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Kalipso Chalkidou



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Kalipso Chalkidou

Visiting Faculty, Berman Institute for Bioethics,
Johns Hopkins University, Baltimore, MD; NICE International,
National Institute for Health and Clinical Excellence, UK
kalipso.chalkidou@nice.org.uk

Abstract: This paper reviews the role and functions of the National Institute for Health and Clinical Excellence (NICE) in the context of assessing the Health Impact Fund (HIF). It highlights areas in which NICE's experiences are relevant to the HIF. NICE has been an important, transformational organization, and its ten-year history offers many lessons for the HIF.

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The views expressed here are my own and do not represent NICE or the NHS.

1. INTRODUCTION

This paper reviews the role and functions of the National Institute for Health and Clinical Excellence (NICE) in the context of assessing the Health Impact Fund (HIF). It highlights areas in which NICE's experiences are relevant to the HIF. NICE has been an important, transformational organization, and its ten-year history offers many lessons for the HIF.

The HIF is a proposed mechanism for reorganizing the way that pharmaceuticals are paid for, in order to increase both innovation and access, especially for uninsured populations in relatively poor countries. The essence of the HIF is that an international fund would be established, paying out a fixed amount annually for registered innovative pharmaceutical products. Registering would be optional for patentees. Registrants would agree to sell registered products at the marginal cost of production, and would be eligible for a 10-year stream of reward payments from the HIF, based on the registered product's assessed global health impact during each year. The amount paid each year would be equal to the amount of the fund times the percentage of health impact assessed for that product out of all registered products. Firms would be expected chiefly to register products for which the profits available by charging high prices would fail to reflect the potential health benefits of the product because, for example, most potential consumers were uninsured and poor. Since health impact reward payments would be based on assessed health impact, the HIF would rely heavily on the measurement of health effects. For a complete discussion of the HIF, see the Health Impact Fund website at www.healthimpactfund.org.

The paper proceeds by providing some background to NICE, and then examining its operations.¹ It then explores how NICE's experiences are relevant to the HIF.

¹ The discussion of NICE is based on a report sponsored by AcademyHealth: Kalipso Chalkidou and Gerard Anderson, *Comparative Effectiveness Research: International Experiences and Implications for the United States*, AcademyHealth, Washington, DC, July 2009, <http://www.academyhealth.org/content.cfm?ItemNumber=2841&navItemNumber=2933>.

2. THE ROLE OF NICE IN ENGLAND

Establishment and Evolution

The British National Health Service (NHS) was established in 1948 as a publicly financed (mostly through general taxation), single-payer system providing free universal access to health care. In 2005, the UK spent £83 billion, a little over 8 percent of its gross domestic product (GDP), on healthcare, including central and local government expenditure. As a point of reference, the Organisation for Economic Co-operation and Development (OECD) average was slightly higher at 9 percent.² The OECD figure is the equivalent of \$2,724 per capita (purchasing-power parity adjusted), almost one-third of what the US spent in 2005. Every year, the UK spends about £8 billion (or 10 percent of its healthcare budget) on branded drugs and another £3 billion on generics.

NICE was formally launched in March 1999³ to perform three core functions, which continue to be its main objectives today:

- a. To reduce unwarranted variation in practice across the UK, through the development and dissemination of best-practice standards, clinical guidelines based on the best available evidence of what works and for whom;
- b. To encourage fast diffusion and even uptake of high-value new technologies and medical innovations;
- c. To ensure that tax-payers' money invested in the NHS by the government is spent so that *health benefit is maximized* through considering not only the comparative clinical benefits but also the cost-effectiveness of alternative technologies and services. To the extent that NICE's cost-effectiveness threshold reflects NHS's productivity across all services, the maximisation of health benefits can be achieved through NICE's decision-making.⁴ However, this principle is not rigidly applied in that other factors such as societal values or legislation may influence the final decision. Most recently, NICE

² OECD, *OECD Health Data 2007*, OECD, Paris, 2007.

³ Frank Dobson, UK Secretary of State for Health, "Secretary of State's Speech Launching NICE," March 31, 1999, <http://tinyurl.com/3k2tak>.

⁴ Culyer AJ, McCabe C, Briggs A, Claxton K, Buxton M, Akehurst R, Sculpher M, Brazier J. Searching for a threshold, not setting one: the role of the National Institute for Health and Clinical Excellence. *Journal of Health Services Research and Policy*. 2007;12:56-8.

issued guidance to its committees to value life extensions near the end of life more highly than improvements in quality or life extension for chronic diseases.⁵ Budgetary impact considerations do not directly influence decision-making but may be considered in the process for decisions with significant budgetary implications, as in these cases the decision-making committees tend to be more averse to uncertainty.

In 2005 NICE's remit was expanded to include health promotion and disease prevention. NICE guidance is now issued not only to the NHS, but also directly to local authorities, education and transport boards, employers and other parties with a stake in preventative public health interventions.

In an environment of high levels of unwarranted geographical and socio-economic variation, uneven adoption of innovative treatments and lack of nationwide professional standards of best practice, NICE was established with the explicit objectives of (a) improving quality and (b) ensuring the NHS obtains value for its investment in health technologies. The latter is not synonymous with cost-containment. During the first 10 years of its existence, NICE has been proactive in promoting a significant *additional* investment in high value healthcare services.

Evidence-Informed Policy Making: Building on Existing Capacity

NICE in the U.K is a consumer of research to inform coverage decisions and to set quality standards across the NHS, rather than a direct *generator* of research evidence. Indeed, NICE's success has depended to a large extent on the pre-existing infrastructure that produced the necessary evidence, mostly in the form of systematic reviews and evidence syntheses that informed economic evaluations, upon which coverage and policy decisions are based. Of course, NICE's needs have resulted in increased government funding of comparative effectiveness research (CER) activities through public agencies, namely the National Institute for Health Research. The funded CER is mostly comprised of evidence syntheses and economic modelling rather than prospective clinical trials because of time constraints. However, prospective evidence generation through trials and observational studies is becoming an increasingly important activity, especially in the context of evaluating pharmaceutical products.

⁵ NICE, "Appraising Treatments which May Extend Life, at the End of Life," NICE, 2009, <http://www.nice.org.uk/aboutnice/howwework/devnicetech/endoflifetreatments.jsp>.

NICE extensively uses research from the NHS Research and Development program,⁶ which commissions “research focused on the needs of patients and the public” and develops “evidence to inform and underpin health and social care policy.” The NHS R&D program includes a health-technology assessment program and a horizon-scanning service, both commissioned by the Department of Health to address NICE’s needs with regard to evidence syntheses and topic prioritization, respectively. Furthermore, NHS R&D provides financial support to the Cochrane Collaboration, supports research into methods of critical appraisal and economic evaluation and helps build professional capacity through fellowship training programs across major universities in the UK.

In addition to NHS R&D, which supported the development of NICE’s technology appraisals’ program, the NICE clinical guidelines program builds on a pre-existing network of professional guideline development, based across England’s Royal Medical and Surgical Colleges. NICE maintains this network through contracting the Colleges and their affiliated teams of systematic reviewers and, more recently, health economists, to produce NICE guidelines. Having the Royal College or professional association brand alongside NICE’s brand on the clinical guidelines improves the buy-in by health professionals working in the health service and makes it easier to incorporate relevant material in post-graduate education curricula.

The Decision-Making Process

NICE was set up to help the NHS make evidence-informed decisions as to the most clinically effective and cost-effective applications of specific technologies and broader clinical disease management practices. In this context, the synthesis and critical appraisal of the available evidence (*assessment phase*) is one input in the broader decision-making process that generates final recommendations (*appraisal phase*). NICE’s core objective is to make decisions based on the best available evidence.

NICE typically does not, however, encourage evidence generation through prospective research into existing uncertainties. This is a major limitation of the NICE model that the HIF can potentially address through making the link between evidence and financial rewards more direct. To the extent that evidence for new technologies is more readily available than for old

⁶ UK Department of Health, *Research for Health: A Research and Development Strategy for the NHS*, HMSO, London, 1991.

existing ones and that new drugs are also more likely to have some accompanying evidence than non-registered technologies with a designated sponsor, there is a bias for assessing and hence possibly recommending newer pharmaceutical technologies over existing ones or non-pharmaceutical interventions and services. Furthermore, the latter—that is, service-delivery models—are much harder to evaluate using randomised controlled trials (RCTs) or are much less frequently the subject of economic analyses, which further biases the whole process towards those technologies where the evidence base is already there. This bias is further aggravated by the fact that only NICE’s recommendations on pharmaceuticals and (less frequently) devices are required to be implemented. In contrast, local health authorities have an option to implement public health interventions or clinical management approaches recommended by NICE.

However, as discussed earlier, responsive links exist between publicly funded entities dedicated to evidence generation (the Medical Research Council, or MRC, and the National Institute for Health Research, NIHR) and NICE. The UK’s Department of Health commissions, on behalf of NICE, NIHR to undertake (a) horizon scanning to inform the topic selection process; (b) evidence synthesis including a systematic review of the evidence and decision analysis modelling or a critique of manufacturers’ models, to inform the development of guidance on the use of specific technologies and (c) starting in 2007, real world trials with prospective evidence collection (as opposed to retrospective analysis of existing data) to address specific uncertainties identified during the guidance development process that will inform future updates of the guidance. Similarly, MRC receives public funding to support a responsive research stream into methodologies for developing NICE guidance including modelling tools for making conditional coverage decisions and ways for incorporating equity considerations into the decision-making algorithm. At the same time, NICE contracts with professional Royal Colleges to synthesize and critically appraise the evidence for informing the development of clinical practice guidelines. A similar process is followed in the case of guidance on disease prevention and health promotion, where NICE contracts with academic centres based at UK universities to undertake similar functions for informing the production of public health guidance.

During the assessment phase different evidence from various sources is synthesized and used to develop a decision analysis model as appropriate. NICE has developed explicit guidance as to the type, format and sources of evidence that decision-making committees consider during the appraisal process. This evidence includes good quality meta-analyses and systematic reviews

of RCTs, head-to-head RCT comparisons of the technologies under consideration and also different types of non-experimental studies, such as prospective cohorts, registries and epidemiological analyses.⁷ NICE has a fairly pragmatic approach to evidence—instead of a rigid adherence to evidence hierarchies,⁸ each question is considered individually and the best available evidence identified, critically appraised and used. Unpublished evidence deemed to be either academic or commercial “in confidence” information can also be considered, though NICE encourages stakeholders to keep such submissions to a minimum, requires full justification of the confidential nature of such evidence, and expects that the evidence will be put in the public domain upon, for example, the licensing of a technology or the publication of an academic analysis. Finally, NICE also commissions and reviews patient surveys and patient and professional expert opinion through focus groups or testimonies.

Furthermore, given the increasing pressures for making timely decisions in the NHS, NICE’s approach to CER is driven by evidential synthesis rather than primary research, allowing consideration of multiple sources of evidence; extrapolation beyond the usually short time-horizons of RCTs; incorporation of the epidemiological data specific to the UK population such as baseline risk or usual treatment patterns; consideration of alternative comparators and costs; and quantification of uncertainty and of the implications of making the wrong decision, issues hardly addressable through a single RCT.

Increasingly, NICE is experimenting with decision options linking policy and practice recommendations to evidence generation whereby reimbursement decisions are subject to supplementary evidence as to the relative effectiveness of various technologies being produced

⁷ For a classification of different types of research and definitions of trial types see the Cochrane Collaboration website: <http://www.cochrane.org/resources/revpro.htm>.

⁸ According to traditional evidence hierarchies, randomized controlled trials (and systematic reviews of randomized trials) always score higher in terms of quality than observational studies such as a register of a new surgical procedure or a drug. However, such adherence to hierarchies has had various adverse effects over the years, especially on organizations such as NICE that use evidence to inform real life decisions. NICE abandoned the grading of recommendations based on the underpinning “quality” of the evidence used to inform them. Important priorities for implementation are often based on what may be considered low quality evidence. For example, no RCT was ever conducted for the beneficial effects of steroids in case of anaphylactic shock or of thioxine in moixloedema (Paul Glasziou, Iain Chalmers, Michael Rawlins, Peter McCulloch, “When Are Randomised Trials Unnecessary? Picking Signal from Noise,” *British Medical Journal* 334, no. 7589 [2007], 349–351). Furthermore, such grading often biased implementation support towards interventions with a good evidence base which may not always be desirable especially if there are budgetary restrictions. Finally, evidence hierarchies are scientifically inept and underdeveloped for decisions other than assessing comparative effect size. Side effect profiles of treatments for example are rarely based on RCTs. Michael Rawlins, Harveian Oration 2008, “De Testimonio: On the Evidence for Decisions about the Use of Therapeutic Interventions,” Royal College of Physicians, London, October 16, 2008, <http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=262>.

and evaluated by NICE. Such “conditional reimbursement” decisions are particularly relevant in circumstances of increased uncertainty, as is the case with new drugs at the time of receiving marketing authorization or with diagnostic tests and surgical procedures which are usually accompanied by limited evidence of impact on health outcomes.

Consideration of Costs

“Even if NHS funding is significantly increased that single truth will remain...resources do not stretch to satisfying the demands placed on them by everyone. No healthcare system in the world begins to meet, and match, the aspirations of all those who work in it or use it.” Sir Michael Rawlins, Chair of NICE, 1999.

An important aspect of the NICE approach to CER is the inclusion only of cost considerations from the NHS perspective. Broader indirect societal costs can be considered in exceptional circumstances where such costs are likely to be significant. For example, in the case of Alzheimer’s Disease, carers may incur substantial costs in looking after family members suffering from the disease. Such indirect costs are not routinely considered because they are borne by government departments other than the Department of Health and/or individuals, and, therefore, do not come out of the Health budget. However, NICE’s perspective is currently under review.

NICE considers the cost-effectiveness of technologies when making coverage recommendations, by requesting the calculation of an incremental cost-effectiveness ratio (this is usually defined as the additional cost per Quality-Adjusted Life-Year or QALY) at the assessment phase. The NICE decision-making committees then consider this ratio in addition to other non-quantifiable considerations such as equity implications or the availability of alternatives, in a deliberative fashion. Deliberations are now increasingly recorded and are mostly held in public. There are no written rules about how impact on equity and other non-utilitarian considerations should be accounted for. Instead, NICE relies on its committees to make these judgements, based on Social Value Judgements guidance.⁹ This guidance is informed by NICE’s Citizens’ Council, a form of citizens’ jury which meets twice each year to tackle

⁹ NICE, *Social Value Judgements: Principles for the Development of Nice Guidance*, 2nd ed., NICE, London, 2008, <http://www.nice.org.uk/aboutnice/howwework/socialvaluejudgements/socialvaluejudgements.jsp>.

questions such as whether age should be taken into account when making decisions or whether orphan drugs deserve a special premium. Gradually, a sort of case law has developed that forms the basis of future decisions. For example, NICE committees approved a seemingly cost-ineffective technology that delayed intubation for patients with motor neurone disease on grounds of the severity of the disease. They also approved the use of a drug for malignant mesothelioma, a disease affecting patients who worked in mines in the 1960s to the 1980s. This is a diminishing group of relatively poor patients who were affected by an environmental hazard inadequately understood and controlled at the time. The committee decided that on grounds of equity this technology should be made available for this group.

In one case, NICE asked its committees explicitly to consider altering the weight of QALYs. The case relates to whether a higher weight should be applied to drugs that extend life for terminally ill patients. No final decision has yet been reached, but the issue has attracted considerable attention, including in Parliament.¹⁰

The upper threshold range applied by NICE is between £20,000 and £30,000 per QALY for new technologies. There is limited empirical evidence upon which to base the threshold range. It was initially based on anecdotal evidence of the ICER of adoption decisions by local purchasers. More recently, program budgeting and marginal analysis data released by the Department of Health has made it possible to estimate the substitution rate (or the NHS productivity) at the local level across all types of intervention, including technologies, surgery or inpatient stay. According to these analyses the NICE threshold range is broadly compatible with the NHS return on investment in major disease areas such as cancer and cardiovascular disease.

NICE analyses do not consider affordability directly; instead, they provide budgetary impact analyses for all recommendations in order to support implementation. NICE requires that its committees exert greater caution and expect higher levels of certainty around the expected incremental cost effectiveness ratio when the budgetary implications of a recommendation are significant. This may create more pricing flexibility for industry for drugs targeting small groups of people (orphan drugs). However, NICE's approach is a way to address concerns about higher developmental costs for less frequently used technologies whilst reducing the likelihood that the NHS will have to bear high costs for potentially ineffective technologies affecting large

¹⁰ UK Health Select Committee, Report on Top-Up Fees, April 30, 2009; see paragraph 58: <http://www.publications.parliament.uk/pa/cm200809/cmselect/cmhealth/194i/194i08.htm#a21>.

population groups. Affordability concerns are addressed through the appropriate calibration of the threshold range, which, however, carries significant informational and methodological challenges.

Supporting and Assessing the Uptake of NICE Guidance

When NICE was first established, implementation was explicitly excluded from its remit. However, as unwarranted variation (what is known in the UK as “postcode prescribing”) persisted despite national guidance, implementation of NICE recommendations became a government priority and a number of measures were introduced to improve uptake. This included the three-month funding direction introduced in 2003, making it mandatory for commissioners to make available the funds necessary for implementing any positive NICE recommendation, and the establishment in 2004 of a NICE Implementation Directorate, recently the fastest growing part of the organization. The Implementation Directorate has developed a number of tools and interventions for supporting the uptake of guidance at the local level, including audit criteria, educational tools, a network of “implementation consultants” operating at the local level, guides to changing provider behaviour, budget impact tools adaptable to the local setting and a “forward planner” to help commissioners plan ahead for upcoming NICE guidance. The Implementation Directorate is also responsible for collating and sharing case studies of best practice in implementing NICE guidance and also for developing and maintaining a database of uptake studies from across the UK (www.nice.org.uk/ernie). On the 60th anniversary of the NHS, an NHS Constitution was established for the first time, with the explicit objective of making treatments recommended by NICE an entitlement for all those living in England, in another effort to tackle regional variation in uptake of recommended care.

It is methodologically challenging to assess the impact of NICE guidance on practice patterns and, even more so, on health outcomes. The lack of a control group and the multitude of government policies and other, often non-health-related factors confounding the relationship between the use of CER through NICE in the UK context and observed health trends, make attributing causality impossible. For example, NICE may affect pricing considerations by industry long before a product reaches the market. So it would be hard to show NICE’s impact on spending and outcomes using historical controls in the NHS given the multitude of factors influencing use of services and government investment in healthcare. However, there are

numerous case studies that show the impact of the use of CER to inform coverage decisions on unwarranted variation in practice and the speed of diffusion of new treatments across the NHS. According to a report by the National Director for Cancer, the uptake of cancer drugs appraised by NICE increased by almost 50 percent across the country between 2003 and 2005 and geographical variation in use dropped from 3–8 fold to 2–3 fold over the same period. Another national report showed that NICE advice for the use of multidisciplinary teams for managing lung and colon cancer patients was taken up by over 95 percent of providers across the service.

NICE adoption decisions have an estimated aggregate cost of £0.8–1.2 billion per year; in 2006–2007, NICE guidance absorbed more than a tenth of the growth in healthcare spending across the NHS. Over the same period, the price of episodes of care (the equivalent of the US Disease Related Groups) used by the NHS was adjusted upwards by almost 1 percent. This is expected to increase significantly as new cancer drugs, all of which are now subject to NICE appraisals, are included in the price list. It is very hard to assess whether spending would have been higher or lower had there not been a NICE; however, the government's explicit objective was for NICE to target additional funding towards good value innovation rather than to cut costs.

Perhaps the greatest contribution of NICE has been to raise awareness amongst the general public, the media and also professionals and industry of the importance of making evidence-informed healthcare resource allocation decisions in a transparent, inclusive and methodologically robust way. In their 2008 parliamentary enquiry into NICE, the multi-partisan Health Select Committee concluded:

NICE does a vital job in difficult circumstances. The development of more and more health technologies and procedures, alongside rising patient expectations and the ageing population, is going to make it even more difficult in the future. Healthcare budgets in England, as in other countries, are limited. Patients cannot expect to receive every possible treatment. Demand outstrips resources and priorities have to be determined. In other words rationing is essential, and NICE has a key role to play. Given the difficult environment, NICE requires the backing of the Government.

NICE must not be left to fight a lone battle to support cost- and clinical effectiveness in the NHS.”¹¹

¹¹ UK Health Select Committee, Report on NICE, December 17, 2008; see summary: <http://www.publications.parliament.uk/pa/cm200708/cmselect/cmhealth/27/2702.htm>.

3. APPLYING NICE METHODOLOGY IN A LOW INCOME SETTING

The basic principle of the Health Impact Fund (HIF) is simple: annual reward payments for the pharmaceutical firms that opt into the scheme would be directly proportionate to their products' global health impact (measured as QALYs) every year for the first 10 years of their being on the market. In return, firms would retain their patent rights but would have to make their product available at marginal cost of production (or marginal cost plus a small mark up to cover distribution costs, where appropriate). Perhaps the most crucial and most challenging aspect of the HIF idea is how health impact would be measured in practice.

The methodology for measuring costs and effects of medical technologies, and then making a judgment as to the value for money of these technologies in a given healthcare system, is being applied by agencies around the world to inform investment decisions. The Pharmaceutical Benefits Advisory Committee in Australia (PBAC), NICE in the UK, and the Swedish Council on Technology Assessment in Health Care (SBU) in Sweden are examples of such agencies, as are the Canadian Agency for Technologies in Health (CADTH), the Deutsche Agentur für Health Technology Assessment beim Deutschen Institut für Medizinische Dokumentation und Information (DAHTA@DIMIDI), the Institute for Quality and Efficiency in Health Care in Germany, and the Drug Effectiveness Review Project (DERP) in the US. Below, using NICE in the UK as a case study, we discuss some of the methodological, practical, governance and informational challenges of and opportunities for achieving a reliable, efficient and reproducible assessment mechanism across countries and for different products and populations. The list below is not exhaustive.

1. Aspects of NICE's function in the NHS/UK that could be transferred/adapted to a low income setting

- 1.1. Measure of health impact: NICE uses the QALY as a measure of health outcome, which combines both mortality and morbidity in a single number. However, there are a number of concerns regarding its theoretical underpinnings, the practicality of getting the right valuations, and the QALY's equity implications. For example, there are objections to its basic theoretical assumptions of constant proportional trade-off (i.e., patients are risk-neutral in that they experience [or value] additional units of life/quality the same way

regardless of when this gain (or loss) occurs) and additive independence between health states (i.e. people's preferences for health states are not affected by the sequence in which health states occur); difficulties with eliciting quality of life relevant to local populations; concerns that the QALY discriminates unfairly against both young and old people; objections that it takes no account of distributional issues; concerns that EQ 5D (the scale used to describe health states) may not adequately capture all relevant dimensions for some disease types; and there are still questions as to who should be responsible for valuing health states (patients or the general public). DALYs, or Disability-Adjusted Life-Years, may be more readily available in low-income settings, but they have their own problems. Overall, the QALY, for all its faults is a well-tested, simple tool with a large literature supporting its use in different settings. It is continuously developed methodologically and it has extensive survey data from around the world that can be readily used to inform analyses. While criticizing the QALY or DALY is easy, what is not so easy is to argue that there is a more suitable measure reflecting social values, including market demand.

- 1.2. Operational principles: The appraisal side of the decision-making process is separate in the NICE model and follows on from the evidence synthesis undertaken by technical staff. The appraisal stage involves a series of value judgements, both scientific (e.g., around the hierarchies of evidence and data quality) and social (e.g., around the distributional impact of an investment decision). These judgements are made by clinicians, academics, lay people, industry and payers in the NICE process and are governed by core principles of transparency, inclusiveness, independence, contestability and timeliness. In the context of NICE and the NHS, these principles translate into the following:

Transparency: NICE is committed to making all information, including formal analyses and patient testimonies, used to make decisions, the methods and processes for doing so and the actual deliberations and disagreement in the process, in the public domain. Commercial and academic in-confidence data are still accepted and protected; however, their volume is kept to a minimum.

Inclusiveness: All relevant stakeholders are involved in the process of developing individual decisions and the methods and processes for reaching such decisions. Different ways of involving people are constantly being tried and improved (or abandoned), such as consultation via the web, participation in committees, expert testimonies, citizens' juries, focus groups and general opinion surveys.

Independence: NICE is funded by government, but government's involvements in NICE's work is limited to helping set its work programme (and hence the accountability link is maintained). Independence in developing its own methods and processes and in applying those to individual decisions is of paramount importance. Government can comment on NICE's work as any other stakeholder.

Contestability: In the context of technology appraisals, all decisions, positive and negative, can be challenged through a public appeals mechanism, whereby stakeholders including insurers, industry, clinicians and patients can challenge a draft decision mostly on grounds of process and NICE's remit. The appeal is heard by an independent committee and, if upheld, leads to the decision being reconsidered.

Timeliness: NICE is constantly striving to ensure that the needs for scientific rigour and broad consultation are balanced against the need for timeliness of recommendations. This has been a challenging task.

- 1.3. Scientific value judgements will still need to be made in the context of the HIF by the technical branch that develops the general guidelines for health-impact assessment and by the assessment branch that applies these guidelines to specific technologies. It is important that the process of making these scientific value judgements (both at the technical- and assessment-branch levels) is transparent and consultative and is based on robust (tested) scientific principles. The critical appraisal process is based on a series of scientific value judgements. For example, the choice of modelling or of observational data, the choice of head-to-head randomized controlled trials or indirect comparisons, and the choice of strict evidence hierarchies are all scientific value judgements that affect the content of the final decisions.

NICE has worked extensively on the assessment of clinical and cost effectiveness evidence and this experience can be shared with HIF technical colleagues. For example,

NICE's approach to critical appraisal includes the adoption of an adapted version of GRADE¹² to include costs and a markedly less "elitist" attitude to traditional evidence hierarchies. The problem of, for instance, applying a treatment effect size from a randomised trial carried out for licensing purposes in the US to different populations in a middle income country may not be that dissimilar from making a series of assumptions when trying to extrapolate from the same trials to the UK setting. (In the latter case the baseline risk and epidemiological data are likely to be of better quality, but this is discussed below). WHO CHOICE is a useful database and the Disease Control Priorities project¹³ has produced significant amounts of data applicable to lower income settings.

- 1.4. Social value judgements: Certain social value judgements need to be made explicit at the technical branch level for the assessment branch to be able to apply those to individual decisions. These judgements include the total size of the Fund (which will determine the threshold, or the relative size of the rewards subject to demand from product manufacturers, based on the multiplier for the proportion of health impact shown to have been achieved by a certain product in a given year); the distributional weights of QALYs (i.e., whether QALYs going to more severely ill patients or to those in poor rural areas should be overweighted); and other non-utilitarian considerations, such as decisions to overweight or underweight certain QALYs, (e.g., whether to overweight orphan disease QALYs), need to be made explicit at the technical branch level for the assessment branch to be able to apply those to individual decisions. Opting for equal QALY weights irrespective of who receives those is a value judgement in itself, and the rationale for reaching such a conclusion should be made clear as well as the implications of doing so (e.g., incentives for sponsors to target "easy" QALYs, say, in populations that are easier to reach and where drug distribution systems already exist).
- 1.5. Methodological problems include surrogate endpoints, indirect comparisons, sensitivity analysis and quantifying uncertainty. NICE often has to base its decisions on surrogate endpoints. This may be necessary in the HIF context until new data becomes available. There is a risk that the application of surrogate endpoints or indirect comparisons, when

¹² The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group: <http://www.gradeworkinggroup.org/index.htm>.

¹³ The Disease Control Priorities Project: <http://www.dcp2.org/page/main/Home.html>.

head-to-head trial data are not available, will discourage further generation of relevant evidence. This risk needs to be taken into account, possibly through making on-going rewards conditional on the production of further relevant data (e.g., through Phase IV trials). For a discussion of a selection of key methodological issues see the NICE methods manual.¹⁴

- 1.6. An (addressable) challenge in the UK system is identifying, calculating and including all relevant costs in the analysis. In a low-income country, costs potentially borne by the local health system (e.g., the cost of treating side effects or the time of expert nurses administering a drug) should be considered in addition to outcomes, so that the local system does not divert valuable resources to technologies that cost more than their marginal cost of production. Failing to consider such costs may result in inefficiencies, given that local systems in poor (and even richer) settings often lack the analytical capacity, resources and time (and often the information) to select the most cost-effective alternatives when making purchasing decisions and may overlook any resource use implications beyond the marginal pricing cost.
- 1.7. There are more methodological/technical; practical; procedural and ideological obstacles to implementing the NICE approach that are independent of the setting in which this model is applied. Most of these issues are addressed in different ways by NICE in the UK and other agencies around the world and are hardly unique to the HIF concept. They are likely to become more significant as the HIF gains traction in settings where some actors are at risk of losing out from a change in the status quo.

2. Aspects of NICE's function in the NHS/UK that would be hard to apply in a low-income setting

- 2.1. Informational requirements: NICE relies on high quality information on epidemiological and demographic data for the UK population, quality of life estimates, observational and experimental studies undertaken in the UK or EU setting, and data on local unit costs and resource use costs. (The final data set may not be required if the HIF only considers outcomes, however.) In poorer countries such data may not be available. For example,

¹⁴ See the manuals at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp.

data on the baseline risk of incidence of chronic diseases are scarce in low-income countries. This is a problem that the HIF will have to deal with.

- 2.2. Local buy-in and direct link to the respective health system: the HIF is by definition a centralised “service.” The HIF would be centrally managed and would not necessarily require local engagement other than maybe to retrieve relevant data to inform the assessments. Even this could be achieved by HIF teams travelling across countries. One of the reasons NICE has survived so far in the UK, despite the fact it has had to make a number of unpopular decisions, has been the fact that it has managed to engage with relevant players in the NHS and has established itself as an integral part of the healthcare service. This aspect of the NICE model would not be applicable at a global level, but this may not be relevant to the success of the HIF idea to the extent the HIF will not be denying access to drugs. On the other hand, the interpretation of evidence submitted to the HIF by pharmaceutical registrants will be key in defining the size of the reward. Possible disagreements may lead to companies pulling out of the scheme and negative publicity, which may be best addressable through an inclusive process that allows for consultation and meaningful challenge.
- 2.3. Technical capacity to undertake the technical, assessment and audit functions: NICE has benefited from an extensive and growing network of academic experts who help to develop methods and apply these to individual technologies in the UK. The HIF will require such capacity to undertake its technical, assessment and audit functions. It would be interesting to think about whether such capacity would have to be centralised or whether part of it could or ought to be devolved to individual countries or regions. Currently there is a significant shortage of technical expertise in low-income countries and transition economies and building such capacity takes time and resources. Other issues requiring consideration include the opportunity cost of training and employing expert staff in the HIF and the most appropriate remuneration rates to avoid perverse effects.
- 2.4. Multi-stakeholder involvement: Another aspect of the NICE model is the involvement of different parties throughout the process of making decisions. The HIF’s centralised and almost exclusively technical focus may not require or allow such engagement. It may be

that such a purely technocratic solution (whereby the social value judgements have already been agreed at the inception stage) is the most efficient way of going about improving both drug development and access for poor (and possibly richer) countries. However, there may be room for such engagement at the technical guidelines development stage or in the context of a raising awareness campaign amongst stakeholders (funders, service users, governments, industry).

3. Aspects of NICE’s function that could be strengthened through a HIF approach in low- and medium-income countries

- 3.1. The greatest advantage of the HIF, assuming it is successful, would be its direct link to primary data generation, a link that is currently relatively weak in the UK system. If rewards are based on direct evidence of health impact, pharmaceutical registrants will have incentives to invest in pragmatic trials and to generate local evidence for local decisions. Issues of how to manage uncertainty at the early stages of diffusion of a technology, the timeliness of randomised trials, the cost of doing primary research and potential bias in the design, interpretation and publication of trial findings when these are sponsored by the technology registrant remain, but at least the link between decision-making and research is made explicit with the latter a requirement for the former.¹⁵
- 3.2. NICE’s technology appraisals increasingly rely on single comparator (rather than multiple comparators within a class). The HIF will hopefully address this issue by including all relevant (drug and non-drug) comparators in its evaluations.
- 3.3. Because the HIF will operate under a predetermined fixed budget, there is no need to assess willingness to pay per unit of outcome and no risk that inflationary pressures of such a normative approach to rewarding health benefit would tend to crowd out other

¹⁵ The bias in using sponsor-generated evidence could be addressed by supporting the emergence of a special class of evidence-generating firms (similar to existing contract research organisations [CROs] but with better governance in terms of conflict of interest management—e.g. many CROs are owned by pharmaceutical companies). Industry would have to hire such firms to do the trial and/or analyses for them; and such firms could be accredited with the HIF in terms of governance and vested interests and would, of course, lose their accreditation if they engaged in inappropriate activities. In the UK, academics tasked with secondary analyses of existing studies work both for NICE and for industry. As long as this process is adequately managed (e.g., at NICE, an academic working for industry on a specific submission is not allowed to sit on a NICE committee considering this drugs or to work with NICE In evaluating this submission) it is helpful in that it addresses limited capacity issues and improves the quality of submissions by industry and the ability of academics (when they work for NICE) to identify and question suspect claims.

interventions. (There will always be, however, an opportunity cost of investing in the HIF rather than an Advance Market Commitment or a different model.) Despite a fixed healthcare budget in the UK, there is some distortion because of a mandatory funding direction for drugs but not other cost effective services such as prevention and because of the lack of a “real” NICE budget.

- 3.4. NICE in the UK has no direct powers to negotiate prices (the HIF reward equivalent). The HIF will have direct responsibility for defining the size of the reward for each participating technology based on evidence of health impact. This feature of the HIF provides a strong incentive for industry to provide the necessary data to convince the HIF of the value of its drugs. This incentive may trigger lobbying and marketing to increase the uptake of drugs with some health impact in order to maximise the reward (which may have distorting effects on local priorities—e.g., resources locally diverted to support pharmaceutical use rather than other services which makes local resource-use assessment critical). Another form of lobbying may be towards influencing the assessed health-impact-assessment process; however, this lobbying should be subject to much better control (to the extent it can be evidence-based) than the current prescription habits of individual clinicians subject to detailing or patients subject to direct-to-consumer advertising in rich economies such as the US.
- 3.5. Current restrictions that prevent NICE from recommending off-licence indications that may be cost-effective and at times better supported by evidence compared to new and more expensive licensed drugs limit NICE’s potential for advising the NHS on the most cost-effective treatments. The HIF may be able to address this to the extent that firms will be encouraged to invest in clinical trials to support new indications for older drugs with no “patent potential” and make relevant claims over HIF rewards. This would address a key practice problem whereby many doctors prescribe with little evidence of effectiveness and efficiency because there is little commercial incentive to engage in clinical trials for new uses for older drugs. The incentive the HIF provides to conduct clinical trials of new uses for old medicines has the potential not only to unlock new uses for many older drugs but also to improve the quality of what is currently very extensive, unproven, off-label prescribing. This would also remove the restriction placed upon those working on the demand side (such as NICE) to only consider licensed indications

when there is good evidence of comparative clinical and cost effectiveness to support off-label use of older drugs. Thus, the HIF could improve practice both by encouraging the generation of primary research on older and supposedly unpatentable technologies and by empowering payers to use such evidence where available.

- 3.6. Recently launched flexible pricing arrangements and patient access schemes (pay for performance for drugs) subject to new evidence (per indication and subgroup) have a lot in common with the HIF approach and are becoming increasingly popular in countries such as the UK and Canada. The role of NICE in these schemes in the UK is to inform the assessment of the “reward” (or price) based on evidence of effectiveness. However, there are two weaknesses: (a) such schemes or requests for flexible (upward) pricing can only be initiated by industry rather than by users or payers of these technologies and (b) the data generated are owned by the technology sponsors (even though often these schemes are run by the NHS and use NHS patient data). It is not clear how the HIF can directly address these problems.

4. Possible challenges in implementing the HIF that are not directly linked to the NICE model

- 4.1. Audit: Assessing health impact will require information on rates of usage, including prescribing by indication and population subgroup, dispensing data and credible data on adherence to medication by individual patients. These data are hard to get in the UK and likely even harder to acquire in a poorer setting where the incentive to game the system is strong and the success of the HIF is dependent on how well the assessment reflects reality.

NICE in the UK has developed a methodology for establishing current use (for budget impact assessment analysis).¹⁶ The lack of information is the greatest weakness of this approach, though it is better to make an educated guess than to avoid confronting the problem. Furthermore, gradually, suppliers such as IMS Health are working towards improving the uptake monitoring systems given the demand from the UK’s Department of Health. If such a demand were generated by sponsors or the HIF in low-income

¹⁶ NICE, *Methods Guide: Developing Costing Tools*, NICE, London, 2008, http://www.nice.org.uk/usingguidance/implementationtools/costingtools/costing_tools.jsp?domedia=1&mid=F3E04B99-19B9-E0B5-D46097AFA4B0DCE6.

countries, then it is possible that the informational infrastructure would gradually improve.

- 4.2. Procurement and distribution issues; counterfeit drugs, illegal mark-ups/back market; parallel trade; governments' unwillingness to part-take: These are all issues related to drug access in low and middle income settings and are not directly relevant to the method for establishing the size of the reward and assessing health impact.