So many questions, so few answers

In "An unfinished trip through uncertainties", an article published in 2004 in the *British Medical Journal*, Alessandro Liberati described his own life-threatening illness – multiple myeloma requiring two bone marrow transplantations – and the anguish of not having sound research on which to base decisions on his treatment. He talks to Les Olson on the urgent need for better integration of research and treatment.

Courtesy of Alessandro Liberati

Alessandro Liberati

Alessandro Liberati is associate professor of medical statistics at the Medical School of the University of Modena and Reggio Emilia in Italy. After periods of research in the United States of America at Harvard University and the University of California, Los Angeles, in 1994 he founded the Italian Cochrane Centre, of which he is the director. He collaborates with the Regional Health Care Agency of Emilia Romagna on the organization of research programmes and also serves on national and international research committees. He has had more than 180 papers published in peer-reviewed journal

Q: When you first developed symptoms of multiple myeloma, you were disappointed to find that available research was not very helpful in deciding what to do. One reason you identified for this lack of information was that research is too often driven by academic competition. How can we avoid that?

A: We need to move forward on several fronts. We need to increase awareness of the misalignment between the research that is done and what needs to be done. Few people understand how much waste there is in research – research on questions that have already been answered, research on irrelevant questions, and so on. Those who use research – health practitioners and patients – need to be involved in setting priorities and designing research.

When I had to decide whether to have a second bone-marrow transplant, I found there were four trials that might have answered my questions, but I was forced to make my decision without knowing the results because, although the trials had been completed some time before, they had not been properly published!

This should not happen. I believe that research results must be seen as a public good that belongs to the community – especially patients. Several practical changes are needed: more public funding and so more public control of research, more integration of research into clinical practice, and routine use of all sound research results in everyday practice. Every clinical encounter should be an occasion for contributing, in some way, to new knowledge.

Q: Evidence-based medicine - "the routine use of all sound research results in everyday practice" - has become a standard for medical care in many parts of the world. But guiding treatment by research requires patients to expose themselves to the uncertainties inherent in the statistical nature of research results. How can we help people deal with these uncertainties?

A: This is a difficult question, and there are no universally valid answers. There are lots of uncertainties – about diagnosis, prognosis, the impact of treatment, the effects of illness on everyday life, and so on. Each of us feels differently about these uncertainties, so not only are the answers different for different people, but also different for the same person confronting a range of uncertainties.

A good starting point would be a general appreciation of the central place that uncertainty has in the patient's experience. When I had my first transplant I had to have a long-term catheter placed in a vein. Although this was, objectively, far from the worst thing I experienced, I recall vividly the anguish I felt, simply because of the uncertainty about why and for how long the catheter would be needed.

Q: What can we do for patients for whom research results are not relevant because their disease is rare or they fall outside the common age range?

A: We simply *must* invest in more and better research for these groups. That this will take time and money cannot be an excuse for leaving people to suffer.

Q: You have also identified commercial pressures as a reason why research does not provide the answers patients need. How can we balance commercial pressures with research goals?

A: Commercial research will always leave important questions unanswered, because, for example, people who manufacture drugs will never pay for trials of non-drug treatments. The research agenda is systematically biased by commercial funding. If the research questions you ask are biased, so are the answers. Unfortunately, many members of the medical profession have abandoned the notion that they, rather than pharmaceutical companies, should design research trials. The first GISSI (*Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico* – Italian Group for the Study of Survival in Myocardial Infarction) trial in the early 1980s was designed by doctors, and *then* support was sought: the researchers were the owners of the trial.

Another example of bias is that pharmaceutical companies do few head-to-head comparisons of treatments. Such comparisons are very important for doctors and patients, but the risk is that a new, expensive drug may turn out to be no better – or even worse – than the one to which it is compared. However, last year the US Government allocated US$ 1.1 billion to a new comparative effectiveness research programme to fund this kind of research that companies do not support. Italy also has a funding programme to support non-commercial research on drugs. In running this programme, the Italian Medicines Agency has found that research priorities can only be challenged by guarantees of long-term funding of re-

search infrastructure. Short-term project funding is not sufficient.

Q: Where do a society's values and beliefs fit into evidence-based decision-making?

A: Policy should be informed by evidence, not dictated by it: values and beliefs are an essential part of the decision-making process. The key principle is transparency of decision-making: there is nothing wrong with saying that evidence alone is not enough. This means that more and better research is needed. It also helps to distinguish between broad and narrow areas of policy. For example, if we look at the question of whether we should use nuclear energy for power generation, there are advantages and known risks – such as waste disposal – and there are suspected risks, but balancing the risks and benefits is not a scientific question: it is one of values and preferences. But when it comes to the evaluation of a specific drug, I find it hard to justify going beyond scientific arguments.

Q: What can we offer patients who are not participating in research projects, but for whom the only options are new or unproven treatments?

A: When you have a serious disease for which there are no effective treatments, you want to have a chance and so you are more interested in what might work than in what definitely works. A patient's threshold for accepting that a treatment is worth trying is likely to be lower than the threshold of scientific proof. From a public health perspective, however, we do not want to pay for something that does not work when the money could be used for something that does work.

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We need to acknowledge that "works" is not a value-free term. To return to the example of nuclear energy, it definitely "works" as a way of generating electricity, but that does not mean we are obliged to say it is something we want to use. It is also not a matter of saying that scientists are right about what counts as proof that something "works" and patients are wrong, but of fairly and transparently incorporating their different perspectives in decision-making.

Q: You have said that it is not enough for research to be done: patients have to have access to the results in a form they can use. How might researchers do better when presenting their results to the public?

A: We need to improve how scientists present results, how journalists address the public and how the public assesses what scientists tell them. People need a simple set of questions to ask every time results are presented; patients can ask their doctor these same questions. Scientists should understand that it is unethical to present the results for a treatment as relative risk reductions instead of absolute risk reductions because that misleads people into thinking the results are much better than they really are. ■