Social Values and Health Priority Setting Case Study

Title of Case Study	**Mifamurtide for the treatment of osteosarcoma in the UK**
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Case Summary (approx. 350 words) Please include information here about why the case is of particular interest	Some medical interventions, particularly those that benefit the young, provide benefits over a long period of time. When appraising such interventions, the practice of NICE in the UK is to discount their costs and benefits. One such example is mifamurtide. Mifamurtide is a medicine that can be used in conjunction with other medicines in the treatment of osteosarcoma. Although osteosarcoma is the most common form of bone cancer, it is nonetheless a rare condition, with only around 150 new cases per year being reported. It particularly affects the young. NICE appraised mifamurtide in 2010 (NICE, 2010). The appraisal concluded that mifamurtide was clinically effective when used with other medicines, raising survival rates in those treated with the drug after 7.9 years to 78% from 71% in the control group. However, the NICE appraisal concluded that, although mifamurtide was clinically effective, it was not cost-effective as measured by the ratio of benefits to costs. Because the majority of treatment costs are incurred in the first year, whereas the benefits are added to an already potentially long (around 60 years) survival time, estimating the ratio of incremental benefits and costs is affected by the discount rate applied to the benefits. For example, if there is no discounting, the ICER value is approximately £24,371, whereas if the costs and benefits are discounted at the currently standard rate of 3.5%, the ICER value is £56,606. Such sensitivity to the application of discounting to health outcomes raises difficult issues of ethics and social values and is therefore of particular interest in this respect.
1. Facts of the case Please include information on as many of the following as are relevant to the case: • At what condition is the intervention, program or service aimed? • What are its effects? Eg. Is it curative, preventative, palliative, life-prolonging, rehabilitative? • Is there a relevant comparator? If so how does this intervention, service or program compare to the alternative? Include ICER estimates/QALY costs if relevant. • What are the significant features about the condition and/or about the patient	**Facts of the case** • Mifamurtide is a treatment for bone cancer (non-metastatic osteosarcoma). It is authorised for use in 'children, adolescents and young adults for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection' (NICE, 2011). It is used in conjunction with multi-agent chemotherapy treatments. • The clinical and cost effectiveness of mifmurtide was assessed in comparison to the existing regime of multi-agent chemotherapy alone. • Mifamurtide increases survival rates and length of survival: 78% of those treated with Mifamurtide survived past 7.9 years in comparison to 71% of the control group. • Two features of the treatment are significant: 1) Mifamurtide allows 7% of patients to survive longer than 7.9 years, when otherwise they would not survive; 2) past 7.9 years, the survival period for those treated with the drug is long - around 60 years - so its benefits stretch into the future. • The patient population is predominantly young - up to 30 years of age. • Although osteosarcoma is the most common form of bone cancer, it is nonetheless a rare condition, with only 150 new cases per year. • Benefits of the intervention are consistent across the patient population. • The ICER of the intervention was calculated initially to be £56,700 per QALY, using a

population in this case? Eg. patient population is very young, very old, condition is rare, life-threatening, life-limiting etc. • How are the benefits of the intervention distributed across the patient population and/or across time? • What is the cost or budget impact of the intervention/service/ programme? • What is the nature and strength of the evidence about the outcomes of the intervention, service or programme? Eg. randomized clinical trials, evidence on patient-related outcomes. • How did the issue about this case arise - for example, from clinical practice, from a policy setting, from a topic selection process?	discount rate of 3.5% for both costs and benefits. These discount rates were considered by NICE Appraisal Committee and it was suggested that this case met special conditions in NICE's 'Guide to the methods of technology appraisal' whereby a discount rate of 1.5% for health benefits could be used (NICE, 2011a). This reduced the cost per QALY of Mifamurtide to £36,000. This adjustment in the discount rate for health benefits was significant in the final decision to approve the intervention.
2. Policy decision: process Please include information on as many of the following as are relevant to this case: • What stages/institutions were involved in the decision making process? • Is legal context important in this case? If so, in what way? • Who was involved? Eg. key stakeholders, the public, professionals, industry, patients, governmental or non-government policy actors. • How were they involved, and at what stages of the process? • Was there disagreement between any of the parties involved in the decision process? • Do any rules or frameworks exist to guide decision making? If so, were they followed in this instance? • Do mechanisms exist for challenging the decision at any stage of the process? • How, if at all, is the decision process or the decision itself publicized?	**Policy decision: process** The case of Mifamurtide was considered by the UK National Institute for Health and Clinical Excellence (NICE), according to the rules of its Single Technology Appraisal process. The process was as follows in this case: • Evidence on Mifamurtide was obtained by NICE from the drug's manufacturer, Takeda UK. • This evidence was critically reviewed by an independent Evidence Review Group (ERG) (in this case, the School of Health and Related Research, University of Sheffield). • NICE invited clinical specialists, NHS commissioning experts and patient experts to attend Appraisal Committee meetings to consider the intervention, and to provide their views in writing. Details of all stakeholders invited to attend meetings were made available on the NICE website. • The Appraisal Committee met to consider the evidence for the intervention - the meeting was open to the public and the press (NICE publishes a notice of the meeting and a draft agenda on its website 20 days before the meeting date). • Patient experts at the appraisal committee meeting stated that diagnosing and treating osteosarcoma has a significant impact on patients and their families and friends. This includes disruption of family life, strain on family relationships, additional stress at work and financial pressures, and a negative effect on the health of families, friends and carers. The patient experts and clinical specialists stated that there had been few developments that had improved treatment outcomes for osteosarcoma over the past 20 years, and that any improvement in overall survival from adding mifamurtide to standard chemotherapy was clinically significant and important. • An appraisal consultation document summarising the evidence and views that were considered by the Appraisal Committee and its provisional recommendations were published for public consultation. • The Appraisal Committee finally decided to approve the intervention for its licensed indication as a treatment for osteosarcoma. The Final Appraisal Document containing the Committee's decision was sent to relevant stakeholders, offering them the opportunity to

	appeal. • No appeal was raised, so the Final Appraisal Document was published on the NICE website in October 2011.
3. Policy decision: content	**Policy decision: content**
Please include information on as many of the following as are relevant to this case: • What decision was made about the intervention, service or program, if any? • What values were relevant in the case or in the decision itself? For example, values of cost-effectiveness, clinical effectiveness, justice/equity, solidarity or autonomy. How did they affect the decision itself? • Was the way in which these values were balanced affected by any specific features of the case? For example, end of life considerations, age of patients, impact on carers, disease severity, innovative nature of the intervention, social stigma or cultural sensitivity? • Did the case challenge established guidance or 'decision rules'? Eg. on cost-effectiveness, cost thresholds, age discrimination etc. If so, in what way? • Were any health system-wide considerations influential in the decision? For example, displacement of old technologies, professional practice issues, or infrastructure/feasibility considerations.	• The intervention was approved. The main considerations taken into account were as follows: • *Clinical effectiveness* Based on data from randomized controlled trials, the NICE Appraisal Committee concluded that a regime of postoperative multi-agent chemotherapy *plus* Mifamurtide may be more clinically effective than postoperative multi-agent chemotherapy alone. There was uncertainty around the size of Mifamurtide's effect, particularly in the context of the standard treatment regimen used in the NHS, but on the balance of all the evidence NICE concluded that Mifamurtide represented a clinically effective therapy (NICE, 2011b) • *Cost effectiveness* The ICER of Mifamurtide was initially estimated at £56,700 per QALY gained, including a patient access scheme which made the drug available for free for a certain number of treatments. This figure was arrived at using a 3.5% discount rate for costs and benefits which is standard in all UK public accounting (see Discussion section below for further details). £56,700 per QALY is considerably higher than the £30,000 per QALY threshold that NICE unofficially operates, and would therefore be likely to be rejected on the basis of the rules on cost-effective ratios usually operated by NICE. One of the reasons for this apparently high cost was the rate at which the benefits of the intervention were discounted because they occur in the future (see discussion section and references, below, for further details). In short, the higher the discount rate, the more expensive a treatment will appear if its benefits occur largely in the future. This case challenged the £30,000 threshold usually employed by NICE. However, the NICE Appraisal Committee recognized the impact of the 3.5% discount rate for the health benefits of Mifamurtide on its high ICER ratio and suggested a clarification to the 'Guide to the methods of technology appraisal' issued by the Board of NICE, as follows: 'where the Appraisal Committee has considered it appropriate to undertake sensitivity analysis on the effects of discounting because treatment effects are both substantial in restoring health and sustained over a very long period (normally at least 30 years), the Committee should apply a rate of 1.5% for health effects and 3.5% for costs' (NICE, 2011b). The Committee discussed whether these criteria were met in the case of mifamurtide. It noted that mifamurtide is a treatment with curative intent that increased the overall survival from 71% to 78% compared with chemotherapy alone in the whole trial. It also noted that patients who are cured are expected to have a long and sustained benefit and regain normal life expectancy. The Committee concluded that both criteria were met and a discount rate of 1.5% should be used for health effects. This resulted in a manufacturer's best-case probabilistic ICER of £36,000 per QALY gained (NICE, 2011b). • *Innovation and disease rarity* The Committee accepted that mifamurtide plus chemotherapy may represent a potentially valuable new therapy and that the mechanism of action offered by Mifamurtide was novel. It acknowledged that few advances had been made in the treatment of osteosarcoma in recent years and mifamurtide could be considered a significant innovation for a rare disease (NICE, 2011b).

	• *Adequacy of capturing health-related quality of life in economic analysis* The Committee heard from patient experts that supporting a young person with osteosarcoma has a profound impact on the health-related quality of life of the family and friends of the person affected, particularly when treatment is not successful. For example, parents and siblings may develop mental health problems and family relationships may be strained. The Committee concluded that these are very important issues affecting the health-related quality of life of those close to the person with osteosarcoma which should be taken into account but on this occasion had not been adequately captured in the economic analysis. The Committee concluded that the combined value of these factors, in addition to the potential uncaptured QALY benefits, meant that mifamurtide could be considered a cost-effective use of NHS resources. (NICE, 2011b).
4. Discussion Please use this space to reflect on, for example: • The reasons or values explicitly used in making the decision. Do these reflect any institutional decision rules or statements of value, for example commitments to equality, non-discrimination or fairness? Do they reflect wider social, moral, cultural, religious values, and if so how? • Considerations not explicitly taken into account in the decision, but which may nonetheless have been important 'background' factors. These might include, for example, public opinion, political sensitivity, moral sensitivity, and international reputation, as well as cultural, social, moral, religious or institutional norms. • The impact of the decision making process on the decision itself, if any. • Any issues relating to implementation. For example, whether access may be restricted by capacity issues, even if the intervention, service or programme is provided on a 'universal' basis. • Anything else you think significant or interesting about the decision.	**Discussion** The following were the key positive reasons for accepting the intervention: • Length of treatment benefit • Ability of the intervention to return patients to normal functioning and lead a 'fulfilling life' • Restoring normal life expectancy • Innovative nature of the intervention for a rare disease • Absence of other recent advances in treatment for osteosarcoma • Impact of the disease on families of patients with osteosarcoma Many of these reasons seem to turn substantially on the clinical benefits of the intervention and its ability to restore normal functioning for the patient - NICE states as one of the primary aims of its guidance to 'promote good health and prevent ill health', so use of these reasons are not surprising. However, the emphasis not only on survival rates but also on the quality of life that is restored also reflects NICE's position, state in its Social Value Judgments, that 'mere survival is an insufficient measure of benefit' and that healthcare should be concerned with improving people's quality of life, and not just prolonging it (NICE, 2008;17) There seem to be considerations of fairness at work in recognition of the innovative nature of a drug for a disease that is rare AND for which there have been few advances in treatment over recent years. In NICE's statement of Social Value Judgments (NICE, 2008; 18), principle 3 states that 'Decisions about whether to recommend interventions should not be based on evidence of their relative costs and benefits alone. NICE must consider other factors when developing its guidance, including the need to distribute health resources in the fairest way within society as a whole'. This principle seems to have been at work here not only in that cost-effectiveness was not the only factor taken into account (in fact, the established discounting rule used in cost-effectiveness estimates was amended in light of the 'merits' of the case) but also in terms of distributing health resources fairly. If few advances in treatment have been achieved over recent years, then it may be thought fair that when a new treatment does come along, patients are given the opportunity to benefit from it. In terms of opportunity costs, it might be thought fair that resources are used to offer such opportunities to osteosarcoma sufferers rather than offering *more* benefits to patient groups who have already enjoyed many recent advances in treatment. Other values which played an important part in considering the intervention were:

- Cost-effectiveness
  - Opportunity costs and discounting

One of the basic reasons why NICE uses cost-effectiveness analysis is to recognise and incorporate the principle that money spent for the benefit of one group of patients does not unfairly disadvantage another group on whom the money would otherwise have been spent.

Whereas in many circumstances opportunity costs raise issues of fairness between two patient groups in the present, in the case of this intervention, the issue of fairness is between groups of patients now and groups of patients in the future, given the length of time over which the health benefits of this drug stretch. This is an issue of distribution of resources, and therefore Principle 3 of the Social Value Judgments is relevant, although in this instance in regard to opportunity costs in distribution of resources to patient groups now or patient groups in the future.

The idea of discounting is that benefits obtained in the future are worth less than benefits obtained today (for details see Weale and Clark, 2011). Therefore applying the same value to treatments for future and current patients would incur potentially unfair opportunity costs to current patients: the thought here is that the value of future benefits should thereby be discounted. However, the effect of discounting is to make interventions such as Mifamurtide, whose benefits stretch into the future, look more expensive in QALY terms than other drugs whose benefits occur today.

However, from the perspective of fairness in distribution of resources, we may also ask why a QALY gain in twenty years' time should be counted any differently from a QALY gain now. It could be argued that just as where a patient lives should not affect the health benefits they receive, nor should the date at which they receive them. For further discussion on the issues of social value raised by discounting, see Weale and Clark, 2011.

  - Cost thresholds

The initial ICER of £56,700 per QALY put Mifamurtide beyond NICE's £30,000 per QALY threshold. Whilst this threshold might is an important decision rule in NICE policy making, in practice, it is modified by other considerations such as the constraints of anti-discrimination and equalities legislation, and by the special attention given to end of life considerations and rare diseases, amongst others. In previous discussions, the Citizens' Council (NICE Citizens' Council, 2008) has identified up to fourteen special or exceptional circumstances that might modify the application of a simple ICER threshold.

In the case of Mifamurtide, the issue was not simply one of making an exception to the £30,000 threshold on grounds of, for instance, rarity of disease, but rather recognizing the *impact* that another decision rule - discounting benefits at 3.5% - had on the ICER of Mifamurtide, putting it beyond the £30,000 threshold. The issue is then whether discounting at the 'decision rule' rate of 3.5% is appropriate given the other features of the particular case. In the case of Mifamurtide, the Appraisal Committee took the view that the 3.5% rate was not appropriate, for reasons associated with other non-cost related features of the intervention and of osteosarcoma.

- Clinical effectiveness

It is interesting to note that there was some uncertainty with regard to the independent effect size of Mifamurtide but that this was thought not to be substantial enough to prevent it from being approved. However, further research was recommended to determine the size of the drug's effect.

	Social values not explicitly taken into consideration, but which may be relevant to the case: • Age of patients Patients with osteosarcoma are predominantly young - up to 30 years of age. However, the Appraisal Committee's decision states that it 'considered that no different recommendations were made for the patient population within the licensed indication, that is, the recommendations are not based on age and do not vary according to the age of the patient' (NICE, 2011). The decision not to take age into account in the appraisal reflects the position arrived at by the NICE Citizen's Council that 'health should not be valued more highly in some age groups than in others' (NICE, 2008;23). It is a common intuition that children deserve special consideration because they have yet had few years of life but have many potential years ahead of them, and that they should therefore give them special consideration in health priority setting. One reaction to the case of mifamurtide might be, therefore, that it is a special case simply because the patient group in question consists of children - but this was clearly not the reaction of the Appraisal Committee. Given that for many of the patient group, the drug extends the already long lifetime which is secured by the existing chemotherapy treatment, the fact that they are children when they receive mifamurtide is not of itself important since the benefits they receive do not come until much later in their lives. That is to say, if they did not receive mifamurtide, 71% of osteosarcoma patients would be expected to survive until the age of 60 anyway - the drug makes no difference as to whether this 71% of children live to adulthood or not. It is only of benefit to them in terms of giving them added years of life at the age of 60, not at the ages of 6 or 16. However, paying attention to the fact that osteosarcoma patients are at an early stage of their lives may be important in relation to the compound nature of discounting which was significant in the Appraisal Committee decision in terms of the effect it had on Mifamurtide's ICER. This is for the following reason: if the patient group in question were on average 50 years old, and were expected to live until age 60, there would only be 10 years of benefits to discount; osteosarcoma patients however are children and young people and are expected to live until age 60 - there are therefore many more years of benefits to discount. This means that the osteosarcoma patients appear to be expensive in cost-effectiveness terms partly in virtue of the fact that the period of discounting is so long, and this in turn is in virtue of the fact that the patients are children - there is simply a longer period over which benefits are discounted than if they were people in middle-age. So the problem here is not that children should be given special consideration and are not being given that consideration, but rather more straightforwardly that they are being actively disadvantaged because they are children and have many years of life ahead of them. So, whilst the age of the patients in question in this case was not a reason in itself in the appraisal process, it was inevitably a background factor because of the effect of discounting health benefits in a case where the patients in question are children with a long life expectancy ahead of them and therefore many years of benefits to discount.
5. References/Links to relevant documents	
	NICE (2011a) ***Clarification to the Clarification to section 5.6 of the Guide to Methods of Technology Appraisals*****. Available at:** **http://www.nice.org.uk/media/955/4F/Clarification_to_section_5.6_of_the_Guide_to_Methods_of_Technology_Appraisals.pdf**

	NICE (2008) *Social Value Judgments*. Available at: http://www.nice.org.uk/media/C18/30/SVJ2PUBLICATION2008.pdf NICE (2011) *TA235 Osteosarcoma - mifamurtide: guidance.* Available at: http://publications.nice.org.uk/mifamurtide-for-the-treatment-of-osteosarcoma-ta235