Social Values and Health Priority Setting Case Study

Title of Case Study	**Lapatinib for the treatment of advanced or metastatic breast cancer**
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Case Summary (approx. 350 words) Please include information here about why the case is of particular interest	Lapatinib is a drug for treatment of patients with incurable cancer: they are at the end of their lives. The case was considered in light of the 'end of life' criteria introduced by NICE in 2009, designed to be used when appraising life-extending treatments for patients with short life expectancy, in order to take account of the potentially higher cost of innovative interventions for small patient groups with incurable conditions. At its first appraisal, the NICE Committee determined that lapatinib did not qualify for all of the end of life criteria: whilst it met the requirements that the patient population had a life expectancy of less than 24 months, and that is was a small population (less than 7000), it did not meet the criteria for extending life for more than 3 months. Thus end of life weightings could not be applied to the ICER ratios for the drug, and it was judged not to be cost-effective for use in the NHS. At an appeal by the manufacturer against this point of the decision (amongst others), the NICE Appeal Panel accepted the objection that the Appraisal Committee's interpretation of the 3 month life extension rule had been too restrictive. It suggested that there could be 'exceptional' or 'compelling' cases where the 3 month life extension criteria could be applied more flexibly, although it did not state how 'exceptional' or 'compelling' should be defined. On reconsidering lapatinib after this appeal, a second Appraisal Committee decided that it qualified for all of the three end of life criteria, including that of life extension. However, even with the end of life weighting, it judged that lapatinib was still not a cost-effective use of NHS resources. The case raises interesting general issues over the application of decision rules, but also interesting specific issues around NICE's end of life criteria and how 'exceptional' and 'compelling' cases might be defined in a patient group which is already identified as being 'exceptional' and in 'compelling circumstances'.
1. Facts of the case	**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?	Lapatinib is a treatment for advanced or metastatic breast cancer. It has a marketing authorization specifically for the treatment of patients whose tumours overexpress the human growth factor receptors ErB1 and ErbB2 (also known as HER1 and HER2) and who have progressive disease and have already received prior interventions including anthracyclines, taxanes and therapy with trastuzumab for metastases. Carcinoma of the breast which over expresses ErbB2 (HER2) is associated with a worse prognosis and a shorter life expectancy than other forms of breast cancer.

• 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 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?	*Clinical effectiveness* The manufacturer's analysis included several different comparators including capecitabine monotherapy, vinorelbine monotherapy, trastuzumab monotherapy and trastuzumab combination therapy. The manufacturer reported details of one randomised controlled trial. This open-label trial enrolled women with HER2-overexpressing advanced or metastatic breast cancer, who had received prior therapy, which included anthracyclines, taxanes and trastuzumab in the advanced or metastatic setting. Patients were randomised to receive treatment with lapatinib plus capecitabine or capecitabine alone. 198 patients were enrolled in the lapatinib plus capecitabine group and 201 patients in the capecitabine monotherapy group. The primary outcome measure was time to progression, and the secondary outcomes were overall survival, progression-free survival, overall tumour response rate, clinical benefit rate and duration of response. Median time to progression was reported as 27.1 weeks for lapatinib plus capecitabine compared with 18.6 weeks for capecitabine monotherapy. Median progression-free survival was reported as 27.1 weeks for the lapatinib plus capecitabine group compared with 17.6 weeks for the capecitabine monotherapy group. However, there was no statistically significant difference in median overall survival: 67.7 weeks for lapatinib plus capecitabine and 66.6 weeks for capecitabine monotherapy. *Cost* The cost of lapatinib treatment is £57.45 per day, or £20,969 per year. The cost of a 21-day cycle of capecitabine treatment is £244.00 per cycle or £4238 per year. This gives a combined cost of lapatinib plus capecitabine of approximately £25,207 per year. *Cost effectiveness* There are various estimates of cost-effectiveness, according to the different comparators, as follows: • The ICER of lapatinib plus capecitabine compared with vinorelbine monotherapy gave an ICER of approximately £79,000 per QALY gained. • The ICER for lapatinib plus capecitabine in comparison with trastuzumab monotherapy was approximately £24,000 per QALY gained, but this did not take into account the comparison of trastuzumab with capecitabine (trastuzumab is usually used in combination with capecitabine) for which the ICER was approximately £109,000 per QALY. • The manufacturer also used a 'blended comparator', which weighted the costs and QALYs of all of the lapatinib comparators (that is, capecitabine-, vinorelbine- and trastuzumab-containing regimens) to produce a single ICER of approximately £61,000 per QALY gained for lapatinib plus capecitabine in comparison with all comparators. (NICE, 2009a)
2. Policy decision: process	**Policy decision: process**
Please include information on as many of the following as are relevant	Lapatinib was appraised using NICE's Single Technology Appraisal process.

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?	However, there were a number of appeals from the manufacturer, GlaxoSmithKline (GSK). As such, the timeline of the appraisal process was as follows: **January 2009:** The appraisal of lapatinib was considered at a fourth meeting of the Appraisal Committee **March 2009:** The first Final Appraisal Decision (FAD) was issued. **June 2009:** The hearing of GSK's appeal to NICE in respect of the first FAD. This appeal was on several grounds of procedural unfairness of NICE's, including NICE's ruling out of the use of trastuzumab as a comparator, and the timing of announcements on the introduction of the end of life criteria, as well as on what GSK suggested was an overly restrictive interpretation of the end of life criteria - notably the 3 month life extension element (see GlaxoSmithKline Notice of Appeal, 8 June 2009; see also Discussion section, below) **July 2009:** The decision of the Appeal Panel was issued; the Panel found in favour of GSK on one point of appeal and a second point of appeal in part, with both points relating to the application of the new Guidance on End of Life Treatments. The appraisal was therefore returned to the Appraisal Committee. **September/October 2009**: The fifth meeting of the Appraisal Committee took place and a second negative Appraisal Committee Decision was issued on 21 October 2009. **November 2009**: The sixth meeting of the Appraisal Committee to consider this appraisal took place. **December 2009**: A draft Final Appraisal Determination was sent to the NICE Guidance Executive, who requested that the Appraisal Committee should give further consideration to the appraisal in the context of potential cost savings to the NHS if lapatinib were used in place of trastuzumab-containing regimens. **February 2010**: The seventh meeting of the Appraisal Committee took place. **May 2010**: The final (and currently applicable) FAD is issued recommending that lapatinib *does* qualify for application of end of life criteria, but that it does *not* provide sufficient benefits to justify its costs and therefore remains unsuitable for use in the NHS.
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,	*Clinical effectiveness* The Committee discussed the clinical effectiveness of lapatinib plus capecitabine presented in the main RCT. It noted that lapatinib plus capecitabine was associated with an improved time to progression, progression-free survival and other secondary outcomes compared with capecitabine monotherapy. *Cost effectiveness* The ICER of lapatinib plus capecitabine compared with vinorelbine monotherapy gave an ICER of approximately £79,000 per QALY gained. The Committee specifically considered the estimates of cost effectiveness that included the patient access scheme comparing lapatinib plus capecitabine against capecitabine and vinorelbine monotherapy. The Committee noted that the ICERs were approximately £70,000 and £55,000 per QALY gained, respectively. The Committee noted that the ICER for lapatinib plus capecitabine in

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.	comparison with trastuzumab monotherapy was approximately £24,000 per QALY gained, but that this did not take into account the comparison of trastuzumab monotherapy with capecitabine for which the ICER was approximately £109,000 per QALY gained. The Committee considered that, although the analysis presented by the manufacturer suggested that lapatinib plus capecitabine compared with trastuzumab-containing regimens was cost effective in the base case, the incremental analysis demonstrated that it was based on a comparison of capecitabine with trastuzumab which was not cost effective. The Committee was mindful that there was uncertainty about the effectiveness of trastuzumab-containing regimens, but considered that even if future evidence on the effectiveness of trastuzumab plus capecitabine demonstrated that it was more cost effective than had been assumed, this would only increase the ICERs for lapatinib plus capecitabine in comparison. Therefore, the Committee concluded that the results of the manufacturer's cost-effectiveness analysis in this situation were unsupportable, and the Committee could not, on this basis, recommend lapatinib plus capecitabine as a cost-effective use of NHS resources. The Committee also examined the economic analysis from the manufacturer that used a blended comparator, which weighted the costs and QALYs of the lapatinib comparators (that is, capecitabine-, vinorelbine- and trastuzumab-containing regimens) to produce a single ICER of approximately £61,000 per QALY gained for lapatinib plus capecitabine in comparison with all comparators included in the economic analyses. The Committee was not persuaded that it was appropriate to combine independent health technologies to produce a single estimate of cost effectiveness nor that the economic analyses that compared lapatinib plus capecitabine with a blended comparator were appropriate. Specifically the Committee was not persuaded that it was acceptable to include treatments in the blended comparator approach which, when considered individually, were not cost effective. Therefore, the Committee did not consider that the cost-effectiveness analyses using a blended comparator could form the basis of a decision on the appropriate use of NHS resources. *Patient Access Scheme* The Committee noted that the proposed patient access scheme (section 3.18) had been applied to the blended comparator. The Committee was aware that the manufacturer proposed to pay for the costs of lapatinib for the first 12 weeks of treatment for all people eligible for treatment, as part of this scheme. The Committee recognised that the patient access scheme reduced the ICER, using the blended comparator, from approximately £61,000 per QALY gained to approximately £16,000 per QALY gained. The Committee did not consider that applying the patient access scheme to the blended comparator was appropriate because of its views on the acceptability of the blended comparator as an appropriate basis for making recommendations about the cost effectiveness of lapatinib *Other benefits* The Committee considered the wider benefits that may be associated with lapatinib. These include providing a range of technologies for the treatment of advanced or metastatic breast cancer and the fact that lapatinib is taken orally. The Committee recognised the importance of patient choice, but considered that lapatinib could not be recommended in the absence of evidence of cost effectiveness. Therefore, the Committee was not persuaded that the benefits

associated with the mode of administration of lapatinib or the importance of patient choice should alter their decision about lapatinib being an appropriate use of NHS resources.
(NICE 2009a)

End of life considerations
In the first appraisal determination (NICE, 2009a) - that is, before GlaxoSmithKline's first appeal - the following is the Committee's assessment of whether the end of life criteria apply to lapatinib:

- The Committee understood that the main RCT reported a median overall survival for patients receiving capecitabine monotherapy of approximately 15 months (65.9 weeks) and, thus, it met the criteria for short life expectancy.

- It is estimated that approximately 2000 patients with HER2-overexpressing metastatic breast cancer per year are receiving second- or third-line chemotherapy and are therefore eligible to be offered treatment with lapatinib. In this respect lapatinib met the criteria for small patient population.

- The Committee observed that the trial data suggested that lapatinib plus capecitabine extends survival relative to capecitabine alone. However, it noted that the main RCT reported a gain in overall survival of approximately 1.9 months which did not reach conventional levels of statistical significance.

- The Committee was also mindful of the results from the economic model, but noted that this provided an estimate of life years gained of 0.19 reflecting a gain in overall survival of approximately 2.3 months. Therefore, the Committee did not consider that the size of the possible benefit was in keeping with the supplementary advice from NICE for consideration of life-extending, end-of-life treatments.

- The Committee was not persuaded that lapatinib fulfilled the criteria for consideration of end of life treatments, and it concluded that the use of lapatinib was not a cost effective use of NHS resources, and recommended that lapatinib should only be used in the context of further research.

However, consideration of the end of life criteria in relation to lapatinib changes in the second appraisal determination issues in May 2010: the Committee decides that all of the end of life criteria, *including* that of life extension (the only criteria *not* accepted in the first appraisal in 2009, and one of the points of appeal by GSK) are applicable to lapatinib. However it judges that, even with the application of the end of life weights, the ICER ratio of lapatinib of £54,900 (revised in light of new evidence from GSK) remains too high.

The following is the relevant section of the second appraisal (NICE, 2010) in respect of the life extension criteria and final judgement of ICER ratios:

> "The Committee then considered the updated survival data provided by the manufacturer and the alternative analyses that adjusted for crossover

	and baseline prognostic factors. The Committee noted that the revised unadjusted estimate of overall median survival benefit was 2.4 months. The alternative analyses, variously adjusting for crossover and baseline prognostic factors, gave estimates in the range of 2.7 to 4.3 months. The Committee noted that where presented the confidence intervals were wide, extending down to 1 month or less. The Committee heard from the DSU that it considered that the methods used to adjust for crossover may have led to some bias in the estimates and that there were alternative methods that might be more valid and might give different estimates. The Committee was not therefore persuaded that the adjusted estimates of overall survival presented by the manufacturer led to estimates that were any more valid than the unadjusted estimate of 2.4 months, and certainly did not provide robust evidence that the extension of life provided by lapatinib was 3 months or greater. However, the Committee noted that there was a minor chance that lapatinib plus capecitabine might offer an increase in overall survival of 3 months compared with capecitabine alone. It therefore concluded that it should consider the ICERs presented by the manufacturer in light of the end-of-life considerations." (NICE, 2010; para. 4.21) The Committee considered the further revised economic evaluation presented by the manufacturer. The Committee noted that the ICER in the further revised base case, including the patient access scheme, was £59,400 per QALY gained. The Committee also noted that the modelled overall survival benefit from lapatinib treatment in the further revised base case was 3.5 months. The Committee discussed the extra weight that might be considered acceptable for a potential increase in life expectancy of 3 months taking into account the unique and innovative aspects of lapatinib, patient need, and previous appraisals where judgements were made taking into consideration the end-of-life supplementary advice, to allow the cost-effectiveness estimates to fall within the range that is normally accepted as a cost effective use of NHS resources. The Committee concluded that the magnitude of additional weight that would need to be assigned to the QALY benefits for the base-case ICER of £59,400 per QALY gained to fall within the current threshold range was not acceptable. The Committee further concluded that the magnitude of greater weight that would need to be given to the QALYs gained in the later stages of terminal disease, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy person of the same age, was also not acceptable." (NICE, 2010; para. 4.23)
4. Discussion	**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	An interesting issue arose in this case around the interpretation of the life extension element of the end of life criteria. This was one of the main points in GlaxoSmithKline's appeal against NICE's first appraisal determination, and it seems to have influenced the way in which the Appraisal Committee considered the applicability of the life extension criteria, as reflected in the second appraisal determination (NICE, 2010; see excerpts from paras. 4.21 and 4.23 above). The following is the relevant section of the appeal by GSK in response to the

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.	first appraisal determination (it is worth quoting in full, but <u>note particularly point 2</u>, later referred to in the Appeal Hearing as the 'proportionality argument'): "GSK believes that the way in which NICE's Supplementary Advice was applied by the Appraisal Committee, in the context of its consideration of lapatinib at paragraphs 4.19 - 4.21 of the FAD, was unfair. In particular the criteria listed in NICE's Supplementary Advice include a requirement that the treatment should offer "*an extension to life, normally of at least an additional 3 months, compared with current NHS treatment*". The way in which this criterion was interpreted by the Appraisal Committee in the appraisal of lapatinib was highly restrictive; the Appraisal Committee concluded, at paragraph 4.19 of the FAD that the trial data for lapatinib offered an overall survival advantage of 1.9 months compared with capecitabine alone, which did not reach conventional levels of statistical significance and that, accordingly, the size of the possible benefit was not in keeping with NICE's Supplementary Advice. The Appraisal Committee therefore seemingly considered that no further consideration of the Supplementary Advice was required in the context of the appraisal of lapatinib. This was unfair for the following reasons: 1. An inflexible application of the requirement that a treatment should extend life by at least three months is inconsistent with NICE's procedures: the Supplementary Advice provided only that this should "normally" be the case. 2. In addition, an inflexible approach also fails to take into account the very variable life expectancies that may be encompassed within a category of patients who have less than 24 months to live. By way of example, where a patient has only three months to live, a doubling of that life expectancy arguably represents a greater treatment benefit than an extension of life of three months in a patient who, in the absence of treatment, could expect only 23 months of life. The median survival in the capecitabine monotherapy arm of the pivotal lapatinib trial in this indication was 15 months. The fact that an extension of life of approximately two months from 15 months (the position in the lapatinib trial) is proportionate to an extension of life of three months from 24 months (as provided in NICE's Supplementary Advice) has not seemingly been considered by the Appraisal Committee at all. In fact, where patients who have received fewer than three chemotherapy regimens are considered, as submitted for consideration by the Appraisal Committee on 21 January 2009, a lapatinib containing regimen produces a median survival advantage of 32.2 weeks, over twice the three month period specified by NICE in its Supplementary Advice. 3. The criticism by the Appraisal Committee that the survival advantage associated with lapatinib in the pivotal trial in this indication did not reach conventional levels of statistical significance (paragraph 4.19 of the FAD), failed to take account of the fact that recruitment to the trial was halted early as a result of the superior results associated with lapatinib treatment. The Committee noted, at paragraph 3.2 of the FAD, that enrolment to study EGF100151 was discontinued in view of the emerging data showing increased time to disease progression (the primary endpoint) associated with lapatinib therapy. It was deemed unethical to continue the study in light of this positive benefit seen with the use of lapatinib. Accordingly, the study may have been

underpowered to detect certain secondary endpoints (such as overall survival) and subject to confounding as a result of cross over from the capecitabine arm of the study (paragraph 3.4 of the FAD). Paradoxically, therefore, it is by virtue of lapatinib's proven superior efficacy that it has not been possible to demonstrate a statistically significant improvement in overall survival. It is clearly unfair that the most effective treatments, with the best early trial results, are less likely to satisfy NICE's criteria for more flexible consideration by the Appraisal Committee.

4. NICE's Supplementary Advice does not consider the additional costs associated with prolonging life in patients who will live only a short time - excluding the costs of the technology under consideration - and this has not been taken into account by the Appraisal Committee in the context of this appraisal. Almost invariably, a patient with a short life expectancy will require additional health and/ or social services support in terms of nursing care, medical consultations, hospital costs and the costs of medicines that alleviate symptoms - before the costs of health technologies directed towards the disease under consideration are considered. Therefore the survival benefits associated with lapatinib treatment affect the assessment of cost-effectiveness - before any costs associated with the drug itself are considered. Even if lapatinib is provided at zero cost the cost utility ratio in comparison to capecitabine alone is still £11,000/QALY - i.e. employing NICE's methodology, the very benefits associated with use of lapatinib, mean that it appears less cost effective than a comparator."
(GlaxoSmithKline Notice of Appeal, March 2009)

The response by the NICE Appeal Panel was as follows (NICE, Appeal Hearing on Lapatinib, July 2009):

"As regards the 'proportionality argument', the Appeal Panel found that the Committee's approach was correct. The amount of life extension required by the Supplementary Policy is not to be varied relative to the overall life expectancy of the patients in question. First, there is no sanction for this in the policy itself. Secondly, it would have the result of placing an ever increasing value on shorter and shorter periods of extension, depending on how close to a patient's probable death the extension was obtained. Although….it was very understandable that a patient and their family and friends might argue for this, it was not a logical position from a broader NHS perspective." (para. 44)

However, the appeal panel go on in para. 46 to say:

"However, the Appeal Panel did not accept the Committee's approach to the meaning of the requirement that life extension should be 'normally of at least an additional 3 months, compared to current NHS treatment.' The Appeal Panel concluded that the Appraisal Committee was not correct to have read that as requiring a minimum of an average of three months in absolutely every case. It would, in compelling circumstances, be open to the Appraisal Committee to accept an average value of less than three months."

And they continue in para. 47:

"In deciding what constitutes a compelling circumstance, it would have to be borne in mind first that all patients to whom the Supplementary Advice might

	be applied are in …a parlous situation. All will be facing the end of life, with all that that entails. That is not a 'compelling circumstance' in itself. Something over and above the features common to all or many end of life cases would be required before the Committee could justify accepting a mean benefit of less than three months. The Supplementary Advice is itself already a policy dealing with a departure from normal policy in exceptional circumstances. Clear and strong justification would be required for an exceptional departure from what is already an exceptional policy, particularly if the departure is more than nominal. It might be that such compelling circumstances would almost never be present. Nonetheless, the Committee was mistaken to have thought that it had no discretion at all to apply the Supplementary Advice where the mean survival benefit is shown to be less than three months." In para. 48 the Appeal Panel allowed the appeal on this point "in so far as the Committee should consider whether, exceptionally, a life extension of less than three months might be acceptable in this case." A paper prepared for the NICE board in 2009 drew attention to the issue of 'exceptionality' and invited the board to consider the nature of what "exceptional" might mean (NICE, 2009b; para. 2.7). It does not seem that clarifications on this are publicly available as yet, but the question of what an 'exceptional' case or 'compelling circumstances' might be in already 'exceptional' and 'compelling' circumstances is an interesting one.
5. References/Links to relevant documents	
	GlaxoSmithKline Notice of Appeal, March 2009. Available at: http://www.nice.org.uk/nicemedia/live/11731/44499/44499.pdf NICE Guidance Executive (2010) Lapatinib for women with previously treated advanced or metastatic breast cancer Available at: http://www.nice.org.uk/nicemedia/live/11731/47060/47060.pdf NICE (2010) Final Appraisal Determination: Lapatinib for the treatment of women with previously treated advanced or metastatic breast cancer. Available at: http://www.nice.org.uk/nicemedia/live/11731/49197/49197.pdf. NICE, Appeal Hearing on Lapatinib, July 2009. Available at: http://www.nice.org.uk/nicemedia/live/11731/44808/44808.pdf NICE (2009a) Final Appraisal Determination: Lapatinib for the treatment of women with previously treated advanced or metastatic breast cancer. Available at: http://www.nice.org.uk/nicemedia/live/11731/43476/43476.pdf NICE (2009b) Update Report on the Application of the End of Life Supplementary Advice in Health Technology Appraisals. Available at: http://www.gserve.nice.org.uk/media/835/8E/ITEM7EndOfLifeTreatments.pdf