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Review

Executive summary

Choosing between randomised and non-randomised studies: a systematic review

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Health Technology Assessment
NHS R&D HTA Programme

Executive summary

Background

Studies that compare healthcare interventions can be divided into those that involve randomisation of subjects between comparison groups, and those that do not. The former, in its commonest form the randomised controlled trial (RCT), is seen by many as the 'gold standard' as it should ensure that subjects being compared differ only in their exposure to the intervention being considered. The RCT has been criticised, however, with some arguing that design features tend to exclude many individuals to whom the results will subsequently be applied. Furthermore, practitioner and patient preferences may influence the outcome of treatment and cause the results to be misleading. These criticisms have led some to advocate the use of non-randomised designs.

Objectives

This review explored those issues related to the process of randomisation that may affect the validity of conclusions drawn from the results of RCTs and non-randomised studies.

Methods

The review was based on a series of systematic reviews involving structured searches of databases. Details of the methods used are described in the main report. Four research questions were addressed.

- Do non-randomised studies differ systematically from RCTs in terms of treatment effect?
- Are there systematic differences between included and excluded individuals and do these influence the measured treatment effect?
- To what extent is it possible to adjust for baseline differences between study groups?
- How important is patient preference in terms of outcome?

Results

Previous comparisons of RCTs and non-randomised studies

Eighteen papers that directly compared the results of RCTs and prospective non-randomised studies were found and analysed. No obvious patterns emerged; neither the RCTs nor the non-randomised studies consistently gave larger or smaller estimates of the treatment effect. The type of intervention did not appear to be influential, though more comparisons need to be conducted before definite conclusions can be drawn.

Several reasons emerged as to why RCTs might produce a greater or lesser estimate of treatment effect than non-randomised studies. A greater effect may occur in RCTs if patients receive higher quality care or are selected in a way that gives greater capacity to benefit. A lower estimate of treatment effect may occur if:

- patient selection produces a study population with less capacity to benefit than would be the case in non-randomised studies
- strong patient preference exists against a particular treatment in an unblind RCT, thus reducing the treatment effect
- non-randomised studies of preventive interventions include a disproportionate number of people with greater capacity to benefit
- publication bias exists; negative results are less likely to be published from non-randomised trials than from RCTs.

Exclusions

The number of eligible subjects included in the RCTs ranged from 1% to 100%. Reasons for exclusions may be medical (e.g. high risk of adverse events in certain groups) or scientific (selecting only small homogeneous groups in order to increase the precision of estimated treatment effects). Blanket exclusions (e.g. the elderly, women of childbearing potential) are also common in RCTs.

Large clinical databases containing detailed information on patient severity and prognosis have been used instead of RCTs, and where database subjects are selected according to the same **inclusion** criteria as RCTs, the treatment effects of the two methods are similar.

Participation

Most RCTs failed to document adequately the characteristics of eligible individuals who did not participate in trials. However, RCTs were more

likely than non-randomised trials to include university and teaching centres and this may have exaggerated the treatment effect measured in the RCTs.

Participation in RCTs differed between studies of treatment interventions (subjects tended to be less affluent, less educated and more severely ill and therefore had greater capacity to benefit from treatment) and those evaluating preventive interventions (more affluent, better educated and generally healthier and therefore had less potential to benefit than eligible subjects who declined to participate).

Adjusting for baseline differences

Adjustment for differences in baseline prognostic factors in non-randomised studies often changed the treatment effect size but not significantly; importantly, the direction of change was inconsistent. Most of the case studies were too small to draw conclusions but where this was possible, the superiority of one treatment over another was probably a function of the patients' clinical characteristics.

Patient preference

Only four papers directly addressed the role of patient preference on trial results. However, preference could account for some of the observed differences between RCTs and non-randomised studies.

Conclusions

Results of RCTs and non-randomised studies do not inevitably differ, and the available evidence suffers from many limitations. It does, however, suggest that it may be possible to minimise any differences by ensuring that subjects included in each type of study are comparable. The effect of adjustment for baseline differences between groups in non-randomised studies is inconsistent but, where it is done, it should involve rigorously developed formulae. Existing studies have generally been too small to assess the impact of such adjustment.

Implications for policy

While a high level of exclusion may have some advantages for those conducting an RCT, it also has important implications for policy. In particular, there is a risk of denial of effective treatment to those who might benefit but who have been excluded from the RCTs, and delay in obtaining definitive results because of low recruitment rate. In addition, there is a danger of unjustified extrapolation of results to other populations, and it is concluded that it should **not** be assumed that summary results apply equally to all potential patients.

Recommendations for research

Conducting research

- A well-designed non-randomised study is preferable to a small, poorly designed and exclusive RCT.
- RCTs should be pragmatic by including as wide a range of practice settings as possible. Study populations should be representative of all patients currently being treated for the condition.
- Exclusions for administrative convenience should be rejected.

Interpretation

- Heterogeneity of populations and interventions should be addressed explicitly. Practitioners should apply caution when extrapolating to populations that differ from those included in RCTs.
- For both study designs, authors should define their reference population, state the steps taken to ensure the study population is a representative sample or explain how it differs. They should also give details of patient and centre participation and the characteristics of eligible individuals who did not participate.
- Further research is required on patient characteristics, long-term follow-up, participation of centres and practitioners and patient preference.

Publication

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NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

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The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will, in England, be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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