How Does it Work and What are the Implications for the U.S.?

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EXECUTIVE SUMMARY

OVERVIEW OF NICE

The growing emphasis on evidence-based decision-making in health care, especially regarding health technologies, has generated notable debate and discussion in the U.S. around establishing a more formalized process or system for collecting comparative effectiveness information. The National Institute for Health and Clinical Excellence (NICE) in the U.K. is the most discussed and debated system currently in operation. NICE represents the most sophisticated national attempt to systematically review the value, or relative costs and benefits, of various treatments. While NICE has been commended for various aspects of its review and appraisal processes, from the inclusion of stakeholders to rigorous use of evidence, it has not operated without controversy. Concerns abound regarding the methods employed during the appraisal and review process, the role and utility of cost-effectiveness evidence in decision-making, and the resulting impact on outcomes and access to health care.

In broad terms, NICE serves as an “arms-length” organization that provides national guidance on the promotion of good health and the prevention and treatment of various health conditions. Specifically, NICE’s remit is to consider both clinical and cost-effectiveness in developing its guidance. When it was established and during the majority of its existence, NICE has produced three types of guidance, including technology appraisals, clinical guidelines, and interventional procedures. In mid-2005, NICE also assumed the responsibilities of the Health Development Agency (HDA), which provided the Institute with authority to develop guidance on public health interventions or programmes.

Regarding its role in health care decision-making, NICE guidance essentially serves a quasi-law function in the National Health Service (NHS) and broader health care system. Beginning in January 2005, technology appraisals are supported by mandate, in that the NHS in England and Wales are now legally obligated to provide funding for medicines and treatments recommended by NICE. Specifically, if NICE guidance supports that a particular technology be made available by the NHS to a certain patient group(s), then associated health care organizations are obligated to implement such recommendations. Moreover, NHS organizations are required to do so within three months of the date the guidance is issued.

Topic Selection and Prioritization

To prioritize assessments and initiate the guideline development process, NICE receives suggested topics from a number of sources. In general, the Department of Health (DH) commissions NICE to develop clinical guidelines, guidance on public health, and technology appraisals, while topics for the interventional procedures program are submitted directly to NICE, usually by clinicians. However, topics for potential NICE guidance are also derived from health professionals; patients; the general public; manufacturers; and, within NICE itself. NICE compiles and maintains a list of all submitted topics, which aids in ensuring transparency.

Guidance Development

Guidance development entails a number of key processes, from topic selection to systematic review of evidence and consultation on draft guidance. Several aspects inherent to NICE’s procedures lend themselves to an effective deliberative process, many of which are focused on ensuring the highest degree of transparency and the participation of a wide range of stakeholders. NICE’s engagement of a broad representation of stakeholders, from multiple sectors and disciplines, serves to introduce a variety of perspectives into the appraisal and decision-making process. This is particularly helpful when reaching consensus on conflicting evidence or recommendations; making such judgments typically requires knowledge of the scientific literature, realities of clinical practice, and underlying social values. Moreover, as there is a paucity of scientific evidence about patient treatment preferences and viewpoints on issues such as equity and fairness in health care, it is important to involve a
variety of stakeholders in the process to elicit such perspectives. At the implementation stage, a high level of stakeholder involvement increases public and professional ownership in the guidance, which enhances the likelihood that it will effectively guide decision-making and clinical practice.

**Guidance Dissemination and Implementation**

NICE employs different mechanisms to disseminate its guidance, from publication on its website to distribution to local decision-makers. Adequate and timely communication and implementation is crucial, as guidance is only effective if it is indeed used by decision-makers to make health policy and/or provision decisions. This is especially true in the case of NICE, whereby its guidance carries significant weight, in terms of NHS funding of and access to health technologies. However, existing evidence suggests that the uptake of NICE guidance is often slow, patchy, and without adequate incentives for implementation. There are several factors that are considered to impact whether or not NICE guidance is fully implemented, including local political drivers, lack of provider support, deficient knowledge and understanding of the assessment process, media and patient group pressure, limited mechanisms for accountability, and poor financial planning of local decision bodies.

**RELEVANCE TO THE U.S.**

In the U.K., NICE is constituted as a Special Health Authority within the NHS. Therefore, it has an ‘arms-length’ relationship with government, although all its funding comes from the DH. Experience from the U.K. and elsewhere suggests that an appearance of independence is important for HTA agencies or entities, as the findings of HTA reports are often controversial. A survey of general practitioners in the U.K. showed that NICE was perceived as being independent from industry, but not independent from government. Also, when NICE guidance is considered by the media, the Institute is normally referred to as ‘the government’s health watchdog’ or, occasionally, as ‘the NHS’s rationing body’.

In the U.S., the primary decision affecting the governance, funding, and organization of any HTA entity would be where it is located. That is, should it be a new Federal agency, part of an existing agency, or outside of government? Regardless of the governance arrangement(s), any public HTA entity will likely end up informing decisions of a variety of payers, even if the entity is only charged with informing the decisions of the Federal Government. Indeed, currently the HTAs generated for the Medicare Coverage Advisory Committee (MCAC) decisions are posted on the CMS website and are available for consultation by private health plans.

**Remit for HTA Agency**

On the international level, NICE is probably in a minority among HTA entities in having such a clear remit to consider cost-effectiveness. The recent debate in the U.S. has been conducted using the term ‘comparative effectiveness’. For many commentators, the study of comparative effectiveness would involve consideration of clinical outcomes only, usually through the conduct of clinical trials, comparing relevant technologies in a real life (i.e., routine practice) setting. On the other hand, some commentators acknowledge that an assessment of comparative effectiveness could also consider costs.

**Scope of Analyses**

As the debate about comparative effectiveness progresses in the U.S., the breadth, or restriction, in the scope of the required analyses will be a critical issue. At one end of the spectrum, the HTA effort could focus solely on the funding and conduct of clinical trials to compare alternative technologies. Unlike most of the trials currently funded by industry (e.g., Phase III for drugs), these trials are likely to compare two or more widely-used therapies, enroll large numbers of patients, and have long-term follow-up. They are also likely to be quite costly, so their number will be limited, even with the budgets currently being proposed for the comparative effectiveness
initiative, which at present range from $4-6 billion a year. The current funding level for NICE is more modest (around $50 million), but crucially the Institute does not commission primary research, such as comparative clinical trials. Rather, it relies on systematic reviews of the existing literature, in addition to economic modeling. The main reason for this is the emphasis on the timeliness of the assessment. That is, since a decision has to be made (on the appropriate use of a health technology), the principal need is to develop the best possible guidance given currently available data.

If, in the U.S., the emphasis in ‘comparative effectiveness’ assessment were to be on large, long-term, controlled trials, this would have to be developed under a scheme similar to ‘coverage with evidence development’, since the technologies would have to be approved for funding in order to allow such trials to take place. Under ‘coverage with evidence development’, funding for the technology to be studied is contingent upon participation in the clinical trials. Therefore, more discussion of the design of such schemes, including study requirements, funding and risk-sharing arrangements (if any) is urgently required.

**Setting Priorities**

Priorities for assessment by NICE are set by the government in the U.K., according to published criteria. If any HTA entity in the U.S. were also servicing the decision-making needs of the Federal Government, a similar process could apply. For example, the topics could relate to those technologies for which coverage decisions are required. If an HTA entity in the U.S. were seeking to be relevant to a wider range of health care decision-makers, the nature of the process for setting priorities is less clear, although many private health plans also cover Medicare enrollees.

**Assessments vs. Appraisals**

NICE makes a clear distinction between assessments, where only the technical analysis is undertaken, and appraisals, where the evidence is evaluated and the decisions made. The Institute relies heavily on expert committees in its decision-making processes (e.g., Appraisal Committee, Guideline Review Panels) and this adds somewhat to the appearance of independence. The experts are a mixture of academics (across several disciplines including medicine, statistics, and economics), NHS decision-makers, and patient representatives. There is no reason why a similar approach should not work for an HTA entity in the U.S., although it may be more of a challenge to secure adequate representation from the various decision-making groups.

A more fundamental issue in the U.S. context is whether an HTA entity would have a decision-making role at all, given the diverse nature of the health care system. It is possible, indeed more likely, that the responsibilities of any entity in the U.S. would cease at the assessment stage. Assessments could then be made publicly available, for the various payers to use (or not use) as they see fit.

**SUMMARY AND CONCLUSIONS**

Although the increased use of HTA in the U.S. may lead to a more cost-effective use of health care resources, it will also increase the burden on industry to produce data. In addition, to the extent that HTA is linked to decisions about the pricing and reimbursement of medicines, it will lead to greater controls on the prescribing and use of drugs. These wider considerations are beyond the scope of this project. Although there are considerable differences between the health care systems in the U.K. and the U.S., several important lessons can be drawn from the U.K. experience with the NICE model.
1. **Independence of HTA Entity**

   The governance and organization of any HTA entity is critically dependent on whether its role is to serve the decision-making needs of one major payer or the needs of many decision-makers in a diverse system. However, whatever its governance and organization, it is important that any HTA entity is as independent as possible.

2. **Consider All Health Technologies**

   In order to make the broadest impact, an HTA entity should consider all health technologies (not just drugs). Priorities for topics need to be set in an explicit manner and assessments should be rigorous and transparent, conducted in accordance with a clear set of methods guidelines.

3. **Involve All Major Stakeholders**

   Any HTA entity should make strenuous efforts to involve major stakeholders in the development of methods guidance, the scoping of individual assessments and in commenting on the results of studies. Early and consistent involvement of technology manufacturers is particularly important, as they play a major role in conducting the studies on which the assessments are based. Ideally, assessments should be carried out by independent research groups, under the general direction of the HTA entity, and should be as transparent as is possible.

4. **Broaden Types of Evidence and Improve Methods Synthesis**

   There needs to be a debate in the U.S. about the pros and cons of focusing the HTA effort on the conduct of additional large, long-term randomized controlled trials, versus investing more effort in improving the methods of evidence synthesis using available data. There also needs to be discussion of how the production of more evidence on health technologies is linked to decision-making, perhaps through a system of ‘conditional reimbursement’.

5. **Avoid Narrow Focus on Clinical Outcomes**

   More discussion is required about the ways of incorporating economic factors in assessments, in order to provide relevant information for decision-makers in the U.S. context. A focus on clinical outcomes alone is inappropriate as it may exclude important advantages and disadvantages of health technologies, such as impacts on quality of life and savings in other healthcare resources. On the other hand, calculation of a single (incremental) cost-effectiveness ratio may not be very helpful, given the great diversity across the U.S. in health care budgets, practice patterns, and cost levels.

6. **Provide Evidence Interpretation, Not Guidance**

   Finally, the most appropriate focus for an HTA entity in the U.S. is on undertaking high quality assessments (i.e., interpretation of the evidence), rather than *appraisals* (i.e., the production of guidance for decision-makers). The objective should be to produce high quality *assessments* that will enable various decision-makers to undertake an appraisal from their own perspective.
PROJECT BACKGROUND

The growing emphasis on evidence-based decision-making in health care, especially regarding health technologies, has generated notable debate and discussion in the U.S. around establishing a more formalized process or system for collecting comparative effectiveness information. While different options are presently being formed, the National Institute for Health and Clinical Excellence (NICE) in the U.K. is the most discussed and debated system currently in operation. NICE represents the most sophisticated national attempt to systematically review the value, or relative costs and benefits, of various treatments. While NICE has been commended for various aspects of its review and appraisal processes, from the inclusion of stakeholders to rigorous use of evidence, it has not operated without controversy. Concerns abound regarding the methods employed during the appraisal and review process, the role and utility of cost-effectiveness evidence in decision-making, and the resulting impact on outcomes and access to health care.

In the context of current discussions in the U.S., the National Pharmaceutical Council (NPC) commissioned a project to LSE Health to examine NICE and its operations, and the implications for comparative effectiveness reviews in the U.S. As described in further detail below, the project addresses the organization and procedures of NICE; evidence requirements and methods; stakeholder and public perceptions of its operations (especially among manufacturers and related industry entities); and, potential implications for similar processes in the U.S. context.
OVERVIEW OF PROJECT

The project will be completed in four separate phases:

• **Phase 1** entails an overview of NICE, encompassing its 1) governance and organization, 2) topic selection procedures, 3) evidence requirements and assessment methods, and 4) guidance dissemination and implementation.

• **Phase 2** provides an in-depth investigation of the third area of focus in Phase 1 – evidence requirements and assessment methods.

• **Phase 3** involves an analysis of public comments on NICE recently submitted to the House of Commons Health Select Committee, focusing on key stakeholder perspectives on the appraisal process and broader NICE operations.

• **Phase 4** examines the potential application of NICE procedures and standards to the U.S. landscape, and identify those factors or forces unique to the U.S. marketplace, in comparison to the U.K. and other EU Member States, where applicable. In particular, the implications of such a model on incentives for innovation and overall health care will be explored and examined. While the focus will be on comparative effectiveness, as currently debated in the U.S., this phase will also examine the opportunities and challenges of cost-effectiveness evaluation should such a proposal be put forth and deliberated in the future.

Each phase of research builds upon each other to provide a comprehensive review of the NICE model and its relative strengths and weaknesses.
PHASE 1: Review of the Organization and Procedures of NICE

INTRODUCTION

Health technology assessment (HTA) is increasingly employed by countries as a tool to more effectively regulate the diffusion and utilization of health technologies. The growth of HTA principally originated from the rapid uptake of costly health technologies, beginning in the 1970s, and the resulting concern among policy-makers about the ability and willingness of payers and the public to pay for them (Jonsson & Banta, 1999). At the same time, there was increased scrutiny of health care rationing decisions and a growing consumerist approach, both of which called for decision-making processes that were more accountable, transparent, and legitimate. As such, a more comprehensive approach was needed to help decision-makers set priorities and obtain maximum benefit from limited resources, without compromising the ethical and social values underpinning health systems (Hutton et al., 2006). The resulting growth and development of HTA reflected the demand for well-founded information to support decisions regarding the uptake and expansion of health technologies. Based on these needs, many EU Member States have established HTA systems over the last 20 to 30 years, while others (e.g., Eastern European countries) are currently under development or discussion. The U.S. was one of the first countries to institute HTA, in the late 1970s, through the congressional Office of Technology Assessment. However, this effort was abandoned and only recently are new proposals for establishing a national HTA capability being considered.

The National Institute for Health and Clinical Excellence (NICE) in the U.K. is often considered the most sophisticated national attempt to systematically review the value, or relative costs and benefits, of various treatments. In fact, as argued by Smith (2004), NICE may prove to be “one of Britain’s greatest cultural exports”. Under the broader rubric of developing guidance on health technologies and interventions, NICE has played a pivotal role in 1) identifying those new treatments that offer the best value for money; 2) enabling evidence of clinical and cost-effectiveness to inform judgments on such value; 3) discerning the recommended use of technologies; and, 4) supporting and facilitating health care innovation (Culyer, 2006).

While frequently deemed one of the leading bodies dedicated to health technology evaluation, its operations and procedures have not been without controversy since its inception in the late 1990s. The debate surrounding NICE reflects the most important issues regarding the broader field of HTA – concerns pertaining to priority-setting, stakeholder involvement, economic evaluative methods, and impacts on health care decision-making.

In order to understand the complexities of the NICE model and its relative strengths and weaknesses, this first of four deliverables provides a broad review of its origination and development, organization, core domains of operation, and principal procedures in producing guidance.

INCEPTION, DEVELOPMENT, AND REMIT OF NICE

The need for HTA in the U.K. emerged as a policy priority due to rising health care costs, especially related to health care technology, and increased variation in health care services (Woolf & Henshall, 2000). During the time around NICE’s inception, a key political issue in England and Wales was ‘postcode rationing’, where new and expensive technologies where applied differently in some localities across the U.K., creating inequities in patient access and variation in the quality of services. Given that decisions about the adoption/non- adoption of new health technologies were made largely at the local level, the adoption of and access to treatments depended upon local perceptions and decisions about value for money and budgetary impact. A White Paper published in 1997
brought many of these issues to the fore, highlighting the need to increase quality of care and reduce variations in services, particularly through the introduction of standards and the identification of key interventions for certain patient groups.

In attempts to address such objectives, NICE was created in 1999 to promote clinical excellence within the National Health Service (NHS) by reducing the variation in the uptake of new health technologies and help control costs (Newdick, 2005). Upon its creation, it was hoped that a more formalized and central role for HTA in priority-setting and policy-making processes would lend to improved access and quality of care, greater efficiencies, and a more pervasive reliance on evidence-based medicine. Along with other mechanisms, such as the National Service Frameworks (NSFs) and waiting time guarantees, it denoted an important strategy for regulatory quality and control, as well as the protection of equitable rights to health care.

In broad terms, NICE serves as an “arms-length” organization that provides national guidance on the promotion of good health and the prevention and treatment of ill health. NICE’s remit is to consider both clinical and cost-effectiveness in developing its guidance. When it was established and during the bulk of its existence, NICE has produced three types of guidance, including technology appraisals, clinical guidelines, and interventional procedures. However, as a result of the Department of Health’s 2004 on-going review of its various arms-length bodies, NICE also assumed the responsibilities of the Health Development Agency (HDA) in mid-2005, which provided the Institute with authority to develop guidance on public health interventions or programmes. Principally serving as a cost-cutting measure, the absorption of the HDA by NICE was estimated to result in administrative cost-savings of approximately £3.5 million.

Regarding its role in health care decision-making, NICE guidance essentially serves a quasi-law function in the NHS and broader health care system. In this capacity, guidance is employed to direct clinical practice, establish national standards, and inform decisions on the funding of medicines and treatments. Moreover, it plays a role in improving the capacity and capability of health care organizations, systems, and the wider health workforce to deliver high value, quality care. Overall, NICE guidance is advisory and much is left to local discretion, in terms of its adoption and implementation. However, as of January 2005, technology appraisals are supported by mandate, in that the NHS in England and Wales are now legally obligated to provide funding for medicines and treatments recommended by NICE. Specifically, if NICE guidance supports that a particular technology be made available by the NHS to a certain patient group(s), then associated health care organizations are obligated to implement such recommendations (Mason & Smith, 2005). Moreover, they are required to do so within three months of the date the guidance is issued. The mandate is a result, in part, to the well-publicized “postcode lottery” debates around disparate funding of treatments.

The purview of NICE recommendations differs for each type of guidance. Guidance with regards to public health focuses and applies solely on England, while guidance pertaining to health technologies and interventional procedures covers England, Wales, and Scotland. Regarding the latter, guidance is developed with advice from NHS Quality Improvement Scotland on implementation in the context of the health service in Scotland. The recommendations in clinical guidelines pertain to England and Wales only.

In terms of audience, all guidance is targeted towards practitioners and policy-makers in the NHS, local health authorities, education, private and voluntary sectors, and the general public. To meet the information needs of various stakeholders, NICE has increasingly broadened its dissemination channels and platforms; facilitated stakeholder involvement in the assessment process; and, enhanced public availability of key documents regarding its operations and procedures. In addition to furthering the application of its guidance, these mechanisms have been incorporated into NICE’s core operations in an effort to improve the transparency, accountability, and accessibility of HTA processes.

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1 The NHS Quality Improvement Scotland is an umbrella organization for the Scottish Medicines Consortium (SMC), which similar to NICE, advises on the clinical effectiveness and cost-effectiveness of all newly licensed medicines.
The following sections explore many of these issues in further detail, covering a number of key areas in NICE operations and developments:

- Governance and organization
- Topic selection and priority-setting procedures
- Assessment processes and procedures
- Guidance dissemination and implementation

**GOVERNANCE AND ORGANIZATION**

NICE is organized across three principal entities: the Board (including a Senior Management Team), Directorates, and Centres. Figure 1 below depicts the organizational structure of NICE.

**FIGURE 1: Organizational Structure of NICE**
The Board is composed of executive and non-executive Directors, with a diverse array of experience and interests in health care. Under the umbrella of the Board, there are also several sub-committees with varying administrative responsibilities, including the Audit Committee, Citizens Council Committee, Remuneration and Term of Service Committee, and the Risk Management Committee, in addition to two key councils, the Partners Council and the Citizens Council.

Appointed by the Secretary of State for Health in England and the National Assembly in Wales, the Partners Council assumes a statutory duty to meet annually to review the Institute’s Annual Report. The Council also provides a forum for the exchange of ideas, concepts, and future plans related to NICE operations. Members of the Council come from various organizations, including patient groups, health professionals, NHS management, quality assurance entities, industry, and trade unions. For example, current members are represented by the UK Public Health Association, College of Occupational Therapists, British Medical Association, Association of British Insurers, among many others. The Citizens Council assists NICE decision-making by offering views of the public on key issues informing the development of guidance, especially with regards to social values and judgments, such as equity and need. For example, it considered the economic and social issues surrounding orphan drugs. While participation is open to the broader public, the aim of the council is to provide involvement from stakeholders not typically represented in the assessment process. Therefore, NHS employees, patient groups, representatives of lobbying organizations, and industry are not allowed to participate on the Citizens Council. The approximately 30 members are determined by independent facilitators with no direct association with NICE.\(^2\) The Council normally meets twice annually, discussing a particular topic(s) of interest, such as the role of age in decision-making on NHS funding. NICE employs feedback from the Council by 1) creating a framework on the scientific and social value judgments used to guide the work of independent groups and experts, and 2) reviewing methodologies used to develop its guidance.

The Senior Management Team consists of the Chief Executives and Directors of the Institute, whom meet regularly as part of the process of on-going guidance production. Finally, the various Directorates conduct research and development to improve the methods used by NICE to produce guidance, manage publication and dissemination activities, and ensure the application of guidance.

The key structures of NICE include the three different centres - Centre for Health Technology Evaluation, Centre for Clinical Practice, and Centre for Public Health Excellence. The centres assume a principal role in developing and coordinating the guidance development process.

The **Centre for Health Technology Evaluation** develops guidance on the use of new and existing medicines, treatments, and procedure within the NHS. The work of the centre involves three primary entities, including the Interventional Procedures Advisory Committee (IPAC), independent academic centers, and the Technology Appraisal Committee.

The IPAC includes NHS health professionals and other individuals familiar with key issues affecting patients. The Committee also collaborates with specialist advisors, nominated by relevant health professional bodies.

NICE often commissions an independent academic centre, called Technology Assessment Group (TAG) or centres to prepare assessment reports for consideration by the Technology Appraisal Committee. In particular, NICE collaborates with the following organizations (NICE, 2004a):

- Health Economic Research Unit and Health Services Research Unit, University of Aberdeen
- Liverpool Reviews and Implementation Group, University of Liverpool
- Centre for Reviews and Dissemination and Centre for Health Economics, University of York
- Peninsula Technology Assessment Group (PenTAG), Peninsula Medical School, Universities of Exeter and Plymouth

\(^2\) To date, council members were chosen from around 4,000 individuals responding to a public call for participation.
• School of Health and Related Research (ScHARR), University of Sheffield
• Southampton Health Technology Assessment Centre (SHTAC), University of Southampton
• West Midlands HTA Collaboration, Department of Public Health and Epidemiology, University of Birmingham

In addition, the Centre also contains the Technology Appraisal Committee (TAC). The TAC is an independent entity with membership drawn from the NHS, patient organizations, academia, and industry, and is the primary decision-making body in the production of guidance on new health technologies. Members are typically appointed for a three-year term, and allocated to one of three branches within the Committee. While the TAC represents the views of its varied membership, its advice is intended to be separate of any vested interests.

In addition to the aforementioned, the Centre confers with various ‘consultee organizations’, ranging from national patient groups, health professional bodies, and manufacturers of the technology under review. Such entities are able to submit evidence during the evaluation process, comment on the appraisal documents, and appeal against the TAC’s final recommendations. Moreover, the Centre relies on ‘commentator organizations’, which are represented by manufacturers of comparator products, NHS Quality Improvement Scotland, and research groups working in the relevant topic area. These bodies can comment on evidence and other documents used or produced by the appraisal process, but cannot submit evidence.

The Centre for Clinical Practice offers guidance on the appropriate treatment of specific diseases and conditions within the NHS. Among other things, these clinical guidelines interpret and provide guidance on how to implement the NSFs. To help manage the development and publication of guidelines, the Centre relies on the support of National Collaborating Centres (NCCs), which represent the Royal Medical Colleges, professional bodies, and patient organizations. The seven NCCs oversee different disease areas, such as cancer, mental health, and chronic conditions. To develop a guideline, the Collaborating Centre establishes a Guideline Development Group, containing members with expertise in systematic review, evidence appraisal, clinical and cost-effectiveness assessment, and patient issues. Registered stakeholders are invited to nominate members of the group and provide input on guidelines.

In addition to the aforementioned, the Centre also has a number of Guideline Review Panels, typically consisting of four or five members (including a chair and deputy), that serve to validate the final guideline. In particular, they review how and the extent to which any comments received during the consultation process were considered in the final guideline.

Where possible, the Centre collaborates with the Scottish Intercollegiate Guidelines Network (SIGN) in guidance development, in order to avoid duplication of effort and ensure compatibility in NHS guidance. In addition, collaboration enhances both bodies’ ability to address as many of the clinical areas of concern to practitioners and patients as possible.

The Centre for Public Health Excellence develops guidance on the promotion of good health and disease prevention. To support the production of guidance, the Centre is organized into five Public Health Programme Development Groups (PDG), each headed by an Associate Centre Director. The groups cover behavior change, community engagement, maternal and child nutrition, physical activity and environment, and smoking cessation. The PDGs are responsible for supporting the development of public health guidance by scoping topics, engaging with stakeholders, organizing reviews of guidance, managing public consultation, and devising final recommendations (NICE, 2006a). The Directors, who are leaders in the field of public health, provide support and direction to the respective groups on generating evidence and developing guidance. In addition, they manage any work completed by collaborating centres. The membership of each PDG includes researchers and practitioners, representatives of the stakeholders on the topic under evaluation, and individuals supporting the general public, as appropriate.
An independent Public Health Interventions Advisory Committee is also part of the Centre, with responsibility to review and interpret evidence on the effectiveness and cost-effectiveness of public health interventions. It also produces recommendations on the use of public health interventions in the NHS, local government, and broader public health arena. The Committee is assisted by Specialist Advisors, who are clinicians nominated or approved by professional bodies. In some cases, experts on a particular topic are invited to participate in meetings and a Review Body, represented by universities and an academic hospital, often provides systematic reviews of interventional procedures and collects relevant data.

While there are different arms of NICE, as described above, collaboration between the various centres is encouraged and increasingly commonplace. For example, the outputs of one centre are occasionally used in the guidance produced by the other bodies (e.g., technology appraisals are often incorporated in, or updated by, clinical guidelines). This coordination allows for a more coherent presentation of advice to stakeholders and efficient use of resources and expertise within NICE.

In terms of overall governance, it is important to acknowledge that NICE collaborates with other HTA bodies in the U.K. Namely, the National Coordinating Centre for Health Technology Assessment (NCCHTA) provides support to NICE by managing TAG contracts and contributing to Single Technology Appraisals (described in further detail below) by commissioning Technology Assessment Reports (TAR), which appraise submissions from manufacturers. Beyond the NCCHTA, NICE works with the National Horizon Scanning Centre, UK Cochrane Centre, and Joint Committee for the Review of Vaccines.

Table 1 below summarizes the governance and organization of NICE.

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<th><strong>TABLE 1: Governance and Organization of NICE</strong></th>
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| **Entity responsible for reviewing HTA evidence for priority-setting and decision-making** | Department of Health (DH)  
NICE: Advisory Committee/Program Development Group (Public Health), Appraisal Committee (Health Technologies), Advisory Committee (Interventions), and Guideline Review Panels (Clinical Guidelines). |
| **Agenda-setting body(s)** | Primarily, DH in collaboration with NICE. |
| **Areas for HTA** | Medicines, medical devices, diagnostic techniques, surgical procedures, and health prevention/promotion activities. |
| **Reimbursement requirements and limitations** | Not relevant, except that the implementation of guidance on technology appraisals is mandatory. |
| **Stakeholder involvement** | Broad participation from a variety of stakeholders – health professionals, patient groups, general public, manufacturers, professional associations, methodological experts, etc. |
| **National collaboration** | Primarily, Centre for Reviews and Dissemination and NCCHTA. Other entities are also involved in HTA, including academia, the DH, National Horizon Scanning Centre, UK Cochrane Centre, UK National Screening Committee, and the corporate sector. |
| **International collaboration** | EuroScan, HTAi, WHO Health Evidence Network (NCCHTA), EUnetHTA, INHTA, and Guidelines International Network. |
TOPIC SELECTION AND PRIORITY-SETTING PROCEDURES

To prioritize assessments and initiate the guideline development process, NICE receives suggested topics from a number of sources. In general, the Department of Health (DH) commissions NICE to develop clinical guidelines, guidance on public health, and technology appraisals, while topics for the interventional procedures program are submitted directly to NICE, usually by clinicians. However, topics for potential NICE guidance are also derived from public health professionals, patients, and the general public; manufacturers; and, within NICE itself. The public, including patients and health professionals, can suggest a topic for guidance by completing a form (either on-line or in hard copy) and submitting it to NICE. For manufacturers, topic requests are submitted to the National Horizon Scanning Centre, who informs the DH of key new and emerging technologies that might need to be evaluated by NICE. NICE compiles and maintains a list of all notified procedures, which aids in ensuring transparency.

As a result of a public consultation process in mid-2006, NICE was given responsibility for the initial stages of the topic selection process on behalf of the DH. Once a topic is submitted, NICE initially reviews the suggestion for appropriateness. NICE also consults with manufacturers about draft remits and scopes of particular technology appraisals prior to the topic selection process. Subsequently, the topics are filtered according to several selection criteria set forth by the Department. The list of selection criteria was created in July 2006, following a public consultation process. Specifically, the stated criteria include (NICE, 2006b):

- Burden of disease (population affected, morbidity, mortality)
- Resource impact (cost impact on the NHS or the public sector)
- Clinical and policy importance (whether the topic falls within a government priority area)
- Presence of inappropriate variation in practice
- Potential factors affecting the timeliness for the guidance to be produced (degree of urgency, relevancy of guideline at the expected date of delivery)
- Likelihood of guidance having an impact on public health and quality of life, reduction in health inequalities, or the delivery of quality programs or interventions.

A panel composed of experts in the relevant topic area, generalists with a substantial knowledge of health service and delivery, public health professionals, and patient representatives review the topic suggestions according to the aforementioned criteria. The panel’s recommendations are then reviewed by Ministers at the DH, who hold responsibility for the final decision regarding which topics are referred to NICE for the development of guidance.

In terms of the topic selection process, there is some outstanding criticism that NICE disproportionately focuses evaluations on new pharmaceuticals, compared to other (and older) health technologies and interventions. However, a recent study by Linden et al. (2007) found that of technologies reviewed between 2000 and 2006, 53% were new and 75% were pharmaceuticals. Based on this evidence, criticisms of the bias toward new technologies are somewhat unfounded. However, (new) pharmaceuticals are certainly over-represented in the programme compared with devices and procedures. This may be due to the need to review more pharmaceutical products relative to other technologies or the fact that review methodologies are more advanced in terms of pharmaceuticals.

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3 Appropriateness measured by whether the topic: 1) is within NICE’s remit, 2) has already been covered by guidance, 3) represents an emerging public health issue, and 4) represents an ultra-orphan disease.
Moreover, there has been debate over the transparency of the topic selection process. Following any scoping exercises, NICE and the DH collate feedback and prepare recommendations to Ministers on which technologies should be included in the next wave. However, as the recommendations are not released to stakeholders, there has been a criticism that transparency is lacking regarding the rationale and criteria behind the recommendations. For instance, following a call for topics, it is often unclear why certain technologies have been selected for appraisals, and why particular assessment processes (e.g., multiple vs. single technology appraisal) or clinical guidelines are considered most appropriate for the technology or intervention under question. In addition, increased attention has been given to the time required to make final appraisal referrals to NICE. While consultations on referrals can indeed be a useful and required exercise, the process can take several months before final recommendations are made, which may lead to delays in assessing new technologies and, in general, can create inefficiencies in NICE operations.

Consequently, there has been a push for 1) enhanced breadth of technologies reviewed, 2) greater transparency in the topic selection process, and 3) reduced time required to select topics by the DH and relevant Ministers. To the latter, it has been suggested that final decisions on topic selection be made within one to three months of each published call.

Table 2 below summarizes NICE topic selection processes and criteria.

<table>
<thead>
<tr>
<th>TABLE 2: NICE Topic Selection Processes and Criteria</th>
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<tbody>
<tr>
<td>Governance of topic selection</td>
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<tr>
<td>Criteria for topic selection</td>
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<td></td>
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<tr>
<td>Criteria for assessment</td>
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<tr>
<td>Criteria outlined or publicly-available</td>
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</tbody>
</table>
ASSESSMENT PROCESSES AND PROCEDURES

Depending on the type of guidance, NICE employs slightly different assessment processes and procedures. In general, most guidance development begins with the topic selection process, as previously described, followed by registration of stakeholders (e.g., professional organizations, research and academic institutions, industry, general public) with an interest in participating in guidance development process. Subsequent steps in the process broadly include 1) preparation of the project scope, 2) systematic review of evidence or appraisal, 3) drafting of guidance, 4) consultation of the draft guidance, 5) finalization of the final guidance, and 6) approval and issuance of guidance. The principal processes and procedures by type of guidance are delineated below.

TECHNOLOGY APPRAISALS

NICE produces three different versions of technology appraisals: full appraisals, quick reference guides, and information for the public. Each version targets different stakeholder groups, from the NHS and health professionals (full appraisals and quick reference guides) to patient groups and a lay audience (information for the public). The key steps are outlined below (NICE, 2004a, NICE, 2004c, NICE, 2004f).

Step 1: Production of Provisional List of Appraisal Topics (by the DH)

Step 2: Identification of Consultees and Commentators

Step 3: Preparation of the project scope

- A scoping workshop, with participation of key stakeholders, is held to discuss and finalize all project scopes. Moreover, every scope is subject to a 4-week consultation period, whereby a broader stakeholder community can review and comment on the scope (publicly accessible via the NICE website).

Step 4: Preparation of the Appraisal

- The Technology Assessment Group is formally commissioned, in conference between NICE and the NHS HTA Programme, to prepare the report upon issuance of the final scope and list of consultees and commentators.

- Manufacturers are requested to submit available evidence on clinical and cost-effectiveness. To uphold transparency, all evidence pivotal to the Appraisal Committee’s decision is typically made publicly available. However, NICE accepts unpublished evidence under agreement of confidentiality, or commercial-in-confidence data. Confidence restrictions are expected to be kept to a minimum and must be supported by acceptable justification. Evidence requirements and submission processes will be discussed further in Phase 2.

Step 5: Development of the Assessment Report

- The Technology Assessment Group reviews the clinical and cost-effectiveness of the technology based on a systematic review of the literature and manufacturer submissions.

- Evidence on both therapeutic effect and cost-effectiveness is considered. In terms of cost-effectiveness, the Assessment Group examines the following areas: a technology’s benefit on the course of disease; impact on patients’ quality of life and the value of those impacts in relation to the

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4 A project scope outlines a clear definition of the topic; identifies relevant care settings, health delivery systems, and providers; ascertains the policy context; develops key questions to be answered by the assessment; specifies outcomes measures and comparators; and, substantiates clear timelines. An initial literature search and development of a conceptual and analytical framework help inform and guide preparation of the scope.
preferences of the general population; and, the effect of the technology on resource use and the valuation of those effects in monetary terms. Where relevant and available, evidence on acceptability, appropriateness, feasibility, and equity are also taken into account.

• Beyond the existing literature and manufacturer submissions, the Assessment Group will also consult with clinical and methodological experts in gathering evidence for the report. An economic model may also be produced by manufacturers and the Assessment Group in support. This often creates issues around methodological congruency and transparency and ownership, as the data and methods used by various groups may differ. Many times the manufacturer model may not get considered by the Assessment Group or included in the TAR. This may be a result of 1) bias against manufacturer models (both in terms of technical rigor and potential conflict of interest), 2) desire to keep an arms-length from industry, and 3) preferences of the Assessment Group to develop and use their own model(s).

• The Assessment Report is not a comprehensive review of all the information on a given technology, but is a focused review of the evidence pertinent to the defined scope. The extent to which the Assessment Group employs submitted evidence depends on how closely it aligns with the criteria defined in the protocol and follows recognized methodological guidance.

• Upon completion of the report, it is submitted to NICE and, subsequently, forms the basis of the appraisal.

• NICE also contacts the consultees and commentors to inform them of the availability of the report for review and comment.

• Typically, a timeframe of approximately 36 weeks is allocated for completing the report.

**Step 6: Development of the Evaluation Report**

• The Assessment Report and other evidence and comments put forth by the consultees and commentators are combined in an Evaluation Report.

• The report does not propose recommendations on the use of the technology for the NHS; rather, recommendations are developed that form the guidance document.

**Step 7: Production of the Appraisal Consultation Document (ACD)**

• The Evaluation Report is submitted to an independent committee, the Appraisal Committee, for consideration. The Committee reviews the evidence, and nominated clinical specialists and patient experts participate in a committee meeting, where they can respond to and pose questions.

• The Committee then sets forth their recommendations in the ACD. The recommendations regard the clinical and cost-effectiveness of treatment for the use within the NHS. It is also within the remit of the Committee to recommend against the use of treatment, in cases where the benefits for patients are unproven or not cost-effective. Making recommendations on the pricing of the technology(s) is not currently within the remit of the Committee.

• In appraising the evidence, the Committee considers a breadth of factors:
  – Nature and quality of the evidence
  – Effectiveness and adverse events in different subgroups of patients
  – Risks and benefits of the technology from the patient’s perspective
  – Position of the technology in the overall care treatment pathway
– Implications for health care programmes by the adoption of the new technology
– Appropriateness of the comparator technology or technologies, as perceived by NHS takeholders
– Estimates of cost-effectiveness (e.g., Quality-Adjusted Life Year (QALY))
– Robustness of economic methods
– Broad clinical and policy priorities
– Extent of health need
– Effective use of available resources
– Role in encouraging innovation that will benefit NHS patients.

• The ACD highlights the key evidence used in the appraisal process and highlights any areas of contention or uncertainty. It is made available to the consultees and commentators, health professionals, and the public for comment. The comment period spans a four-week period.

• In the event that new data become available during the appraisal process that materially impacts the (provisional) recommendations set forth in the ACD, the Committee may choose to re-formulate the ACD for additional rounds of consultation.

**Step 8: Production of the Final Appraisal Determination (FAD)**

• The Appraisal Committee reviews the comments on the ACD and then renders its final recommendations in the FAD. The FAD is subsequently submitted to NICE for final approval, a process spanning about 14 weeks.

• Consultees are given the opportunity to appeal against the FAD or the general conduct of the appraisal process. Grounds for appeal include 1) NICE has failed to act in accordance with its published appraisal procedures, 2) the FAD does not adequately reflect submitted evidence, and 3) NICE has exceeded its remit. At the discretion of the Appeal Committee, appellants are afforded an oral submission of complaint.

**Step 9: Issuance of Guidance**

• If there are no appeals or one is not upheld, NICE officially issues the guidance to the NHS, patients, and the public.

In addition to the aforementioned appraisal procedure (termed ‘multiple technology appraisals’ or ‘MTAs’), NICE developed a Single Technology Appraisal (STA) process in 2005 for the review of single technologies for a sole indication. This process was introduced in response to criticisms surrounding the length of time taken by the MTA process.

For an STA, most of the responsibility for assembling relevant evidence lies with the manufacturer or sponsor, and the process is employed for new pharmaceutical products close to market launch. The decision as to whether the appraisal of a technology is appropriate for the STA process is made during the topic selection stage (see above). Selection is typically based on such factors as the complexity of current standard treatments and the likelihood that a sufficient evidence base resides with the sponsor. The STA process is used to ensure that NICE is able to issue guidance to the NHS on new technologies quickly after their introduction into the UK market.

The STA process is similar to that of the full MTA appraisal process, as previously described. However, in terms of the former, only evidence submitted by the manufacturer is formally considered in the independent review. Moreover, formal consultation procedures take place only if the Appraisal Committee’s preliminary recommendations are substantially more restrictive than the terms of the license indication under appraisal (NICE, 2006c). The timelines for the STA process also differ (NICE, 2006c). Specifically, STAs require less time to pro-
duce the guidance, approximately 39 weeks, from initiation of the appraisal to publication. However, the timeline for STAs isn’t substantially compressed and with any delays in the appraisal or appeals, it could approach the duration required for an MTA.

In cases where the appraisal is tracking regulatory approval, the first Appraisal Committee meeting is organized subsequent to a positive opinion by the European Agency for the Evaluation of Medicinal Products (EMEA). The minimum time from regulatory approval to publication of the guidance is between 6 and 13 weeks.

To date, the STA process has been applied only to drugs, mainly regarding cancer drugs.

**Clinical Guidelines**

NICE produces four versions of its clinical guidelines: full guidelines, NICE guideline, quick reference guide, and information for the public. Similar to guidance on technology appraisals, the difference between the various versions primarily concerns the extent of detail needed to meet the information needs of different stakeholder groups. In addition to topic selection and registration of stakeholders, as previously discussed, the key steps are outlined below (NICE, 2006d, NICE, 2006e).

**Step 1: Preparation of project scope and work plan**

• Similar scoping process as technology appraisals. However, the National Collaborating Centre (NCC) commissioned to develop the guideline prepares the scope.

• Following the scope, a work plan is devised to specify methods, timelines, and cost. The work plan forms an agreement between NICE and the NCC for development of the guidance.

**Step 2: Establish Guideline Development Group**

**Step 3: Systematic Review of Evidence**

• Evidence from searches of electronic databases and via information submitted by stakeholder organizations is reviewed.

• The Guideline Development Group consults with a health economist(s) to provide advisement of economic issues, a review of economic literature, and recommend economic analysis (e.g., modeling), where needed.

**Step 4: Drafting of the Guideline**

• Draft recommendations, as set forth by the Guideline Development Group, are prioritized according to 1) impact on patient outcomes, 2) influence on reducing variation in practice, 3) ability to lend to more efficient use of NHS resources, and 4) capacity to effectively move patients through the care pathway.

**Step 5: Consultation on the Draft Guideline**

• At minimum, there is one consultation period for registered stakeholders to comment on the draft guideline.

• Following the consultation period(s), a Guideline Review Panel reviews the guideline to ensure accountability of stakeholder commentary.

**Step 6: Production, Approval, and Issuance of the Final Guidance**

• The Guideline Review Panel finalizes the recommendations and sends draft guidance to the NCC to produce the final guidance.

• NICE then approves the guidance (in approximately 18 months) and disseminates to the NHS, patients, and the public.
In addition to the aforementioned process, NICE has recently instituted ‘short clinical guidelines’, which are designed to address clinical questions that do not meet topic selection criteria for a traditional clinical guideline (or technology appraisal), but where more urgent guidance would be beneficial. The shorter guideline is developed in the same manner, but within a condensed timescale, typically between nine and 11 months.

Public Health Interventions

NICE produces two types of guidance: public health intervention guidance and programme guidance. While there are a few minor differences between the production of the two types of guidance, the main processes are similar, as outlined below (NICE, 2006a). The first three initial steps, topic selection, registration of stakeholders, and preparation of the project scope, coincide with technology appraisals and clinical guidelines.

**Step 1: Systematic Review of Evidence**
- A review of the existing evidence and an economic appraisal is completed. The economic component is typically conducted if the topic is deemed a priority area (e.g., major resource implications are present, current public health practice is challenged or lacks consensus among health care professionals).
- The review may be conducted by NICE or an external research body.
- A synopsis of the review is created and disseminated to registered stakeholders for comment.

**Step 2: Drafting of the Guidance**
- The Public Health Interventions Advisory Committee reviews the synopsis and drafts the guidance. Recommendations are based on several factors, including the strength of supporting evidence, importance of outcomes, health impact, cost-effectiveness, and other considerations (e.g., inequalities, feasibility).

**Step 3: Consultation (1-month) on the Draft Guidance**

**Step 4: Conduct of Fieldwork**
- The draft guidance is tested via meetings with practitioners in the field. At least four to five full-day meetings with 30-35 practitioners are convened, and these take place across a variety of geographic regions.
- Meeting reports are drafted in a technical document and submitted to the Advisory Committee.

**Step 5: Production, Approval, and Issuance of Final Guidance**
- The Advisory Committee reviews the technical document and comments from the consultation period, and produces the final guidance.
- NICE then approves the guidance (in approximately 13 months) and disseminates to the NHS, patients, and the public.

NICE also has a process for developing guidance on interventional procedures. However, as the course of action is similar to public health interventions and clinical guidelines, it will not be covered in detail.
Table 3 presents a select range of both published and planned (or in progress) NICE guidance over the last 5 years. Since 2004 alone, NICE has completed over 280 guidance.

<table>
<thead>
<tr>
<th>Public Health Guidance</th>
<th>Interventional Procedures Guidance</th>
<th>Technology Appraisals</th>
<th>Clinical Guidelines</th>
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<tbody>
<tr>
<td><strong>Published</strong></td>
<td><strong>Planned</strong></td>
<td><strong>Published</strong></td>
<td><strong>Planned</strong></td>
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<tr>
<td>Physical activity</td>
<td>Alcohol &amp; schools intervention</td>
<td>Deep brain stimulation for tremor and dytonia</td>
<td>Biopolar disorder – new drugs</td>
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<tr>
<td>Smoking cessation</td>
<td>Mental health &amp; older people</td>
<td>Insertion of biological slings for stress urinary incontinence</td>
<td>Crohn's disease – infliximab</td>
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<tr>
<td>Workplace smoking</td>
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<td>Laparoscopic Partial nephrectomy</td>
<td>Obesity – orlistat</td>
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<tr>
<td>Substance misuse</td>
<td></td>
<td>High-intensity Focused Ultrasound for prostate cancer</td>
<td>Sepsis (severe) – drotrecogin</td>
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<tr>
<td>Preventing STDs and pregnancy in those under 18</td>
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<td>Anthroscopic knee washout</td>
<td>Breast cancer – gemcitabine</td>
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<tr>
<td></td>
<td></td>
<td>Cryotherapy for renal cancers</td>
<td>Ischaemic stroke (acute) – alteplase</td>
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<td>Drug misuse – naltrexone</td>
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Table 4 summarizes an overview of key NICE assessment processes and procedures.

**TABLE 4: Overview of Key NICE Assessment Processes and Procedures**

| Key steps in the assessment process | • Preparation of project scope  
• Systematic review of evidence/appraisal  
• Drafting of the guidance  
• Consultation  
• Finalization of the guidance  
• NICE approval and issuance of guidance |
| Evidence reviewed* | • **Technology appraisals**: Clinical and cost-effectiveness evidence.  
• **Clinical guidelines**: Existing literature, information submitted by stakeholder organizations, existing economic literature or original analyses.  
• **Public health guidance**: Evidence briefing (review of reviews); systematic review of primary data; existing, published primary research; and, new primary research, where available.  
• Interventional guidance: Primarily published, peer-reviewed literature. |
| Duration required to conduct assessments** | • **Technology appraisals**: ~54 weeks (MTAs); ~39 weeks (STAs)  
• **Clinical guidelines**: ~72 weeks (full); ~40 weeks (short)  
• **Public health guidance**: ~52 weeks  
• **Interventional guidance**: ~46 weeks |

* Detailed discussion of evidence requirements and technical processes of review will be included in Phase 2, with a primary focus on technology appraisals.

** Standard timelines, given no problems or appeals. If either of these occurs, the duration of the assessment can be longer.

**GUIDANCE DISSEMINATION AND IMPLEMENTATION**

The guidance produced by NICE are employed on a number of different levels. Specific uses include:
• Develop treatment standards for health organizations
• Inform and guide decision-making among patients and consumers
• Guide actions to meet government indicators and targets for health improvement and reduce health inequalities
• Improve communication between patient and providers
• Guide education and training of health professionals
• Reduce treatment and practice variation
• Inform decision-making regarding NHS funding and resource allocation
• Guide the development of treatment pathways for new procedures and interventions
To facilitate the dissemination of guidance, all publications are focused on the needs of different stakeholder groups – from government and NHS decision-makers, health professionals, patients, and the general public. While all guidance is published online, NICE also sends copies to key stakeholders and end-users, including local government organizations, health professionals working in the area covered by the guidance, NHS staff responsible for clinical governance, and consultants in relevant specialties. Moreover, NICE informs the broadcast and print media about newly published guidance and participates in various HTA international organizations and professional societies, such as Health Technology Assessment International (HTAi).

As previously noted, the Secretary of State for Health has instituted a mandatory requirement that Health Commissioners make funds available for implementation of technology appraisal guidance within 3 months of publication. Following issuance of NICE guidance, NHS Quality Improvement Scotland (QIS) reviews the guidance for implications and validity for NHS Scotland. The NHS boards in Scotland, however, are not obligated to provide funds for the implementation of NICE guidance.

To aid the implementation process of all its guidance, NICE has established an implementation program. Each set of guidance is assigned an implementation team, who collaborates with those involved in the development process, and communications and field-based teams, to ensure targeted dissemination to various audiences; engage with the NHS, local government, and the wider community; evaluate uptake of NICE guidance; and raise awareness of NICE guidance.

Moreover, NICE provides a number of tools to support the implementation of guidance, all of which are available via the website. Such aids include (NICE, 2006f):

- **Forward Planner** – Summarizes published and forthcoming NICE guidance, and explains which sectors are likely to be impacted.
- **Slide sets** – Highlights key messages from the guidance and makes recommendations for implementation.
- **Audit criteria** – Assists organizations to execute baseline assessment and monitor associated activities.
- **Costing tools** – Helps assess the financial impact of implementing NICE guidance.
- **Implementation advice** – Points to sources of support, resources, etc.
- **Commissioning guides** – Provides support for local commissioning and needs assessment.
- **ERNIE database** – The Evaluation and Review of NICE Implementation Evidence (ERNIE) Database provides details on how NICE guidance is being used.

In addition to offering implementation tools to stakeholders, NICE tracks the implementation of its guidance by local organizations.

NICE conducts a re-evaluation of appraisals every 4 years for health technologies, every 4 to 6 years for clinical guidelines, every 3 years for public health guidance, and every 1 to 5 years for STAs. As described above, NICE incorporates a formal appeals process for technology appraisals only. To date, there have been over 40 appraisals subject to appeal.

Table 5 summarizes NICE procedures for guidance dissemination and implementation.
### Table 5: NICE procedures for guidance dissemination and implementation

<table>
<thead>
<tr>
<th>Channels for HTA results dissemination</th>
<th>NICE website, publications, international HTA organizations, media, and dissemination/implementation tools provided to stakeholders (via NICE website).</th>
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</thead>
<tbody>
<tr>
<td>Use of HTA results</td>
<td>Develop standards; guide patient care decisions; inform strategies to meet government indicators and targets; support decision-making regarding NHS funding and resource allocation; and, guide education and training of health professionals.</td>
</tr>
<tr>
<td>Evidence considered in decision-making</td>
<td>See HTA Topic Selection and Analytic Design section.</td>
</tr>
<tr>
<td>Any reported obstacles to effective implementation</td>
<td>Insufficient funding, lack of health professional support, inadequate structure to support implementation amongst the trusts, duplication of effort during appraisal process, timelines, etc.</td>
</tr>
<tr>
<td>Formal processes to measure impact</td>
<td>Yes</td>
</tr>
<tr>
<td>Processes for re-evaluation or appeals</td>
<td>Re-evaluation: every 4 years (technology appraisals), every 4-6 years (clinical guidelines), every 3 years (public health guidance), every 1 to 5 years (STAs). NICE can set an accelerated timeline for technology appraisal re-evaluations. NICE incorporates a formal appeals process for technology appraisals.</td>
</tr>
<tr>
<td>Accountability for stakeholder input</td>
<td>Yes, several opportunities for stakeholder submission of evidence, review, and comment.</td>
</tr>
<tr>
<td>Transparent/public decision-making process</td>
<td>Yes, information regarding most appraisal and decision-making processes is publicly-available via the NICE website.</td>
</tr>
</tbody>
</table>

### CONCLUDING SUMMARY OF NICE’S OVERALL STRENGTHS AND WEAKNESSES

Overall, NICE and its programs for developing guidance are unique and represent a policy embodiment of evidence-based medicine. As discussed by Culyer (2006), NICE promulgates a deliberate process that elicits and combines various types of evidence and from different sources in order to develop guidance. Several aspects inherent to NICE’s procedures lend themselves to an effective deliberative process, many of which are focused on ensuring the highest degree of transparency and the participation of a wide range of stakeholders. Such characteristics include:

- Open Board meetings that take place bi-monthly around England and Wales.
- Broadly set membership of the Technology Appraisal Committee (as well as other committees).
- Existence and participation of a Partners and Citizens Council.
- Extensive consultation and comment opportunities throughout the appraisal process.
- Implementation of an appeals procedure.
- Frequent and close collaboration with external review bodies, such as the NCCs, TAGs, and the Royal Colleges.
- For the most part, public availability of key documents, thereby aiding overall transparency.
NICE’s engagement of a broad representation of stakeholders, from multiple sectors and disciplines, serves to introduce a variety of perspectives into the appraisal and decision-making process. This is particularly helpful when reaching consensus on conflicting evidence or recommendations; making such judgments typically requires knowledge of the scientific literature, realities of clinical practice, and underlying social values. Moreover, as there is a paucity of scientific evidence about patient treatment preferences and viewpoints on issues such as equity and fairness in health care, it is important to involve a variety of stakeholders in the process to elicit such perspectives. At the implementation stage, a high level of stakeholder involvement increases public and professional ownership in the guidance, which enhances the likelihood that it will effectively guide decision-making and clinical practice.

At the same time, however, there is debate and scrutiny as to whether NICE most effectively utilizes stakeholders in the review process. For example, in terms of patients, while NICE has established patient and public involvement programmes to provide information and support to patients and the broader public (and, is certainly one of the most progressive HTA bodies in this regard), the precise influence of various groups on the guidance process and resulting decision-making is unclear (Bridges & Jones, 2007). A greater role for industry representatives has also often been promulgated. However, this is often controversial, due to concerns that greater collaboration between NICE and sponsors/industry may influence the objectivity and transparency of the assessment process, particularly with regards to evidence submissions and resulting recommendations. On balance, the general benefit of manufacturer involvement is recognized; however, such participation should be as transparent as possible.

In terms of the methods NICE employs or promulgates, there are both advantages and drawbacks. In general, methods are transparent and standardized across appraisals (and, other forms of guidance). However, in particular to topic selection, while the transparency of the nomination and decision-making process has improved recently, greater clarity and openness is needed on the rationale and criteria behind topic selection and recommendation. STAs raise further questions around these issues, as the criteria for selection and how they may differ from the MTA process isn’t necessarily clear. Moreover, as there is a slight bias toward the evaluation of new pharmaceuticals, increased focus should be placed on other treatments (e.g., devices, public health interventions), especially given continued growth in technological innovation and advances in prevention strategies.

As previously mentioned, the timeframe between topic referral and the initiation of the appraisal process can pose issues. If too lengthy, there is concern that beneficial technologies will be delayed from entering the market. Since, if a NICE appraisal is planned, NHS organizations are reluctant to introduce the technology until the guidance is issued. Furthermore, a lengthy process upfront may place time pressures on the relevant groups and stakeholders towards the end of the appraisal process. To that end, the current timeframe is structured to permit incorporation of new information toward the end of the process, without necessarily allowing time for sufficient review and critical appraisal. On balance, however, a shorter period may render it difficult for relevant stakeholders to assemble the appropriate evidence, as the key questions posed by the assessment aren’t necessary clear prior to the finalization of the project scope. It is therefore important for NICE to balance transparency and collective participation with efficiency. In addition, continued focus should be given to more speedy and efficient production of guidance, where appropriate and without compromising a thorough and open process. As addressed previously, STAs were introduced in hopes of meeting these aims at the Institute. As a relatively new process, however, many of the elements of the STA process have yet to be fully tested in practice and there is question as to whether the STA model will indeed deliver more timely decisions. This may also be a factor if the resources dedicated to STAs will detract from the appraisal of other products (through the MTA process).

With regards to the actual appraisal process, one potential drawback of the NICE approach is an unnecessary duplication of effort. For example, as manufacturers and the academic (TAG) group often work in apparent isolation, difficulties may ensue if conflicts regarding the available evidence are resolved only late in the appraisal
process. Specific strengths and weaknesses of NICE methods, including the appraisal process, will be explored in greater detail in Phase 2.

If the appraisal process isn’t sound and transparent, the likelihood of appeal increases. In particular, appeals often ensue as a result of a lack of (balanced) stakeholder consultation, divergent recommendations from different regional decision bodies (i.e., NICE vs. the Scottish Medicines Consortium), and an over-reliance on cost rather than efficacy considerations. Particular to the appeals process, there are criticisms that the grounds for appeal are drawn too narrowly and that the membership of the appeal panels should be confined to individuals with no formal connection to NICE. There tends to be a general perception that the number of appeals has increased over time. However, the absolute number of appeals and the proportion of appeals to guidance in a given year have remained relatively constant. To date, approximately 42% of all appeals allowed have been upheld by NICE. A recent appeal challenged the findings in a NICE technology appraisal that recommended drugs to treat Alzheimer’s disease only for patients of moderate severity. This appeal was not successful, and the NICE findings were then challenged in a judicial review. As a result of the review, recommendations regarding use of the drugs were unchanged, but NICE was required to clarify how its guidance should be applied to groups such as people with learning disabilities or whose first language is not English. Issues about the NICE appeals process are addressed in more detail in Phase 2.

Lastly, the success of guidance implementation can either hinder or facilitate the effective use of the recommendations set forth by NICE. While the implementation of guidance is not necessarily standardized or stringent, there is some evidence of influence, such as the mandated 3-month requirement. However, a significant hurdle to effective implementation is securing funding to offer recommended technologies and interventions within a resource-constrained environment. Given a fixed budget scenario facing local health care systems in the NHS, mandatory uptake of NICE guidance may require local trusts to forego other possibly higher priority investments or make cutbacks in other key activities. In this sense, there is significant tension between local and centralized decision-making, in terms of understanding local circumstances and opportunity costs in balance with the need for national, standardized guidance across the U.K. In addition, restrictions in the use of a technology, as outlined by NICE guidance (a somewhat common outcome), frequently pose a challenge to implementation, especially when compared to more straightforward “go/no go” decisions. This can delay the finalization and uptake of guidance.

A study by Sheldon et al. (2004) found that implementation of NICE guidance was mixed, by technology and location. For example, the use of orlistat and taxanes grew rapidly following publication of guidance, although compliance among NHS organizations appeared to be inconsistent across a range of guidelines. Compliance is likely contingent upon the extent to which NHS organizations are prepared for NICE guidance and have established structures and processes to manage implementation. To that end, implementation of NICE guidance is likely to be improved if the guidance is clear and based on an understanding of clinical practice and/or the policy process, in addition to being well-supported in terms of funding and professional involvement. Responsibility for ensuring that NICE guidance meets the needs of policy-makers and other key stakeholders requires collaboration from key constituencies, such as industry and patients, so that the decision-making process is more acceptable, relevant, and transparent.
PHASE 2: Technical Review of the Evidence Requirements and Assessment Methods of NICE

INTRODUCTION

NICE employs a rigorous process to evaluate the relative costs and benefits (cost-effectiveness or ‘value for money’) of selected health technologies and interventions. The technical and methodological aspects of the HTA process are pivotal not only for a robust, evidenced-based evaluation, but also for the successful acceptance and implementation of the guidance. Without a sound appraisal process, subsequent decisions and guidance are more likely to be challenged by key stakeholders, including patients, manufacturers and sponsors, and policy decision-makers. Beyond technical rigor, the transparency of and consistency across assessments are also key components of an accurate and standardized process.

NICE is considered one of most sophisticated HTA agencies, especially in terms of methodological processes and development. In particular, the Institute has promulgated standards and guidelines for evidence requirements and economic evaluation, and is one of the few agencies that integrally involves stakeholders in the assessment process and has instituted a formal appeals process. Moreover, while further improvements could be made regarding the transparency of some of its procedures (e.g., topic selection), NICE has made significant strides in this area by making most key documents publicly-available and detailing the assessment and appraisal processes. NICE also supports methodological development, by offering training opportunities and fellowships to HTA personnel and funding research on new economic evaluation methods. In a similar sense, it has been responsive to areas of technical or methodological concern, such as the timeliness of guidance, with the recent introduction of Single Technology Assessments (STAs). Despite the advances in HTA methods put forth by NICE, there still remain areas of continued debate, particularly in relation to the methods of cost-effectiveness analysis. Key issues include the use of models, the derivation of QALYs, and approaches for characterizing uncertainty (e.g., probabilistic sensitivity analysis).

This second of four deliverables provides a technical investigation of the principles and methods of the NICE assessment and appraisal process, including the evidence required to effectively and appropriately evaluate a given technology or intervention. The standards and methods by which NICE obtains and reviews evidence is examined, with areas of controversy and uncertainty regarding its processes highlighted. While the previous phase discussed all areas of guidance, the following review will focus on technology appraisals, in particular.
OVERVIEW OF NICE TECHNOLOGY APPRAISAL METHODS

While slightly different assessment processes and procedures are used for the various types of guidance (e.g., clinical guidelines, technology appraisals), three principal phases are generally involved: 1) scoping or selection, 2) assessment, and 3) appraisal. Figure 2 provides an illustration of the three phases.

FIGURE 2: Three Main Phases of Technology Appraisals

In the scoping or selection phase, NICE determines the specific questions to be addressed for each technology appraisal, in order to define the key issues of concern or interest and the questions to be addressed by the Appraisal Committee when considering the clinical and cost-effectiveness of the technology. The consultees and commentators, as outlined in the previous report, are consulted during this process and their comments inform any necessary revisions to the initial draft scope. The final scoping document outlines the boundaries of the appraisal and the parameters to be investigated. The scope is further developed into a protocol for the technology assessment. Further, the scoping process provides an opportunity to discuss methods and pertinent technical considerations, normally in a Scoping Workshop, in which all the main parties are involved.

The assessment phase is a systematic and independent evaluation of the relevant evidence available on a technology, with the overarching aim to produce an estimate (and, any examination of uncertainty) of its clinical and cost-effectiveness for a specific indication. The assessment is comprised of two distinct, but mutually-dependent, components: 1) a systematic review of the evidence and 2) an economic evaluation. The assessment process requires an understanding of the appraisal question and the context within which it is to be addressed (e.g., current paradigms of care and any available alternative technologies or treatments) and appropriate methods of comparing the technologies. The assessment, therefore, consists of an objective analysis of the quality, findings, and implications of the available evidence, as it relates to the appraisal question(s) and broader context. Strengths, weaknesses, and gaps in the evidence are identified and evaluated.

This is also the phase where the manufacturer or sponsor of the technology has the opportunity to make a submission of evidence, in accordance with guidelines set forth by NICE. In the original process (now known as multiple technology assessments or ‘MTAs’), the manufacturer submission may or may not influence the approach followed by the independent Assessment Group. In STAs, however, the Assessment Group mainly critiques the manufacturer submission.
The appraisal phase involves the consideration of outputs of the assessment process within the context of additional information supplied by consultees, commentators, clinical specialists, and patient experts. The Appraisal Committee considers the evidence put forth by the Assessment Report (described in the Phase I deliverable) and from other sources. The Committee then formulates an appraisal decision, applying judgments on the importance of a range of factors that differ from appraisal to appraisal. While there is a boundary between the assessment and appraisal phase, it is not precisely defined and judgment in the assessment process about, for example, choice of outcome measures to be investigated will influence the appraisal process.

Each of the three phases are examined in further detail below.

**SCOPING PROCESSES**

As discussed in the Phase 1 report, the Department of Health and the Welsh Assembly Government provide NICE with a final remit for appraisals. Upon selection of the topic(s), NICE defines the details of the appraisal (what it will and will not examine) through a scoping process (Figure 3). The primary aim of the scope is to provide a framework for the appraisal, which is used to shape and guide the review. The scope defines the issues of interest (e.g., patient population) as clearly as possible and sets the boundaries for the work undertaken by the Assessment Group and the Appraisal Committee.

**FIGURE 3: Overall Scoping Process for Technology Appraisals**

As depicted above, NICE commences an initial scoping exercise by conducting a preliminary search of the literature and working with the Assessment Group. Potential consultees, commentators, and clinical specialists are then consulted on the draft scope and invited to participate in a subsequent scoping workshop. The scoping workshop involves the Assessment Group, all provisional consultees and commentators, the Department of Health, the Welsh Assembly Government, and other interested and relevant parties. Workshops seek to generate
discussion on the scope of the appraisal from different perspectives. In particular, participants of the workshop discuss and define the relevant issues to be considered during the appraisal, including the:

- Clinical problem and relevant clinical pathways
- Current best treatments (if known)
- Comparator technologies
- Key health outcomes, including quality of life
- Key clinical and economic studies
- Potential structure for models developed to assess cost-effectiveness

Following deliberations, a final appraisal scope is substantiated and, where relevant, a review protocol for the Assessment Group is developed.

The final scope outlines and defines key parameters of clinical and cost-effectiveness to be addressed by the appraisal. As presented in Table 6, such parameters include the 1) clinical problem and the relevant target population(s) or subgroup(s), 2) technology and settings of application, 3) relevant comparator technologies, 4) principal health outcome measures, 5) cost measures, 6) time horizon, and 7) other considerations/issues.

<table>
<thead>
<tr>
<th>TABLE 6: Appraisal Parameters Outlined in the Scoping Process</th>
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<tbody>
<tr>
<td>PARAMETER</td>
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<tr>
<td>Clinical problem and patient population(s)</td>
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<td>Technology and application</td>
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<td>Relevant comparator technologies</td>
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<td>Principal health outcome measures</td>
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<td>Cost measures</td>
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<td>Time horizon</td>
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<tr>
<td>Other considerations/issues</td>
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ASSESSMENT PROCESSES

Upon referral to NICE of a group (or ‘wave’) of technologies, the Institute issues timetables for appraisals of each technology within the group. For each individual appraisal, NICE initiates the process by formally inviting consultee and commentator groups to participate in the appraisal process, and issues a final remit and scope.

Evidence Requirements and Submissions

NICE subsequently requests the submission of evidence relevant to the technology under appraisal. According to NICE, “consideration of a comprehensive and high-quality evidence base is fundamental to the appraisal process”. To meet this objective, the Institute encourages the submission of evidence on a number of aspects of care, of various types and from multiple sources. Such evidence must be robust and the analysis and interpretation thereof be as transparent as possible. To that end, the evidence submitted to NICE is required to be 1) relevant to the issue under consideration, addressing target patient groups, comparators, analysis perspective, and measured outcomes; 2) comprehensive and complete; 3) inclusive of pertinent study design information and parameters; and, 3) appropriate for the purpose of the appraisal (examining clinical benefit and/or cost-effectiveness and quality of life. Any analyses or models submitted must also be methodologically sound and minimize any bias (e.g., via explicit presentation of study inclusion and exclusion criteria). Moreover, given that there are typically deficiencies in the available evidence base, any limitations must be explicitly stated, including any attempt to overcome such uncertainties.

The evidence is submitted directly to NICE, normally to the Technical Lead. Subsequent to receipt, NICE gives the evidence to the Assessment Group. Prior to making submissions, the perspective and presentation of evidence may be discussed with the Appraisal Programme Director and/or the Technical Lead. However, there are limits to the extent to which the Institute’s staff can engage with stakeholders (particularly, manufacturers/sponsors) in discussions about evidence submissions.

To ensure a comprehensive repository of evidence, the Institute normally allows and requests evidence from a variety of stakeholders, including manufacturers or sponsors of the technology, patient groups, healthcare professionals, and clinical specialists or patient experts. For manufacturers and sponsors, they are required to identify all evidence relevant to the appraisal. This includes a list of all sponsored or known studies, in the form of all clinical trials, follow-up studies, and registry evidence. It also includes unpublished and part-published evidence (e.g., unpublished clinical trials, abstracts) not in the public domain and commercial-in-confidence data. Unpublished and part-published evidence must be critically appraised, with accompanying sensitivity analyses, where applicable. NICE will accept unpublished evidence under agreement of confidentiality (‘commercial-in-confidence’ information) or if it might affect future publication rights (‘academic-in-confidence’ information). To ensure transparency, NICE encourages pivotal evidence to be publicly-available and, ideally, available to the Committee, consultees, and commentators. As such, ‘confidence’ restrictions are expected to be kept at a minimum and, if required, must be supported by acceptable justification. If the technology is undergoing regulatory approval, manufactures are required to make available sufficient detail of the clinical trial evidence, in order to facilitate the appraisal.

All of the evidence is provided to the Institute in a submission package. Specifically, the submission package should a complete list of all studies concerning the health technology by manufacturers or known to them; an
executive summary; a main submission addressing 1) aims of treatment and current approved indications for the technology, 2) assessment of clinical effectiveness, 3) assessment of cost-effectiveness containing NICE’s reference case analysis (described in further detail in subsequent section), 4) assessment of resource impacts, 5) appendix of data and supporting materials, 6) appendix of excluded evidence and justification thereof, and 7) electronic copy of cost-effectiveness model.

Table 7 presents the breadth of evidence typically submitted and accepted by other key stakeholder groups.

<table>
<thead>
<tr>
<th>Stakeholder Group</th>
<th>Evidence Requirements/Submissions</th>
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<tr>
<td>Patient Groups</td>
<td>Evidence includes any information obtained from patients and/or caregivers that may inform the appraisal. NICE is particularly concerned with capturing a range of patient views on, and experiences of, living with a condition and the impact of a technology on a patient’s symptoms and physical, social, psychological, and emotional state. To provide a balanced view, NICE is also interested in obtaining patient perspectives on living without the technology. In particular, the dimensions of patient evidence include perspectives on: • Effectiveness of the technology • Appropriateness of the technology • Acceptability of the technology • Impact of a technology on physical and psychological symptoms, disability, function, long-term outlook, quality of life and lifestyle. • Equity issues • Costs to the patient (financial and other) Patient evidence must be presented in a synthesized manner and have a balance of positive and negative views.</td>
</tr>
<tr>
<td>Healthcare Professionals</td>
<td>Evidence can be submitted by the Royal Colleges, specialist societies, professional bodies, and NHS organizations. Most healthcare professional provide views of the technology within the context of current clinical practice (not typically available through the existing literature). Submissions usually address the following issues: • Patient group variations • Appropriate use of outcome and surrogate measures • Relative significance of side effect profile and clinical benefits • Treatment pathway(s) • Current best alternative treatments • Published clinical guidelines and impact of possible guidance on care delivery and the education and training of NHS staff</td>
</tr>
<tr>
<td>Clinical specialists and patient experts</td>
<td>Clinical specialists and patient experts are nominated by participating consultees and commentators to act as expert witnesses to the Appraisal Committee and provide oral evidence. These representatives must not have any personal financial involvement with the manufacturers or sponsors of the technology. In advance of the Committee meeting, the experts submit a written personal view of the role of the technology and its use in the NHS. They also provide oral evidence during the meeting. However, the experts do not participate in Committee discussions on the content of the Appraisal Consultation Document (ACD). Oral views inform the debate on the following dimensions: • Variations in clinical practice (e.g., geographical, patient subgroups) • Requirements to support guidance implementation • Perceived benefits and potential risks of the technology • Parameters related to starting and stopping use of the technology • Impacts on the education and training of NHS staff</td>
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The following section details the type of evidence preferred and normally accepted by NICE, across the areas of relative treatment effects, cost-effectiveness, and other appraisal considerations.

**Evidence on Relative Treatment Effects**

Evidence on relative treatment effects is broadly categorized into experimental and observational studies. NICE considers experimental studies with high internal and external validity, and stated inclusion and exclusion criteria, the most reliable, followed by various types of observational studies, as depicted in Figure 4 below.

**FIGURE 4: Hierarchy of Preferred Study Designs**

In terms of Level 1, RCT evidence, NICE strongly prefers head-to-head studies that directly compare the technology and the selected (appropriate) comparator. Where no such trials are available, consideration is given to indirect comparisons, subject to thorough and fully described analysis and interpretation. In some appraisals, there will also be available systematic reviews and meta-analyses of RCTs, which may be considered in parallel with the primary evidence. Depending on the appraisal scope, robust systematic reviews can be considered at the top of the evidence hierarchy. Despite being the preferred study design, the quality of the RCT is considered, particularly with regards to external and internal validity. Related issues include method of randomization, rate of follow-up, trial size, selected outcome measures, and generalizability.

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5 Treatment effect defined as the difference between the health state or quality of life that would be expected on average by patients receiving the technology and the health state or quality of life of the same group were they to receive alternative care.

6 RCTs are designed to minimize bias or confounding effects in order to isolate the effects of a single variable in a well-defined patient group. The outcome of the trial measure the estimated magnitude of benefit and risk associated with the technology relative to the comparator (or control).
Level 2 through 4, or non-RCT, evidence is considered more susceptible to bias, including publication, retrieval, selection, performance, measurement, and attrition biases, although these issues are more characteristic of studies lower in the hierarchy. More than one source of observational evidence is required, where possible, to assure the validity of conclusions drawn regarding relative effectiveness. Moreover, the implications of potential selection bias associated with the use of non-RCT evidence are usually required to be assessed in sensitivity analyses.

However, even where definitive primary studies exist, there are limitations that must be considered. For example, the elderly and other patients with co-morbidities are often excluded from clinical trials, even though these patients are major consumers of medical products. Additionally, trials do not always collect a full range of economic data (e.g., indirect costs, health utility measures) and the study time horizon is often too short to detect longer-term outcomes. To supplement available clinical data, findings from different types of studies should be combined or synthesized. This is especially the case in consideration of ascertaining cost-effectiveness, where evidence from sources other than RCTs is usually required, such as long-term outcomes (e.g., mortality) and intermediate and long-term side effects (adverse or beneficial). Alternatively, other types of studies (e.g., case series, registries) may be preferred to RCTs for different policy questions. For instance, modeling is useful when making decisions under uncertainty.

Evidence on Cost-Effectiveness

Evidence for the economic evaluation of a product include the quantification of its effect relative to the comparator treatment on the course of the relevant disease and the impact of such effects on patients’ health-related quality of life (HRQL). The valuation of these impacts should reflect the preferences of the general population. In terms of costs, evidence includes quantifying the effect of the technologies on resource use in terms of physical units, where possible or applicable. The valuation of these effects should be in monetary terms using appropriate prices and unit costs. Costs should also represent those most relevant to the NHS and PPS. Evidence on cost-effectiveness is obtained from original analyses and findings from systematic reviews of existing published literature.

Evidence on Other Appraisal Considerations

In addition to evidence on therapeutic benefit and relative value, or cost-effectiveness, other issues are considered. These areas of concern include:

- **Acceptability, appropriateness, and preference** – Even in cases where a health technology has established treatment effect and cost-effectiveness, it may not be acceptable to patients and providers. For example, the frequency, intensity, or nature of side effects, route or frequency of administration, design, or ethical implications associated with a particular technology can significantly impact preferences for uptake and use.

- **Feasibility and impact of use** – Certain organizational factors can impact upon patients and/or those providing care, in terms of the feasibility and impact of implementation. For example, adopting a technology may require additional resources, in terms of staff time or human capital. Consequently, organizations may need to recruit additional staff or a different staff mix to meet such demands.

- **Equity** – NICE is one HTA agency that explicitly considers equity, as defined by how the effects of a health technology may deliver differential benefits across the population. The recommendations of NICE are intended to apply across the whole of England and Wales, regardless of place of residence or employment. A recent appraisal on Imatinib for the treatment of chronic myeloid leukemia in the chronic phase and in the accelerated and blast crisis (for patients not treated earlier with Imatinib) phases highlights considerations of equi-
ty (Rawlins & Culyer, 2004). Imatinib was found to be cost-effective in the chronic phase, with a similar cost-effectiveness ratio for the accelerated phase. While use of Imatinib in the blast crisis phase resulted in a higher ratio, denial of treatment availability to such patients was considered unfair. Patients at this advanced stage could reasonably have expected to be afforded the opportunity of treatment with Imatinib at an earlier stage of their condition; a lack of access would have been due to failings in the health care system. Therefore, on grounds of equity, it was considered that Imatinib be made available to patients in the blast crisis phase who had not previously been treated with the drug.

A variety of types of evidence on these dimensions can be submitted. Most evidence derives from a variety of sources, and encompasses both quantitative and qualitative data. Examples of relevant evidence sources include literature reviews, adverse effect/adherence/continuation data, patient surveys, case studies, implementation and evaluation studies, and summarized testimonies from clinical specialists and patients. In particular to equity considerations, evidence might come from generated utility weightings applied in health economic analyses, societal values elicited through population surveys and other methods, studies on differential uptake of a technology or variations in disease risk or incidence.

**Estimating Therapeutic Benefit, Cost-Effectiveness, and NHS Impact**

As outlined in Phase 1, an Assessment Group critically reviews the available evidence (from published information and manufacturer submissions) regarding the clinical and cost-effectiveness of a technology(s). The base of information reviewed can be categorized by two primary domains of evidence: 1) evidence synthesis (e.g., systematic review, meta-analysis, and patient-level and summary data) and 2) decision analysis (e.g., modeling, probabilistic analyses).

To frame and guide the assessment, the Assessment Group follows NICE guidelines for economic evaluation (NICE, 2004a,c). The guidelines aim to enhance the quality, transparency, reproducibility, and consistency of the analytical approaches used in assessments. The guidelines can be found at: http://www.nice.org.uk/page.aspx?o=201971 and http://www.nice.org.uk/page.aspx?o=201973.

The overarching principles of the guidelines set forth that all evidence must be identified, quality assessed and, where possible or appropriate, pooled against an explicit, justifiable, and reproducible framework. The framework suggested by NICE for estimating clinical and cost-effectiveness includes several core aspects, but is grounded in the concept of the reference case. According to NICE, the reference case (NICE, 2004a):

“… specifies the methods considered with an NHS objective of maximizing health gain from limited sources. Submissions to the Institute should include an analysis of results generated using these reference case methods. This does not preclude additional analyses being presented where one or more aspects of methods differ from the reference case. However, these must be justified and clearly distinguished from the reference case.”

In the valuation of a given technology, there are several different possible methodological approaches (e.g., analysis perspective, classifying HRQL) that can impact the outcome of the technical analysis. In efforts to move toward a consistent process, the reference case specifies the methods considered by the Institute to be most appropriate for the purpose of the Appraisal Committee and consistent with NHS objectives. Submissions to NICE should include an analysis of results using the reference case methods; however, this does not preclude the presentation of other additional analyses. Table 8 outlines the key elements related to the reference case and accompanying analysis requirements.

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7 The Assessment Group comprises a panel of independent, academic experts from one of a number of centres commissioned by the National Coordinating Centre for Health Technology Assessment (NCCHTA).
### TABLE 8: Summary of the Reference Case and Analysis Requirements

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<thead>
<tr>
<th>Element of HTA</th>
<th>Reference Case</th>
<th>Description</th>
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<tbody>
<tr>
<td>Defining the decision problem</td>
<td>Scope developed by NICE</td>
<td>• Statement of the decision problem requires a definition and justification of the technologies being compared and the relevant patient group(s). This coincides with the agreed-upon scope.</td>
</tr>
<tr>
<td>Comparator</td>
<td>Current best alternative care or therapies routinely used in the NHS.</td>
<td></td>
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<tr>
<td>Costs</td>
<td>NHS and PPS</td>
<td>• All direct costs to the NHS and PPS. May include travel and other public sector costs, but does not typically include productivity costs. Wider set of costs (e.g., social opportunity costs) are included if expected to impact results. These costs must be reported separately from NHS/PPS costs.</td>
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<tr>
<td></td>
<td></td>
<td>• Where actual costs paid differs from the public list price (in the case of pharmaceuticals, medical devices), the public list price should be used.</td>
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<td></td>
<td></td>
<td>• Primary source of costs and prices: any current official listing published by the Department of Health/Welsh Assembly Government. Use of all cost data must be justified.</td>
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<td></td>
<td></td>
<td>• Value added tax (VAT) is excluded from all economic evaluations, but included in budget impact calculations.</td>
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<tr>
<td>Outcomes</td>
<td>All health effects on individuals</td>
<td>• All direct health effects. However, indirect health effects, if any, should be noted. Wider set of effects are included if expected to impact results.</td>
</tr>
<tr>
<td>Type of economic evaluation</td>
<td>Cost-effectiveness analysis</td>
<td>• Cost-effectiveness analysis considered the most appropriate form of economic evaluation to establish whether differences in costs between treatments can be justified in terms of changes in health effects. Cost-effectiveness is expressed by an Incremental Cost-Effective Ratio (ICER), which compares the incremental cost of an intervention with the corresponding incremental health improvement.</td>
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<tr>
<td></td>
<td></td>
<td>• Cost-benefit analysis may be used in specific situations, principally in the case of non-reference case analyses. For example, cost-benefit analysis may be particularly useful when non-health consequences are important in an evaluation.</td>
</tr>
<tr>
<td>Synthesis of evidence on outcomes</td>
<td>Based on systematic review</td>
<td>• Synthesized review should include consider relevant patient populations, normal clinical circumstances, clinical outcomes, and comparison with relevant comparators. Analysis should include measures of both relative and absolute effectiveness, appropriate measures of uncertainty, and data from all relevant studies.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• A protocol of inclusion/exclusion study criteria must be followed to reduce risk of bias and enhance reproducibility of the review. Each study included in the review must be subject to critical appraisal. This also extends to non-published and part-published evidence.</td>
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<tr>
<td></td>
<td></td>
<td>• Synthesis of outcomes data through meta-analysis is appropriate, provided there is sufficient relevant and valid data that use measures of outcome that are comparable. The characteristics and limitations of the data must be fully reported.</td>
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<td>• In cases where a single appraisal includes a number of related technologies, both separate and combined analysis of benefits should be undertaken.</td>
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### TABLE 8: Summary of the Reference Case and Analysis Requirements

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<thead>
<tr>
<th>Element of HTA</th>
<th>Reference Case</th>
<th>Description</th>
</tr>
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<tr>
<td>Measure of health benefits</td>
<td>QALYs</td>
<td>• Health effects should be expressed in terms of quality-adjusted life years (QALYs). The QALY is considered the most appropriate generic measure of health benefits that reflects both mortality and HRQL effects.</td>
</tr>
<tr>
<td>Description of health states for QALY</td>
<td>Health states described and measured using a standardized and validated method of preference elicitation for health state valuation</td>
<td>• Value of changes in patients’ HRQL (i.e., ‘utilities’) should be based on a generic instrument public preferences.</td>
</tr>
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</table>
| Method of preference elicitation for health state valuation | Choice-based methods (e.g., time trade-off, standard gamble) | • The EQ-5D is the choice of instrument promulgated by NICE. However, as it is not appropriate in all contexts, it is not required to the exclusion of other methods that meet underlying criteria. Any choice of instrument must be justified.  
• Additional (non-reference case) analyses may be submitted where patients’ HRQL has been measured using disease-specific instruments, provided justification is possible. This also applies to utility values based on patient, rather than public, preferences. |
| Source of preference data | Representative sample of the public | • Reliable UK population preference values are preferred. |
| Modeling | Often required to generate estimates of clinical and cost-effectiveness | • Modeling is most frequently required when 1) patients participating in trials do not represent the typical patients likely to use the technology, 2) intermediate outcomes are used rather than effect on HRQL and survival, 3) relevant comparators have not been used or trials do not include evidence on relevant subgroups, and 4) long-term costs and benefits extend beyond the trial follow-up period.  
• Must followed accepted guidelines, and all assumptions and data sources must be fully documented and justified. In addition, probabilistic sensitivity analyses must be run on models. |
| Time Horizon | Period over which the main differences (in health effects and costs) between technologies are expected to be experienced. | • A lifetime time horizon is typically used, particularly in the case of treatments for chronic disease. This time horizon is also required to quantify the implications of any differential mortality effect between alternative therapies. For a lifetime time horizon, modeling is often necessary, and should reflect alternative assumptions about future treatment effects.  
• A shorter time horizon is justified when there is no differential mortality effect, and differential costs and HRQL relate to a relatively short period. |
| Discount Rate | Annual rate of 3.5% (costs and effects) | • Should reflect the present value of the stream of costs and benefits accruing over the time horizon. When results are potentially sensitive to the discount rate, sensitivity analysis should vary between 0% and 6%. |
| Sub-Group Analyses | Separate estimates of clinical and cost-effectiveness for each relevant subgroup of patients. | • Aimed to capture the level of benefit (and resulting costs) from treatment that differs between patient groups. There should be clear clinical justification and biological plausibility for (where appropriate) the definition of patient subgroups and the expectation of differential effect.  
• May also include the analysis of pre-protocol populations (as a valid subgroup), which comprises individuals who completed the trial according to the pre-specified trial protocol. |
As previously noted, information on the estimated impact of the implementation of NICE guidance on the NHS and the PSS, where appropriate, is required by the Institute. Analysis of impact includes potential technology uptake and resulting effects on population health, resource use, and costs. The objective of ascertaining NHS impact is to support the national and local bodies (e.g., Department of Health) when planning the implementation of NICE guidance.

First, evidence-based estimates of current treatment utilisation and expected rates of uptake of the appraised and comparator technologies in the NHS must be supplied. Second, NICE also recommends that an estimation of health impact in a given population be included. All analyses are required to account for underlying epidemiological patterns and appropriate levels of access to diagnosis and treatment services in the NHS. Third, direct implications for various units of resource provision, where applicable, should be ascertained in the impact analysis. Such resource impacts may include staff numbers and hours, training and education, support services, and service capacity or availability of facilities (e.g., hospital beds, diagnostic services). Any potential constraints on the resources required to support the implementation of the technology must be highlighted and addressed. Finally, estimates of net NHS costs are required to be disaggregated by appropriate organizational (e.g., NHS, hospital) and budgetary (e.g., drugs, staffing, capital) domains, where possible. The cost information should be based on published cost analyses or recognized publicly-available databases or price lists.

**Development of the Assessment Report**

The systematic synthesis of available evidence (literature and manufacturer/sponsor submissions) is used to develop the Technology Assessment Report (TAR). It is derived from, and falls under, the auspices of the Assessment Group.

Upon completion of the report, it is submitted to NICE and is employed as the basis for the appraisal. To that end, the TAR is an integral part of the input into the appraisal, but it is not the only evidence that informs the Appraisal Committee’s evaluation of a technology. The appraisal process is outlined in more detail in the following section. NICE then contacts the consultees and commentators to inform them of the availability of the report for comment.
The TAR and other evidence and comments put forth by the consultees and commentators are combined into an Evaluation Report. The report does not propose recommendations on the use of the technology for the NHS; this is the responsibility of NICE following comprehensive review of all considerations. Rather, recommendations are developed that form the guidance on the use of the technology.

Figure 5 presents a summary of the assessment process.

**FIGURE 5: Summary of the Assessment Process**

<table>
<thead>
<tr>
<th>Assessment Group</th>
<th>Manufacturer/sponsor submissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAR</td>
<td>Other submissions upon request</td>
</tr>
<tr>
<td>Assessment Group may reply to comments</td>
<td></td>
</tr>
</tbody>
</table>

- **Consultee and Commentators**
- **Consultee submissions**
- **TAR**
- **Comments on AR**
- **Selected clinical and patient experts submit written views**
- **Overview**
- **Submissions and Comments on TAR**
- **Institute**
- **Consultee**

### APPRAISAL OF THE EVIDENCE

As described in Phase 1, the Appraisal Committee is an independent advisory board that makes recommendations (positive or negative) to NICE regarding the clinical and cost-effectiveness of treatments for use within the NHS. Of note, it is not within the remit of the Committee to render recommendations on the pricing of technologies to the NHS.

To develop the Appraisal Consultation Document (ACD), the Appraisal Committee meets with the Assessment Group and invited clinical specialists and patient experts (nominated by the consultees). While these groups assist the Committee by clarifying aspects and outstanding issues of the assessment and providing clinical and personal views on the technology, respectively, they do not assist in the drafting of the ACD. Prior to drafting the ACD, lead members of the Committee make a presentation to introduce the topic of the appraisal. The presentation usually provides an overview of the target condition(s)/indication(s), including any relevant epidemiological information; the given technology and its position in the treatment pathway; the evidence of clinical effectiveness and cost-effectiveness; and, any other key issues considered central to the discussion.
Table 9 displays the key factors taken into account by the Appraisal Committee when judging the therapeutic benefit and cost-effectiveness of a technology.

### TABLE 9: Key Factors in the Appraisal Process

#### Clinical Effectiveness

A) Nature and quality of the evidence
   - Consider full range of the hierarchy of evidence
   - Analysis from the Assessment Group, written submissions, views of experts and specialists

B) Uncertainty generated by the evidence & differences between the evidence submitted for licensing and that related to the effectiveness in clinical practice.

C) Consideration of possible differential or greater risk of adverse events in different patient subgroups.

D) Risks (adverse effects) and benefits of the technology from the patient's perspective.

E) Position of the technology in the overall pathway of care.

F) Availability of alternative treatments.

#### Cost-Effectiveness

A) Technology in consideration of overall resource availability to the NHS:
   - Implications for other broad health and clinical priorities and programs that may be displaced by adoption
   - of the new technology.

B) Strength of supporting clinical effectiveness evidence; degree of clinical need of the patients with the condition under consideration.

C) Quality of the evidence and any modeling:
   - Use of quality clinical evidence vs. theoretical modeling in estimating cost-effectiveness
   - Robustness of the structure and assumptions made in the economic model(s)
   - Committee’s preferred modeling approach, accounting for all the economic evidence submitted and critique of any manufacturer models
   - Appropriateness of comparator technologies

D) Range and plausibility of the ICER(s) generated by models.

E) Broad balance of benefits and costs

F) Long-term interests of the NHS in encouraging innovation.

With specific regard to cost-effectiveness, for many review and related review bodies, interpreting the result of analyses can be problematic, making it difficult to decide whether to adopt a particular treatment. As a result, a cost-effectiveness or “willingness-to-pay” threshold can be employed to serve as a general decision rule for ascertaining which treatments represent good value for money. An intervention’s cost-effectiveness ratio is often compared to the threshold in order to recommend inclusion or exclusion in the benefits package. However, interventions may be adopted despite having an unfavorable ratio, if other factors (e.g., disease burden) are a consideration. However, few countries, including NICE, use a formal or fixed threshold, or at least do not make such a decision rule explicit. In fact, it remains uncertain whether NICE employs a threshold. Both recent comments by NICE officials and particular guidance, as in the case of Orlistat, indicate a threshold ranging £20,000-£30,000

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8 The Committee does not consider the affordability of the new technology, but does account for the efficient use of available healthcare resources. It is NICE’s remit to judge whether something out to be purchased from within the resources made available to the NHS.
per QALY (Culyer et al., 2007; Devlin & Parker, 2004). However, NICE has maintained that there is no formal, fixed threshold. Rawlins and Culyer (2004), the Chair and Deputy Chair of NICE, respectively, suggest that NICE bases decisions primarily on cost-effectiveness ratios below £20,000 per QALY, with the likelihood of rejection increasing with higher ratios. Given a ratio of £20,000 per QALY (or higher), NICE makes more explicit reference to other factors to judge the acceptability of the technology. Such factors include the degree of uncertainty in the calculation of ICERs, the innovative nature of the technology, particular features of the condition and the patient population, and the wider societal costs and benefits, where appropriate. While it has been asserted that NICE should employ an explicit, formal threshold, Culyer et al. (2007) argue that doing so is beyond the remit of the Institute, as it does not set the NHS budget. Rather than a ‘threshold-maker’ or ‘threshold-taker’, NICE serves as a ‘threshold-searcher’, where the threshold is ‘logically implied by the combination of technologies that are available and the budget’.

Following sufficient review of all available evidence, the Appraisal Committee then derives a provisional decision and related recommendations on the technology for the ACD9. Figure 6 depicts the range of potential decisions derived by the Committee.

**FIGURE 6: Decision Matrix for New Health Technologies**

<table>
<thead>
<tr>
<th>Cost-effective given existing evidence</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adopt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Request additional evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revisit decision</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>YES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adopt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No requirement for additional evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review decision if other evidence emerges</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If there are any outstanding uncertainties with regards to the clinical effectiveness evidence or the provisional assessment of cost-effectiveness, it may request additional information or suggest that further research be undertaken before even a provisional decision is rendered. Requiring additional information is usually appropriate given certain conditions: 1) probability of making the wrong decision based on current evidence base, 2) cumulative effect of parameter uncertainty, 3) implications of a wrong decision in terms of health and resources. These factors can be considered to determine the value of seeking additional information. Furthermore, if evidence is forthcoming during the appraisal that leads the Appraisal Committee to question the original remit,

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The Committee is not normally expected to make recommendations regarding the use of pharmaceuticals outside currently licensed indications, as published in the manufacturer’s product profile (Summary of Product Characteristics). However, the availability of evidence relating to such ‘off license’ use is not precluded from consideration during the assessment phase and may inform the deliberations regarding licensed use of such products.
scope, or assessment, then it may advise NICE that the guidance document should clearly delineate the limitations of the appraisal and offer potential changes to the scope of the review.

Based on the preliminary recommendations put forth by the Appraisal Committee, the ACD is prepared by NICE’s in-house appraisals team, in discussion with the Committee Chair and the Appraisal Committee. Upon a final draft, it is sent out for official consultation to consultees and placed on the Institute’s website. The ACD, most notably with regards to the ‘Preliminary Recommendations’ and ‘Considerations’ sections, which outlines the key evidence considered in crafting the recommendations and highlights key aspects of the assessment and subsequent deliberations, is integral to the NICE process. To that end, the credibility of the guidance produced by the Institute is dependent upon the transparency of the Appraisal Committee’s decision-making process. Accordingly, the ACD must be as explicit, standardized, and clear as possible.

After the comment period (approximately one month), the Appraisal Committee reviews submitted comments from consultees, commentators, and the website consultation on the ACD. In the event that new data becomes available during the appraisal process that materially impacts the provisional recommendations set forth in the ACD, the Committee may choose to re-formulate the ACD for additional rounds of consultation. Such data would typically include the new trial data, new analysis or modification of the economic model, and changes in the licensed indications of the technology. Beyond the availability of data, the Appraisal Committee also considers the impact of the comments on issues for effective implementation (e.g., extent of any changes in current clinical practice) and opportunities for additional research.

The NICE appraisals team (again, in consultation with the Committee Chair and the Appraisal Committee) then renders its final recommendations in the Final Appraisal Determination (FAD). This constitutes the point at which the preliminary recommendations, as set forth in the ACD, become guidance. Similar to the ACD, the FAD outlines all evidence and issues of consideration pivotal to the appraisal process.

NICE, specifically its Guidance Executive, assumes responsibility for final review of the FAD and its distribution to the consultees; this process spans approximately 14 weeks. As highlighted in Phase 1, consultees can appeal against the FAD or the general conduct of the appraisal process during specified time period (the appeal period). Grounds for appeal encompass 1) NICE has failed to act in accordance with its published appraisal procedures, 2) the FAD does not adequately reflect submitted evidence, and 3) NICE has exceeded its remit. NICE does not normally consider appeals against the merits or content of the determination reached by the Appraisal Committee or FAD. However, as indicated, an appeal can be made if the consultees consider the FAD to be ‘obviously and unarguably wrong’, ‘in defiance of logic’, or ‘so absurd that no reasonable Appraisal Committee could have reached such conclusions’ (NICE, 2004f).

At the discretion of the Appeals Committee, appellants are afforded an oral submission of complaint, in addition to any written submissions. The appropriate Appeal Panel, drawn from members of the Appeals Committee (particularly, non-executive directors of the Institute), normally hears an appeal within 10 weeks of the appeal being lodged. During the Panel meeting, a limited number of the public and press can participate, but must obtain permission from NICE beforehand. If an appellant discloses any confidential information, the Appeal Panel allows such submissions to be heard in the absence of public participants (e.g., other appellants, the public, press) only if such information is necessary in order for the appellant to be able to make an effective submission. In consideration, NICE balances the disclosure of confidential information with the need for transparency and fair process.

Following the hearing, the Appeal Panel renders its decision to NICE, typically within one month. If an appeal is required and upheld, the Appraisal Committee may need to further review the appraisal or require additional evidence from consultees, clinical specialists, patient experts, and the Assessment Group. In the case of no appeals, or where one is not upheld, NICE officially issues the guidance.

All stakeholders want reassurance that NICE has done as much as possible to identify a cost-effective use for a given technology. Past history suggests that if stakeholders perceive that the appraisal lacked an open, fair, and
uniform process, guidance is more apt to be appealed. For example, in 2006, stakeholders lodged appeals against draft guidance on the use of drugs to treat Alzheimer’s disease (i.e., not mild disease). The Appraisal Committee recommended that donepezil, galantamine, and rivastigmine should only be considered options in the treatment of people with moderate Alzheimer’s disease. Memantine was not recommended as a treatment option for those with moderately-severe to severe Alzheimer’s disease, except as part of clinical investigations. One of the main points of contention and dissatisfaction with the evaluation amongst stakeholders was the issue of transparency of the models used in the appraisal. In particular, manufacturers claimed that the use of models lacked transparency and that NICE was not open with industry in terms of explicitly demonstrating the reasons for potential differences in the results and conclusions drawn from models submitted by involved parties (e.g., the Assessment Group and various manufacturers). The appeal was not upheld by NICE and was subsequently challenged in court. Based on the judicial review, the core of the guidance regarding use of the drugs remained unchanged. However, NICE was required to clarify how its guidance should be applied to groups such as people with learning disabilities or whose first language is not English, as the original guidance was deemed “discriminatory”.

Beyond issues of transparency, appeals often ensue as a result of a lack of (balanced) stakeholder consultation, divergent recommendations from different regional decision bodies (i.e., NICE vs. the Scottish Medicines Consortium), and an over-reliance on cost rather than efficacy considerations.

Particular to the appeals process, there are criticisms that the grounds for appeal are drawn too narrowly and that the membership of the appeal panels should be confined to individuals with no formal connection with NICE. Stakeholder perceptions of the appeal process will be examined in further detail in Phase 3.

While there is a perception that the number of appeals has increased over time, the absolute number of appeals and the proportion of appeals to guidance in a given year has remained relatively constant, and even declined since the early 2000s. Between 2000 and 2007, the average appeal rate was about 37%. More specifically, over the period of NICE’s existence the Appraisal Committee’s final draft recommendations have been subject to 43 appeals (Table 10). To date, all the panels’ decisions have been unanimous and almost half of all allowed appeals have been upheld on one or more grounds.

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Published Appraisals</th>
<th>Appeals Submitted</th>
<th>Appeals Allowed (withdrawn or dismissed after hearing)</th>
<th>Appeals Upheld</th>
<th>Appeals Dismissed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>17</td>
<td>8</td>
<td>8 (0)</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>2001</td>
<td>14</td>
<td>5</td>
<td>4 (1)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2002</td>
<td>24</td>
<td>11</td>
<td>10 (1)</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>2003</td>
<td>19</td>
<td>4</td>
<td>4 (0)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2004</td>
<td>13</td>
<td>5</td>
<td>2 (3)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2005</td>
<td>6</td>
<td>3</td>
<td>3 (0)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>2006</td>
<td>20</td>
<td>6</td>
<td>6 (0)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>2007</td>
<td>6</td>
<td>1</td>
<td>1 (0)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>119</td>
<td>43</td>
<td>38 (5)</td>
<td>16</td>
<td>22</td>
</tr>
</tbody>
</table>

10 Data obtained from NICE’s comments submitted to the Health Select Committee. Data does not include appeals against final draft guidance, which have been upheld on appeal, but have yet to be published.
Figure 7 presents a summary of the appraisal process.

**FIGURE 7: Summary of the Appraisal Process**
As described in Phase I, NICE developed a Single Technology Appraisal (STA) process in 2005 for the review of single technologies for a sole indication. STAs were designed to speed up the issuance of guidance to the NHS (compared to MTAs), particularly in terms of those products close to market launch as well as life-saving new treatments.

The STA process is similar to that of the full, MTA appraisal process, as outlined above. However, in terms of the former, only evidence submitted by the manufacturer is formally considered in the independent review. Moreover, formal consultation procedures take place only if the Appraisal Committee’s preliminary recommendations are substantially more restrictive than the terms of the licensed indication(s) of the product under appraisal (NICE, 2006c). As shown in Table 11, the timelines for the STA and MTA process also differ. Specifically, STAs require less time to produce the guidance, approximately 39 weeks, from initiation of the appraisal to publication, compared to 54 weeks for MTAs. However, the timeline for STAs isn’t substantially compressed and with any delays in the appraisal or appeals, it could approach the duration required for an MTA. Stakeholder perceptions of if and how the STA process has impacted the timeliness of publishing technology guidance will be explored in Phase 3 of this project.

**TABLE 11: Timelines for MTA versus STAs**

<table>
<thead>
<tr>
<th>Weeks</th>
<th>MTAs</th>
<th>STAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Organizations invited to participate as consultees and commentators. Consultees invited to make submissions. Professional and patient consultees invited to nominate clinical specialists and patient experts.</td>
<td>Manufacturer/Sponsor submission requested; consultee statements invited.</td>
</tr>
<tr>
<td>2</td>
<td>Manufacturer/Sponsor submission of decision problem received; nominations of experts requested from all non-manufacturer/sponsor consultee and commentators.</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Evidence submissions and consultee comments received; start of report preparation by the Evidence Review Group (ERG).</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Request for clarification send to manufacturer/sponsor.</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Submissions received by consultees.</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Submissions from manufacturers and sponsors sent to Assessment Group.</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Selected clinical specialists and patient experts invited to attend Appraisal Committee meeting and asked to submit a written personal perspective.</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>ERG report received.</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Committee papers compiled and sent to Appraisal Committee.</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Positive opinion required at this point for STA to proceed; Appraisal Committee meeting to develop ACD.</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>ACD consultation begins; marketing authorization or regulatory approval issued.</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>ACD placed on NICE website for public comment.</td>
<td></td>
</tr>
</tbody>
</table>
To date, NICE has initiated more than 25 STAs, primarily applied to cancer drugs. For example, Herceptin, indicated for early-stage HER2-positive breast cancer, was one of the first products to be appraised under the STA process (guidance published in late 2006). Increasingly, NICE is moving towards the use of STAs; most of the appraisals referred to NICE by the Department of Health as part of the 12th, 13th, and 14th wave are to be carried out as STAs. A broader range of indications, such as diabetic retinopathy and rheumatoid arthritis, is also encompassed in planned STAs.

### TABLE 11: Timelines for MTA versus STAs

<table>
<thead>
<tr>
<th>Weeks</th>
<th>MTAs</th>
<th>STAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>ACD distributed to consultees and commentators for 15 working days during which consultee can appeal.</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>ACD consultation ends.</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>TAR received by NICE.</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>Appraisal Committee meets to develop FAD.</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>TAR sent to consultees and commentators for comment.</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Selected clinical specialists and patient experts submit personal perspectives.</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Comments on TAR from consultees and commentators received by the Institute.</td>
<td>FAD distributed to consultees and commentators for 15 working days during which consultee can appeal.</td>
</tr>
<tr>
<td>36</td>
<td>Evaluation Report compiled and sent to Appraisal Committee.</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Appraisal Committee meeting to develop ACD.</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>Anticipated publication (if no appeal).</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>ACD distributed to consultees and commentators for 4 weeks’ consultation.</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>ACD posted on Institute’s website for 3 weeks’ public comment.</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>Appraisal Committee meeting to develop FAD.</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>FAD distributed to consultees and commentators.</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>FAD posted on NICE website.</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>Close of appeal period (if no appeal, guidance published within 6 weeks).</td>
<td></td>
</tr>
</tbody>
</table>
KEY ISSUES SURROUNDING NICE EVIDENCE REQUIREMENTS AND METHODS

The following section provides a summary review of the key issues, across methods and processes, regarding the technical aspects of NICE’s procedures.

Methods

Trials vs. Models

While RCT evidence is strongly preferred by NICE (as well as by the majority of HTA agencies), there are limitations to their use (or, over-reliance) in economic evaluation. For instance, trial follow-up periods are often shorter than the time horizon where the main differences in health effects and costs between technologies are expected to be experienced. Trials also compare selected options, but not all possible strategies, many of which may be viable treatment options or routine therapy. Moreover, trials do not always collect a comprehensive range of economic data (e.g., health utility measures), which can hinder the use of RCT data in cost-effectiveness analyses. Finally, trials are often undertaken in multiple locations, many of which are outside the UK or country of interest.

In addition to some of the methodological limitations of RCTs, there may simply be a lack of available data, which can hinder assessments. For example, NICE commonly assesses technologies (primarily drugs) in the same class, through the MTA process. Although this approach can lead to greater efficiency and comparability across similar products, it is often associated with problems resulting from a lack of head-to-head studies and manufacturer burden to demonstrate additional benefits (Drummond, 2006). The latter issue is also true of STAs, which place more emphasis on analyses submitted by the manufacturer and less on external review.

Models are often used to address some of these issues, particularly in the context of ascertaining cost-effectiveness. They are particularly helpful in addressing non-UK case-mix and clinical practice data, a lack of resource data, and short trial time horizons. Additionally, models can account for different levels of uncertainty in key decision parameters through the use of probabilistic analyses. However, in order to appropriately account for some of the limitations of RCTs, models must be technically sound and accurately reflect the complexities of particular diseases and interventions. Within the context of modeling, findings from different types of studies (e.g., observational studies) can be combined or synthesized to supplement available clinical data and best fit different policy questions.

Use of QALYs

QALYs are increasingly considered to be the principal measure of health gain, as they reflect both mortality and quality of life effects. Moreover, QALYs allow for comparability within an evaluation (e.g., efficacy vs. adverse events) and between potential decision options. They also provide a consistent basis for comparison of the value for money from different health technologies through the derivation of the incremental cost per QALY ratio.

However, there are also drawbacks or criticisms of the use of QALYs as the primary indicator of cost-effectiveness. First, it has been argued that the use of QALYs can put individuals with long-term conditions at a disadvantage over those with life-threatening conditions, as products that extend life (survival benefit) will often result in favorable cost per QALY ratios, even if they do not guarantee a high quality of life. In relation, elderly patients may be at disadvantage (Harris, 2005). Second, some view the EQ-5D, a generic tool for assessing health gain for the incorporation in QALY analyses, to be simplistic and relatively insensitive to important changes in quality of life that are important to patients (Krahm et al., 2007). Other posited limitations of the QALY include limited account for the impact of disease and its treatment on carers and/or the immediate family of the patient, in addition to broader societal benefits derived from treatment, such as the ability to continue/return to work.
**Indirect and Mixed Treatment Comparisons**

A key methodological issue surrounds the difficulty with adequately synthesizing the available evidence, especially if a variety of evidence is required in lieu of RCTs. When there is no or insufficient direct evidence from RCTs, indirect comparisons may provide useful or supplementary information on the relative efficacy of competing interventions. In terms of indirect and mixed treatment comparisons, there is a need to estimate many different parameters (e.g., treatment effects, quality of life, costs), from a number of divergent information sources. NICE ensures for a robust process by requiring that sources of evidence be identified and accounted for in a systematic manner. For example, all analysis parameters, sources, and justification for use are required to be documented. However, these approaches are potentially subject to bias; while methods (e.g., meta-analysis) have improved, additional progress is needed to take account different study designs, varying study quality, and possible heterogeneity.

**Subgroup Analysis**

NICE uses subgroup analysis to predict the effect of certain patient characteristics (e.g., age, sex, ethnicity) on cost-effectiveness. While the Institute suggests that modeling of subgroups of patients is appropriate, there are no recommendations as to which variables are considered ethical. Outlining clear criteria for subgroup analyses, based on specific variables, could help to incorporate social values into decision-making in an explicit, transparent, and consistent way.

**Accounting for Uncertainty**

NICE requires probabilistic sensitivity analysis to account for or characterize uncertainty in estimates of costs and benefits. Typically, sensitivity analyses are required on all variables that could potentially influence the overall results, or on a subset of parameters that may be more imprecise in nature. The stipulation for sensitivity analyses comes from the need to test or verify the robustness of the findings, primarily through understanding the joint contribution of parameter uncertainty on overall decision uncertainty. This is especially important in the case of assessments for new technologies, where the necessary data for evaluations is seldom clear.

In 2005, NICE began to require the use of probabilistic sensitivity analysis with all models submitted to the Institute. Given the types of decisions faced by NICE, the use of probabilistic methods has been supported. This approach addresses some of the limitations of standard sensitivity analysis, better meets the need to propagate joint parameter uncertainty (in relations to decision uncertainty), and provides a starting point, through the quantification of decision uncertainty, for assessing the value of additional research. In fact, NICE has been at the forefront of advancing these types of methods.

Given the variation in assessments and the inherent uncertainty of the assessment process, the choice of parameters used in sensitivity analyses is important. As there are a wide range of possible parameter distributions, it is important that the choice and rationale of inputs be substantiated and well-documented, in order to enhance transparency and potential replication. This is particularly true when more than one entity is involved in the development and analysis of models.

In terms of HTA methods, NICE has served as a model for technical development and has spurred growth in new assessment approaches, such as probabilistic analysis. This has been aided by steady funding for training fellowships and the recruitment of skilled health economic personnel. Moreover, the Institute has been at the forefront of methodological guideline development, and has supported continuous revision of such guidelines as new methods become available and debated. For example, in March 2007, NICE initiated a formal review process of its methodology for technology appraisals. The review will focus on areas where methods have evolved over
the past three years or where NICE’s methodological approach has been questioned. These areas include evidence synthesis, exploring uncertainty, identifying subgroups and exploring heterogeneity, and estimation of costs, among other topics.

**Processes**

**Exchange/Non-Exchange of Models**

It is common for models developed by both manufacturer and the Assessment Group to be submitted for a given assessment. This often creates issues around methodological congruency and transparency and ownership, as the data and methods used by various groups may differ.

One area of debate is the uptake of manufacturer models submitted to NICE. Manufacturer models normally get submitted to the Technical Lead at NICE and then passed along (with other submitted evidence) to the Assessment Group. The Assessment Group may or may not take the manufacturer model into account or include it in the TAR. This may be a result of 1) bias against manufacturer models (both in terms of technical rigor and potential conflict of interest), 2) desire to keep an arms-length from industry, and 3) preferences of the Group to develop and use their own model(s).

Another issue relates to the availability of the models put forth by the Assessment Group. While the Assessment Group has full access to the economic models produced by manufacturers, the models developed by the Assessment Group are often ‘locked’. This may stymie the verification of such models and the overall transparency of assessments. To ensure a transparent and technically robust process, full disclosure is needed regarding how estimates of cost-effectiveness are derived and any discrepancies between manufacturer and the Assessment Group models.

**Commercial-in-Confidence Data**

As previously indicated, NICE accepts unpublished evidence under agreement of confidentiality, or commercial-in-confidence data. To ensure transparency, NICE encourages key evidence to be publicly-available and, ideally, available to the Appraisal Committee. Consequently, confidence restrictions are expected to be kept to a minimum and must be supported by acceptable justification. However, NICE tends to be fairly relaxed with allowing manufacturer requests for confidence (i.e., removing such data in relevant assessment reports). At minimum, a structured abstract may be requested to be made available for public disclosure. However, it has been argued that allowing confidential material as part of the decision-making process obscures the transparency of decisions and possibly jeopardizes the quality of the NICE assessment process. There is also the question of conflict of philosophy and values given the public commitment of NICE to transparency. As such, it is important for NICE to collaborate with industry to achieve an appropriate balance between confidentiality and adequate information exchange and transparency.

**Deriving at the Adoption Decisions**

Processes for deriving at the adoption decision are another key issue in the assessment process. For a sound and transparent decision process, there is a need to appropriately define the various decision constraints. In NICE’s case, this normally relates to the budget constraint, as considered in relation to cost per QALY ratios. In accounting for this constraint, however, there are arguments that opportunity costs should be explicitly quantified. This argument is based on the notion that a review of the costs and benefits of a health technology in isolation of examining the associated opportunity costs is insufficient to address issues of efficiency of resource use. Without the consideration of such opportunity costs, the assessment process may lead to increases in NHS expenditures without evidence of health gain, greater inequalities in access to services, and problems pertaining to the sustainability of public funds for new technologies (Birch & Gafni, 2007).
Moreover, in addition to the NHS budget, many stakeholders have asserted that NICE should consider other constraints (e.g., capacity, equity, political) and adopt a broader definition of value or benefit. For example, this was an issue regarding the NICE guidance on Alzheimer treatment, as the British Alzheimer’s Society posited that NICE failed to account for the costs of carers and the increase in the use of unlicensed antipsychotic drugs given implementation of the decision.

Other considerations related to the adoption decision include adequately accounting for and quantifying any uncertainty related to the decision (e.g., expected costs of making a wrong decision, in terms of resources and health gains forgone) and assessing the value of additional research or evidence. In addition, while NICE produces guidance at a national level (in accordance to a national health service), local variation in resource capacity and patient populations, for example, can pose issue to the appropriateness of the decision and subsequent implementation.

**Timing of Assessments**

The time required to conduct assessments and publish guidance is subject to pressure from ensuring comprehensive evaluations, while concurrently providing timely information to decision-makers, providers, patients, and other stakeholders. NICE has been responsive to concerns regarding the timing of assessments and the resulting impact on the decision-making process and patient access, principally through the introduction of the STA process. For example, the STA appraisal of Herceptin for adjuvant breast cancer was not only one of the fastest appraisals undertaken by NICE, but also one which produced guidance within weeks of EMEA licensing.

Despite its potential to speed up the publication of NICE guidance, there are a number of concerns regarding STAs. For example, in order to reduce the time of the assessment process, the extent of opportunity for stakeholders to comment on the output of the Assessment Group has been reduced. To that end, the Expert Review Group (ERG) report, which is an assessment of the manufacturer’s submission and forms the basis of deliberations, is not made available to manufacturers and other stakeholders before it goes for consideration by the assessment panel. The absence of this critical step may undermine the consultative nature of STAs for developing guidance and lead to subsequent delays if any discrepancies need to be addressed later in the process. There is also question as to whether the STA model will indeed deliver more timely decisions, and if the resources dedicated to STAs will detract from the appraisal of other products.

The STA program should be monitored and evaluated for effectiveness and the impact on access to new technologies. Moreover, as more STAs are being referred to NICE, it will be important to ensure that NICE is appropriately resourced to ensure an acceptable turnaround time for assessments.
INTRODUCTION

In early 2007, the Health Select Committee of the House of Commons initiated an inquiry into NICE, given growing public concern about the availability of various treatments in the NHS. As part of the investigation, the Committee put forth a call for comments from a variety of stakeholders, including manufacturers, patient and professional associations, healthcare providers, and the general public\(^\text{12}\). The topics of inquiry requested by the call encompassed the following areas of interest:

- Existing level of, and changes in, public confidence in NICE.
- Perceptions regarding how NICE has impacted access to treatments.
- Degree of independence and objectivity in assessment processes and related decision-making.
- Balanced consideration of a range of evidence, from costs and effectiveness to broader, social concerns (e.g., equity, particular patient subgroups).
- Adequate use of economic evidence in coverage and reimbursement decisions.
- Appropriateness of employing maximum thresholds (“value cut-offs”) in decision-making.
- Perspectives on the existing appeal system.
- Timeliness of guidance development and public dissemination.
- Comparisons between NICE, the Scottish Intercollegiate Guidelines Network (SIGN), and the Scottish Medicines Consortium (SMC).
- Effectiveness of guidance implementation, with a focus on technology appraisals and clinical guidelines.

The Committee received a total of 92 submissions from a wide range of stakeholders. Table 12 presents the stakeholders who submitted evidence.

\(^{12}\) Comments were collected between early February and late March 2007.
### TABLE 12: Stakeholders Submitting Evidence to the Health Select Committee

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<tr>
<th>STAKEHOLDER</th>
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<td>NICE</td>
<td>Motor Neurone Disease Association</td>
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<td>Academy of Medical Sciences</td>
<td>Myeloma UK</td>
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<td>Alzheimer’s Society</td>
<td>UK Myeloma Forum</td>
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<td>American Pharmaceutical Group</td>
<td>National Childbirth Trust</td>
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<td>Amgen</td>
<td>National Infertility Awareness Campaign</td>
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<td>Archimedes</td>
<td>National Osteoporosis Society</td>
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<td>Arthritis and Musculoskeletal Alliance</td>
<td>National Rheumatoid Arthritis Society</td>
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<td>Association of British Healthcare Industries</td>
<td>NHS Confederation</td>
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<td>Association of the British Pharmaceutical Industry</td>
<td>Novartis Pharmaceuticals UK Ltd</td>
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<td>AstraZeneca</td>
<td>Pelvic Pain Support Network</td>
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<td>Beat</td>
<td>Pfizer</td>
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<td>Bioindustry Association (BIA)</td>
<td>Rarer Cancers Forum</td>
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<td>Bowel Cancer UK</td>
<td>Roche Pharmaceuticals</td>
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<td>Breakthrough Breast Cancer</td>
<td>Roy Castle Lung Cancer Foundation</td>
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<td>Bristol-Myers Squibb Pharmaceuticals Ltd</td>
<td>Royal College of Midwives</td>
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<td>British Association for Counselling and Psychotherapy</td>
<td>Royal College of Nursing</td>
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<td>British Medical Association</td>
<td>Royal College of Physicians of Edinburgh</td>
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<td>British Psychological Society</td>
<td>Royal College of Pediatrics and Child Health</td>
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<td>British Society for Rheumatology</td>
<td>Royal College of Psychiatrists</td>
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<td>Cancerbackup</td>
<td>Royal National Institute of the Blind (RNIB)</td>
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<td>Cancer Research UK</td>
<td>Sanofi-Aventis</td>
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<td>Continence Foundation</td>
<td>Schering Health Care Limited</td>
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<td>Cystic Fibrosis Trust</td>
<td>ScotME</td>
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<td>Deltex Foundation</td>
<td>Servier Laboratories</td>
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<td>Diabetes UK</td>
<td>Sirtx Medical</td>
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<td>Joint Epilepsy Council of the UK and Ireland</td>
<td>South Asian Health Foundation</td>
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<td>Ethical Medicines Industry Group</td>
<td>Specialised Healthcare Alliance</td>
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<td>European Medicines Group</td>
<td>Wyeth Pharmaceuticals</td>
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<td>FEmISA</td>
<td>Dr. Daphine Austin</td>
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<td>GlaxoSmithKline</td>
<td>Professor Michael Barkham et al.</td>
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<td>Helped the Aged</td>
<td>Dr. Imogen Evans, Mrs. Hazel Thorton, and Sir Iain Chalmers</td>
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<tr>
<td>Hepatitis C Trust</td>
<td>Professor Malcolm Hooper</td>
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<tr>
<td>Improving Surgical Outcomes Group</td>
<td>Dr. Chris Hyde</td>
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<tr>
<td>Institute for Innovation &amp; Valuation in Health Care</td>
<td>Doris Jones</td>
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<td>Johnson &amp; Johnson</td>
<td>Gay Lee</td>
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<td>KCI Medical UK</td>
<td>Michael Lee</td>
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<tr>
<td>Kidney Cancer UK</td>
<td>Professor Ragnar Lofstedt and Frederick Bouder, King’s College London</td>
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<tr>
<td>Leukemia Care</td>
<td>Dr. Tom Marshall, University of Birmingham</td>
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<tr>
<td>Lifeblood: The Thrombosis Charity</td>
<td>Dr. Catherine Meads, University of Birmingham</td>
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<td>Lilly</td>
<td>Sandra Simkin</td>
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<td>25% ME Group</td>
<td>Dr. Keith Syrett, University of Bristol</td>
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<td>ME Association</td>
<td>Peter Telford</td>
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<td>Medical Technology Group</td>
<td>Dr. David Thomson</td>
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<td>Medtronic Ltd</td>
<td>John Walsh</td>
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<td>Merck Serono</td>
<td>Miss Rose A. Woodward</td>
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Of the total submissions, 51 (55%) were from patient or provider/medical associations, 21 (23%) from manufacturers or industry representatives, 17 (19%) from individual members of the public, and 3 (3%) from other (Department of Health, NICE, and NHS Confederation).

This third of four deliverables provides an analysis of stakeholder perspectives on NICE and its overall processes. The report also discusses trends toward stakeholder acceptance of NICE methods and decisions, in addition to suggested recommendations for improvement. The evaluation of comments will be addressed according to the following categories: Organization and Process, Methods, Decision-Making and Implementation, and General Perceptions.

ORGANIZATION AND PROCESS

NICE’s remit and governance

The majority of stakeholders support the overall role of NICE in informing and supporting decisions regarding the use of health technology and broader public health interventions in the NHS, and acknowledge that the Institute has positively benefited the population in England and Wales. Along these lines, they acknowledge that NICE has evolved into an internationally-recognized center of excellence for health technology appraisals and has maintained a notable level of respect for having a thorough, fairly inclusive, and high quality guidance development process. In addition, as NICE guidance is increasingly becoming a key, if not determining, factor by which primary care trusts (PCTs) allocate their limited resources, the importance of the Institute will likely increase.

It was recognized that NICE has a challenging and complex charge of providing guidance that ensures equitable access to medicines and other health technologies, all within the confines of NHS budgetary constraints and an ever-increasing number of new, innovative treatments. Moreover, many stakeholders realize that NICE is currently operating in a difficult environment, where the ability of the NHS to meet patients’ expectations is increasingly being questioned, concurrent with a growing emphasis on greater patient choice. As stated by the UK Department of Health, “giving people more choice and control over the treatment and service they receive will…remain a key priority as we continue to develop health and social care services that put the patient first” (Department of Health, 2006). However, patient choice is often limited by NICE guidance, especially in cases where treatment is expensive (e.g., MS, cancer) and the supporting evidence is uncertain or unavailable. Consequently, in the viewpoint of many stakeholders, these objectives are in direct tension with one another and make it increasingly difficult for NICE to successfully meet its objectives and retain public confidence in its operations.

Stakeholders also noted some existing ambiguity regarding NICE’s role and remit, both in terms of its level of independence and its overall objectives in the NHS. To the former, several stakeholders, particularly patient organizations, consider NICE to be insufficiently independent and influenced unduly by government (or, key politicians) and powerful special interest groups. In the view of one commentator, NICE increasingly creates “policy-based evidence”, rather than “evidence-based policy”. A few organizations provided the example of Herceptin to illustrate that NICE is indeed influenced by political pressures and external factors, resulting in mixed signals about its independence. To that end, many felt that this encourages special interest groups to challenge NICE and its decisions and lends a lack of clarity as to its lines of accountability.

The majority of commentators suggested that NICE has assumed an implicit, if not explicit, rationing function, where its recommendations on specific technologies or interventions stem directly from questions of affordability, as opposed to patient need and benefit. This perception may be due, in part, to the fact that many aspects of economic evaluation are beyond the understanding of the general public (and, in fact, many health care professionals), and this heightens the suspicion that NICE essentially serves as a rationing arm of the NHS.
Consequently, it is often viewed that NICE has extended beyond its original and intended remit, by placing economic concerns above (short- and long-term) therapeutic benefits and broader social considerations (e.g., quality of life, equity). A majority of stakeholders maintained that such perceptions have deleteriously impacted public confidence in the Institute, marginalized patients and providers, and deterred innovation in the UK (see ‘General Perceptions’ and ‘Decision-Making and Implementation’ for further commentary regarding these concerns).

Finally, several stakeholders commented on recent proposals for an expanded role for NICE, as set out in the Cooksey Review of UK health research funding (Cooksey, 2006), and the Office of Fair Trading (OFT) report regarding the Pharmaceutical Pricing Regulation Scheme (Office of Fair Trading, 2007). In particular, the OFT proposes a central role for NICE in defining a pharmaceutical’s value, as a critical input into determining the price the NHS will pay for a particular medicine (so-called ‘value-based pricing’). The initial observation of several commentators, most notably industry representatives, is that while the principle of value-based pricing merits examination, the practicalities of how such a system would work are highly complex. Moreover, there is an overarching belief that NICE is not ready or currently equipped to assume the enhanced role envisaged by OFT. As such, stakeholders feel strongly that a thorough review of NICE and a blueprint for future reforms must be in place before any wider role for the Institute is seriously considered.

**Stakeholder Involvement**

The general sentiment of the commentators is that NICE is to be commended for including a wide range of stakeholders in the assessment process. However, most consider there to be significant room for improvement. For example, while the Institute encourages and accepts evidence from patient experts, in practice it may be difficult for them to play a meaningful role in the process. Many stakeholders feel that patient experts (e.g., lay members of the Appraisal Committee or Guideline Development Groups) have difficulty with complex summaries or tables of evidence presented, especially if there is no accompanying explanation of the various study results and any flaws in corresponding research designs. This is especially true of the presentation of health economic evidence, which is often too technical for non-specialists. In addition, several stakeholders commented that in their experience with NICE, patients were merely “token participants”, somewhat marginalized, and that any evidence submitted on their behalf was not taken seriously, especially if their viewpoints differed from the findings of the Appraisal Committee.

Aside from patient experts, NICE appoints clinical experts to participate in each appraisal, intended to represent wider medical opinion. However, some commentators felt that many of the “experts” are derived from an unrelated medical field or have no actual experience of using the product under question. A committee that includes experts in the field in question is more likely to have necessary expertise and produce meaningful guidance. Furthermore, such a committee will give far greater credibility to the overall process in the view of providers, patients, and the general public.

The majority of industry stakeholders maintained that manufacturers should be invited to attend the Appraisal Committee meeting, given that many sponsors have spent years amassing the evidence upon which NICE guidance is based and other stakeholder groups (e.g., patients) are invited to attend. Their lack of involvement to date is considered inherently inequitable and, in some cases, resulting in unnecessary revision and appeals. Moreover, it denies the Appraisal Committee the opportunity to address any outstanding questions regarding the available evidence. To that end, manufacturers assert that if they were able to convene with NICE earlier, particularly during the scoping process, they could better ensure that the required evidence is built into on-going clinical studies. At present, there is no opportunity to discuss data requirements early on in the assessment, as well as key issues that arise throughout the process, particularly following Appraisal Committee meetings.
For all stakeholders, it was suggested that NICE give greater consideration for the logistics of fully participating in the assessment process. It is often difficult for manufacturers, providers, and patients to attend all-day meetings, especially if currently employed. Moreover, for some patients who are either economically-disadvantaged or ill, it may be difficult to either attend key meetings or even access relevant meetings notices via the Internet.

**Transparency of Process**

Many stakeholders felt that adequate transparency is crucial to secure and maintain public confidence in NICE and its processes. The call for greater transparency includes the remit and objectives of the Institute (and, any underlying policy or political motivations), topic selection, use of stakeholder evidence and related requirements, criteria used in decision-making, and priorities for guidance implementation. As noted in the previous reports, transparency is pivotal for stakeholder acceptance of NICE processes and subsequent decisions. In relation, establishing clear lines of accountability is also important, which some stakeholders consider currently lacking and a cause of frustration when patients are denied access to treatments.

**Key Stakeholder Recommendations**

- Better communication is needed regarding the role and remit of the Institute, in addition to what treatment is appropriate in order to eradicate any misconceptions and temper patient and public expectations. Moreover, NICE should clarify the processes undertaken when producing guidance.

- NICE should more appropriately balance cost-containment concerns with health and broader social considerations.

- Increased provision of early dialogue between companies and NICE would ensure a more efficient process and allow timely discussion on methods and data. This would ultimately facilitate the appraisal process, limit inaccuracies, and reduce the number of appeals. Dialogue with manufacturers should involve both the Assessment Groups (MTAs)/Evidence Review Groups (STAs) and the Appraisal Committee, and be continuous throughout the assessment process. This type of feedback loop is especially needed with regards to STAs.

- Training should be given to key staff of the Collaborating Centers on how to present technical evidence to groups that include lay representatives.

- Stakeholder comments on draft guidance or guidelines and associated responses should be made more prominent on the NICE website, in order to enhance the transparency of operations.

- If patient experts are indeed consulted, then NICE should report on the relative impact their evidence and input had on the final outcome of the appraisal.

- NICE should incorporate greater flexibility and accommodation in the practical logistics of stakeholder involvement.

- All NICE processes, from its remit and role to the criteria used in decision-making, should be as transparent as possible.
METHODS

Topic Selection

Comments were mixed regarding the topic selection process. Some stakeholders supported the recently revised topic selection process (as of September 2006), whereby NICE has authority to render the final determination on assessment topics. Nevertheless, many hold concerns that this new process is not sufficiently transparent (this also pertains to the previous process) and needs further refinement. For instance, having recently introduced new topic consideration panels, NICE now publishes the notes of their meetings on its website. In their present form, however, the notes are insufficiently detailed, with respect to understanding why certain decisions were made. Moreover, while the extensive consultation is a useful exercise, it may take many months before final referrals are made. This can, therefore, result in increased delay to the assessment of new technologies and is inefficient for the Institute.

Alternatively, other stakeholders contended that the new process compromises the independence of the topic selection process and lends to less transparency. Following the scoping exercise, the topic recommendations are not released to stakeholders, which inhibits transparency as to the rationale and criteria behind the recommendations. Ultimately, when a new wave of assessments is announced, it is often unclear why certain technologies have been selected for appraisal. It is also unclear why certain processes – multiple or single technology appraisals, or clinical guidelines – are considered most appropriate for the technologies under review.

As an alternative to the new process, a few stakeholders felt that NICE should not have authority over initial topic selection. To that end, a body independent of NICE should be given a mandate to determine which topics are to be taken forward and at what point in time in the NICE process. Several commentators asserted that without an independent and transparent topic selection process, NICE could be subject to criticism that high profile or notably political treatments and conditions are given precedence over equally essential, but less well known, treatments and conditions.

Finally, as noted in previous reports, several stakeholders commented that NICE should have greater focus on the assessment of potential areas of disinvestment in current treatments, as opposed to considering new technologies.

Evidence requirements and review

As raised in the previous report, one key concern is that there is too much weight given by NICE on evidence resulting from RCTs, especially for certain therapeutic areas that are significantly under-funded in terms of clinical research or for which a notably small patient population exists (e.g., psychological therapies, orphan diseases). The reliance on a limited range of evidence may disadvantage patients through restricting patient choice for, and access to, a range of interventions, as well as over-resource treatments that may not be appropriate for all patients. Consequently, many stakeholders felt that RCTs should be complemented by other methodologies, such as observational studies, auditing, benchmarking, and case studies. Such alternative evidence may more appropriately illuminate important issues of product use in routine or “real world” settings. In this sense, the relationship between RCT evidence and systematic data collection from routine settings and the role of qualitative research need to be reviewed in order to improve the NICE evaluation process (and its hierarchy of evidence), so as to make NICE guidelines relevant and applicable to the NHS. For further explanation of some of the limitations of RCTs, refer to the Phase 2 report.

In a similar vein, NICE has increasingly suggested that manufacturers carry out new RCTs to provide further evidence about a product and, in some instances, has recommended use “only in the context of research”. At the time of these requests, however, it is often too late in the process to design a clinical trial to meet the needs of patients in the UK. Stakeholders felt such recommendations reflect the Institute’s poor understanding of the
realities of commercial pressures driven by licensing and patient regulation. With earlier collaboration with industry, however, these issues could be ameliorated.

Many manufacturers also felt that the Institute has excessively high expectations regarding the quality and quantity of clinical and health economic data available prior to, or by, product launch. Often, the necessary data can only be gathered once the treatment has been routinely used in the NHS setting. In the view of a number of stakeholders, unreasonable expectations regarding the available evidence results in “all-or-nothing” or “yes-no” decisions. This can have deleterious impacts, such as denying patients access to important treatment advances. Moreover, limiting patient access early in the product lifecycle means that learning and incremental innovation through normal clinical experience will either not occur or be delayed.

A particular concern for innovative companies is that NICE’s approach to cost-effectiveness analysis is often based on limited data generated too early in a product’s life cycle. This can lead to greater levels of uncertainty, especially in highly innovative products. Some stakeholders, especially those involved in the device industry, felt that there is a real risk that smaller companies will either be penalized for failing to generate sufficient health economic data, or forced to use limited data from RCTs that will produce uncertain outcomes.

Cost-effectiveness analysis and QALYs

The majority of submitted stakeholder comments touched upon some aspect of the health economics component of the NICE methodological process. The overarching view was that NICE is overly and inappropriately reliant on QALYs, or cost per QALY, as a measure of cost-effectiveness and product value. These sentiments are in consideration of the fact that QALYs are not always objective, can change over time, and do not take into account the indirect and broader social benefits of a new therapy, such as productivity gains or reduction in caregiver burden. In addition, the generic (rather than disease-specific) approach required by NICE and used in QALY calculations is relatively insensitive to incremental changes in quality of life and does not fully reflect the range of benefits are important to patients. Such methods also tend to disadvantage those treatments that improve patients’ quality of life, rather than extending life expectancy. By implication, patients with chronic conditions, including cancer, and elderly patients are most likely to be disadvantaged (Harris, 2005). These patient groups may gain particular benefit from even short periods of (higher quality) additional life. Consequently, in the view of many stakeholders, QALYs are just one, albeit integral, source of evidence that should be considered as part of a full assessment of the value of a medicine. Other than those factors previously mentioned, other criteria (identified by stakeholders) that should be evaluated include clinical benefit, unmet medical need and the priorities of the patient population, the nature of the therapeutic market and other available treatments, the perspective of medical specialists, and affordability concerns and effects on macro-economic growth.

Another issue related to cost-effective analyses concerns the availability of the models developed by Assessment Groups. While the Assessment Group has full access to the economic models produced by manufacturers, the models developed by the Assessment Group are often ‘locked’ (i.e., the impact of varying key assumptions cannot be explored). Several stakeholders, particularly manufacturers, felt that this inhibits the verification of such models and the overall transparency of assessments. To ensure a transparent and technically robust process, full disclosure is needed regarding how estimates of cost-effectiveness are derived and any discrepancies between manufacturer and the Assessment Group models. A lack of accessibility and the open exchange of models will continue to fuel challenges to NICE decisions. Indeed, the lack of access to the Assessment Group model was one of the main issues in the recent judicial review of the NICE appraisal of Alzheimer’s drugs.

In relation to the use of models, some commentators felt that NICE should make greater allowance for the uncertainty inherent in analyses using longer-term time horizons (e.g., chronic conditions), especially since it is not possible to assess the cost and quality of life benefits of long-term conditions via RCTs.
Inclusion and calculation of costs

Another methodological concern of stakeholders pertains to the inclusion and calculation of costs. The major complaint is that appraisals do not give full consideration to wider healthcare and societal costs outside of narrow definitions of the NHS budget(s). This, in turn, skews the focus of the analysis from the perceptions of patients and their carers. Such expenses include those costs related to a reduction in overnight hospital stays, decreased staff time downstream in the treatment pathway, or residential care costs. Commentators asserted that all these broader costs should be considered during the appraisal process, even if these considerations do not ultimately impact upon the final guidance outcome.

It was also suggested that NICE appraisals should reflect the full value of medicines to the UK, rather than the NHS alone. Such an approach would focus on “episodes of care” as a way to recognize the full cost and value of an intervention, the overall patient outcome, and the corresponding costs and benefits incurred across the healthcare system.

Timing of assessments/speed of guidance

The timing of assessments is a significant concern for almost all stakeholders. While many commentators consider the process too slow, there is recognition that this is due, in part, to the complexity and depth of the task at hand, especially with ample stakeholder consultation. However, this must be tempered with the need to ensure that guidance is published in a timely fashion, in order to provide patients with access to innovative products and the best healthcare services. It is also important so that guidance maintains relevance and that evidence used in the review is not quickly superseded with new information.

Many commentators consider the newly-introduced STA process as a possible solution to addressing such issues. In fact, some stakeholders inferred that an early appraisal process is an important model for the future, with MTAs for a single disease offering a complimentary approach for reviewing the treatment of a disease area. The latter process would occur at a time when a substantially larger evidence base is available, subsequent to drug licensing when more clinical trials have been published, and both clinical and cost-effectiveness data are likely to be more definitive.

Despite the potential merits of STAs, many stakeholders also expressed concern. First, the existence of STAs should not disadvantage drugs being appraised by NICE that are not selected for this process. Further, apprehension exists that there is not sufficient time available during the STA process for adequate consultation, especially prior to the meeting of the Appraisal Committee, which may result in stakeholders casting challenge toward resulting decisions. Apart from being inconsistent with the MTA process, the majority of manufacturers felt that the opportunity for them to correct inaccuracies in an STA is particularly important, as the Evidence Review Group report is based solely on industry submission. Consequently, many stakeholders stated that appeal is the only route to make corrections or revisions to the assessment. Moreover, several commentators suggested that the high number of negative recommendations at the first stage of the STA process demonstrates that Appraisal Committees are uncomfortable making positive recommendations based on the range of data typically available early in the lifecycle of a product. In the view of many stakeholders, NICE needs to be more realistic about what evidence can be provided at early stages and to accommodate a greater degree of uncertainty. Risk sharing agreements and early access agreements may need to be considered in this context.

To that end, there was some consensus that assessments performed close to the time of market launch are problematic, as the data required to form an informed judgment are not often available at this time; such evidence can only be gathered through extensive use of the product in a real-life setting. For example, long-term outcomes or survival data will not generally be available at this stage. Appraisals begun at this point cause significant problems for the manufacturer and can result in unnecessary additional resource burdens.
Consequently, it was suggested that NICE enhance its flexibility in the timing of appraisals close to launch. Other commentators supported early guidance at the time of launch, with a subsequent re-evaluation post-launch, in order for patients to gain timely access to treatments and provide adequate incentives to industry for innovation. A few stakeholders took these suggestions another step, suggesting that NICE be involved at a much earlier stage in the drug development process.

**Orphan products and specialized patient populations**

Another theme related to NICE methods arising from the comments concerns the consideration of orphan products and populations, or other specialized patient populations. Namely, the combination of limited data at launch and relatively high per-patient costs means it is challenging for orphan medicines to meet NICE cost and QALY criteria. Higher cost estimates may be due to higher costs for clinical development costs (even with fewer patients, as patients are more difficult to recruit and a greater number of research centers may be needed), pharmacovigilance, medical information, and manufacturing, compared to other medicines. Moreover, there are relatively small patient populations, which make it difficult for companies to achieve a return on investment.

Consequently, several stakeholders felt that it is counterintuitive to apply the same appraisal methodology to products indicated for rare diseases with small patient numbers and where clinical practicalities restrict the quantity and type of available data. To that end, many commentators felt that treatments falling under ‘orphan status’ when considered by NICE have fared particularly poorly when reviewed using standard methodology. Based on an analysis performed by the UK Office of Health Economics (OHE) (OHE, 2007), as of January 2007, NICE had appraised 16 FDA/EMEA-designated orphan medicines, of which it rejected four (25%), recommended nine (56%) for restricted use, and recommended three (19%) for general use. In comparison, of the 116 non-orphan drugs appraised by NICE, seven (6%) were rejected, 56 (48%) recommended for restricted use, and 53 (46%) were recommended for general use. Consequently, it was suggested that the current methodology for appraising orphan drugs (for diseases affecting fewer than 5 in 10,000 people) and ultra-orphan drugs (for conditions affecting less than 1 in 50,000 people) requires re-evaluation, with the use of distinct methodologies and decision rules focusing more on unmet need, innovation, clinical effectiveness, and budget impact. Of note, recently, the responsibility for issuing guidance on drugs for ultra orphan diseases has been given to a government committee dealing with specialized services.

Moreover, it was suggested that NICE is out-of-step with Europe and the U.S. when it comes to the definition and treatment of orphan drugs in the valuation process, as the former categories orphan products into two categories, orphan and ultra-orphan drugs, as mentioned above. Several stakeholders suggested that NICE revise its definitions to be congruent with EMEA and FDA definitions.

**Other methodological concerns**

There were a number of other methodological concerns put forward by stakeholders that did not fall under a coherent theme. These considerations are outlined below:

- The wide range of methodological approaches employed by different Assessment Groups can result in significant uncertainty in the accuracy of results and reproducibility between different appraisals. To that end, many stakeholders commented that the quality of reviews varies considerably between Assessment Groups, with some reports lacking fairness and balance.

- In some cases, it may not be possible to demonstrate cost-effectiveness, particularly in areas that have suffered from historically low levels of innovation and where comparators are old, generic, and very inexpensive. NICE should examine new or different methods to account for such issues.
• It may be a waste of resources to apply the same extensive and time-consuming appraisal methods to a drug that may cost the NHS a maximum of £1-2 million a year, as is applied to a “blockbuster” treatment that might cost tens or even hundreds of millions of pounds.

• When NICE announces a specific product to be reviewed, some PCTs refuse to fund a technology until the guidance is produced; a phenomenon deemed the “NICE blight”. The Department of Health should develop policy mechanisms to ensure patients are not denied new treatments in the period NICE is evaluating a technology or if NICE chooses not to review a particular product (see the ‘Decision-Making and Implementation’ section for further discussion of this issue).

• The practice of disclosing new evidence in the Final Appraisal Determination (FAD) should be discontinued. Rather, there should be a requirement that upon significant change following the Appraisal Consultation Document (ACD), a revised ACD should be issued for consideration, in order to allow for comment and to reduce the likelihood of appeals.

• The lack of depth and detail of explanation in the ACD and FAD is a particular problem, given that it is difficult to enter into a dialogue with NICE outside of the consultation process. Better explanations should be provided as to how a decision was reached in ACDs and FADs – “considered not appropriate” is not sufficient.

Key Stakeholder Recommendations

• More attention should be focused on further reducing the time required to make final topic referrals to the Institute. Furthermore, greater transparency regarding the methodology, rationale, and criteria for the topic selection process should be introduced.

• RCT data should be supplemented with a broader range of quantitative and qualitative data.

• Manufacturers should be integrally involved in defining evidence requirements.

• NICE should adopt a more pragmatic approach to the assessment of cost-effectiveness, and should consider taking into account cost per life year gained analyses, particularly in the appraisal of end of life therapies.

• NICE should adopt the definition of orphan disease status, as defined by EU and U.S. regulations, and that rarer diseases should be appraised through a separate process, where a higher cost-effectiveness ratio is employed and additional criteria are considered, including clinical efficacy, unmet need, total costs to the NHS, and patient quality of life issues.

• The STA process should be used for new products being introduced into the NHS, while MTAs should be limited to reviewing products with significant “real-world” data. However, NICE should ensure that STAs and MTAs inter-relate, where applicable, to guard against confusion of providers and patients regarding which piece of guidance to follow.

• As a technical matter, the word limit of STA submissions should be expanded to ensure they are sufficiently comprehensive.

• Further research is needed to develop more robust, inclusive, and transparent methodologies for valuing medicines. Such methods need to acknowledge the variations in patient response to medicines and the limitations of applying population-level models to individuals.

• An independent review of the quality of Assessment Group/Evidence Review Group reports should be conducted, including recommendations pertaining to accountability for quality, production of a detailed methods manual for STAs, and the introduction of a more robust quality control system.
DECISION-MAKING AND IMPLEMENTATION

Assessing product value

The majority of comments related to making decisions about product value surrounded the perceived narrowness of the criteria on which NICE bases its recommendations. While stakeholders acknowledged that cost-effectiveness information is a necessary component of determining the relative value of treatments, it is not sufficient and other factors should be taken into consideration. Such factors include clinical benefits, side-effect profile, ease of use, quality of life, medical need and national clinical priorities, patient preferences, equity, and innovative characteristics. Moreover, some comments inferred that long-term vision is lacking in NICE decisions, as long-term savings achieved from medical technologies are often ignored.

In relation, several commentators took issue with NICE’s (implicit) use of a decision rule or maximum cost-effectiveness threshold, stating that it had become a “de facto affordability threshold”, “not within the Institute’s intended remit”, and “arbitrary”. Even with a threshold in place, it was suggested that the rationale and method of its determination should be much more transparent, and that the balance of factors taken into account by NICE in appraising a technology should be duly clear and more consistent across valuations.

Other considerations related to the adoption decision include adequately accounting for and quantifying any uncertainty related to the decision (e.g., expected costs of making a wrong decision, in terms of resources and health gains forgone), as some stakeholders felt that the NICE process does not sufficiently acknowledge that assessing cost-effectiveness is an imprecise science, based on a variety of inputs and assumptions, and that for any product, there is a range of plausible cost-effectiveness ratios. Further, how NICE accounts for this uncertainty tends to be unclear. This exposes the process to the suspicion that it is driven principally by subjective judgments (e.g., affordability), rather than objective criteria.

The use of a threshold for rare and chronic diseases was also a cause of concern for stakeholders. Evidence compiled by the Office of Health Economics (OHE) demonstrates that appraisals of treatment of rare and chronic diseases, including cancers, are statistically more likely to be rejected by NICE, compared to standard treatments. It was the general consensus amongst those commenting on rare and chronic diseases that a higher cost-effectiveness threshold be applied in these cases. In fact, NICE recommended that separate decision rules and higher QALY threshold, up to £300,000 per QALY, would be required to enable the assessment of ultra-orphan drugs. With orphan products, however, NICE suggests that it is possible to apply the current methodology to their appraisal; many stakeholders disagree with this contention. Without a higher threshold, such patients will continue to be disadvantaged by the NICE process. This argument was also extended to cancer patients, where patient populations may be small and new treatments notably expensive.

Implementation of guidance

All submitted comments expressed significant concern regarding the implementation of NICE guidance, with many stakeholders deeming this to be a key issue for the Institute, in terms of its effectiveness, efficiency, and public credibility. Indeed, it was agreed that the uptake of NICE guidance is slow, patchy, and without adequate incentives for implementation.

It is recognized that NICE appropriately acknowledges that implementation is an issue and has made strides to address the problem, most notably that positive guidance (at least that resulting from Technology Appraisals) are to be accompanied by mandatory funding within 3 months of the guidance being published. However, these efforts have not adequately improved the implementation of guidance, with significant variation in their uptake and funding amongst different PCTs in the UK. This, in turn, has maintained or even exacerbated (in the view of most stakeholders) the “post-code prescribing” that NICE was intended to rectify. In addition to lending to inequitable access to treatments for patients, as stated by commentators, “it is an inefficient use of NHS resources
to have an appraisal system in place that is not fully implemented or prioritized by PCTs” and “guidance has no impact on patient care unless it is implemented”. In addition, the guidance contained in Clinical Guidelines is not mandatory, so it stands even less chance of being implemented.

There are several factors that are considered to impact whether or not NICE guidance is fully implemented, several of which have been noted and discussed in the previous phases of this report. Such contributory issues include local political drivers, lack of provider support, deficient knowledge and understanding of the assessment process, media and patient group pressure, lack of a whole systems approach to implementation, minimal reinforcement of compliance or accountability, and poor financial planning. To the latter, studies commissioned by NICE specifically examined the financial planning of local bodies, and found inappropriate use of allocated funding, lack of horizon scanning for future NICE guidance, and poor planning (Audit Commission, 2005). The organizations reviewed perceived that NICE guidance was unaffordable, but where robust implementation systems were in place, funding was found not to be the biggest barrier.

A related problem noted by many stakeholders concerns the fact that, despite some of the aforementioned issues, NICE guidance carries significant weight. As a result, if NICE recommends against a technology, or there is no available guidance for a particular new treatment, then it proves extremely difficult for that product to receive funding by the NHS (as previously noted, often termed “NHS blight”). Several commentators asserted that in their experience, the NHS is increasingly using the absence of NICE guidance as a reason for the unavailability of some treatments to patients. In many instances, PCTs will not fund treatments that have not been reviewed by NICE or are currently in the review process, regardless of available evidence supporting the value of the product. Other stakeholders felt there are bureaucratic hurdles put in place, particularly when a treatment is new to the market, rendering it difficult for providers to prescribe the product to patients. All of these issues can be heightened if a new treatment is never selected for NICE review or if an appraisal takes several years to complete. The Department of Health recently re-issued guidance (Good Practice Guidance) clarifying that a lack of NICE guidance was not an acceptable reason to refuse funding. However, it remains to be seen whether the guidance will have any impact; a situation that stakeholders contend should be closely monitored.

In the current environment of limited resources, stakeholders appreciate that NICE cannot feasibly monitor the implementation of all guidance. However, further progress must be made to this end and will likely require improved collaboration between the Department of Health, NICE, patient and professional groups, and local decision-makers. The majority of commentators called for an increased role of the Healthcare Commission (a body that audits the performance of NHS management) in reviewing the local implementation of guidance and for further resources to be directed to NICE’s Implementation Directorate, which provides support to PCTs on the practical and financial consideration of implementation. To the former, many stakeholders called for the Commission to put in place a more rigorous measurement and inspection system to provide an accurate and clear picture of both the quality and extent of implementation. While the Commission’s Annual Health Check provides the basis for the monitoring of NICE guidance implementation, it does not appear to be a sufficiently high priority for the Commission and, at present, NICE does not receive specific feedback about the uptake of guidance.

Given that the Annual Health Check presently takes the form of merely ensuring that processes are in place to potentially implement guidance, more attention needs to be directed to actually measuring tangible evidence of implementation. One stakeholder suggested that PCTs be required to record how emerging guidelines were factored into relevant decisions and planning efforts, in order to facilitate horizon scanning and compliance. The efforts of the Healthcare Commission could also be enhanced by a stronger, on-going relationship between NICE and the affiliated implementation groups subsequent to the publication of guidance.

Other recommendations to improve the implementation of guidance include more stringent sanctions toward PCTs for non-compliance of the 3 month funding mandate; “joined up” commissioning and financial
incentives (e.g., inclusion of an implementation component in the QOF [Quality and Outcomes Framework, an annual reward and incentive program detailing GP practice achievement], automatic inclusion of NICE-approved treatments in local formularies); and, including adherence to NICE guidance as a fundamental part of broader NHS performance measures and related frameworks.

**Appeals process**

Similar to many issues related to NICE, stakeholders acknowledge both strengths and weaknesses of the current appeals process. Although they applaud the Institute for having a formal, relatively open system of appeals, there is much room for improvement, with several commentators requesting review and revision of the process. First, the majority of stakeholders took issue with the independence and composition of the Appeals Panel. They strongly contend that the Panel should not be comprised of individuals affiliated with NICE; rather, an independent entity should review all appeals. Without this independence from NICE, appeals are likely to be seen as lacking transparency and fairness, and result in diminished public acceptance of decisions and confidence in the Institute. Moreover, in spite of the fact that the majority of appeals relate to the interpretation of cost-effectiveness, there is no health economist on the Panel; a problem that stakeholders indicate suggests a deficiency in expertise in addressing the complex issues raised by assessments.

Second, the criterion for appeal, where the conclusion in the FAD is so arguably wrong to be “perverse”, is considered by stakeholders to be an extremely high and unreasonable hurdle. To that end, NICE appeal procedures do not allow for any review of the scientific/technical methods of its recommendations. While appeals are permitted under the three principal grounds (refer to the Phase 2 report for explanation of the grounds for appeal), these do not include a challenge based simply on differences in scientific opinion. The effect of this limitation is that there is no possibility within NICE procedures for a challenge to be brought forth, where a conclusion appears to be incorrect, but is not necessary perverse.

According to several stakeholders, this situation appears to be exacerbated by several circumstances:

1) Guidance may be changed between the ACD and the FAD and, in such circumstances, there may be no possibility to submit a challenge to the substantive scientific conclusions that are expressed for the first time in the FAD;

2) In situations where new evidence is presented in the FAD and consultees have no opportunity to consider or challenge the new data; and,

3) There is an absence of any review of the substantive conclusions presented in the FAD, only the procedure or process by which it was reached.

In addition, many manufacturers consider it inequitable that challenge to the substantive conclusions expressed in the FAD is not possible at appeal, as they have had not opportunity to attend earlier meetings with the Appraisal Committee to ensure that their case is fairly and accurately represented. Rather than limiting appeals to criteria of “perversity”, it was suggested that recommendations be reviewed on the grounds of “reasonability”, allowing differences in scientific opinion to be openly discussed and considered if the decision is unreasonable in light of the submitted evidence.

Third, there are some concerns with the appeals process itself. One issue relates to the involvement of the Appraisal Committee in the appeals process. Following a successful appeal, an appraisal will often be returned to the Committee for further consideration. However, the Committee asked to perform this task is the same as the group that previously produced the unfavorable FAD, raising the possibility of impartiality. There is also disagreement about the standard approach taken at appeal hearings where if more than one appellant is present, each party may respond to questioning only when its particular point of appeal is under consideration. In circumstances where several appellants may raise similar points of appeal, this may mean that an appellant
is prevented from engaging with issues relevant to its own appeal. One stakeholder noted that this occurred during the recent Alzheimer’s disease appeal, where issues relevant to the clinical trial data of one manufacturer were raised by one of the professional groups, rendering the manufacturer concerned unable to comment on its own clinical trial data. Similarly, in some cases, particularly where there have been several appellants present at an appeal hearing, the panel has not given adequate time for all the issues to be adequately explored.

Finally, several stakeholders expressed apprehension that the appeals process is “never-ending”, serving to delay decisions, facilitate tensions between stakeholder groups and stakeholders and NICE, and, ultimately, harm patients in need of treatment and healthcare services. In fact, several commentators maintained that, at present, the appeal system is the only available mechanism to redress limitations in NICE processes. Rather than use the appeals process as a “last resort”, of sorts, this tendency might be ameliorated if many of the issues surrounding transparency, stakeholder representation and participation, and current evaluation methods are adequately addressed and improved.

**Key Stakeholder Recommendations**

- NICE should adopt a broader definition of product value, beyond a narrow focus on the cost per QALY.
- Different cost-effectiveness thresholds for different treatments, depending on the type of product and patient population (as in the case of orphan drugs) should be employed and such thresholds should be made explicit.
- The use of the QALY and cost-effectiveness thresholds should be debated in public and further explored for methodological validity.
- NICE should adopt an approach, whereby a drug that is being appraised early in its lifecycle is not completely rejected on the basis of insufficient evidence of cost-effectiveness. More creative solutions to establishing value following launch should be considered.
- When NICE issues guidance recommending that a technology not be used routinely in the NHS, it should define “non-routine use” and a set of “exceptional case” circumstances. This will ensure consistency of use and decrease the current “post-code prescribing”.
- Overall, the decision-making process needs to be more transparent. Otherwise, NICE decisions will continue to be challenged.
- The Department of Health must ensure that patients requiring treatment with non-NICE reviewed medicines are not discriminated against and have access to necessary treatment. This situation should be monitored alongside the successful uptake and implementation of NICE guidance.
- Mandatory funding within three months of guidance production should be extended to Clinical Guidelines.
- A thorough review should be undertaken to assess the impact of the NICE implementation team, and to the value to the NHS.
- NICE (Implementation Directorate) should provide more guidance to PCTs as to where the resources required to implement guidance are to be derived, in order to potentially avoid placing PCTs in a position of having to cut back on existing, non-assessed interventions, which may in fact represent better value for money.
- To increase the independence and credibility of the appeal process, it should be separated from NICE, with the Appeal Panel constituted entirely of non-NICE personnel.
- NICE should judge criteria other than the “perversity” of decisions for appeals, allowing differences in the scientific or technical quality and accuracy of the evidence underpinning the decision to be debated and considered.
• NICE should adopt a more flexible approach towards the hearing of appeals, with a willingness to hear sub-
missions from other appellants in response to points of appeal, in the format that is used or the hearing, and 
in the time permitted for adequate consideration of the issues raised.

• The impact of HTA and the NICE process, in particular on the sustainability of health technology innovation 
in the UK, should be thoroughly reviewed. Unless this is addressed, there is a real prospect that the develop-
ment and introduction of new technologies will be drastically reduced in the UK, especially in disease areas 
where common practice is to use off-patent products. Moreover, areas of unmet need will continue to be 
untouched by innovation. This is particularly an issue for the device industry.

GENERAL PERCEPTIONS

NICE vs. SMC and SIGN

The comments on comparisons between NICE and the SMC and SIGN were somewhat limited, compared to 
many of the aforementioned issues. Of the available commentary, however, several stakeholders considered the 
SMC to employ a more flexible, timely, and open process of engagement with stakeholders. The SMC is also 
viewed as less process-driven than NICE and more willing to discuss the content of submissions through the 
assessment. Moreover, as discussed above, in the event of a negative decision, many stakeholders consider their 
only recourse to be lodging a formal appeal to NICE. The SMC, in contrast, provides justification for why it has 
not recommended a particular treatment for use in Scotland and allows manufacturers to resubmit, where new 
evidence may be available. Some stakeholder suggested that following the SMC model would reduce the num-
ber of formal appeals to NICE.

In terms of SIGN, it was viewed favorably as compared with NICE, particularly in respect of its processes for 
synthesizing peer-reviewed evidence into clinical practice guidelines, and the rate of subsequent acceptance and 
uptake by clinical professionals and NHS organizations. In addition, relevant SIGN documents were considered 
more succinct and better supported for use by the incorporation of quick reference guides for clinicians. 
Compared with NICE, SIGN was also deemed as having a more robust method for ensuring that all pertinent 
healthcare professionals are engaged in guideline development. Finally, another advantage of the SIGN process is 
that its program of work is selected according to clinical priorities and the availability of evidence, and is agreed 
upon in concert with the (Scottish) Health Department, which serves to build professional and public confi-
dence. Nevertheless, a few weaknesses of SIGN were also raised, namely that its guidelines do not consider evi-
dence on cost-effectiveness. Stakeholders also expressed that SIGN and NICE duplicate a great deal of work. In 
particular, a situation where there are two “national guidelines” offering conflicting advice on the same clinical 
condition should be avoided.

Other stakeholder issues related to comparisons between these entities, including differences in their respec-
tive decisions and guidance, which hinder public confidence and trust. Many stakeholders and the general pub-
lic do not understand why the same treatment may be available in neighboring Scotland, but not in England and 
Wales. This problem is likely intensified by public (and provider) confusion regarding the various remits and 
lines of accountability. NICE should provide better explanation of how the remits and responsibilities of the var-
ious entities differ and the reasons underpinning the derivation of different conclusions.

Other sources of public confidence (or lack thereof)

A number of the key factors influencing the level of public confidence in NICE have been discussed in prior 
sections of this report. However, there are a few more general noteworthy issues that deserve mention. First, the 
media is viewed as playing a principal role in both facilitating or hindering public trust and support.
Stakeholders acknowledge that the media have an interest in sensationalizing stories and distorting select NICE decisions, which effectively damages public confidence and encourages scrutiny. According to one commentator, seeing angry patients and their carers carrying condemnatory placards and circulating petitions leaves a “powerful emotional image” on the public, providers, industry, and policy-makers. The media also tends to emphasize negative decisions and related controversies, without a balanced attribution of the positive impact NICE guidance has on patient access to new treatments and improved health outcomes. Media coverage pertaining to recent decisions, such as beta-interferon for Multiple Sclerosis, imatinib for Leukemia, trastuzumab for Breast Cancer, and various drugs for Alzheimer’s Disease, certainly illustrates this point. The media has also played upon concerns that the pharmaceutical industry possesses too much influence over the NICE decision-making process, creating suspicion of conspiracy and conflict of interest among patients and the public. Media attention, however, can also have the positive effect of encouraging more members of the public to be engaged in the work of NICE.

Public confidence in NICE decisions appears to also be influenced, in part, by general attitudes regarding the NHS. As briefly discussed previously, there is the perception that decisions in the NHS, both nationally and at the PCT level, are being driven far more by cost-containment objectives than by health considerations. Members of the public witness individual PCTs cutting services, and NICE is intimated as part of that process - a primary cause of the refusal of treatment to individual patients. Consequently, several stakeholders contended that government officials and local decision-makers should be more forthcoming and open about the financial challenges facing the NHS and provide political and financial support for NICE and the critical role it plays in the broader healthcare system.

These concerns are likely enhanced by a growing awareness of the variation in treatment availability across the UK. Beyond the neighboring borders of Scotland, there is the perception amongst stakeholders and the wider public that some treatments routinely available to patients in Europe and the U.S. are being denied to patients in the NHS as a result of NICE. As such, the Institute is seen as not sufficiently meeting its principal objectives of accelerating the uptake of effective new technologies and reducing or eliminating geographical disparities in their use. In the words of many stakeholders, “post-code prescribing remains a very real phenomenon” and serves to “deteriorate public support” of NICE.

**Key Stakeholder Recommendations:**

- The different roles and remits of NICE, SMC, and SIGN need to be clarified and better communicated to stakeholders and the general public. Moreover, differences in decisions between these entities should be better explained and justified.
- Greater collaboration between NICE, SMC, and SIGN should ensue to avoid duplication of effort and create efficiencies in topic selection and evidence review.
- NICE should work more collaboratively with the media and increase their public relations activities to secure a more positive public image and more effectively highlight its positive and important contribution to patients and the broader healthcare system.
- By ensuring that NICE processes are transparent and fair, and its decisions are clearly communicated, the Institute may improve public confidence and recover any lost credibility.
- Greater financial and political support should be given to NICE, and government officials should be more open about the financial pressures facing the NHS. Patients and the general public need to better understand the realities of priority-setting, considering the increasing rate of new technologies, not all of which can be fully funded within the NHS budget. This is a situation this is likely to worsen, with the termination of the substantial increase in NHS expenditures witnessed in recent years.
• To enhance public perceptions of NICE, its guidance should better reflect clinical practice and patient and provider perspectives.

• The allowance of earlier appraisals, more timely guidance publication, and improved implementation of guidance are a few key actions toward more effectively addressing “post-code prescribing”.

CONCLUDING REMARKS

The stakeholders’ comments illustrate that even with an HTA entity as sophisticated as NICE, many problems remain. Even within areas where NICE could be considered to be better than most HTA entities (e.g., involvement of stakeholders, transparency in decision-making), many criticisms were made. This suggests that it is impossible to devise a national approach to HTA that will satisfy the needs of all the key parties. Several important themes can be identified in the stakeholder comments, as highlighted below. These overarching issues provide a backdrop to the analysis in Phase 4 on the implications of the NICE approach for the U.S.

Lack of independence

Despite the ‘arms length’ organizational structure of NICE and its use of expert committees, it is still perceived by many stakeholders as being too closely aligned to government, operating a rationing agenda. It is difficult to see how this perception could be dispelled, since it is the nature of HTA that some recommendations will be negative, thereby denying patients’ access to care that is effective, if not cost-effective. However, the perception is fuelled by the fact that NICE is solely dependent on government for funding.

Assessment methods

Although stakeholders acknowledge that NICE undertakes rigorous assessments, many perceive these to be undertaken from too narrow a perspective. This criticism has a number of elements, including a) an excessive reliance on data from RCTs, to the exclusion of data from observational studies; b) too much focus on the quality-adjusted life-year (QALY), as the measure of the social benefit of healthcare interventions; and, c) a narrow perspective for costs, excluding those falling on patients and their families. Many of these features of NICE’s methods derive from the remit given to it from government, reinforcing the point about lack of independence made above. Also, the concerns about the narrow perspective for decision-making are enhanced by NICE’s perceived strict adherence to a cost per QALY threshold.

NICE is currently reviewing its methods guidelines, with the aim of producing a new set of methods by the end of 2007. Among the areas being reviewed are health-related utility measurement, equity and social value judgments, and estimation of costs.

Lack of transparency

Although NICE would claim that, in many ways, its procedures are transparent, it is clear that stakeholders feel that greater transparency is required. In response, one potential change for NICE to consider (and, which has been suggested) would be to hold discussions of the evidence in Appraisal Committee meetings in public. However, there are currently no plans to make ‘unlocked’ versions of the assessment group models available, especially now that the challenge to the practice of withholding models was not successful in the recent Alzheimer’s judicial review.

Inadequate stakeholder involvement

Holding some parts of the Appraisal Committee meetings in public would meet some of the concerns of manufacturers about lack of involvement. However, there is still a concern that manufacturers are not involved early enough, or in a sustained manner. Many stakeholders felt that this was particularly important, given the
manufacturer’s role in producing and interpreting the clinical data. There were also residual concerns about securing adequate clinical and patient input to NICE’s assessment and appraisal processes. NICE does have patient representatives on all of its advisory committees, but given the technical nature of much of the discussions, it is clearly difficult for patient participation to be effective.

**Delays in issuing guidance**

Many stakeholders were concerned about the time taken in issuing NICE guidance, particularly as there is evidence that decision-makers delay the introduction of new treatments pending NICE’s decision. Of course, some of the other stakeholders concerns, such as the need to consider a broader range of evidence and the need to involve stakeholders more fully, may serve to increase further the time required for assessments. In addition, there were suggestions that the introduction of STAs, the main mechanism employed to reduce the time for assessments, is not without its problems.

Central to the concern about delays is the fact that patients are often denied access to new therapies while the assessments take place. In the UK, this is because payers feel that once new technologies are introduced, it is subsequently difficult to remove them if further evidence suggests that they are not cost-effective. This suggests that consideration needs to be given to developing approaches for introducing new technologies that better integrate the decisions on funding with the accumulation of evidence. That is, HTA should become a more continuous process, not a ‘one shot’ attempt around the time of product launch.

**Uneven implementation of guidance**

Despite the fact that implementation of the guidance from NICE technology appraisals is mandatory within 3 months, and numerous other attempts to increase the implementation of guidance, there is plenty of evidence to indicate that implementation is uneven. Many stakeholders argue that positive guidance is often less implemented than negative guidance, because of its obvious funding implications. Some of the difficulties observed in the UK, with its global healthcare budgets, may not be so apparent in systems that tie reimbursement to particular procedures. Nevertheless, all parties agree that if resources are to be invested in HTA, the results of studies should be implemented.

These difficulties will be revisited in Phase 4, where the implications of the NICE model for the U.S. are examined in detail.
PHASE 4: Implications of the NICE Model for the U.S.

INTRODUCTION

It is well-known, in health policy circles, that the devil is in the detail and that policy solutions are very context-specific. Therefore, it is highly unlikely that the NICE model could simply be uplifted and transported to the U.S. In particular, the NICE model, and many similar approaches in other European countries, reflects a policy response designed to meet the needs of a predominantly public, single payer, healthcare system. This contrasts sharply with the U.S., which has a multifaceted healthcare system, involving public, private not-for-profit and private for-profit payers.

More fundamentally, there are important social and cultural differences between the UK and U.S., which may impact on efforts to introduce a NICE-type model. These include the willingness to accept explicit restrictions on the access to services, which is arguably greater in the UK, and the concern about extensive government involvement in healthcare, which is arguably greater in the U.S. (Kohut and Stokes, 2006). Another major difference between the U.S. and Europe, which partly reflects these cultural differences, is the much greater level of patient co-pays in the U.S. healthcare system, especially for pharmaceuticals (Cohen et al., 2007; Cohen et al., 2006).

Even so, it should be noted that the U.S. health care system already has several jointly operating HTA entities. The Effective Health Care program (EHC) at the agency for Health Care Research and Quality, includes a collection of research centers that review existing evidence or generate new evidence and analytic tools. The Centers for Medicare and Medicaid Services (CMS) has the Medicare Coverage Advisory Committee (MCAC), each of the 50 state Medicaid programs has some form of HTA procedure for drugs (the state of Washington recently extended its HTA program to also cover devices, diagnostics, and procedures), and 13 states participate in the Drug Effectiveness Review Project. Also, many private health plans and pharmacy benefit managers (PBMs) operate HTA programs.

However, despite the differences between the UK and the U.S., much can be learned from the successes and failures of NICE, and these lessons will be important to acknowledge as the debate on the role of health technology assessment (HTA) progresses in the U.S. Here the comments are organized under the following headings: governance, funding, and organization; assessment methods; decision-making processes; and communication and implementation of guidance.

GOVERNANCE, FUNDING, AND ORGANIZATION

Structure and composition

In the UK, NICE is constituted as a Special Health Authority within the National Health Service (NHS). Therefore, it has an ‘arms-length’ relationship with government, although all its funding comes from the Department (Ministry) of Health.

Experience from the UK and elsewhere suggests that an appearance of independence is important for HTA agencies or entities, as the findings of HTA reports are often controversial. A survey of general practitioners in the UK (Conn, 2006) showed that NICE was perceived as being independent from industry, but not independent from government. Also, when NICE guidance is considered by the media, the Institute is normally referred to as ‘the government’s health watchdog’ or, occasionally, as the ‘the NHS’s rationing body’.
Therefore, despite its quasi-independence, NICE is perceived as pursuing a payer’s agenda. However, on occasions it does make recommendations that are, at best, inconvenient for government. For example, it twice rejected beta-interferon for multiple sclerosis. Fearing a political backlash, the government brokered a risk-sharing scheme with the manufacturers, in order to ensure that the drugs were available for patients (Department of Health, 2002).

NICE also takes other measures (discussed below) to increase public perceptions of independence. These include the use of expert committees, extensive patient representation on its committees, and stakeholder involvement.

In the U.S., the primary decision affecting the governance, funding, and organization of any HTA entity would be where it is located. That is, should it be a new Federal agency, part of an existing agency, or outside of government (Wilensky, 2006; Orszag 2007)? Subsequently, it would need to be decided whether the entity was to be charged with informing the decisions of Federal Government alone, or the decisions of a wider range of payers.

In the former case, one could imagine a relationship similar to the one NICE has with the Department of Health in the UK. On the other hand, if any HTA entity were to be providing guidance to a broader range of healthcare decision-makers, a wide range of funding and organizational options would be possible. These could include a mixture of public and private funding, and/or a 'virtual institute', involving a collaboration of several existing public and private organizations with expertise in HTA (Orszag, 2007). Regardless of the governance arrangement(s), any public HTA entity will likely end up informing decisions of a whole range of payers, even if the entity is only charged with informing the decisions of the Federal Government. Indeed, currently the HTAs generated for the MCAC decisions are posted on the CMS website and are available for consultation by private health plans.

The precise nature of any HTA entity in the U.S. is likely to be determined to a large extent by the outcome of the November 2008 elections. However, two observations can be made. First, it is difficult for any organization to develop an appearance of independence if its funding comes from a single source. From this point of view, multiple funding sources are preferred. Secondly, even where the HTA entity is charged with informing public decisions alone, it can also influence decisions in other sectors. For example, in Canada, the Common Drug Review (CDR) was established by the Federal Government, under the stewardship of the Canadian Agency for Drugs and Technologies in Health (CADTH). The Federal government does not control the funding and availability of drugs. However, the outcomes of the CDR are influential in the decisions of the various Provincial formularies, although the various provinces clearly take local factors into account (McMahon et al., 2006). Therefore, it would be unwise to assume that the influence of any HTA entity would be confined to a single sector of the healthcare system.

Remit

Regardless of the structure and composition of any new HTA entity in the U.S., a critical feature would be its remit. NICE’s remit is to consider all health technologies and it seeks to apply the same methods of assessment to each. This is thought to be more policy-relevant than concentrating on one sector (e.g., drugs), although in practice a substantial proportion (around two-thirds) of NICE technology appraisals have been of pharmaceuticals. Although the appraisal of devices, procedures, diagnostics, and public health interventions tends to be more challenging that the appraisal of drugs, it would make sense to have the same broad remit for any HTA entity in the U.S.

The other element of an HTA entity’s remit is the scope of the assessments it is asked to carry out. In particular, should it focus only on clinical outcomes (e.g., effectiveness), or should it also consider cost-effectiveness? In the UK, NICE’s remit clearly obliges it to consider both clinical and cost-effectiveness. The Institute takes this remit seriously and includes an explicit economic component in its analyses (with the exception of investigation-
al procedures). In practice, economic considerations have played a greater role in the guidance emanating from technology appraisals than that resulting from clinical guidelines or public health appraisals. This is mainly because of the increased difficulty in addressing the economic issues in the latter two programs, due to the breadth of the topics and the lack of available data.

On the international level, NICE is probably in a minority among HTA entities in having such a clear remit to consider cost-effectiveness. Other examples of entities with a similarly clear remit would be the national drug formulary committees in Australia, Canada, and several European countries. In contrast, many agencies have a remit to promote ‘quality in health care’, ‘care of an international standard’, or care that ‘is reasonable and necessary’. In these situations, problems arise if there is uncertainty over how to interpret the remit.

The recent debate in the U.S. has been conducted using the term ‘comparative effectiveness’. For many commentators, the study of comparative effectiveness would involve consideration of clinical outcomes only, usually through the conduct of clinical trials, comparing relevant technologies in a real life (i.e., routine practice) setting (Wilensky, 2006). On the other hand, some commentators (MedPac, 2007; Orszag, 2007) acknowledge that an assessment of comparative effectiveness could also consider costs. The definition given by MedPac is the one of the clearest and most comprehensive. It cites the AcademyHealth (2005) definition that ‘Comparative-effectiveness analysis evaluates the relative effectiveness, safety and cost of medical services, drugs, devices, therapies and procedures used to treat the same condition’. It also states that such studies may include:

- Clinical outcomes, including traditional clinical endpoints, such as mortality and major morbidity;
- Functional endpoints, such as quality of life, symptom severity, and patient satisfaction; and,
- Economic outcomes, including the cost of health care services and cost-effectiveness.

In contrast to the MedPac definition, the majority of observers and policy initiatives employing ‘comparative effectiveness’ deems that considerations of costs and cost-effectiveness should be considered by the payer, not the evaluator. Indeed, the term ‘comparative effectiveness’ may have emerged and gained traction precisely because it avoids the mention of costs.

As the debate about comparative effectiveness progresses in the U.S., the breadth, or restriction, in the scope of the required analyses will be a critical issue. At one end of the spectrum, the HTA effort could focus solely on the funding and conduct of clinical trials to compare alternative technologies. Unlike most of the trials currently funded by industry (e.g., Phase III for drugs), these trials are likely to compare two or more widely-used therapies, enroll large numbers of patients, and have long-term follow-up. They are also likely to be quite costly, so their number will be limited, even with the budgets currently being proposed for the comparative effectiveness initiative, which at present range from $4-6 billion a year (Wilensky, 2006). The current funding level for NICE is more modest (around $50 million), but crucially the Institute does not commission primary research such as comparative clinical trials. Rather, it relies on systemic reviews of the existing literature, in addition to economic modeling.

A narrow definition of ‘comparative effectiveness’, excluding cost-effectiveness, has some appeal within the U.S. context. In particular, since healthcare organization, clinical practice patterns, costs, and, importantly, perspectives differ among the various payers, a centralized calculation of the cost-effectiveness of health technologies may have little meaning. Even in the context of one payer (e.g., CMS), it might be argued that the consideration of cost-effectiveness is not admissible within its remit.

On the other hand, some feel quite strongly that costs should be considered, although such sentiments are generally promulgated by academics rather than decision-makers. In a recent interview (Tunis, 2007), David Eddy said ‘I believe that our failure to explicitly consider costs in medical decision making is the single greatest flaw in our health care system’ and that ‘if we are not allowed to consider cost, there is no way to determine the
value of any activity. We end up recommending everything that has any benefit, no matter how small. Nevertheless, it has been suggested that cost-effectiveness is an implicit consideration in some policies and private plans (Neumann and Sullivan, 2006).

The other, more practical argument is that cost-effectiveness considerations may eventually feature in decision-making, even if they are not explicitly considered. However, without a formal consideration of all the relevant economic factors, cost criteria might be considered inappropriately.

The best example of this comes not from NICE, but from Germany, where the newly established Institute for Quality and Economic Efficacy in the Health Sector (IQWiG), was asked to provide advice to the Joint Federal Committee (Gemeinsamer Bundesausschuss, or G-BA) on the relative merits of insulin analogues as compared with regular insulin. At the time, the remit of the Institute did not include a formal consideration of cost-effectiveness, so the comparison was limited to the clinical evidence, obtained from randomized controlled trials. The conclusion of the study was that all types of insulin were equally effective in controlling blood glucose levels.

Since the conclusion was one of comparative efficacy, the G-BA saw little reason to pay a premium price for insulin analogues. The problem was that the study, appropriately conducted within the Institute’s narrow remit, ignored most of the potential advantages of insulin analogues, which mainly relate to their greater potential to avoid hyperglycemic events and the associated costs and health outcomes. Therefore, if a formal consideration of cost-effectiveness is to be excluded, it is important that any differences between health technologies, in terms of their impact on quality of life and other healthcare resource use, are estimated as part of the analysis. Otherwise, there is a risk that the eventual ‘cost-effectiveness analysis’, which must surely be conducted at some point in the decision-making process, will be a simple comparison of acquisition costs of the alternative technologies with the narrowly-defined clinical effects.

**ASSESSMENT METHODS**

**Priority-setting and scoping**

Priorities for assessment by NICE are set by the government in the UK, according to published criteria. If any HTA entity in the U.S. was also servicing the decision-making needs of the Federal Government, a similar process could apply. For example, the topics could relate to those technologies for which coverage decisions are required. If an HTA entity in the U.S. were seeking to be relevant to a wider range of healthcare decision-makers, the nature of the process for setting priorities is less clear, although many private health plans also cover Medicare enrollees.

One clear message from the NICE experience is the importance of the scoping stage. This is where the decision problem is specified and the basic design of the assessment determined. Also, by defining the alternatives to be compared, NICE also identifies which technology manufacturers will be approached to make a submission (see below). As in the case of priority setting, the scoping process is likely to be simpler if only the decision-making needs of the Federal government are being considered. It may not be possible to specify a single analysis capable of meeting the needs of all the different payers in the U.S., who may currently be sanctioning different treatment practices. However, it should be noted that the Federal Government is not a monolithic payer, and is not focused only on the elderly. As such, the lines drawn between the responsibilities of the various payers are not always so clear or distinct.

**Methodological guidelines**

NICE, along with many other HTA entities (Tarn and Smith, 2004), has specified methodological guidelines for its assessments (NICE, 2004). These guidelines serve several purposes, including standardizing assessments and increasing transparency.
Although several aspects of the prescribed methods have been the subject of debate, the majority view in the UK is that it is better to have guidelines than not. However, an important feature of the NICE guidelines is that they embody the ‘reference case’ concept, first proposed by the Panel on Cost-Effectiveness in Health and Medicine (aka, the Washington Panel) established by the U.S. Public Health Service (Gold et al., 1996). The principle behind the reference case approach is that alternative analytic approaches are not excluded from consideration, as long as an analysis consistent with the reference case is also reported. Manufacturers submitting to NICE favor this approach; if they feel that they can improve upon the reference case, then they can submit an additional analysis. On the other hand, the reference case provides a clear statement of the minimum requirements.

As mentioned above, several aspects of NICE’s methodological guidelines have been the subject of debate. The most controversial aspects have been the perspective for costing (which currently excludes productivity costs, costs on other government budgets, and costs falling on patients), the expression of health outcomes in terms of QALYs, the use of models to synthesize indirect comparisons in the absence of head-to-head studies, the ex-post analysis of patient subgroups, and the mandated use of probabilistic sensitivity analysis. These items were discussed in more detail in Phase 2.

If an HTA entity were established in the U.S., it is likely that similar methodological debates would take place. Therefore, it would be necessary to establish a process to develop methodological guidelines that have the approval of the key parties (e.g., major payers and technology manufacturers). This effort would probably build on existing proposals, including the Washington Panel’s reference case and the AMCP Format (AMCP, 2002).

**Assessment process**

NICE’s assessments are mostly based on secondary research (i.e., systematic reviews and economic models), as opposed to primary research, such as large prospective studies. The main reason for this is the emphasis on the timeliness of the assessment. That is, since a decision has to be made (on the appropriate use of a health technology), the need is to develop the best possible guidance given currently available data.

NICE recognizes that, in many instances, the data are imperfect. Therefore, the Institute often makes recommendations for further research (Mason et al., 2006). However, these recommendations are not normally binding on any party, including the manufacturer. Nevertheless, since NICE is committed to reviewing its guidance after a period of 3 years, manufacturers sometimes consider it worthwhile to gather more data after the product is made available on the NHS, in order to strengthen their submission when the technology is reappraised.

Only rarely are such requests for further research made mandatory. One example is the risk-sharing scheme for beta interferon mentioned above. Another is the British Society of Rheumatology Biologics Registry, which was set up at the request of NICE following its positive guidance on the use of the first two TNF inhibitors for the treatment of rheumatoid arthritis. The notion of ‘conditional reimbursement’, where a new technology is approved for use on the condition that further data are gathered, is of increasing interest both within the UK and U.S. Of course, CMS already has its program of Coverage with Evidence Development (CMS, 2006; CMS, 2005).

If, in the U.S., the emphasis in ‘comparative effectiveness’ assessment were to be on large, long-term, controlled trials, this would have to be developed under a scheme similar to coverage with evidence development, since the technologies would have to be approved for funding in order to allow such trials to take place (Under coverage with evidence development, funding for the technology to be studied is contingent upon participation in the clinical trials). Therefore, more discussion of the design of such schemes, including study requirements, funding and risk-sharing arrangements (if any) is urgently required (Garrison et al., 2007; Drummond, 2007). Beyond trials, other thought leaders envision the primary use of evidence syntheses of existing trials, complemented by retrospective data, where possible. To that end, the Medicare Modernization Act of 2003 contains language and funding for comparative effectiveness research that is now conducted by AHRQ, but the funding only permits syntheses.
Another important feature of NICE’s assessment process is that technology manufacturers are invited to submit a dossier of data and analyses, consistent with the Institute's methodological guidelines. Most manufacturers welcome this opportunity, as it provides them with the possibility to present the advantages of the product on their own terms. Under the NICE model, company submissions are regarded as an important part of the process. With the increased emphasis on STAs, which relies more heavily on evidence submitted by the manufacturer, they are becoming even more important. However, not all HTA entities provide for manufacturer submissions. In the U.S. context, drug companies are invited to submit dossiers to the Drug Effectiveness Review Project (DERP), which states that 'submitting a correctly completed dossier will ensure that the evidence submitted by a company will be fully reviewed (DERP, 2007).

One important aspect of manufacturer submissions is that they often contain commercial-in-confidence data (e.g., the results of clinical trials which have not yet been published). NICE welcomes this in its technology appraisal program, as it may otherwise struggle to obtain such data. However, in return, NICE commits to keep the data confidential, until such a time as the manufacturer says it can be released. Often this does not pose a problem, in that over the time span of an appraisal, the confidential data may often be published before the Appraisal Consultative Document (ACD) is circulated. Nevertheless, there are occasions when NICE has to request the release of confidential data, if these are central to interpreting its guidance. This is important, given the need for transparency in NICE’s decision-making (see below). In contrast, the submissions made to the DERP in the U.S. are publicly available, so manufacturers typically exclude commercially sensitive information.

NICE commissions assessments from independent outside bodies (mainly academic groups), although it does have a substantial internal staff to oversee and steer the HTA process. Given the controversy surrounding HTA findings, the process of independent external review is considered to be an important feature of the NICE process. It is particularly important in the case of MTAs, where there may be several manufacturers’ submissions, each of which may come to a different conclusion. External review is still a feature of the STA process, although there are some concerns that it may not be as thorough or inclusive, given the shorter timeframe and the lower level of resources available to the reviewers.

In the U.S., any HTA entity would be wise to rely fairly heavily on external review, given the wide range of perspectives present in the healthcare system. There is also a large body of health services research expertise to draw upon in existing public and private organizations. Therefore, however the HTA effort in the U.S. is organised, it should be done in a way that provides sufficient funding for thorough, scientific assessments to be conducted. In the UK, NICE pays its independent assessment groups around $250,000 for each full (multiple) technology assessment and around $90,000 for each STA. This is quite generous given that these assessments are largely based on secondary research and do not involve prospective data collection.

**DECISION-MAKING PROCESSES**

**Assessment versus appraisal**

NICE makes a clear distinction between assessments, where the technical analysis is undertaken, and appraisals, where the evidence is evaluated and the decisions made. The Institute relies heavily on expert committees in its decision- making processes (e.g., Appraisal Committee, Guideline Review Panels) and this adds somewhat to the appearance of independence. The experts are a mixture of academics (across several disciplines including medicine, statistics, and economics), NHS decision-makers and patient representatives. There is no reason why a similar approach should not work for an HTA entity in the U.S., although it may be more of a challenge to secure adequate representation from the various decision-making groups, some of which are in competition with one another.
A more fundamental issue in the U.S. context is whether an HTA entity would have a decision-making role at all, given the diverse nature of the U.S. healthcare system. It is possible, indeed more likely, that the responsibilities of any entity in the U.S. would cease at the assessment stage. Assessments could then be made publicly available, for the various payers to use (or not use) as they see fit.

**Involvement of stakeholders**

NICE has arguably led the way in the involvement of key stakeholders in its decision-making processes. The main stakeholders are the technology manufacturers, professional societies, patient organizations, the NHS, and the Department of Health. All stakeholders have the opportunity to comment at key stages in the appraisal process. As mentioned in Phase 2, although this involvement sometimes has the result of slowing down the appraisal process, it is generally regarded as a positive feature. Indeed, on some occasions, NICE guidance has been changed as a result of stakeholder comments. Therefore, this might be a feature to promote in any HTA effort in the U.S., even if the HTA entity only performed assessments, as opposed to issuing guidance.

If they feel their comments have been ignored, stakeholders have the opportunity to appeal against NICE’s decisions, mainly on the grounds that procedures were not properly followed. Although hard to substantiate, this has probably had the impact of reducing the number of legal challenges to NICE guidance.

**Formulation of guidance**

Following consideration of the evidence, NICE produces guidance for the NHS. As mentioned above, this may not make sense in the U.S., unless such guidance were to take account of the many and varied decision-making contexts in the U.S. healthcare system.

NICE often distinguishes between patient sub-groups in terms of cost-effectiveness and may recommend the new technology for some groups, but not others. This may not be as acceptable in the U.S., since it would likely be conceived as discriminatory. However, it is worth remembering that, in the presence of patient co-pays, a technology can be made available to all in the U.S., providing the patient pays a substantial portion of the cost. Therefore, it may be possible, and acceptable, to discriminate by applying differential co-pay levels to different sub-groups. Such arrangements already exist in some 3-tier pharmacy benefit programs. This is not an option for NICE, since it operates within the confines of the British NHS, where there are only limited co-payments.

**Need for transparency**

The need for transparency arises from the fact that NICE is a public body and therefore has to be accountable. Similar needs may arise if an HTA entity in the U.S. were a Federal agency, for example.

It is worth noting that NICE seeks to be transparent both in its assessments and its decision-making. Transparency in assessment methods and processes may also be important in the U.S., even if the various resulting decisions may not be so transparent. For example, decision-making in for-profit health plans is unlikely to be transparent, as a result of commercial sensitivities.

**Cost-effectiveness threshold**

Over time NICE has come to base its decisions on a cost-effectiveness threshold, representing the maximum amount it is willing-to-pay for a QALY (i.e., unit of health gain). This has been made explicit by the Chair and Deputy Chair of NICE and is said to be in the region of £20,000 to £30,000 per QALY (Rawlins and Culyer, 2004).

No such threshold exists for any public body in the U.S., but in the health economics literature, a threshold of $100,000 per QALY is often referenced. Of course, in the U.S., it is likely that the threshold, if one exists, will differ among the different sectors of the healthcare system, according to the level of budget available.
If there were ever an HTA entity in the U.S. issuing guidance (e.g., to CMS), it would probably be possible to infer a threshold from the decisions made, even if one were not explicitly stated (Devlin and Parkin, 2004). However, as mentioned above, it is probably more likely that an HTA entity will restrict its role to undertaking assessments, rather than making appraisals.

**COMMUNICATION AND IMPLEMENTATION OF GUIDANCE**

NICE devotes considerable effort to the communication and implementation of its guidance. Also, the implementation of NICE’s technology appraisals is mandatory in the NHS. Even so, implementation of NICE guidance is patchy. The biggest problems arise when the guidance indicates use of the technology for some patient groups and not others. Manufacturers often argue that the NHS, given budgetary constraints, finds it easiest to implement negative NICE guidance. In general, one might expect the implementation of HTA findings to be easier in the U.S., since this could be linked to coverage decisions, although no doubt difficulties would arise in practice.

Within the U.S., it is likely that any HTA entity will have an extensive communication strategy, most likely for the results of its assessments, rather than guidance. How different decision-makers would react to this remains to be seen. It is already known that many payers in the U.S. consult the NICE website, but the influence this has on decision-making is unclear. One option for some plans would be to use technology assessments as one way of engaging with enrollees about the trade-offs between more coverage, the extent of co-pays, and the level of premiums.

Finally, as mentioned earlier, NICE revisits all its guidance with a default period of 3 years. Out-of-date assessments or out-of-date guidance can be potentially harmful, so periodic updating would need to be a feature of any HTA process in the U.S. Over time, more may be learned from NICE about the appropriate frequency of updates in different fields.

**SUMMARY AND CONCLUSIONS**

Although the increased use of HTA in the U.S. may lead to a more cost-effective use of healthcare resources, it will also increase the burden on industry to produce data. In addition, to the extent that HTA is linked to decisions about the pricing and reimbursement of medicines, it will lead to greater controls on the prescribing and use of drugs. Therefore, the first consideration for industry is whether or not it should support the broader introduction of HTA in the U.S. This will depend on assessments of whether the growing interest in HTA can be countered and the possible alternative policies that payers may pursue if the broader implementation of HTA is abandoned.

These wider considerations are beyond the scope of this project. Rather, the focus here is on what industry should do if, for whatever reason, HTA, along the lines of the NICE model, were to be introduced to a greater extent in the U.S. Although there are considerable differences between the healthcare systems in the UK and the U.S., several important lessons can be drawn from the UK’s experience with the NICE model.

First, the governance and organization of any HTA entity is critically dependent on whether its role is to serve the decision-making needs of one major payer or the needs of many decision-makers in a diverse system. In the UK, the role and remit of NICE is fairly clear. In the U.S., much will depend on whether any HTA entity is estab-
lished primarily to serve the decision-making needs of the federal government (e.g., CMS), or a broader range of needs. However, whatever its governance and organization, it is important that any HTA entity is as independent as possible.

Secondly, in order to make the broadest impact, an HTA entity should consider all health technologies (not just drugs). Priorities for topics need to be set in an explicit manner and assessments should be rigorous and transparent, conducted in accordance with a clear set of methods guidelines.

Thirdly, any HTA entity should make strenuous efforts to involve major stakeholders in the development of methods guidance, the scoping of individual assessments and in commenting on the results of studies. Early and consistent involvement of technology manufacturers is particularly important, as they play a major role in conducting the studies on which the assessments are based. Ideally, assessments should be carried out by independent research groups, under the general direction of the HTA entity, and should be as transparent as is possible.

Fourthly, there needs to be a debate in the U.S. about the pros and cons of focusing the HTA effort on the conduct of additional large, long-term randomized controlled trials, versus investing more effort in improving the methods of evidence synthesis using available data. There also needs to be discussion of how the production of more evidence on health technologies is linked to decision-making, perhaps through a system of ‘conditional reimbursement’.

Fifthly, more discussion is required about the ways of incorporating economic factors in assessments, in order to provide relevant information for decision-makers in the U.S. context. A focus on clinical outcomes alone is inappropriate as it may exclude important advantages and disadvantages of health technologies, such as impacts on quality of life and savings in other healthcare resources. On the other hand, calculation of a single (incremental) cost-effectiveness ratio may not be very helpful, given the great diversity across the U.S. in health care budgets, practice patterns, and cost levels.

Finally, the most appropriate focus for an HTA entity in the U.S. is on undertaking high quality assessments (i.e., interpretation of the evidence), rather than appraisals (i.e., the production of guidance for decision-makers). The objective should be to produce high quality assessments that will enable various decision-makers to undertake an appraisal from their own perspective.
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