

Summary: Exception from Informed Consent

Introduction and Experience

My name is Richard Dutton. I am the Chief of Anesthesiology at the R Adams Cowley Shock Trauma Center in Baltimore, part of the University of Maryland system. Unlike most of those providing commentary, I do not represent any other organization or company. I have had significant experience “in the trenches” of Emergency Services research and would like to share some of that with you.

The Shock Trauma Center (STC) is the busiest trauma center in the country. As the centerpiece of Maryland’s state-wide trauma network, the STC is both a primary resource for trauma in the Baltimore area and a secondary referral center for critically injured patients anywhere in Maryland or the surrounding states. We serve an estimated population of about 6 million. I am proud to work at the STC, and I am proud every time our system saves a life. Yet this is only a small part of our contribution. Beyond the care of individual patients, we are obligated to push at the boundaries of science, and we are obligated to share what we have learned with others. One life saved today in my hands should mean hundreds or thousands of lives saved around the world in the future. Our motto is “to heal, to teach, and to discover.” As the largest, the busiest, and the best-organized trauma center in the country, my colleagues and I feel this as a moral imperative. If we aren’t constantly trying to do better, then we aren’t doing our jobs.

I came to the STC out of the United States Navy specifically because of my interest in resuscitation of dying patients. In the past 12 years I have initiated or participated in more than a dozen IRB-approved clinical trials in emergency care. Every one of them had to address the question of informed consent, and this was the major logistical hurdle in many of them. The requirements of 21-CFR 50 have a strong impact not only on the studies that use community consultation, but also on many studies that do not. Specifically:

- The Baxter sponsored diasparin cross-linked hemoglobin study of the mid-1990s was one of the first to use the provisions of 21-CFR 50. We participated in that trial, and I cared for several patients who received the trial product. The University’s experience with community consultation included at least one bad event, when a poorly attended meeting at a local church turned into an inflammatory (and poorly informed) article in the newspaper the next day. Fortunately, more reasoned discussion followed, and we were allowed to continue our participation in the trial until it was closed.
- At about the same time we started our own investigator-initiated and internally funded study of deliberate hypotension in actively hemorrhaging trauma patients. This therapy, which required immediate application at the time of admission to be effective, was well supported by animal data and one large human trial (completed before 21-CFR 50), and was already in use by many of our surgeons and anesthesiologists. Initially, the IRB told us we would need to pursue community consent, but it was subsequently decided that both therapies were within the existing standard of care. We were therefore allowed to conduct a prospective comparison of these therapies under a policy of waived initial

consent, with a “consent to continue” as soon as possible thereafter from the patient or family. This study eventually enrolled 110 patients over several years, and contributed to the body of knowledge that has made this approach to hemorrhagic shock the current worldwide standard.

- We have also conducted half a dozen prospective trials of early monitoring devices for shock and traumatic brain injury (TBI) in the past decade, funded by the NIH, the DoD, or private industry. The protocols for these studies are all similar. The device is applied to the patient at the earliest moment in the field or in the Trauma Resuscitation Unit, data is gathered, and this data is subsequently compared to “gold standard” diagnostics such as the serum lactate level (for hemorrhagic shock) or the cranial CT scan (for TBI). Because the devices are non-invasive, and because the data collected is not used for clinical decision making, the IRB has allowed these trials to proceed with a waiver of informed consent. Patients are notified subsequently about their inclusion in the trial and given the chance to withdraw from study. Any data already gathered is destroyed.
- Five years ago we began using recombinant human coagulation factor VIIa as a rescue therapy for patients with intractable hemorrhage, and we I started work with the manufacturer to design a prospective trial of its efficacy. Due to safety concerns the initial trial of FVIIa in trauma patients was conducted outside of the United States. Results were positive, and a worldwide trial is underway. At present this study is proceeding in the United States using a conventional mechanism for obtaining consent from a legally authorized representative (LAR). Although the protocol allows for enrollment in the study up to the time of the 8th unit of red blood cell transfusion, this window is functionally very small in the kind of patients who are likely to benefit from the drug, and enrolling adequate numbers of patients for study will certainly be difficult.
- I am also participating as a Steering Committee member and principal investigator in the ongoing RESUS trial of pre-hospital use of a hemoglobin-based oxygen carrier (HBOC) for patients in hemorrhagic shock, sponsored by the US Navy. This trial has yet to receive FDA approval, in part because of the risk-benefit standards imposed by the provisions of 21-CFR 50.

It is on the basis of these experience that I wish to comment on the existing standards of 21-CFR 50, and make some suggestions for improvement.

The Nature of Traumatic Injury

In creating the Maryland trauma system and the Shock Trauma Center four decades ago, Dr. R Adams Cowley coined the term “The Golden Hour” to express the truism in trauma care that good patient outcomes depend on the speed with which injuries are diagnosed and treated. The STC was built with this concept in mind – the Resuscitation Unit immediately adjoins both the radiology suite and the Operating Rooms – and is staffed accordingly, with specialist surgeons, anesthesiologists, nurses, technicians, and consultants immediately available to care for seriously injured patients.

The “need for speed” creates a very serious conflict with the respect for individual autonomy that underlies 21-CFR 50. We know for a fact that more rapid control of hemorrhage leads to better outcomes. We know that early and aggressive prevention of secondary brain injury is critical to functional status after TBI. We have reams of animal data suggesting promising new therapies for these patients, yet translational research has lagged considerably, because these are the exact patients that are nearly impossible to enroll in research trials. Here’s why:

Patient Issues:

- No time for complicated discussions (cannot interrupt therapy)
- Need for endotracheal intubation and mechanical ventilation
- Altered mental status in hemorrhagic shock
- Altered mental status in TBI (by definition)
- Intoxication and substance abuse (in about half of all trauma victims)
- Language barriers (in about 10% in our area)
- Need for pain medication and sedatives
- An inherently coercive environment

Family / LAR Issues:

- Must be found and notified of the traumatic event
- Must arrive at the Trauma Center (may be hundreds of miles away)
- Must be brought up to speed on clinical events
- Must have or assign decision making authority
- Must overcome language barriers
- Must overcome emotional distress, grieving
- Must have enough time for a discussion
- Must not feel coerced

Over the years, we have developed some data on these topics that illustrate the issues. From our experience with multi-institutional trials, we estimate about a 50% recruitment rate for studies in which we have to have a serious or complex discussion with a family during the first hours after admission. It seems obvious, but is worth stating, that trauma happens by surprise. In the first hours after a serious injury, family members are coping with grief, guilt, disruption of their lives and schedules, serious financial problems, and legal entanglements. When we looked back at our experience with deliberate hypotension, a protocol in which the active portion of the investigation was already completed before we could possibly talk with the family, we found that the average time to complete notification of enrollment and get the patient or family’s permission to continue data collection was five days (unpublished data). This seems too long, but as one of those engaged in the process I have a good understanding of why it was so. We are compassionate individuals, and sought to talk with the family at a time when they could understand the medical issues involved, understand the context of the research we were conducting, and make an informed decision. In fact, the family was frequently so devastated by the patient’s injury that it was easier for us to wait for the patient to recover enough to talk with us than to pursue the conversation with the LAR. This raised the interesting and still unanswered

question of whether it is appropriate to wait for a delayed consent from the patient (greater individual autonomy) or attempt early communication with the LAR.

Also as part of the deliberate hypotension study we conducted a planned call-back of the first 50 enrolled patients, at an average of 6 months following study enrollment. Typical of the population, we were actually able to get in touch with less than half of the patients or their surviving family members. Only two had any recollection of discussing a research study during their hospitalization. Interestingly, all of those we talked to supported our research efforts, supported the use of waived consent, and were accepting of having participated.

Over the past decade we have enrolled more than 1,000 patients in various monitoring trials that operated under a waiver of consent but required subsequent notification of the patient / LAR, and provided an opportunity to “opt-out.” Although most of these subjects were enrolled while clearly incompetent (after TBI or intubation), the few who participated while awake had the benefit of a short discussion with the research nurse or PI before the monitoring took place. We have not had a patient refuse to participate in this setting, especially once they knew that the device itself was non-invasive. In our community at least, patients understand that we (the STC) are striving to find new ways to help them. Most are grateful for an opportunity to help out. In the incompetent patients where this discussion is taking place later, or when we are mailing them a description of the study after discharge, we have also had very few refusals (less than 0.5%). Most have come when the patient has died of their injuries, and the family is still in chaos.

More recently, as a benefit of increased research infrastructure, we have begun an internally-funded prospective survey of all STC admissions, asking the basic questions: “Could this person give informed consent?” “Why not?” and “When was a family or LAR available?” Over the past six months we have surveyed 2,011 primary trauma admissions. As of mid-November, the top-line results were that 43% of admitted patients would have been unable to consent for themselves, due to brain injury, intoxication, shock, or a language barrier. Of the 865 patients who could not consent for themselves, 441 (51%) had no available and acceptable LAR within 3 hours of admission. The second phase of this study is now underway, linking this data to the Trauma Registry to determine what the degree of “consentability” will be for various populations of interest, including patients with severe TBI, patients with active hemorrhage, and patients with particular injury patterns (e.g. victims of T-bone motor vehicle collisions, patients with isolated open tibial fractures, patients receiving uncrossmatched red blood cells). We hope to publish these data soon.

Recommendations

These are complicated issues, and I do not present myself as an expert in medical ethics. While I do respect individual autonomy, I also believe that research in trauma patients is essential, and I believe there are ways that the current exception from consent process can be improved. The following are my suggestions:

- 1) *Form a single national body to advise the FDA, investigators, and individual IRBs, on exception-from-consent issues.* This body would allow for concentration of expertise in one

place, thus avoiding the frequent problem for investigators of having to educate local IRBs as much on the consent process as on the scientific specifics of a given study. This body would also be a resource to investigators, by clarifying and standardizing practices, and to the scientists of the FDA. Although national review of waiver-of-consent trials would be mandatory, approval of studies would still require local IRB review, because only the local IRB can assess how the study will fit with the population and culture of the community. Having the “blessing” of a respected national body will facilitate this process, however, and will give the IRB confidence that proposed ongoing-consent and community notification procedures are appropriate.

2) *Provide public access (such as a web site) to information about waiver-of-consent trials, and the communities they are present in.* While community consultation regarding these trials often does not reach the necessary target audience, or is lost in the noise of other advertising, interested members of the public should have an easy means to learn more. I support making the protocols themselves available. Issues this serious demand transparency. The same National Advisory Board outlined above could be responsible for establishing and maintaining this web site.

3) *Clarify the language of the existing standards.* It would be beneficial to provide concrete examples of interpretation of language in the existing policy. Words and phrases such as “impracticable,” “important research,” and “likely to have a benefit” have been distressing investigators, IRBs, and even the FDA itself for the past decade. Even the definition of “community” has led to controversy and confusion.

4) *Adopt a policy of “rolling consent.”* Patients and families who have suffered medical emergencies are under a great deal of stress. The consent process should recognize this. Initially, appropriate studies should be allowed to enroll patients following very brief communications, not interfering with ongoing care. For example, the paramedic might say to the wife of the patient in the field something like “We are studying ways to improve care in patients like your husband. I can’t take the time to explain it fully now, but would you have any objection to him participating in an approved research study if he were eligible?” Assuming the patient’s wife was willing, this would begin a conversation that would continue for days or even weeks, until the patient and his family could be fully informed regarding the specifics of the study, and could formally grant informed consent for continued participation. The essence of the plan is presenting study information at a time and pace that it can actually be understood, with three key understandings:

- Discussion about the study will not delay indicated care.
- Further information about the study will always be available, if the patient or family asks for it.
- Any refusal at any point in the discussion will remove the patient from study.

Our experience at the STC suggests that most patients would be willing to work with a mechanism like this. Over time, public acceptance of this mechanism should increase as trust develops in the policies for approving research projects and the high-profile people (the national advisory board) who are involved.

5) *Make research results publicly available.* Scientific results should be made public, of course, but so should the “social” results. How many patients refused to consent? How many objected to the mechanics of consent? How many had a clear understanding of the research process a year later? Which were the communication strategies that worked best? Would the patient or family participate again? By requiring this kind of ongoing review, information can be collected that will guide us empirically towards the most effective means of completing research in emergency care, while still satisfying the needs of the population.

Summary

A waiver of consent mechanism is essential for necessary research in trauma care. During the past hour 18 US citizens have died from injury. To lower this number we must find ways to develop public confidence in a consent process that both enables critical research and protects the rights of the individual.

Thank you for inviting my opinions. I am available for further discussion with any interested parties at rdutton@umaryland.edu

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