

Clinical trials without consent: some experiments simply cannot be done

Michael C Kennedy

THREE ARTICLES in the Christmas issue of the Journal,¹⁻³ responding to media coverage of a proposed clinical trial,⁴ failed to address the objections raised to conducting the trial without patient consent. The proposed trial, the *Royal North Shore (RNSH) and Ambulance Regional Study of a Stenting Strategy as an Alternative to Lytic/Medical Therapy in Acute Myocardial Infarction (RARE SALAMI)*, was to be conducted in Sydney's Northern Area Health Service. The aim was to compare two regimens of management of patients with acute myocardial infarction and determine whether, despite some additional transit time, diverting ambulances past local hospitals (where patients would receive thrombolytic treatment) and on to the services at RNSH (where patients would be treated with percutaneous coronary intervention) would be beneficial to patients (Box 1).¹ The trial would involve the ambulance service, RNSH and the emergency departments of four district hospitals within the health area. Senior medical staff from two of the emergency departments were among those who expressed concerns in the media reports.⁴

Diversions from standard treatment

Inherent in the trial were a number of diversions from standard treatment and procedures. These included contravening the standard advice provided to the community regarding emergency cardiac care — to attend the nearest hospital emergency department as quickly as possible; interference in established therapeutic networks and ongoing therapeutic relationships, including relationships with hospitals; and, most importantly, delays in time to treatment.

Delays in time to treatment were to be caused by:

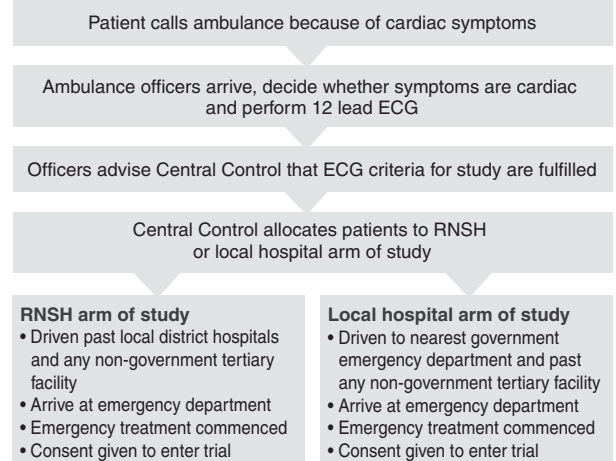
- Performing a resting 12-lead electrocardiogram (ECG) at the point of ambulance pick-up of patients with cardiac symptoms for the purpose of the selection and allocation of trial subjects;
- Informing the allocating person at the ambulance control centre of the computer report of the ECG and awaiting randomisation;
- Transport of subjects randomised to the experimental group past hospitals with facilities for thrombolytic treatment and a private tertiary hospital providing acute invasive cardiac procedures, thereby adding up to about 40 km of suburban roads to the emergency dash.

Manly Non-Invasive Cardiac Laboratory, Manly, NSW.

Michael C Kennedy, MD, FRACP, Consultant Physician; and Research Associate, Department of Clinical Pharmacology, St Vincent's Hospital, Darlinghurst.

Reprints: Dr Michael C Kennedy, Manly Non-Invasive Cardiac Laboratory, Level 4, 22 Darley Road, Manly, NSW 2095. drmkenn@ozemail.com.au

1: Proposed sequence of events for a trial to compare two regimens of management for acute myocardial infarction



RNSH = Royal North Shore Hospital.

- Adding uncontrolled clinical variables (eg, intercurrent illnesses) and location difficulties caused by heavy traffic at peak periods, a lift bridge and intermittent road closures due to environmental hazards (eg, low-level flooding, bushfires).

Opposition to the trial

It was evident from all the *MJA* articles that many people within the profession and in the community opposed the trial. There are several reasons for this opposition, including:

- local geographical issues of transport and the present distribution of health services;
- issues of risk and inconvenience for patients;
- methodological issues such as experimental design, rationale and execution of the trial; and
- no provision for meaningful consent before entry into the trial.¹⁻⁴

Despite this opposition, at the time of the media investigation the trial was about to be implemented. Members of the community and hospital and ambulance staff not wanting to be involved in the trial were about to be included. Indeed, in the period between the media reports and the Christmas issue of the *MJA*, one metropolitan council included in the trial area formally documented its view in relation to the proposed trial and conveyed this to the relevant ethics committee.⁵ The following motion was carried unanimously:

Council opposes the conducting of medical trials on any member of the community without their full informed consent — this particularly applies in the treatment of cardiac conditions.

Patient consent

In the *MJA* articles it was proposed that “ethics committees (can) assume the responsibility of giving consent on behalf of patients”,¹ and that, “almost by definition, people in the midst of life-threatening medical emergencies, who may be unconscious, in shock, in extreme pain or delirious, surrender their normal sentient ability to consent”.² However, this denies one of the cornerstones of medical ethics — the patient’s right to self-determination.

This is not to say that clinical trials should be discarded. Experimenting on patients, often in the form of a clinical trial, is an essential element of evaluating drugs and therapeutic innovations. Patients are patients because they present for and need treatment. They are entitled to a treatment that is tried and true — in this case, standard rescue protocols for myocardial infarction — and, unless otherwise indicated, they must reasonably trust that that is what they are getting. Accordingly, medical staff and, in this case, ambulance personnel are obliged to provide such care. Service organisations and clinician-researchers may experience tension between their obligation to provide a certain type of treatment and the need to divert from accepted standards for research purposes.

Fortunately, there are guidelines to ease this tension and to chart the correct course of action. The Nuremberg Code of 1947⁶ is the modern forerunner of these guidelines. It has the appeal of being a simple 10-point code and, until 1964, when the World Medical Association (WMO) produced its first set of guidelines (the Declaration of Helsinki), was the only code of its kind. Subsequently, there have been revisions of the WMO’s Declaration⁷ and the development of various national codes, including the Australian National Health and Medical Research Council (NHMRC) statement on research involving humans. The NHMRC’s 1999 National Statement⁸ is currently the primary guide to clinical research in Australia. As with other guides, it emphasises the importance of fully informed consent and sets out the circumstances in which patients can be included in clinical trials without their knowledge or consent.

Criteria for proceeding without consent

Consent is reviewed in considerable detail in the NHMRC Statement on Ethical Conduct in Research Involving Humans.⁸ Statements relating to areas where consent is either waived or considered not necessary appear in paragraphs 1.11, 6.9, 14.4, 15.8, 16.13 and 17.1 and 17.2. Paragraphs 14.4, 15.8 and 16.13 relate to identifiable data, tissue samples and genetic issues. Interestingly, even in survey-type activities where consent is not required, Part 17 ensures there should be no element of deception. Part 6 considers emergencies, intensive care, terminal care, those with impaired capacity for communication, those highly

2: Summary of National Health and Medical Research Council guidelines for research without consent

Paragraph 1.7

If a participant lacks competence to consent, a person with lawful authority is provided with the information and exercises that choice.

Paragraph 6.9

When conformity to the principle of consent (paragraph 1.7) is not feasible, and neither the participant nor the individual’s representative can give consent in advance, a Human Research Ethics Committee may approve a research project without prior consent provided the proposal

- (a) is not contrary to the patient’s interest;
- (b) does not place the patient at any more risk than that which is inherent in the patient’s condition;
- (c) is based on a valid hypothesis; and
- (d) the patient, the patient’s relatives and legal representatives will be informed as soon as possible and given the choice to continue the experiment or withdraw the patient.

3: Summary of FDA Guidelines for research without consent

1. Life-threatening situation, available treatments unproven or unsatisfactory and an experiment, including the use of placebo, is needed to answer the question.
2. Consent not feasible because (a) of the medical condition, (b) it must be administered before an authorised person can give consent, (c) it is not possible to identify subjects before the condition occurs.
3. Subjects may benefit because (a) they are in a life-threatening situation, (b) animal or preclinical studies show the potential for benefit, (c) the risks are reasonable allowing for what is known about the condition.
4. The study could not be conducted without a waiver.
5. The time window for the experimental intervention is defined and during this time the investigator is committed to finding the subject’s duly authorised representative rather than proceeding without consent.
6. Community consultation before the study to explain risks and expected benefits.
7. Public disclosure of the results.
8. Independent monitoring of the results.
9. The subjects (or their representatives) are informed as soon as possible as to their inclusion in the study.

dependent on care, and the unconscious (see summary in Box 2). In relation to emergency situations, the vulnerability of patients and relatives is acknowledged, as is the inability to obtain consent. When research may produce a “. . . reduction of potential benefits”, Part 6.9 gives specific guidance, stating that the research should not be contrary to the patient’s interests; must be based on valid scientific hypotheses; must ensure that the patient/relatives are able to give consent or withdraw the patient from the research as soon as reasonably possible; and, most importantly, must ensure that there is no increased risk to the individual. Leeway has been allowed for proceeding with experimental techniques without consent when a number of the conditions are met. The essence of these can be summarised as follows:

- The choice is between essentially no treatment and experimental treatment;
- The experimental treatment offers the chance of benefit and no greater harm; and
- There are reasonable grounds for assuming that the patient would consent if he or she were able to.

Similar leeway has been allowed by the Food and Drug Administration (FDA) in the United States. The FDA undertook review of this area in response to concerns expressed by researchers that “. . . current rules are making high quality acute care research difficult or impossible to carry out when the need for such research is increasingly recognized”. As a result, regulation 50.24 became effective in 1996.⁹ These guidelines are summarised in Box 3.

While institutional ethics committees may interpret the FDA guidelines differently for specific treatments,¹⁰ the circumstances that allow waiver of consent in emergency situations are similar to those outlined by the NHMRC. They include proceeding with acute resuscitation that is experimental at the time of a cardiac arrest when standard treatment has failed; trialling the acute use of a neuroprotective agent when a patient arrives in the emergency department in a deeply comatose state; or, as recently reported, the administration of standard anticonvulsants by ambulance personnel.¹¹

Will patients be harmed?

The downside of any clinical experiment is that the hypotheses may turn out to be wrong and patients may be harmed. The *RARE SALAMI* trial requires delaying accepted efficacious cardiac treatment in emergency situations in which there is a very high mortality rate in the first hours. The hypothesis that no harm will be done to the patients is put forward in one of the articles as a foregone conclusion,¹ but doctors with a working knowledge of local practicalities of the catchment area were clearly not convinced by these arguments,⁴ and neither were the intended research subjects, their representatives and statutory authorities, who were moved to formalise concerns.^{1,5} Such situations are succinctly covered in the Nuremberg Code. Point 5 states:

No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

Conclusions

Komesaroff is correct in stating that this imbroglia provides several important lessons about process.³ In addition, it is a reminder of the need to guard against confusing “consent to treatment” with “consent to research”, and to avoid distorting what the guidelines say. This applies particularly to what the NHMRC National Statement says about consent for research in persons highly dependent on medical care. Finally, it is most important to remember what calling an ambulance is all about.

With regard to consent, the trial cannot be imposed on an unwilling community and unwilling doctors. It should not proceed until the following conditions are met:

1. At the community level

- There is factual agreement between the researchers and the community as to the time delays involved;
- There is broad agreement within the profession as to the risk to patients;
- There is agreement between researchers and the local community, including local general practitioners and specialists, as to the disruptions that would be caused by the trial;
- Arrangements are in place to detect and make good any harms caused; and
- The community agrees that the benefits of the project to their community are worth the costs to the community.

2. At the level of individual research subjects

- All persons in the communities involved with the trial have been informed of the details of the proposal, including the risks and benefits to research subjects, by means of mailing and public meetings, and their comprehension of the information has been established by a survey; and
- There are provisions for opting out and confirmation of informed consent at the point of first contact by ambulance personnel.

This is informed consent in action. Without it, some experiments simply cannot be done.

Acknowledgements

The author wishes to thank the four *MJA* reviewers and Judith Kennedy for helpful suggestions.

References

1. Rasmussen HH, Hansen PS, Koyama Y, et al. Trial of a trial by media. *Med J Aust* 2001; 175: 625-628.
2. Chapman S. Media milking of sacred cows: a heart-stopping tale. *Med J Aust* 2001; 175: 629.
3. Komesaroff, PA. Clinical research in the emergency setting: the role of ethics committees. *Med J Aust* 2001; 175: 630-631.
4. Ryle G. A trial of the heart. *Sydney Morning Herald* 2001; 29 March: 11.
5. Pittwater Council. Mayoral minute. July 2, 2001.
6. The Nuremberg Code (1947). *BMJ* 1996; 313: 1448.
7. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. October 2000. Available at: http://www.wma.net/e/policy/17-c_e.html (accessed June 2002).
8. National Statement on Ethical Conduct in Research Involving Humans. Available at: <http://www.health.gov.au/nhmrc/publications/humans/contents.htm> (accessed June 2002).
9. Department of Health and Human Services. Food and Drug Administration Office of the Secretary. 21 CFR Part 50, et al. 45 CFR Part 46. Protection of human subjects and waiver of informed consent requirements in certain emergency research; Final rules: 51497-51531. *Federal Register (FR)*, 61 FR 51498, October 2, 1996.
10. Silverman H, Chandros S, Sugerman J. Variability among institutional review boards' decisions within the context of a multicenter trial. *Crit Care Med* 2001; 29: 235-241.
11. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med* 2001; 345: 631-637.

(Received 9 Jan, accepted 3 Apr 2002)

□