Willingness to participate in Research on Medical Practices and the implications of the ‘investigational misconception’ for informed consent

Benjamin Wilfond MD
Seattle Children’s Research Institute
Treuman Katz Center for Pediatric Bioethics
Center for Clinical and Translational Research

University of Washington
Institute of Translational Health Sciences

David Magnus PhD
Stanford University
Stanford Center for Biomedical Ethics
The Stanford Center for Clinical and Translational Research and Education (Spectrum)
COLLABORATORS
Stanford
- Steve Alexander MD
- David Rosenthal MD
- Glenn Chertow MD

University of Washington
- Kris Patton MD

Seattle Children’s
- Raj Munshi MD
- Steve Seslar MD

Booster Shot Media
- Gary Ashwal
- Alex Thomas MD

PRIM&R
- Elisa Hurley PhD
- Kimberly Hensle Lowrance

Turner Research Network
- Anne Breese PhD
- John Turner

Providence Medical Research Center
- Radica Alicic MD

ROMP Study Team

Investigators
- Mildred Cho PhD (Stanford)
- Melissa Constantine PhD (U Minn)
- Maureen Kelley PhD (Seattle Children's)
- Diane Korngiebel DPhil (UW)
- Sandra Soo-Jin Lee PhD (Stanford)
- David Magnus PhD (Stanford)
- Benjamin Wilfond MD (Seattle Children's)

Consultants
- Alex Capron LLB (USC)
- Michael Green MD (Penn State)
- Nancy Kass ScD (Hopkins)
- Steve Joffe MD MPH (U Penn)

Research Managers
- Adrienne Meyer MPA
- Stephanie Kraft JD
- Katie Porter JD MPH

Research Staff
- Ellen Kuwana MS
- Cyan James PhD
- Emily Rosenthal
- Bryant Phan
- Isabelle Wijangco

Secondary Investigators
- Doug Diekema MD MPH (Seattle Children's)
- Thomas Gallagher MD (UW)
- Philip Lavori PhD (Stanford)

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Research Questions

**Empirical**: What do the public and regulators think about the ethical implications of randomization within usual clinical practices?

**Normative**: How should these attitudes influence policy about approaches to informed consent?
Important Distinction

- ROMP—Research on Medical Practice
  - Research to determine which commonly utilized treatments are best
  - Umbrella for pragmatic trials, point of care randomization, LHS, CER, and potentially QI

- RENT—Research to Evaluate New Treatments
  - Research on an investigational or new drug or intervention
  - May include PCT in Phase III of development
ROMP Products to Date

- 5 Empirical papers
- 4 Normative commentaries
- 3 Videos
Publications


The ROMP Ethics Study

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

This is Anthony. He has high blood pressure.

He sees his physician, Dr. Anderson.

Hmm... well, we've tried diet and exercise. I think I know a medication that might help.

She prescribes Anthony "Medication A" to help lower his blood pressure.

But "A" isn't the only choice...

A different doctor might have prescribed Anthony a different medication.

A is good!

B is good!

C is good!

Research on Medical Practices (ROMP) attempts to answer this question by comparing A, B and C.

What is Research on Medical Practices?

Often many medications are approved for a single medical condition. Think of high blood pressure. for
## ROMP Study Populations and Methods

<table>
<thead>
<tr>
<th>IRB</th>
<th>Public</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB members</td>
<td>patients (and parents) via cardiology and nephrology clinics and research registry</td>
</tr>
<tr>
<td>3 (n= 22)</td>
<td>10 (n = 53)</td>
</tr>
<tr>
<td>n=10</td>
<td>n=15</td>
</tr>
</tbody>
</table>

### Focus Groups
- Seattle/Stanford

### Cognitive interviews
- Seattle/Stanford

### Surveys
- Closed and open responses

### 1500 PRIM&R members randomly selected
- n = 601 (40%)

### Nationally representative sample via Research Now
- n=1095

### Patients from subspecialty clinics in Spokane WA
- n=120 (53%)
## Cross sectional population survey

<table>
<thead>
<tr>
<th>Content</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attitudes about trust their in doctor and health system</td>
<td>Instrument developed following focus groups and refined in 13 cognitive interviews</td>
</tr>
<tr>
<td>3 Videos interspersed with questions</td>
<td>Videos revised following focus groups</td>
</tr>
<tr>
<td>• Knowledge of ROMP</td>
<td>Collaboration with Turner Research</td>
</tr>
<tr>
<td>• Attitudes about research</td>
<td>• Recruitment using Research Now</td>
</tr>
<tr>
<td>3 Scenarios</td>
<td>• Nationally representative by geography, age, gender, race/ethnicity</td>
</tr>
<tr>
<td>Scenario based questions</td>
<td>• Web-based entry (Qualtrics)</td>
</tr>
<tr>
<td>• Notification and permission preferences</td>
<td></td>
</tr>
<tr>
<td>• Attitudes about risk</td>
<td></td>
</tr>
<tr>
<td>• Willingness to participate in ROMP</td>
<td></td>
</tr>
<tr>
<td>4 open ended questions</td>
<td></td>
</tr>
</tbody>
</table>
Research scenarios

- Medical record review scenario
  - Clinicians decide between 3 approved medications based on their own judgment

- Randomization scenario
  - All newly diagnosed patients are randomly assigned
  - Patients and their doctors know which drug the patient has received
  - Clinicians provide usual medical follow-up and change the medication if patients
    - Experience an adverse effect
    - Fail to respond clinically
    - Request a change
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; Cynan 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 impractical. These attitudes are not aligned with proposed regulatory guidance.

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

Ann Intern Med. doi:10.7326/M15-0166
For author affiliations, see end of text.
Willingness to Participate

- Asked if willing to participate after each scenario
- For scenarios with randomization, asked if they would give permission for **family member** to participate
- Open ended questions about willingness to participate offered following these scenarios
  - Randomized hypertension (self)
  - Randomized hypertension family member)
  - Randomized “more serious condition” (self)
Open Ended Responses

- Removed nonresponsive or nonsensical responses
  - 113 from hypertension scenario (self)
  - 135 from hypertension scenario (family member)
  - 154 from more serious condition scenario (self)
- Completed open ended responses questions:
  - 742 for hypertension scenario (self)
  - 720 for hypertension scenario (family member)
  - 701 for more serious condition scenario (self)
- 1658 responses combined from those willing
- 505 responses combined from those unwilling
Analysis

• Content analysis by 4 team members to inductively develop code book
• Entire team iteratively reviewed and revised
• Two coders made final revisions to code book
• Each of them independently coded half the responses
• Inter-rater reliability calculated on 20% of all response answers
• Cohen’s kappa of .84 (nearly perfect agreement on all codes) calculated using Dedoose software
Limitations

• Panel sample may not representave
• Hypothetical interest
• Text responses rather than interviews
<table>
<thead>
<tr>
<th></th>
<th>All survey respondents (n=1095)</th>
<th>Respondents who answered at least one open-ended question (n=834)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% male)</td>
<td>49.0</td>
<td>46.3</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-26</td>
<td>7.9</td>
<td>6.1</td>
</tr>
<tr>
<td>27-44</td>
<td>37.4</td>
<td>34.9</td>
</tr>
<tr>
<td>45-64</td>
<td>37.2</td>
<td>39.7</td>
</tr>
<tr>
<td>65+</td>
<td>17.6</td>
<td>19.3</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>74.0</td>
<td>75.3</td>
</tr>
<tr>
<td>Asian</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>African American</td>
<td>13.1</td>
<td>12.4</td>
</tr>
<tr>
<td>Other/multiracial</td>
<td>10.1</td>
<td>9.6</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>16.1</td>
<td>14.3</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>13.9</td>
<td>11.7</td>
</tr>
<tr>
<td>Some college/associate’s degree</td>
<td>30.5</td>
<td>31.6</td>
</tr>
<tr>
<td>College graduate</td>
<td>34.4</td>
<td>34.3</td>
</tr>
<tr>
<td>Graduate/professional school</td>
<td>21.2</td>
<td>22.5</td>
</tr>
<tr>
<td>Household income</td>
<td></td>
<td></td>
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<tr>
<td>Less than $30,000</td>
<td>16.5</td>
<td>14.8</td>
</tr>
<tr>
<td>$30,000-$55,000</td>
<td>23.2</td>
<td>23.4</td>
</tr>
<tr>
<td>$55,000-$95,000</td>
<td>29.5</td>
<td>29.6</td>
</tr>
<tr>
<td>$95,000 or more</td>
<td>30.8</td>
<td>32.2</td>
</tr>
<tr>
<td>Self-reported health status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>18.3</td>
<td>18.0</td>
</tr>
<tr>
<td>Very good</td>
<td>40.7</td>
<td>42.1</td>
</tr>
<tr>
<td>Good</td>
<td>29.0</td>
<td>28.1</td>
</tr>
<tr>
<td>Fair</td>
<td>10.8</td>
<td>10.7</td>
</tr>
<tr>
<td>Poor</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Prior clinical research participation</td>
<td>9.2</td>
<td>8.5</td>
</tr>
<tr>
<td>Have children</td>
<td>63.2</td>
<td>64.0</td>
</tr>
</tbody>
</table>
### Willingness to participate (n=1095)

<table>
<thead>
<tr>
<th>Method</th>
<th>Condition</th>
<th>Prospective participant</th>
<th>% willing to participate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical record review</td>
<td>Hypertension</td>
<td>Self</td>
<td>80.6</td>
</tr>
<tr>
<td>Randomization</td>
<td>Hypertension</td>
<td>Self</td>
<td>72.9</td>
</tr>
<tr>
<td>Randomization</td>
<td>Hypertension</td>
<td>Family member</td>
<td>74.2</td>
</tr>
<tr>
<td>Randomization</td>
<td>More serious condition</td>
<td>Self</td>
<td>67.4</td>
</tr>
<tr>
<td>Randomization</td>
<td>More serious condition</td>
<td>Family member</td>
<td>63.1</td>
</tr>
<tr>
<td>Reason</td>
<td>n (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>--------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefit to others</td>
<td>934 (56%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical benefit to the participant</td>
<td>317 (19%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safe</td>
<td>159 (10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug similarity</td>
<td>156 (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trust in a specific physician or institution</td>
<td>130 (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable view of randomization</td>
<td>127 (8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ability to switch medications</td>
<td>112 (7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditional on transparency and information</td>
<td>68 (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditional on a patient’s ability to make an active choice</td>
<td>33 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misconceptions about ROMP</td>
<td>30 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No added risk beyond usual care</td>
<td>28 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General or institutional trust or mistrust</td>
<td>21 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curiosity</td>
<td>17 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason</td>
<td>n (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>--------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsafe</td>
<td>178 (35%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfavorable view of experimentation</td>
<td>136 (27%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desire for physician control over treatment decisions</td>
<td>60 (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfavorable view of randomization</td>
<td>37 (7%)</td>
<td></td>
<td></td>
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<tr>
<td>Conditional on a patient’s ability to make an active choice</td>
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<tr>
<td>Privacy or confidentiality</td>
<td>24 (5%)</td>
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<td>21 (4%)</td>
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</tr>
<tr>
<td>Doubt in drug similarity</td>
<td>8 (2%)</td>
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</tbody>
</table>
Major themes for willingness to participate

• Perceived benefits
• Perceived risks
• Trust
• Randomization and experimentation
• Informed consent
• Misconceptions about ROMP
Perceived Benefits (others or themselves)

- “help other patients”
- “benefit the greater good.”
- “We have to find some way to improve the system, why not me as a guinea pig?”
- “Maybe by participating in this research it could help me and other patients with the right medication.”
- “be one medicine closer to my cure.”
Perceived Risks (Willing)

- “little added risk”
- “I have no objections to using this type of research as long as it doesn't affect my health.”
- “there doesn't seem to be a huge difference in the drugs”
- “not really any different than my doctor guessing at which medication is best for me.”
- “As the video has shown there is a form of randomization already occurring, with doctors prescribing medicines based on personal info.”
Perceived Risks (Unwilling)

• “It’s too risky”
• “I wouldn't want to gamble with serious side effects.”
• “People may react differently to each medication.”
• “It is one thing to play the randomization research game for [blood pressure], but strokes are nothing to mess with.” [explaining why willing to participate for one scenario, but not “a more serious condition.”]
Trust (willing)

• “If they felt it wasn't safe then I don't think they would have me do it. I trust my doctor.”

• “I trust the healthcare community enough to participate in research using randomization so long as I am given information about the process.”

• Would participate “only after discussion with my physician, not a representative of a health system or insurance company.”
Trust (Unwilling)

• “great in theory, but I want to know my doctor looked at all the options, and picked the medication that is best for ME.”
• I don’t trust the drugs”
• “I don’t trust randomization.”
• “You would have to put your trust in more people and I simply no longer trust our health care system.”
Randomization and Experimentation (positive)

• Randomization is “more objective”

• “the gold standard”
Randomization and Experimentation (Neg)

• Randomization: “It creates more variables, red tape, and is not patient centered in my opinion.”

• “I want the right medicine the first time using my doctor's experience with my condition. I don't want to experiment.”

• “I don’t believe humans should be experimented on!”

• “Are you kidding, randomness in treating me for perhaps a grave medical condition, or creating side conditions as a result of using a random approach to treatment...ludicrous!”
Informed Consent (Willing)

• Participation often conditional on transparency and being informed and sometimes on ability to consent
• “so long as I am given information about the process,”
• “if my doctor was to explain everything and tell me the risks.”
• “As long as I receive informed consent, I would do so in the name of science.”
Informed Consent (Unwilling)

• “I would need to know further information and at this time I don't know enough to say yes.”
• “I would only participate if I have signed a document.”
• “I can take the risk for myself, but I wouldn't decide that for another person.” (explaining unwillingness for family member participation)
Misconceptions

• No need to do research on human subjects to know what works
• “My physician knows what is best for me as individual” (regardless of state of knowledge)
• Investigational Misconception
Investigational Misconception

- Confusion of ROMP—research that evaluates and compares common medical practices, with
- Research to evaluate new treatments (RENT)—including placebo controlled randomized trials of new treatments or drugs
Investigational Misconception

- “if no one tests the new drugs, no one will know if they are effective”

- Some wanted to participate so that they could get access to new drugs:
  - “If it is the only way to get medication for said condition, it's worth it.”

- Others feared receiving unproven medications:
  - “I would just prefer to be given a medication that has already been proven to work.”
Investigational Misconception

- RENT vs ROMP often conflated—difficult to correct misconception
  - Use of animated videos
  - Supplemented by explicit language explaining ROMP
- Research = placebo controlled trials
- Assumption that research requires doing something different than would otherwise have taken place
- Efforts to educate public to avoid therapeutic misconception may have been more successful than appreciated
Investigational Misconception

• May be reinforced by standard template language by IRB’s (aimed at avoiding therapeutic misconception)
• Could be very confusing and problematic if patients or decision makers fundamentally misunderstand the nature of the activity
  • Undermine consent
  • Create hurdles to recruitment based on misunderstanding
  • Contribute to regulatory confusion
• Further research on the Investigational Misconception to explore its dimensions and to determine if interventions can be developed to mitigate the problem in ROMP
Emily Littella: What's all this fuss I hear about the Supreme Court decision on a deaf penalty? It’s terrible! Deaf people have enough problems as it is!

Chevy Chase: That’s death penalty, Ms Littella, not deaf....death.

Emily Littella: Oh, well that's different. Never mind!
A randomized study of multimedia informational aids for research on medical practices: Implications for informed consent

Stephanie A Kraft¹, Melissa Constantine², David Magnus³, Kathryn M Porter¹, Sandra Soo-Jin Lee³, Michael Green⁴, Nancy E Kass⁵, Benjamin S Wilford¹ and Mildred K Cho³
Video Development – “A New Kind of Research”

- Create materials appropriate for the cultural context and health literacy of patient participants
  - “How is my medical record being used?”
  - “Library of Medical Information?”
- Develop simplified illustrations capable of effectively conveying information across cultural and linguistic barriers
- Conduct patient testing and incorporate feedback into revisions