importance of the objective is in proportion to the inherent risk to the participant. Delayed treatment of acute mania is associated with considerable acute and long-term morbidity from both illness and its secondary consequences (Post, 2000). Randomising a patient with acute mania to the placebo arm of a 3-week trial leads to considerable delay in treatment.

In this trial 145 patients with acute mania were assigned to the placebo arm. We consider it unethical and inhumane to treat 145 patients with acute mania with placebo. All future trials concerning the efficacy of a medication for acute mania should use an arm with one of the proven medications as a comparator and not include a placebo arm.

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World Medical Association (1989) *World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects*. http://www.fda.gov/oc/health/helsinki89.html

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Authors' reply: Dr Srinivasan *et al* are in error when they state that this trial (Khanna *et al*, 2005) could not have been conducted in a high-income country. Johnson & Johnson conducted this trial in India at the same time as two trials in other countries (including the USA) as part of a global effort to obtain registration for risperidone monotherapy in bipolar mania. (Hirschfeld *et al*, 2004; Smulevich *et al*, 2005). Quality investigators and sites were chosen and approval from research ethics boards and participant consent were obtained at each site.

We categorically reject the implication that a clinical trial in India is medically inferior or ethically suspect. The investigators and sites in India were comparable in scientific quality and adherence to ethical guidelines to their peers globally. Any suggestion to the contrary is unwarranted, and fosters prejudice by creating a distorted perception of Indian clinical scientists and centres of research.

Below are our responses to the other questions raised by Dr Srinivasan *et al*:

> Why was a placebo used?

Placebo-controlled trials expose the lowest number of patients to a potentially ineffective (new) treatment, while also providing valid data on adverse events attributable to the treatment.

> How did patients give their informed consent during an episode of acute mania?

In this study, patients or a family member provided informed consent as required in the protocol. Patients with psychiatric illness, including mania, can give informed consent: capacity to consent or withhold consent is not automatically lost because of illness.

> Where were the trial sites? Who were the participants? What were the adverse events? How were seven patients from the placebo group lost to follow-up?

The study was conducted at eight sites in India, as reported in the *Journal* article (page 229); participants were those experiencing an acute exacerbation of symptoms of mania and are described in Table 1 (page 231); adverse events are reported on pages 232–233; as in all clinical trials, a few participants could not be contacted at follow-up. In this study, 3% of participants were lost to follow-up, which is in line with previous studies of mania (Sachs *et al*, 2002; Yatham *et al*, 2003).

> Was the wash-out period medically and morally justified?

Stable patients who were responsive to their current medication were not enrolled in this trial. Patients who were enrolled were symptomatic despite their current medication (suggesting that they were not responsive to the treatment) or because they had spontaneously discontinued medication. In order to successfully assess the trial medication, it was necessary that they discontinue their current suboptimally effective medication. This is scientifically and ethically justifiable.

> Do the authors who are not drug company employees have any competing interest to declare?

The two authors who were not Johnson & Johnson employees had no conflict of interest related to this study.

> Was the trial conducted according to the Declaration of Helsinki? Why did the authors cite the 1989 revision of the Declaration and not a more recent revision?

The trial was conducted in accordance with the principles originating in the Declaration of Helsinki. Reference to the 1989 version of the document was made since this was a commonly cited version at the time the study preparations were underway (1999–2000).

Drs Murtagh and Murphy refer to 'serious shortcomings' in our report. These are said to include omitting crucial details of the process of randomisation, interrater reliability and masking. In addition, 'the most worrying aspect of the trial was the use of a placebo in the control group and apparent absence of any ethical approval to proceed with this study'.

There were no such 'shortcomings' in the trial itself but not all methods were detailed in our report. On page 229, we wrote, 'Randomisation was stratified by the presence or absence of psychotic features at baseline, manic or mixed episode, and by treatment centre. After randomisation and the initiation of treatment (baseline), patients remained in hospital for at least 7 days'. On page 230, we wrote, 'Investigators were trained in the use of each of these instruments and certification was required for those administering the YMRS'. Furthermore, page 229 states, 'Signed informed consent was obtained for all participants and the study was conducted according to the *Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects*, in the 1989 version of the Declaration of Helsinki'. The study had the approval of national and local research ethics boards. These are standard descriptions of such procedures and are similar to those provided in many published reports of clinical trials.

A placebo control was necessary to establish the effects of medication because people with mania manifest response to placebo which is of variable magnitude. The true efficacy of risperidone in this trial was incontrovertibly established over and above the effects observed with placebo.

Similarly, the safety of risperidone can only be appropriately assessed in the context of adverse events in the placebo arm. Furthermore, patients could be withdrawn from the study and treated in an open-label

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manner at any time. The appropriate use of placebos in clinical trials for bipolar disorder has recently been reviewed by Vieta & Carné (2005), who point out that the regulatory agencies (Food and Drug Administration, European Agency for the Evolution of Medical Products) and consumer associations support their use to ensure that ineffective drugs are not authorised for this condition.

Basil *et al* question why data from a site that was withdrawn because of concerns about data quality were included in the safety analyses. It is a conventional procedure in clinical trials to omit efficacy data but not safety data from such sites. They also question the 'legitimacy' of the informed consent obtained from the patients. It is our experience that patients with severe illness are capable of giving their informed consent to participate in a trial. Capacity to consent is not automatically lost because of a symptom score on the Young Mania Rating Scale.

Basil *et al* question the ethics of including a placebo arm in the trial. A placebo group was included because patients with mania generally show a high and variable placebo response, making it difficult to identify their responses to an active medication. Placebo-controlled trials are valuable in that they expose the fewest patients to potentially ineffective treatments. In addition, inclusion of a placebo arm allows a valid evaluation of adverse events attributable to treatment *v.* those independent of treatment. For these reasons, regulatory agencies (Food and Drug Administration, European Agency for the Evaluation of Medicinal Products) and the consumer associations support the use of placebo controls (Vieta & Carné, 2005).

Most (83%) of the placebo patients had been receiving treatment for bipolar disorder for at least 30 days before being hospitalised for the treatment of severe acute mania. This indicated that their current treatments were not adequately treating their symptoms and illness. Thus, as expected, a high response to placebo was shown by these patients. Significant improvements *v.* baseline were seen on each of the efficacy measures in patients receiving placebo or risperidone. For example, improvements in YMRS total scores at week 3 end-point were −10.5 (s.e.=1.3) in patients receiving placebo and −22.7 (s.e.=1.1) in patients receiving risperidone ($P<0.001$ *v.* baseline in both groups). The proportion of placebo patients whose severity of illness (Clinical Global Impression scale) was rated as 'not ill', 'mild', or 'very mild' increased from 1% at baseline to over one-third (37%) at end-point (the increase was from 0% to 72% in the risperidone group).

Declaration of interest

B.L., F.G., M.E. and M.K. are employees of Johnson & Johnson Pharmaceutical Research and Development, which supported the study.

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Editor's reply: We thank our correspondents for pointing out an important issue that we need to address more assiduously in our reviews of papers. We agree fully that the *British Journal of Psychiatry* needs to ensure that a greater policy of openness towards low- and middle-income countries is not accompanied by any lowering of ethical standards.

However, there are clear divisions of opinion here. When the protagonists for each of these make their eloquent arguments, it may seem strange that any should remain rather uncomfortably on a rickety fence when the alternative certainties are so much more inviting. Well, we are still wobbling because we feel it is right to wobble. The two sides of this argument, put crudely, are (a) it is unethical to exploit patients in low-income countries for studies that would never be allowed to proceed in rich countries, and (b) research performed for a global scientific community has to provide general evidence, not specific to one group or country, and so worldwide efficacy studies are necessary.

Drs Murtagh & Murphy, Basil *et al*, and Srinivasan *et al* all allege, directly or indirectly, that the patients in India have been selectively exploited for research purposes and this is fundamentally unethical. Patel (2006) also asks whether there is a personal financial aspect to the trial that has been undeclared. The allegation that 'this trial could not have been conducted in a high-income country but may have been conducted in India because regulatory requirements could be fulfilled there' (Srinavasan *et al*) is a serious charge.

However, the case for the trial is also strong. Although Basil and his colleagues suggest that 'all future trials concerning the efficacy of a medication for acute mania should use an arm with one of the proven medications as a comparator', regulatory bodies such as the Food and Drug Administration insist on at least two placebo-controlled studies that demonstrate superiority of the index drug over placebo in order to get a licence approved. Although one may criticise the Administration for this requirement, it is scientifically unimpeachable and is a general one for drug treatments. A very similar trial has also been carried out in the USA in which risperidone was also compared with placebo treatment (Hirschfeld *et al*, 2004) (and which should have been disclosed with the paper of Khanna *et al*, 2005). The findings suggest that when risperidone is licensed for the treatment of mania it is possible to argue that both these positive trials represent an advance in patient care. A subsidiary argument, a practical one not always well-received in ethical circles, is that participation in a research study can, and should be, a proper and ethical way of providing good patient care, exemplified by the recent comments of Phillips *et al*

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