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Commentary

May I have your consent? Informed consent in clinical trials – feasibility in emergency situations

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Abstract

Clinical researchers in acute emergency settings are commonly faced with the difficulty of satisfying the conventional ethical requirement of obtaining informed consent, whilst ensuring a representative group of patients is recruited into studies. We discuss our own experience in addressing institutional ethical requirements to obtain informed consent in a multi-centre trial, recruiting highly agitated patients in the emergency setting in Melbourne, Australia. We suggest that, through the application of existing ethical and legal frameworks and pre-emptive communication with the key stakeholders in ethics committees, hospital insurers and legal representatives, a balance can be struck between ethical and legal requirements on the one hand, and the integrity of the research question, on the other.

Keywords

Consent; psychiatric emergency; emergency

'A 33-year-old male, of average build, is brought into the Emergency Department (ED) by police. He is severely agitated, aggressive, is threatening staff and kicking doors. An internal hospital alert is called and security staff are mobilised. De-escalation measures have failed and you see an urgent need for chemical restraint (drug sedation) to reduce the risk of harm to the patient or others. The need for sedation deems the patient eligible for inclusion into a clinical trial which compares several drug alternatives in this setting. Before proceeding with immediate study drug administration, what are the issues relating to informed consent? The patient is clearly incompetent to consent and no next of kin or legal representative is available. How can consent be obtained in these circumstances?'

This vignette outlines a typical scenario we have been faced with in the conduct of a study currently underway in three EDs across Melbourne, Australia. The study aims to assess

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the efficacy of sedating agent regimens, with the primary outcome being the time taken to achieve adequate sedation. Simply excluding all such patients would severely compromise our study both in terms of the number of patients recruited and the generalisability of the sample. It would become biased towards those less severely ill. In anticipation of such scenarios, we engaged in pre-emptive discussions with local institutional research ethics committees and legal representatives regarding how to work within their frameworks to deliver the imperatives of this study. This paper describes that process and outlines some clinical scenarios we have faced in the conduct of the study thus far. However, first, we expand on the context in which the study is being conducted.

ACUTELY AGITATED PATIENTS IN THE ED SETTING

Highly agitated patients are unable to make informed decisions regarding treatment options or informed consent for participation in clinical research. Accordingly, the value of consent obtained from such patients is questionable. Furthermore, consent obtained under such conditions may be similar to involuntary submission (Lewin et al. 2006). Other investigators evaluating treatments for acute agitation have also acknowledged the difficulty in obtaining meaningful and truly informed consent prior to enrolment into the study (Damsa et al. 2008; Nobay et al. 2004; Martel et al. 2005; Knott et al. 2006; TREC Collaborative Group, 2003).

One approach to dealing with this has been to take consent from the patient after the intervention has been instituted. This provides patients with an opportunity to withdraw (as is their right), data are then destroyed and the patient is excluded from analyses. However, difficulties arise with obtaining patient consent post enrolment in studies such as ours, as a considerable proportion of patients with underlying mental illness may need to be sedated for extended periods after their ED visit. They may be transferred to an acute psychiatric unit or another institution prior to recovery from sedation or behavioural disturbance. The logistical difficulties in tracing these patients and approaching them at an appropriate time would be considerable or not possible. Patients who are sedated due to the effects of recreational drugs or alcohol are commonly belligerent and uncooperative even upon discharge. It is not uncommon that they leave against medical advice or abscond.

Furthermore, selection bias may still be introduced by failing to obtain consent from patients who, when incapacitated, were randomised and administered the study drugs. Those patients able to provide informed consent are likely less agitated than those unable to provide consent. Secondly, inability to consent and use data already collected on some patients (due to ongoing mental illness, refusal, loss to follow up) would result in additional patients being randomised and administered the study drugs. Consequently, the number of patients randomised may be well in excess of the required sample size. This outcome would be undesirable from the patient perspective and would add cost, logistical difficulties and delays to the study. Indeed, these factors present ethical issues in their own right. Finally, all patients randomised should be included in the analysis under the 'intention to treat' principle. If consent cannot be obtained subsequently, this principle is technically breached and additional selection bias may be introduced.

An alternative to 'post hoc' consent is to approach a family member to act as a surrogate for decision making. This approach has been sanctioned and has a place in certain research scenarios (American Medical Association, unpub. report, 2004: http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion8081.shtml). However, again, there are logistical difficulties in obtaining informed consent from family members or other 'responsible persons' prior to sedation, in a study such as ours. The greatest barrier is their lack of availability at the time an emergency intervention (i.e. rapid sedation) is required. Also, there is the possibility that the patient may blame the family member for having 'given' consent to such an intervention, on their behalf.

RESOLVING THE REQUIREMENTS FOR INFORMED CONSENT

There is no single strategy for managing the process of obtaining emergency consent, due to variability in hospital and institutional ethics committees' policies, and local legislation. The issues surrounding informed consent are complex and specific. Fortunately, there is provision for waiver of consent in such circumstances. However, this process can be protracted, and requires consultation amongst all key stakeholders including the study principal investigator, study site investigators, hospital staff members involved in the study, institutional ethics committees, hospital insurers and legal representatives. There is potential for patient and public involvement in the design of such clinical studies to help investigators improve the study methodology and protocol development. Such studies may be better accepted by participants regardless of their capacity to provide informed consent at the time of entry into the trial. This might serve to minimise the potential for bias, secondary to the subsequent withdrawal of patient consent.

In terms of our study, we decided proactively to engage the aforementioned stakeholders from all the participating sites, early in the study design and ethical application process. After the initial institutional ethics application, a meeting was convened with the chair of the institutional ethics committee, a representative of the hospital, a lawyer representing the hospital insurers and the study investigators. At this meeting, the inherent difficulties of obtaining informed consent from this particular patient group, the medical condition and study design were discussed with respect to the feasibility of obtaining informed consent pre- or post-sedation, either from the patient themselves or a legal representative. At the conclusion of the meeting, all parties were satisfied that the local legislation (The Victorian Guardianship and Administration Act 1986) satisfactorily covered the absence of patient consent for the purpose of this study. This decision was accepted by the institutional ethics committees of all participating institutions, and ethical approval was granted. Specifically, the Human Research Ethics Committee (HREC) consulted section 4.4.6 of the National Statement on Ethical Conduct in Human Research (National Health and Medical Research Council et al. 2007) in their deliberations and was satisfied that the conditions for waiver of consent were met. The National Statement (2007) acknowledges that 'in emergency care research, recruitment into a research project often has to be achieved rapidly...' and states that '...consent for the research may be waived provided the conditions of paragraph 2.3.6 (page 24) are satisfied.' A set of nine conditions are outlined under paragraph 2.3.6, one of which is that HREC must be satisfied that 'it is impracticable to obtain consent (for example, due to...accessibility...)' (National Health and Medical Research Council et al. 2007).

While specific legislation or national statements on human research will differ depending on the location of practice and research, the process of prompt identification of the key stakeholders in resolving consent issues and the arrangement of meetings can be generally applied in different practice settings. Through prompt proactive engagement of stakeholders, much time was saved in extensive electronic communication, delays in waiting for replies and responding to requests for clarifications. In our experience, this was critical in achieving an efficient outcome for all parties. Given the complexity of this issue, every effort should be undertaken to convene a meeting with all stakeholders in attendance. It also provides an opportunity to discuss and examine existing acts and regulations, which may be a challenge to interpret.

EXISTING LEGAL AND ETHICAL FRAMEWORKS

The enrolment of such patients into clinical research is governed by medical ethics, state and federal legislation. The World Medical Association Declaration of Helsinki (2008), the European Directive on clinical trials (European Parliament, 2001) and the Nuffield Council documents on bioethics suggest that

non-consenting patients are permitted in trials on two grounds: where no other context exists in which to answer the question and where all trial participants get clear therapeutic benefit from whichever arm they are randomised to (Huf et al. 2002). The World Medical Association Declaration of Helsinki (2008) offers provisions for studies to proceed even when informed consent is not provided by the patient or a legally authorised representative, given that the reasons for involving subjects with a condition that renders them unable to give informed consent is stated in the research protocol and is approved by the institutional research ethics committee.

With respect to the management of behavioural disturbance, there are variations in mental health legislation between the US, UK, Australia and New Zealand. However, the respect for individual autonomy and the use of least restrictive management practices is consistent amongst all legislation (Phillips et al. 2009). Such legislation allows provisions for the admission, assessment and treatment of people unable to make medical treatment decisions for various reasons to avoid posing danger to themselves or others.

EDs provide an easy entry point for people with mental health problems, including those temporarily incapacitated due to external factors including intoxication of drugs and alcohol, and situational crisis. Generally, under all Australian and New Zealand mental health acts, doctors are empowered by legislation to detain a mentally ill or incapacitated person who is in need of assessment and treatment. (Phillips et al. 2009).

In Australia, each state is governed by state mental health legislation. Specifically, in Victoria, Australia, the legal requirements for the emergency medical treatment of such patients is set out in Section 42A of the Guardianship and Administration Act 1986 (Vic) (GAA), where 'a registered practitioner may carry out... treatment on a patient without consent...if the practitioner believes on reasonable grounds that the treatment is necessary, as a matter of urgency...to save the patient's life; or to prevent serious damage to the patient's health'. The provision for the recruitment of patients who lack the capacity to provide informed consent for the purposes of medical research, are set out in Section 42E of the GAA. Within the GAA, a 'medical research procedure' is defined as 'a procedure carried out for the purposes of medical research, including, as part of a clinical trial, the administration of medication or the use of equipment or a device'. Studies that satisfy this definition may be acceptable in the absence of informed consent. However, this would depend on individual and locally specific circumstances.

SUMMARY AND CONCLUSIONS

Medical ethical documents and legislation are in place to protect individuals and provide guidance to conduct clinical research. Current medical ethical statements provide some provision for clinical research to proceed without prior patient consent. However, these should be interpreted alongside legislation that is relevant to the study-site(s) and applied to support study protocols and institutional ethical submissions. Early facilitation of meetings with key stakeholders is important to ensure an understanding of study intentions and to resolve any queries surrounding informed consent for the specific patient group under study. This will lead to more speedy ethical approvals and improve the efficiency of clinical research in such settings. There are regulations which permit waiver of informed consent in specific circumstances in the United States, Canada and Australia (Largent et al. 2010). However, researchers should be aware, that whilst patients may lack the capacity to provide informed consent to participate in research, this does not mean that such patients may be automatically recruited into clinical studies. Investigators must be familiar with the legislation that offers provisions to proceed with their research prior to obtaining patient consent.

In conclusion, whilst resolving the need for informed consent in an emergency clinical research setting can be challenging, satisfactory resolution that respects ethical and legal considerations is possible.

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