Involving patients in enrolment decisions for acute myocardial infarction trials

Seriously ill patients requiring emergency treatment are unlikely to be able to give full informed consent for a clinical trial, but Neal W Dickert and Franklin G Miller argue that this does not mean that they shouldn’t be involved in enrolment decisions at all.

Neal W Dickert assistant professor 1 2, Franklin G Miller senior faculty member 3

1 Department of Medicine, Emory University School of Medicine, Atlanta, GA 30322, USA; 2 Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta; 3 Department of Bioethics, National Institutes of Health, Bethesda, MD, USA

Controversy over informed consent for clinical trials in acute ST elevation myocardial infarction (STEMI) has existed for over 30 years.1–3 How can a patient with dyspnoea and angina in need of emergency percutaneous coronary intervention possibly make an informed, considered decision about whether to enrol in a clinical trial? Some authors have argued that seeking consent for research in this context is not only impracticable but unethical.4 Nevertheless, it has remained standard practice to ask STEMI patients or surrogates to consent to enrolment in trials. The recent Unfractionated Heparin versus Bivalirudin in Primary Percutaneous Coronary Intervention (HEAT-PPCI) trial, in which patients were randomised without prospective consent, has forced a re-examination of this long simmering question.5–7 This discussion is particularly timely given the growing emphasis on pragmatic comparative effectiveness trials that integrate clinical care and research. We contend that the principle of respect for persons supports involving patients in enrolment decisions for trials, even when trials pose few risks and patients cannot give valid consent.

Consent related challenges in emergency care research

Prospective informed consent is a general ethical requirement for most clinical research, but research in acute illness must sometimes be conducted without it. For example, most countries and international guidelines permit waiving consent for clinical trials in conditions like cardiac arrest and traumatic brain injury, when patients are unconscious and surrogates cannot provide consent within an appropriate timeframe.5 The creation of regulatory frameworks to accommodate these situations is an important ethical achievement and has facilitated substantial progress in treating severely ill patients. The challenge in trials for STEMI and many other illnesses is that patients are typically conscious and not sufficiently impaired to preclude all involvement in enrolment decisions. At the same time, randomisation must take place within minutes of arrival at hospital. These are highly stressful circumstances and many patients have severe symptoms.

In response to these challenges, HEAT-PPCI investigators employed a “deferred consent” strategy. Patients were not consulted about the initial enrolment and randomisation decision regarding choice of anticoagulant but were asked later to give consent for collection of follow-up data. The central arguments for using this approach were that prospective consent would have been invalid, would have delayed treatment and enrolment, and was unnecessary because both trial arms used approved treatments and posed no risks beyond standard practice.5 6 These issues require a nuanced analysis that focuses on the potential reasons for involving patients in enrolment decisions in the first place, including respect. The optimal approach must also be driven by robust evidence about patients’ preferences and expectations.

Respecting patients

Consent in STEMI research has not been extensively studied, but several studies have shown that patients’ understanding of trial details is often poor and that patients confuse medical care with trial enrolment.10–12 These challenges are well known in many research contexts. Interestingly, most data suggest that patients still feel that they are able to participate in enrolment decisions, prefer to be consulted rather than having decisions made for them.10 11–13 Typical rates of refusal in STEMI trials are not well described, but in several recent studies, 10–15% of patients declined enrolment.14–16 Their reasons for refusal are not known. These refusal rates are far lower than for most clinical trials but are higher than the exceedingly low rate of “deferred consent” in HEAT-PPCI. In that trial only four of 1829 enrolled patients were reported to have refused or withdrawn deferred consent. This suggests that the trial probably enrolled some patients who...
would have declined if offered the opportunity. Because the decision to provide consent for follow-up data collection is fundamentally different from that for prospective consent to randomised treatment assignment, the fact that few enrolled patients declined to provide deferred consent cannot be considered to indicate acceptance of initial enrolment. The term deferred consent is unfortunate in this respect because it invites conflation of decisions made before and after enrolment. Available data thus support the claim that valuable ethical goals may be advanced by patient involvement that constitutes less than valid informed consent. Most concretely, involving patients prospectively offers them some opportunity to decline enrolment. Although clinical treatment can sometimes be legitimately provided against incapacitated patients’ objections if it is in their best medical interests, refusals to participate in research should generally be respected regardless of how well informed the patient may be. Participation in clinical trials is generally not obligatory, and in most cases, patients are not enrolled unless they, or their surrogate, are capacitated and agree to give consent. Two other respect driven goals may be advanced by patient involvement in enrolment decisions. Firstly, upfront disclosure provides transparency. This can potentially enhance the trust of patients and the public and may prevent patients from feeling “duped” into enrolment. Secondly, even when valid informed consent may be impossible, some involvement in enrolment decisions may make patients feel that they were treated in a caring manner and that their dignity was appreciated. These concerns are important in the context of serious acute illness. Little is known about what strategies best advance these goals or meet patients’ expectations in trials of emergency treatment. However, there is no basis for presuming that not involving them prospectively is the only ethical solution, as has been suggested. Instead, we need to explore limited and context specific ways to involve patients in enrolment decisions.

Risk is only part of the issue

One function of consent is to justify exposing patients to risks arising from the study. Valid consent allows people to authorise those risks and helps to ensure that acceptance of those risks is consistent with their values and goals. Some comparative effectiveness trials, however, pose no risks to patients beyond the risks of standard clinical care. Does it follow that soliciting prospective consent for research is unnecessary in such studies? A central premise of the argument against prospective consent in HEAT-PPCI has been the absence of research risk. Patients were randomised between two approved anticoagulants; it is not normal clinical practice to tell them which of these medications they receive, and patients had no reason to prefer one medication over the other. These features would make a compelling case for waiving prospective consent if it were not possible for patients to have any involvement in the enrolment decision. However, the absence of research risks (or presence of very low risks) does not negate the potential ethical advantages of patient involvement described above, particularly for advancing respect. Additionally, if involvement is meaningful in low risk trials, it is even more important when interventions under evaluation pose larger risks or when major differences exist between treatment arms (such as trials comparing procedural with medical interventions).

Methods for limited involvement

There remains an important practical question. How can investigators involve patients prospectively while randomising them within minutes of arrival? Several strategies could be pursued. One option is the informed refusal approach, in which limited information is provided about the key features of a study. This approach may be represented by the common practice of using highly abbreviated consent forms and scripts. Whether this strategy is practical within the time constraints of a trial in STEMI patients is uncertain, but other partial involvement strategies have been described. The TASTE-MI trial, for example, used a simple oral consent script. Similarly, in the IMMEDIATE trial, a pre-hospital trial of glucose-insulin-potassium versus placebo in STEMI, patients who were clearly incapacitated were not enrolled, and eligible patients were read a brief script by paramedics which allowed them to decline enrolment. Their assent was considered to be sufficient for initial randomisation. Finally, a strategy that may be particularly appropriate in low risk comparative effectiveness trials is a simple opt-out process, whereby eligible patients are told of the study and that they will be enrolled unless they wish to be excluded. The box gives an example of an opt-out script for HEAT-PPCI that would have taken less than a minute to read.

Some patients and populations in STEMI trials will not be able to be meaningfully involved in decisions. For example, many patients who have had a cardiac arrest or are in severe cardiogenic shock have profound cognitive impairment. In these circumstances, surrogate decision makers may play a role in enrolment decisions, although many time and stress related limitations to consent apply to surrogates as well as patients. There are also circumstances when conducting valuable research is impossible with prospective consent, and severely ill patients should not be arbitrarily excluded from enrolment when studies are examining important questions for their management. This is the purpose of regulations allowing exceptions from consent for research in emergency settings. Our argument here is simply that involvement in enrolment decisions, when possible, should be facilitated and should match patients’ expectations and preferences.

Need for evidence

We have argued that respect for persons provides good reasons to involve STEMI patients in enrolment decisions, even when this falls short of valid consent. We have also argued that limited strategies may accomplish some ethical goals without delaying enrolment or treatment. However, there are no data on the effect of any of these processes on patients’ actual decisions or experiences. The ideal strategy should be driven by evidence and not speculation. Do patients actually prefer to be involved? Do they prefer opt-in or opt-out processes? What is the effect on enrolment rates? What pieces of information are critical to patients who would want to refuse? And do patients think differently about participation in comparative effectiveness trials than they do about trials of new drugs? Answering these questions is essential to develop strategies that meet the needs of both patients and researchers. This can be done by embedding ethics studies within trials in STEMI and similar conditions in order to assess whether different strategies cohere with patients’ expectations and express respect to patients. Information from such studies can then be used to provide guidance on how best to involve patients in these decisions. Such guidance is currently lacking within national and international guidelines and
regulations for trials in which there are unavoidable barriers to informed consent but do not meet the criteria for waiving consent.\(^2\)\(^{22}\)

We conclude that abandoning all prospective patient involvement in STEMI trials and similar situations is premature, may not best meet the demands of respect for persons, and is not the only solution. Rather, we must reframe patient involvement to advance achievable goals while acknowledging its limitations.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare NWD receives research salary support from the Greenwall Foundation Faculty Scholars Program. FGM worked on this manuscript while he was an employee of the National Institutes of Health. The opinions expressed are the views of the authors and do not necessarily reflect the policy of the National Institutes of Health, the Public Health Service, or the US Department of Health and Human Services.

Contributors and sources: ND is a cardiologist and bioethicist. FM is a bioethicist. Both authors have a longstanding interest in the ethics of clinical research and informed consent. Both authors participated in the conception of this project, and both authors contributed to the literature review. NWD took primary responsibility for initial drafting of the manuscript. Both authors contributed to editing of the manuscript and preparation for submission.

Provenance and peer review: Commissioned; not externally peer reviewed.

---

1 Smith HL. Myocardial infarction—case studies of ethics in the consent situation. Soc Sci Med 1974;8:399-404.
2 Tognoni G, Geraci E. Approaches to informed consent. Control Clin Trials 1997;18:621-7; discussion 61-6.
3 Gammelgaard A. Informed consent in acute myocardial infarction research. J Med Philos 2004;29:417-34.
4 Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;1:397-402.
5 Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single-centre, randomised controlled trial. Lancet 2014;384:1846-58.
6 Shaw D. HEAT-PPCI sheds light on consent in pragmatic trials. Lancet 2014;384:1826-7.
7 Wood S. HEAT-PPCI: Heparin beats bivalirudin in STEMI, amid heated debate. Heartwire 2014 Apr 1.www.medscape.com/viewarticle/822927.
8 Van Belle G, Mentzelopoulos SD, Aufderheide T, May S, Nichol G. International variation in policies and practices related to informed consent in acute cardiovascular research: results from a 44 country survey. Resuscitation 2015;91:76-83.
9 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.
10 Gammelgaard A, Mortensen OS, Rossel P. Patients’ perceptions of informed consent in acute myocardial infarction research: a questionnaire based survey of the consent process in the DANAMI-2 trial. Heart 2004;90:1124-8.
11 Gammelgaard A, Rossel P, Mortensen O. DANAMI-2 Investigators. Patients’ perceptions of informed consent in acute myocardial infarction research: a Danish study. Soc Sci Med 2004;58:2315-24.
12 Williams BF, French JK, White HD. Informed consent during the clinical emergency of acute myocardial infarction (HERO-2 consent substudy): a prospective observational study. Lancet 2003;361:918-22.
13 Dickert NW, Fehr AE, Lianos A, Sickluna VM, Samady H. Patients’ views of consent for research enrollment during acute myocardial infarction. Acute Cardiac Care 2015;17:1-4.
14 Frisvård O, Lapidot B, Olveronika GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med 2013;369:1587-97.
15 Selker HP, Beshansky JR, Sheehan PR, et al. Out of hospital administration of intravenous glucose-insulin-potassium in patients with suspected acute coronary syndromes: the IMMEDIATE randomized controlled trial. JAMA 2012;307:1925-33.
16 Thiele H, Zeymer U, Neumann FJ, et al. Intracoronary balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012;366:1287-96.
17 Levine RJ. Deferred consent. Control Clin Trials 1991;12:546-50; discussion 51-2.
18 Dickert NW, Kass NE. Understanding respect: learning from patients. J Med Ethics 2009;35:419-23.
19 Kass N, Faden R, Tunis S. Addressing low-risk comparative effectiveness research in proposed changes to US federal regulations governing research. JAMA 2012;307:1589-90.
20 Kim SY, Miller FG. Informed consent for pragmatic trials—the integrated consent model. N Engl J Med 2014;370:765-72.
21 Dickert NW, Lianos A, Samady H. Re-visiting consent for clinical research on acute myocardial infarction and other emergent conditions. Prog Cardiovasc Dis 2012;55:251-7.
22 Department of Health and Human Services. Code of Federal Regulations. Title 45: public welfare. Part 46: protection of human subjects. 2009. www.hhs.gov/ohrp/policy/ohrpregulations.pdf.

Accepted: 11 June 2015

Cite this as: BMJ 2015;351:h3791

© BMJ Publishing Group Ltd 2015
Summary points

- Informed consent is difficult to obtain in clinical trials for STEMI and other acute conditions.
- Nevertheless, involving patients in enrolment decisions may advance important respect related ethical goals.
- Several methods exist to allow patients some say over whether enrolment occurs.
- Research is needed to determine what processes most effectively meet patients’ goals and needs.