

# Premature stopping and informed consent in AMI trials

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Clinical trials give rise to ethical dilemmas, especially in the acutely ill, but we take issue with two points raised in a recent comment on a specific acute myocardial infarction (AMI) trial. The commentators judged that the trial most likely could, and therefore should, have been terminated much earlier. By analysing the problem statistically we arrive at results that go against their intuitive judgment—they also see it as mandatory to update the patient information sheet as trial results accrue and trends begin to emerge. In our view, interpreting subtle trends and borderline *p*-values must rest with data monitoring boards, not patients. Moreover, patients with AMI or in other medical emergencies need very simple instructions. Empirical studies of the consent process confirm that the idea of a genuinely informed consent is problematic in such cases.

In their “coalface” comment,<sup>1</sup> Fernando Verdú-Pascual and Ana Castelló-Ponce (V&C) bring up the eternal theme of “randomised clinical trials [being] a source of ethical dilemmas”. One can only agree. They focus on two issues, on which we shall comment in turn: early termination of promising trials, and informed consent in acute myocardial infarction (AMI) trials.

The trial that prompted their comment compared immediate angioplasty with thrombolytic treatment for AMI, enrolling 220 cases over a period of five years.<sup>2</sup> Verdú-Pascual and Castelló-Ponce observe that it may be inadmissible to continue a trial if early results point to a clear cut therapeutic benefit, and they feel that, in the angioplasty report, the results are such that “we can suppose that after studying half the sample, the results already pointed towards significant differences between the two treatments”. *But is that really so?*

In-hospital death was the primary endpoint and is also the endpoint that came out significant: three patients died out of 109 in the angioplasty group against 12 out of 111 on thrombolysis. Quoting always one-sided *p*-values to avoid ambiguity, we obtain  $p = 1.8\%$  (as  $z = 2.103$ ,  $\chi^2 = z^2 = 4.42$  on one degree of freedom; or by Fisher's test); multiply by two to obtain the customary two-sided *p*.

Now, halfway into a trial, each count is roughly one half its final value. It is easy to see that the  $\chi^2$  is then also one half its final value (or slightly smaller). In the present case that implies:  $z = 2.103/\sqrt{2} = 1.49$  (or slightly smaller), leading to a *p* as high as 6.9% (or slightly larger). One may, in fact, calculate the exact chance that a significant trend was present midway, say after recruitment of 55 patients to each arm, under the usual assumption that matters do not change during the study. With a serial numbering of the case records in the angioplasty file, any of the 109 positions is then as likely as any other to hold one of the three deaths. Similarly for the thrombolysis file. By examining the  $4 \times 13 = 52$  possible data sets, ranging from (0,0) [all deaths occurred later on] to (three, 12) [all deaths in the first half], and subjecting each data set to Fisher's test, we find that the chance of non-significance ( $p > 0.025$ ) is 86%, and the chance of *p* exceeding 0.05 is 70%. There is thus a good-majority chance that the midway data would *not* have led to a verdict in favour of angioplasty—which is contrary to what V&C suspected.

If, instead, one focuses on six months survival, the difference turns out to be non-significant, emphasising, in another way, the importance of not closing one's eyes too hastily in science.

Undeniably, the concern about undue continuation of trials is a genuine ethical concern. It is a matter of altruism (what sacrifice are THEY entitled to expect from ME?) in the context of uncertainty and uncertainty-reducing research, a topic which one of us once tried to develop in a formal model.<sup>3</sup> In the trial cited, however, the trends are too weak to spark such concerns.

Incidentally, there does exist a class of techniques for orderly discontinuation of trials; textbooks discuss them under keywords such as “sequential trial” and “interim analysis”. On the other hand, one should never stop a trial just because right now—after 77 or 117 cases—the results look convincing: the statistical risk of arriving at erratic conclusions will rise and get out of control.

Turning to informed consent, V&C doubt that it is morally right not to inform potential research subjects about the preliminary trends of a trial. As the proper evaluation requires both statistical and medical expertise, however, the assessment of whether or not it is safe to join a trial should rest with the data and safety monitoring board, which is there precisely to protect patients from undue risks. It seems to be a misguided homage to autonomy to involve patients in such intricacies—and all the more so in relation to AMI patients, because the emergency circumstances call for brief, simple and clear information. The *p*-value game does not belong in the emergency ward.

Moreover, V&C are concerned about the prospect of obtaining valid consent from patients in an imminent life-endangering situation. This important issue has been addressed empirically in the AMI context.<sup>4–8</sup> These studies indicate that due to pain, anxiety, sedatives and lack of time the informed consent in AMI trials is indeed less informed than in non-emergency trials. Thus, the essential ethical issues in relation to informed consent in AMI research concern 1) the fact that patients who participate in AMI trials consent (or decline) on the basis of a limited comprehension of the trial, and 2) whether it is acceptable at all to involve patients in a consent process in the emergency situation. If the debate about the ethics of AMI research is to be advanced,

patients' experiences with the consent process in such trials need to be studied in more detail.

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