Deferred consent

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Emergency research

- Autonomy of the patient and guaranteeing patient wishes’
- Protection against discomfort, harm, risk, exploitation

- Prospect of potential benefit
  - Studies comparing interventions with clinical equipoise
Delay in clinical research
Dexanabinol in Traumatic Brain Injury

(861 patients enrolled in the study)
Delay in clinical research
Dexanabinol in Traumatic Brain Injury

Therapeutic window from animal studies

Prior consent in emergency research can result in selection bias

Deferred Consent

A New Approach for Resuscitation Research on Comatose Patients

Norman S. Abramson, MD; Alan Meisel, JD; Peter Safar, MD

JAMA 1986;255:2466-2471

“obtaining consent to continue with an experimental therapy after administration of that therapy has already begun”

After lengthy deliberations, 15 of the 16 participating American institutions approved the deferred consent mechanisms. Because of cultural and philosophical differences from the United States, approval of the deferred consent mechanism was more easily obtained in the eight participating European hospitals.
**Waiver of consent**

USA and Europe

- US Federal Code of Regulation accepted emergency research to be performed without informed consent in 1996
  - necessity to explain the protocol to the relevant community

- European Council Directive in 2001 required written informed consent and a waiver of consent was not possible
  - some countries did not comply (Belgium, France, The Netherlands, Spain and Germany) where others did (Denmark, Ireland, Portugal and UK)

  ✓ surrogate (spouse, legal representative, (independent-dependent) physician) may provide consent
Waiver of (prior) consent

Public view

- Public views supports exceptions on informed consent in emergency situations
  - survey in 530 people: 88% prior information is required § 49%
  - enrollment in emergency situation is acceptable § 70% would not object to be enrolled without prior consent
1. Can proxies give a valid judgement for consent or refusal on immediately on admission?
Proxy consent

- Proxies are not always available in first hours of admission
- Emotional nature of the emergency situation limits the reliability of proxy consent
- Comprehension of provided information is limited in emergency situations
- Families are in psychological stress and have limited effective coping mechanisms
- Families want to know about diagnosis, prognosis and uncertainty influences their reactions, actions and strategies
Proxy consent

- Decision making competence
  - factual understanding
  - evidencing a choice (consent or refusal)
  - reasoning and appreciation of the situation

Family members are probably (temporarily) incompetent in these 3 points and are not likely to provide valid proxy consent during the acute phase.

Thursday, March 22, 12
Informed consent in clinical trials in critical care: experience from the PAC-Man Study

Sheila E. Harvey
Diana Elbourne
Joanne Ashcroft
Carys M. Jones
Kathryn Rowan

3.3% refused consent retrospectively
0.7% refused consent despite prior consent of relatives
Waiver of (prior) consent
Effect on recruitment

- Randomization within 3h from start of septic shock
- 7 months: inclusion rate 4 /mo (expected 10p /mo)
- 300 patients randomized
  - 10 patients gave informed consent (10%)
  - 70 relatives gave informed consent (23%)
  - 220 no informed consent (74%) before start of the study (following amendment for waiver of consent)
  - Survivors asked to sign informed consent afterwards
Waiver of (prior) consent
Effect on recruitment

- CRASH trial: effect of steroids in head injuries § 4000 patients randomized
- 78 hospitals: waived consent - 38 hospitals: consent required

![Graph showing time to randomisation and no randomisations per month for waived and non-waived consent.](Emerg Med J 2004;21:703)
2. What to do with the data when the patient dies before consent
Deferred consent in emergency intensive care research: what if the patient dies early? Use the data or not?

1. Introduces selection bias
2. Violates the intention-to-treat principle of the primary analysis
3. Validity of proxy consent in these situations is ethically questionable
4. Very few patients/relatives object to the use of already obtained data in emergency situations
5. Using the data will not “harm” the patient or relatives if confidentiality and privacy are assured
6. Jeopardizing results of the study might harm future patients and society
7. Devalues the “contribution” made by the subjects entered with consent
8. Confronting bereaved relatives with consent procedure represents additional burden
9. The individual’s decision about the privacy of their medical information is not absolutely binding if the processing is necessary and proportionate for ‘the protection of health’, if sufficient safeguards apply or if it is necessary and proportionate for the goals of medical research
Study completed before consent obtained

- Study on the effect of early goal (lactate) directed therapy following ICU admission
  - therapeutic protocol lasted for 8h
  - study procedures for 72h following start of the study
- Deferred consent accepted by the Ethical Committee
  - 10% of the patients died before consent could be obtained
  - In another 5% of the patients consent could not be obtained within 72 hours
**Inability to obtain deferred consent due to early death in emergency research: effect on validity of clinical trial results**

DOI 10.1007/s00134-010-1988-0

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Lactate group</th>
<th>Relative risk (95%CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td><strong>In-hospital mortality: unadjusted analysis - % (n)</strong></td>
<td></td>
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<tr>
<td>All patients (n=348)</td>
<td>43.5% (77/177)</td>
<td>33.9% (58/171)</td>
<td>0.78 (0.60-1.02)</td>
<td>0.067</td>
</tr>
<tr>
<td>Excluding early death (n=309)</td>
<td>33.8% (51/151)</td>
<td>28.5% (45/158)</td>
<td>0.84 (0.60-1.18)</td>
<td>0.32</td>
</tr>
<tr>
<td>Excluding all missing deferred consent (n=289)</td>
<td>33.1% (46/139)</td>
<td>28.7% (43/150)</td>
<td>0.87 (0.61-1.22)</td>
<td>0.42</td>
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</table>

|                     |               |               |                       |         |
| **In-hospital mortality: adjusted analysis - hazard ratio (95% CI)** |               |               |                       |         |
| All patients (n=348) | 0.61 (0.43-0.87) |               |                       | 0.006   |
| Excluding early death (n=309) | 0.80 (0.53-1.21) |               |                       | 0.28    |
| Excluding all missing deferred consent (n=289) | 0.81 (0.53-1.25) |               |                       | 0.35    |

Chi-square test

Cox’s proportional hazards analysis
Stratified by: center and sepsis group
Adjusted for co-variables: age, sex, APACHE II and SOFA
Deferred consent

When the patient dies before consent, ask the family?

- Proxy represents the patient during treatment however this ends when the patient dies and thus their autonomy is limited but not absent
  - Information of these proxies is usually indicated
  - Informing the proxies and asking consent may introduce selection bias
- The consent in research is focused on participation (risks, harm, benefit etc) not so much on use of data
- Patients have a legal right to see their data however proxies do not have patients’ rights after the death of the patient and so no legal right to see research data
- Proxies do not have to consent on the use of data at this point
## Deferred Proxy Consent Practice

<table>
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<tr>
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<th>Lactate Interventional</th>
<th>NGAL Observational</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
<td>n=362</td>
<td>n=550</td>
<td>n=856</td>
</tr>
<tr>
<td>Deferred Proxy Consent</td>
<td>273 (75.4%)</td>
<td>494 (89.8%)</td>
<td>767 (89.6%)</td>
</tr>
<tr>
<td>Deferred Proxy Refusal</td>
<td>14 (3.9%)</td>
<td>4 (0.7%)</td>
<td>18 (2.1%)</td>
</tr>
<tr>
<td>No consent</td>
<td>75 (20.7%)</td>
<td>52 (9.4%)</td>
<td>127 (14.8%)</td>
</tr>
</tbody>
</table>

Crit Care 2009;13(suppl 1):S196 - Poster 488
Recommendations

- Waiver and deferred (proxy) consent has an ethical basis in emergency research
- Approach the relatives with information about the research and ask for consent when this is ethically valid to do so
- Study data can be used before consent can be obtained (including the situation the patients has died) when sufficient privacy measures are applied
  - time limit of 72h (or use of independent physician)
  - inform general practitioner
  - report to local ethical committee
Deferred proxy consent in emergency critical care research: Ethically valid and practically feasible

Diagram:
- Start study procedures
  - Proxy present or available within appropriate time frame?
    - Yes → ethically valid to inform and ask for consent?
      - Yes → inform proxy and ask for consent a.s.a.p.
        - Yes → obtained
        - No → refuse
      - No → wait until valid to inform and ask for consent
    - No → wait until present
  - No → study procedures already finished or patient died?
    - Yes → inform proxy and ask for consent a.s.a.p.
    - No → use data
- Continue study use data
- Stop study no use of data
- Do not ask for consent inform proxy use data

> 72h