The following recommendation was made by the Clinical Recommendations Committee (CRC), at the meeting held on 10 December 2009.

Recommendation 16/09: In the absence of other specific NICE or SMC guidance, the DHSS will make decisions on the use of any new orphan or ultra orphan drug/intervention following the principles and processes that are in place through the CRC.

Approved by the Minister on 17 February 2010.

POLICY:

Orphan Drugs

Introduction

1. Prevalence and characteristics of orphan diseases in Europe

Estimates of the number of rare diseases vary, but the European Agency for the Evaluation of Medicinal Products (EMEA) estimates that between 5000 and 8000 distinct rare diseases may exist, and states that five new diseases are described every week in the medical literature. The number of identified rare diseases is increasing, "an apparent conundrum that is explained by our increasing understanding of the underlying patho-physiological mechanisms, resulting in the separation of broad disease categories into smaller and more well-defined disease entities".

The Orphanet report: *Prevalence of rare diseases. A bibliographic survey, February 2008* notes that the exact prevalence of many diseases is difficult to assess and estimates should be regarded as indicative rather than definitive. Figures for some 1700 diseases are presented, but prevalence rates (per 100,000) are estimated for only about 520 of these. The remainder are described in terms of the number of published cases or families affected, reflecting their extreme rarity.

A prevalence of less than 1 in 50,000 is commonly used to distinguish between rare and very rare diseases in the UK. The term ultra-orphan disease (nominally less than 1 in 50,000) is not defined in legislation, but is used by the National Institute for Health and Clinical Excellence (NICE) to categorise diseases affecting a total of <1000 people in England and Wales.

Only about 270 of the diseases for which prevalence rates are presented in the Orphanet report have prevalence above the 1 in 50,000 level and so may be described as orphan diseases. The remainder may be termed ultra-orphan diseases, and most of these are extremely rare.

Some 80% of rare diseases have identified genetic origins. Symptoms of some rare diseases may appear at birth or during childhood, or during adulthood. All paediatric cancers and most congenital malformations are classed as rare diseases. The table below summarises the number of drug designations by therapeutic area:

Therapeutic area	Number	Percent
Solid tumours	106	24
Oncohaematology	79	18
Neurology	31	7
Transplantation	26	6
Inflammation	24	5
Infectious diseases	23	5
Cystic fibrosis	22	5
Respiratory	19	4
Cardiovascular	18	4

From the Table above it is evident that there is a resource risk if a clear policy is not in place for Orphan drugs.

Some of the very high cost orphan drugs (used to treat Orphan diseases) have been creating ethical problems for the funders of healthcare and challenging prioritisation processes across Europe. This paper and proposed policy is about using a carefully structured approach so as to support a local commissioning decision on expensive orphan drugs for rare conditions. It is also about the politics of following through a rational process for a drug that appears to work but is clearly not cost effective. Are there any special criteria to justify funding? If not, can a reasonable process that resists legal challenge be followed? What are the vested interests and pressures? The high costs of these drugs have posed practical funding dilemmas for some UK NHS Trusts e.g. one course of drugs for Nocturnal Hemoglobinuria can cost over £250 000 per annum.

The introduction of new, high price treatments such as orphan drugs inevitably focuses everyone's attention on the resource pressures they may create. The need for rationing may now be widely accepted but the way this should be done is the subject of heated debate. The number of high-cost treatments and increasingly vocal interest groups makes the task of allocating resources one of the most politically sensitive and complex issues facing any part of the DHSS.

A report from a recent international workshop on "the reality of orphan medicines" characterised the present climate as: "distinguished by hope, fear and frustration. Hope for rare disease sufferers and their families who see scientific breakthroughs with the potential to alleviate severe, life-threatening and chronically disabling diseases. Fear on the part of those responsible for commissioning new treatments who are anxious about the pressures of a proliferation of high price drugs on their already constrained budgets. Frustration for patients, researchers and companies, for whom policy contradictions and delayed decisions hold up the development and availability of new treatments".

2. Scope of policy

The draft policy focuses on the criteria that should be used when considering the commissioning of a new orphan drug by the DHSS.

3. Orphan drugs

3.1 Definition

European Union legislation defines an orphan drug as one that could treat a disease with a prevalence of less than five per 10,000 of the population (i.e. less than 40 cases on the Isle of Man). This approximated to a maximum of 185,000 cases across the then 15 member states of the European Community. Many orphan drugs are given marketing authorisation by the European Medicines Evaluation Authority (EMEA), which then allows them to be marketed across the EU countries. This definition includes tropical diseases uncommon in Europe but widespread in other parts of the world.

3.2 Background

EU orphan drug legislation was enacted in 1999 so as to encourage pharmaceutical companies to develop new drugs for diseases with small numbers of patients. In return for investing in specific new drugs companies could undertake research trials with a lower level of outcomes, have support from the EMEA and any such new drugs would have an extended patent life.

3.3 The importance of the natural history of the disease

To understand fully the role and impact of a new treatment it is important to understand the natural history of the disease. Research on some of the rare diseases is lacking probably because of the small numbers of patients and the lack of effective treatments. Many genetic diseases, such as the Lysosomal Storage Disorders (LSDs), are genuinely uncommon and there is a lack of knowledge of the natural course of these diseases. Typically with a disease such as one of the LSDs a patient with the serious form would develop increasingly severe symptoms in mid-life and possibly die 10 years later. However, not all patients with the missing gene develop the disease or a severe form of it. Without fully understanding the natural history it is difficult to understand the long-term outcomes of a new treatment such as Enzyme Replacement Therapy (ERT) for LSD.

3.4 The use of surrogate markers in research

When pharmaceutical companies have researched these orphan drugs, the trials have produced a limited evidence base, mostly using surrogate or substitute markers such as biochemical tests rather than clear patient or clinical benefits such as increased survival. There are often uncertainties around the links between improving the results of surrogate markers (a biomarker intended to substitute for a clinical endpoint that may not be measurable or desirable e.g. death from CHD, instead we use cholesterol level as an endpoint or the use of CD4 as a measure for severity of HIV infection instead of death) and whether survival or the quality of life is changed over the long term. This uncertainty is reflected by a special statement from the Scottish Medicines Consortium (SMC) on orphan drugs that refers to the uncertainties in the available evidence.

4. Current issues in funding orphan drugs

4.1 Drug pricing and opportunity costs

As a means of assessing funding priorities for drugs (and services) it has become increasingly common to evaluate drugs using a combination of the clinical effectiveness, the side effects and cost effectiveness. All of these criteria for evaluation are inter-related and are important areas that would contribute to a formal HTA if one is commissioned. Cost effectiveness provides a technical way of looking at the opportunity costs if one treatment is to be seen as a priority over another. Typically the cost per QALY (Quality Adjusted Life Year) is used by health economists. Although not a perfect tool and subject to ongoing debate it does allow comparisons to be made. NICE tends to recommend treatments for funding in the NHS if they are below £20,000 per QALY, although in special circumstances NICE may recommend treatments at levels up to £30,000 per QALY. With some of the orphan drugs costing £250,000 per patient per year the cost per QALY has been estimated at levels between £200,000 to over £1 million per QALY. An alternative way of thinking about the opportunity costs is to directly compare what is already funded e.g. for £250 000 10-12 renal dialysis patients could be funded and we know exactly what benefits those patients would achieve in terms of increased survival and improved quality of life.

4.2 Variation in commissioning policies

Normally the National Institute for Health and Clinical Excellence (NICE) would be asked to look at important new drug developments and evaluate their use in the NHS. In producing guidance NICE would commission an HTA as a basis for further consideration of the drug or service. NICE has evaluated several technologies with orphan drug designation and has approved some and judged others to be cost effective but it has not considered those orphan drugs considered to be very high cost.

NICE has submitted an “informal paper” to the Department of Health (DH) regarding the appraisal of orphan drugs (2006). It redefines an additional group as “ultra-orphan” drugs for very rare diseases (even less than 5 per 10 000 population) and which have very high costs. The DH UK is reported as not having responded to this informal paper. However, at present, the DH selection criteria for the referral of topics to NICE specifically exclude ultra-orphan diseases. Therefore these very expensive orphan drugs will not have a NICE assessment to produce guidance for the NHS in spite of the possibility that the annual costs to UK NHS for one drug might range from £30 million upwards or exceeding £250 000 per annum per patient.

A NICE orphan drug paper makes some assumptions and generalisations to suggest that other criteria may be appropriate to commission orphan and ultra orphan drugs. These criteria are not well defined and seem to focus around the severity of the diseases. This would appear to be a variation of what has been called the “rule of rescue” and not necessarily appropriate for commissioning across a wider population where any opportunity costs are likely to apply to other patients with severe diseases. The “rule of rescue” is a term that is used to suggest that patients who are more easily identifiable are more likely to receive treatment as a result of a more sympathetic and emotive response from health professionals, the media, the public and politicians. The Scottish Medicines Consortium (SMC – in some ways comparable to NICE) usually evaluates orphan drugs as they are licensed and applies comparable commissioning criteria to that used for other new drugs. Consequently many of these, such as some of the Enzyme Replacement Therapies (ERT) for treating Storage disorders, are not being funded in Scotland whilst in England, where NICE has not been given any orphan drugs of this type to appraise, all the

ERTs have been funded. Wales ha also adopted its own approach to dealing with these expensive drugs via the All Wales Medicines Strategy Group.

5. Prioritisation and a decision making framework

The DHSS has a statutory responsibility to provide healthcare and to remain within its designated budget. It is acknowledged that not all new technological developments can be funded within this budget and so it is necessary to have a process for determining the priorities for funding. To help ensure that any process is fair and reasonable it is necessary to have a decision making framework that will cover ethical considerations and the criteria by which a technology might be assessed – the CRC is part of this framework on the Isle of Man.

5.1 Commissioning criteria

The starting point is the information used to assess a new treatment and an HTA, if merited, will provide an objective overview of this information. This is expected to cover clinical effectiveness, safety and cost effectiveness. Cost effectiveness gives a comparative tool for consideration of the opportunity costs. At CRC we broadly follow the QALY/ICER (Incremental Cost Effectiveness Ratio) system used by NICE for valuing the clinical and cost effectiveness of interventions. However, in adopting funding policies for particular drugs or interventions, CRC may deviate from the NICE financial limits where there are good reasons to do so e.g. local financial constraints. Any new orphan drug should be capable of being evaluated using the same criteria as are used for other new drugs. Using comparable criteria to other new technologies will allow relative priority to be determined. In this way new orphan drugs can be considered to be the same as any other new technology. Other points that might merit special consideration are addressed later in Appendix 1.

5.2 Ethical principles

Broadly four principles can be considered, if needed, when making a decision. These are particularly helpful when there is potential conflict between different priorities. Beneficence – ensure that there is some benefit; non-maleficence – do no harm; autonomy – patient involvement in any clinical decision; distributive justice – considering the wider public good. These aspects are considered within NICE's *Social Value Judgements*.

6. Clinical Trials

The DHSS should not have to pick up the funding of patients who are finishing pharmaceutical company sponsored drug trials or the costs for "compassionate funding" unless prior arrangements have been made. It should be seen as the responsibility of those initiating therapy to ensure that there is either an exit strategy or that ongoing treatment is provided.

Orphan drugs are high cost interventions which the DHSS will be required to consider from time to time. The DHSS (through CRC) should broadly follow the QALY system, recommended by NICE and most other medicine evaluation agencies, for valuing the clinical and cost effectiveness of interventions but, in adopting funding policies for particular interventions, it may deviate from NICE strict financial limits where there are compelling reasons to do so e.g. local politics or resource constraints. However the CRC does not have to accept that additional DHSS investment is necessarily justified simply because a medical condition is rare or serious. An approach which approves differential investment for those with rare conditions would place a value on the lives of patients with rare conditions which is higher than those with more common conditions, and this would not be fair. The DHSS and CRC should recognise that, from time to time, they will have to

consider very high cost interventions. The DHSS may conclude that the intervention is not cost effective even if the intervention were clinically effective to save or extend the lives of patients e.g. as we have already done for some new cancer drugs. The usual condition for the CRC is that where a decision is made that an intervention is not to be routinely funded, the CRC will consider exceptional cases where funding may be provided. If the CRC is faced with an intervention (drug or service) which it considers is not ever likely to be cost effective because it would require investment which is significantly greater than the QALY system recommended by NICE, the CRC should be entitled to classify the intervention as one where it will not normally consider individual exceptions to the policy i.e. low priority or "no funding". The DHSS and CRC does not wish to raise expectations of patients and their families by a referral to the Exceptions Committee if, whatever the individual clinical or social circumstances of the patient, an investment at that level e.g. QALY of £250 000 for an individual patient cannot be justified. In some circumstances the CRC should still be prepared to consider individual cases if the anticipated cost for that individual would be significantly less than the anticipated cost for other patients with the same diagnosis who could benefit from the same treatment. The CRC should also keep the general funding policy for such an intervention under review and be prepared to reconsider the CRC`s overall policy with respect to the intervention if an application were made for funding for an individual patient.

Summary

This is a support paper outlining why the DHSS, Isle of Man should consider that new orphan drugs should be assessed in a comparable way to other new drug treatments and healthcare technologies. This will allow the prioritisation for funding of new treatments in a fair and reasonable way that is understandable and allows public scrutiny.

APPENDIX 1

Special considerations:

1. Rarity

The rarity of a disease is not considered to be grounds for allowing any available new treatments to be assessed differently to any other new treatments. There are debates around whether orphan drugs constitute special cases for commissioning but it is difficult to understand why rarity alone might mean that funding is weighted towards the orphan disease treatments. To argue that rarity is a valuable criterion in its own right would seem to put it in the category of the "rule of rescue". This term implies that people find it difficult to refuse funding of treatments because they can more easily identify the patients and identifying with the patients as opposed to weighing up the opportunity costs for other patients who are not so readily identifiable. In many cases the values and judgements behind the rule of rescue can become mixed up with media and political pressures. This has sometimes embarrassed UK NHS Managers into agreeing funding that is not consistent with the normal processes of evaluation or prioritisation. In my opinion, there are no clear or apparent reasons why rarity alone should alter the assessment of the clinical and cost effectiveness of a new treatment and its subsequent prioritisation against other new treatments.

2. Severity

The severity of a disease is not considered to be grounds for permitting any available new treatments for that disease to be assessed differently to any other new treatments for other severe diseases. In some cases, such as within NICE's Citizen's Council, it has been argued that severity as a part of a rare disease is important. However, it is clear from a knowledge of prioritisation decisions in the UK NHS, NICE, SMC and in other national evaluation agencies that treatments for patients with severe diseases may, or may not, be funded depending on the assessment of the clinical and cost effectiveness. Hence treatments for severe diseases should be assessed with comparable criteria and using a clear decision making framework. Funding decisions should not be swayed by an emotional reference to severity or rarity because that will ignore opportunity costs for other groups within a population and this will lead to unfair decision-making processes.

3. Geographical variation in funding

Statutory organisations with funding responsibilities need to make their own assessments of new treatments based on considerations of the evidence and a knowledge of the available local resources. Some variation in funding decisions is inevitable as different populations have different healthcare needs and different financial allocation systems. Hence it is highly likely that there will be variation among the priorities of different healthcare commissioners in different areas of the UK. The "Postcode lottery" will always exist unless strict control is exercised by a central unit in Government and this will not happen while such organisations as NHS PCTs and Scottish Boards are responsible and accountable for their own budget allocations. There are often legitimate reasons for so called "post code" lotteries but the way it is portrayed by the media and patient interest groups makes it an emotive topic.

4. "Rule of rescue"

The ability to identify patients or specific groups with a disease (usually rare and severe) who might benefit from any available new treatment should not be considered to be grounds for permitting any available new treatments to be assessed differently to any other new treatments. Using clinical and cost effectiveness criteria to assess new treatments will allow the prioritisation of these treatments in a fair and reasonable manner so that opportunity costs are able to be considered in a balanced objective way. The literature on orphan drugs and treatment of rare diseases makes a number of references to the rule of rescue. It is sometimes advanced as part of the counter arguments to a perceived over-dependence on economic evaluation.

The West Midlands NHS commissioned a report on the ethical issues of distributive justice and resource allocation, with specific reference to the provision of Enzyme Replacement Therapy (ERT). The author, Dr Sheehan, describes the purpose of his report as "to critically examine the various moral pressures that pull or push in resource allocation decisions". A substantial portion of it considered the 'rule of rescue'.

Dr Sheehan describes the rule of rescue as a "general empirical fact" describing a human tendency to respond compassionately and without reference to direct or opportunity costs when the lives of identified individuals are in danger. He concludes that it is descriptive not prescriptive, and states: "the Rule of Rescue is not to be understood as a moral principle ...", and "It is a mistake to speak of the Rule of Rescue as an imperative ...", that is a rule that *ought* to be followed.

Some contributors to the report dismiss the rule of rescue entirely e.g. "The debate around orphan drugs must recognize that the 'rule of rescue' is not in fact a rule, but rather a concept that explains the observed instinctive emotional reactions of individuals to tragic

events or circumstances. The process of putting a name to the sentiment and showing that it is prevalent, does not make it a valid basis for policy."

NICE have advised that "considerable care" should be taken when applying the rule of rescue, which they describe as "an understandable human impulse …" with "some broad public support".

5. Equity with other expensive treatment funding decisions

It is expected that the NHS will offer "standard care" for any patient with a disease whether or not a new treatment is funded. The NHS position, when a new treatment is not funded, is sometimes perceived by outsiders as being that there is no treatment at all available for that patient. This is not the case and the NHS will always be expected to offer reasonable care to a patient.

The argument that new high cost treatments should be funded because other high cost treatments have been funded in the past is not a fair one. Other high cost treatments that have been previously funded have not had a decision making process similar to the one agreed by the DHSS in 2008 and the precedents should not, therefore, be regarded as appropriate for new treatments in the future. It is important to ensure consistency of future decisions about expensive drugs or services.

6. Orphan drugs challenge ethics

The treatment of rare diseases draws attention to the lack of agreement about the ethical principles that should underlie resource allocation. Decisions demanding complicated trade-offs between benefits, risks, direct and opportunity costs, always involve judgement and these judgements invoke theories of distributive justice either explicitly or implicitly.

Some will argue that restricting the availability of orphan drugs means that patients who have a rare condition risk being left untreated. However, the opportunity cost of funding expensive orphan drugs is that a far greater number of patients with a more prevalent (common) disease are denied treatments that are more cost effective. This contraposition raises important questions on equity, and goes to the heart of what is considered to be socially just.

Rare diseases will not fare well under utilitarian approaches – minorities are side-lined if the aim is the greatest good for the greatest number – and the high price of orphan drugs means they are unlikely to be able to 'jump the cost-effectiveness hurdle'.

This makes some people uncomfortable. It looks as though the distribution that is given by the cost-effectiveness/QALY approach is not just, as we would ordinarily think of justice or fairness. The utilitarian approach could be deemed to be out of step with the belief that caring and equity are important.

In recent years there has been increasing recognition that moral theory provides a framework for thinking about resource allocation but does not prescribe action. More attention is now paid to the importance of political procedure, recognising that the way that decisions are made is very important to their democratic acceptability. The concept of 'accountability for reasonableness' argues that, in the absence of consensus about ethical principles, priority setting is legitimate if it is generally agreed that the procedure is fair. This is in tune with calls for public bodies to be accountable for their actions, to be open about their decisions and decision-making processes, to be consistent in their approach, and to avoid discrimination.

7. Orphan drugs at the intersection of several problem areas

It is probably not helpful to think of "an orphan drug problem". Instead, the issue of orphan drugs may be regarded as occupying the intersection of a number of other, potentially problematic, areas. These are:

- A growing demand for priority setting in general, and the management of new treatments in particular, to be governed by explicit principles, process and criteria for decision-making.
- Difficulties with the methodology and criteria for assessment of high price treatments, be it an orphan drug, a new transplant technique, or a medical physics innovation.
- Management of patients entering into and coming off clinical trials.
- Response to lobbying, challenges to decisions, and sophisticated use of the media to influence policy.

None of these problems is unique to orphan drugs, or the treatment of rare diseases, but the resolution of problems in these areas generally would dispose of the perceived 'orphan drugs problem'.

Policy Proposal:

In the absence of other specific NICE or SMC guidance, the DHSS will make decisions on the funding of any new orphan or ultra orphan drug in the same way and using the same principles and processes as are used to decide on any other new drug or technology or intervention i.e. CRC process.

The DHSS (CRC) will require orphan and ultra orphan drugs to satisfy assessments such as safety and clinical and cost effectiveness, just as these are required of treatments or interventions for more common conditions. This is in line with an ethical commissioning framework that supports consistent decision making across different areas of health care. In this way the residents of the Isle of Man can be sure of fair and reasonable decisions being made on their behalf.

The DHSS will not fund drugs with little proof of clinical effectiveness nor with cost effectiveness estimates that are significantly different to the commonly accepted NICE QALY thresholds that are considered to be an appropriate use of NHS resources.

As is the case with other treatments and interventions that are not routinely offered, in the case of orphan or ultra orphan drugs that the DHSS decides are a low priority for funding, the DHSS will give careful consideration to any application for the use of such a drug arising from the exceptional circumstances of an individual patient.

Dr P Emerson
CRC December 2009

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