Clinical effectiveness and cost effectiveness of zanamivir (Relenza): translating the evidence into clinical practice, a National Institute for Clinical Excellence view

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The UK National Institute for Clinical Excellence (NICE) is charged with the duty of providing informed guidance on clinical practice (clinical effectiveness and cost effectiveness) to patients and health professionals. The Appraisal Committee through its process of review of evidence advises NICE on the clinical effectiveness and cost effectiveness of new and existing technologies and their appropriate use within the National Health Service in England and Wales. The appraisal process takes into account both published and unpublished evidence as well as input from professional and patient and carer groups when coming to its decisions. The appraisal of a new technology often has to bridge the gap between the evidence required for licensing purposes and that needed to provide pragmatic advice to practising clinicians. The appraisal of zanamivir (Relenza) is an excellent working example of this difficult and important process.

Keywords: influenza; zanamivir; National Institute for Clinical Excellence; appraisal; clinical; cost effectiveness

1. BACKGROUND

The UK National Institute for Clinical Excellence (NICE) was originally set up in order to address major issues that were identified in three government consultation papers: (i) *A First Class Service*; (ii) *Putting Patients First: Quality Care and Clinical Excellence*; and (iii) *Faster Access to Modern Treatment*. The main areas of concern identified were:

- (i) slow uptake of therapeutic innovations (technologies) of potentially great benefit to patients;
- (ii) different judgements taken in different parts of the country on the interpretation or significance of the evidence regarding a particular technology, resulting in variations in access for patients to the new treatments and the widespread perception of inequity;
- (iii) wasteful use of resources as treatments may be used outside the range of circumstances in which they are clinically cost-effective, at the expense of alternative uses of those resources which could give greater benefits to patients.

The objectives of NICE are principally to 'provide informed guidance on clinical practice (clinical effectiveness and cost effectiveness) to patients and health professionals'. This guidance should be based on the best evidence (e.g. from clinical trials) that is currently available but must also be informed by expert opinion from both specialist health-care professionals and patients and carers.

NICE's appraisal process which has been established to produce this guidance is summarized below. The process

takes into consideration the Secretary of State's directions to NICE to consider:

- (i) the broad clinical priorities for the National Health Service (NHS);
- (ii) the degree of clinical need of patients;
- (iii) the broad balance of benefits and costs;
- (iv) guidance on resources likely to be available;
- (v) effective use of available resources;
- (vi) the encouragement of innovation.

The evidence base that is required by the regulatory bodies for initial licensing of a new drug treatment (i.e. evidence of efficacy and toxicity) is different from that needed in making an appraisal of its clinical effectiveness and cost effectiveness in practice (table 1). This difference results in an 'evidence gap' that can often leave clinicians without pragmatic evidence on which to make therapeutic decisions in particular circumstances not currently covered by the published evidence.

The Department of Health (DoH) and the National Assembly for Wales (NAW) refer technologies to NICE for appraisal. The following considerations determine their topic selection:

- (i) Is the technology likely to result in a significant: health benefit, taken across the NHS as a whole, or impact on other health-related government policies, or impact substantially on NHS resources?
- (ii) Is NICE likely to add value by issuing national guidance?

Table 1. HTA: efficacy versus effectiveness.

(The different requirements of the evidence needed for licensing and appraisal of health technologies often leads to the development of an 'evidence gap', which may leave health-care professionals making day-to-day clinical decisions on the basis of inadequate evidence.)

efficacy (licensing)	effectiveness (appraisal)
explanatory trials	pragmatic trials
highly selected populations	few exclusions
comparator commonly placebo	comparator current (best) practice
outcomes, clinical endpoints of morbidity, mortality, adverse events 'what it says on the packet'	outcomes, patient focused, downstream resource implications the real-life effect

2. THE PROCESS

The process of a NICE appraisal is unique worldwide. It takes 8–12 months from initiation of a new request for appraisal to the final issuing of guidance to the NHS in England and Wales (figures 1 and 2).

For the appraisal process, an independent academic group conducts a systematic review of published evidence and the manufacturers' submissions. In addition the process involves, as consultees, the national bodies that represent health professionals, the national patient and carer organizations and the manufacturers of the technology.

Consultees also prepare submissions of evidence. They are consulted on the provisional determination and have an opportunity to appeal against the final determination. The professional and patient and carer organizations nominate experts to inform the process, who attend the initial meeting of the Appraisal Committee. The consultees in the zanamivir (Relenza) appraisal are listed in table 2.

3. THE QUESTION

The DoH and NAW asked NICE to 'provide guidance on the clinical effectiveness and cost effectiveness of the use of zanamivir in the treatment of influenza'.

This request was based on the recognition of the importance of influenza as a national health issue, but also the potential innovative importance of the neuraminidase inhibitors in both the treatment and prevention of influenza.

4. THE ISSUES TO BE CONSIDERED

During the appraisal five main issues regarding the clinical research evidence base for zanamivir and its use in the NHS were considered. These were derived from the assessment report, the consultees' submissions and the verbal and written reports provided by the experts nominated for the day from professional and patient and carer organizations.

- (i) Effects on the disease process. The health gain that may accrue from shortening an influenzal illness and

the relevance to both an individual and the community at large of a reduction of the acute phase of the illness by 1–2 days.

- (ii) Effects on complications. The potential overall health gain from reduction of secondary complications, particularly serious respiratory tract infection. In addition evidence of a reduction of overall mortality.
- (iii) Effects on primary care. General practice consultation rates were of particular relevance. The potential for an 'overwhelming' increase in consultation rates that may occur with unrestricted access to zanamivir and its inappropriate prescription to individuals unlikely to benefit (see point (v) in this list). In addition the use of community resources including district and practice nurses and social care were considered, with particular regard to the importance of influenzal illness in the elderly and in those in residential care.
- (iv) Effects on secondary care. Reduction in hospitalization rates and reduction in costs of treating complications of influenzal illness in secondary care have a major impact on the cost-effectiveness analysis. The potential for improved efficiency of usage of hospital beds during the winter period by avoiding admissions for complications of influenza is important when considering the overall use of health-care resources.
- (v) Targeting of specific treatment groups. Two subgroups were considered of particular importance:
 - (a) Treating high-risk (at-risk) patients—defined as those individuals who, as the result of their age or underlying medical condition, may experience a more prolonged and/or severe course of illness, or may suffer complications as the result of an influenza virus infection. This includes individuals with chronic respiratory disease (including chronic obstructive pulmonary disease and asthma) requiring regular medication, with significant cardiovascular disease (excluding individuals with hypertension), who are over the age of 65 years, who are immunocompromised, or who have diabetes mellitus. These are also the groups of patients who are currently recommended as priority targets for the national influenza immunization programme.
 - (b) Avoiding unnecessary therapy in those who are unlikely to benefit by treating preferentially individuals with true influenza versus those with 'influenza-like illness' (ILI). The method of identifying this target population is currently based on a combination of presentation with a characteristic clinical symptom complex in the presence of high levels of influenza virus 'circulating' in the community. The definition of when influenza is circulating is based on the results from regular 'on-going' audit of general practitioner consultations and the number of isolates of influenza virus identified by the Public Health Laboratory Service.

5. THE EVIDENCE

Eleven placebo-controlled randomized trials were identified of the use of zanamivir at the licensed inhaled dose,

Figure 1. The NICE model of HTA comprises two stages. The first is 'assessment' of the evidence base, both published and unpublished, usually provided by an externally commissioned academic group. The second 'appraisal' incorporates a series of inputs from clinical experts, health-care professionals and patient groups during which guidance is formulated and uniquely, worldwide, feeds directly into national policy making and the provision of advice to the NHS in England and Wales.

Figure 2. The NICE appraisal process. The appraisal process takes approximately 12 months from the initiation of a request to appraise a technology from the DoH and NAW to final production of guidance for the NHS. This includes a consultation period with interested parties on both the provisional and final appraisal determinations. The appraisal process was reviewed and updated in February 2001. The revised process is available on NICE's Web site (www.nice.org.uk). Revisions include the real-time publishing of provisional and final determinations on the Web site. AD = appraisal determination.

involving more than 3000 individuals drawn from Europe, North America, the southern hemisphere and Japan. Subgroup analysis was derived from an evidence base for at-risk adults (some 800 individuals). This was based on subgroup analysis of individuals in nine all-adult trials.

The importance of rapid and accurate diagnosis and the early initiation of therapy (within 48 h of the onset of symptoms) were highlighted.

On average, the duration of symptoms was reduced by 1–2 days in all treated patients and this was similar in the overall pooled analysis of 'at-risk' individuals. Evidence on the time taken to return to normal activities and reduction in complications was less robust.

Evidence of an effect on overall mortality or reduction in hospitalizations was either not significant or absent.

The importance of surrogate endpoints, in particular the prescription of antibiotics in the 'at-risk' group was

Table 2. Consultees during the zanamivir (Relenza) appraisal.

(Consultees prepare submissions of evidence, are consulted on the provisional determination and have an opportunity to appeal the final determination (note there were no appeals during this appraisal). The professional and patient and carer organizations also nominate experts to inform the process and attend the Appraisal Committee meeting.)

British Medical Association
 British Geriatrics Society
 British Lung Foundation
 British Society for Antimicrobial Chemotherapy
 British Thoracic Society
 Faculty of Public Health Medicine
 National Asthma Campaign
 Public Health Laboratory Service
 Royal College of General Practitioners
 Royal College of Paediatrics and Child Health
 GlaxoWellcome UK

considered very carefully. Thus in the clinical trial population as a whole, respiratory events during an episode of ILI requiring antibiotics were significantly reduced by approximately 28% in those taking zanamivir compared with placebo. The analysis of the 'at-risk' group was underpowered and did not show a statistically significant effect. However, the reduction in complications requiring antibiotics was consistent with that seen in the total adult population and was considered by the review team and the Appraisal Committee to be a true effect.

Cost-effectiveness models for the use of zanamivir in the UK were reviewed cautiously. The model used considered the clinical effectiveness estimates outlined above, the costs of additional consultations with general practitioners and the costs of hospitalization. The models also incorporated realistic assumptions about the proportion of those who might, in practice, be prescribed zanamivir, who would actually have influenza A or B and hence who would be most likely to benefit. The results of this analysis demonstrated:

- (i) an incremental cost per quality adjusted life year (cost/QALY) of £38 000 for all adults when influenza is circulating;
- (ii) an incremental cost/QALY of £9300 to £31500 for at-risk adults when influenza is circulating.

6. THE GUIDANCE

On the basis of the Appraisal Committee's recommendations, NICE's guidance to the NHS in England and Wales was that listed here.

- (i) For otherwise healthy adults with influenza the use of zanamivir is not recommended.
- (ii) Zanamivir is recommended, when influenza is circulating in the community, for the treatment of at-risk adults who present within 36 h of the onset of ILI and who are able to commence treatment within 48 h of the onset of these symptoms.

- (iii) Based on the evidence from clinical trials, at-risk adults are individuals falling into one or more of the following categories:

- age 65 years or over;
- chronic respiratory disease (including chronic obstructive pulmonary disease) requiring regular medication;
- significant cardiovascular disease (excluding hypertension);
- immunocompromised;
- diabetes mellitus.

- (iii) Community-based virological surveillance schemes should be used to indicate when influenza is circulating in the community.
- (iv) The guidance does not cover the circumstances of a pandemic or a widespread epidemic of a new strain of influenza to which there is little or no community resistance.
- (vi) Effective targeting of zanamivir for the at-risk adult population with a high incidence of true influenza is essential to maximize both the clinical effectiveness and cost effectiveness of this therapy.

Implicit in this guidance was the recognition of the paramount importance of the national immunization programme, which should be the first line of defence against influenza for at-risk patients. In particular, at-risk groups are recommended to be immunized against influenza before every winter.

7. FUTURE RESEARCH

An important aspect of the appraisals process is both the identification of the 'evidence gap' (previously referred to in § 1) and indicating ways in which this may be filled by appropriate future research. In the case of zanamivir several areas of continuing uncertainty were discussed by the Appraisal Committee and suggested as topics for future research in the final guidance.

The absence of hard data on major 'relevant' endpoints, e.g. overall mortality, serious complications and the need for hospitalization, was of particular concern. The need for randomized control trial (RCT) evidence in this area was therefore highlighted in the guidance to the NHS. The difficulties involved in producing this evidence were also recognized in that a study of sufficient power to produce a significant result would take some time, probably requiring several influenza seasons to complete, and might need to be set up on an international basis.

In addition, and as a minimum requirement, it was suggested that prospective clinical audit programmes should routinely record the number of at-risk individuals with ILI symptoms who present in primary care and are treated with zanamivir, and what proportion of these are influenza-positive. Such audit programmes should also enable the collection of data relevant to the endpoints of the need for hospitalization and overall mortality, which would supplement the requirements for an RCT although not completely replace them.

Other areas of potential future research discussed included:

- (i) comparisons of zanamivir with alternative treatments, e.g. amantadine and other neuraminidase inhibitors;
- (ii) the use of alternative delivery systems, i.e. oral versus inhaled formulations;
- (iii) the prospect for prophylactic use of these drugs;
- (iv) the feasibility and importance of near patient testing for 'true' influenza as a means of more effectively targeting treatment.

8. DISCUSSION

Although health-technology assessment (HTA) is undertaken in many countries, NICE's appraisal process is unique worldwide for a number of reasons including:

- (i) transparency of objectives, process and documentation;
- (ii) consultation with stakeholders from a wide variety of interested parties including industry sponsors, professional groups and patients and carers;
- (iii) direct feed of the output of the appraisals process into policy making in health care;
- (iv) independence of the advisory committee from both the NICE executive and 'political' influence;
- (v) formulating guidance on the basis of a balance of both clinical benefits and cost effectiveness.

The time-scale of the appraisals process is short enough to ensure that the guidance produced is pertinent and relevant to current clinical practice, but long enough to allow detailed and wide-ranging consultation. In addition, all guidance is issued with a 'shelf-life', which ensures that NICE will revisit the appraisal within a predetermined time-scale. This is usually 12 or 36 months, depending on the likelihood of the availability of new evidence on the technology or the emergence of competing or complementary therapies that may influence the guidance as initially issued.

The differences between the evidence required for the licensing of a new technology, particularly a pharmaceutical, and that which is needed to determine its clinical effectiveness and cost effectiveness in everyday practice is often significant. The appraisal of zanamivir has been an important example of that 'evidence gap' and the need for the production of guidance to health-care professionals which is pragmatic and current in that situation.

Further information on the appraisal of zanamivir and of NICE's work in general is available on the Web site www.nice.org.