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Ethical Considerations for Conducting a Randomized Controlled Trial in Transport

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Abstract

Although recent studies support the rapid transfer of patients experiencing time-sensitive emergencies, limited data exist to support the use of air transport for non-urgent patient transfers. The nature of medical transport and the heterogeneity of patients who are transferred present unique challenges in designing and conducting clinical research trials that could contribute to the evidence-based decision-making for patient care and transport. The current regulatory framework presents several barriers to conducting such research in the medical transport setting. We present a hypothetical study that randomizes patients to either ground or air transport as an exemplar. We discuss informed consent, risk, and the impracticality of conducting community consultations in a medical transport setting. Finally, recommendations for potential changes to current regulations are presented. These are directed at facilitating the conduct of emergency research through a system of oversight that integrates characteristics of quality improvement and health services research.

Keywords

research ethics; medical transport

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Introduction

Developing an evidence base for the science of medical transport will require an extensive amount of research focused on patients who are acutely ill or injured and require transfer. The barriers to and difficulties of conducting research with critically ill or injured patients have been extensively explored in the literature¹⁻³. However, to date little progress has been made in facilitating research and modifying regulatory environments to enable the ethical conduct of research in this vulnerable population⁴. Notwithstanding the challenges, we are obligated to the public to continually improve practice and conduct the required research to allow us to inform patients, surrogates, and other clinicians regarding whether, when, how, and why critical care transport services should be provided⁵. The purpose of this paper is to explore the current barriers to conducting research in the transport setting.

Some of the most vulnerable patients are those who are ill or injured and require medical care that is not available at their current location. Definitive intervention requires moving these patients by ambulance, helicopter, or fixed-wing aircraft to the most appropriate center for further medical care. Yet, the effect of the transfer itself on patients both during and after transfer remains poorly understood. Recent studies support the transport of patients who are experiencing time-sensitive emergencies such as trauma⁶ and myocardial infarction^{7,8}. For these patients, use of the shortest transfer time to definitive care, which frequently is air transport, is non-controversial. Alternatively, several studies have reported worse outcomes for critical care patients who undergo interfacility transport in situations in which intervention is not time-sensitive^{9,10}. A primary question that remains unresolved involves how to optimally move non-urgent patients.

The current regulatory environment severely limits the feasibility of conducting research in critically ill or injured patients primarily due to the requirement for informed consent. Waiving the requirement for informed consent using the emergency research waiver requires that community consultations be conducted. This presents several hurdles that may prove challenging for research conducted in a medical transport setting. Additionally, health care delivery is evolving into a learning health care system (that blurs the distinction between comprehensive data collection required to support today's electronic medical records and quality reporting systems), with activities that would have been previously labeled as research¹¹. The conventional criteria that differentiates clinical practice from research is considered by some as no longer applicable¹¹.

In this paper we will explore the barriers to conducting emergency research under the current regulatory framework, using a hypothetical study that proposes to randomize patients to either ground or air transport as an exemplar. We will specifically focus on informed consent, risk, and the impracticality of community consultations. We will then propose several recommendations for possible changes to the current regulations to enable the conduct of emergency research while maintaining our moral obligation to uphold patient safety and respect their rights.

Background

Approximately 400,000 patients are transferred by helicopter, with another 150,000 transferred by fixed-wing aircraft each year in the United States¹². In addition, there are 264 registered ground critical care ambulances that also transport patients¹², however, the annual number of completed ground patient transfers in the United States on an annual basis is not currently available. The primary justification for using air transport is to reduce the out-of-hospital time that patients experience, especially for patients being transferred between intensive care units (ICU). The importance of out-of-hospital time stems from the assumption that while patients are in the transport environment, they are at increased risk for physiological compromise due to the stressors of transport, limited resources available for care, the potential for equipment failure, and limited capability of the providers to respond if physiologic decompensation occurs. To date, this assumption has not been confirmed; there have been no reports of increased complication rates or increased mortality during ground transport when compared to air.

There are multiple factors that contribute to high use of elective (i.e. not time sensitive) helicopter transfers. Emergency rooms may request that a complicated patient be transferred out as quickly as possible, in order to relieve busy departments of the resource-intensive patient. Another factor is the consideration of distance. Transport protocols often use trip distance as a deciding factor –with longer trips increasing the likelihood of helicopter use, regardless of the patient's condition or needs, reflecting the assumption that faster is better.

The high rate of air transport may suggest that the prevailing approach is to err on the side of caution and request helicopter transport under the assumption that it is superior to ground transport both in the care provided and the outcomes achieved. To date, we noted only one review of a large series of transfers that found a 2% increase in the likelihood of a critical event for every 10 minutes of an urgent medical transfer when cared for by varying levels of paramedics¹³. Another study suggests that the distance of transport may present greater risk for minor adverse events¹⁴. In their discussion of healthcare regionalization, Singh and MacDonald¹⁵ note that the actual health impact and risk of transferring critically ill patients to a higher level of care within a regionalized health system is not precisely known.

With exception of time-sensitive diagnoses, there is currently no evidence to support that non-urgent patient transfers conducted by critical care transport teams, especially those staffed with advanced providers (e.g. nurse practitioner, physician), experience similar risk. Recent evidence suggests that even time-sensitive patients being transported for surgical intervention over long distances experience an improved physiologic state both during and after transfer with improved clinical outcomes when transferred by advanced practice critical care transport teams to high volume quaternary hospitals¹⁶. Lack of compelling evidence creates the conditions for clinical equipoise regarding the efficacy of helicopter versus ground transport for non-urgent interfacility transfers.

Example Study

Several methodological approaches could be used to answer the question of differences in morbidity and mortality for patients who are transferred by helicopter versus ground. The

choice of method depends on several factors, including the feasibility of conducting the study. One option would be to design a rigorous prospective observational study that creates matched cohorts of like patients and compares them based on the mode of transport. Robust statistical analyses, using propensity scoring and matching with sensitivity analysis can provide similar results to the gold standard results of a randomized clinical trial^{17,18}. The primary benefits of conducting an observational study include the correspondence with real-world conditions, negating a primary criticism of clinical trials that have strict inclusion and exclusion criteria limiting generalizability of study findings. However, observational designs are vulnerable to selection biases and the possibility that unobserved covariates could have an effect on the outcome under study.

The threat of selection bias is a primary concern in answering the specific research question of interest here. Selection bias, reflected in providers' and systems' decisions for mode of transport, presents a major barrier that can be controlled via randomization of mode of transport. Even though an observational study design could be used to investigate differences in outcomes, the heterogeneity of patients, referral processes, and provider preferences could confound study conclusions and require very large samples to obtain sufficient subjects for matching. Therefore, for the purposes of this paper, we will explore the feasibility of conducting a randomized clinical trial.

In this hypothetical trial, the study population would include patients who are referred for transfer, who have a non-urgent diagnosis, and who would, under standard care, be equally likely to be transported by ground as by air. A common example of a patient who would fall into this category would be a patient with respiratory failure who was intubated and stabilized in a small hospital emergency department or ICU and is being transferred to a larger tertiary care hospital. Enrolling patients like this into a randomized trial will be the example case for discussion.

Informed Consent

The primary issue in conducting research in emergency and critical care settings is the requirement to obtain informed consent. Although progress has been achieved with the addition of the emergency research waiver of consent amendment in 1996¹⁹, major regulatory barriers still remain both in the United States, and similarly in Europe²⁰ where limited emergency research is conducted at the present time.

The challenges of obtaining informed consent for patient enrollment have been discussed^{3,4,21–25}, and are applicable to the conduct of this trial. There are several considerations to explore for this trial related to obtaining informed consent. The primary practical or logistic consideration concerns the inability to prospectively identify subjects who are referred for transfer, and who are usually at outside hospital locations. The only possible method of obtaining consent for enrollment would be to call the patient or surrogate prior to dispatching the mode of transport to retrieve the patient. Although possible in some instances, the phone call option would rarely be feasible because many patients in these situations lack decisional capacity and surrogate decision-makers are often not available at the time of the referral call. An alternative option would be to obtain informed consent from

the patient or surrogate once a transport team arrives at the referring facility. However, post-arrival consenting is not a reasonable option because if a patient or surrogate refuses participation, another transport team and alternative mode of transport may have to be dispatched depending on the first mode that is assigned. This would entail increased cost and inappropriate allocation of resources.

Another possibility would be the application of the emergency research consent waiver (ERCW). Under current regulations, the ERCW under section 46.101(i), of 45 CFR 46²⁶ may or may not apply, depending on the circumstances of when the transfer decision is made, and who is available to participate in the decision to transfer. Most non-urgent patient transfers originate from either an emergency department or ICU, and as Luce²⁵ states, these patients typically are not in a true emergency and therefore would not be eligible for research under the emergency waiver. In our example case, the patient has already experienced the acute episode, received airway intervention and is stable, and now requires transfer for a higher level of care.

Implementation of this trial would still face a major challenge even if we were to only include patients who are urgent transfers and thus were appropriate for application of the ERCW. To meet the requirements of the ERCW, community consultations are required, and this poses a significant barrier - how to adequately define the community that would be involved in the study. Most tertiary-based transport programs serve large regions of a state, with many serving a multi-state area. Any attempt to simplify or reduce the region down to only a few communities would greatly reduce the practicality of conducting this trial and the probability of capturing an adequate sample size of a specific patient population in a reasonable time frame.

Shah and Sugarman's²⁷ work has identified that the primary concern voiced by the public during community consultations is the ability to refuse participation in a trial. We will address this concern in the considerations for future directions. Having established that the options of obtaining consent prior to the initiation of the transport mission, at the time of transport team contact with the patient, and the possible use of ERCW are not feasible, we propose that a waiver of the consent requirement is justified. Waiving consent requires us to carefully evaluate the risks of the trial and the justification for waiving the standard consent requirement.

Balancing Risk with Benefit

The well-established moral obligation to respect the right of competent persons to decide for themselves whether or not to participate in research and the duty to prevent or minimize harm (risk) are closely related. As the degree of risk or burden increases, the stringency of the requirement for consent increases. In justifying the proposed waiver, we will first evaluate the degree of risk.

There are two ways in which subjects may be exposed to added risk through research participation in this hypothetical trial. They are: (1) the research presents less net clinical benefit and/or overall greater risk, and (2) because the research protocol dictates which

intervention a patient receives, different risks are entailed than would occur under standard care¹¹.

The underlying thesis to the first claim is that research with patients requires special oversight because it is less likely than clinical practice to be in the patient's best clinical interests and more likely to impose added clinical risk¹¹. Although this assertion may be true in clinical interventions where risk is known or is probably greater compared to established standards of care, the same cannot be said for our hypothetical protocol evaluating a specified mode of transport.

Limited data exist to suggest that patients benefit when transferred by helicopter⁶ as compared to ground. Most research conducted on transported patients focuses on time-sensitive patients where time of transfer has been the primary outcome. However, when we remove time as the exposure of interest as would be the case for non-urgent transfers, we then have to shift our focus to other factors that could be affecting patient outcome. A common assertion is that air transport crews provide higher quality care as compared to ground teams and that the overall out-of-hospital time is reduced when transferred by helicopter, thus improving patient outcomes.

There is some evidence to suggest that there may be a difference in quality of care between air and ground transport, particularly in regards to airway management^{28,29}. However, this evidence comes from situations in which airway intervention is being performed in time-sensitive emergencies. However, the majority of transport teams who conduct inter-hospital critical care transport are comprised of the same crew composition, usually a nurse and paramedic. Sometimes the same personnel staff both modes. An important factor that has not been addressed in the literature is the possible physiologic effect of the mode of transport on the patient.

Air transport may in fact subject patients to increased risk related to features of the helicopter flight, such as barometric pressure, or vibration, and present a more difficult environment for care as compared to the ground environment. Other potential risks of air transport include but are not limited to increased noise, on-scene and environmental hazards, or risk of crash. Ground transport may be subject to some of the same risks as air transport, with the exception of barometric pressure changes. An additional risk specific to ground transport could include prolonged response times or total trip times due to traffic conditions. However, we have not found current published data to substantiate the claim that increased complications are related to the amount of time patients spend out-of-hospital during non-time-sensitive critical care transport. Thus, given the available evidence we cannot reasonably assume that air transport improves outcomes for non-urgent patient transfers, nor that it presents more or less risk when compared to ground transport. If, then, we have clinical equipoise, we should consider the next issue of interest.

The second claim related to the imposition of risk is that research protocols dictate which interventions a patient will receive, in contrast to usual clinical decisions which are presumed to be solely directed by judgment of what is in the best interest of that patient. This second distinction is increasingly becoming irrelevant in today's healthcare

environment. Kass et al¹¹ provide several examples that illustrate the constraints that are placed on a clinical provider's ability to deliver patient care. There has been a surge in the development of standardized care protocols such as early goal directed therapy for sepsis^{30,31}. These protocols, as do other evidence-based protocols, recommend treatment strategies that are based on the effectiveness of that treatment for the average patient. While successful, these protocols, especially those that are developed and directed by a specific hospital, may limit providers' choices in treatment options. While standardized guidelines are presumably based on data that established best practice for similar patient populations, clinicians may encounter individual patients for whom they judge the guidelines ought not to be applied.

To the extent that there are sanctions and barriers that constrain the ability to use individual judgment in individual cases, decisions regarding a specified intervention may not, in fact, be directed entirely by the individual assessment of what is in that specific patient's best interest. In fact, the rationale behind guidelines is precisely the assertion that individual clinician judgments may be idiosyncratic and ought not always to be the deciding factor in choice of interventions.

The research protocol for this hypothetical randomized trial directs enrollment of a subject into one of two options. Both options are currently considered acceptable interventions when patients require transfer. The protocol does not introduce a third, or new, option with unknown efficacy or unknown risks. Similar to clinical treatment guidelines, this randomized trial relies on a protocol, not assessment of individual patient characteristics or clinician preference, to direct choice of intervention. While these features of standard care and research protocols are thus similar, it may be argued that enrollment in research does limit flexibility more so than do practice guidelines. Therefore, flexibility can and should be designed into research protocols as well¹¹. Flexibility of the proposed research protocol for providers, patients or surrogates can be addressed through an opt-out option. That is, clinicians and potential subjects, if they have decisional capacity (or their surrogates if available) can be provided with information and the opportunity to "opt out," thus preserving some ability to respect idiosyncratic preferences of either clinicians or potential subjects.

We have reviewed the current moral distinctions of risk that patients are subjected to when enrolled in clinical research. That said, factors that have been used for quite some time are becoming less relevant in today's rapidly changing learning healthcare environment. They continue to hinder the conduct of research in emergent and critical care patient populations. An updated, more relevant framework is necessary to guide the development and monitor the conduct of research in today's healthcare settings.

Implications

Local IRB

Under current institutional review board (IRB) review and guidelines the proposed hypothetical study would not likely be approved as it proposes to circumvent the currently accepted approaches to conducting emergency research. However, review of the criteria for

waiver or alteration of informed consent in sections 45 CFR 46.116(c)(2) and 45 CFR 46.408, reveals that this proposed study should, with the justification provided, be granted a waiver from the standard informed consent requirements.

Federal regulations (45 CFR Part 46) currently recognize four justifications for waiving the informed consent requirement. The four criterion include: (1) the research involves no more than minimal risk to the subjects, (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects, (3) the research could not practically be carried out without the waiver of alteration, and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation¹⁹. Criterion 1 and 2 - we have provided evidence that randomizing patients to either ground or air transport will involve no more than minimal risk and will also not affect the rights and welfare of subjects. Criterion 3 – we have provided evidence that this randomized trial could not be practically conducted any other way, including community consultation or obtaining consent during any phase of the transport process.

Criterion 4 specifically guides the flexibility that must be considered when designing and conducting a study as currently proposed. Specific to this study design and process, an information sheet would be used. The information sheet would be carried by the transport crew and provided to the patient or surrogate upon the team's arrival, prior to transport. The one page sheet would contain the relevant information related to the planned use of randomized choice of transport mode and also contain an "opt-out" clause. The opt-out clause will provide the provider, patient, or legal surrogate the ability to decline transport by the randomized method and request that the alternative mode be used, assuming that the alternative mode is available (e.g. weather permitting for helicopter transport). The opt-out clause enables the provider discretion to override the randomization of the mode of transport in certain circumstances (e.g. a small free-standing emergency department is over-crowded and lacks the resources to continue caring for a critically ill patient – justifying expeditious arrival of the transport crew and transfer of the patient).

In order to avoid delay, the physician requesting transport could be provided the opt-out option when initially requesting the transport. Providing the referring physician the opt-out option could be an important feature for transports originating from regional or out-of-state hospitals and could influence the referring provider's willingness to participate in randomization. An additional step to address possible concerns about delay in transfer would be to randomize the patient at the time of the referral call and provide an estimated time-of-arrival if the patient is randomized to ground transport, thus providing the referring provider the ability to opt-out of the study and choose air transport.

Review of the criteria for waiver or alteration of consent¹⁹ supports the conclusion that this protocol would meet the strict criteria for acceptable waiver of consent. Challenges remain with varying interpretations of the criteria between IRBs, and more specifically between experienced high-volume IRBs versus low-volume IRBs. Consistent interpretation, review, and approval of emergency research protocols like the proposed randomized trial can be achieved through changes in policy and governing bodies' guidelines.

Policy

While we have focused our discussion here on a hypothetical study, the arguments presented illustrate the deeper issues related to the short-comings of the current research regulatory system. At present, the framework for protection of human subjects draws a distinct line between research and quality improvement initiatives. Health services research, such as the hypothetical project discussed here, has been viewed as “research” and regulated in the same manner as classic clinical trials. Quality improvement, on the other hand, receives no standard oversight and is not subject to federal regulation.

As health care systems have adopted a progressively stronger orientation towards becoming “learning environments,” there has been growing recognition of the need to reconsider how best to assure ethical conduct in investigations designed primarily to improve systems of care. There is ongoing debate about the precise boundaries between research and quality improvement and where health services fits. Nevertheless, there is general consensus that the current regulatory system presents barriers that impede careful evaluation of organizational systems of care, while providing inadequate protection of patients from well-intended but risky changes in clinical and management systems^{32–34}. In the example discussed here, failure to rigorously evaluate the effects of ground versus air transport for non-urgent transfers has the potential to continue to expose patients to unrecognized risks and contributes to rising healthcare costs.

In 2011 the Department of Health and Human Services initiated the Advance Notice of Proposed Rulemaking process for the *Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators (ANPRM)*³⁵. The ANPRM contains recommendations to update the definitions of what qualifies as research and to also create less burdensome review processes. The public commenting period has ended and comments are available for viewing online^{36,37}. Currently the ANPRM has not progressed past the public comment period.

The recommendations for streamlining IRB review contained in the ANPRM could move us forward in meeting our duty to continuously examine and improve processes of care, while providing adequate protection of patient rights and patient safety. Most of these include some provision for developing a system of oversight designed around the typical characteristics of quality improvement and health services research, rather than stemming from the framework of traditional clinical trials. Developing this alternative system requires explicit recognition of the obligations of both providers and patients to contribute to the common good of improved health care delivery, thoughtful balancing of the principles of beneficence and autonomy, and precise examination of risks.

As described here, our hypothetical study would not expose patients to any known increase in risks, is consistent with the current standard of care, continues to allow choice of both patient and physician through the opt-out mechanism, and involves no deception. It thus poses no added risk and preserves an appropriate level of autonomy. In addition, the study addresses an important aspect of care and has the potential to contribute to significant improvement in cost and effectiveness of transport services for patients. However, requiring

that the study meet the current standard of informed consent would make the study non-feasible.

Conclusion

The current regulatory system provides significant barriers to the conduct of investigation of care processes, such as transport methods. We suggest that revisions to the current regulatory oversight policies could be incorporated to facilitate needed research while protecting patient rights. The transport community must play an active role in developing policy that specifically addresses and enhances the conduct of ethical research in transport settings.

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