Developing a Participant-Centric Consent Process for ADAPTABLE

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Adaptable

The Aspirin Study

pcornet

Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE)

- Objective: To compare effectiveness & safety of two commonly-used doses of aspirin (81 / 325 mg) in high-risk patients with coronary artery disease
  - Primary effectiveness endpoints: Composite of all-cause mortality, hospitalization for MI, or hospitalization for stroke
  - Primary safety endpoint: Hospitalization for major bleeding
- First demonstration project to be conducted through PCORnet, the National Patient-Centered Clinical Research Network
  - Enroll 20k patients through Clinical Data Research Networks

Features of ADAPTABLE

- ADAPTORS: Patient leaders for ADAPTABLE Trial
  - Patient representatives from each participating CDRN
  - Have experience taking aspirin and history of heart disease or enrichment factors for trial eligibility
  - Serve on the Steering Committee
- National model for new research paradigm, learning health care systems
  - Enhance capacity to conduct much-needed health research studies more quickly and efficiently, less expensively, and with greater potential impact than is now possible
  - Model for effective, participant-centric informed consent

ADAPTABLE Study Process

Screening of CDRN EHR data with computable phenotype

Outreach to prospective participants with trial introduction and link to ADAPTABLE web portal

Web-based, electronic informed consent

- Information in text and video format, English & Spanish
- Focused questions to promote consent comprehension

Confirm eligibility; randomization to aspirin dose

Electronic follow-up (~30 months)
Survey every 3–6 months, supplemented with EHR/CDM/claims data

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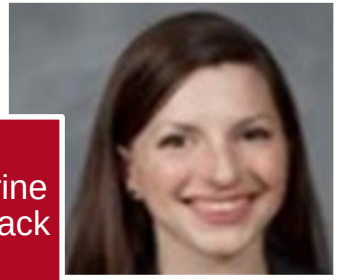
Today's Presentation:
- Empirical development of participant-centric consent form and comprehension tool

Duke Program for Empirical Bioethics: ADAPTABLE Consent Team

Laura Beskow



Catherine Hammack

Kevin McKenna

Zach Lampron

Martina Bresciani

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Informed Consent: The Challenge

Consent forms are “becoming ever more intimidating, and perhaps inhibiting rather than enhancing participants’ understanding. Participants may not even read them, much less understand them.”

Hastings Center Report (2008)

Calls for Simplified, Participant-Oriented Consent

"Consent forms would no longer be able to be unduly long documents, with the most important information often buried and hard to find. They would need to give appropriate details about the research that is most relevant to a person's decision to participate in the study, such as information a reasonable person would want to know, and present that information in a way that highlights the key information."

Federal Notice of Proposed Rulemaking (2015)

Informed Consent: Pragmatic Trials

Randomization:

- When existing evidence does not suggest that one intervention is better, randomization per se does not increase/decrease risks
- Participant perceptions (hypothetical about pragmatic RT for HPT drug):
  - Cho et al. *Ann Intern Med* 2015: "Compared to just having your doctor prescribe medications, how much additional risk do you think that there is to you from this research?"
    - 23% no additional risk, 63% a little, 16% a lot
  - Nayak et al. *Ann Intern Med* 2015: "Patients who participate in the randomized study face greater risks than patients who receive usual care."
    - 35% disagreed, 42% neutral, 23% agreed
- Regardless whether disclosure is needed to *protect* participants, should be disclosed as a matter of *respect* (when consent is needed)

Wendler D. *J Gen Intern Med* 2015; Lantos et al. *Clin Trials* 2015

Informed Consent: Pragmatic Trials

Risks of Research / Standard Care / Underlying Condition:

- OHRP Draft Guidance (2014): Reasonably foreseeable *risks of research* include the already identified risks of the standards of care being evaluated as a purpose of the research, when the risks being evaluated are different from the risks some of the subjects would be exposed to outside the study
- Critique (Lantos & Spertus *NEJM* 2014; The Editors *NEJM* 2014):
  - Implies studies of widely used treatments are always inherently riskier than those treatments would be if offered outside a research protocol
    - Prospective participants will suffer false impression that there is known net difference in risks that can be avoided by not enrolling

http://www.hhs.gov/ohrp/newsroom/rfc/comstdofcare.html

Empirical Development of ADAPTABLE Consent Form

Track Record of Empirical Research on Informed Consent, Participant Perspectives

Protocol + Regulatory Requirements

Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE)

We are asking you to join a research study called ADAPTABLE. The information below explains the study so you can decide if you want to take part or not. Please read it carefully and take all the time you need to decide. Feel free to talk it over with your family, friends, and doctor. If there is anything you do not understand, be sure to ask questions.

Comment [CMH1]: 45 CFR 46.116(a)(1): Study involves research

Comment [CMH2]: 45 CFR 46.116(a)(8): Voluntariness

Comment [CMH3]: 45 CFR 46.116: Sufficient opportunity to consider whether or not to participate, minimize coercion/undue influence

WHY IS THIS STUDY BEING DONE?

For more than 40 years, doctors have been telling patients with heart disease to take aspirin. For these patients, taking aspirin every day can lower the risk of heart attacks and strokes.

Millions of Americans who have heart disease already take either regular (325 mg) or low-dose (81 mg) aspirin. Many studies have shown that both doses work and both are generally safe. The most common side effect of aspirin is an upset stomach. Aspirin can also make you bleed more easily. In rare cases (about 5 in 1,000 people), it can cause dangerous bleeding in the stomach, brain, or other places.

Comment [CMH4]: 45 CFR 46.116(a)(2): Risks/discomforts

Even though both doses of aspirin are widely used, no one knows which is better. Regular aspirin has a higher risk of bleeding than low-dose aspirin. But no one knows if low-dose aspirin is both safer and works just as well as regular aspirin to prevent heart and blood vessel problems.

The goal of ADAPTABLE is to try to find out which dose of aspirin is better for patients like you who have heart disease. Patients who join this study will take either low-dose or regular aspirin every day. That way, we can learn which is better in terms of reducing the risk of heart attacks, strokes, bleeding, and death.

Comment [CMH5]: 45 CFR 46.116(a)(1): Purpose of research

45 CFR 164.508(c)(1)(iv): Purpose of the requested use/disclosure

We expect 20,000 patients with heart disease from across the U.S. will take part in ADAPTABLE.

Comment [CMH6]: 45 CFR 46.116(b)(6): Approximate number of subjects involved

Pragmatic Trial Considerations

- Introduction / Purpose of the Study: Benefits & risks of aspirin
  - Featured prominently up front
- Procedures: Randomization
- Risks of the Study:
  - Computer will assign dose (not you or doctor)
  - Assigned dose may differ (higher or lower) than currently take

Focus on Readability

	Original	Current
Length	4 pages	4.5 pages
Flesch-Kincaid grade level	7.2	7.3
Flesch-Kincaid reading ease *(100-point scale; the higher the score, the easier it is to understand)*	69	70
Passive sentences *(active sentences are easier to understand)*	4%	5%

Helpful Resource: PRISM Readability toolkit (https://www.grouphealthresearch.org)

Participant Input – Cognitive Interviews

- Questions asked about each consent form section:
  - Tell me in your own words what you understand this section to be saying
  - Is there anything confusing?
  - Is there anything you especially like/find especially concerning?
  - Is there extra information, details here that you think are not needed?
- Conducted in person and by phone (Jun 2015)
  - Exempt under 45 CFR 46.101(b)(2)
  - Publication in process

Participant Input – Cognitive Interviews

- Participant Characteristics (n=10)
  - Iterative; two rounds of 5 interviews each **
  - Patients with heart disease: 7 women / 3 men, 6 white / 4 black
    - ADAPTORS and Duke cardiology patients **
  - Age range: 55 – 85+
  - Education: High school/GED – Master's degree

*** Realities of real-time development for actual study*

Participant Input – Cognitive Interview Results

Overview:

- High degree of objective and subjective understanding
- Appreciated lack of “legalese”, efforts to simplify with patient input
- Little identified as extraneous detail that could be removed

Participant Input – Cognitive Interview Results

Overview:

- High
- Ap
  inp
- Littl

"Good job of introducing study, good use of plain language, organized well, easy to read. It covers everything I would think of as a patient. I've participated in studies like this before, this is one of the best consent forms I've read; they are usually too technical, hard to understand. When people don't understand, they just go forward instead of asking questions. Many think some study details don't apply to them, or that too much detail is offered, and it can sometimes be scary to some people."

Participant Input – Cognitive Interview Results

Overview, continued:

- Some questions / concerns about:
  - Language required by regulations (e.g., written withdrawal)
  - Role of treating physician
  - Confidentiality (e.g., SSN) → *optional*
  - Lack of compensation → *$25*

SECTION: Introduction

WHY IS THIS STUDY BEING DONE?

For more than 40 years, doctors have been telling patients with heart disease to take aspirin. For these patients, taking aspirin every day can lower the risk of heart attacks and strokes.

Millions of Americans who have heart disease already take either regular (325 mg) or low-dose (81 mg) aspirin. Many studies have shown that both doses work and both are generally safe. The most common side effect of aspirin is an upset stomach. Aspirin can also make you bleed more easily. In rare cases (about 5 in 1,000 people), it can cause dangerous bleeding in the stomach, brain, or other places.

Even though both doses of aspirin are widely used, no one knows which is better. Regular aspirin has a higher risk of bleeding than low-dose aspirin. But no one knows if low-dose aspirin is both safer and works just as well as regular aspirin to prevent heart and blood vessel problems.

The goal of ADAPTABLE is to try to find out which dose of aspirin is better for patients like you who have heart disease. Patients who join this study will take either low-dose or regular aspirin every day. That way, we can learn which is better in terms of reducing the risk of heart attacks, strokes, bleeding, and death.

Comments on Purpose of the Study

- *"My husband takes a baby aspirin every day and I take a full-dose aspirin every day and I've never, never had anyone tell me why, even though I've asked his doctor and my doctor." [CA01]*
- *"The fact that patients have been prescribed aspirin for over 40 years and there is not completely definitive information on all the potential outcomes and what dosage is best, it is good to know we can resolve that. I didn't know such questions existed, I thought it was all figured out by now." [CA02]*

Comments on Risks of Aspirin

- *"I think you did a really good job; you addressed the concerns with the medication, with the bleeding … I think those things are important. There's always a risk in anything, there's very few things without risk in life, but it's worth it to get the information." [QA03]*
- *"It says 'it can cause dangerous bleeding in rare cases, about 5 in 1,000' – it makes you stop and think a little bit. When I see where it says it can cause 'dangerous' bleeding, I would wonder about that. What do you mean by dangerous, like uncomfortable or that it can cause my death? In what way would it be dangerous?" [CA02]*

SECTION: Procedures

WHAT WILL YOU ASK ME TO DO?

If you agree to join ADAPTABLE, here is what will happen:

. . .

3. The computer will assign you to take either regular aspirin or low-dose aspirin. Neither you nor your doctor will choose which dose of aspirin you will take. Rather, the computer will assign one or the other randomly. This means every patient has a fair and equal chance of getting either dose of aspirin.

   The reason to use chance, rather than choice, to assign the dose of aspirin you will take is because no one knows which is better for patients like you. Assigning patients randomly helps make sure that the group that takes each dose is about the same. That way, at the end of the study, we can be pretty sure that any differences in health are because of the dose of aspirin—not because the groups were different from the start.

Comments on Randomization

- *"I don't have a problem with it at all. That way you can't sway it one way or the other … Everybody's got the same chance." [CD01]*
- *"I think that's better. Because then the doctors who are doing the study aren't just giving it to one group of people – everyone has an equal chance to see if the aspirin will help." [CD02]*

SECTION: Risks

WHAT ARE THE PHYSICAL RISKS?

Even though doctors do not know which dose of aspirin is better, they agree that between 75-325 mg daily is a good idea for most patients with heart disease. The two doses we will compare—low-dose (81 mg) and regular (325 mg) aspirin—are both widely recommended by doctors today.

There are no extra risks from taking aspirin as part of this study compared to taking aspirin as part of your usual care. The main differences are:

- In this study, the computer will assign which dose of aspirin you will take every day
- If you already take aspirin as part of your usual care, you might be assigned to take a different dose (higher or lower) than the one you take now

There will be no other changes to your medical care based on being in the study. If you have side effects or other concerns during the study, you and your doctor are free to decide that you should take a different dose of aspirin or stop taking it altogether.

If you have any questions or concerns about starting aspirin or changing your dose, be sure to talk to your doctor.

Comments on Risks

Interview Question: How do you feel about the risks of taking a daily dose of aspirin as part of this study, compared to the risks of taking a daily dose of aspirin outside of this study?

- *"It's the same. The only thing is you may be helping somebody else along the line." [CD01]*
- *"There are a lot of people taking aspirin anyway, it's an individual preference. I think there is greater risk for some people who weren't taking it prior to the study." [CD08]*

Empirical Development of ADAPTABLE Comprehension Tool

Assessment of Consent Comprehension

- FDA guidance: eConsent processes "may be enhanced by including questions … that help assess the subject's understanding and awareness of the consent materials"

- Disclosure vs. comprehension: Comprehensive knowledge of every detail disclosed in consent form is not necessary

  "Investigators do not need to disclose, and potential participants do not need to understand all there is to know about research. Not only is there too much to know, but much of what there is to know is not necessary to give valid informed consent."

  Wendler & Grady (2008)

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM436811.pdf

ADAPTABLE Consent Comprehension

- Systematic identification of essential information (e.g., Delphi process) versus “the horror factor”
- 8 multiple-choice items:

CONCEPT	ADDRESSED BY:
Purpose	Q1. ADAPTABLE is a research study. The main reason for doing this study is because, for patients who have heart disease, no one knows: …
Procedures, Duration	Q6. If you join this study, you will be asked to take a certain dose of aspirin every day for 3 years. How will this dose be assigned? … Q8. In addition to taking aspirin every day, researchers will ask you to do all of the following except: …
Risks	Q3. Does taking aspirin every day involve any risks? …
Benefits	Q7. What is one reason why patients with heart disease might want to take part in this study? …
Confidentiality	Q5. The information collected for this study will be stored for an unlimited amount of time for researchers to use. How does this affect your privacy? …
Withdrawal	Q4. If you decide to join the study but later change your mind, what should you do? …
Voluntariness	Q2. Who can decide whether you will take part in this study? …

https://cft.vanderbilt.edu/guides-sub-pages/writing-good-multiple-choice-test-questions/

ADAPTABLE Consent Comprehension

- Vanderbilt's guide to writing good multiple choice questions *
  - Effective stems, effective answer options
  - Bloom's taxonomy
- Not a "quiz" – framed as:

  "Now we will ask you a few questions to help make sure we did a good job explaining what people need to know about ADAPTABLE. Doing your best to answer the questions is a good way to be sure you understand the study before signing up!"
- Goal: Reinforce key concepts to help prospective participants make informed decisions

* *https://cft.vanderbilt.edu/guides-sub-pages/writing-good-multiple-choice-test-questions/*

Example 1

ADAPTABLE is a research study. The main reason for doing this study is because, for patients who have heart disease, no one knows:

- ☐ whether taking aspirin has any side effects
- ☐ which of two commonly-used doses of aspirin is better
- ☐ if a new, experimental alternative to aspirin is safe

Example 1

ADAPTABLE is a research study. The main reason for doing this study is because, for patients who hav eart disea e, no one knows:

- ☐ whether taking aspiri
- ☐ which of two c er
- ☐ if a new, experim

CORRECT!

Doctors already know that the most common side effects of aspirin are upset stomach and increased risk of bleeding. **The main reason for doing this research is to find out whether 81 mg or 325 mg aspirin is <u>better</u> at reducing heart attacks, strokes, bleeding and death**. Both of these doses are commonly used; we are not testing any new drugs in this study.

Example 2

If you join this study, you will be asked to take a certain dose of aspirin every day for 3 years. How will this dose be assigned?

- ☐ My doctor will choose my dose for me.
- ☐ I will choose the dose I want to take.
- ☐ A computer will choose my dose by chance.

Example 2

If you join this study, you will be asked to take a certain dose of aspirin every day for 3 years. How will this dose be assigned?

- ☐ My doctor will choose my d[illegible] for
- ☐ I will choose the dose I wa[illegible]
- ☐ A computer will choo[illegible]

CORRECT!

Neither you nor your doctor will choose which dose of aspirin you will take. Rather, **the computer will assign you to one dose or the other by chance.** It is important for the study that you take the dose that you are assigned.

Participant Input – Cognitive Interviews

- Questions asked about each item:
  - What kinds of things did you think about when selecting your answer?
  - How did you arrive at final answer – remember, guess, answer obvious?
- Conducted in person and by phone (Sep 2015)
  - Exempt under 45 CFR 46.101(b)(2)
  - Publication in process

Participant Input – Cognitive Interviews

- Participant Characteristics (n=14)
  - Iterative; two rounds of 7 interviews each **
  - Patients with heart disease: 5 women / 9 men, 12 white / 2 black **
    - ADAPTORS and cardiology patients in Durham, NC; Little Rock, AR; central PA; and Huntsville, AL
  - Age range: 45 – 79
  - Education: High school/GED – Master's degree

*** Realities of real-time development for actual study*

Comments on Comprehension Tool

- *"I thought it was well done … I think the information you've provided – while there's a lot – that it's essential for the patient to know it." [QA03]*
- *"I thought it was very clear, it's very simple to read … I like it." [QD14]*
- *"[The quiz] summed the consent form up pretty good … It was nice and short." [QA05]*

Proposed Consent Process Questions

- How would you rate the amount of information provided in the ADAPTABLE consent process?
  - 5-point scale: Way too little → Way too much
- How would you rate your understanding of the information provided in the ADAPTABLE consent process?
  - 5-point scale: Poor → Excellent
- How would you rate your experience with ADAPTABLE's web-based consent process?
  - 5-point scale: Poor → Excellent
- What were the most important reasons why you decided to participate [or not] in ADAPTABLE?

Discussion

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Adaptable

The Aspirin Study

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