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EDITORIAL

Randomized Trials or Population-based Registries

New methods introduced for treatment or prophylaxis have to be better, safer, simpler and/or cheaper than the old ones. The new method could derive from pharmacological research, invention of new techniques or observations from registries. Today it is rarely a question of dramatic or all-or-none effects. Therefore, properly designed studies must be performed to show differences in effect. The classical method is the randomized controlled trial (RCT), but data can also be derived from observational studies or registries, both types of studies having, strengths and weaknesses. The researcher and clinician must be familiar with those aspects and possible flaws in design and analysis.

The clinical problems are how to draw the proper conclusions from RCTs, how to transfer results into the relevant clinical setting and how to analyze whether the outcome in real life is similar to that of the RCTs. Treatment indications are likely to be broader and exclusion criteria likely to be less strict. An RCT should only be performed if there is a true uncertainty about the value of one treatment versus another.[1] This is also an ethical prerequisite with the aim to increase knowledge for better care of patients. The benefit and disadvantage of a treatment must be balanced.

An RCT is truly experimental with random allocation of the participants to exposure. In most studies only one factor is varied. Correctly performed, the RCT has a high internal validity. This is a safe way to compare treatments and avoid as far as possible the influences of selection bias and various confounders. The background and prognostic factors are kept balanced. The control group allows us to assess possible causal associations, especially when the causal chain between intervention and outcome is short. The patient material is homogenous and well defined and the procedures, treatments and outcome measurements are well controlled. It is almost always possible to identify and randomize patients in a grey area of uncertainty.[2] The criteria set up by authorities such as Food and Drug Administration (FDA) and European Agency for the Evaluation of Medical Products (EMEA) should be adapted also in non-pharmacological studies.

The strictly defined RCT situation may differ from clinical reality, resulting in poor external validity and generalizability. The clinicians must ask how applicable the results are to patients in their practice. Selection mechanisms and criteria for inclusion and exclusion may make the inclusion rate very slow and prolong the study period, casting doubt on the clinical relevance of the study results. A logbook of consecutive patients with reasons for exclusion is important. The flow of patients and selection mechanisms must be transparent.

RCTs rarely take into consideration changes over time, which could be due to factors outside the study situation, and sometimes the results may be obsolete, when the study is finalized. This is especially true in studies on new devices with rapid technical development. Surrogate endpoints are often used, the clinical relevance of which are dubious. A surrogate must correlate with clinical outcome as well as with the effect of the intervention.[3] When the outcome event is rare, multicentre trials may be a solution. Inclusion of low risk patients dilutes the frequency of end points. The tendency not to publish small trials is serious, because they will fall outside systematic reviews and meta-analyses, which may distort the conclusions. RCTs are expensive. Financial support from the industry may influence the results in an industry-positive way, even when the studies are blind. The majority of RCTs are designed to study effect and rarely to study infrequent side effects, adverse events and complications. Sometimes this may not even be possible because the complications are not known beforehand or very rare. Most RCTs are dimensioned to study short term effects, whereas many patient groups have chronic diseases, atherosclerosis being one example. Many problems are difficult to study with a blind design, such as technical innovations, surgical techniques, etc. This increases a danger of bias, and blinded outcome assessment should be used.[4,5] Instead of being transparent the reporting of RCTs may be incomplete and inaccurate. The CONSORT

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statement (CONsolidated Standards Of Reporting Trials) has introduced a checklist and flow diagram of essential items to be included when reporting RCTs.[6–8]

The results of an RCT are less likely to be generalizable if the outcome of the intervention is highly dependent on the provider or the clinical setting such as in surgery, as compared to drug treatment.

Various types of registries exist, including those administered by industry to monitor performance of new devices or drugs. In population-based registries with a large number of individuals, the impact of a new therapy can be evaluated. Dynamics over time can be followed as well as the influence of developing technologies and long-term effects. Registry studies give the opportunity to analyze the external validity of RCTs and can generate hypotheses. It is possible to identify risk factors, prognostic factors etc., which are important to handle in the design of RCT trials. Case-control studies are particularly effective, when rare events are to be studied, since those events have already occurred when the study is initiated. If a case-control is performed nested in the cohort of a registry, risk factors are recorded prospectively in the registry. Thus, the major weakness of case-control studies are dealt with. Survival analysis can be undertaken, linkage being made to population registries.

The design, however, is not experimental and data on exposure to a specific treatment or action may be uncertain. The patient material is heterogeneous and sometimes difficult to control for confounding factors. The effect of confounders does not diminish with increasing size of the study. Moreover, it is only possible to control confounders that are known. Factors of importance may change over time. There is an obvious risk for selection bias. One criticism is the sometimes small impact on patient care because of poor feedback to the profession and inertia in the system. The organizers of a registry must guarantee a dynamic feedback to the users. Underreporting in registries can be a problem. Non-registered patients often have a worse outcome, underlining the importance to maintain a high registration rate. Registry data may be misused to introduce new treatment or products without relevant RCTs. This is not possible with pharmacological products and should not be concerning technical devices.

Over the years, there have been several examples of results from registries or observational studies leading to rather firm conclusions about treatments, which have not been able to confirm in RCTs. One example is the lower risk of coronary events and progression of coronary lesions with vitamin E intake as suggested in population-based studies.[9–11] This effect was neither confirmed in the HOPE trial[12] nor in a metanalysis on 52 000 patients (HOPE).

After RCTs and systematic reviews showing a beneficial effect of ß-blockers in elderly patients undergoing surgery,[13–15] a population based cohort study showed one ß-blocker (atenolol) to be superior to another (metoprolol) in reducing myocardial infarction and death.[16] An RCT directly comparing these two ß-blockers in unlikely to be performed.

In vascular surgery the technique of endovascular aneurysm repair (EVAR) is a contemporary example how the medical profession sometimes is slow and inefficient in assessing new treatments. Since the technique was described, several minor studies reported promising results. The EUROSTAR voluntary register was launched 1996 to record outcome of patients treated with EVAR. Reports indicated that the median aneurysm diameter was 5.7 cm meaning that around half of the registered patients had an aneurysm size that would not merit operation according to common standards. With such a skewed selection of patients generalizibility of findings could be questioned. There is a similar UK based registry, RETA, also from 1996, five years results recently reported.[17] Not until fifteen years after the introduction of EVAR results of major RCTs were published.[18–20]

When results of RCTs are made public, the potential impact outside the study situation must be evaluated. An example is what happened with carotid endarterectomy in Sweden when the results from the Asymptomatic Carotid Surgery Trial (ACST) were made public. After the first report, the number of carotid endarterectomies for asymptomatic disease started to increase and the increase has continued. The results in the Swedish Vascular Registry concerning postoperative mortality and permanent neurological morbidity are not inferior to the results in the RCTs, which is reassuring.[21]

Both economic and patient resources must be optimally used to give clinical useful information. The size of the effect is often obtained in the RCTs, but questions on how representative and relevant outcome are equally important.

RCTs and registry studies are both needed and are complementary (Fig. 1). Their respective advantages and disadvantages must be known both by those designing the studies, by those analyzing the data, and by those reading about the results. The scientific problem must be clearly defined and the optimal study and statistical methodology used. Registries can complement data from RCTs to analyze treatment effect and rare side effects on a population basis.

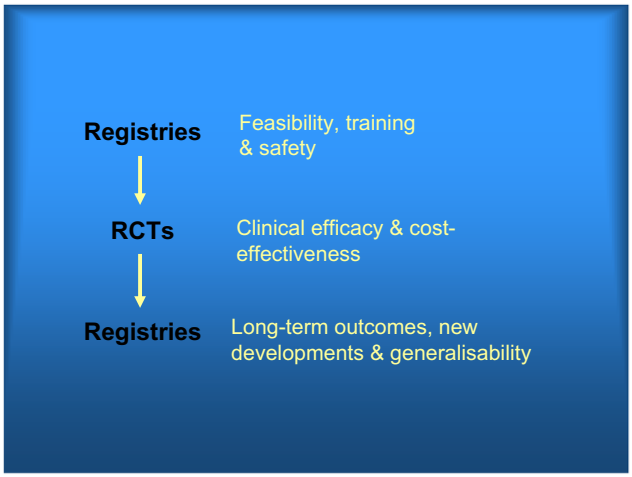

Fig. 1. "Tracker" design for new technologies.

Transferring best evidence based on research findings to best medical practice is difficult.[22] A population-based registry may be helpful in analysing the ways in which this implementation is successful or not. When results from RCTs are compared with those from population-based registry studies it is important to analyze differences in background factors which could offer explanations of differences in outcome. One model which has been shown to work reasonably well in vascular surgery, when national results are compared, is to apply the POSSUM physiology score as shown by the Audit and Research Committee of the Vascular Surgical Society of Great Britain and Ireland.[23]

Conclusion

With well defined scientific questions in combination with adequate design and analysis as well as awareness of strengths and weaknesses, both RCTs and population based registry studies do give significant information. Both designs require external and internal validation assuring that patients not randomized, or not registered, do not introduce bias. Finally, it is not a question of either/or – we need both.

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