

## **Responses to questions from the Review of UK Health Research from Iain Chalmers, Editor, *James Lind Library*, 24 July 2006**

Email: [ichalmers@jameslindlibrary.org](mailto:ichalmers@jameslindlibrary.org)

### **Question 1**

#### ***1.1 What are the strengths and weaknesses of the MRC and NHS R&D programmes at present?***

The MRC and NHS R&D programmes differ in a number of ways, and both have strengths.

The MRC programme has existed for nearly a century, and so it has had decades of opportunity to earn international respect and to accumulate a number of very important 'research trophies'. These include some very important clinical trials, many of them based on successful international collaboration and coordinated by internationally respected research units such as the MRC Clinical Trials Unit in London and the Clinical Trials Service Unit in Oxford. The MRC's relative independence from political interference has sometimes been relevant: one of the most important MRC trials in recent years - the Heart Protection Study - was opposed for political reasons by the Department of Health. However, although the MRC often draws attention to examples from its clinical and epidemiological research when presenting its work to the public, the UK Clinical Research Collaboration's Health Research Analysis shows that 80% of MRC funding is for basic underpinning and aetiological research, with a very modest element of the remainder spent on applied clinical research. I am not aware of any formal analysis of the effectiveness of this balance of investment.

A commentary by Peter Rothwell in the current issue of the *Lancet* (2006;368:262-266) raises important questions about funding for practice-orientated clinical research. The UKCRC analysis has shown that less than 10% of **total** research funding is on clinical research. This funding pattern has existed for decades, and because it left the NHS poorly served by the research community, it prompted the House of Lords to make the recommendations that led to the establishment of the NHS R&D Programme in 1991. The Programme has always had a very substantially smaller budget than the MRC, but I believe it has used its limited resources well. The NHS R&D Programme is a global leader in supporting systematic reviews of existing applied research - work which has served the NHS well because of its fundamental importance in developing clinical guidelines and cost-effectiveness assessments for NICE. The Programme has also been successful in commissioning clinical trials across a very wide range of health conditions and intervention types, many done under the aegis of the Health Technology Assessment Programme, which has also established a substantial international reputation in only a decade. Interestingly, the NHS R&D Programme has also commissioned what I believe to be the largest programme of methodological research in the world, including research

relevant to assessing the validity of animal models for human disease and treatment (see <http://www.pcpoh.bham.ac.uk/publichealth/nccrm/publications.htm>)

In 2003, I made available to those preparing the BIG-T and AMS reports on clinical research an analysis of the characteristics of non-commercial clinical trials (subsequently published as Chalmers et al. 2003). This showed (i) that the NHS R&D Programme had commissioned trials in disease areas and of intervention types which had been almost completely ignored by the MRC and the medical research charities; and (ii) that there had been a dramatic fall in the number of non-commercial trials, particularly trials supported by the DH/NHS R&D Programme. This reflected, in part, Alan Milburn's decision to abolish regional health authorities, thus abolishing with them the R&D Programme's main responsive funding stream.

Those responsible for the BIG-T and AMS reports on clinical research are probably in the best position to assess whether the overall ratio of basic to applied research funding across the MRC and the NHS R&D Programme is likely to address the crisis in clinical research which both reports identified as a matter of serious concern. However, I agree with Peter Rothwell's conclusion that the current ratio of basic to applied research funding is unlikely to address the crisis in clinical research or the information needs of the NHS.

In a final comment in response to this element of Question 1 I want to draw attention to some examples of constructive interaction between the MRC and the NHS R&D Programme.

- The Department of Health provided core funding for National Perinatal Epidemiology Unit; the MRC provided funding for many of the clinical trials in the Unit's portfolio of perinatal trials (which became the largest programme of perinatal trials in the world during the 1980s).
- Systematic reviews of treatments used in intensive care were funded by the NHS R&D Programme through its core support of the Cochrane Injuries Group. These led to an MRC-funded, multinational trial (CRASH), which showed that, for three decades, we have been killing patients with acute traumatic brain injury by giving them steroids.
- MRC-funded sociological investigations made important input to the design of a NHS HTA-funded trial (ProtecT) on the treatment of early prostate cancer. This MRC-sponsored qualitative research helped to make successful a study which was widely predicted to be impossible.
- Regional NHS R&D funding was used to assess the feasibility of a randomized comparison of intravascular and open surgical management of intracranial arterial aneurysms. The success of the feasibility study led to a successful MRC-funded main study (ISAT), and helped to promote an appreciation of randomized trials among interventional radiologists.

### ***1.2 How do each of these support the research and training needs of the NHS, social care, industry and academia?***

Both the MRC and the NHS R&D Programme have training fellowship schemes relevant across the spectrum from basic to applied research in health and social care.

As a largely responsive programme, the MRC can restrict its funding to individuals and groups with established track records and correspondingly low risk of failure. In these circumstances calling for “funding to be awarded on the basis of excellence” is natural and unproblematic, but it has tended to reinforce current patterns of funding, and has resulted in limited coverage of the health problems seen and interventions used in the NHS.

By contrast, as a largely commissioned programme wishing to extend the reach of research to areas not traditionally covered, the NHS R&D Programme has had to take greater investment risks. The consequence, however, is that it has fostered the development of research skills in areas like physiotherapy in which no strong research tradition had previously existed. The focus of the NHS Programme has probably also contributed more than the MRC to a general improvement in research awareness and critical research appraisal skills. These contributions may not always reflect research excellence, but they are essential if a research culture is to become embedded within and across the whole of the NHS.

### ***1.3 Does more need to be done?***

Yes. I am encouraged that the MRC has recently increased its investment in clinical research and has started to fund methodological research. In addition, I have it on good authority from within the MRC that it is, at last, going to begin to fund systematic reviews which, for over a decade, it has required of applicants requesting funding for support for new clinical trials.

After wide consultation, the NHS R&D Programme has presented some radical and exciting plans in ‘Best Research for Best Health’, and I am glad that these have been welcomed publicly by the Secretary of the MRC and other influential people. However, although Haldane did not (as some have implied) call for government departments to eschew direct commissioning of research to inform their policy needs, the NHS R&D Programme has clearly suffered both from ministerial neglect and from political interference, such as that which led the Department to oppose proposals for the Heart Protection Study, and to the collapse of the NHS’ regional and investigator-led R&D capacity. One of the most important challenges facing the Cooksey Review is how to preserve the many good features of the NHS R&D Programme – including accountability - while protecting the programme both from political neglect and from political interference.

Finally, in response to Question 1, I want to express my hope that, in whatever new arrangements are put in place for managing the single fund, successful features of current arrangements will be protected, in particular:

- Independent as well as commissioned systematic reviews
- Commissioned, non-commercial clinical trials
- Promotion of research strength and innovation in neglected areas

## **Question 2**

### ***2.1 What do you believe are the key scientific challenges facing health research in the UK over the next decade, and how might the UK Government best help address those challenges?***

The key scientific challenge is to build, systematically, on what is known already, both to guide practice and policies within the NHS, and to inform the design of new research. For example, one of the most important advances over the past 20 years has been discovery of the importance of aspirin for reducing risks associated with cardiovascular disease. These were identified when a UK-led initiative assembled individual patient data from all the relevant controlled trials in the world in systematic reviews. Not only did these systematic reviews guide clinical decisions, they also informed the design of new trials, for example ISIS-2, which showed that a small dose of aspirin reduced the risk of premature death after myocardial infarction by 20%.

Although these principles have become more widely adopted in recent years by clinical researchers – particularly those involved in late phase clinical research - they have not been observed sufficiently within animal research and early phase clinical research. Not only is this scientifically indefensible, it may also be a reason for the high failure rate of drug discovery programmes.

The government can help ensure that these principles are observed by assessing compliance with existing requirements to review systematically what is known already before embarking on new research, and extending these requirements to areas in which they are currently being ignored.

### ***2.2 What do you believe are the key organisational challenges facing health research in the UK over the next decade, and how might the UK Government best help address those challenges?***

Of the many good suggestions within ‘Best research for best health’, promoting an evaluative, research-conscious culture within the NHS seems to me to be key. The government can encourage adoption of this culture in a number of ways. Specifically, government could (i) ask NICE to make greater use of the option to recommend that inadequately evaluated treatments should be used only within a research framework until

more was known about their advantages and disadvantages; and (ii) provide the funding and incentives to support the research needed.

***2.3 What do you believe are the key challenges underpinning training, and how might the UK Government best help address those challenges?***

Promoting wider appreciation of the importance of acknowledging uncertainties - about the validity and relevance of animal models, the effectiveness of current approaches to translational research, the validity of diagnostic strategies, and the effects of treatments and organisational models of service delivery – and understanding the strategies required to address these uncertainties.

***2.4 What do you believe should be the Government's objectives for health research, and why?***

To produce knowledge which can be used to protect and improve the health of individuals and the population more generally – because this objective should be an element of government policy in all nations which wish to be regarded as civilized.

**QUESTION 3**

***3.1 What should be the Government's priorities for health research?***

Prioritization of health research will always be contentious (as will be made clear by the responses to whatever priorities are suggested by the Cooksey review!). Because most investment in health research is made either by research councils and charities operating responsive (investigator-led) funding schemes, or by industry commissioning research for its needs, government must consider how to support the many important gaps left by these arrangements (a point made in the report of the House of Commons Health Committee on the influence of the pharmaceutical industry). I have referred above to the success of the NHS R&D Programme. Both NICE and the NHS Health Technology Assessment Programmes have open invitations to suggest questions that their respective programmes should address. The Department of Health and the MRC have both contributed funding for creating the Database of Uncertainties about the Effects of Treatments ([www.duets.nhs.uk](http://www.duets.nhs.uk)), and the James Lind Alliance ([www.lindalliance.org](http://www.lindalliance.org)) which is endeavouring to promote greater attention within the research community to patients' and clinicians' unanswered questions about the effects of treatments. Both Department of Health, the MRC and the NHS Health Technology Assessment Programme have said that they will take account of priorities identified in this way. In addition to taking patients' and clinicians' priorities into account in research priority setting, the government needs to make explicit the criteria and processes it uses to choose among competing priorities.

### ***3.2 Is there anything the Government should stop doing or funding?***

The government sometimes comes across as too ready to challenge others to improve their efficiency without setting an example itself. Government should stop funding costly initiatives without building in scientifically robust evaluations. For example, many of the initiatives introduced following public health white papers (health action zones, health improvement plans, the Sure Start programme, and so on) were introduced without well designed evaluations. As a result, it remains unclear whether they are an effective use of limited resources. The government's repeated management reorganisations of the NHS are a further example of inadequately and irresponsibly under-assessed initiatives.

Within clinical care within the NHS, the government should be more ready to insist that inadequately assessed treatments should only be used within the context of well-designed research. The fiasco following NICE's defensible decision about drugs for multiple sclerosis and more recently over herceptin could have been avoided had the government been prepared to stick to the principles which it claims led it to create NICE. As suggested above, encouraging NICE to make greater use of the option to recommend that treatments only be used within the context of research would not only help to produce the information needed by the NHS, but also promote a research-aware culture within the Service.

### ***3.3 What is the Government not doing or funding that it should do?***

See above.

### ***3.4 In the absence of further sources of support, what can the Government do to release the necessary funds?***

Government should cease its massive investment in unevaluated initiatives and increase its support systematic reviews of what can be known from existing research, as it has envisaged in 'Best research for best health'. A analysis of NIH clinical trials recently published in the Lancet (Johnston et al. 2006) suggested these studies were highly cost-effective investments because of the introduction of new practices or cessation of unhelpful practices. It was pointed out in subsequent correspondence that systematic reviews are likely to be even more cost-effective (Glasziou et al. 2006).

## **QUESTION 4**

***How should decisions be taken on the balance between the long-term economic and social benefits of a high quality biomedical research base; and the needs for research to improve healthcare and other public services? What is the appropriate balance between public funding for investigator-led and priorities led research? How do we***

***balance funding for basic science, translational science and applied science? Is this something that should vary over time? What mechanisms should be used to make judgments about this balance?***

Because of the very unsatisfactory quality of the evidence to inform answers to these questions, I feel unable to offer any more comments of possible relevance than I have already mentioned above and in my covering letter.

## **QUESTION 5**

***5.1 In your experience, how have the results of publicly-funded health research in the UK been used in the development of new treatments***

As has been pointed out by others, although progress in developing treatments is sometimes ‘from bench to bedside’ it can work in the other direction too. One of the clinical trials coordinated by the National Perinatal Epidemiology Unit, funded by the Department for International Development and WHO, was designed to compare three treatments for eclamptic convulsions – magnesium sulphate, diazepam and phenytoin. Magnesium sulphate had been used in the USA for nearly a century but rarely in the UK, which had used diazepam and, more recently, the anti-epileptic drug phenytoin. Some neuroscientists regarded the use of magnesium as an anticonvulsant as ludicrous, because no mechanism was recognized through which it could have anticonvulsant activity. The results of this pragmatic clinical trial showed that (dirt cheap) magnesium sulphate is superior to the more expensive alternatives; but I gather that it has also led to a re-evaluation of the role of magnesium in ictal activity by neuroscientists. This insight may lead to better treatments for epilepsy.

***5.2 In your experience, how have the results of publicly-funded health research in the UK been used to influence / change wider policy and healthcare practices?***

The clear results of the trial mentioned above changed the practice of British obstetricians very rapidly (Jones et al. 1998), as did the results of the MRC-funded ISIS-2 trial among British cardiologists. Both these trials were large enough to provide very clear answers. Similar effects can be achieved with systematic reviews and meta-analyses of the results of a number of similar trials, as happened for example with tamoxifen in breast cancer, aspirin in cardiovascular disease, and prenatal corticosteroids prior to premature delivery.

Investment by the MRC in large trials and by the NHS R&D Programme and NICE in systematic reviews has had a massive impact on the development of clinical guidelines, and these have sometimes been reflected in changes in clinical practice such as those mentioned above. However, it cannot be assumed that strong evidence from research will necessarily impact on practice. For example, organization of effective services for patients experiencing a stroke and its after-effects has lagged years behind publication of

systematic reviews showing the beneficial effects of organized stroke care (stroke units) on mortality and residual disability (Langhorne and Dennis 1998).

Eighteen months after the results of the MRC CRASH trial had been published in the Lancet, I wrote to the Minister for Health asking who was responsible for ensuring that no patients admitted to the NHS with acute traumatic brain injury were receiving systemic steroids. Her answer made clear that existing mechanisms for ensuring that NHS patients would benefit from new research findings were far from satisfactory.

### ***5.3 What lessons can usefully be learned to improve the uptake of advances in science and medicine?***

I share the belief of others that great improvements in health could be achieved if existing research evidence were to be applied more effectively. There has been pitifully little investments in the information systems needed to make relevant research evidence and information about ongoing trials available to clinicians and patients at the time they need it. The National Library for Health ([www.library.nhs.uk](http://www.library.nhs.uk)) provides an excellent gateway, but it needs more resources. Furthermore, more and better research is needed to understand how to improve implementation, and this very challenging field of research deserves much greater attention and support than it has received. During my tenure as chair of the advisory committee for the MRC Health Services Research Collaboration one of the world's leading investigators in this field – Professor Jeremy Grimshaw - was lost to a senior post in Canada when the MRC indicated that it was not willing to invest in this kind of research.

## **QUESTION 6**

***How might better links be forged between 'basic', translational and applied researchers, working across the whole field of health research, from the laboratory bench to the front line of the NHS? How might better links be forged across disciplines, e.g. with engineers, physicists, and social scientists?***

I have illustrated earlier how the assumption that links needed are unidirectional - from the laboratory bench to the front line of the NHS – is unhelpful. A possible reason for the disappointing dividends from massive investment in drug discovery programmes is because the clinical perspective in much basic science has been lost. Clinicians could be mandatory partners in most basic science grants to make sure of a clinical perspective.

As the House of Commons Health Committee pointed out, there is a particular need for support of research on non-drug interventions. This was also emphasized by Charles Warlow, professor of neurology in Edinburgh, in his BMJ editorial on the MRC report 'Clinical Trials for Tomorrow': "Government agencies and charities must not abdicate funding to the commercial sector. There are far too many noncommercial interventions

that need to be tested, such as non-patented drugs, surgery, devices, physiotherapy techniques, and so on.” (Warlow 2003).

## QUESTION 7

### ***How can the Government encourage translation, entrepreneurship and innovation in health research to improve public services in the UK?***

I have been encouraged to believe that the Cochrane Collaboration, which I am told now involves participation by well over 12,000 people all over the world, is an example of entrepreneurship and innovation in health research which has impacted positively on public services in the UK and elsewhere. With some reluctance, I draw on my personal experience of the development of this organization (Chalmers 2003).

During the 1980s, the Department of Health provided core funding for me and some other staff in the National Perinatal Epidemiology Unit. We never had contracts for longer than five years and extensions were based on satisfactory external assessments. This core funding allowed us the flexibility to develop new projects. One of these was a pilot study to develop methods for preparing, maintaining and disseminating (on paper and electronically) the results of research about the effects of healthcare interventions in pregnancy, childbirth and early infancy.

After the NHS R&D Programme had been initiated by Michael Peckham, I submitted a proposal for funds to establish a small centre (a ‘Cochrane Centre’) to facilitate the extension of these methods beyond the perinatal field. I asked for 5 years with a review after 3. I am told there was considerable scepticism about my proposal among members of Michael Peckham’s main advisory committee (the Central Research and Development Committee). However, he took the plunge and told me he would provide funds for three years with a review after 18 months, and I accepted this. After targets had been agreed with Steering Group chaired independently by Professor Martin Bobrow, I was left alone with almost complete freedom to use the budget assigned to me in whatever way I felt would secure the centre’s agreed objectives.

I think two features of this experience may be relevant to the question you have posed. First, peer review is innately conservative and suspicious of new ideas. I doubt that the pilot study that we completed successfully within the National Perinatal Epidemiology Unit, would have survived a standard peer review process. The proposal for the Cochrane Centre probably only survived peer review because Michael Peckham was very familiar with the success of the pilot study.

The second feature that may be relevant was that, with one brief episode at the National Perinatal Epidemiology Unit which nearly led me and some of my colleagues to resign, the Department of Health made no attempt to micro-manage my work. I really was left alone to pursue ‘blue skies’ health services research!

## QUESTION 8

***How can UK health research funding be most effectively used to provide the appropriate infrastructure for basic, translational and applied research, whether funded by the UK public sector or other sectors? How can UK health research funding be most effectively used to support the work of NICE, facilitate innovation and collaboration with industry, and address market failures in the application of healthcare?***

As suggested in my covering letter, the following serious problems need to be confronted:

- Failure to address biased reporting of research
- Failure to cumulate evidence scientifically
- Failure to establish valid measures to assess returns on investment in research

## QUESTION 9

***What lessons should the UK learn from other countries in making the proposed changes to the institutional arrangements for the funding of health research?***

I have insufficient knowledge of arrangements in other countries and their relevance to the UK to be confident about answering this question. However, the director of the Mario Negri Institute in Milan, Silvio Garattini told me in May about a recent development in Italy which I believe deserves serious consideration. The Agenzia Italiana per il Farmaco (AIFA) is the first European drug regulatory agency to fund independent clinical research on proprietary and unregistered drugs. This is because new legislation now requires pharmaceutical companies operating in Italy to contribute a fee corresponding to 5% of their annual advertising and promotion costs (salaries excluded) to “a central pot for independent, publicly funded clinical trials.” This has already allowed AIFA to complete a call for approval in three areas of clinical research: orphan drugs, head to head comparisons of drugs in randomized controlled trials, and translational research. All the research proposals received have been assessed by independent, international referees, and 54 projects were approved last March for a total budget of approximately 40 million euros. I understand that a second call will be launched very soon. The results of these studies will help AIFA’s regulatory activity, and will encourage independent clinical research in Italy. The UK should consider establishing a comparable scheme.

## QUESTION 10

***In implementing the single fund for health research, to what extent should the MRC and DH / NHS R&D be merged or brought together? And to whom should the single,***

***ring-fenced fund be accountable? Please provide reasons and any supporting evidence for your response.***

Pass! Except to say that, as with any reorganization, it is important to avoid trying to fix what isn't broken (Oxman et al. 2005), and to monitor carefully the outcomes of any changed arrangements. I have tried without success for four years to persuade the MRC and the DH to update information about the characteristics of clinical trials provided to the BIG-T and AMS working parties on clinical research (Chalmers et al. 2003). Not only should this simple descriptive information be collected and published on an annual basis. It would also be worth planning to repeat, perhaps in 3 years' time, the survey of research investment done by the UK Clinical Research Collaboration. Indeed, it might be worth establishing a small unit to duct relevant 'research on research', to improve understanding of how to assess value for investment in research.

#### **QUESTION 11**

***To what extent does the success of recent innovations in health research (e.g. Clinical Research Networks) and the proposed structures rely on the new Connecting for Health NHS IT system, and to what extent should it do so?***

I think it is appropriate to challenge the assumption in this question – that the National (Cancer) Research Network has been successful. What is the answer to the question “What - *of relevance to patient care* - has NCRN-supported research added to what was already known?” As Rothwell (2006) writes in the current Lancet, “the much vaunted initial doubling in numbers of cancer patients entering ‘clinical trials’ in England after the introduction of the NCRN in 2001 was, in fact, mainly accounted for by non-randomised observational and genetic studies of various kinds.”

However the success of the Clinical Research Networks are judged, it is clearly possible to do useful clinical research without any dependence on Connecting for Health. For example, the NHS Central Register has made possible greatly superior long term follow-up rates of study participants in the UK than are possible in the United States. Indeed, I have been rather surprised that so little has been made of this feature of research capacity in the UK. I suppose this must be because industry is not particularly interested in the long term effects of its products. Whether Connecting for Health will help to improve the research needed by the NHS remains to be seen.

#### **QUESTION 12**

***Given that NHS R&D is currently devolved, but that the work of Research Councils is not, how can these functions work best together to maximise the health and economic benefits to the UK?***

The Health Departments already share funding for certain core research resources and projects. The ones with which I am familiar are the UK Cochrane Centre and the Centre for Reviews and Dissemination in York. These existing examples suggest that, given willingness to collaborate when collaboration is needed, pragmatic solutions are possible.

## References

Chalmers I (2003). The pre-history of the first Cochrane Centre. In: Bosch X, ed. Archie Cochrane: Back to the front. Barcelona, 242-253.

Chalmers I (2005). Academia's failure to support systematic reviews. *Lancet* 365:469.

Chalmers I, Rounding C, Lock K (2003). Descriptive survey of non-commercial randomised trials in the United Kingdom, 1980-2002. *BMJ* 2003;327:1017-1019.

Glasziou P, Djulbegovic B, Burls A (2006). Are systematic reviews more cost-effective than randomised trials? *Lancet* 367:2057-8.

Johnston SC, Rootenberg JD, Katrak S, Smith WS, Elkins JS (2006). Effect of a US National Institutes of Health programme of clinical trials on public health and costs. *Lancet* 367:1319-27.

Jones P, Johanson R, Baldwin KJ, Lilford R, Jones P (1998). Changing belief in obstetrics: impact of two multicentre randomised controlled trials. *Lancet* 352:1988-9.

Langhorne P, Dennis M (1998). *Stroke units: an evidence based approach*. London: BMJ Books, 1998

Oxman AD, Sackett DL, Chalmers I, Prescott TE (2005). A surrealistic mega-analysis of redisorganisation theories. *Journal of the Royal Society of Medicine* 93:563-568.

Rothwell P (2006). Funding for practice-orientated research. *Lancet* 368:262-266.

Warlow CJ (2003). Clinical trials for tomorrow funded by the MRC. *BMJ* 327:240-1.