

High quality clinical research: how doctors and trusts can take advantage of the R&D budget

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Clinical research

Clinical research performed on individuals is less easily circumscribed than basic medical science performed in the laboratory or epidemiological studies of populations. The conference consensus appeared to be that clinical research describes the study of applied physiology, clinical observations and patient experience. Such research places improvements in our understanding of basic medical sciences in a relevant clinical context and allows scientific progress to be translated into useful clinical applications. The provision of effective and financially efficient health care for large populations requires an understanding of what lies between the laboratory and epidemiology.

There was rather less agreement about the well-being of clinical research, the skills necessary to perform it and the role of medical graduates. Professor Dieppe put forward the view that the United Kingdom had a formidable tradition of clinical research, especially in applied physiology, but that this area was in decline. It is difficult to quantify the amount of clinical research that is taking place but the number of higher degrees awarded may be a surrogate marker for this activity¹. The reasons for this perceived decline are not clear. Clinical research is often confounded by patient variability. However, there is little evidence that basic medical science research is less rigorous than clinical research or easier to perform.

A historical perspective on the rather artificial division between clinical and basic medical science was outlined by Professor Borysiewicz. In the nineteenth century, Claude Bernard sought to divide 'observers' from 'experimentalists'. In the early years of the twentieth century Haldane's influence led to the foundation of clinical departments, ensuring that physical separation reinforced the dichotomy between clinical and basic medical science. A stigma associated with merely documenting observations may continue to be reflected unjustly on clinical research. The clinical observations of the last millennium are not equivalent to modern clinical research and peer-reviewed funding is now unlikely to be available for exclusively descriptive work.

Professor Borysiewicz's own work on human

papilloma viruses and cervical neoplasia provided an example of high quality, contemporary, clinical research: by integrating clinical, epidemiological and laboratory studies, advances in each field influenced the evolution of work in the others. As basic science illuminates clinical problems and directs research on individuals, so clinical and epidemiological observations helped to generate hypotheses, whose molecular basis could be tested in the laboratory. The multi-disciplinary nature of the team and the numerical predominance of scientists over physicians did not impede the project, although progress has taken its time. The therapeutic 'payoff', in this case, clinical studies of human papilloma vaccines in pre-invasive and invasive cancer, arrived many years after work began².

The role of medical graduates in clinical research is not clear. If medical graduates are to function as project managers, how much do they need to know about techniques they themselves do not perform? This question is equally important when considering molecular biology, applied physiology or statistics. Clearly the limitations of any analytical techniques are important when designing experiments. However, medical graduates are expensive to employ and training doctors to duplicate the skills of scientists consumes valuable resources. There are limited opportunities for training in clinical research and the length of time between formulation of hypotheses and publication makes establishing a track record a lengthy process. The criteria to identify the clinician-scientists of the future, the numbers required and the structure and funding of their training have been addressed by the Academy of Medical Sciences³.

General qualities of research proposals

The demand for funding for medical research continues greatly to exceed supply. This is likely to be true whatever the source of funding. Most of the qualities necessary for successful applications to the NHS R&D budget are the same as for any other funding body.

The attributes of high quality research proposals were not disputed. A clear hypothesis should be able to be addressed and answered by a robustly designed proposal with a feasible timescale. Appropriate skills

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and resources should be available to the investigators who should have a record of delivering results. Collaboration between research groups and between different professions within such groups is likely to enhance proposals.

Industry is a major investor in health care R&D and an industrial view was provided by Dr Belcher. Ascertainment of patients is enhanced by the use of patient databases, but it remains important to plan for realistic rates of loss of patients from any clinical study. Industry may be able to support clinical studies by funding additional staff and equipment and this may aid recruitment and follow-up. However, performing clinical studies in the UK is expensive and there is considerable variation in costs between different units. An increasing number of clinical trials are performed in areas with lower costs such as Eastern Europe and South America.

The standards adopted by governmental regulatory bodies are more demanding than those required for peer-reviewed publication and this may go some way to explain the concentration of statistical expertise in the pharmaceutical industry and the paucity of statisticians employed in the NHS or in academic medicine.

With this in mind, the design of studies and the use of appropriate statistical methodology were examined by Professor MacRae. The origin of observed differences and the design of studies to minimise bias secondary to allocation or assessment methods were clearly illustrated with examples. The dangers of uncritically accepting interim analysis, sub-group analysis, multiple comparisons and meta-analysis were highlighted. Any uncertainty about analysis, policies and the pitfalls of each approach, were demonstrated by examining an imaginary trial of the benefits of mountain climbing in acute ischaemic heart disease. The tyranny of the p-value attracted comments from the audience. The ease with which Professor MacRae was able to find examples of over-interpretation of observed differences in highly regarded, peer-reviewed journals serves to emphasise the value of expert statisticians when planning a research project.

Conference programme

■ **Introduction: From proteins to policy**

Professor Paul Dieppe, University of Bristol

■ **What does the NHS R&D programme want from you?**

Dr Russell Hamilton, NHS Executive South West

■ **Defining and planning a clinical research project**

Dr Glyn Belcher, Takeda Euro Research & Development Centre Ltd

■ **Making it work - best use of appropriate expertise**

Professor Kenneth MacRae, University of Surrey Postgraduate Medical School

■ **Clinical research in action**

Professor Sir Leszek Borysiewicz, Imperial College School of Medicine, London

NHS Research and Development (R&D) funding

The Department of Health (DoH) spends in excess of £500m a year on R&D. Although a number of research programmes are directly commissioned, most of this sum is allocated to NHS providers to pay the service support costs of research⁴. In 2000/2001, a total of 376m was allocated to 317 providers; individual providers received between £2,600 and £42m. The circumstances under which the NHS will support non-commercial externally funded R&D by meeting associated patient care costs are described in partnership agreements. Well established partnerships exist with research councils, the European Union, government departments and research charities.

The organisation of the NHS R&D programme is presently being modernised⁴. A single stream of funding existed between the inception of the programme and February 2001. As part of the programme of modernisation the R&D budget will, in future, be divided into two streams; NHS priorities and needs funding (PNF) and NHS Support for Science (SfS). The burden of morbidity and mortality associated with cancer, cardiovascular disease and mental health and the costs of delivering services in these areas, have led to the DOH identifying these areas as current priorities. However, it is clearly important to look to the future and PNF funding will address future needs as well as current priorities. The consultation period on the DoH proposals for the operation of the NHS Support for science is now complete and responses are being considered.

Recent changes in the organisation of commissioned research have established three principal areas – Health Technology Assessment (HTA); Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT). These will replace earlier programmes relating to NHS priorities or to specific disease areas, the majority of which are no longer commissioning new projects. In addition to the national programme, each NHS regional office has an R&D Directorate with responsibility to distribute R&D findings, to identify and fund local priorities and to develop the local R&D infrastructure. Perhaps the most important change that has been introduced in the current modernisation is the introduction of research governance.

Research governance

‘This country is fortunate to be able to draw upon a wide range of research within the health and social care systems. Most of this is conducted to high scientific and ethical standards. However, recent events have made us all painfully aware that research can cause real distress when things go wrong. The proper governance of research is essential to ensure that the public can have confidence in, and benefit from, health and social care research.’

Lord Hunt of Kings Heath,

Introduction to the DOH Research Governance Framework

The trend to give greater weight to the autonomy of patients and their relatives has been driven forward by a number of high

profile examples of the failures of current practice. Many difficulties may be related to issues of transparency and consent. The research governance framework (RGF) published by the DoH aims to ensure that research is conducted to high ethical and scientific standards⁵. The RGF sets standards, details the responsibilities of individuals researchers, outlines the delivery systems and describes local and national monitoring systems.

The conflict balance between autonomy and beneficence in the context of clinical research is delicately balanced. Public debate has concentrated on the use of stored or retained human tissues and organs but stored clinical data are also a valuable resource. Analysis of patient data, both in case records in referral centres for rare diseases and in computerised databases such as the General Practice Research Database (GPRD), may provide the substrate for hypotheses that are subsequently tested *in vitro* or in populations. Limiting access of researchers to patient materials may prevent valuable insights into rare diseases. Adopting the research governance framework and scrupulous adherence to the practical standards it recommends may protect individual researchers and the reputation of clinical research. Funding from NHS R&D or any other body is unlikely to be directed to proposals that fall outside the RGF.

Conclusion

The NHS R&D budget will fund high quality research that concerns questions relevant to the priorities and needs of the NHS. Successful applications are likely to satisfy the scientific and ethical targets of the new research governance framework.

References

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- 5 *Department of Health Research Governance Homepage*. <http://www.doh.gov.uk/research/rd3/nhsrandd/researchgovernance/govhome.htm>.