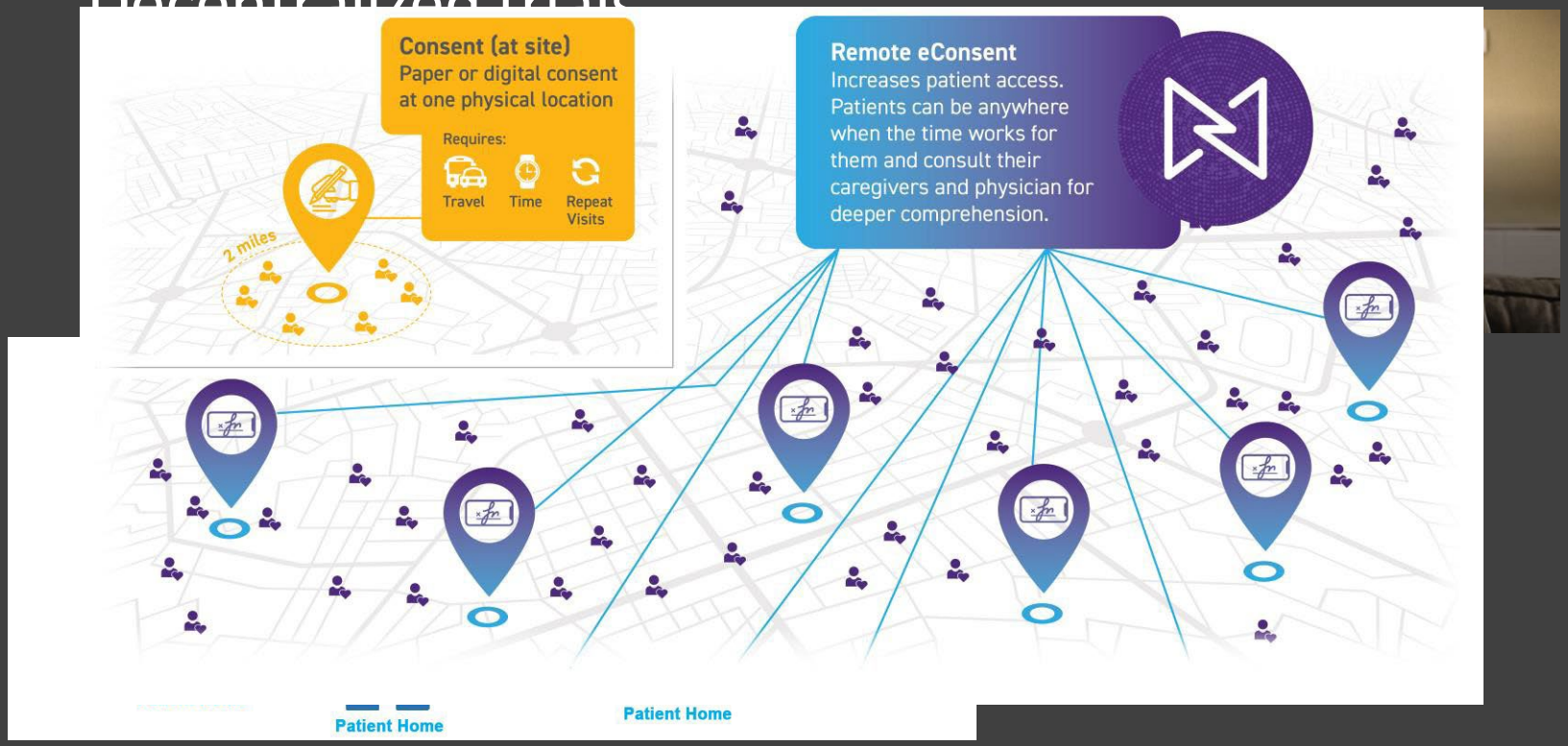
SUPPLEMENTARY INFORMATION:

I. Background

"…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."

Decentralized trials

Decentralized trials



Informed Consent

Table 1. Components and Challenges of Informed Consent with Traditional Paper Forms and Electronic Methods.

Component	Traditional Paper Informed Consent	Electronic and Digital Informed Consent	Challenges and Areas for Research
Disclosure	Information is written, usually on paper Discussion with investigator takes place, usually face to face	Consent can involve electronic information, multimedia information, video graphics, and interactive computer interfaces Investigator can be remote in time or place from participant	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
Understanding	Investigator and participant discuss information Participant asks questions Investigator assesses understanding, in some cases using questions, structured quizzes, other methods	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	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[47]
Voluntariness	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	Some electronic systems facilitate participant control Participant can easily sign off or disengage Participant can decline	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
Authorization	Paper consent document is signed Copies of document are kept in records	Options might include clicking agreement or an electronic signature Records of agreement are kept electronically	It may be difficult to verify the identity of the authorizing person

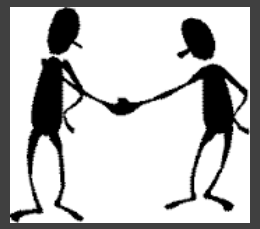
Conclusions

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