Research and practice coming together

The advent of personalized medicine is bringing clinical research and practice closer together

Philip Hunter

In the early days of synthetic drugs, just after the discovery of penicillin, doctors knew very little about pharmaceuticals and simply followed the manufacturer's 'advice' when prescribing them for patients. This made sense in a period when pills were almost worshipped as panaceas for whatever ailment they were supposed to treat. Over time though, clinical experience revealed a more nuanced picture; the efficacy of drugs increasingly had to be balanced against side effects and other factors, including the development of resistance to antibiotics and eventually cost. These factors put the onus on doctors to make appropriate prescriptions, weighing all the information. To do so, it became necessary for doctors to know about both the benefits and side effects of drugs—in other words, to be informed about the results of clinical research. This development led to calls for closer links between clinical research and the medical front line; it also enabled the rise of patient advocacy groups, as well as increasing efforts to involve both general practitioners (GPs) and hospital doctors more closely in clinical trials.

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In Europe, these activities have culminated in a report, *Forward Look Implementation of Medical Research in Clinical Practice*, published in May 2011 by the European Medical Research Councils (EMRC) and the European Science Foundation (ESF; www.esf.org). It is focused in

particular on the flow of information from research to doctors, but its 10 recommendations also include a call for greater patient involvement in improving evidence-based guidelines for clinical trials. Furthermore, the review highlights the issue of reporting bias in clinical trials, which can obscure a realistic picture of the efficacy of a drug compared with its risks. One of the recommendations was therefore to promote rigorous reporting of all clinical studies, whereas another was to "strengthen shared national and international open access databases on protocols, data, reports, systematic reviews and health technology assessment."

The key point of the ESF/EMRC report, however, is that research and medical practice should be brought closer together, according to Liselotte Højgaard from the University of Copenhagen, Denmark, who is also chair of the EMRC and the report. "You should do [clinical] research and practice in the same department, with the same people doing both," Højgaard said. "We now know that research-based patient treatment is best." This coupling of research and practice would ensure that treatment is up-to-date and reflects the latest evidence. "In some cases, the application of medicine both in hospitals and general practice has become out of date, and this will get worse in the age of personalised medicine," Højgaard explained. "I think therefore it is most important that we secure faster feedback and it is a question of those in charge of GPs taking responsibility and ensuring that evidence-based medicine is used." She suggested that Europe as a whole should follow the lead of Scandinavian countries, which have recognized academic medicine as a field of expertise: "In the Nordic countries we have university

professors of general practice, and we have practice doctors who are affiliated with the university and who do research."

Norway, for instance, established the Norwegian Knowledge Centre for Health Services in Oslo dedicated to exchanging information between research and medical practice independently of pharmaceutical companies or any other commercial interest. This is a very important development that should act as a cue for other countries, commented Günter Ollenschläger, head of the German Agency for Quality in Medicine in Cologne, and a board member of the International Society for Evidence-Based Healthcare. "A key bridge between research and medical practice is reliable knowledge transfer, independent from industry," he said, and recommended the establishment of an independent trust centre for knowledge transfer similar to the Norwegian Knowledge Centre. "Such an entity should work in the fields of knowledge appraisal, as well as of production, dissemination, implementation and evaluation of evidence-based guidance for health professionals and the public," he added. Expectations are that such a centre should also develop tools and methods, such as electronic aids for doctors in clinical decision-making, and guidelines to help policy-makers manage the process of knowledge transfer.

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It is important that this process of knowledge transfer is itself properly regulated to ensure that it does not become a source of biased information, according to Frank Rockhold, senior vice president for global clinical safety and pharmacovigilance at GlaxoSmithKline (GSK), one of the largest manufacturers of pharmaceuticals and vaccines. "There should certainly be a drive to make medical research and publications an important influence over the practice of medicine, as long as there is someone, regulators perhaps, who can integrate available information," he said. "No physician or patient should make a decision to use or not use a medication on the basis of a single publication, and the interests of the patient must be the driver."

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Ollenschläger conceded that making knowledge transfer work will bring challenges, because there will always be conflicts of interest between the various parties involved, including researchers, healthcare providers, the pharmaceutical industry and patients through patient advocacy groups. In Europe this could be a task for the ESF, Ollenschläger suggested. "The ESF should be pro-active in promoting the ideas involved in knowledge transfer, especially with respect to its membership. Dealing with the conflicts of interests among their members and its functionaries should become a main issue."

Conflicts of interest are not confined to drug companies, which want to push their own products, thereby emphasizing benefits and downplaying side effects. They can also arise through the desire of medical researchers to pursue fundamental questions that might not be relevant to patients and doctors, according to Sulev Kõks, professor of physiological genomics at the University of Tartu in Estonia. "A problem is that the projects scientists undertake are often too fundamental and have very limited practical relevance," he said. "Scientists should build their projects on more relevant and clinically important questions." This requires a change of mindset among

scientists, but this in turn will not happen unless researchers are more directly and continuously exposed to the medical frontline, Kõks added. It might require not just organizational changes, but also structural modifications to hospitals and research buildings to accommodate interaction between medical practice and research. "The fastest way to achieve this change is to reshape research centers and labs such that scientists and doctors share rooms on an everyday basis," Kõks concluded.

In Estonia, this thinking has led to the formation of the National Centre for Translational and Clinical Research in Tartu. "We also have more specialized activities as well, and the University of Tartu has founded the Centre for Translational Genomics in order to facilitate the implementation of genomics in clinical practice and to implement personalized medicine," Kõks explained. "This centre combines different -omics technologies, that is genomics, proteomics and metabolomics, to give very detailed and complex descriptions of different human pathologies. It provides the input for clinical trials and for decision-making."

Whatever the setting in which they collaborate, researchers and clinicians should not lose sight of the actual clients of clinical research and practice. "Patients are the absent stakeholder in clinical research. Yet their questions are usually timely and appropriate. It would be a great advance to involve them in clinical research design," said Rosa Sicari, from the Consiglio Nazionale delle Ricerche Institute of Clinical Physiology in Pisa, Italy. "I work in a highly patient oriented research center. Patients have always perceived this as bringing added value to their care. They feel more involved if their suggestions are included in project designs."

At the same time, major drug companies such as GSK have also been taking greater account of patients and physicians when designing studies. "We involve expert physicians early in the clinical trial design process to ensure that our clinical trials are relevant and meaningful to clinicians," commented Judith Ng-Cashin, GSK's head of medical excellence and quality in research and development. "We often involve patient advocacy groups early on to ensure relevance for the patients we aim to serve. We are always looking to improve how we engage physicians and patients in this process."

Patient involvement can change not only the focus of medical research, but also the way in which clinical trials are conducted, with potentially profound implications for medical practice. Randomized, controlled, double-blind trials were designed to avoid bias from patients or the doctors involved in a study, but their impersonal nature can discount a vital aspect of healing, which is confidence. This point has been made by a well-known advocate for patient involvement in research, Hazel Thornton from the Department of Health Sciences at the University of Leicester in the UK. She has argued that the focus on the role of chance rather than choice within clinical trials can create negative feelings in patients and thereby affect the outcome significantly. Thornton became involved in patient advocacy when being treated for breast cancer in the early 1990s and was invited to participate in a clinical trial after having a piece of breast tissue removed. The experience led her to conclude that the way such trials were conducted left patients feeling isolated with no treatment plan and faced with having to make a choice over whether to participate or not without any expert guidance. This took away the important therapeutic confidence in the treatment.

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Since then, Thornton has published books on the subject and has been involved in advocacy initiatives, including the James Lind Alliance, a non-profit group established in 2004 to bring together patients, carers and clinicians to identify and prioritize the top 10 'unanswered questions' about the effects of treatments that they think are most important (<http://www.lindalliance.org/>). Thornton argues that patients want to reduce uncertainties in their treatments as far as possible so that they can feel more confident in them.

There are also good clinical reasons for patient involvement in research, exemplified by the example of an AIDS trial in the 1990s. At the time, the drug zidovudine had been recently introduced for treating AIDS, with good evidence of a beneficial effect in patients with advanced disease. The obvious question was whether using

zidovudine earlier in the course of HIV infection might delay disease progression and further improve survival. As a result, trials began in the USA and Europe to test this possibility. The US trial was halted early on when a possible but still uncertain beneficial effect had been found. With the active participation and agreement of patient representatives, the European trial continued until a different conclusion emerged: that zidovudine used early in the course of infection did not seem to confer any benefit, but did elicit unwanted side effects (Concorde Coordinating Committee, 1994). This led to the more appropriate prescription of zidovudine only after AIDS symptoms had started to occur.

Another aspect of clinical trials that has attracted attention from patients and researchers concerns the use of placebo to measure the effectiveness of drugs. Although placebo is important, its use has become excessive in some cases to the detriment of patients, according to Silvio Garattini, founder and director of the Mario Negri Institute for Pharmacological Research in Italy. "You have many cases, let's say in the field of diabetes, where you

have already tested a drug many times in association with another drug. Then that should be the comparator and not the placebo," he said. The point is that when a drug is already well established, any new drug should be tested against that one, rather than giving some patients a placebo without clinical efficacy. "Here I think it is very important that people comply with the Helsinki Declaration [a statement of ethical principles for medical research: www.wma.net], which makes it very clear that you can use the placebo only when you don't have other drugs available," Garattini explained.

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This point is particularly relevant for so-called non-inferiority trials, which are used to test new drugs to treat a condition against which well-proven drugs are already available. "The idea is that it is better to have a few choices than only one, since each drug is not active on every patient," Garattini said. Such new drugs are

tested on the non-inferiority hypothesis, which means demonstrating in clinical trials that they are at least as effective as the existing ones. To do this properly the new drug has to be tested against a placebo in a group of patients suffering from a disease or condition. "If you do a correct study in terms of non-inferiority, you have to use a placebo," Garattini explained. "So you get a group of people obliged to use a placebo when there is already a drug that would be useful for them."

This is an ethical problem that could be resolved by testing the new drugs only in patients who are resistant to the existing ones. In that case, such patients would not be denied an effective drug during the clinical trial and the results would be more relevant because they would identify new drugs shown to work in people who are resistant to existing ones.

Moreover, it requires even more thorough education of patients about risks, benefits and alternatives before they can give informed consent to their participation. Here again, pressure from patient advocacy groups could be effective in ensuring that non-inferiority trials are conducted ethically. The issue is also reflected

indirectly in the ESF/EMRC guidelines, which call for clear evidence on the comparative effectiveness of new drugs and other technologies before approval.

Taken together, the 10 recommendations in the ESF/EMRC report cover all the key points needed to make clinical trials more accountable, effective and reflective of societal needs. Whether they will be properly implemented remains to be seen, with one sticking point being funding in

the current financial climate. A main aspect of the report is to encourage transparency and independent assessment of drugs, which, by definition, requires the creation of public resources that have so far often been provided by the pharmaceutical companies.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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