NHS organisation statement template

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Primary Care Trusts (PCTs) provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a PCT perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: [redacted]

Name of your organisation **Oxfordshire PCT**

Please indicate your position in the organisation:

- commissioning services for the PCT in general?
- commissioning services for the PCT specific to the condition for which NICE is considering this technology?
- responsible for quality of service delivery in the PCT (e.g. medical director, public health director, director of nursing)?
- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)?
- other (please specify) **Responsible for the implementation of NICE guidance within the organisation**

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Hepatocellular cancer (HCC) is treated with hepatic resection and for a small minority of patients with liver transplantation. These may be curative.

Other treatments which have been suggested; percutaneous ablation, radiofrequency ablation, chemoembolism, systematic chemotherapy with doxorubicin, cisplatin, fluorouracil. None has been found conclusively to prolong survival.

To what extent and in which population(s) is the technology being used in your local health economy?

- is there variation in how it is being used in your local health economy?
- is it always used within its licensed indications? If not, under what circumstances does this occur?
- what is the impact of the current use of the technology on resources?
- what is the outcome of any evaluations or audits of the use of the technology?
- what is your opinion on the appropriate use of the technology?

Sorafenib for HCC is not locally funded and is not in the formulary of our major provider.

The PCT has received 4 requests in the last 12 months to use sorafenib for HCC through the individual patient request route. All were within the licensed indication. The requests recognised in at least one case that the treatment would be palliative. One patient had received a resection for haemochromatosis not HCC. The 4 patients had received a variety of other treatments; radiofrequency ablation (more than once) – 2 patients, doxorubicin – 1 patient and considered in another, intra-hepatic nemorubicin/cisplatin – 1 patient, ECF (epirubicin, cisplatin + 5FU) – 1 patient, tamoxifen – 1 patient. No requests were funded because exceptionality of condition/ capacity to benefit had not been shown.

No local outcome evaluations or audits have been reported.

In our initial view there is little place for this high cost technology which has a reported median overall survival of 2.9 months (no range reported) and no statistically significant impact upon time to symptomatic progression. However the evidence has yet to be reviewed fully at the Oxfordshire Priorities Forum which might return a different opinion.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

This is difficult to assess. Some patients are currently entered into trials and all receive a variety of different treatments with little published evidence of increased survival rates.

Patients receiving sorafenib for HCC might need to be assessed at clinic more frequently for adverse events.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

This technology is only suitable for use in a specialist setting by a team experienced in the delivery of care to patients with HCC. This is an oral therapy and few additional resources are anticipated unless progression free survival is measured radiologically.

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

Oxfordshire (pop approx 610,000) saw 29 new cases of HCC in 2003-05 (minimum 4 cases, max 13 per year). It has been locally estimated that 30-40% of new cases seen across South Central SHA (196 in the same period, population approx 4 million) might have been suitable for potentially curative treatments. Not all of the remaining patients would have been suitable for treatment with sorafenib (i.e. disease had progressed too far). The South Central Priorities Support Unit has suggested a cost impact across South Central SHA in year 1 (assuming treatment duration of 26 weeks) of approx £650,000 rising to £2.2 – 2.75 million by year 5 (using model described in Scottish Medicines Consortium report).

HCC is a rare condition within the UK; South Central figures for new cases show considerable variation from year to year but there does appear to be an increase in cases – this may be a statistical artefact but may reflect an increase in numbers of people with risk factors. There is considerable variation in incidence across the world and future impact on numbers of new cases arising in patients who may have been exposed to risk factors in their country of origin should be considered. Potential future impact of the increased incidence in hepatitis B and hepatitis C should also be taken into account.

Drug costs are high (over £14,000 for 23 weeks treatment). The important figure for this PCT is cost per life year gained. Time to progression seems to have little significance unless accompanied by an improvement or stabilisation in the quality of the patient's life and this has not been shown to be significant.

The treatment should not be accepted simply because it is the only potential treatment. We would expect recognition of real benefit to patients.

The technology is licensed for HCC but the SHARP trial patients had good liver function (Child-Pugh) and ECOG performance status. Selection of patients should be taken into account and maximum length of treatment.

If the treatment were recommended, we would expect to see criteria for withdrawal of treatment i.e. a definition of disease progression beyond which treatment should be withdrawn.

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

Within the next 5 years all monies apportioned to implementing NICE technology appraisals will need to be 'cost neutral' to the organisation as a whole. We do not anticipate increased funding for cancer therapies. Thus any spending on this technology will compromise spending in other areas. In the past increased costs have been offset by cutting primary and community care services. In the future it is likely that savings will be expected from the services where a new technology is to be implemented.

Would there be any need for education and training of NHS staff?

None identified

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.

We would hope to see;

- **appraisal of time to symptomatic progression compared with time to progression and whether the latter reflects patients quality of life**
- **the range of overall survival and not just the median survival**
- **If there are sub-groups of patients identified who might respond better to treatment than others.**

Patient/carer organisation statement template

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

About you

Your name: Stella Pendleton

Name of your organisations: Rarer Cancers Forum and Hepatitis B Foundation UK

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- X an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc) **Executive Director of Rarer Cancers Forum and Website Manager/Nurse Advisor, Hepatitis B Foundation UK**
-
- other? (please specify)

What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?

1. **Advantages**

(a) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make.

The key aspect is improved survival in a cancer with a notoriously poor prognosis. This technology is the only systemic treatment shown to be effective in patients with advanced hepatocellular carcinoma.

In a review of 100 randomised studies reported in the last 30 years, no other anti-cancer agents have been recorded as demonstrating consistent survival benefit (Llovet et al, 2008). Thirty years is a long time to wait for a new treatment but hopefully NHS patients will soon be able to benefit from this innovative technology.

(b) Please list any short-term and/or long-term benefits that patients expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example family, friends, employers)
- other issues not listed above.

- ***Phase III trial data suggest that patients receiving this technology are likely to live around three months longer, with median survival of 10.7 months compared with 7.9 months in placebo group. These are median figures so some patients will survive for longer than 10 - 11 months.***
- ***Three months extra may not sound much to people with a longer life expectancy. However, people with hepatocellular carcinoma have an extremely poor prognosis and those three extra months are very precious indeed for many patients and their families.***
- ***This technology is a real lifeline to patients awaiting liver transplantation. It can act as a bridging treatment, keeping them alive longer and so improving their chances of having a liver transplant, with the potential for a significant improvement in life expectancy.***
- ***This technology offers hope which is a key factor in good mental health***

What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition? (continued)

2. **Disadvantages**
Please list any problems with or concerns you have about the technology.
Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

- ***The most common side effects are diarrhoea, rash, alopecia and hand-foot skin reaction but these do not occur in all patients.***
- ***Diarrhoea affects three out of 10 people, is usually mild and can be controlled with medication.***
- ***Hand-foot reaction is uncomfortable. It affects two out of 10 people. However, topical applications and practical advice about avoidance of pressure may help to relieve discomfort.***
- ***Rash, or red, dry itchy skin occurs in about three out of 10 people - Topical applications may help relieve symptoms.***
- ***Alopecia occurs in two to three people out of 10***

(Figures from Cancer Research UK)

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

4. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

- ***For patients awaiting liver transplantation, the technology may be critical in tiding them over until they can have their surgery and the hope of significantly improved life expectancy.***

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.

- ***Doxorubicin, cisplatin or biological therapies***

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

- ***Improved survival***
- ***Technology is taken orally which is a great advantage to patients***

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

Research evidence on patient or carer views of the technology

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine NHS care reflects that observed under clinical trial conditions.

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?

Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

- ***It would offer hope of significantly improved survival for patients and their families***

What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

- ***Patients would die earlier than need be. Without having the extra months of life afforded by this technology, some patients eligible for liver transplantation would die before a donor organ could be found.***

Are there groups of patients that have difficulties using the technology?

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.

Hepatocellular carcinoma is increasing and is likely to increase as the prevalence of hepatitis B and C increases. There is no vaccine against hepatitis C. Although still regarded as a relatively rare cancer, nevertheless according to Cancer Research UK, one in every 100 cancers diagnosed in the UK is a primary liver cancer. So the need for this technology will increase.

There is, unfortunately, stigma attached to hepatocellular carcinoma and a too ready tendency to link it with alcohol misuse and so regard it as self-inflicted. However, many people will need this technology because they were infected with hepatitis B virus from their mothers at birth. Others have genetic diseases such as haemochromatosis or alpha 1 antitrypsin deficiency. Wilson's disease is rare, but increasingly patients are surviving into adulthood with pre-existing hepatic cirrhosis (Ryder, 2003).

But whether or not patients' lifestyles contributed to their disease they are all human beings facing a very dismal prognosis and in need of all the compassionate help they can get.

Reference: Ryder, S.D. (2003) Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults, Gut,52(Suppl III):iii1–iii8

Professional organisation statement template

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: Royal College of Nursing

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **employee**
- other? (please specify)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

Nurses working in this area of health considered the invitation to submit professional statement for this health technology appraisal. They have indicated that they do not have any information to submit at this stage.

The RCN will participate in the next stage of this health technology appraisal.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Professional organisation statement template

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

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To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] RCP Registrar submitting on behalf of:

Name of your organisation: NCRI, RCP, RCR, ACP, JCCO

Coordinated by Dr John Bridegewater (nominated clinical expert of the above bodies)

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **YES**
- other? (please specify)

What is the expected place of the technology in current practice?

The liver cancer incidence trend for the UK has increased from 2.5 to 3.9 per 100,000 persons between 1993 and 2005 (http://info.cancerresearchuk.org/cancerstats/). The majority of these will be hepatocellular carcinoma (HCC). Although relatively uncommon in the UK with an incidence of approximately 3100 new cases per year, it is much more a global problem, being the 6th most common cancer primarily because of endemic Hepatitis B infection. In the UK, the aetiology is related more to Hepatitis C and other forms of cirrhosis, primarily alcohol. Although vaccination is available for HBV, there will be a significant lag time for those who are already infected. No vaccination is currently available for HCV. Prognosis for liver cancer is poor so incidence and mortality patterns are very similar.

In the UK, HCC is diagnosed early in 30 to 40% of patients allowing potentially curative treatments, such as resection and liver transplantation and locoregional techniques such as radiofrequency ablation ((Bruix, 2005)Figure 1). Five-year survivals of 60 to 70% can be achieved however advanced disease has a dismal prognosis, owing partly to the underlying liver disease and lack of effective treatment options. Although doxorubicin or platinum based regimen have been used, no systemic therapy has convincingly improved survival in patients with advanced HCC(Lai, 1988; Yeo et al., 2005).

Bruix, J.M.S. (2005). Management of hepatocellular carcinoma. *Hepatology*, **42,** 1208-1236.

Lai, A.S (1988). Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. *Cancer*, **62,** 479-483

Yeo, W (2005). A Randomized Phase III Study of Doxorubicin Versus Cisplatin/Interferon {alpha}-2b/Doxorubicin/Fluorouracil (PIAF) Combination Chemotherapy for Unresectable Hepatocellular Carcinoma. *J. Natl. Cancer Inst.*, **97,** 1532-1538.

The advantages and disadvantages of the technology

Sorafenib is a small molecule that acts by inhibiting the Raf-1/B-Raf, vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptor β (PDGFR-β) kinases and as such has a wide-ranging activity (Wilhelm et al., 2004). After encouraging phase 2 data (Abou-Alfa et al., 2006) a series of randomised studies were initiated (table 1).

Table 1

Trial	Doxorubicin/Sorafenib* (n=98)	SHARP (n=602)	Asian (n=226)
OS	13.7m vs 6.5m	10.7m vs 7.9m	6.5m vs 4.2m
PFS	6.9m vs 2.8m	5.5m vs 2.8m	2.8m vs 1.4

*21% increase AUC Doxorubicin

The lead study is the SHARP study (Llovet et al., 2008) in which 602 patients with good Child-Pugh status were randomised to Sorafenib or placebo. The population was primarily European and 70% had extrahepatic disease or vascular invasion. The study was stopped prematurely by the DMC at the 2nd interim analysis following 321 events when a clear survival benefit (10.7m vs 7.9m) was demonstrated. The primary excess of toxicities in the Sorafenib arm were diarrheoa and hand-foot syndrome.

The Asian study (presented at ASCO this year but not yet published) used an identical design and was again stopped early following analysis of the SHARP data. The demographics of this population is known to differ: a greater proportion have HBV-related disease, there was more extrahepatic spread, BCLC C patients , patients with ≥4 sites disease and patients with lung disease. The benefit was correspondingly less but nevertheless significant and of major clinical importance.

The doxorubicin study was designed as a randomised phase 2 and completed accrual of 98 patients although there was a recommendation to close the study following the SHARP interim analysis. The population was similar to the other studies being Child-Pugh A and ECOG 0-2. These data have been presented at the ECCO meeting in September 2007 but not yet published. Survival improved from 4.8 to 8.6 months with no appreciable increase in toxicity from Sorafenib.

Although the smaller studies are unpublished the data support and reinforce the benefit of Sorafenib for Child-Pugh A ECOG 0-2 patients with advanced HCC. The studies may be criticised for their size and the regrettable but necessary early stopping but were otherwise well conducted and conceived studies. They may also be criticised (as the SMC do) for not improving the time to symptomatic progression but this may be a function of the instrument used to measure this function.

Abou-Alfa, G.K (2006). Phase II Study of Sorafenib in Patients With Advanced Hepatocellular Carcinoma. *J Clin Oncol*, **24,** 4293-4300.

Llovet, J.M. (2008). Sorafenib in Advanced Hepatocellular Carcinoma. *N Engl J Med*, **359,** 378-390.

Wilhelm, S.M., (2004). BAY 43-9006 Exhibits Broad Spectrum Oral Antitumor Activity and Targets the RAF/MEK/ERK Pathway and Receptor Tyrosine Kinases Involved in Tumor Progression and Angiogenesis. *Cancer Res*, **64,** 7099-7109

Any additional sources of evidence

Implementation issues

In my view this drug should be offered to all good performance status patients with advanced HCC and it should be the basis upon which to base further clinical trials.

The primary implication issue is that of cost.