Consent - A Different Standard for Research?

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How Does Consent Differ?

*Clinical Care vs. Research Participation*

1. Not a signature on a form – “process” that continues throughout the study
2. How SDMs are Approached – important
3. Patient participation is voluntary and optional
4. Balance: Benefit vs. Harm
5. Other forms of consent (waived, deferred, two physician)
How Does Consent Differ?

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1. Not a signature on a form – process that continues throughout the study

<table>
<thead>
<tr>
<th>Clinical Care</th>
<th>ICU Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature (except emergencies)</td>
<td>Signature (except waived)</td>
</tr>
<tr>
<td>Procedure/Intervention</td>
<td>Process</td>
</tr>
</tbody>
</table>
Research Consent - A Different Standard?

“A Process”

• Investigators have an obligation to regularly reassess whether
  • (i) continued participation is desired
  • (ii) ongoing participation is in patients best interests

For example

• “Delayed consent” must be sought when patients regain decision-making capacity

• Participation should be reassessed in light of emerging evidence

ATS Guidance Document, 2004 170:1375-84
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2. How SDMs are Approached – important

<table>
<thead>
<tr>
<th>Clinical Care</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>SDMs Approached (90%)</td>
</tr>
<tr>
<td>Discussion (clinical encounter related to patient care)</td>
<td>Discussion (research encounter often perceived as separate from patient care)</td>
</tr>
</tbody>
</table>

3. Patient participation is voluntary and optional

<table>
<thead>
<tr>
<th>Clinical Care</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended by physicians/allied health care providers</td>
<td>REBs caution against recommendations/coercion</td>
</tr>
<tr>
<td>Necessary</td>
<td>Optional</td>
</tr>
</tbody>
</table>
In Ontario, the Personal Health Information Protection Act advises that ‘researchers should not make contact with consent providers, directly or indirectly, unless custodians (physicians taking care of the patient, nurses or social workers) first obtain the individual’s consent to be contacted’

Some research ethics boards (REBs) mandate physician involvement in introducing research to SDMs.
A multicentre study of pediatric recruitment processes found significantly higher consent rates when research personnel were introduced by a member of the clinical team.

Menon K, ICM 2012; 38: 153-9
The Approach Trial

138 SDMs randomized

1 incorrect randomization

137 SDMs randomized with intent to approach

67 SDMs with a physician introduction (84 eligibility events)
- Randomized, No Approach
  - Randomized, Approached Consent Provided
  - Randomized, Approached Consent Declined
  - Randomized, Approached Consent Provided & Declined

70 SDMs with a non-physician introduction (78 eligibility events)
- Randomized, No Approach
  - Randomized, Approached Consent Provided
  - Randomized, Approached Consent Declined
  - Randomized, Approached Consent Provided & Declined

No reply returned
Approach Trial: RCT Results

- Mixed Methods Study (RCT + nested qualitative study); N=138 SDMs
- Pilot RCT comparing MD introduction vs. Non-MD introduction of research to SDMs in the ICU.
- Achieved all pre-specified feasibility metrics (missed few MD introductions, identified low protocol violation rates, approached most SDMs) evaluating potential threats to study validity.
- High average comfort, satisfaction and acceptance scores between- MD and non-MD groups among participants.
- No difference in consent rates between approaches or based on study risk (investigator or SDM-assigned).
- SDMs introduced by an MD were significantly more likely to provide consent when a patient status update was provided.
Approach Trial: Qualitative Results

- In the nested qualitative study (n=14; 7 MD and 7 non-MD), we found:
  - Poor SDM recall of MD involvement
  - SDMs perceived that physician time would be better spent providing patient care
  - Several participants ‘perceived’ benefits to MD involvement
    - (i) enhancing the credibility of research
    - (ii) providing reassurance, comfort and confidence during decision-making
    - (iii) ensuring broad awareness of patient participation by the clinical team
Approach Trial: Qualitative Results

What was important to SDMs?

1. The personality and professionalism of the person approaching them
2. The importance of timing (when not in crisis) and having space to make decisions
3. Personal responsibility in their role as SDM
4. A need to appraise the risks and benefits of participation and evaluate the potential benefit to the patient or others
5. Personal and patient values toward research
6. Trust in the healthcare team
7. Knowledge of the voluntary nature of participation
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4. Balance: Benefit vs. Harm

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<tbody>
<tr>
<td>Net benefits &gt; Net risks</td>
<td>Net balance (risks vs. benefits) largely unknown</td>
</tr>
</tbody>
</table>
Research Consent – A Different Standard

“Balance Between Benefit vs. Harm”

• Some therapeutic studies have the potential to benefit participants, others have no therapeutic potential or the potential to cause harm.

• Critically ill patients are at risk of morbidity, mortality and intervention-related complications.

• Necessary to weigh risk-benefit ratio

• Should disclose/discuss study interventions that have the potential to benefit the patient vs. those that do not

ATS Guidance Document, 2004 170:1375-84
Why substitute decision makers provide or decline consent for ICU research studies: a questionnaire study

Fig. 1. SDMs’ reasons for consenting for an ICU research study (N = 68)
The Approach Trial: Risks vs. Benefits

<table>
<thead>
<tr>
<th>SDM Rationale for Providing Consent</th>
<th>MD Introduction</th>
<th>Non-MD Introduction</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Will benefit from participation (benefits &gt; risks)</td>
<td>14</td>
<td>17</td>
<td>31</td>
</tr>
<tr>
<td>Have a strong desire to help others (future patients, medical community)</td>
<td>13</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>Want to advance medical knowledge and science</td>
<td>5</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Desperate to try anything</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Loved one would want to participate</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>I trust the medical team</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>I wanted to please the medical/research teams</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Consent Study (n=26 SDMs)
Research Consent – A Different Standard

“Balance Between Benefit vs. Harm”

• One approach is to categorize risk for ICU research

A) Interventions not involving greater-than-minimal risk

B) Interventions involving minor increase over minimal risk (likely to yield generalizable information)

C) *Interventions involving greater-than-minimal risk and the prospect of direct benefit to the patient

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<tr>
<td>Patient (norm) /SDM or parental consent/assent</td>
<td>Patient/SDM Consent (norm)</td>
</tr>
<tr>
<td>MD consent (emergency)</td>
<td>Deferred, Waived, 2 MD consent</td>
</tr>
</tbody>
</table>
A study involving hypothetical scenarios found that ICU survivors preferred consent for their research participation to be obtained from their SDMs.

A study involving SDMs found that while SDMs were willing to be involved, they were often uncomfortable making consent decisions with at least 75% of SDMs wanting to speak to an ICU physician about research participation.

Scales DC, ICM 2009: 35:1703-12
Barrett KA, ICM 2012; 38:1616-23
Other Forms of Consent - Definitions

• “A waiver of consent is present when a given research intervention is initiated without a prospective genuine consent from either the patient or a proxy.”

• “Deferred consent: Consent obtained after the patient has been included in an ongoing research protocol.

• The after the fact consent relates specifically to the patient’s continued participation in the study.
“Other Forms of Consent” – Waived

3 circumstances where WAIVED Consent may be appropriate

1. Observational research
   - no intervention or minimally interventional
   - specimens collected during usual care

2. Emergency/Acute Care research
   - TCPS 2 (3.7.7) impracticable to carry out research/cluster trials

3. Minimal risk trials (?)
   - REBs and legislators require convincing!
   - May 2014 European directive: “low intervention” research – prior consent remains mandatory.

Lemaire F, CRJ 21(5); 271
Tri Council Policy

• TCPS 2 refers to both circumstances (a waiver of consent or exemption from informed consent) in section 3.7.
• Research involving medical emergencies (deferred consent specific to situations involving medical emergencies) in section 3.8 below.
• “When a previously incapacitated participant regains capacity, or when an authorized third party is found, consent shall be sought promptly for continuation in the project, and for subsequent examinations or tests related to the research project.”
TCPS2 - Article 3.7 – Waived Consent

“Article 3.7 The REB may approve research without requiring the participant’s consent where the REB is satisfied, and documents, that all of the following apply:

- (a) the research involves no more than minimal risk to the participants
- (b) the lack of the participant’s consent is unlikely to adversely affect the welfare of the participant
- (c) it is impossible or impracticable to carry out the research and to answer the research question properly if prior consent is required
- (d) whenever possible and appropriate, after participation, or at a later time during the study, participants will be debriefed and provided with additional pertinent information........ at which point they will have the opportunity to refuse consent
- (e) the research does not involve a therapeutic intervention, or other clinical or diagnostic interventions.
Waived Consent

RCT of septic patients (n=300) comparing Hydrocortisone and Fludrocortisone vs placebo for 7 days

*Inclusion rate: 4 pts/month (before waiver) – increasing to 10 pts/month (after amendment)

Consent obtained from
- patients (3%)  
- next of kin (23%)  
- 74% (could not contact relative)

Annane D. ICM 2004;30:321-4
Research Consent – A Different Standard

“Other Forms of Consent” – Waived

3 circumstances where WAIVED Consent may be appropriate

1. Observational research
   - no intervention or “minimally interventional”
   - specimens collected during usual care
2. Emergency/Acute Care research
   - TCPS 2 (3.7.7) impracticable to carry out research/cluster trials (entire groups are randomized)
3. Minimal risk trials (?)
   - REBs/IRBs/legislators require convincing!
   - May 2014 European directive: “low intervention” research – prior consent remains mandatory.
TCPS2 – Article 3.8 – Deferred Consent

**Article 3.8** The REB may allow research that involves medical emergencies to be carried out without the consent of participants, or of their authorized third party, if all of the following apply:

1. (a) a *serious threat to the prospective participant requires immediate intervention*;
2. (b) either no *standard efficacious care exists* or the research offers a *realistic possibility of direct benefit* to the participant vs. standard care;
3. (c) the *risk is not greater than that involved in standard efficacious care, or it is clearly justified by the prospect for direct benefits to the participant*;
4. (d) the prospective participant is *unconscious or lacks capacity to understand the risks, methods and purposes of the research project*;
5. (e) *third party authorization cannot be secured in sufficient time,* despite diligent and documented efforts to do so; and
6. (f) *no relevant prior directive by the participant is known to exist.*

When a previously incapacitated participant regains capacity or when a third party is found, consent shall be sought for continuation in the project, and for subsequent examinations or tests related to the research project.
Deferred Consent

Research participants’ opinions of delayed consent for a randomised controlled trial of glucose control in intensive care

Abstract

PURPOSE: Critically ill patients are often unable to give informed consent to participate in clinical research. A process of delayed consent, enrolling patients into clinical trials and obtaining consent as soon as practical from either the participant or their substitute decision maker, has sometimes been used. The objective of this study was to determine the opinion of participants, previously enrolled in the NICE-SUGAR study, of the delayed consent process.

METHODS: This observational study was conducted from 2009 to 2010 in the ICU of a tertiary referral hospital in Australia. Participants who were enrolled in the NICE-SUGAR study with delayed consent who survived, were cognitively intact, and proficient in English were posted a questionnaire regarding their opinion of the delayed consent process. The questionnaire was returned by post, fax, email, or completed during a telephone interview.

RESULTS: Of 298 eligible participants, 210 responded, with an overall response rate of 79%. Delayed consent to participate in the NICE-SUGAR study was obtained from participants (57/210; 27.1%) or the substitute decision maker (152/210; 72.4%). Most respondents (195/204; 95.6%) would have consented to participate in the NICE-SUGAR study if asked before enrolment; most (163/198; 82.3%) ranked first “the person who consented on their behalf for the NICE Study” as most preferred to make decisions, should they be unable; and most (177/202; 87.6%) agreed with the decision made by their relative.

CONCLUSION: Delayed consent to participate in a clinical trial that includes critically ill patients is acceptable from research participant’s perspectives.
Survey of the General Public

- Objective: To ascertain the attitudes and views of the general public towards *different consent models* for participation in *RCTs* in critically ill adults

- Design: Developed, pilot tested and administered a questionnaire

- Study population: 221 members of the general public

- Study location: A summer student administered the questionnaire in public settings in downtown Toronto (U of T campus, Dundas Square, Nathan Phillips Square)

- Questionnaire: Specifically referred to RCTs and different approaches to obtaining consent that could be used for enrollment if respondents were *unconscious* (critically ill)
Scenario 1

“YOU have a substitute decision maker who comes to the ICU within 24 hours. How comfortable would YOU be being enrolled in this trial protocol if it used the following ways of obtaining consent for YOUR participation?”

1a) YOUR SDM is asked to provide consent for YOU. If the SDM consents, the research team will enroll you. If YOU later regain capacity, YOU will be asked for informed consent.

1b) YOUR SDM is asked whether you would “object to participating”

1c) Your are enrolled in the trial and consent will be DEFERRED until YOU regain capacity to make decisions. At that time YOU will be asked for informed consent.
SDM Exists

Frame of Reference

SDM provides consent, patient approached when capacity regained

SDM asked if you would "object to participating"

Deferred to patient
SDM Exists but Not Available

“YOU have family but the hospital staff are unable to reach them in time to enroll you in the trial. How comfortable would you be being enrolled in this trial if it used the following ways of obtaining consent for YOUR participation”

2a) Your **attending** Critical Care physician (not involved in the trial) is asked to provide consent.

2b) Two physicians (**your attending and another physician** – neither or whom are involved with the trial) are asked to provide consent.

2c) Two physicians (**neither of whom are involved with the trial or your care**) are asked to provide consent.
SDM Exists but Not Available

“YOU have family but the hospital staff are unable to reach them in time to enroll you in the trial. How comfortable would you be being enrolled in this trial if it used the following ways of obtaining consent for YOUR participation”

2d) YOU are enrolled in the trial and consent will be deferred until YOU regain capacity.

2e) Consent is waived for YOU to participate in the trial.
SDM Exists but Not Available

Comfort Levels Across Scenario 2

- Scenario 2a
- Scenario 2b
- Scenario 2c
- Scenario 2d
- Scenario 2e

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Comfortable</th>
<th>Neutral</th>
<th>Uncomfortable</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>60%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>2b</td>
<td>50%</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>2c</td>
<td>70%</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>2d</td>
<td>40%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>2e</td>
<td>50%</td>
<td>20%</td>
<td>30%</td>
</tr>
</tbody>
</table>
No SDM Exists

Comfort Levels Across Scenario 3

- **Scenario 3a**
  - Comfortable: 40%
  - Neutral: 20%
  - Uncomfortable: 10%

- **Scenario 3b**
  - Comfortable: 50%
  - Neutral: 15%
  - Uncomfortable: 5%

- **Scenario 3c**
  - Comfortable: 60%
  - Neutral: 10%
  - Uncomfortable: 5%

- **Scenario 3d**
  - Comfortable: 45%
  - Neutral: 20%
  - Uncomfortable: 5%

- **Scenario 3e**
  - Comfortable: 50%
  - Neutral: 20%
  - Uncomfortable: 10%

Legend:
- Green: Comfortable
- Yellow: Neutral
- Red: Uncomfortable
No SDM Exists

- Would YOU want to be considered for participation in the trial at all?

<table>
<thead>
<tr>
<th>Scenario</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDM Exists</td>
<td>74.1%</td>
<td>25.9%</td>
</tr>
<tr>
<td>SDM Exists/Not Available</td>
<td>63.8%</td>
<td>36.2%</td>
</tr>
<tr>
<td>No SDM Exists</td>
<td>69.9%</td>
<td>30.1%</td>
</tr>
</tbody>
</table>
Summary

- When an SDM is present and available - slight preference for SDM to be involved in consent decisions.

- Most participants were comfortable participating in a trial under alternative consent models (SDM asked if they would object to participating, deferred consent)

- When an SDM is appointed but not available – majority of participants were comfortable with waived consent as a preferred consent model.

- When no SDM exists - participants expressed preference for four consent models:
  - Attending physician (not involved with the trial)
  - Two physician model (1 involved in care; neither involved in trial)
  - Waived consent
  - Deferred consent
Conclusion: ICU Research Consent

Need to balance

**Interests of vulnerable patients**

- Participant safety and well-being
- Ethical conduct

**vs.**

**Need for rigorous clinical research**

- Generalizable results (< 5% in CCCTG studies)
- Timely identification of beneficial/harmful Rx
- Not deny vulnerable patients the opportunity to benefit from research participation

- Investigators, REBs, hospitals and granting agencies have a mandate to conduct high quality, scientifically rigorous, and ethically sound research to ensure that timely and effective care is provided to critically ill patients.

- Maintain the public’s confidence in our competence, our work, & ethics.

- Researchers need to ensure that participants understand potential risks & benefits.

- Consider more liberal approaches for patients who can not offer first person consent in specific situations.
Thank You
• article 28-3 says: “Any subject, or where the subject is not able to give informed consent, his or her legally designated representative may...withdraw from the clinical trial at any time...Without prejudice to Directive 2001/20/EC, the withdrawal of consent shall not affect the activities carried out and the use of data obtained based on consent before its withdrawal”
No SDM Exists

“ You have no family. A SDM has not been appointed for you. How comfortable would YOU be being enrolled in this trial if it used the following ways of obtaining consent for your participation”

3a) Your attending Critical Care physician (not involved in the trial) is asked to provide consent.

3b) Two physicians (your attending and another physician – neither of whom are involved with the trial) are asked to provide consent.

3c) Two physicians (neither of whom are involved with the trial or your care) are asked to provide consent.
No SDM Exists

“You have no family. A SDM has not been appointed for you. How comfortable would YOU be being enrolled in this trial if it used the following ways of obtaining consent for your participation”

3d) YOU are enrolled in the trial and consent will be deferred until YOU regain capacity.

Deferred Consent means that the research team can enroll you in the trial and YOU will be approached later and asked whether you would have agreed to participate in the trial and to use your study data.

3e) Consent is waived for YOU to participate in the trial.

Waived Consent means that consent to participate is not required for emergency research provided that you require immediate intervention, the research offers a real possibility of benefit to you compared to usual care, and the risk of causing harm to you is not greater than usual care.
Attitudes of the General Public Toward Alternative Consent Models

By Karen E. A. Burns, MD, Nora M. Magyarody, BSc, Mark Duffett, BScPharm, Rosane Nisenbaum, PhD, and Deborah J. Cook, MD