to measure Bill's height first, then visit Bob and measure his height, and then compare the two heights. Instead of learning the difference in height directly you learn the absolute height of each and use that to compare.

Which method is better? The back to back comparison eliminates some possible errors because you have both subjects under observation at once (which allows easier control of time of day, posture, and so on) and it requires you only to measure accurately the difference in height, which is less subject to measurement error than measuring each individual's height. On the other hand, measuring each individual's height gives more information than just measuring the difference. For example, from just the difference you could not say whether either Bill or Bob was tall.

But suppose that Bill and Bob are not in the same place and you lack an accurate measuring device. You might be able to say that either Bill or Bob is tall, but you are unlikely to know each of their heights with enough precision to know who is taller. This situation—an indirect comparison—is the one we usually face when we conduct placebo controlled trials. One might think that a placebo comparison, like a measuring tape, enables you to measure efficacy against a meaningful zero point. Thus if two treatments are both compared with placebo we know their efficacies both absolutely and relatively, just like knowing the absolute heights of Bill and Bob. This assertion is correct in principle but not in practice.

Placebo controlled studies are usually designed to find out only whether a new treatment is significantly better than placebo. Because the placebo effect is usually considerably different from that of an effective treatment a study does not have to be very large to find a significant difference. As a result, we may be able to say that the treatment beats placebo, but we can say little about how efficacious it is—that is, our estimate of its effect will have a wide confidence interval. The result is not like measuring height with a measuring tape: it is more like a hazy visual assessment of height that can conclude only that someone is short or tall.

To estimate comparative efficacy or to show equivalence there is no escape from designing studies that are much larger than the usual placebo controlled studies. We could either have large placebo comparison studies or omit the placebo group and have comparative trials of just the two effective treatments.

It is fortunate that we can assess comparative efficacy without placebos because when an efficacious treatment already exists it is unethical to assign placebo treatment to patients.⁵ Doing so violates the ethical principle of equipoise, a state of uncertainty regarding which of the treatments studied is better.⁶ Without equipoise any therapeutic trial is unethical, and if equipoise is lost during a trial we must stop the trial for ethical reasons.

Equipoise does not suffice, however. The Declaration of Helsinki states, "In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method."⁷ Allegiance to using placebos has apparently prompted some writers to criticise the Declaration of Helsinki, which may be interpreted as precluding the study of any new treatment.^{2, 8} After all, how can a treatment be the best proved method if it needs to be studied? The answer is that equipoise between the new treatment and the existing treatment makes it ethical. But assigning a placebo is unethical unless placebo is thought to be as good a treatment as exists.

If we adhere to these ethical guidelines placebo controlled trials should become infrequent as medical knowledge accumulates. Then the scientific method of comparing active treatments against one another will be essential to understand. Towards that end Jones *et al*, their homage to placebo controls notwithstanding, have contributed a lucid description of the principles behind equivalence trials.³

KENNETH J ROTHMAN
Professor of public health

Section of Public Medicine and Department of Epidemiology,
Boston University School of Medicine,
Boston, MA 02118, USA

1 Hill AB. Medical ethics and controlled trials. *BMJ* 1963;i:1043-9.

2 Collier J. Confusion over use of placebos in clinical trials. Better guidelines needed. *BMJ* 1995;311:821-2.

3 Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to show equivalence. *BMJ* 1996;313:36-9.

4 Turner JA, Deyo RA, Leiser JD, Von Korff M, Fordyce WE. The importance of placebo effects in pain treatment and research. *JAMA* 1994;271:1609-14.

5 Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *N Engl J Med* 1994;331:394-8.

6 Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987;317:141-5.

7 World Medical Association. Declaration of Helsinki IV. In: Annas GJ, Grodin MA, eds. *The Nazi doctors and the Nuremberg Code: human rights in human experimentation*. Oxford: Oxford University Press, 1992:339-42.

8 Lasagna L. The Helsinki Declaration: timeless guide or irrelevant anachronism? *J Clin Psychopharmacol* 1995;15:96-8.

Measuring diastolic blood pressure in pregnancy

Use the fifth Korotkoff sound

The measurement of diastolic blood pressure during pregnancy offers plenty of scope for error. Most people still use a mercury sphygmomanometer, with all the pitfalls that are familiar outside obstetrics—"white coat" hypertension, digit preference, cuff size, differences between arms, and poorly calibrated equipment. To these should be added the influence of posture and gestation in a pregnant woman, so any advance in getting it right is to be welcomed. There is now good evidence to support using the fifth Korotkoff sound when measuring diastolic blood pressure in pregnancy.

Although measuring blood pressure and detecting hypertension remain at the core of antenatal monitoring, there has long been uncertainty about whether to record diastolic pressure as the point when the sounds muffle (Korotkoff phase IV) or when they disappear (phase V). The World Health Organisation recommends the use of phase IV,¹ while phase V is advised in a consensus report from the United States National Heart, Lung, and Blood Institute.² Phase V is closer to "real" diastolic blood pressure as recorded intra-arterially in pregnancy³ and is routinely

used outside pregnancy.⁴ However, it has been argued that phase V is not suitable for use during pregnancy because in many women the sounds never disappear.⁵ This assertion now seems to be unfounded. In a prospective study of 1194 nulliparous women blood pressure was measured five times at each of five different gestation times between 20 weeks and delivery.⁶ Among the more than 25 000 readings in the sitting position, Korotkoff phase V was unobtainable in just three. The discrepancy between this finding and the earlier claims of frequent failure to obtain a phase V reading may well be a consequence of difference in technique: pressing the stethoscope diaphragm tightly on to the brachial artery will lead to a very low diastolic blood pressure being recorded.

Measurement of phase IV presents real problems of reproducibility. Diastolic blood pressure was recorded by two observers in a total of 556 readings in 58 women (42 hypertensive and 16 normotensive) at various stages of pregnancy.⁷ The observers agreed on the presence of muffling in less than a third of cases and both found it harder to identify

phase IV in the hypertensive women than in the normotensive women. The question of reproducibility has now been rigorously assessed, with pairs of observers sitting in separate booths but using a shared cuff.⁸ The first part of the study involved two pairs of research staff each making 340 measurements from 85 pregnant women with a wide range of blood pressures. The fifth Korotkoff sound was heard simultaneously on every measurement, was never lower than 40 mm Hg, and readings were in agreement to within 5 mm Hg in 86% of cases. In contrast, the fourth sound was identified simultaneously in only a fifth of readings, and overall agreement within 5 mm Hg occurred in only 16% of cases. In the second part of the study five pairs of clinical staff undertook the same simultaneous recording in 80 pregnant women with the same dismal outcome for Korotkoff phase IV, which was heard by both observers in only 16% of cases, compared with 100% for phase V with no reading below 40 mm Hg.⁸

There seems little reason to continue the policy of using phase IV diastolic blood pressure in pregnancy when phase V is easier to obtain, more reproducible, and closer to intra-arterial pressure. The reading should be taken with the woman sitting quietly, using a cuff of appropriate size, and with the stethoscope diaphragm applied lightly to the arm. Blood pressure should be recorded to the nearest 2 mm Hg.

Having accurately determined the diastolic blood pressure, the next step is to interpret its prognostic importance. The watershed of 90 mm Hg is more than two standard deviations

from the mean throughout gestation,⁹ but it has its limitations. Such a reading may be of little importance in a woman with mild essential hypertension, yet it may signal dangerous hypertension in someone who began pregnancy with a diastolic pressure of 50 mm Hg. The diastolic blood pressure in pregnancy should therefore be seen in the overall medical and obstetric context of the individual woman.

PETER RUBIN
Professor

Department of Medicine,
University Hospital,
Queen's Medical Centre,
Nottingham NG7 2UH

- 1 WHO Study Group. *The hypertensive disorders of pregnancy*. Geneva: World Health Organisation, 1987: 1-114. (Technical Report Series 758.)
- 2 Lindheimer MD. Hypertension in pregnancy. *Hypertension* 1993;22:127-37.
- 3 Brown MA, Reiter L, Smith B, Buddle ML, Morris R, Whitworth JA. Measuring blood pressure in pregnant women: a comparison of direct and indirect methods. *Am J Obstet Gynecol* 1994;171:661-7.
- 4 Petrie JC, O'Brien ET, Littler WA, de Swiet M. Recommendations on blood pressure measurement. *BMJ* 1986;293:611-5.
- 5 MacGillivray I, Rose GA, Rowe B. Blood pressure survey in pregnancy. *Clin Sci* 1969;37:395-407.
- 6 Lopez MC, Belizan JM, Villar J, Bergel E. The measurement of diastolic blood pressure during pregnancy: which Korotkoff phase should be used? *Am J Obstet Gynecol* 1994;170:574-8.
- 7 Blank SG, Helseth G, Pickering TG, Wast JE, August P. How should diastolic blood pressure be defined during pregnancy? *Hypertension* 1994;24:234-40.
- 8 Shennan A, Gupta G, Halligan A, Taylor DJ, de Swiet M. Lack of reproducibility in pregnancy of Korotkoff phase IV as measured by mercury sphygmomanometer. *Lancet* 1996;347:139-42.
- 9 Stone P, Cook D, Hutton J, Purdie G, Murray H, Harcourt LNA. Measurement of blood pressure, oedema and proteinuria in a pregnant population in New Zealand. *Aust N Z J Obstet Gynaecol* 1995;35:32-7.

Misdiagnosing the persistent vegetative state

NEP 13

An apparently high rate of misdiagnosis demands critical review and action

Diagnosing the persistent vegetative state is important and sometimes difficult. Patients who retain some degree of awareness must be recognised if their quality of life is to be maximised and inappropriate withdrawal of tube feeding prevented. On p 13 Keith Andrews and colleagues present a retrospective study of the clinical records of 40 patients admitted over three years to a single unit specialising in the rehabilitation of patients with profound brain damage.¹ The authors conclude that 17 of these patients were misdiagnosed. Patients in the persistent vegetative state seem to be awake with their eyes open but show no evidence of awareness, but the 17 misdiagnosed patients were able to communicate consistently using eye pointing or a touch sensitive buzzer. Such an apparently high rate of misdiagnosis raises important concerns about the accuracy of the diagnosis of the vegetative state and related syndromes of severe brain damage.¹ It also demands a critical review of the study's methods.

One important question is whether the sample of patients is representative. This seems unlikely since, as the authors point out, their unit is the only one in Britain specialising in the management of this group of patients. It is also important to distinguish late recovery from late discovery of consciousness. Patients who start regaining consciousness several months after the injury (late recoveries) should not be confused with patients who may have been conscious for some time before the discovery (late discoveries). The authors state that none of the misdiagnosed patients were vegetative at the time of admission, but it is not clear how such a conclusion can be reached with certainty, especially when 10 of the 17 misdiagnosed patients were admitted to the unit less than 12 months after injury.

Another question is whether the methods used to identify awareness were valid. In my experience rehabilitation units often develop "unique" ways of communicating with patients that only they can master. If the "touch sensitive buzzer switch system" is as useful and reproducible as this article suggests, it should be made available to other rehabilitation units, which in turn should be able to reproduce these authors' results. Video-tapes of the buzzer in operation would help to demonstrate to others the usefulness and reproducibility of this system. Until such validation occurs, I must view the buzzer system with some scepticism.

Diagnosing the persistent vegetative state can be aided by neurodiagnostic tests such as computed tomography, magnetic resonance imaging, electroencephalography, and positron emission tomography. These could have helped to explain why some patients had such severe motor impairment as to appear unconscious. In particular, they could help to distinguish the persistent vegetative state from the locked in syndrome, in which patients are severely motor impaired but have relatively normal consciousness. Such patients would be likely to have minimal cerebral cortical atrophy on computed tomography and magnetic resonance imaging, and positron emission tomography would show nearly normal cerebral cortical metabolism of glucose and oxygen (or at least much higher than in patients in a vegetative state). Both the multi-society task force on the vegetative state in the United States^{2,3} and the working group of the Royal College of Physicians in Britain⁴ stated that these neurodiagnostic studies have some use in the diagnosis. It is unfortunate that Andrews *et al* did not make use of them.