



The *Academy of*
Medical Sciences

Strengthening Clinical Research



A report from the
Academy of Medical Sciences

October 2003

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This report is published by the Academy of Medical Sciences and has been endorsed by its Officers and Council. Contributions by the Working Group and respondents to the call for evidence are made purely in an advisory capacity. The Review Group added a further 'peer-review' stage of quality control to the process of report production.

The members of the Working Group and Review Group and the respondents participated in this report in an individual capacity and not as representatives of, or on behalf of, their individual affiliated hospitals, universities, organisations or associations (where indicated in the appendices). Their participation should not be taken as an endorsement by these bodies.

Contents

	Page
Summary	7
Recommendations	9
Chapter one: <i>Historical perspective, international comparisons, opportunities and challenges</i>	11
Chapter two: <i>Strengthening the clinical research base in the NHS</i>	17
Chapter three: <i>Clinical trials and population-based health research</i>	23
Chapter four: <i>Experimental medicine</i>	27
Chapter five: <i>Building collaboration and trust</i>	29
Chapter six: <i>Proposal</i>	33
<hr/>	
Appendix one: <i>Acronyms and abbreviations</i>	37
Appendix two: <i>References</i>	39
Appendix three: <i>Working Group and Review Group members</i>	43
Appendix four: <i>Terms of reference and work plan</i>	45
Appendix five: <i>The Wellcome Trust Clinical Research Facility based at Western General Hospital, Edinburgh</i>	47
Appendix six: <i>A funding framework for establishing a National Network for Clinical Research</i>	49

Summary

Dramatic progress has been made in the last 20 years in elucidating fundamental mechanisms of disease and creating new therapeutic and diagnostic opportunities. Much of this progress has emerged from the application of the laboratory sciences, molecular and cell biology, to resolving the biochemical basis of disease. However, there is now a substantial gulf between basic discoveries and converting such discoveries into innovations that directly benefit patients or prevent disease. This translational gap can only be bridged through the successful application of clinical research, testing and evaluating new concepts and interventions at the bedside and in carefully managed clinical trials. Put simply, clinical research has not kept pace with the advances in basic scientific discovery and this disadvantages patients.

Although clinical research encompasses a large number of activities this Academy report has specifically identified two major areas that require urgent attention. The first of these is **experimental medicine**, clinical investigation directed at establishing disease causation and 'proof-of-concept' - testing the validity and importance of new discoveries or treatments in patients or healthy volunteers. The second is large-scale **clinical trials** of all new forms of healthcare intervention. In these two areas in particular there is a serious lack of activity and capacity in the UK.

At present the ability to undertake this type of research is severely limited by a number of factors:

- a lack of appropriate facilities and infrastructure
- a lack of appropriately trained clinical scientists and a career structure to support them
- inadequate funding support for experimental medicine and all types of clinical trials
- a failure to utilize the opportunity provided by a National Health Service (NHS) to generate high quality clinical data for such studies
- the increasingly complex and bureaucratic legal and ethical frameworks in the UK and EU

This report highlights the need to re-establish the capacity to undertake clinical research in the UK. It has profound implications for the effective management of a modern NHS, for patients who require new interventions for their disease, and also for those attempting to develop novel treatments or diagnostics in the biotechnology and pharmaceutical industries. Any attempt to energise this activity will require the joint efforts of the Department of Health (DH), the Department of Trade and Industry (DTI), the Department for Education and Skills (DfES), the Medical Research Council (MRC) and the major medical charities. The Academy has attempted to identify some of the crucial limiting factors that have disabled this activity in recent years and has made specific recommendations as to how they might be corrected.

In Chapter 6 we set out a series of proposals which we believe will remedy some of the problems, and help the UK take its rightful place in leading improvements in clinical care. Chapters 2-5 provide the background reasoning.

Recommendations

Recommendation 1: Create a National Network for Clinical Research within the National Health Service to create and support excellence in clinical research

The National Network for Clinical Research (NNCR) should have the status of a **special health authority** and support the development of clinical trials and translational research networks focused on the seven main causes of morbidity and mortality. A new funding structure, extending the framework established for cancer through N-TRAC and NCRN to six other major disease areas,¹ would greatly enhance the capacity for clinical trials and translational research in the NHS. The NNCR could ensure that resources were appropriately targeted at the necessary infrastructure and would also fund specific research commissions by the NHS, taking account of the needs of the National Institute for Clinical Excellence (NICE).

Two major aims for the NNCR would be to:

Develop clinical research facilities. These facilities are necessary for the support of experimental medicine. Only a limited number of these facilities are realistically sustainable but these should be identified and supported through properly costed overhead streams accompanying programmatic grants from the major funding bodies including the MRC, the NHS, major charities, and the biotechnology and pharmaceutical industry.

Develop the infrastructure and culture needed to support high quality clinical trials within the NHS. The decline in this activity must be reversed and this will involve commitment of the funders - the MRC, DH, DTI, major charities, and industry. It will be necessary to develop new trial methodology for use in chronic disease. Research in these areas will increasingly be based in Primary Care and this will need to be considered when creating new infrastructure funding mechanisms.

Recommendation 2: New Office of Science and Technology funding should be made available through the Medical Research Council to support the programmatic aspects of clinical research

Such funding should include support for clinical trials and provide a specific funding stream for experimental medicine and for the training of clinical scientists.

Recommendation 3: Improved career structures and incentives for those undertaking clinical research

More support should be made available to NHS doctors of all grades undertaking clinical research. Specifically, support should be available to 'buy out' significant time to allow clinical researchers to undertake research whilst continuing to participate in routine patient care activities within the NHS.

For those clinical researchers employed within the universities, recognition must be found within the Research Assessment Exercise and appropriate measures devised to measure success and impact.

Recommendation 4: Improve the regulatory environment needed to support clinical research within the NHS and promote public involvement

Ensure that the importance of clinical research in developing a modern evidence-based NHS is fully recognised. A significant expansion in clinical research can only be successful if the population recognizes and embraces the value of such research and if individuals are willing to be active participants. In exchange any patient wishing to participate in a clinical study should have the opportunity to do so. The NICE and the DH should encourage public debate on involvement in research as part of developing an effective health service.

¹ The six disease areas discussed are: neurodegenerative disease, musculoskeletal disease, cardiovascular disease and stroke, respiratory disease, mental health and diabetes, in addition to cancer which is already covered by N-TRAC. See Chapter 6 for details.

Create a National Ethical Code for informed consent relating to patient data. This would simplify access to patient records for ethically approved research projects that would have no direct impact on the individual patient, but which would provide invaluable data for large-scale research of disease in cohorts, for therapeutic monitoring studies and for health services research.

Encourage development of European Clinical Research Networks. This would greatly enhance the potential of new investment in clinical research and would avoid duplication of effort. It could also help in persuading regulatory authorities to recognise the importance of clinical research for the health of the population and strike a realistic balance between the needs of research and the needs of regulation.

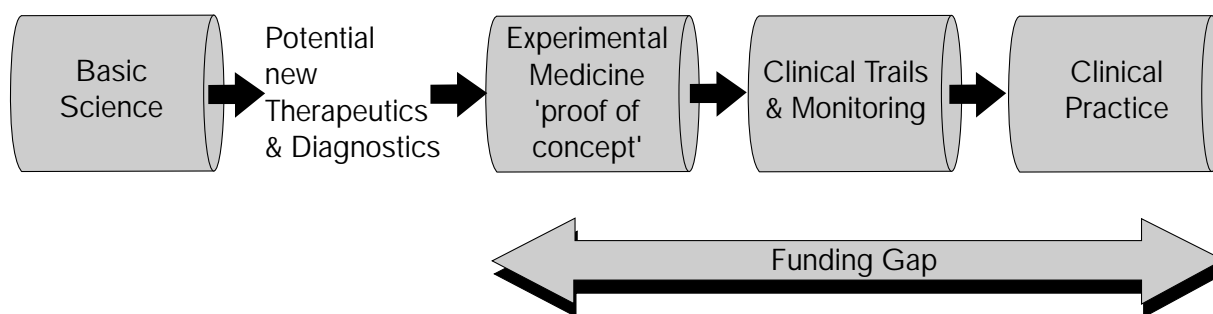
Recommendation 5: The NHS should support its clinical research activities with 1.5% of its turnover, so returning to the original goal of the R&D programme

This target reflects an original, but unachieved, goal of the NHS Research and Development (R&D) programme when it was conceived in the early 1990's. Given the importance of an appropriate knowledge base for the cost effective delivery of health care, this figure compares favourably with R&D budgets in the commercial sector that range from 1-16%. A failure to build investment in research to this level over the next 10 years will disable the NHS through a lack of specific information, independently generated, about the benefits that may or may not be derived from therapies, both old and new. The figure of 1.5% would fund the recommendations made in this report. The funding would be introduced step-wise over a period of 10 years.

Chapter one - *Historical perspective, international comparisons, opportunities and challenges*

- 1.1 Historically, clinical research has been a highly esteemed academic activity in the UK. This was reflected in the substantial investment by the MRC and the role of the clinical research board through the management of its research portfolio. But by the 1970s worldwide, a decline in clinical research had begun. This was due in part to the lack of technology needed to go beyond relatively simply clinical physiology and an inability to address the more fundamental aspects of the major chronic diseases. In contrast to the technological barriers that confronted clinical scientists, there was a dramatic change in the capacity to undertake laboratory research at a cellular and molecular level, especially with the discovery of the basic tools of molecular biology in the 1970s, which allowed genes to be manipulated and transferred between cellular populations. Three decades later the application of molecular genetics and, more recently, human genetics to analysing disease, has transformed our understanding of basic biomedical disease processes. This surge in activity in the molecular sciences eclipsed research activity in clinical science.
- 1.2 The revolution of molecular and cell biology, and major advances in imaging science, have provided many more tools to study human disease and there is now an urgent need to re-establish expertise and active programmes in clinical science. Many of the methodologies now available allow the stratification of previously poorly-defined diseases into more discrete mechanistically organised subsets. These methodologies significantly advance our ability to diagnose and monitor disease and herald a new era of experimental medicine. Importantly, however, re-emergent experimental medicine must move beyond the classical clinical physiology of the last era of clinical science and fully exploit the potential of the new investigative imaging and molecular tools to elucidate understanding of human disease.
- 1.3 Access is needed to fully staffed and properly equipped clinical research facilities. A host of new therapeutic opportunities emerging from academic programmes and industry need to be evaluated. Such an evaluation is needed for effective translation of new ideas into clinical practice. At present, few countries are equipped with the infrastructure, manpower, or programmatic support to make this happen. The UK is impoverished in this arena, as these experimental studies have often failed to gain support from funding organisations and there has been failure to develop the required infrastructure.
- 1.4 In addition to the lack of infrastructure and expertise in experimental medicine, there is also a crisis in the area of late-stage clinical trials. Although much of the fundamental methodology for undertaking such trials was developed in the UK, there remains a paucity of sources of support for these activities. This reduction in clinical research activity, funded by all sources, has been documented (Chalmers *et al.*, BMJ in press) and the reduction in clinical trial activity has profound effects on the ability of the NHS to make knowledge-based decisions and will slow the access of patients to effective new therapies. A further constraint on the UK's activity in clinical trials is the lack of appropriate clinical research networks. Although some such networks have developed in an *ad hoc* fashion, and a cancer network has been established successfully through the NHS, N-TRAC and the NCRN programmes, these need to be developed more generally.
- 1.5 Failure to maintain these two areas of research activity, experimental medicine and clinical trials, is having serious consequences for the clinical research base in the UK. The lack of capacity in these areas will mean that the translation of basic science discovery into clinical practice will be hindered. This in turn will call into question the societal merits of basic biomedical research

The Biomedical Research Pipeline



leading to a clinical environment unattractive for innovation in biotechnology, and will disadvantage patients and the NHS. The revitalisation of clinical science is therefore crucial for the viability of the entire health care and biomedical research enterprise.

disciplines including hospital-based and specialty medicine, primary care medicine and diagnostic subspecialties, such as laboratory medicine and radiology.

Academia and the NHS

Scope of the Report

1.6 The Academy of Medical Sciences voiced concerns about the future of clinical research in the UK at a meeting with the House of Lords Science and Technology Select Committee in November 2001 and subsequently decided to undertake a study of the issues. This report is part of that evaluation. It focuses on the major issues limiting clinical research nationally. It does not address in detail more general issues relating to the strengths and opportunities for biomedical research. In compiling this report the Academy has taken a broad approach to the issues under discussion as they affect the UK and has not dealt with the needs of the individual administrations in Scotland, Wales and N.Ireland.

1.7 Although the definition of clinical research is potentially broad, the Academy has intentionally limited the discussion to experimental medicine and the enabling technologies that have created a renaissance in this field, and to clinical trials of established and novel therapies and diagnostics. These two major areas require improved infrastructure and workforce capacity as well as programmatic support. They bridge many clinical

1.8 Clinical research, unlike much other research in the UK, falls between two institutions - the universities and the NHS - and requires major academic institutions to support and integrate their activities with those of the NHS. There will be a limited number of places within the UK with the capacity to undertake truly rigorous and cutting-edge experimental medicine and these are all likely to occur in centres offering both academic and clinical excellence. Clinical trial networks, on the other hand, should be spread widely around the country in academic and NHS institutions with access to substantial patient populations and where there is a willingness to engage in this type of research activity. The N-TRAC model has demonstrated, through its network, that these centres are likely to be widely dispersed.

1.9 In order to integrate NHS priorities and academic programmes, coordination will be required between the major funding agencies and the NHS. Any facilities provided will only succeed if they are financially neutral (or beneficial) in relation to the hospital trusts that house them. Academic institutions similarly will be reluctant to take on the task of supporting clinical research unless they receive appropriate resources.

Industry issues

1.10 In the UK, the pharmaceutical and biotechnology companies dominate industrial R&D activity (DTI, 2002) contributing 37% of all industry R&D. UK pharmaceutical R&D intensity² is 14.6% compared to 2.2% for all sectors. The most recent data from the Industry Association; The Association of the British Pharmaceutical Industry, (ABPI, 2003) show that pharmaceutical R&D funding in the UK continues to increase but the ABPI warns that the UK should not be complacent and should take heed of the intense competition from other countries.

1.11 Companies fund significant amounts of basic and clinical research in universities and NHS facilities. Their research contribution is not just financial: companies provide significant intellectual input to their academic partnerships and play a major role in research training. Industry is also a major beneficiary of the training that takes place in the public sector and is particularly keen to acquire individuals trained in clinical research and experimental medicine skills.

1.12 Companies have expressed concerns over the last decade about the decline in the UK as an attractive location for clinical trials, specifying fragmented research trial capacity, long start-up times, low patient recruitment rates, high and variable costs as well as regulatory constraints and a less welcoming culture than other countries (Poste, 2001)³. Some of these issues are being addressed by joint Government-industry initiatives in the UK and EU⁴, and there is now joint UK Government-pharmaceutical industry commitment to publishing annual performance indicators of the attractiveness of the UK as a location for pharmaceutical company research (DH, 2002).

1.13 It is also becoming accepted within industry that early-stage 'proof-of-concept' studies to evaluate

medicines in patient populations represent a crucial stage in the drug-discovery/development process. These studies occur after toxicology studies have been completed and help establish the potential biological activity of new compounds in humans. Although some pharmaceutical companies have their own clinical research facility to accommodate these experimental medicine protocols, many are done in conjunction with academic institutions. This allows industry to bring substantial clinical expertise to the problem and also provides access to many of the new enabling technologies and imaging methodologies that indicate which surrogate measures of efficacy might be useful in their later-stage studies. Experimental medicine, conducted in this way, has the potential to accelerate drug discovery and produce safer and more effective medicines.

1.14 Issues relating to experimental medicine and clinical trials capacity are particularly important for biotechnology companies which often do not have the capacity to undertake clinical research.

1.15 It is important for industry, academia and the NHS to do more together to identify key skills and match these to key disciplines, for example in clinical pharmacology (DH, 2001; DH/ABPI, 2003), and to share learning on what works best for interdisciplinary and translational research in public-private models.

International comparisons

1.16 The UK is not alone in identifying organisational weaknesses in clinical research. A broad analysis of resources for clinical research at the European level in one key area, cardiology, indicated the need for much better collaboration and coordination of research structures. Suggested remedies included creating a European analogue of the National Institutes for Health in the United States (US NIH), developing pharmaceutical company-

² Defined as investment as a proportion of sales

³ For example: the USA and Canada

⁴ For example: the Pharmaceutical Industry Competitiveness Task Force (DH, 2002b), Biosciences Innovation Growth Team (BIA, 2003), G10 Medicines Group (G10, 2002) and the Health Innovation Task Force.

university partnership models, and raising the profile of the contribution made by clinical research to disease management (Bassand *et al*, 2002).

1.17 The Organisation for Economic Cooperation and Development (OECD) has also noted the importance of the university/health service interface where, through partnership, research informs practice. Therefore, there is a need to integrate education, research and healthcare - the tripartite mission (OECD November meeting, 2002). A shared problem across the OECD membership are the different planning timescales for education/research and for service delivery: universities tend to concentrate on the future but hospitals on the present. If clinical centres are to play their part in the wider network across health and social care and contribute to economic development, then strategic challenges must be faced relating to R&D priorities and their performance criteria.

1.18 The encouraging example of Canada is of particular interest. The Canadian Institutes of Health Research (CIHR) were established in 2002 to replace the Medical Research Council of Canada and to broaden the scope of health research⁵. The CIHR created mission-based institutes similar to the US NIH, although there is no intramural component. The institutes operate in 'virtual' mode. Inception of the CIHR has stimulated both dramatic growth in the research budget and overt linkage with innovative goals for healthcare. There is new commitment to building research partnerships - with policy-makers, patient groups and industry. Innovation goals have been further progressed by the launch of the Canadian Foundation for Innovation (CFI) to support infrastructure.

1.19 In Europe, too, Germany has now clearly recognised the lack of infrastructure and support

for large-scale clinical trials. It is currently developing plans to establish a large clinical trial network that will be supported by substantial infrastructure as well as programme grant support. It is envisioned that this will provide benefits for the health care system as well as create opportunities for further inward investment from the pharmaceutical and biotechnology industry (Seibert-Grafe, 2003).

1.20 In the US, the NIH is currently discussing a new plan (McLellan, 2003) that will probably lead to significant redirection of NIH funds in favour of clinical research. A recent report from Institute of Medicine (IOM) proposes the enlargement of clinical research centres into a National Centre for Clinical Research and Research Resources (NRC/IOM, 2003). US opinion-leaders have identified many problems of the clinical research enterprise⁶ (Rosenberg, 2003; Sung *et al*, 2003; IOM, 2003) that were found to impede both the translation of basic science into clinical studies and of clinical studies into medical practice. The IOM recommended urgent resolution of the four central challenges:

- public participation
- information systems
- workforce training
- funding

1.21 A similar sense of crisis in the US pervades the recent report from The Commonwealth Fund (CMWF, 2003) and their recommendations for the research future of the Academic Health Centres cover a similar area to the IOM⁷. While it is premature to dwell further here on which particular elements of the rescue packages recommended for the US might be most applicable to the UK's clinical research crisis, the parallel developments in US healthcare research policy will provide a continuing source of intelligence and an instructive basis for comparison.

⁵ It focuses on medical, clinical, population and health services research, and training future researchers.

⁶ These included: insufficient funding, fragmented infrastructure, regulatory burden, incompatible databases, shortage of qualified investigators and of willing participants

⁷ These areas are: interdisciplinary research structures, priorities for funding to include public health and health services research, translational needs, informatics, industry relations, ethical review and human subject protection.

Challenges in building the UK clinical research base

1.22 The NHS is one of the most knowledge-intensive organisations in the UK. For the effective management of the organisation, there must be access to robust data defining the most appropriate and efficient diagnostic and therapeutic interventions for all patients at any stage of their disease progression. The successful and cost-effective management of the NHS requires that it generates its own source of R&D information. An organisation providing such data would have many potential benefits, in addition to providing the NHS with the sort of information it needs to make decisions about health care interventions. To achieve this it is necessary to embrace a culture that recognises the importance of evidence and implements such evidence widely and efficiently across the NHS. This culture of evaluation is unlikely to develop unless there is support, resource and encouragement for participation by health practitioners and patients in the rigorous evaluation of therapeutic options.

1.23 A commitment to NHS R&D was made in 1994. At that stage, the decision was taken to separate the funding stream to allow R&D to be funded up to a level of 1.5% of NHS turnover. This initiative, however, has never truly fulfilled its potential (McNally *et al.*, 2003). Less than 20% of the current resources allocated to NHS R&D are actually spent funding scientific projects and, although there are notable successes, for example, Genetics Knowledge Parks and N-TRAC, a culture of evaluation does not pervade the NHS nor is there the necessary information available for organisations such as NICE to perform adequately. There is a requirement, therefore, to reconsider how R&D is supported within the NHS and to ensure that it receives the priority so that the delivery of health care in the UK is efficient and cost effective.

1.24 Major problems relating to experimental medicine and clinical trials are at the heart of this report. The gap that currently exists between research funded by NHS R&D and that funded by the other public research funders is acute in these areas. The relative lack of money for investigator-led, early clinical research has knock-on effects for research training and the development of practical and interpretative skills. At the same time, there are concerns that funding support for clinical trials has all but disappeared in the UK (Chalmers, BMJ in press).

1.25 The Working Group reviewed various options for change. In evaluating the models of best practice, they identified alternative ways of addressing the current inadequacies in research infrastructure, training and funding. Broadly, the UK could emulate US-style centralised research facilities based on academic health centres⁸ (most appropriate for experimental medicine) or could introduce a more 'distributed' model, whereby multiple institutions capitalise on individual strengths (ideal for clinical trial networks). Such models assume that research beds can be protected, which is a notorious problem. In this report the Academy has not attempted to specify the remedies in detail but rather identify ways of delivering coordinated activity⁹, together with the further development of evidence-based health care and healthcare policy¹⁰, leading to an increasingly intelligent provision of healthcare.

1.26 In discussing the case for more funding, the Academy recognises the need to describe how a more effective R&D enterprise will emerge¹¹. There will be pressure to link increased investment with some measurement of the returns it yields; the research community should therefore prepare for increasing demands of accountability and methodologies should be developed to enable such accountability. Increased public funding, and subsequent commitment to

⁸ As currently is being developed by the Wellcome Trust in their Millennium Centres initiative.

⁹ Through support for experimental medicine, clinical trial recruitment and the other research objectives detailed in Chapters 1 and 6.

¹⁰ Building on current processes such as NICE, The Health Technology Assessment (HTA) and Health Protection Agency (HPA).

¹¹ Such work is currently getting underway. For example the recent NHS work relating to paediatrics.

interdisciplinary and translational research and to NHS ownership of research training, will create an opportunity for partnership with industry research, creating a yet more effective system for delivering value.

1.27 Although it has not considered the issue in detail, the Academy recommends further exploration of the relationship between the public sector research funding strategies, potential new sources of money¹³, and private sector funding. In this context it is also important that the Academy's recommendations are taken together with the recommendations from others, in particular the Pharmaceutical Industry Competitiveness Task Force (PICTF), the Bioscience Innovation and Growth Team (BIGT) and the House of Commons Trade and Industry Inquiry on the Biotechnology Industry.

¹² For example that of the Higher Education Funding Councils (HEFCs), Office of Science and Technology (OST), NHS, research charities and EU.

¹³ From Regional Development Agencies and other UK/European Innovation/Development funds.

Chapter two - *Strengthening the clinical research base in the NHS*

Background and definition of the field

- 2.1 Clinical research refers to the scientific activity directed at understanding the clinical features of disease and evaluating, through measurements at the bedside, a range of therapeutic and diagnostic interventions. The molecular study of disease has been driven by many technological advances and has resulted in a remarkable expansion in medical research, increasingly fuelled by developments such as the sequencing of the human genome and our ability to systematically study proteins, RNA, DNA and small molecules, using the tools and newly-formed databases associated with the field of genomics.
- 2.2 The revolution in molecular medicine has acted as a powerful magnet for young scientists and continues to be immensely attractive both as a career and as a target for grant support from the major funding agencies and has tended to draw trainees away from applied clinical research. The advances that are now beginning to emerge from these molecular studies must eventually be tried and tested in patients if they are to provide the benefits that this technology has long promised. There remains a significant gap between scientific discovery in the laboratory and its application in patient care. Clinical research is necessary to ensure that these exciting innovations are eventually implemented. At present, there is insufficient capacity in the NHS for this form of clinical science to be used to translate basic discoveries into diagnostics or therapeutics that would benefit patients.
- 2.3 A variety of factors have led to a substantial reduction in the capacity to undertake clinical science in the NHS. They include a lack of appropriate infrastructure for clinical research within the NHS (both in terms of clinical investigation units and the necessary infrastructure, such as IT required to network centres together for larger scale trials), a lack of available time to allow NHS clinical staff to participate in these activities, a lack of training opportunities and career structure for individuals who want to undertake a career as clinical investigators and, most importantly, a lack of research funding for bedside research into disease. Furthermore, it must be recognised that the field of clinical research has changed significantly as a result of many of the technologies that have become available over the past twenty years. Clinical research is now greatly facilitated by the availability of a range of enabling technologies that allow much more precise evaluation and assessment of biochemical variables in diseased individuals. New methodologies have been successfully applied to identify important intermediate phenotypes in disease. For example, modern imaging technologies using Positron Emission Tomography (PET) or Magnetic Resonance Imaging (MRI) have allowed disease phenotypes to be characterised, even when they may be pre-symptomatic or found in only a sub set of diseased patients. Such approaches will be essential in understanding the role of genetic variation in altering predisposition to diseases and drug responses.
- 2.4 Similarly, the quantification of surrogate disease markers, such as viral load, that have emerged from molecular techniques has greatly strengthened the ability to investigate the role of new therapeutic interventions in a range of viral diseases. The molecular medicine revolution has also bred a whole range of new and important diagnostic and therapeutic interventions such as DNA-based genetic testing, disease classification based on transcript profiling, structurally based drug design and gene therapy. In a sense, the dramatic expansion in molecular medicine has created a crisis in clinical research by producing a pipeline of new interventions and technologies that need now to be evaluated in a clinical setting.
- 2.5 There is an international dimension to this crisis in clinical research. The lack of researchers in clinical science has been the subject of much

discussion in North America, where both Canada and the USA have experienced a similar dramatic expansion in the molecular sciences. Multiple reports, including that of the Association of American Medical Colleges Task Force on Clinical Research (AAMC, 2000), have argued that the lack of clinical research infrastructure and the failure to train an adequate number of clinical scientists is disabling the entire medical research effort. Similar concerns have been expressed in Europe (G10 Medicines Group, 2002).

2.6 The UK, however, has a special reason to be concerned about its failings in this arena. The NHS is highly dependent on critical evaluation of a range of new diagnostic and therapeutic interventions that may be required over the next twenty years. As a healthcare system that is free at the point of delivery and organised according to nationally agreed standards, access by patients to new interventions needs to be rapid, but based on independent data demonstrating efficacy. This makes the requirement for expanding an R&D base within the NHS even more imperative than elsewhere.

2.7 The DH responded to the House of Lords (HoL, 1995) report a decade ago by setting up NHS R&D that was distinct from other forms of medical research in the UK. The creation of the programme of NHS R&D provided an opportunity to build clinical research directed at improving the welfare of patients and also informing the NHS about therapeutic alternatives and interventions in a rigorous way. But NHS R&D now has only approximately £70 million per annum of programme funds¹⁴ to directly support clinical research and development for the benefit the Health Service (Pattison, 2003). This represents 0.1% of NHS turnover, which is considerably less than other nationally supported health care systems. The recent decision to reduce DH manpower supporting NHS R&D and to reorganise it, provides a significant opportunity to alter both the size and the shape of research and development within the NHS.

Beneficiaries of a strong national clinical research programme

2.8 *Patients*

The major beneficiaries of research and development within the NHS will undoubtedly be the patients. A culture within the NHS that values and rewards careful and thoughtful evaluation of different practices will inevitably raise the standard of clinical practice. It is recognised that patients involved in clinical trials benefit from the application of the rigorous protocols that are a necessary function of this scientific culture. The same culture also improves the performance of health care professionals throughout their institutions. A clinical research infrastructure would allow patients in the NHS to have relatively early access to effective novel therapeutic interventions and help clinicians in the Health Service become familiar with their benefits. At the same time it would ensure early recognition of ineffective or unsafe new treatments. It follows that it should be the ambition of the NHS to have a sufficient level of clinical research within its constituent institutions so that any patient wishing to participate in a clinical trial would have the opportunity to do so. The success of the UK clinical trials for all children with acute leukaemia led to progressive improvements in therapy that has few parallels in modern medicine. We should look to having a similar structure within the NHS for most other common diseases.

2.9 *The NHS*

Decision-making and prioritising therapeutic and diagnostic alternatives requires the best possible information, which in turn requires appropriate clinical research infrastructure and programmatic research support. The NHS will be confronted repeatedly with a range of demands for its limited resources. As was recognised with the introduction of NICE, there is no alternative except to make decisions based on thorough evaluation of patient populations (DH, 1998a).

¹⁴ Additional money is provided for specific initiatives e.g.: NCRN and N-TRAC.

2.10 Expanding the research culture in the NHS would greatly improve the way it functions. Evaluation needs to be fundamental to the thinking of all professionals in the NHS. The additional infrastructure required for these research activities (new IT infrastructure as well as new imaging technologies) would make a major contribution to the efficient and effective delivery of health care.

2.11 *Clinical scientists*

This type of scientist is already an endangered part of the workforce due to the lack of career structure and research support. The loss of these individuals should be of serious concern to the NHS, for they are the key workforce responsible for addressing challenging questions about applications of new technologies. Strong support for clinical research should provide the necessary opportunities to ensure that the careers of these individuals are protected and that time and resources are available to enable them to undertake their activities.

2.12 *Basic science community*

Over the past twenty years, a compelling case has been argued for the expansion of UK capacity in basic biomedical research. It was recognised that the new tools that accompany modern biomedicine should enable discoveries to be made that would profoundly influence our ability to diagnose and treat human disease. The basic science community has delivered substantial insights into disease mechanisms and much understanding of basic biological processes. Now the challenge is to realise the benefits for patients. Failure to do so will ultimately impact negatively on the basic science community and, indeed, basic scientists are among the strongest advocates for translational research.

2.13 *Industry*

One of the strongest components of the British economy is the pharmaceutical and biotechnology sector. Their activities are dependent on interactions with academic research programmes

and on their ability to evaluate new therapies. The most important requirements are access to experimental medicine to help develop 'proof-of-concept' studies for new interventions, and clinical trial resources that utilise modern enabling technologies. There is an increasing need to access large patient populations for phase III studies. The clinical trial infrastructure required for these studies to occur should bring substantial resources into the NHS, utilising and benefiting willing patients throughout the service. Both the pharmaceutical industry and the biotechnology industry have argued that the NHS, potentially the most important and powerful arena for the development of new therapies, is an asset whose potential has not been sufficiently realised. It follows that an enhanced research infrastructure would transform the viability of UK-based health care industries. Thus a re-emergence of high quality clinical research is an essential part of wealth creation through bioscience and would simultaneously improve the lot of patients in the NHS.

The scope of NHS-based clinical research - experimental medicine and enabling technologies for clinical science

2.14 *Experimental medicine*

Detailed evaluation of small numbers of patients has historically proved crucial in improving our understanding of disease, introducing techniques for the measurement of disease progression and for evaluating the potential of novel therapies. One excellent example of how experimental medicine has transformed the therapeutic options in inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease, is the introduction of antibodies to tumour necrosis factor (TNF). These biological agents emerged from the study of TNF cytokines, which was thought to mediate the inflammatory response in autoimmune diseases. Pioneering work by Professors Maini and Feldmann at the Kennedy Institute demonstrated on a small number of

patients the potential therapeutic efficacy of anti-TNF intervention in rheumatoid arthritis (Elliot *et al.*, 1994). These observations have led to the successful development and implementation of an entirely new therapeutic modality. It seems likely that many similar opportunities exist, particularly with the technologies now available to a clinical investigator.

2.15 *Early Phase (I, II) clinical trials*

There are many examples of diseases where a cascade of new therapeutic interventions has dramatically altered the prognosis, AIDS being one of the best examples. New therapeutic options are changing the outlook of many patients with cancer: e.g. Imatinib for chronic myeloid leukaemia, bevacizumab for colorectal cancer and gefitinib for non-small cell lung cancer. The NHS has contributed rather erratically to early phase studies. This position could be transformed were the NHS equipped with an appropriate clinical research infrastructure. Many such interventions could potentially emerge from academic, NHS-based research activities. For example, most of the major gene therapy programmes in the UK are not based in industry, but in order to prove the efficacy of these therapies, patient populations and Phase I and II infrastructure must be available for clinical scientists to study their effects. A further example is the development of DNA-based vaccine strategies for infectious diseases. Much of this work is being undertaken in academic centres and has shown early promise. Not only are these approaches likely to be effective for important causes of morbidity in western populations, but they may also have profound effects in preventing and treating those diseases for which there is no clear commercial imperative, as is the case for many diseases of the developing world.

2.16 *Evaluation of novel diagnostic methodologies*

Genomics and genetics are likely to reveal many potentially useful diagnostic tests. The ability to screen large numbers of DNA variants, RNA species, proteins and small molecules (genetics,

transcript profiling, proteomics and metabonomics) will lead to the identification of many disease-susceptibility determinants and markers that predict or anticipate the onset of disease or which can be used for monitoring progression or response to therapy.

2.17 It will be important to evaluate such potentially important diagnostic tests and to develop the methodology necessary to have them carried out in routine clinical settings. With each diagnostic test, practical issues relating to technology, high throughput analysis and related ethical and legal issues need to be considered. This approach is exemplified by the work of the Genetics Knowledge Parks, which are attempting to bridge the translational gap between basic genetic research and its implementation in clinical practice. Many more such activities will be required to evaluate other diagnostic methodologies and to absorb them effectively into the clinical service if they prove to be worthwhile, or eliminate them if their clinical value is limited.

2.18 *Characterisation of intermediate phenotypes or surrogate markers for disease*¹⁵

Much of the new technology available for patient evaluation and diagnosis provides opportunities for identifying disease markers that can be used to track disease onset or progression. Analysis of viral load in HIV or hepatitis C provides one such example of disease monitoring. Modern methodologies for imaging also provide a new approach to this form of translational medicine. Dramatic advances have been made in MRI and PET. New methodology, such as Magneto Encephalography (MEG), provides additional approaches to characterising disease phenotypes. These methodologies have profound implications for the management of common disease and for the evaluation of new therapies

¹⁵ This includes medical imaging.

Experimental medicine	Clinical trials and population based science
<ul style="list-style-type: none"> • ‘Proof of concept’ studies • Early Phase (I and II) studies • Evaluation of novel diagnostic methodologies • Characterisation of intermediate phenotypes or surrogate markers for disease • New technologies and technology assessment 	<ul style="list-style-type: none"> • Disease networks • Late Phase (III) clinical trials • Drug and disease monitoring • Genomic epidemiology • Health services research

Translational research: component areas

2.19 *New technologies and technology assessment*

The craft-related specialties have a particular role to play in clinical research. These specialties have undergone innovation and development as new surgical tools and techniques have been introduced, for example, endoscopic surgery has transformed many aspects of surgery. But these innovations require evaluation before they are disseminated throughout the service. The left ventricular assist devices, a technology which NHS-based surgical researchers have been instrumental in developing, demonstrate the need for evaluation to assess their merits and to prepare the NHS for their introduction. No other body is better positioned to fund this sort of research that is essential both for the improvement of patient care and for the proper management of a dynamic NHS.

The scope of NHS-based clinical research - clinical trials and population health research

2.20 The ability to deploy clinical resources in such a way as to tackle specific common diseases is an

important part of a clinical research strategy. Organisational units based around individual groups of diseases provide one mechanism to facilitate a whole range of translational clinical research projects. The National Cancer Research Network (NCRN) phase III-IV trials and N-TRAC provide model examples of such a structure. They coordinate the implementation of large clinical trials between major centres and provide support for the collection of tissue samples and their characterisation; and promote the development of interdisciplinary programmes focused on specific disease entities, such as genotyping typing methodologies for pharmacogenetic and prognostic applications in colorectal cancer. The success of this programme indicates that such translational networks could, and should, be developed for common diseases, such as coronary artery disease, diabetes, stroke, neurodegenerative diseases and mental illness. Such networks would establish the infrastructure to ensure that the NHS could support its own clinical trials, as well as supporting clinical trials emerging from the biotechnology or pharmaceutical sector. Such networks could also facilitate the introduction of novel diagnostics, underpinning a range of other translational activities.

2.21 *Late Phase (III) clinical trials*

Large-scale (Phase III) clinical trials remain the most important single means of evaluating novel therapies. These trials are usually funded by industry although a minority of studies have been funded by the DH or the MRC. With the wealth of new therapeutic opportunities, these Phase III studies provide both an opportunity for the NHS to conduct independent studies and for industry to fulfil its regulatory requirements. Patients registered in Phase III clinical studies on the whole do significantly better than those who are not involved. Phase III studies promote good clinical practice and have a widely beneficial effect on the quality of clinical activity. The Academy believes that all patients should have the opportunity to participate in randomised clinical trials. Healthcare providers need to obtain as much independent clinical trial data as possible

to ensure that their funding decisions are as well informed as possible. Decision making about therapeutic alternatives within the NHS and organisations such as NICE need better utilisation of the NHS for Phase III clinical trials. Phase III studies require significant infrastructure support and, because of their size, are almost invariably multicentre studies. Translational networks¹⁶ would help facilitate the coordination at a national level of studies of the major diseases and, with appropriate coordination and management of patients in major centres in the UK, most patients would, if they chose, have the opportunity to participate. In theory, there is probably no health care system better placed than the NHS to undertake these large-scale trials; in practice few are currently undertaken due to the lack of skilled personnel and infrastructure.

2.22 *Drug and disease monitoring*

It has been recognised that, even after successful licensing of therapeutic interventions, ongoing monitoring is often necessary to evaluate the benefits of such therapies and to identify rare but important complications. This long-term prospective monitoring is therefore necessary for the safety of patients. Only a publicly funded health care system has the capacity and resources required for large-scale follow-up studies. For example, the recent long-term follow-up programme for β -interferon will be the only means of demonstrating whether this therapy has sustainable benefits for patients¹⁷ with multiple sclerosis (NICE, 2002).

2.23 *Genomic epidemiology*

The interface between genetics, genomics and epidemiology will provide some of the most important insights into the underlying mechanisms of disease and may provide information about lifestyle or other environmental determinants of disease. Only within the NHS will it be possible to undertake studies of the scale and scope necessary to characterise both biological markers and environmental determinants, while providing appropriate

infrastructure needed to support such activities. The Biobank project represents one such opportunity. With the provision of better IT infrastructure within the NHS and the use of cohort design, it should be possible to follow large subsets of the population. This will promote a better understanding of the environmental and biological influences on disease and should improve treatment.

2.24 *Health services research*

There is a substantial body of research that needs to be undertaken to ensure the successful operation of the many components that make the NHS function effectively. This includes a whole set of issues relating to activities within both hospitals and general practice and includes the activities of medical and paramedical staff at all levels within the Health Service. A rigorous approach to health services research could have profound economic implications and is an essential component of the NHS managerial function.

¹⁶ For example: NCRN and N-TRAC.

¹⁷ In an identifiable sub-group, β -interferon therapy cannot be used to treat all patient groups.

Chapter three - *Clinical trials and population-based health research*

3.1 Historically the UK has had an outstanding record in developing much of the methodology used to undertake many forms of population-based health research, including clinical trials. The development of methodology for large-scale clinical trials, large prospective cohorts and meta-analyses have all emerged from the UK population health community.

3.2 These activities have also in the past delivered very substantial contributions to the health of individuals in this country. For example, the pioneering observations of the role of smoking in the aetiology of lung cancer and heart disease has led, in the UK, to one of the most effective smoking control programmes in the world and, compared with our neighbours in Europe, a dramatic reduction in the incidence of lung cancer. Similarly, large-scale clinical trials have robustly informed the NHS about decisions it takes regarding the application of old and new therapeutic or diagnostic interventions, ensuring these are founded on a strong evidence base and, hence, provide real cost effectiveness in the way the service is run. For example, the Heart Protection Study provided, for the first time, quantitative data on the profound effect of the use of statins in all individuals at risk of cardiovascular disease or stroke regardless of cholesterol levels (HPSCG, 2002). This has profound implications for both patients and the NHS. Other examples include the trials that have gradually refined the therapy of acute childhood leukaemia, one of modern medicine's greatest achievements, or trials of the use of cognitive therapy in the management of mental illness.

3.3 Despite this remarkable track record and the proven ability of this methodology to enhance the welfare of patients and the efficient decision making within the NHS, there has been a crisis in the support and funding of clinical trials

within the UK over the past five years (Chalmers, in press). Whilst the ability of these trials to produce high quality data that could be used to determine cost-effectiveness had been demonstrated, even before this crisis, inadequate resources were available to ensure these studies could address the host of unresolved questions from across the breadth of medical care.

3.4 Importantly, these population-based studies incorporate not only acute care, hospital-based services, but also involve a major contribution from community-based sites, including primary care. Primary care based clinical science has the capacity to evaluate data relating to individuals in the community who may not currently be the recipients of healthcare. It is also likely that existing and future prospective cohort studies, which will provide us with much information about the role and interaction between the environment, genetics and disease, will be based in a primary care setting.

A National Network for Clinical Research

3.5 Despite the general lack of existing infrastructure and capacity to pursue clinical trials, there are some examples of structures that could be replicated or expanded. The NCRN and the N-TRAC provide effective examples of how major centres around the country can be brought together to perform large-scale clinical trials and translational research activities. These networks will ensure that the speed and quality of data that is generated around the evaluation of many of the new therapies for cancer is significantly improved. This model provides a structure on which to base other networking programmes. Programmes that link centres with expertise in stroke, ischemic heart disease, mental

health, neurodegenerative diseases, diabetes, respiratory disease and bone and joint disease, provide a framework on which to build clinical trial and clinical research capacity in the UK. Experience from the cancer model suggests that relatively modest investment yields disproportionately large returns.

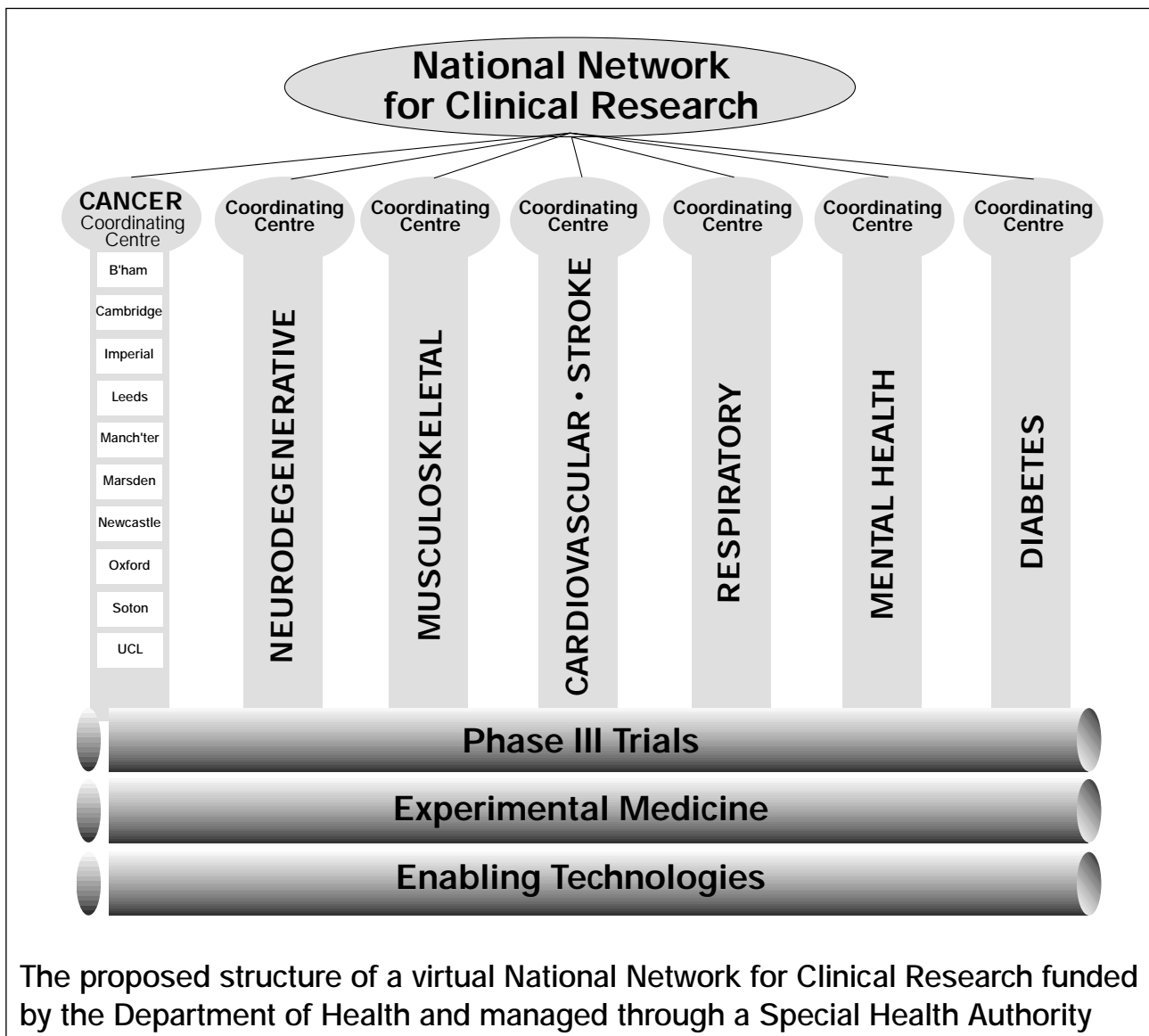
3.6 The expansion of disease specific networks and infrastructure to facilitate large-scale clinical trials would be one of the remits of a National Network for Clinical Research (NNCR) funded through the NHS. This entity would have the capacity to link major centres around the UK into clinical trial networks, supplying them with the necessary administrative and support staff to allow rapid ascertainment of patient populations and facilitate

entry into large-scale studies. The NNCR would both fund the infrastructure and provide support for individual trials as determined by the needs of the NHS or identified by NICE. Many of these clinical trials could be partnered with other funding agencies such as the MRC and the major charities. The major role of the NNCR would be to ensure the provision of infrastructure.

Major objectives in re-establishing a clinical trials framework in the UK

3.7 Infrastructure

There is a profound lack of organisation and infrastructure needed for development of clinical trial protocols. This infrastructure requires the



identification and support of network participants with the administrative staff and research nursing staff necessary to undertake large-scale studies. This strategy would facilitate subsequent programme support for a range of clinical trials as the infrastructure need not be replicated.

3.8 Certain individual centres have established such networks already, for example the Clinical Trials Service Unit in Oxford has a substantial network of sites around the country capable of recruiting patients for clinical trials in cardiovascular disease. Most of these networks, however, remain *ad hoc* and fragile, requiring central commitment and coordination from the DH.

3.9 The second component of infrastructure that needs investment is the IT infrastructure within the NHS. As long as this remains fragmented and dysfunctional, it will be extremely difficult to undertake many large-scale, population-based prospective studies, patient monitoring studies, and clinical trials. Current plans to improve IT within the NHS must take into account the needs of research (DH, 1998b).

3.10 *Workforce development and career structure*

Clinical trials and population-based health research, both in the hospital setting and in primary care, are at risk because of the lack of adequate training positions for young clinicians and the lack of long-term support for senior scientists who wish to undertake this activity as a career. Positions in academic general practice are almost impossible to fill at the present time and even senior posts in population-based health specialties have been difficult to recruit to in recent years. This reflects both the funding uncertainties of this area of work and the lack of funded training positions for individuals with these specific interests.

3.11 There is a need to correct the current deficit in training positions for young clinicians and the lack of long-term support for senior scientists wishing to pursue a career in clinical trial and population based health research. This requires

attention to funding training and career grade posts by both Higher Education Funding Council for England (HEFCE) and the NHS.

3.12 *Ethics and governance framework*

Population-based health research is data-dependent. Many studies have demonstrated that large datasets produce more robust information on clinical trial outcomes and on population-based health studies. The opportunities being created by the NHS Information Strategy could potentially provide substantial advances in this field. However, these are significantly inhibited by the constraints placed on the use of data for health research.

3.13 Concerns about these limitations on access to data have been discussed elsewhere by the Nuffield Trust in its report “Learning from Experience: Privacy and the Secondary Use of Data in Health Research” (Nuffield Trust, 2002). The Nuffield Trust focused on key matters of societal control and proposed three options for the secondary use for data research: (i) use of personal data with consent from the subjects; (ii) anonymisation of data before use but with the general acceptance that reversible anonymisation will be needed, that systems must be effective and secure and data must be difficult to re-identify without authorisation; (iii) the use of personal data without explicit consent under a public interest mandate. The Academy strongly supports this approach and commends it to Government.

3.14 It is the Academy’s view that the UK should attempt to avoid an overly bureaucratic system where privacy concerns represent a growing barrier to participation in research. There is little evidence that the concerns of individuals related to data protection in other spheres necessarily extend to access of their health data for the general benefit of advancing health care research. An appropriate level of consent must be achieved alongside important considerations of privacy. These issues of data protection will be highlighted by the availability of an electronic data record

within the NHS that will significantly challenge existing ethical and governance framework in that the information found therein has enormous potential for improving health. The Nuffield Trust recommendations would, if adopted, go some way to meeting these objectives.

3.15 The activity of multiple research ethics committees also presents challenges to the further development of large-scale population-based protocols. Diverse outcomes from multiple reviews of the same protocol provide a threat to the conduct of large-scale multi-centre trials and widespread studies in genetic epidemiology (McWilliams *et al.*, 2003). The approach taken by the health centre research ethics committees should be strengthened and extended.

3.16 *Methodological issues*

There remains an urgent requirement for methodological developments in this area. Although randomised controlled clinical trials are highly effective at measuring outcomes in some diseases, they are difficult to conduct in many of the chronic diseases. This is relevant to both common chronic diseases (multiple sclerosis, Alzheimer's disease, rheumatoid arthritis etc.) and relatively rare disorders that nevertheless constitute a major public health burden.

3.17 *Programme funding*

The single biggest limitation in the expansion of clinical trials activity, once an appropriate infrastructure is in place, would be the programme funding to support these activities. Although there are clearly multiple potential funders for this activity, few have shown commitment to providing the resource needed to undertake clinical trials in the UK. The annual programme research budget of NHS R&D has fallen to below £70 million for all of its project funding (Pattison, 2003). The MRC has reduced its financial commitment to clinical trials and, although some major charities, particularly the British Heart Foundation and Cancer Research UK, have

shown significant commitment to this area in the past, other charities such as the Wellcome Trust have made little contribution (although the Trust has been a major contributor to other population-based studies such as Biobank) (BHF, 2003; CRUK, 2002; Biobank, 2000). The investment in large-scale clinical trials by industry in this country has also steadily fallen over many years. The lack of coordination and infrastructure, slow patient recruitment, un-coordinated ethical approval structures and relatively high costs have made the UK an unappealing site for inward investment in clinical trials.

3.18 The NHS could provide the best system for clinical trial design and practice, and advantages would accrue to several branches of Government as well as to patients. We recommend therefore that the DH and the NHS, the major beneficiaries, should support the renaissance of this type of research. This would be achieved through the enhanced NHS R&D budget recommended in this report.

Chapter four - *Experimental medicine*

4.1 This activity is in jeopardy in the UK and yet it remains the single most important step in ensuring that the most appropriate diagnostic and therapeutic interventions are developed for the benefit of patients.

4.2 This field has been transformed through access to a number of enabling technologies that allow precise dissection and characterisation of human diseases that can act to provide surrogate markers or intermediate phenotypes for evaluation. Imaging, for example, has dramatically changed in the past ten years, allowing much more detailed characterisation of anatomical structures and the detection of differences in functional activity (fMRI and PET), imaging organs in real time at high resolution (high resolution ultrasound) and establishing the appropriate dose of drugs based on receptor occupancy (PET). Molecular tools such as transcript profiling, proteomics, metabolomics and genetics allow the characterisation of disease prognosis and potentially therapeutic responsiveness in many diseases. Experimental medicine has great potential to enhance both our understanding of disease and to evaluate diagnostic interventions. As an essential part of the process of turning ideas into treatments it is potentially a major source of wealth-creation .

4.3 While much of the innovation which needs evaluation derives from the pharmaceutical and biotechnology industries, these cannot undertake the necessary experimental medicine studies. Such studies require trained clinical scientists, appropriately selected patients and enabling technologies. Innovations will also come from academia, for example, most of the best work in new DNA vaccines has emerged from academic programmes. The 'prime-boost' HIV vaccine programme that is now the leading vaccine candidate worldwide for HIV has emerged

entirely out of Andrew McMichael's vaccine programme funded by the MRC (McMichael *et al.*, 2002). Similar DNA based vaccine programmes for malaria and TB are academically led. Antibody therapy and gene therapy programmes have also historically often been led by academic groups.

4.4 It is imperative therefore to establish a new paradigm for experimental medicine.

Objectives for developing experimental medicine in the UK

4.5 *Infrastructure*

The pressure on NHS service beds has meant that there is little or no available clinical research space within academic centres. One way forward has been indicated by the provision of clinical research facilities funded by the Wellcome Trust. However only a few such centres exist and the maintenance of these facilities remains challenging. They require core administrative staff and research nurses. Most existing facilities are financially insecure as the substantial fixed overhead costs need to be obtained through a research funding stream that is limited at present. The financial activity of a typical centre (Western General Hospital, Edinburgh) is shown in the Appendix 5. We strongly recommend that the NHS should provide funding so that all major medical centres have access to facilities of this kind. In addition to the centres, there is an ongoing requirement to maintain clinically important technology, such as imaging equipment.

4.6 *Career structure and training*

As with clinical trials, there are inadequate training opportunities for young clinicians willing to undertake research in experimental medicine. More training posts in this area need to be

identified and ring-fenced by the NHS. Medical schools-career grade posts will be essential for clinician scientists (AcMedSci, 1999, 2000, 2002).

4.7 *Programme support*

Diverse sources for programme support will need to be harnessed to make this a thriving scientific arena. The MRC should be capable of contributing significantly to the programmatic training support in this area. Similarly, the major charities have shown a commitment to some aspects of experimental medicine and recognise that more funding is needed if this area is to become vibrant again. The DH would itself benefit from supporting aspects of this work, particularly in the field of imaging, technology evaluation and early evaluation of new therapy funding through its NNCR. We recommend that further attention to specific funding by all these bodies should now be given.

4.8 *Industry*

Pharmaceutical companies increasingly look to the clinical academic community for 'proof-of-concept' studies in man for rapid and efficient methods for establishing appropriate dose ranges and for efficient pre-clinical development. The availability of this expertise in the UK would be a significant draw to inward investment in this area and would give companies based in the UK a competitive advantage. For biosciences in particular, geographic proximity is important and so failure to develop these facilities within the UK will have serious detrimental effects on the emerging UK bioscience industry (DTI, 1999). We recommend therefore that these activities should have specific support from the NHS and industry working in concert. The proposed NNCR could assist in ensuring that these activities receive priority.

4.9 *Reward structure*

The conventional reward structure recognised by academic institutions, HEFCE and the major funding agencies is difficult to apply to scientists undertaking experimental medicine. Data emerging from these studies is seldom published in the high-impact journals, such as *Nature*, *Cell* and *Science* and the time required to move through the development and implementation of a single set of protocols is such that productivity can easily be perceived to be low, based on publication rate (NHS and Wellcome Trust, 2001). This underestimates the significant expertise and process required in developing successful experimental design and implementing it in practice. Similarly, this type of activity is often unrecognised within NHS reward systems. Some change in the reward structure for scientists needs to be introduced and we recommend that the relevant Research Assessment Exercise panels take account of this type of research in their appraisals.

4.10 *European Clinical Trials Directive*

The introduction of the European Clinical Trials Directive has the potential to impede the ability of academic institutions to undertake sound, safe and ethically acceptable programmes of research in experimental medicine by imposing on them the same standards that would be needed to obtain eventual market authorisation. This Directive could, therefore, be sufficiently onerous to stifle the growth of academically based experimental medicine or to make it prohibitively expensive for all non-industrial based sponsors. We strongly endorse the UK Government's efforts to ensure that the implementation of this Directive is handled sensitively.

Chapter five - *Building collaboration and trust*

The collaborative nature of clinical research

- 5.1 Few areas of science cross as many boundaries between organisations as does clinical research. Attempts to expand this activity cannot succeed without the wholehearted support of the NHS and the universities, nor are they likely to be successful without the commitment of other funding agencies, including the MRC and the major charities. It is vital therefore that a more robust mechanism for cooperation is developed than exists at present.
- 5.2 Infrastructure must be provided by the NHS, but programme support could come from a variety of sources. Support for training and capacity-building must be jointly shared by all the committed parties, including NHS Trusts and universities. A good example, illustrating the difficult boundaries that need to be managed, is the support of career staff undertaking responsibility for experimental or clinical trials in a hospital setting. These individuals are likely to participate in routine clinical practice, to have university appointments and to need a significant number of sessions 'bought out' to allow them to engage in these forms of clinical research. Such individuals would need a range of parties contributing to their long-term stability and success.
- 5.3 The cost of these ventures will also demand the participation of many parties. Clinical research is costly, in part because of the expense associated with hospital care or, in the case of clinical trials, the size of studies necessary to provide adequate power. Such studies are likely to become more complex as the standard of care improves and the need for larger studies becomes increasingly apparent.
- 5.4 Funding agencies in the UK have not always been effective at surmounting the barriers between their organisations to ensure programmes of research are successfully carried out. However, examples where cooperation has been clearly present are available. One of these is the National Cancer Research Institute, which acts as a forum for all parties funding cancer research in the UK. It has provided an opportunity for collaboration and cooperation, ensuring the portfolio of cancer research related activities is properly balanced. Similarly, the NHS R&D programme and the MRC have cooperated effectively in the past on many clinical trials and, more recently, the DH, the MRC and the Wellcome Trust have collaborated effectively to ensure that the support for the Biobank project was obtained (NHS, 2003; Biobank, 2000). These collaborations need to be built upon. The Academy recommends that a forum be developed for these interactions to be facilitated.

Building trust

- 5.5 A crucial component in the success of any clinical research programme would be the confidence of the general public in the aims and practices of medicine and, more particularly, of this form of science. The challenges faced by science generally are well described in the report of the House of Lords Science and Technology Committee Enquiry (HoL, 2000) and can be summarised as follows:
- there is a crisis of public trust, and assent for research can no longer be assumed
 - public values and attitudes must be heeded, controversial topics can rarely be reduced to sole consideration of the scientific issues
 - there must be a new culture of dialogue and engagement to replace the 'public understanding deficit' model

- presumption of openness and transparency is necessary
- scientists must learn to live with a free press

5.6 The House of Lords report was perceived as initiating a new era, emphasising that ‘increased and integrated dialogue with the public is intended to secure science’s licence to practice, not to restrict it’. There have been subsequent initiatives by the UK Government (BA, 2002) and the European Commission (European Commission, 2002a) on how best to inform and involve the public in science¹⁸. The ESRC public consultation work (ESRC, 2003) includes a survey on recent advances in genetic research and concludes that there is ‘little evidence to support the idea that the presence of more science, scientists and science specialists in the media will increase the public understanding of science’. It goes on to assert: what matters is ‘not so much the science itself, but establishing clear connections between science, policy and the broader public interest’.

5.7 There are few areas of research where public participation is more important than clinical research. This must be viewed as a partnership; the research is designed to provide genuine benefits for human health, but also involves the selfless participation of individuals who may not themselves benefit directly from the research.

5.8 Many of the specific issues for clinical research have recently been examined in the US by the IOM (IOM, 2003), in particular:

- defining and promoting participatory research - covering issues for incentives, academic facilities, conflict of interest considerations, community involvement and specification of model collaborations
- increasing the role of the public in research oversight, particularly the research ethics review process and identification of new

models for human subject protection procedures

- improving the translation and dissemination of the results from clinical research, particularly via patient groups and consensus conferences

Public attitudes and values

5.9 The public is generally unfamiliar with medical research and how it leads to innovation. There are concerns expressed about accountability, regulation of procedures, commercialisation. The ‘public’ is not, of course, homogenous and commentators on negative public sentiment about research have not always properly considered whether the attitude is prevalent or merely attributable to a vocal minority. As part of the process of differentiating public attitudes, it can be useful to identify specific stakeholder groups¹⁹. The role and responsibility of patients is particularly important in addressing the identified impediments to medical research. In this context it is also important to differentiate the particular features of public attitudes to the biosciences.

5.10 *Biotechnology*

Recent data from the EU Eurobarometer study (European Commission, 2002b) shows that the UK is almost the least optimistic in Europe about biotechnology²⁰, although health care applications, e.g. genetic testing, cloning human cells, are perceived as useful and to be encouraged. When the European public are asked ‘who is trusted to tell the truth about modern biotechnology?’ the medical profession is found to be most trusted²¹.

5.11 *Human embryo research*

The UK MORI poll (MRC, 2003) found that 70% of those interviewed supported the use of human embryos for medical research with three-quarters of those respondents taking the view that such work should be limited to treatment for serious disease and fertility research.

¹⁸ The Royal Society has recently set up a working group on best practice in communicating scientific results to the public (RS, 2003).

¹⁹ For example activists, elected representatives, patients/patient interest groups.

²⁰ The UK was just ahead of Greece.

²¹ Outranking consumer organisations and universities and considerably more trusted than the media, government bodies, industry and politicians.

²² The medical profession was not listed as a source of information; university scientists were ranked as the most trusted.

5.12 *Animals in medical research*

The UK MORI poll (CMP, 2002) revealed overall support for experiments on rats, mice and rabbits (and human volunteers), with most acceptance expressed for research for life threatening and debilitating diseases. There was evidence that trust in the regulatory system was eroding and no single professional group was trusted by a majority of those surveyed to provide honest, balanced information²².

Building public and patient trust

5.13 Trust is essential in any successful relationship, including that of the researcher and patient. It has been argued that the recent culture of accountability, intended to increase trust, in fact does the opposite, through excessive bureaucracy and contradictory or unrepresentative targets. What is required instead is better governance without unnecessary centralised micro-management (O'Neill, 2002).

5.14 Thus engaging with patients is important, not just in order to restore confidence or to comply with research governance changes, but also to build trust and change public perceptions of clinical research, in order to:

- promote advocacy in support for research funding and its priorities
- increase participation in the research process and promote accountability, addressing the concern that the UK research agenda does not necessarily match societal priorities for tackling common diseases
- work to reinforce the importance of basic research in understanding the causes of disease
- involve patients in quality of life and impact assessments, to improve the value of research outcomes, and to facilitate dissemination of best practice
- generate commitment to support new opportunities, e.g. data banks, stem cell research, that underpin research advance
- highlight the value of participating in research

to the health services, the economy and the individual (see Chapter 3).

5.15 More needs to be done to explain the procedures for human subject protection in research - and for the research community to challenge the assumptions inherent in new regulatory oversight²³ as necessarily increasing public protection

5.16 Taking forward these recommendations requires commitment to develop informed support for a uniform system of consent for research in the NHS (characterised by opt-out procedures) while avoiding the excessive codification that will inhibit future possibilities. In this context, further attention needs to be given to optimising a role for the Central Office for Research Ethics Committees (COREC) in facilitating public engagement and to ensuring a flexible UK implementation of the EU Clinical Trials Directive.

5.17 A new coherence across the medical research constituencies is required in particular to:

- agree goals for public engagement and identify the performance indicators so as to know when goals are achieved
- share examples of best practice across the research community and with society-at-large
- clarify institutional roles necessary to effect change

Summary

5.18 Initiatives directed at expanding the clinical research base require collaboration on the one hand between governmental and other funding organisations and on the other the whole-hearted support of the public. This is a critical issue for developing a modern evidence-based NHS. It cannot be undertaken solely by the medical research community.

²² The medical profession was not listed as a source of information; university scientists were ranked as the most trusted

²³ For example: the European Directive on Clinical Trials (see Chapter 1).

Chapter six - Proposal

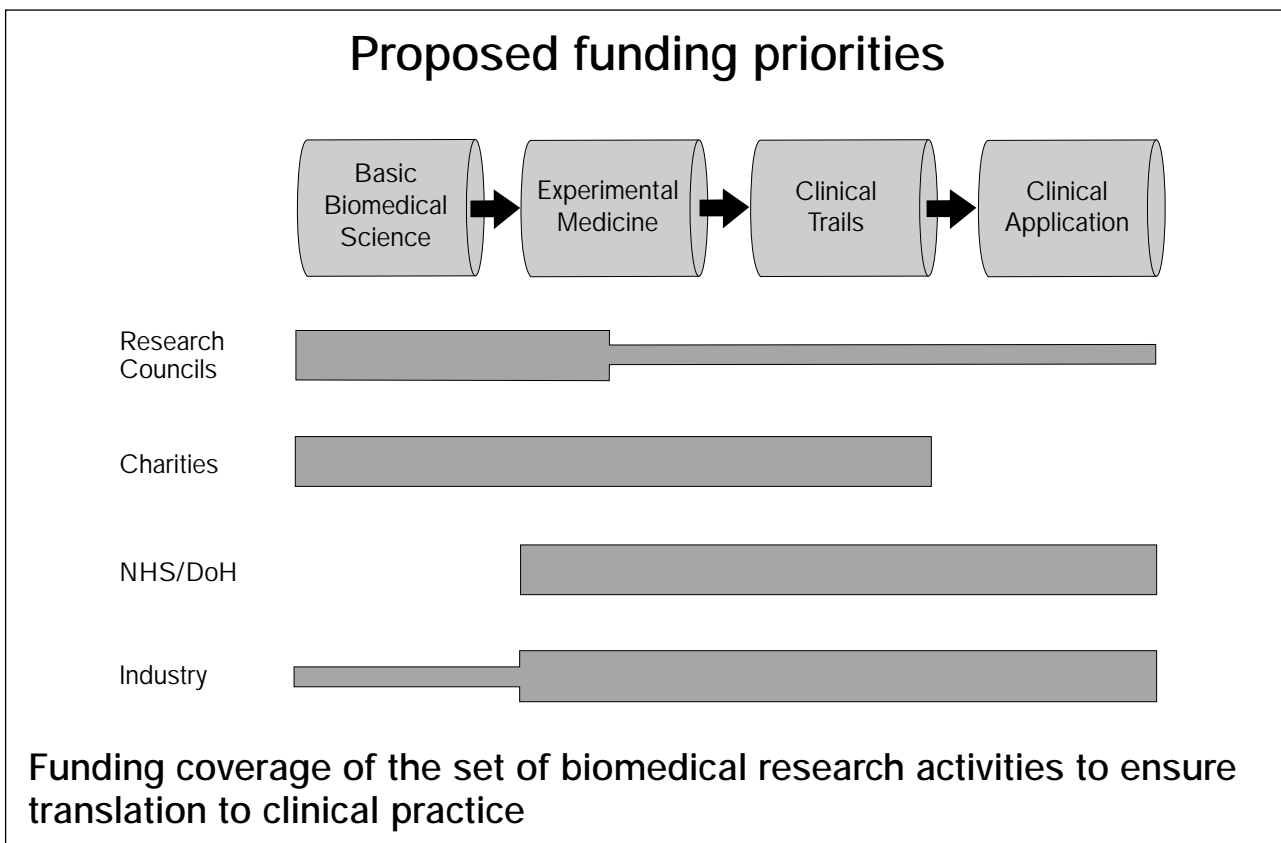
6.1 The Academy believes that in the preceding chapters compelling arguments have been presented indicating that the revitalisation of clinical research is needed for the prevention of disease, the care of patients and for the success of the pharmaceutical, biotechnology and healthcare industries. Revitalisation of clinical research as an important part of the overall research portfolio in science in the UK must now become a priority. Patients in the NHS rely on the translation of basic research to clinical practice to deliver what has been promised by the substantial funding of basic biomedical research programmes over the past twenty-five years. Similarly, health care related industries, the pharmaceutical and biotechnology sectors all depend on this activity if they are to remain competitive and continue to invest in the UK.

6.2 Re-establishment of clinical research requires the co-ordination of funding partners - the DH,

the DfES, the DTI, MRC, the major charities and industry.

6.3 *The DH and the NHS*

Little of the seemingly considerable funds notionally attributed to NHS R&D (£550 million), has been successfully directed at improving the clinical research base in the UK. It is estimated that only £70 million per annum has been used for real grant support (Pattison, 2003) and much of this has been spent on initiatives such as N-TRAC and the NCRN as well as the Genetics Knowledge Parks. The DH must retain responsibility for the infrastructure through which clinical research could be undertaken in the UK. No other body can manage this crucial component of the programme. Similarly, the NHS must be responsible for establishing and facilitating the networks necessary to undertake large-scale clinical trials in a variety of disease areas. The re-creation of a thriving R&D function for the NHS is a central component of the Academy's recommendations.



6.4 The N-TRAC and NCRN models have proved successful in attracting inward investment, creating networks of health care facilities capable of undertaking large-scale trials, facilitating translational research through the establishment of tissue banks and enabling technologies. These structures have already attracted inward investment from the pharmaceutical sector and have enabled the NHS to make decisions about therapeutic and diagnostic interventions being introduced for many forms of cancer.

6.5 The Academy advocates extension of this structure for other major diseases. Each of these major diseases should be supported in a similar way, with capacity to undertake large-scale trials. Appropriate enabling technology, up-to-date trial methodology, and links to experimental medicine protocols would be required. See Appendix 6.

6.6 The Academy suggests six major areas be given priority to be developed along the lines already adopted for cancer. These are: vascular disease (ischemic heart disease and stroke), respiratory disease, mental health, neurodegenerative diseases, diabetes and bone and joint disease. It is further suggested that each distinct area be constituted as a clinical institute that might be organised or co-ordinated together as the National Network for Clinical Research. Such Networks would allow the NHS to expand its clinical research programmes, bringing together the necessary expertise from around the UK and providing the distributed network of trial sites that would give patients in most parts of the country the opportunity to participate in trials should they wish to do so. Success in these major diseases could later be applied to various other disorders particularly those that are relatively rare and need multi-centre participation. Attention is drawn to the immune tolerance network set up by the US NIH to facilitate clinical research into immunological disease²⁴ as an example of the power of this approach. The cost of such a structure would be, based on expenditure of

N-TRAC and NCRN in 2003, approximately £18 million per annum per programme. This programme could therefore be established for £100 million in total, with capacity to expand as it increases its capacity to undertake both translational experimentation and large-scale trials.

6.7 A crucial component of such funding structures is that they must require the NHS to manage and control the infrastructure needed for all clinical research taking place in NHS institutions. This structure, outlined above, would be amenable to an approach to overhead support that would cover the full economic cost of all such activities ongoing in NHS establishments. Although the costs are likely to be substantial, experience with cancer indicates that there are powerful opportunities for better health care and the early adoption of evidenced-based diagnostic and therapeutic measures. Further debate is required on how best this funding stream is to be managed but it is essential that the full cost of providing high quality research is met and that there should be no disincentives for major medical centres to engage in this activity. It seems likely that a combination of overhead support related to the programmes being undertaken, together with core support for clinical investigation facilities, is likely to be the best solution.

6.8 The DH would also need to ensure that positions were available that would allow individuals to undertake career positions in clinical science, dividing their activity between clinical service, experimental medicine or clinical trials. The funding of these positions could come from NHS Trust budgets for supporting service work, and from the Special Health Authority and the NNCR. Such a system would be an incentive for a career in clinical science within the NHS.

²⁴www.immunetolerance.org

6.9 *Proposed National Network for Clinical Research structure*

The most appropriate structure for a NNCR within the DH would be a Special Health Authority. It would have the power and influence to ensure the infrastructure was in place across the NHS and would be sufficiently autonomous to make decisions of scientific priority within its budgetary constraints.

6.10 *Medical Research Council*

Clinical research in the UK cannot thrive without the commitment of the Medical Research Council. The MRC has a distinguished record in supporting, both methodological development and the implementation of large-scale clinical trials. Indeed, most expertise in the area of Phase III studies has emerged from MRC funded programmes. It has also had a creditable track record in providing research training support for young clinical scientists. In the area of experimental medicine and proof-of-concept studies, much less support has been provided, except in specific areas such as vaccine development. However, it has lately recognised the importance of developing expertise in experimental and translational medicine. The Council of the MRC is currently reorganising its Board structure to accord greater priority to translational research and to expand its clinical trial activities as larger, more expensive trials become necessary. No other government agency has the capacity and experience to manage clinical research and the Academy therefore recommends that new funds for such research, other than those dedicated to NHS infrastructure referred to paragraph 6.7 (and managed by the DH) should be allocated to the MRC and ring-fenced for programmes of translational research and training.

6.11 The MRC will have a key responsibility in developing additional capacity for training clinician scientists. The MRC should expand its existing programmes with more emphasis on

experimental medicine, clinical research and clinical trials. The Academy's recent success in securing outstanding young clinical scientists in hitherto neglected areas, including the craft disciplines is noteworthy and could form the basis of a joint programme with the MRC for increasing capacity.

6.12 Programme support for clinical research would be a key component of the MRC's remit. Support for large clinical trials, ideally done in collaboration with the NHS, and for experimental medicine protocols and programmes, would be of special importance for this organisation. An additional important activity best funded from this source is the methodological work that is needed, particularly in the area of clinical trials methodology and the definition of surrogate markers using the new enabling technologies.

6.13 *The Charities*

Medical research in the UK has greatly benefited from the generous support of the UK public through the establishment of a multiplicity of charities such as the cancer research charities and the British Heart Foundation which have played a substantial part in supporting all forms of medical research. However, it is difficult for the smaller charities to support the costs of clinical research and they have been heavily dependent on the infrastructure provided by the NHS. The Wellcome Trust has played an important part in clinical research through its support for training programmes and, latterly, recognising the difficulties faced by clinical research workers, set up five clinical research facilities to which reference has already been made. The medical charities should be encouraged to support research training and should continue to participate fully with the NHS and MRC in the development and activities of the NNCR.

6.14 *Industry*

The commitment to industry is dependent on the appropriate investment and establishment of infrastructure and support for clinical research by others in the UK. Significant success in this field, however, would immediately lead to new inward investment. This has already been demonstrated through the success of the N-TRAC programme and would be similarly successful in other clinical arenas should they exist. The success of this research arena would secure significant competitive advantage for UK-based pharmaceutical and biotechnology industry, both of which have a serious requirement for experimental medicine and for clinical trials. Their support for such a notion is evident in the recent BIGT and PICTF reports.

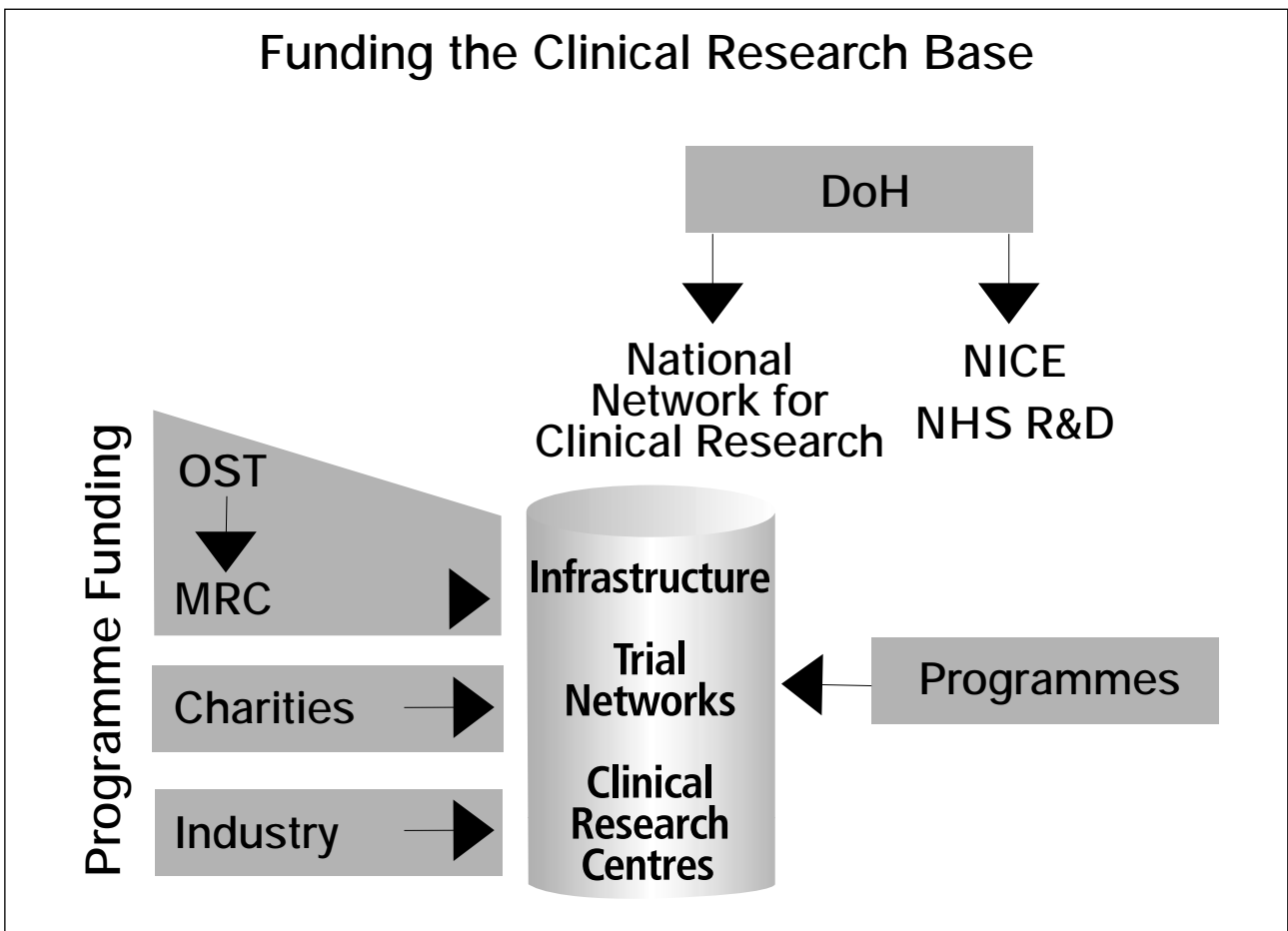
research undertaken in basic biomedical environments over the past twenty-five years. The delivery of some of the exciting observations that have been made in basic science to the bedside would validate the significant investment made in the UK to this activity over many years. It would also have profound benefits for the NHS which needs rigorous data to make decisions about its activities and which also needs to operate in a culture strengthened by the spirit of enquiry and evaluation.

6.16 Patients would ultimately be the major beneficiaries of these efforts, as the delivery of new interventions in a timely and thoughtful way could allow modern biomedicine to have a profound impact on the welfare of many people.

Conclusion

6.15 The Academy believes that clinical research must now become a national priority if the UK is to reap the benefits of the explosion of biomedical

6.17 These opportunities, as well as the possibility of improving UK competitiveness in the pharmaceutical and biotechnology sectors make the expansion of this area a necessity rather than an option.



Appendix 1 - Acronyms and abbreviations

AAMC:	American Association of Medical Colleges	NICE:	National Institute for Clinical Excellence
ABPI:	Association of the British Pharmaceutical Industry	NIH:	National Institute of Health, USA
AcMedSci:	Academy of Medical Sciences	NNCR:	National Network of Clinical Research
AIDS:	Acquired Immunodeficiency Syndrome	NRC:	National Research Council
BA:	British Association	N-TRAC:	National Translational Cancer Network
BHF:	British Heart Foundation	OECD:	Organisation for Economic Cooperation and Development
BIGT:	Biosciences Innovation Growth Team	OST:	Office of Science and Technology
BMJ:	British Medical Journal	PET:	Positron Emission Tomography
CFI:	Canadian Foundation for Innovation	PICTF:	Pharmaceutical Industry Competitiveness Task Force
CIHR:	Canadian Institutes of Health Research	PMedSci:	President of the Academy of Medical Sciences
CMWF:	Commonwealth Fund	R&D:	Research and Development
CMP:	Coalition for Medical Progress	RNA:	Ribonucleic acid
COREC:	Central Office for Research Ethics Committees	RS:	Royal Society
CRUK:	Cancer Research UK	TNF:	Tumour Necrosis Factor
DH:	Department of Health	WGH:	Western General Hospital
DTI:	Department of Trade and Industry	WTCRF:	Wellcome Trust Clinical Research Facility
DNA:	Deoxyribonucleic acid		
ESRC:	Economic and Social Research Council		
EU:	European Union		
FMedSci:	Fellow of the Academy of Medical Sciences		
GCP:	Good Clinical Practice		
HEFCE:	Higher Education Funding Council for England		
HIV:	Human Immunodeficiency Virus		
HoC:	House of Commons		
HoL:	House of Lords		
HPA:	Health Protection Agency		
HTA:	Health Technology Assessment		
IOM:	Institute of Medicine		
JAMA:	Journal of the American Medical Association		
MEG:	Magneto Encephalography		
MRC:	Medical Research Council		
MRI:	Magnetic Resonance Imaging		
NCRN:	National Cancer Research Network		
NHS:	National Health Service		

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Appendix 3 - Working Group and Review Group members

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and in consultation with the Officers of the Academy.

Appendix 4 - Terms of reference and work plan

Terms of reference

To identify, characterise and document impediments to medical research in the UK. The Working Group took an integrated view of basic and clinical research and clarified priorities for action:

- (i) Presenting the evidence that is already available and recommending what further evidence must be collected, in order to quantify the impact of specific issues in the UK (comparing the UK with other countries, where appropriate);
- (ii) Taking account of relevant activities by other bodies, identifying gaps and the particular strategic value added by Academy-based activity;
- (iii) Providing options and recommendations to address the problems identified and advising on a mechanism to track subsequent outcomes.

Timetable

The Working Group first met in October 2002 to agree work plans and responsibilities. Working Group members, supported by the research capacity of the secretariat, provided evidence, analysis of issues and strategic prioritisation, meeting again in December 2002 and February 2003 to collate themes and prepare inputs. A general Call for Evidence was published in February 2003. Working Group review of the draft report was initiated in August and it was decided that the report should focus on clinical research. The Academy's review procedure was initiated and completed in October.

Call for evidence

Inputs to the Working Group were invited via a Call for Evidence placed on the Academy's website, as a global e-mail to all Fellows, and in response to a presentation from the Chairman of the Working Group to a joint Academy/Foundation for Science & Technology event on 30 April 2003, entitled 'Building stronger partnerships in medical science research in the UK'.

The call for written evidence contributions emphasised the need to identify those actions that will make the UK a better location for research, more productive and more attractive to funders. Inputs were invited for the key areas, including funding and governance.

A summary of responses to the Call for Evidence can be found on the Academy's website: www.acmedsci.ac.uk.

Appendix 5 - *The Wellcome Trust Clinical Research Facility based at Western General Hospital, Edinburgh*

The dedicated, purpose-built, Wellcome Trust Clinical Research Facility (WTCRF) sited at the Western General Hospital (WGH), Edinburgh, has centralised core resources and is available to support all types of investigator-initiated studies, including pilot or feasibility studies. Benefits of conducting studies under the auspices of a clinical research facility of this kind include the provision of appropriate structures for quality assurance of data and implementation of Good Clinical Practice (GCP) and Research Governance guidelines. It is the only facility of its kind in Scotland.

The information given here about the WTCRF is intended as an example of a clinical research unit. There is likely to be variability in the details, for example, staff costs, grants etc., of such units, whether existing or planned. The figures and information given are intended as a 'snapshot' of this unit's work, which itself varies according to activity and over time.

The WTCRF clinical space comprise five bedrooms, a day studies area, with five couches and two beds, a research clinic with three consultation rooms, an exercise testing room and a large intensive study room. The core areas, including a 60 seated seminar room, occupy the remaining space, which is approximately half of the building.

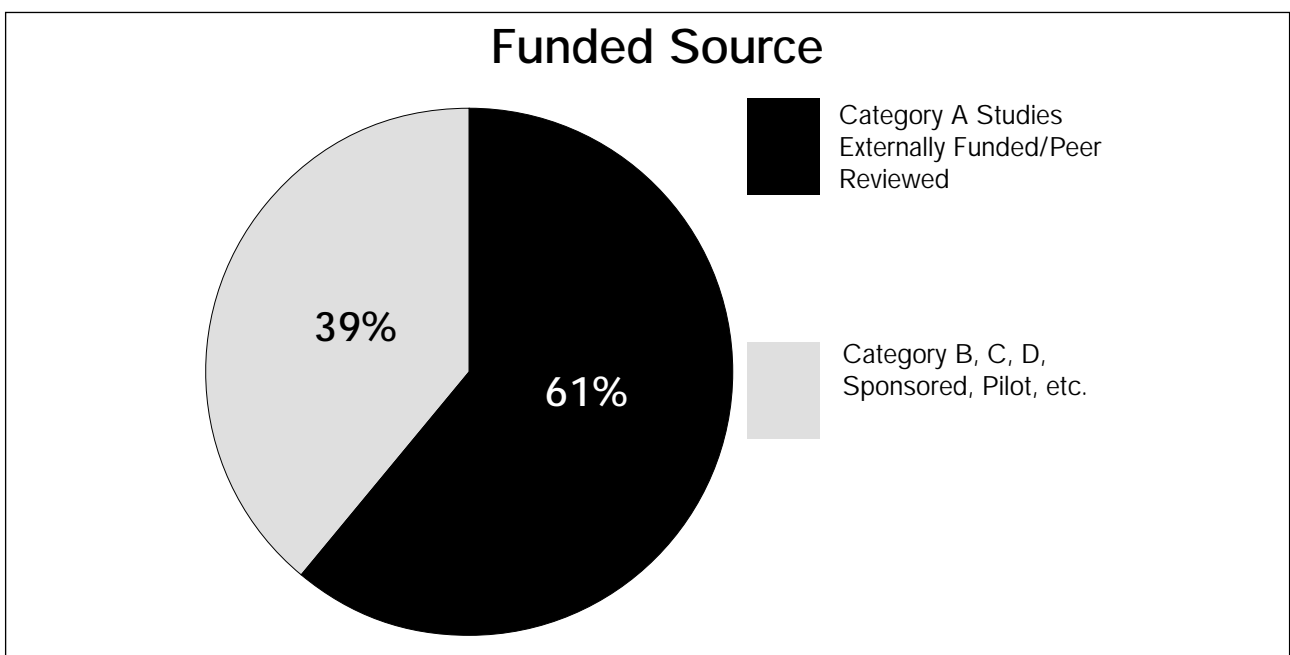
Initially a satellite unit at the Royal Infirmary provided an intensive studies room with fluoroscopy for invasive or complex studies, one bedroom and clinic space. This transferred, and expanded in May 2003, to the new Royal Infirmary of Edinburgh at Little France.

There are also five 'core' areas supporting researchers in:

- epidemiology and statistics
- integrative physiology
- genetics
- image analysis
- mass spectrometry

Funding

	April 2000 - March 2001	April 2001 - March 2002	April 2002 - (projection to March 2003)
Total staff and non staff costs	£212,231	£458,802	£669, 396



Funding of infrastructure and recurrent costs in the future will come largely from NHS R&D allocations (Lothian University Hospitals Trust and Lothian Primary Care Trust) but in the future, importantly, also from research grants.

The WTCRF is available to any researcher with an 'approved' externally-funded, peer-reviewed study (to be known as 'Category A' in future), as well as to those investigators undertaking sponsored, pilot and commercial research (Categories B, C & D). In the period Jan 2001-Dec 2002, studies have been retrospectively categorised with approval given to 34 'Category A' studies and 22 studies in Categories B, C and D, of which 2 were commercial, see below.

There were 21 different grant-funding sources associated with approved studies in this period. The six most frequent grant awards received by applicants are shown below:

Grant awards	No. of studies
British Heart Foundation	14
Chief Scientist Office, Scotland	8
Wellcome Trust	5
Research and Development, Scotland	5
Medical Research Council	3
Chest Heart and Stroke, Scotland	3

Summary

The WTCRF is a streamlined and coordinated facility that optimises the research environment for clinical investigators and is supporting all types of investigator-initiated studies. The central location within a major new teaching hospital ensures ease of access for participants in research as well as for a broad range of NHS Trust and University users. Over 3000 subject visits have occurred in the period and there have been 13 publications, with two studies winning prizes.

Appendix 6 - A funding framework for establishing a National Network for Clinical Research

The Government's programme of work to modernise the Health Service offers an extraordinary opportunity to shape the NHS in a way that supports and levers maximum benefit from recent advances in genomic, proteomic and molecular research for patients and the UK economy. A new National Network for Clinical Research (NNCR) would seize this opportunity through managed distributed clinical research networks covering the seven leading causes of mortality and morbidity in the UK. These networks would provide the infrastructure and training capacity to establish clinical research as a significant platform in the modern NHS, benefiting patients, the Health Service and the parts of the UK economy that contribute to health care innovation.

Resource implications and funding models

The funding model for the new NNCR is based on that of the National Translational Cancer Research Network (N-TRAC). This network was designed to provide infrastructure and training for translational research and for large scale trials and relies on a linked group of centres that co-operate to provide the support, recruitment and technical capacity for clinical research in the cancer area.

The NNCR extends this highly successful model to the other six major areas of morbidity and mortality in the UK, with each having the same basic structure currently in place for cancer. There is considerable room for expansion of the programmatic research that might be undertaken in these networks. The costs associated with this infrastructure are therefore relatively well defined.

1. *CLINICAL RESEARCH NETWORKS:* A funding stream is required to support NHS infrastructure and workforce capability in clinical research through managed distributed networks covering the leading causes of morbidity and mortality in the UK.

- cancer
- cardiovascular disease and stroke
- diabetes
- musculoskeletal disease
- neurodegenerative disease
- respiratory disease
- mental health

For one network:

- a co-ordinating unit, estimated to cost £800k per annum, will be required;
- up to 10 selected network centres, costing £260k per centre per annum, will be required.

For all seven networks:

- seven Co-ordinating Units are required, estimated to cost £5.6 million per annum;
- up to 10 Centres per each of seven networks are required, estimated to cost £18.2 million per annum.

This gives an estimated sub-total cost of £23.8 million per annum for all seven networks.

2. *TECHNOLOGY PLATFORMS:* A second funding stream is required to support the building the network's infrastructure in shared technology platforms. This can be divided into:

- building the infrastructure and capability underpinning the network's shared technology platforms such as tissue resources, imaging, genomics, proteomics, and bioinformatics, with an estimated cost of £15 million per annum. Many of these platforms could be shared between Networks in major centres.
- building the infrastructure and workforce capability underpinning clinical trials, with an estimated cost of £40 million per annum.

This gives an estimated sub-total cost of £55 million per annum.

3. *TRAINING AND EDUCATION:* A third funding stream is required to support building of the NHS's workforce capability through training and education.

- One training and education fellowship is estimated to cost £100k per annum;
- Therefore, for each disease network, ten training and education fellowships will cost an estimated £1 million per annum;
- Over all seven disease networks, the total of 70 fellowships is estimated to cost £7 million per annum.

This gives an estimated sub-total cost of £7 million per annum.

4. *EXPERIMENTAL MEDICINE:* A fourth funding stream is required to build capacity for clinical research in the form of experimental medicine in the NHS. This would support a limited number of clinical investigation centres and the evaluative work that went on in them. This would need to be carefully co-ordinated with investment made by the MRC and medical charities to ensure value added and avoid duplication of activities.

This is estimated to cost £8 million per annum, giving a sub-total of the same value.

5. *DIRECTOR'S OFFICE:* Finally, a funding stream is required to support the NNCR's Director's Office which will include including central programmes of work.

This is estimated to cost £1 million per annum, giving a subtotal of the same value.

Therefore the total estimated cost for the proposed NNCR is £94.8 million per annum. This is given in the table below.

This funding would provide the necessary infrastructure and training capacity within the Health Service. Once in place it could service activities funded by other funders including the MRC, charities, industry and other components of the health service that are required commissioned research to function efficiently (i.e. NICE).

Therefore the total estimated cost for the proposed NNCR is £94.8 million per annum. This is given in the table below:

Funding stream	Estimated cost per annum
Networks	£23.8 million
Building the Network's infrastructure and workforce capacity in shared technology platforms	£55.0 million
Building the NHS's workforce capacity through training and education	£7.0 million
Building capacity for clinical research in the NHS	£8.0 million
Supporting the Networks Director's Office	£1.0 million
Total	£94.8 million



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