

CONSULTATION RESPONSE FOR COOKSEY REVIEW

Principles

- 1.1 The main purpose of applied health research funded by the UK Government is to provide the evidence base to enable the Health Service to deliver the greatest possible health benefit to the UK population from the available resources.
- 1.2 The main component of this is clinical research to quantify the risks, benefits and resource use associated with specific Health Service interventions, investigations or processes of care. These are the issues largely addressed through the HTA programme.
- 1.3 In addition there needs to be work to develop a common understanding of the health benefit that is to be maximised. This involves the consideration of the weights that should be given to different aspects of clinical benefit, equity, access and issues such as the use of appropriate generic health measures, the trade-off between length and quality of survival, issues of perspective and the inclusion of indirect societal costs and benefits.
- 1.4 Once risks, costs and benefits have been determined and priorities agreed, a further aspect to the necessary research involves work around the implementation of appropriate service provision.

Current Issues

- 2.1 The main focus of clinical research investment and publication is randomised controlled trials. However, for a variety of reasons, these may not be possible or may not be the most appropriate methodology in all cases (see notes below).
- 2.2 Research is also largely driven by new pharmaceutical agents and technological developments, which are seen as of more interest from both the commercial and academic point of view.
- 2.3 Considerable resources are invested in identifying areas of new development that are appropriate for future investment. However, there is little scientific basis to the disinvestment decisions that are necessary to fund such developments, with an assumption that savings will be made without significant loss of effectiveness.
- 2.4 The cost-effectiveness threshold used for approval of new technologies is arbitrary and the cost-effectiveness of most current NHS expenditure has not been determined. It may thus be that new developments that individually are seen as cost-effective may reduce the overall effectiveness of the service that is delivered by displacing more cost-effective activities (see example in notes below).
- 2.5 Priority setting often identifies issues that are felt to be of high priority due to cost and/or health impact. However, it is frequently left to those developing the research protocol to determine and justify choices with respect to exact trial methodology, outcome measures and sample size calculations. Applicants for such grants are therefore encouraged to design trials that are achievable in their own setting, there may be a tendency to over estimate recruitment, under-estimate sample size. The process of protocol development is itself unfunded.
- 2.6 There are new and rapidly emerging fields of research relating to economic and pre-trial modelling and value of information analysis that have the

potential to provide a scientific basis for the setting of priorities in health care research and guiding trial design.

- 2.7 New technologies and interventions are often introduced into the NHS in a haphazard way and may become difficult to test through appropriate trials due to widespread adoption on the basis of inadequate data.

Suggestions

- 3.1 **Scoping of research projects.** Having identified areas of high priority there is a place for a separate piece of scientific research to create a scope that identifies the key factors that are drivers for clinical decisions, determines the relevant parameters and sizes of treatment effects that would be critical to the specific decision problem and reviews the appropriate methodology for the circumstances. Depending upon the situation such a project may require a combination of systematic literature review, pre-trial or decision modelling and value of information analysis.
- 3.2 Such a study would be of short duration and low cost compared to an average randomised controlled trial and is likely to have considerable benefits in identifying studies where the results would be unlikely to affect the decision problem or where there are alternative and more appropriate methodologies for quantifying the necessary parameters (see examples in notes below).
- 3.3 **Use of registries for new interventions.** In areas of new rapidly developing technologies there is an important place for the use of registries for new procedures. These are frequently recommended by the NICE Interventional Procedures Advisory Committee and may be very helpful in allowing cost, resource use and risks of new procedures to be quantified for use in pre-trial modelling or cost-effectiveness analysis. They frequently generate useful pilot information that can be used in the planning of studies and may be helpful in tracking changes in the effectiveness of new devices and procedures through the early developmental stages.
- 3.4 Registries also provide a potential means to consider issues around the training and learning curves that are associated with new procedures. Although such registries have been used in the past to good effect it is difficult to secure funding for them from sources such as the HTA or MRC and funding from industry has potential for conflicts of interest or withdrawal of funding when results are not favourable. There is a place for the establishment of a specific funding stream to support registries with sufficient resources to carry out detailed data validation and follow-up.
- 3.5 A regulatory process that only allows the funding of new procedures and treatments when this is linked to the submission of data to registries is likely to result in much more rapid collection of data relating to new procedures. This may well be cost-saving for the NHS as a whole, by providing a mechanism for an orderly and controlled introduction of new technologies.
- 3.6 **Development of standard utility valuations.** An issue which frequently arises in the assessment of cost-effectiveness of new treatments is that clinical trials will measure treatment effects using objective physical parameters or disease specific measures. For decision-making in the NHS, particularly in cost-effectiveness analysis, it is often the estimates of utilities associated with differing health states or disease processes that are least certain and may drive the decision making process.
- 3.7 It would be of great benefit to future analysis if there was work to develop an agreed methodology for identifying utilities associated with outcomes and

health states, and if this was used to generate a library of such measures that could be available as a common data-set for future analyses.

- 3.8 **Prioritising issues relating to potential disinvestment.** There is a need to consider existing technologies and aspects of health service expenditure rather than just concentrating research on new technologies and developments. This would ensure that appropriate disinvestment decisions can be made and that cost-pressures from new developments do not displace more cost-effective use of resources.
- 3.9 **Methodological research.** Research is required to develop uniform policies and processes for determining priorities and incorporating patient preferences, issues of access and equity etc. into NHS decision making.

Notes

Limitations of randomised controlled trials

Over the past 20 to 30 years there has been a rapid development in the concept of evidence based medicine with recognition of the need to base clinical and organisational decisions on best available evidence. This has led to the development of processes for assessing the quality of published evidence and combining these through systematic literature reviews, such as those carried out by the Cochrane Collaboration.

Such reviewing has shown that much of the research that is carried out is of poor methodological quality or does not have sufficient power to provide helpful information thus at best this research is a poor use of resources and at worst may be misleading. Another effect of the move to evidence based medicine has been to put a strong emphasis on methodological quality of research with the randomised controlled trial being seen as the pinnacle of the hierarchy of quality of evidence. Whilst RCT's have some clear advantages there are also a number of disadvantages and areas where RCT's are impractical or misleading. The following are some of the issues that may lead to difficulties in performing high quality RCT's.

- Most studies require the simplification of problems into a dichotomy with two clear treatment choices and may need the aggregation of a heterogeneous population in order to achieve adequate sample size.
- There are often a number of existing or competing new technologies and the choice of experimental and control treatments may be unclear and may be selected in order to try to maximise observed treatment effects.
- Many treatment pathways are complex with interdependence between investigation, treatments and care pathways.
- Problems with recruitment of both subjects and trialists may lead to clinical trials that are carried out by non-representative clinicians or on atypical patient samples.
- Power calculations are often based upon arbitrary definitions of significant effect size without any clear evidence that the result would have an effect on the relevant clinical decision.
- New technologies and invasive procedures present specific difficulties for randomised controlled trials in that they may be operator dependant and may require a learning curve. New procedures or devices are often at a stage of rapid development, creating difficulties in the timing of an appropriate trial.

For all these reasons randomised controlled trials are at their most useful when there is a clear choice between two similar treatments, particularly pharmaceutical agents, but may be very difficult to undertake for more complex aspects of care that involve investigations or compare invasive treatments ¹.

There is a tendency for those who review grant applications or papers submitted for publication to focus on the methodological quality of research and thus to prioritise RCT's for funding and publication. This tends to produce a bias towards those areas in which high quality RCT's are more readily carried out. The result of this is that trials of pharmaceutical agents or high technology new interventions tend to be over represented whilst invasive procedures, investigative techniques and other aspects of care, which account for the majority of Health Service expenditure, tend to be under represented.

Example of possible inappropriate disinvestment

Cost pressures, caused in part by NICE guidance regarding the funding of new technologies, have caused many commissioners to implement recovery plans to meet financial targets. Targets for savings include established treatments that are perceived as low priority. One common example is the suspension of surgery for minor elective operations, including varicose vein surgery. For example, Oxfordshire Commissioning Board has recently decided to stop funding this procedure as part of a recovery plan (<http://www.oxfordcity-pct.nhs.uk/documents/OCBmins10Nov05.pdf>). Varicose vein surgery has been the subject of a recent HTA study ² that showed it to have an incremental cost-effectiveness ratio of around £2,000 per QALY, thus making it a far more cost-effective use of resources than many of the new technologies that will replace it ³.

Example of possibly case for pre-trial modelling

An example of a new and rapidly developing technology is that of endovascular aortic aneurysm repair. Systematic review showed there to be about 20,000 cases reported in the world literature ⁴ and economic modelling based upon published series ⁵ has shown that it is unlikely to prove cost-effective based upon current costs and estimated outcomes. The HTA recently funded a randomised clinical trial at a cost of approximately £1.7M (<http://www.ncchta.org/news/newsitem05061701.htm>) that has confirmed these predictions. It is likely that appropriate pre-trial modelling would have confirmed that the proposed trial was unlikely to provide evidence that would be helpful in informing the decision as to whether the procedure should be adopted by the NHS.

References

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