tion any of this when directly asked by the panel; he did not add this to his evidence later, as he did with other material; and none of this input was acknowledged in the published paper in *Pediatrics*.[2]

We specifically reject the suggestion that our comments about the nursing input were a slur. The nursing sister involved said that she had never undertaken research before the trial and had received limited support. She was accompanied by her husband and a professional representative when she gave evidence, and we expressed in our report considerable sympathy for her position.

We specifically referred to research on issues of recall and were only too well aware of the risk that some of the witnesses may have been pursuing their own agenda, but this does not mean that all parents are wrong and all researchers are right. It means that a governance framework must be in place so that everyone can have confidence, whatever their recall.

It is not in our view desirable or appropriate to debate through this journal all of the points that have been made; much of the matter is still sub judice with the trust and the GMC. We consider our job to be done and will not engage in further debate. The report is a Department of Health report, and that department will be dealing with any further issues arising from it.

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For and against

Clinical equipoise and not the uncertainty principle is the moral underpinning of the randomised controlled trial

The ethical basis for entering patients in randomised controlled trials is under debate. Some doctors espouse the uncertainty principle whereby randomisation to treatment is acceptable when an individual doctor is genuinely unsure which treatment is best for a patient. Others believe that clinical equipoise, reflecting collective professional uncertainty over treatment, is the soundest ethical criterion. Here doctors from two Canadian centres discuss their positions.

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FOR On what ethical grounds may a physician offer trial participation to his or her patient? The answer seems to depend greatly on which side of the Atlantic you reside. In the United Kingdom, the uncertainty principle is widely endorsed.[1 2] However, in North America, clinical equipoise—reflecting collective uncertainty—is the dominant ethical basis.[3] Which of these principles offers the preferred moral underpinning for the randomised controlled trial?

It is widely acknowledged that physicians have a primary duty to promote their patients' welfare. When physicians become investigators, however, other ends such as recruiting enough subjects and retaining them in the trial may conflict with this duty.[4] How can the physician maintain fidelity to the patient and further the ends of a randomised controlled trial? The uncertainty principle offers an appealing solution to this problem.

Uncertainty principle

Physicians who are convinced that one treatment is better than another for a particular patient cannot ethically choose at random which treatment to give, they must do what they think best for the patient. For this reason, physicians who feel they already know the answer cannot enter their patients into a trial. If they think, whether for a wise or silly reason, that they know the answer before the trial starts, they should not enter any patients.[2]

On the other hand, if the physician is uncertain about which treatment is best for a patient, offering the patient randomisation to equally preferred treatments is acceptable and does not violate his or her duty. The uncertainty principle has been successfully used as a key eligibility criterion for large, simple trials.[1 5 6]

But is the uncertainty principle a solid moral basis for the randomised controlled trial? We think not. Under the uncertainty principle it would be difficult, if not impossible, to conclude that a physician ever errs in enrolling a patient in a trial. So long as the physician claims he or she was uncertain, even if madly or incompetently so, he or she cannot be said to be wrong. Recent articles on the uncertainty principle have added "reasonably" and "substantially" to qualify uncertainty.[1 6] But who decides what counts as reasonable or substantial uncertainty? If it is the individual physician—and the uncertainty principle certainly maintains that the proper normative locus for decision making is the individual physician—we are left with the same problem.

Clinical equipoise

Clinical equipoise, on the other hand, recognises explicitly that it is not the individual physician but the community of physicians that establishes standards of practice. According to Freedman, the

> ethics of medical practice grant no ethical or normative meaning to a treatment preference, however powerful, that is based on a hunch or anything less than evidence publicly presented and convincing to the clinical community.

Persons are licensed as physicians after they demonstrate the acquisition of this professionally validated knowledge, not after they reveal a superior capacity for guessing.[3]

Competent medical practice is defined widely as that which falls within the bounds of standard of care—that is, practice endorsed by at least a respectable minority of expert practitioners. The innovation of clinical equipoise is the recognition that study treatments, be they the experimental or control treatments, are potentially consistent with this standard of care. Thus, a physician, consistent with his or her duty to the patient, may offer trial enrolment when there "exists … an honest, professional disagreement among expert clinicians about the preferred treatment."[3]

Clinical equipoise may arise in several ways. Evidence may emerge from early clinical studies that a new treatment offers advantages over standard treatment. Alternatively, there may be a split within the clinical community, with some physicians preferring one treatment and other physicians preferring another. This last scenario is well documented in the published report and calls for a randomised controlled trial to settle which is the better treatment.[7] Clinical equipoise does, however, permit these important randomised controlled trials. It would have physicians respect the fact that "their less favoured treatment is preferred by colleagues whom they consider to be responsible and competent."[3]

Convincing results

The second part of clinical equipoise states: "the trial must be designed in such a way as to make it reasonable to expect that, if it is successfully concluded, clinical equipoise will be disturbed. In other words, the results of a successful trial should be convincing enough to resolve the dispute among clinicians."[3] Clinical equipoise, therefore, generally requires a trial design that will "compare two treatments under the conditions in which they would be applied in practice [and] answer the question—which of the two treatments should we prefer?"[8] In short, clinical equipoise supports a pragmatic approach to the design of randomised controlled trials.

Clinical equipoise … recognises explicitly that it is not the individual physician but the community of physicians that establishes standards of practice

Simplicity

The implications of this are just beginning to be explored. It has already been argued that some trials have too many eligibility criteria, are insufficiently generalisable to the patient population at large, and fail to compare new drugs to best available standard treatment.[9 10 11] Questions related to the determination of sample size and the interim analysis have yet to be explored using the lens of clinical equipoise. For instance, must randomised controlled trials be designed to ensure convincing negative as well as positive results? Might clinical equipoise provide a sound moral basis for decisions to stop trials early? While questions remain, it is already clear that clinical equipoise will lead randomised controlled trial design in the direction of larger, simpler trials.—Charles Weijer, Stanley Shapiro, Kathleen Cranley Glass

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AGAINST Uncertainty on the part of all participants is the principle, moral and practical, required to justify ethically a randomised controlled trial. According to Freedman: "The ethics of clinical research requires equipoise, a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in the trial."[1] But humans have preferences. Equipoise, with its etymological connotation of an equal balance between or among the alternatives to be tested, is a theoretical ideal, almost always impossible to achieve in practice. Freedman recognised that the concept "presents almost insuperable obstacles to the ethical commencement or continuation of a controlled trial." He went on neatly to cut the Gordian knot by rejecting what he called "theoretical equipoise," which he recognised as inherently fragile, difficult to attain, and impossible to maintain, and redefining "clinical equipoise" as a failure of consensus within the clinical community.[1] Thus defined, and thus used by Weijer et al above, "clinical equipoise" is one special case of the

Clinical equipoise [is] a failure of consensus within the clinical community

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uncertainty required to justify a controlled trial. It refers to collective uncertainty among the body of clinicians.

Individual and group morality

Morality, however, is an attribute of individuals as well as of groups. If we grant moral authority to the medical community as a whole, we devalue the responsibility of individual clinicians. Like individuals, the medical community is fallible. While it is often certain, it is not always right, and "certainties" change. Some examples of reversals in my own clinical field of obstetrics include the 19th century belief in the therapeutic value of blood letting and the unwarranted 20th century reliance on pubic shaving and routine enemas for women in labour to reduce the risk of infection.[2 3] It took passionate individuals a long time to shake the complacent collective certainty. Individuals count.

Patient comes first

An ethical physician must do what is best for his or her patients. She cannot participate in a controlled trial if she is certain that one arm is superior to the others and that some of her patients will receive an inferior treatment by participating in the trial. It does not matter whether her certainty is based on formal scientific studies, on personal experience, on anecdote, on tacit understanding, or rules of thumb.[4–6] Whether her certainty is in accord with or diverges from the view of the medical community is irrelevant. Uncertainty is a moral prerequisite for a controlled study. If we know what we should do, we should do it, not study it. Controlled studies are possible and necessary, however, because even though clinicians usually have hunches that one treatment arm is more effective than another, they are often not certain that their hunches are correct. The boundaries (confidence interval) on their hunch may range from much better, through marginally better, down to ineffective, or even frankly harmful. When this is the case "it is time for a trial, and that trial is ethical."[7]

The principle of uncertainty applies even more strongly when it refers to an individual patient, who should not be entered into a trial if any of the treatments that might be allocated would be inappropriate for her.[8] David Sackett illustrates this most poignantly with his confession of the one and only time he felt it necessary to "cheat." Faced with a desperately ill patient, he gave her the treatment that he sincerely and wholeheartedly believed that she needed. His responsibility for the patient's welfare was in direct conflict with his responsibility to the internal validity of the trial. Looking back from the vantage point of today, he justified his action succinctly: "I believe that my action was right in particular, wrong in general." The conflict arose because he "knew" that his patient needed the treatment, and this conviction is just as relevant when it is wrong as when it is right.[8] It could have been avoided if the principle of uncertainty had been incorporated into the trial protocol.

Resolving uncertainty

Herein lies the main lesson. Moral principles are intellectually attractive but ethically deceptive. Sometimes they are in conflict, and sometimes—like all evidence based guidelines—they may not be appropriate. When we are morally certain, we know what to do. When we are uncertain, a controlled trial may help to resolve our uncertainty.—Murray W Enkin

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A memorable patient

A unique case of snake bite

It was one of those midnight calls. My resident called me and said, "Sir, I have a very peculiar case of snake bite. I haven't seen anything like this before."

On reaching the ward, I found a middle aged villager, extremely restless, tachypnoeic, and with his legs and arms jerking intermittently. He had reportedly been bitten by a snake a few hours before. The findings were quite amazing. He was febrile with a temperature of 40°C and a pulse rate of 150/minute. His pupils were dilated, and there was mild local swelling at the bite site.

"What could this be?" I struggled to find the answer to the puzzle. Then, almost unbidden, my pharmacology lecturer's words started ringing in my ears: "As dry as a bone, as mad as a hen, as hot as a hare, and as blind as a bat."

That was how datura (*Datura alba)* poison was described. "That's it."

On inquiry, we found that the patient's relatives had made him drink a preparation made from the locally available datura (known as thorn apple or devil's weed) leaves, which contain atropine as the principal active alkaloid. Their intention was to neutralise the snake venom. The funniest part of the episode was that the snake which had bitten him was not poisonous.

The patient made a complete recovery after a stomach wash and supportive treatment.

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We welcome articles of up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.