Clinical trials and "real-world" medicine

Trial evidence best informs real-world medicine when it is relevant to the clinical problem

CONTROLLED CLINICAL TRIALS provide the most reliable evidence of whether treatments are effective, particularly when the effects of treatment are moderate. Without such trials, ineffective treatments or, even worse, harmful interventions may be accepted in medical practice. Yet medical practice is often not based on clinical trial evidence, because the evidence is considered not relevant or does not exist. Real-world medicine must not only consider the effectiveness of specific treatments, but must do so in the context of patients who have multiple problems and who are often already receiving many different treatments in a setting different from that tested in the trial.[1]

Throughout the history of medicine, many treatments have been considered effective until well-controlled trials demonstrated otherwise.[2] Some recent treatments based on observational data that have been discredited by randomised controlled trials include hormone replacement therapy to prevent coronary heart disease events,[3] vitamin supplements to prevent lung cancer[4] or cardiovascular disease events,[5] and arthroscopic surgery for osteoarthritis of the knee.[6] Although data from observational studies may be of value,[7] these data may sometimes suggest a harmful outcome for treatments that are known, from controlled trials, to be effective, such as blood pressure treatment.[7]

Applying trial results to individual patients

Although clinical trial evidence for the introduction and use of new drugs is widely accepted, the "real-world" uptake is often erratic. For patients with coronary heart disease, the merits of statins, angiotensin-converting enzyme (ACE) inhibitors, β-blockers and aspirin are well recognised from clinical trial evidence, yet these treatments are still significantly underused.[8] The gap between evidence and practice is even wider in other areas.

Evidence is an essential part of good medical practice, but it is not the only information needed for clinical decision-making. Real-world medicine may ignore clinical trial evidence if it does not seem relevant to the clinical problem at hand or if the benefit is uncertain. A drug that shrinks a cancer is not necessarily useful unless it also improves the patient's quality of life or prolongs survival. A treatment that lowers blood pressure or cholesterol has value only if these outcomes are translated into meaningfully fewer cardiovascular events, without a penalty of increased adverse effects.

Hence, evidence from trials is most applicable in practice when the design and the outcomes chosen are directly relevant to real patients, the trials are undertaken against a background of standard medical care, patients in trials are broadly representative of patients in the real world, and evidence from trials is integrated with individual patient characteristics for meaningful risk–benefit assessment.

Absolute differences in risk (or numbers needed to treat) are recognised as most relevant to decision making; yet clinical trial results are often reported as changes in relative risk. For example, recent clinical trial results of breast cancer risk in women taking hormone replacement therapy appeared exaggerated if the increased risks were considered in relative rather than absolute terms. Treatment resulted in a 26% relative increase in breast cancer, which equated to an absolute increase of just 0.08% per year.[3] Nevertheless, the relative treatment effect is of value if applied appropriately (by combining it with the individual's baseline risk), providing a better guide to the absolute effect of treatment in specific patient groups.[1]

Participation

Despite the need for high-quality clinical trials, few patients participate in them, even in areas where trials are common. For example, less than 5% of eligible patients participate in most cancer trials[9] and less than 10% in many cardiovascular trials.[10] Low participation rates raise concerns that the results from trials apply only to select groups of patients. Scant participation is not necessarily a problem if patients are representative, but patients in trials are often narrowly selected because of the eligibility criteria, the setting, or the patients agreeing to participate. Strategies such as public

access to ongoing trials through registers and more pragmatic trial designs are needed to maximise participation and ensure treatments are assessed in a variety of settings.

The need for wider use of clinical trials

Whenever a new drug treatment is discovered that has the potential to help many patients, prevailing systems support well-controlled trials addressing effectiveness and safety. Systems to assess new technologies or interventions other than drugs are equally important, yet more challenging and much less developed. Also lacking are sufficient trials of new devices, health service management decisions, and trials in community or Third World settings.

It has been suggested that clinical trials are too expensive, and funding outside the pharmaceutical industry is limited. A randomised clinical trial, evaluating a moderate treatment effect on important clinical outcomes, may cost from $1 million to more than $50 million. However, this cost needs to be put in the context of healthcare generally (more than $50 billion in Australia each year[11]) and the cost of *not* undertaking trials before deciding which treatments to support. The Australian government has recognised the importance of basing funding decisions for new health technologies (through the Pharmaceutical Benefits Advisory Committee and the Medicare Services Advisory Committee) on the best evidence of the effectiveness, safety and cost-effectiveness of each treatment. But funding more research on the cost-effectiveness of new technologies is also warranted. Specific clinical trials in this context may be much more cost-effective than using funds to introduce therapies on the basis of less reliable evidence.[12] Consequently, a more proactive funding strategy for trials should be considered, extending the model proposed by Glasziou:[13] up to 1% of the national healthcare budget could be used to test new and existing health technologies for which there is inadequate evidence, but potentially large benefits or cost savings.[14]

One approach to monitor and implement some of these strategies is through the use of a comprehensive national trials register to aid the planning of new trials, ensure all trials are identified when evaluating trial evidence, and maximise participation of patients and doctors in ongoing trials.[15]

Many clinical trials already play a central role in everyday clinical practice. However, if we seriously address each of the above issues, health outcomes could be further improved through clinical trials assessing new health technologies and existing treatments in the real world of modern medicine. It is time for us to look at how to make this more of a reality.

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