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Using Comparative Effectiveness Research to Inform Policy and Practice in the UK NHS

Past, Present and Future

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Abstract

Health systems that have fixed budgets and a coherent organizational structure generally have found it valuable to have a dedicated primary research capacity to answer decision-oriented value-for-money questions of particular importance to the system. The UK NHS is one example of such a system. Here, we review the historical evolution of building comparative effectiveness research (CER) capacity in the NHS, describe the current situation, with a focus on how this research is used to inform decisions, and discuss present and emerging challenges. We draw some possible lessons for the US, which is currently considering using CER to inform healthcare policy and practice decisions.

In 2003, Tunis et al.[1] noted that "neither of the major sources of funding for clinical research in the United States – the National Institutes for Health and the medical products industry – has as a primary mission the goal of ensuring that studies are performed to address clinical questions important to decision-makers." Six years on, there has been a significant increase in the discussion about the need to provide better evidence for decision making in the US[2] especially, following a $US1.1 billion commitment to comparative effectiveness research (CER) as part of the American Recovery and Reinvestment Act (ARRA).[3] Indeed, the recently passed health reform establishes a new independent entity, the Patient-Centered Outcomes Research Institute, an independent agency whose primary objective is "… to assist patients, clinicians, purchasers, and policy-makers in making informed health decisions by advancing the quality and relevance of evidence concerning the manner in which diseases, disorders, and other health conditions can effectively and appropriately be prevented, diagnosed, treated, monitored, and managed through research and evidence synthesis …"[4] However, using the generated evidence to inform coverage decisions remains as controversial as ever.[5,6] This backlash against evidence-informed healthcare policy and practice is an oddity specific to the US healthcare system – no other developed or developing healthcare system and its users view evidence as suspiciously as US stakeholders, including the medical technology industry and a large proportion of policy makers.[7] But CER is nothing new.

In the UK, such research has been sponsored by government, in the form of the NHS R&D programme and, later, the Cochrane Collaboration,

and has been formally used to inform decision makers, including local NHS commissioners and central decision-making bodies such as the National Screening Committee and the National Institute for Health and Clinical Excellence (NICE). We discuss the UK NHS example, where research-based evidence on clinical and cost effectiveness (where available) forms an integral component of demand-side decisions about service provision. We look at the historical evolution of the NHS R&D programmes and ongoing developments to secure more public funding for high-priority decision-makers' questions identified by the NHS. Using the NHS as an example, we think it likely that a healthcare system claiming to use its resources to maximize the health benefit of the populations it serves will want to use evidence, especially that generated through high-quality research, in its core business decisions compared with one that treats healthcare as any other good or service.

1. A Short History of Comparative Effectiveness Research (CER) in the UK: Placing Research at the Heart of the Health Service

During the 1980s, health research (mostly basic and clinical) in the UK received public funding through the Medical Research Council (MRC) and, to a lesser extent, the Department of Health and the Economic and Social Research Council. There was little coordination of effort between the different sources of funding, including medical research charities, while the NHS's own research activities played a relatively tangential role in targeting the publicly funded research agenda towards a limited set of questions facing the NHS and government.[8] Research was driven more by the scientific interests of researchers than by policy or the practice-relevant questions of decision makers. There was considerable unwarranted (or, at least, inexplicable) geographical variation in the provision of care and style of practice, attributed by some to a lack of evidence on what 'worked', the lack of a culture demanding such evidence and the lack of a framework empowering professional leaders or policy makers to use what evidence was available.[9,10]

In the 1980s, a seminal review of health research in the UK by the House of Lords Select Committee on Science and Technology highlighted the importance of maintaining and emphasizing the 'public good' nature of health research and its relevance to decision making.[11] The Lords' report concluded "No research system can function efficiently when the principal customer for research (the NHS) has so small a direct input into the initiation of research programmes … there is no lack of push from medical researchers: what is missing is enough pull from the NHS" and recommended the establishment of dedicated structures better to "articulate [the Health Service's] needs and assist in meeting them."[9] The government welcomed the report, as did (most of) the academic community, NHS administrators and health professionals and, in 1991, more than 40 years after the launch of the NHS, an NHS-owned R&D programme was created.[12]

However, the early days of the NHS R&D programme were not without problems. Although the Department of Health budget for research was large, the vast majority of it was used to support, not individual research projects, but the conduct of research commissioned by other funders such as the MRC or medical charities, by providing and maintaining the infrastructure for clinical research.[13,14] This was done by annual subventions to major teaching hospitals but there was little accountability or transparency and, in practice, this funding was often used to support clinical service delivery costs.[15]

To help address these problems, a new government strategy, 'Best Research for Best Health', was launched in 2006.[16] This new strategy reorganized NHS R&D into the National Institute for Health Research (NIHR), whose mission was to create a system in which the NHS supports leading-edge research "… focused on the needs of patients and the public" and the development of evidence "… to inform and underpin health and social care policy."[17] A key word here is 'system' – mutually supporting organizations and programmes funding research, networks facilitating research (e.g. trial recruitment, data collection),

faculty undertaking research (key research staff, established and in training) and operational support functions (e.g. responsible for ethics and governance arrangements).

The strategy secured increased funding for established programmes such as the Health Technology Assessment (HTA) Programme, but also transferred control of the R&D infrastructure support funds from the major hospitals back to the NHS Director of R&D. This funding is now used to run nationwide clinical research networks, which support research such as the conduct of randomized and observational trials on behalf of both public and commercial sponsors, in an accountable manner. One of these networks, that for cancer, has been a model in the UK and abroad; almost one in every eight cancer patients in the UK is enrolled in a clinical trial, the highest trial participation rate worldwide.[18]

The NHS's HTA Programme[19] was established in 1993. Its role is to identify areas of uncertainty about interventions used in the NHS and to evaluate them by directly commissioning research projects – either new primary research or evidence synthesis (see table I) – in contrast with other research programmes such as those of the MRC, which are largely responsive to submissions, depending on researcher interest.[20] This is how CER is conducted in the UK setting.

Identifying NHS priorities on which to commission research is not an easy task. The HTA Programme seeks topics from healthcare professionals, managers and the public, and trawls systematic reviews for areas where uncertainty has been identified. It then uses panels of experts from similar backgrounds to select which of the 1500 topics reviewed each year are most important. 'Policy' customers such as the Chief Medical Officer or National Screening Committee may also suggest important topics: these, almost by definition, carry great NHS importance, but work is required to convert an important topic into an answerable research question. The HTA Programme then advertises the identified topics openly for the research community to respond, and will fund the best submissions. Since 2006, it also operates a researcher responsive arm but the suggestions submitted must pass similar scrutiny for NHS importance before proceeding to scientific review. The research funded may be primary data generation (usually by randomized controlled trials [RCTs] but other designs are also acceptable as appropriate), or secondary analysis of existing data (i.e. systematic review usually accompanied by an economic evaluation).

In late 2006, a Treasury-commissioned review of health research in the UK[21] concluded that the HTA Programme "… has been very successful in its role of Knowledge Production, by providing NHS decision-makers with a high quality evidence base, in meeting needs created by 'R&D market failure' and for its innovation and flexibility." The review also found that "… a substantial proportion of the escalating information needs of the NHS could be met by expanding the HTA programme to enable delivery of large improvements in the quality and efficiency of healthcare in the NHS." The report went on to recommend an expansion of the programme, which has since been funded by government. Its budget has risen from £13 million in 2005, to a planned £88 million by 2011.

The HTA Programme laid some of the ground for the establishment of one of the best known (and often vilified by the US anti-CER camp) CER agencies in the world, NICE.[22-24] The HTA Programme and NICE continue to work closely together: the HTA Programme funds the assessment (i.e. a review of the scientific evidence) of technologies of importance, identified by NICE, in independent academic centres. This allows NICE to go on to undertake appraisal (i.e. the application of judgement to areas of uncertainty where evidence is conflicting or absent, and to consider important issues such as patient choice) before coming to recommendations for NHS practice.

2. NHS R&D Responding to Decision-Makers' Needs: the National Institute for Health and Clinical Excellence (NICE) as an Originator and User of Research

There is a strong case for supporting research into decision-makers' questions in order to resolve uncertainties and inform clinical and policy

Table I. High-priority National Institute for Health and Clinical Excellence (NICE) research questions currently being considered or already advertised or commissioned by the National Institute for Health Research (NIHR) in the UK in the context of 'direct access' launched in 2005. The following priorities were considered and a decision was made to commission them between 2005 and 2007

Topic and date prioritized by NICE to NIHR	Outcome
October 2005	
Psychological interventions for the treatment of moderate and severe depression in children and young people	Project funded and will end late 2015
Pre-operative testing: evidence synthesis, cost effectiveness and value of information analysis	Project funded and will end late 2010
Interventions to help overweight and obese adults to maintain weight loss	Advertised but no suitable applications
Obesity prevention or weight reduction in younger children	Project funded and will end January 2011
October 2006	
Stages of change for smoking cessation	Advertised but no suitable applications
Exercise referral schemes	Not advertised as several similar projects underway
Increasing physical activity levels and increasing smoking cessation	Project funded and will end July 2012
Interferon gamma tests for the rapid identification of active TB	Project funded and will end December 2012
A study of the prognostic value of interferon gamma and tuberculin skin tests for the development of active TB in people with suspected latent TB	Project funded and will end June 2013
CBT and SSRIs in the management of obsessive compulsive disorder and body dysmorphic disorder	Advertised but no suitable applications
October 2007	
Cost effectiveness of routine echocardiographic examination in all newly diagnosed AF patients	Project funded and ended June 2009
Resistant hypertension	Other related projects already underway
Pill-in-the-pocket treatment for AF	Project funded and ended December 2009
Spironolactone vs eplerenone for HF early after an MI	Project funded and ended June 2009
Anticoagulation with antiplatelet therapy in AF	Project funded and will end February 2011
Acetylcholinesterase inhibitors and memantine for psychotic symptoms in dementia	On hold until October/November 2010, when results of other related trials are available
Outcomes of bariatric surgery	Advertised but no suitable applications
May 2009	
Rheumatoid arthritis: adalimumab, etanercept and infliximab	Advertised, awaiting assessment of competitive bids for funding
Irritable bowel syndrome	Advertised, awaiting assessment of competitive bids for funding
Urinary tract infection in children: diagnosis, treatment and long-term management	Advertised, awaiting assessment of competitive bids for funding
Technical patient safety solutions for ventilator-associated pneumonia in adults	Advertised, awaiting assessment of competitive bids for funding
Implantation of miniature lens systems for advanced age-related macular degeneration	Advertised, awaiting assessment of competitive bids for funding
Metastatic spinal cord compression	Advertised, awaiting assessment of competitive bids for funding
Surgical site infection	Advertised, awaiting assessment of competitive bids for funding
Mental well-being and older people	Advertised, awaiting assessment of competitive bids for funding

AF = atrial fibrillation; **CBT** = cognitive behavioural therapy; **HF** = heart failure; **MI** = myocardial infarction; **SSRI** = selective-serotonin reuptake inhibitor; **TB** = tuberculosis.

decisions in healthcare.[1,25,26] The HTA Programme example illustrates this and also some of the difficulties: supporting decision makers to convert vague wishes into researchable questions is time consuming. A second frustration to the Programme and to researchers, professionals and

policy makers is that merely generating and disseminating the evidence is not enough to change policies and to impact on practice. In 1999, the government established NICE, to put a 'front end' to the evidence and support its uptake at the local level. NICE was set up as one of a number of new institutions designed to focus attention on the better use of clinical resources (a process termed 'clinical governance'), to improve quality of care and reduce inappropriate variation,[1] to set quality standards for professionals and to advise the NHS on maximizing return on its investment in new and existing technologies.[28-30] Of these various organizations and initiatives, which included the Commission for Health Improvement and the launch of National Service Frameworks, NICE was to set best practice standards for the management of disease and to determine 'good buys' for the NHS, in transparent and consultative ways, providing research-based information for clinical practitioners and clinical managers. The initial emphasis was on technology appraisal and the creation of authoritative, evidence-informed clinical guidelines. Both – a major developmental step for policy, if not for research – were to explicitly take account of cost effectiveness. Later, surgical and diagnostic procedures and public health (including workplace health and safety) were added. From the very beginning, policy makers appreciated the importance of CER for NICE in three ways.

2.1 Earmarked Funding for Evidence Synthesis

First, NICE, in conjunction with the Department of Health, established a direct responsive connection funded via the HTA Programme with several academic centres around the UK. These conduct evidence syntheses, including systematic reviews, meta-analyses, decision analytic modelling and, occasionally, small-scale primary evidence collection, to inform NICE's advisory committees. Approximately £6 million of NHS R&D money per year is 'earmarked' to address the research needs of NICE through evidence syntheses. To date, more than 170 peer-reviewed evidence syntheses have been completed and published,[19] covering all current NICE programmes.

NICE and the NIHR have directly and indirectly supported the development of methods of subgroup analysis to allow for decisions to take into account factors (such as co-morbidities, sex or race) affecting a treatment's clinical effectiveness related either to the intervention itself (relative effect) or to the underlying disease (baseline risk – absolute effect). For example, in the 2008 update of the NICE *Guide to the Methods of Technology Appraisals*, special consideration is given to how to identify appropriate subgroups and ensure the guidance is granular enough to meet the needs of these groups.[31] Using CER to target subpopulations is also dependent upon appropriate pragmatic study designs with less strict inclusion criteria than explanatory RCTs, that reflect real-world settings.[1]

2.2 Recommending the Use of Technologies Only in the Context of Well Designed Studies

Second, policy makers understood the unevenness of the evidence base and proposed 'conditional coverage' when it was too weak for a definitive 'yes' or 'no' decision: ''In the case of promising interventions not yet supported by sufficiently robust evidence, NICE … will recommend that further research is carried out … indicate in broad terms the questions this research should address and advise clinicians that, in the meantime, they should only use the new intervention as part of … research intended to answer these questions.'' (only in research [OIR]).[32] This option has been much less popular: so far, about 1 in 20 NICE decisions on health technologies have been OIR. A very small proportion of these have led to research being commissioned, such as the evaluation of liquid-based cytology for cervical cancer screening.[33]

The OIR option is similar to the US Centers for Medicare and Medicaid Services 'Coverage

1 There is evidence that NICE has reduced variation in uptake of innovative new drugs, such as cancer drugs, although variation still exists across the NHS.[27]

with Evidence Development'[34] and, in implementing it, NICE and the NHS are faced with similar challenges.[33,35,36] Who pays for the research – public funders or the technology sponsor? Also, who pays for patient access to the new technology outside the research setting or at a time when recruitment to a trial has ended but before results (and thus a policy recommendation) are available? What happens if a technology has no sponsor, as is often the case with preventive or health promotion interventions? What are the mechanisms necessary to ensure the research findings inform guidance updates and practice? And are the findings relevant when the research reports, perhaps several years after the technology has been introduced? What are the criteria for deciding the evidential threshold below which an OIR recommendation is warranted? Is OIR an ethically acceptable option?[37] In the absence of a clear framework, OIR could end up being a 'political fudge', a means for allowing access despite the lack of evidence.[38]

The Multiple Sclerosis risk-sharing scheme, one form of providing drugs in the context of research and the first such scheme to be launched in the NHS, offers useful lessons. The scheme, conceived as a means of improving access to promising new technologies and reducing their price, whilst generating effectiveness evidence and ensuring value-for-money of NHS spending on new technologies with an uncertain evidence base, is a good example of how challenging, politically and methodologically, it is for such schemes to meet their well-intended objectives.[39]

2.3 NICE Research Recommendations: An Integral Part of All NICE Guidance

Third, since its inception, NICE guidance has included sections on research recommendations, the purpose of which is to highlight important evidence gaps whose closure would inform future guidance updates. Over 400 research questions were published as part of all types of NICE guidance between 2005 and 2008 alone (these can be found online[40]).

NICE established an R&D Directorate and an independent R&D Advisory Committee in 2004 to help identify, articulate and prioritize NICE research recommendations, support *de novo* evidence generation and encourage methods development in response to the needs of its advisory committees. However, progress in closing the evidence-based guidance loop has been slow and the NICE R&D Advisory Committee, possibly because of lack of appropriate support and relevant research-funding powers, has been challenged in fulfilling its role. Furthermore, decision-makers' questions require work to turn them into researchable projects, robust prioritization mechanisms are needed to identify those projects worth commissioning and there is always the timeliness challenge: it can take 4–6 years for a research recommendation to lead to the generation of the needed evidence through prospective trials that will then inform guidance reviews and, possibly even further downstream, a change in current practice.

To address some of these challenges, the HTA Programme established, in collaboration with NICE R&D, a 'direct access' process for NICE research priorities. Once a year, following three rounds of prioritization based on explicit criteria, prioritization panels (including NICE and NIHR senior and technical staff, committee chairs and outside experts), review NICE's research recommendations and compile a list of four to eight high-priority questions for further consideration and funding. The questions range from health promotion programmes to surgical interventions and from disease management strategies to new drugs and devices but exclude those that deal with the natural history of diseases, epidemiology or patient views and values. The majority of research questions advertised, commissioned or underway are RCTs to assess the effectiveness (as opposed to efficacy) and value of new and existing interventions in the real-world NHS setting in which these interventions are used. The NIHR has so far committed to funding research into NICE questions through the 'direct access' process. In 2007, NIHR funded a mixed portfolio of comparative clinical- and cost-effectiveness research, including head-to-head prospective trials, observational research and systematic reviews, directly in response to decision-makers' questions, as identified,

articulated and prioritized by NICE and its advisory panels (see table I).

Furthermore, the MRC and NIHR have recently (2009) committed a significant amount of money to addressing methodological research questions directly relevant to the work of NICE, such as ways to elicit and incorporate societal values or to obtain empirical evidence of the threshold and methods for prioritizing research questions using value-of-information analysis.[48]

Despite the efforts of the NIHR and MRC, there remain questions directly relevant to NICE decisions that are not being systematically addressed by any public funding agencies in the UK. Questions on epidemiology and natural history of disease, effective implementation strategies to support the uptake of evidence-informed recommendations or even basic volume data such as appropriately analysed prescription and uptake figures for pharmaceuticals, broken down by indication and patient subgroup, are still in short supply. To a large extent, NICE needs information that is often not seen by the research funding agencies as legitimate research, but rather as audit of current and emerging practices. As long as this ideological divide between research and evaluation or audit persists, and given that NICE does not have a budget to commission the needed 'audit service' to deliver such data, it is unlikely that this information will become available to support NICE's decision-making processes.

3. Recent Developments

NICE was recently given responsibility for the assessment of comparative clinical and cost effectiveness of diagnostics and medical devices, for which there is a relatively underdeveloped regulatory path and, hence, limited evidence of value at the point when these technologies enter the market. In the context of this new diagnostics programme, NICE will be working closely with the NIHR and the NHS to collect evidence of effectiveness and value as these technologies diffuse across the NHS.

Recent reforms in the pricing regime in the UK have made prospective evidence generation an important prerequisite for Patient Access Schemes (PAS) and for flexible pricing. Outcomes-related PAS will allow manufacturers to launch a product at a given price and then revise this price subject to new evidence being generated through its use in the NHS. This was the case with Velcade® for multiple myeloma.[49,50] (The more common, finance-related PAS, on the other hand, are mere price deals and not linked to evidence

Table II. Recent practice-influencing trials funded by the National Institute for Health Research (NIHR) in the UK

Trial	Finding
Bells	Appropriate treatment for Bell's palsy: early treatment with corticosteroids is effective but antivirals are ineffective in treating Bell's palsy[41]
3CPO	Evaluation of non-invasive ventilation in cardiac failure in emergency medicine: in patients with acute cardiogenic pulmonary oedema, non-invasive ventilation induces a more rapid improvement in respiratory distress and metabolic disturbance than standard oxygen therapy but it does not improve short-term mortality[42]
EVAR	Comparison of endovascular vs open repair of abdominal aortic aneurysms: endovascular repair was associated with a significantly lower operative mortality than open repair. But there was no difference in mortality, and endovascular repair was associated with increased rates of graft-related complications and reinterventions and was more costly[43]
VenUS II	Larval therapy for leg ulcers: larval therapy was shown to be no more effective than other available treatments in chronic leg ulcers[44]
CESAR	Conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure: adult patients with severe but potentially reversible respiratory failure should be transferred to a centre with an ECMO-based management protocol to significantly improve survival without severe disability. This strategy is also likely to be cost effective in settings with similar services to those in the UK[45]
NACHBID	Neuroleptics for treating harmful behaviour in adults with intellectual disability: antipsychotic drugs should no longer be regarded as an acceptable routine treatment for aggressive challenging behaviour in people with intellectual disability[46]
CRASH-2	The effect of tranexamic acid on intracranial bleeding among CRASH-2 trial participants. Tranexamic acid safely reduced the risk of death and should be considered for use in bleeding trauma patients[47]

ECMO = extracorporeal membrane oxygenation.

generation.) Flexible pricing allows companies to increase their price if new evidence of superior value than originally assumed is produced and positively assessed by NICE. In the case of both outcomes-related PAS and flexible pricing, NICE will require strong NIHR analytical support (both in terms of evidence synthesis/evaluation of manufacturer submissions and, increasingly, through high-quality research infrastructure and data collection systems).

4. Misaligned Objectives and Other Limitations

Despite the good intentions, the aims of NICE and NIHR are not always well aligned. NICE is under pressure to issue decisions – even when there is considerable uncertainty. The aim of NIHR is to help resolve this uncertainty and make the required evidence available to the NHS. However, prospective trials are time consuming and adoption decisions are often difficult to postpone.[51] NICE's remit confines it to looking at some technologies in a limited way – for instance, in relation to drug therapies, NICE can only consider these in terms of their licensed use. This means that some uses of the technologies cannot be evaluated. For instance, the HTA-funded IVAN (a randomized controlled trial of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation) study[52] examines the use of the licensed but very expensive ranibizumab (Lucentis®) for age-related macular degeneration compared with the unlicensed but similar and less expensive bevacizumab (Avastin®). This is a comparison that the manufacturer (the same for both compounds) will not undertake. However, health systems around the world have asked for this information, leading to the funding of the IVAN study and a very similar study in the US, the National Eye Institute-sponsored CATT (Comparison of AMD Treatments Trial).[53] Even if the results show clinical equivalence at much lower cost, NICE, based on current rules, will be unable to use these results to recommend the less expensive but unlicensed drug. Maybe because of the large budget impact of Lucentis® for the NHS, the Department of Health "… asked NICE to explore with stakeholders what value [NICE] can add in advising the NHS on the clinical and cost effectiveness of Avastin to treat wet age-related macular degeneration." This is the first time the Department has asked NICE to assess the value for money of a technology for an off-label indication in adults.[54] NICE's original decision was approval of Lucentis®. Requiring that it be available to patients across England and Wales hampered recruitment to the IVAN trial and reflected a lapse in coordination between NICE and NIHR. However, Avastin® may become a positive example of where NIHR, NICE and government work together to improve health outcomes and value in the way evidence is generated and applied to decisions on making technologies available in the NHS.

A key third partner that should be involved in evidence generation in the NHS are the Primary Care Trusts – the NHS bodies responsible for healthcare delivery and management of budget at the local level. They are required to support usual NHS costs (including the cost of Lucentis® in the IVAN study, which has to be paid to a central pharmacy supplying blinded drugs for the trial rather than to a local provider). Research arrangements like this often seem to them more of a burden than a mark of excellence and a core component of service provision. Such 'excess' treatment costs borne by Primary Care Trusts undermine the conduct of research in the community/NHS. In the current financial climate, where provision is prioritized, this perception of research as an (expensive) 'optional extra' is likely to become even more pronounced.

5. CER in the US and the UK

5.1 Why Cost Matters

Explicit consideration of comparative cost effectiveness has been a contentious issue in the UK and is highly controversial in the US debate about CER. But cost considerations are inherent to comparing alternative treatment options to make resource allocation decisions. Over the years, the NHS, as an integrated single-payer

system operating with a fixed (albeit fast-growing between 2002 and 2008) budget and serving a defined population, has found it increasingly valuable to have a dedicated primary research (or research commissioning) capacity to answer decision-oriented questions regarding the comparative effectiveness of the services it provides. By 'comparative' here, we mean to imply a comparison between what is provided and what could be provided but is not. The distinction is critical because in such systems the usual objective is related to the health of the population served, and has to do with using the limited budget in such a way that the health gains generated are larger than health gains that *could have been generated* by some alternative pattern of expenditure. The principal objective is thus to maximize the health gains of clients or, equivalently, minimize the opportunity cost of resources in terms of the health gain sacrificed. Achieving this ideal, under either description of it, entails using studies of comparative effectiveness – both of existing procedures (in order to eliminate those with low effectiveness) and of new ones (in order to admit only those that pass a reasonable threshold test). An alternative way of describing the pursuit of this ideal is to ensure that all provision meets, so far as is possible and acceptable in terms of prevailing concepts of fairness, the test of cost effectiveness. We are not advocating here for or against using a specific cost-effectiveness threshold to decide what to pay for. However, getting better value services will require reliable information on risks, benefits and costs to support decisions by payers, providers and/or patients. It is for this reason that the NHS supports economic analysis and cost-effectiveness modelling as part of its internal research portfolio and, through NICE, as explicit inputs in the decision-making process.

On the other hand, in the US, draft CER legislation would explicitly prohibit any CER entity "… from developing or employing a dollars per quality adjusted life year (or similar measure that discounts the value of a life because of a person's disability) as a threshold to establish what health care is cost-effective or recommended" and the Secretary of Health from "… using such measure (or similar measure) as a threshold to determine coverage, reimbursement, or incentives programs." Instead, American policy makers are increasingly opting for 'deals' with pharma[55] rather than an open discussion of how to define, measure and reward demonstrable value. It seems that the closer the US is to establishing institutional structures for undertaking CER, the further it gets from empowering policy makers, payers, patients and professionals from using such research to inform rational decisions.

The latter, in the US, is seen as 'rationing'. Here lies a key cultural difference between the US and the UK. Rationing (or prioritization) in the UK is seen as a tool to ensure fair shares for all in a resource-limited system, the NHS, which is currently enjoying one of its highest levels of public approval since the early 1980s.[56] In the US, which lacks such a history of a unified popular healthcare system, rationing is based instead on ability to pay.

6. CER as a Public Good and the Importance of a Health vs a Payment System

Healthcare R&D (or what we call here CER) has the typical characteristics of a public good: it is non-rival, that is, one person using the good does not result in less of the good being available for use by others,[57] and it is non-excludable, that is, it is practically difficult to prevent people from using it, once available.[58] Indeed, once generated, the benefits of research results accrue to a wide range of audiences, from policy makers and administrators to frontline professionals and individual service users. While intellectual property rights can, through patent protection for example, limit access to knowledge, such restrictions may both compromise the highly effective quality-control mechanism that is peer review and the productivity of R&D investment through allowing wasteful duplication of effort (one of the many weaknesses of the current patent system).[15] As such, CER may not be provided at socially efficient quantities if left solely to the marketplace: to address this market failure stemming from the 'publicness' of CER, there is a strong case for

funding support (but not necessarily production) by central (federal) government.

To address these challenges, the UK has been moving, since the reforms of the 1990s, towards strengthening the demand side for CER, driven mostly by the NHS, its policy makers (such as NICE working with the NIHR and MRC), practitioners (through peer-reviewed, investigator-led proposals) and users (through topic suggestions by the public and participation/consultation of patient organizations in funding committees). At the same time, on the supply side there is now a well developed, albeit not necessarily responsive enough, quasi-market, with competition between academic entities, including university hospitals and medical schools, led by professionals with academic track records, bidding for research contracts. As a result, NIHR has, over the years, funded a series of practise-changing trials (table II).

It may be that the 'public good' nature of CER can explain the lack of success (apart from bright exceptions) of private payers in the US to build an R&D infrastructure capable of addressing their uncertainties. On the public sector side, Medicare, with a lack of finite budget or an explicit definition of 'value' and under constant political pressures from various stakeholders, including industry, patient groups and professionals, has been equally unsuccessful. On the other hand, integrated systems, such as the Department of Veterans Affairs, with fixed budgets, a population perspective and a clear economic argument regarding efficiency, have been significantly better at building a working R&D infrastructure.[59]

Reflecting on whether the example of the establishment of a national healthcare research programme is transferable elsewhere, Nick Black concluded "Clearly, for an approach that integrates R&D into the heart of the health care system, a coherent national system must exist."[9] If a national system is a requirement for functioning CER, the US is a long way away from it. However, there are lessons from specific components of the English reform that could be applied in the US setting: the prioritization process and strong focus on the demand side of R&D; the formal and explicit linking of evidence to decision making through NICE and, more recently, the linking of policy-makers' questions to the national research agenda, through NIHR's direct access and the increasing policy support for conditional coverage decisions ('OIR'). But what made CER an indispensable component of the NHS was not only government support for the generation (through NIHR) and dissemination of CER findings, but the ability of NICE to insist that payers and professionals follow the advice based on such evidence. Increasingly, the input from NICE in the NHS pay-for-performance scheme for primary-care physicians (Quality and Outcomes Framework), in defining provider payment levels through DRGs, in informing provider quality assessment and accreditation through the Care Quality Commission and in driving performance through evidence-based quality standards has meant that CER is viewed as a lot more than just an academic exercise. It has also meant that academics are prepared to commit to undertaking this kind of work (both methods development and actual reviews to inform guidance) as they see it has a real impact fairly quickly, in contrast with most research.[60] This process has not been without its problems. Affected patient groups and specialists almost always object to individual treatments not being provided free by the NHS on grounds of poor value for money; but professional organizations and the Royal Colleges in the UK have been broadly supportive of NICE and the concept of evidence-informed practice. Furthermore, public understanding and support for the work of NICE, as evidenced by the UK media's coverage, with very few exceptions, has been increasing. A series of reports in mainstream newspapers and TV programmes highlight a raised public awareness of the controversial issue of prioritizing health investment based on balance of costs and benefits (e.g. recent reports in *The Independent*,[61] *The Guardian*,[62,63] *The Times*[64] and a BBC documentary entitled 'The Price of Life'[65]).

Most recently, NICE led a broad-ranging debate on innovation and the impact of CER on commercial R&D investment and productivity,[66] an objection frequently raised by those opposing CER in the US. Following a number of technical workshops and commissioned papers;

a wide-ranging consultation with key stakeholders, including industry; a series of media reports; and one independent review, NICE's approach remains to "… convert a proposition that a drug or technology is innovative into a measurable assessment of patient benefit … [and] then to factor that into the value of a drug."[67]

7. Conclusions

Having a healthcare system is a prerequisite in order to 'hard wire' CER into it. Maybe a 'healthcare system mentality', rather than one that emphasizes personal choice and responsibility and seeks to improve efficiency solely through payment incentive mechanisms and cost shifting to service users, is a requirement for CER truly to impact on overall system performance and value. A move towards access to needed care for all Americans may bring about such a mentality change in the US. However, as the recent reaction to the efforts of the US Administration for a healthcare overhaul illustrates, to the extent that CER may undermine revenue streams of providers, insurers, the pharmaceutical and devices industry and healthcare professionals, or access to benefit packages for the well insured, there will always be objections to overt prioritization processes, whatever their scientific basis or ethical rationale.

On the other hand, it may be that competition – but of the right type – is what is really needed rather than more government involvement or even a single-payer system. "Medical information is not unlike the corporate disclosures overseen by the US Securities and Exchange Commission."[68] Maybe, with the right incentives, payers and providers could be convinced to compete on making widely available high-quality, meaningful and relevant information on what works, one step towards making competition in healthcare "a positive sum game."[68] The US experience so far has been rather discouraging.

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References

1. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. JAMA 2003 Sep 24; 290 (12): 1624-32
2. Chalkidou K, Tunis S, Lopert R, et al. Comparative effectiveness research and evidence-based health policy: experience from four countries. Milbank Q 2009 Jun; 87 (2): 339-67
3. American Recovery and Reinvestment Act of 2009, HR1, 111th Cong.
4. Patient Protection and Affordable Care Act of 2010, HR 3590, 111th Cong.
5. Ellicott C. 'I owe my life to the NHS': Stephen Hawking tells US to stop attacking health service. MailOnline 2009 Aug 13 [online]. Available from URL: http://www.dailymail.co.uk/news/article-1205953/NHS-branded-evil-Orwellian-high-level-US-politicians.html [Accessed 2010 Jun 17]
6. Ferner RE, McDowell SE. A model for NICE in the US. BMJ 2009 Jun; 338: b2221
7. Dhruva SS, Phurrough SE, Salive ME, et al. CMS's landmark decision on CT colonography: examining the relevant data. N Engl J Med 2009 Jun 25; 360 (26): 2699-701
8. Culyer AJ. Supporting research and development in the National Health Service: a report to the Minister for Health by a research and development task force chaired by Professor Anthony Culyer. London: HMSO, 1994
9. Black N. A national strategy for research and development: lessons from England. Annu Rev Public Health 1997; 18: 485-505
10. Evans I, Thornton H, Chalmers I. Testing treatments: better research for better healthcare. London: The British Library, 2007
11. The House of Lords Select Committee on Science and Technology, Session 1987-88, 3rd Report. Priorities in Medical Research *[HL 54-I, 54-II & 54-III]*
12. Department of Health. Research for health. London: HMSO, 1991
13. McCollum C. UK National Health Service R&D funding: a bureaucratic nightmare [letter]. Lancet 2003 May 31; 361 (9372): 1906
14. McNally N, Kerrison S, Pollock AM. Reforming clinical research and development in England. BMJ 2003 Sep 6; 327 (7414): 550-3
15. Culyer AJ. Economics and public policy: NHS research and development as a public good. York: The University of York, 1998
16. Department of Health. Best research for best health: a new national health research strategy [online]. Available from URL: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4127127 [Accessed 2010 Jun 17]

17. Department of Health, Research and Development [online]. Available from URL: http://www.dh.gov.uk/en/Researchanddevelopment/index.htm [Accessed 2010 Jun 17]
18. Horton R. Health research in the UK: the price of success. Lancet 2006 Jul 8; 368 (9530): 93-7
19. National Institute for Health Research. NIHR health technology assessment programme [online]. Available from URL: http://www.hta.ac.uk [Accessed 2010 Jun 17]
20. Walley T. Health technology assessment in England: assessment and appraisal. Med J Aust 2007 Sep 3; 187 (5): 283-5
21. Cooksey D. A review of UK health research funding. London: HM Treasury, 2006
22. Klein P. Live or let die. American Spectator 2009 Aug 14 [online]. Available from URL: http://spectator.org/archives/2009/08/14/live-or-let-die [Accessed 2010 Jun 17]
23. Murdock D. Government medicine kills. National Rev Online 2009 Aug 7 [online]. Available from URL: http://article.nationalreview.com/402410/government-medicine-kills/deroy-murdock [Accessed 2010 Jun 17]
24. Of NICE and men. Wall Street J 2009 Jul [online]. Available from URL: http://online.wsj.com/article/SB124692973435303415.html [Accessed 2010 Jun 17]
25. Chalmers I. Minimizing harm and maximizing benefit during innovation in health care: controlled or uncontrolled experimentation? Birth 1986 Sep; 13 (3): 155-64
26. Chalmers I. Well informed uncertainties about the effects of treatments. BMJ 2004 Feb 28; 328 (7438): 475-6
27. Department of Health. Usage of cancer drugs approved by NICE [online]. Available from URL: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4139061 [Accessed 2010 Jun 17]
28. Department of Health. The new NHS. London: Department of Health, 1997
29. Pearson SD, Rawlins MD. Quality, innovation, and value for money: NICE and the British National Health Service. JAMA 2005 Nov 23; 294 (20): 2618-22
30. Rawlins MD. 5 NICE years. Lancet 2005 Mar 5-11; 365 (9462): 904-8
31. NICE. Identifying subgroups and exploring heterogeneity: guide to the methods for technology appraisals [special workshop; online]. Available from URL: http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/selectedfurtherreadingguidetothemethodsoftechnologyappraisal.jsp [Accessed 2010 Jun 17]
32. Department of Health. Faster access to modern treatment: how NICE appraisal will work. London: Department of Health, 1999: paragraphs 33-36
33. Chalkidou K, Hoy A, Littlejohns P. Making a decision to wait for more evidence: when the National Institute for Health and Clinical Excellence recommends a technology only in the context of research. J R Soc Med 2007 Oct; 100 (10): 453-60
34. Tunis SR, Pearson SD. Coverage options for promising technologies: Medicare's 'coverage with evidence development'. Health Aff (Millwood) 2006 Sep-Oct; 25 (5): 1218-30
35. Chalmers I. Addressing uncertainties about the effects of treatments offered to NHS patients: whose responsibility? J R Soc Med 2007 Oct; 100 (10): 440-1
36. Kamerow D. Paying for promising but unproven technologies. BMJ 2007 Nov 10; 335 (7627): 965
37. Pearson SD, Miller FG, Emanuel EJ. Medicare's requirement for research participation as a condition of coverage: is it ethical? JAMA 2006 Aug 23; 296 (8): 988-91
38. Sudlow CL, Counsell CE. Problems with UK government's risk sharing scheme for assessing drugs for multiple sclerosis. BMJ 2003 Feb 15; 326 (7385): 388-92
39. Raftery J. Multiple sclerosis risk sharing scheme: a costly failure. BMJ 2010; 340: c1672
40. National Institute for Health and Clinical Excellence. Key uncertainties in the management and prevention of disease [online]. Available from URL: http://www.nice.org.uk/aboutnice/howwework/researchanddevelopment/keyuncertainties.jsp [Accessed 2010 Jun 17]
41. Sullivan FM, Swan IR, Donnan PT, et al. Early treatment with prednisolone or acyclovir in Bell's palsy. N Engl J Med 2007; 357: 1598-607
42. Gray A, Goodacre S, Newby DE, et al., 3CPO Trialists. Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med 2008; 359: 142-51
43. UK EVAR Trial Investigators, Greenhalgh RM, Brown LC, et al. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med 2010 May 20; 362 (20): 1863-71
44. Dumville JC, Worthy G, Bland JM, et al., VenUS II team. Larval therapy for leg ulcers (VenUS II): randomised controlled trial. BMJ 2009; 338: b773
45. Peek GJ, Mugford M, Tiruvoipati R, et al., for the CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support vs extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet 2009; 374: 1351-63
46. Tyrer P, Oliver-Africano PC, Ahmed Z, et al. Risperidone, haloperidol, and placebo in the treatment of aggressive challenging behaviour in patients with intellectual disability: a randomised controlled trial. Lancet 2008; 371: 57-63
47. CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. Epub 2010 Jun 14
48. MRC and NICE to collaborate for the first time on methodology research programme [press release]. 2009 May [online]. Available from URL: http://www.mrc.ac.uk/Newspublications/News/MRC006081 [Accessed 2010 Jun 17]
49. Department of Health. The 2009 Pharmaceutical Price Regulation Scheme. London: Department of Health, 2009
50. Garber AM, McClellan MB. Satisfaction guaranteed: 'payment by results' for biologic agents. N Engl J Med 2007 Oct 18; 357 (16): 1575-7
51. Chalkidou K, Lord J, Fischer A, et al. Evidence-based decision making: when should we wait for more information? Health Aff (Millwood) 2008 Nov-Dec; 27 (6): 1642-53
52. CTEU Bristol. The IVAN trial: a randomised controlled trial of alternative treatments to inhibit VEGF in Age-related choroidal Neovascularisation [online]. Available from URL: http://cteu.bris.ac.uk/trials/ivan/ [Accessed 2010 Jun 17]
53. National Eye Institute (NEI). Comparison of age-related macular degeneration treatments trials: Lucentis-Avastin trial [ClinicalTrials.gov identifier NCT00593450]. US National

Institutes of Health, ClinicalTrials.gov [online]. Available from URL: http://clinicaltrials.gov [Accessed 2010 Jun 17]

54. National Institute for Health and Clinical Excellence. Department of Health asks NICE to look into Avastin use for eye conditions [press release]. 2010 Mar 30 [online]. Available from URL: http://www.nice.org.uk/newsroom/news/DHasksNICEtolookintoAvastinuseforeyeconditions.jsp [Accessed 2010 Jun 17]
55. Lillis M. Baucus scores a big win for big pharma. Washington Independent 2009 Sep [online]. Available from URL: http://washingtonindependent.com/60782/baucus-scores-a-win-for-big-pharma [Accessed 2010 Jun 17]
56. Appleby J, Philips M. The NHS: satisfied now? In: Park A, Curtice J, Thomson K, et al., editors. British social attitudes, 25th report. London: Sage Publications Ltd, 2009: 25-51
57. Samuelson P. The pure theory of public expenditure. Rev Econ Stat 1954; 36 (4): 387-9
58. Reinhardt UE. An information infrastructure for the pharmaceutical market. Health Aff (Millwood) 2004 Jan-Feb; 23 (1): 107-12
59. Longo WE, Cheadle W, Fink A, et al. The role of the Veterans Affairs Medical Centers in patient care, surgical education, research and faculty development. Am J Surg 2005 Nov; 190 (5): 662-75
60. Cressey D. Health economics: life in the balance. Nature 2009; 461: 336-7
61. Laurance J. NHS watchdog is winning the price war with drug companies. Independent 2009 Dec 21 [online]. Available from URL: http://www.independent.co.uk/life-style/health-and-families/health-news/nhs-watchdog-is-winning-the-price-war-with-drug-companies-1846352.html [Accessed 2010 Jun 17]
62. Bowcott O, Campbell D. Nice backs minimum pricing on alcohol to cut harmful drinking. Guardian 2009 Oct 13 [online]. Available from URL: http://www.guardian.co.uk/society/2009/oct/13/nice-minimum-pricing-alcohol-health [Accessed 2010 Jun 17]
63. Campbell D, Gupta G. Is public healthcare in the UK as sick as rightwing America claims? Guardian 2009 Aug 11 [online]. Available from URL: http://www.guardian.co.uk/society/2009/aug/11/nhs-sick-healthcare-reform [Accessed 2010 Jun 17]
64. Henderson M. We need cancer drug rationing. Times 2008 Aug 16 [online]. Available from URL: http://www.timesonlineco.uk/tol/life_and_style/health/article4539008.ece [Accessed 2010 Jun 17]
65. Wishart A. The price of life [television programme]. London: BBC, 2009
66. National Institute for Health and Clinical Excellence. Kennedy study of valuing innovation. London: NICE, 2009 Jul [online]. Available from URL: http://www.nice.org.uk/aboutnice/howwework/researchanddevelopment/KennedyStudyOfValuingInnovation.jsp [Accessed 2010 Jun 17]
67. Dillon A. NICE and the definition of innovation. In Vivo Blog 2009 Sep [online]. Available from URL: http://invivoblog.blogspot.com/2009/09/nice-and-definition-of-innovation.html [Accessed 2010 Jun 17]
68. Porter ME, Teisberg EO. Redefining competition in health care. Harv Bus Rev 2004 Jun; 82 (6): 64-76, 136

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