

The problem of consent in emergency medicine research

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ABSTRACT

This paper outlines some of the ethical and practical dilemmas of securing true informed consent in resuscitation research in the prehospital or emergency department setting. Possible substitutes to such consent are discussed and evaluated. The *Canadian Tri-Council Policy Statement* guidelines for emergency medicine research are compared to the US Food and Drug Administration rules, and the former are assessed and critiqued. Modifications to the current Tri-Council guidelines are suggested.

RÉSUMÉ

Le présent article dresse un aperçu de certains des dilemmes éthiques et pratiques liés à l'obtention d'un consentement éclairé dans les cas de recherche en réanimation dans un contexte pré-hospitalier ou à l'urgence. Des substituts possibles à de tels consentements sont évoqués et évalués. Les lignes directrices de l'*Énoncé de politique des trois Conseils* pour la recherche en situation d'urgence sont comparées aux règles du Food and Drug Administration aux États-Unis et sont ensuite évaluées et critiquées. Des modifications aux lignes directrices actuelles des trois Conseils sont suggérées.

Key words: emergency medicine, medical research, informed consent, biomedical ethics

Introduction

Especially since the atrocious Nazi experiments during World War II, there has been a growing consensus on the importance of informed consent in human research. Full disclosure of a study's risks and benefits is necessary to protect a subject's autonomy, and the first principle of the *Nuremberg Code* stated that "voluntary consent of the human subject is absolutely essential." However, when the Nuremberg regulations were transformed into the *Declaration of Helsinki* in 1964, Section II ("Medical research combined with professional care") stated explicitly that there may be exceptions to the requirement for informed consent.

Pre-hospital and emergency department (ED) resuscitation research is fraught with ethical dilemmas. One of the

most important of these is the difficulty of obtaining genuine informed consent from research subjects. ED research often takes place when patients are in distress or even unconscious, making a thoughtful discussion of risks and benefits impossible. Yet if such work were abandoned because of the lack of consent, valuable research would be stymied and life-saving therapies never proven. This would particularly affect vulnerable people exposed to acute, life-threatening conditions. Thus, it is crucial to balance the autonomy of research subjects against the need for scientific advancement and societal benefit.

In 1998, the Medical Research Council of Canada (now the Canadian Institutes of Health Research), the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada

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issued a *Tri-Council Policy Statement (TCPS)*¹ to serve as a guideline for Institutional Review Boards (IRBs) approving research proposals. The TCPS addresses emergency health research, and it appears to have been influenced by the US Food and Drug Administration (FDA) regulations. This paper will discuss the ethical issues surrounding consent, then compare and contrast relevant US and Canadian regulations.

Ethical foundations of consent in research

Potential for benefit

Research protocols often use human subjects to evaluate the safety and effectiveness of new treatments. Such protocols are ethical only if there is potential for the subject or future patients to benefit. This requires that the study goals be more than merely of academic interest. Better treatments benefit society by extending life or improving its quality, and the potential for benefit is especially apparent with treatments to prevent imminent death. However, as noted above, without relaxing the requirement for full informed consent, advances in the field of resuscitation could not occur.

Minimal harm and appropriate incremental risk

Research offering the patient no chance of therapeutic benefit should seldom be allowed without consent. Further, in studies where benefit is unlikely, an absolute standard of minimal risk should be a requirement, with no chance of the intervention impeding the institution of necessary treatment. Examples of minimal risk might include the drawing of blood samples or the administration of nontoxic pharmaceuticals, as long as these actions did not delay important care. In cases where an effective standard treatment exists, placebo controls should only be used as an adjunct to standard treatment, never as a replacement for it.

Research in the treatment of life-threatening conditions is necessarily “risky,” since there is always a danger of death or disability if the intervention fails. It therefore seems unrealistic to hold resuscitation research to a standard of absolute minimal risk. Biros and colleagues² proposed the less ambiguous concept of “appropriate incremental risk,” an improvement over the minimal risk standards previously applied to potentially beneficial acute care interventions. They wrote:

“Incremental risk is defined as any potential risk associated with participating in the research protocol relative to the natural consequences of the medical condition, or any potential risk associated with receiving the experimental intervention relative to receiving the standard treatment for the medical condition. Appropriate incremental risk is the

amount of incremental risk that an IRB believes would be acceptable to potential patients.”²

The balance between autonomy and advancement

Although the standard of full informed consent must be relaxed in some instances, the rights and autonomy of the subject must be protected; therefore, the exceptions should be as narrow as possible. Excessively restrictive limitations will inhibit important research, but defined conditions are necessary to ensure that the autonomy of human subjects is respected. In circumstances where full informed consent is unfeasible, investigators should consider one of several alternatives.

Alternatives to standard informed consent

Deferred consent

“Deferred consent” involves enrolling a patient who is unable to consent, then later asking a surrogate decision-maker or the subject (if he or she regains capacity) for consent to continue in the trial. The concept, introduced by Post and Robertson,³ was widely used as a substitute for full consent until 1993, when the National Institutes of Health (NIH)⁴ and the FDA⁵ questioned its legality. In fact, deferred consent is *not* the same as informed consent because, by the time subjects are asked for consent, they have already been exposed to the risks and benefits of the trial.

Leaving aside the issue that deferred consent is only consent to *continue* in a research study rather than *enroll* in it, there is the issue of autonomy. Deferred consent allows researchers to breach the subject’s autonomy by making the enrolment decision themselves, then asking for retrospective approval. If the patient or the surrogate decision-maker objects to the study, it is possible to withdraw from the study but not to ‘undo’ the exposure to the study intervention. Deferred consent cannot be seen as a substitute for full informed consent.

Prospective consent

In some cases, potential study subjects can be enrolled in advance, when they are not in a compromised state and there is adequate time to explain the risks and benefits of the research. Prospective consent is attractive but presents several practical and ethical problems. First, because most catastrophic events (e.g., cardiac arrest) are uncommon, it is almost impossible to prospectively enroll enough subjects to conduct an adequately powered clinical trial. Unless the population at risk is small and discreet, huge numbers of potential subjects would need to be enrolled at insurmountable time and expense. As well, this does not get around the difficulty of obtaining consent at the time of

crisis. If the condition under study is acute and life-threatening, there may not be sufficient time to verify that the potential subject has previously given prospective consent to be enrolled in the research protocol.

Prospective consent is also ethically problematic because potential subjects may not envision themselves having a heart attack or stroke, and risks and benefits may be weighed differently when the danger is a mere theoretical possibility than when the subject is at death's door. In addition, if a long time passes between the time of consent and the time of the trial, the subjects may change their mind. Finally, changes to the protocol or advances in other areas of medical science may out-date their decision. Despite all this, prospective consent may be useful for studies in defined high-risk groups who can imagine themselves in the situation under study.

It is reasonable to consider advanced directives as prospective "refusal of consent." Likely, if a patient does not want aggressive, life-prolonging treatment, she or he would not want an experimental treatment designed to accomplish the same thing.

Surrogate consent

If incapacity or stress precludes full informed consent, researchers may seek consent from surrogate decision-makers. Surrogate consent respects the subject's autonomy, providing the surrogate knows the subject well enough to imagine what his or her decision would have been. While surrogate consent is better than no consent at all, it also has its problems. Finding a surrogate in time to administer emergent intervention may be impossible. If a surrogate is found, the decision to approve aggressive, life-sustaining treatment is difficult, and the outcomes may be more complex than simply life or death. For example, a study could increase the risk of irreversible brain injury while decreasing the risk of death.⁶ It is hard for a surrogate to know what the patient's wishes would be and whether that patient would consent to a clinical study. Such a decision is made even more complex by the stressful context of resuscitation and the rapid response required. In addition, individual values such as altruism and risk-aversion come into play, and there is some potential for abuse. Young people, who are more likely to be surrogates, may be less cautious than older people, who are more likely to be subjects.⁷ Compounding these difficulties is the fact that, at the time of consent, when the surrogate has just been told of the catastrophic situation, they may not be in a state of mind to rationally weigh the risks and benefits of resuscitation research. They may want to assure the subject receives every helpful therapy, yet they may reject out of hand the notion of "experimenting" on their relative at a time of crisis. Either way, the decision would reflect the sur-

rogate's beliefs and values more than those of the subject.

Waiver of consent

Under very limited circumstances, the waiver of consent has been proposed for research in acute care. Contrary to the solutions previously described, a waiver acknowledges that a right is being abdicated for other more important values and does not attempt to be an equal substitute. Despite this, both the new FDA regulations and the Canadian Tri-Council guidelines allow a waiver in some instances.

Arguments for waiver of consent

Similarity with emergency treatment

In the setting where emergent *treatment* is required but informed consent cannot be secured due to incapacity, consent is presumed. Physicians generally assume that patients would want life-sustaining treatment, unless there is evidence of an advanced directive, or the word of a surrogate suggesting otherwise. Some have suggested that emergency research is a parallel situation and that waiver of consent is appropriate. Fost⁸ argues that many "standard" therapies have not been proven in rigorous clinical trials and that, especially in the acute care setting, patients are, in essence, being subjected to unregulated "research." In fact, experimental interventions may have a greater potential benefit with less risk, since these have undergone preliminary study and received investigational review board (ethics) approval, while the often unproven standard therapy may not have. As such, it might be more sensible to presume informed consent for emergency research than for emergency therapy.

Equipose

Equipose is a state of balance or uncertainty that is central to ethical research.⁹ If there is uncertainty which of two treatments is better, then equipose exists. Theoretical equipose requires that the researcher be personally indifferent regarding the merits of each treatment. Clinical equipose requires that a significant group of experts believes in each arm of the research protocol, therefore that neither intervention is viewed as "substandard" treatment based on this relevant community of peers (even if individual researchers have clear preferences). If clinical equipose exists, waiver of consent may be an option, since there are researchers who believe that each possible treatment in the experiment is the most effective.

Reasonable person

Consent is presumed for emergency treatment largely because of the "reasonable person" standard. If a health care

provider has to decide whether to give or withhold therapy, it is best to err on the side of caution: an informed guess as to which choice a reasonable person would likely make. In a well-designed trial, where there is a good chance of benefit and relatively low incremental risk, study subjects are likely to benefit (beneficence). This illustrates Pellegrino's concept of acceptable (weak) paternalism, where physicians substitute their judgement for the patient's not because they believe it to be superior (strong paternalism), but because there is no way to assess the patient's wishes at that time.¹⁰

Arguments against waiver of consent

Problems with the reasonable person standard

The "reasonable person" standard, however, leading to presumed consent in resuscitation research, does not entirely compensate for the possible breach of autonomy. First, it is less likely that a reasonable person would consent to research than to treatment. As outlined above in the discussion of surrogate consent, the decision is more complex and value-laden. Many patients have signed advance directives to refuse heroic treatment, and it is likely that many would similarly refuse heroic (resuscitation) research. It is therefore harder to presume consent in this context. Moreover, a 1996 study of emergency patients showed that only 50% of patients would consent to be involved in an emergency research protocol where the risk was more than "minimal" but the "incremental risk" over minimal was "small."¹¹ This calls into question whether the reasonable person would necessarily consent to research.

Autonomy

Although the subject may not suffer any extra physical injury as a result of being an unwilling participant in a clinical trial, there is still injury to the subject's right to autonomy. The problem of autonomy in resuscitation research has been discussed above.

Summary: a balance between autonomy and reasonable person

Although autonomy is important, it should not be taken as an absolute trump at the expense of all other values. Competing aims ought to be balanced. Allowing a waiver of informed consent in special, limited circumstances, with as many compensatory mechanisms as possible to approximate the consent, is the answer. Both the new FDA regulations and the Tri-Council recommendations attempt such a balance.

The US experience

In the United States, pharmaceutical research protocols must comply with FDA regulations. If the research is funded by the NIH, then Department of Health and Human Services regulations also apply. Neither set of regulations specifically addressed emergency research and, prior to 1996, emergency medicine researchers were often refused ethics approval for emergency research projects because of the inability to obtain valid informed consent.

In October 1994, a coalition of bioethicists, patient advocacy groups, and legal and medical research groups convened to discuss the problem. The outcome was a consensus statement² that suggested regulatory improvements. This led to new FDA and NIH regulations, which took effect in November 1996.¹² The new regulations allow waiver of consent only if the subject's condition precludes informed consent, the condition is life-threatening, available treatments are unproven or unsatisfactory, the research offers the prospect of "direct benefit" to the subject, and the risks and benefits are reasonable in light of the patient's condition and what is known of alternative therapies. In addition, researchers must consult with the community in which the research would occur, publicly disclose the study design and risks prior to the trial, use an independent safety monitoring board, and publicize the study results after completion.¹³

Advance publicity regarding the aims, risks and benefits of a study protocol would put the issue in the minds of potential subjects; and dialogue between researchers and the community can only promote trust and good relations so long as the dialogue is genuine — not merely public relations to "sell" the study to the community. But community involvement is only a partial answer, and the problems described above under "prospective consent" still exist. In addition, vagaries in wording have led to problems.¹⁴ Who is the affected community? What constitutes adequate public notice? How many public meetings are sufficient? Does lack of public participation imply acceptance or poor publicity?

Canadian guidelines – the Tri-Council Policy Statement

The 1998 *Tri-Council Policy Statement: ethical conduct for research involving humans* (TCPS) is a set of guidelines jointly issued by the Medical Research Council, the Natural Sciences and Engineering Research Council and the Social Sciences and Humanities Research Council — three important Canadian research funding bodies.¹ In Article 2.8 of the TCPS, guidelines for research in "emergency health situations" are outlined (Box 1). Although

similar in many respects to the 1996 FDA regulations, they differ in other important areas.

Placebo trials

Box 1 shows that the TCPS considers waiver of consent appropriate if no effective standard care exists, if the risk of harm is not increased and if the research offers a possibility of benefit compared to standard care. In situations where no effective therapy exists, placebo controls are presumably appropriate; however, where a proven effective therapy exists, trials that substitute placebo for standard care would be prohibited. Some researchers might argue that a placebo-controlled trial would be ethical despite the availability of effective standard therapy because subjects randomized to the treatment arm could benefit, but this argument is flawed because item (c) requires that the risk of harm must not be greater than that involved in standard efficacious care or must be *clearly justified* by the direct benefits to the subject. Obviously, neither condition is met: Placebo increases the risk of adverse outcome relative to an effective therapy, and placebo does not provide clearly justifiable benefit to patients. By contrast, trials that compare a new treatment to placebo + standard therapy, would be permitted without consent, so long as the new therapy did not interfere with the standard efficacious therapy, thereby increase the risk of harm.

Appropriate incremental risk

Most emergency therapies carry high risks because of the sit-

uations they are meant to address. Thus the notion of “appropriate incremental risk” was chosen as a standard in this context. Appropriate incremental risk means that the risk must not be greater than that associated with standard, efficacious care *or* must be clearly justified by the likelihood of direct benefit to the patient. If risk is greater, this incremental risk must be commensurate with the possibility of benefit.

It remains unclear whether the guidelines would allow waiver of consent for studies of minimal risk, non-therapeutic interventions; for example, collection of blood samples during a cardiac arrest (where the blood tests offer no possibility of direct benefit to that subject). In this context, the vagueness of the TCPS may be a good thing. Uncertainty will force researchers to ensure that studies are well-designed and of more than academic interest before proposing them to an ethics board. Research ethics boards will be left to interpret these requirements as they see reasonable.

Public notification: FDA and TCPS compared

Unlike the FDA regulations, the TCPS does not mandate public notification or community outreach before a trial begins. Rather, the TCPS includes the rather weak statement that researchers “should include...when feasible or appropriate, one or more of the following [additional safeguards]: ...procedures to identify potential subjects in advance to obtain free and informed consent prior to the occurrence of the emergency situation, consultation with former and potential subjects...”¹

Box 1. Excerpt from Section 2 (Free and Informed Consent), F. Research in Emergency Health Situations, Article 2.8, of the *Tri-Council Policy Statement*¹

Subject to all applicable legislative and regulatory requirements, research involving emergency health situations shall be conducted only if it addresses the emergency needs of individuals involved, and then only in accordance with criteria established in advance of such research by the REB [Research Ethics Board]. The REB may allow research that involves health emergencies to be carried out without the free and informed consent of the subject or of his or her authorized third party if ALL of the following apply:

- A serious threat to the prospective subject requires immediate intervention; and
- Either no standard efficacious care exists or the research offers a real possibility of direct benefit to the subject in comparison with standard care; and
- Either the risk of harm is not greater than that involved in standard efficacious care, or it is clearly justified by the direct benefits to the subject; and
- The prospective subject is unconscious or lacks capacity to understand risks, methods and purposes of the research; and
- Third-party authorization cannot be secured in sufficient time, despite diligent and documented efforts to do so; and
- No relevant prior directive by the subject is known to exist.

When a previously incapacitated subject regains capacity, or when an authorized third party is found, free and informed consent shall be sought promptly for continuation in the project and for subsequent examinations or tests related to the study.

Criticisms: blurring the distinction between research and therapy

The TCPS guidelines share in some respects a widely criticized aspect of the FDA regulations: blurring the line between research and therapy.¹⁶ The TCPS uses language suggesting that the research may constitute therapy. As previously discussed, in research, the physician-researcher acts primarily for future patients, while in therapy, he or she acts for the patient alone. Thus, the distinction between research and therapy must be maintained when dealing with consent issues, since the regulations seem to allow for research that has no chance of benefiting the patient subject.

The TCPS would allow waived consent only if “the research offers a real possibility of direct benefit to the subject.”¹⁷ Further, it suggests that emergency research “shall be conducted only if it addresses the emergency needs of individuals involved.” Unlike the US regulations, the TCPS does not appear to allow a waiver of consent for studies where placebo is substituted for standard care, and placebo-controlled trials seem to be viewed as a type of research that is clearly distinct from “therapy.”

Suggestions for change to the TCPS regulations

The regulations contain many laudable elements. They clarify that “deferred consent” is not valid retroactive consent for study *enrolment*, but rather, that it is consent to *continue* the research. They also clarify that prior directives must be heeded if “relevant” (Box 1). Some may argue that their wording is vague enough to allow researcher to ignore “do not resuscitate” orders because they fail to say, “do not enroll me in a research study.” Practically, however, it is unlikely that any research ethics board would consider such an interpretation reasonable.

The FDA regulations and the TCPS try in different ways to strike a reasonable balance between autonomy and other values in the field of emergency research. Overall, the TCPS is well-drafted, but one suggestion may be appropriate. The TCPS wording blurs the distinction between research and therapy, implying that research studies are, in and of themselves, therapeutic. Perhaps a simple clarification is all that is needed.

Conclusion

Informed consent is important in the therapeutic context, and even more so in the research context, where the physician–patient relationship becomes a researcher–subject relationship, and the researcher has interests beyond those of

the patient. In emergency and resuscitation research, however, full and informed consent is often not possible. Unless we are prepared to prohibit most of the research in this important area, some of the traditional requirements necessary to assure patient autonomy and self-determination must be relaxed in favour of other values.

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