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: Dr Rodney Burnham 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.

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: Sean O'Brien

Name of your organisation:

Are you (tick all that apply):

X 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?

- 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)

- 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.

In my case the technology has stopped the further growth of the tumours and reduced their size. In December 07 I was told that there would be no surgical option for me and that Christmas 07 would probably be my last. Now 15 months on I am on a waiting list to receive a domino liver transplant

(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 conditionI have been taking the drug for 14 months
- physical symptoms None
- pain None
- level of disability None
- mental health Excellent
- quality of life (lifestyle, work, social functioning etc.) Good
- other quality of life issues not listed above None
- other people (for example family, friends, employers)
- other issues not listed above. See Side effects

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 None
- 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 Leaflet which is included in the packaging lists 44 known side effects and separates them into 3 different categories:
Very common
Common
Uncommon

I have experienced nine of the side effects during my time in taking the drug, five in the very common category, three in the common category and one in the uncommon category.

Whilst all are unpleasant and some are persistent I happily accept and tolerate the symptoms given the benefits of the drug.

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?

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.

As far as I am aware there are no other existing 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) Very easy to take
- where the technology has to be used (for example at home rather than in hospital) taken from home two tablets twice daily.
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

No alternative therapy

(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 No
- worsening of specific aspects of the condition None
- difficulty in use (for example injection rather than tablets) Tablets easy
- where the technology has to be used (for example in hospital rather than at home) Home
- side effects (for example nature or number of problems, how often, for how long, how severe).

The side effects which I have experienced over the past 14 months have at times been extreme; those listed in the package leaflet are diverse and can manifest themselves with little or no warning. The support and advice available to me has been limited and is an area which needs addressing in my opinion. When you have the sudden onset of a side effect there is not a single reference point to refer to in order to either address the symptoms or at the very least allay any fears or concerns.

Diarrhoea	Continuously since the beginning – very severe
Weak & tired	progressively over the period
Hair Loss	Lost hair early 2008 – returned December 08
Flushing	Recent development – usually at night
Itching	Very dry skin continuously since beginning

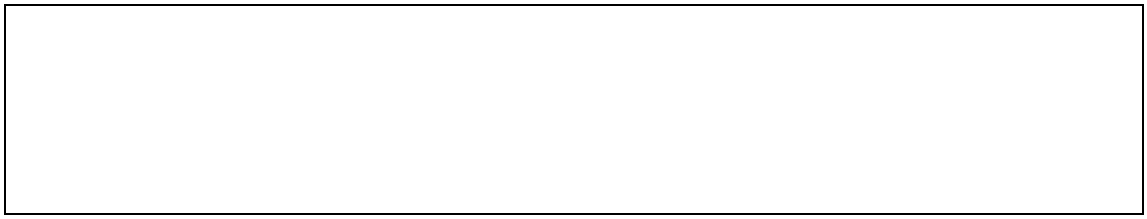
Weight loss	My weight has dropped by five stone
Loss appetite	My appetite has diminished over the 14 months
Inflamed Mouth	I have on and off experienced a very ulcerated mouth
Underactive thyroid	Mildly underactive, diagnosed in 2008

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?

I have been lucky enough to take this drug because I was fortunate enough to have medical insurance and and insurer who are progressive in their thinking. I have personally been at odds with the disparity within the health service concerning this technology because I have been one of the lucky ones. My case clearly highlights that the technology can be life changing and that it should be made available to all those in need. As a person who has lived with cancer now for 4 years I can honestly say that the taking of this drug has been life saving and life changing. By approving this drug and working in association with other medical advances I believe that this drug will not only be used to extend life for short periods of time but that it could also be used as part of a longer term strategy to help people like me regain their life.

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

Lives will be unnecessarily lost and medical advances in treating individuals with liver cancer will be adversely affected

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.

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About you

Your name:
CALUM POLWART

Name of your organisation
CANCER NETWORK PHARMCISTS FORUM, ON BEHALF OF THE BRITISH ONCOLOGY PHARMACY ASSOCIATION (BOPA)

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.)?**
- other? (please specify)

Calum Polwart is Pharmacist for the North of England Cancer Network and Pharmacy Clinical Team Manager for Cancer & Aseptic Services at County Durham & Darlington NHS Foundation Trust. Calum has 10 years experience in oncology and haemato-oncology and is co-author of a book on oral anti-cancer medicines. He also sits on the North of England Cancer Drugs Approvals Group, and has active involvement in the teaching of oncology pharmacists through the Liverpool John Moore Univoersity Post Graduate Programme. Calum is a member of the Cancer Network Pharmacist Forum and a member of the BOPA Committee.

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?

As far as CNPF is aware there is very little access to this treatment across the whole of the UK – principally on the grounds of funding.

We understand that there is over whelming clinical opinion that this treatment should be the treatment of choice in HCC. Although there may be some differences of opinion over which patient group should / should not receive treatment (eg Child Pugh B)

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)?

This treatment should be restricted solely to the specialist setting, under the supervision of a specialist oncology team experienced in the use of Tyrosine Kinase Inhibitors. Treating clinicians MUST provide pharmacy departments with appropriate protocols, and patients will require additional information. This treatment is covered by the NPSA Rapid Response Alert on Oral Anti-cancer Medicines. Prescribing, Dispensing, Administration & Patient Information/Consent must be within the standards set by the NPSA.

It is likely that there will be a resulting increase in workload for oncologists, oncology nurses and oncology pharmacy staff as this patient group has previously been untreated with conventional oncological agents.

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?

There may be a small amount of use through "Exceptional Cases" from PCTs – however there is likely to be diverse definition of Exceptional Cases which will mean even within the small number of Exceptional Cases funded there will be significant variation in clinical presentation with two potentially similar (but 'exceptional') patients in differing geographical locations receiving differing access to treatment.

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.

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?

There are no really meaningful alternative treatments. Without a doubt oral treatment is easier than intravenous therapies. However, oral treatments are not without their risks. Dispensing and prescribing errors are all at least as likely as with intravenous chemotherapies, and over compliance by patients is a common problem with these treatments: patients often failing to suspend their treatment when they experience serious toxicity. For this reason use should be restricted to specialist health professionals experienced in working to oncology protocols, and in following up and monitoring patients on these types of treatment.

Patients are likely to find any additional testing/monitoring acceptable for the potential degree of benefit from the treatment.

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.

This treatment should only be offered in the context of a clearly defined protocol, which should include definitions of stopping rules which may need to consider markers of progression, Child Pugh, toxicity and performance status.

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?

The largest problem with the clinical trials is the lack of clarity of outcomes induced by the cross-over of placebo patients to the therapeutic arm of the study.

The validity of placebo controlled studies in this setting should be kept in mind as most patients, nurses, pharmacist and oncologists can probably tell which patients are on active treatment based on the side effects experienced.

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?

Experience with similar agents in RCC has shown that this is far from an easy tablet based treatment. Patients often experience significant side effects which require specialist intervention. It is therefore essential that the principles outlined in the NPSA Rapid Response Report on Oral Anti-Cancer Medicines are adopted if this technology is adopted. In essence that would mean oncologists (and their supporting specialist multi-disciplinary team) and not-hepatic surgeons or gastro-enterologists supervising patient care.

Development of robust local protocols for dose modification and treatment delays will be essential for safe delivery of this treatment, especially as there is limited UK experience with the agent.

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.

BOPA / CNPF has nothing to add.

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)?

It is unlikely that additional physical resources would be required specifically for this treatment. However, there would be a (relatively small) appreciable training need for oncology nurses and pharmacists – many of whom will never have handled this technology before. It would be possible to deliver that training within the 90 day limit.

On the assumption that a large cancer network would cover a population of 3M, and all patients might be treated at a single centre – around 40 patients per year would be treated. On the assumption that half those patients are on treatment at any one time (6 month duration of treatment), returning monthly to be seen in clinic then this would be the equivalent of 5 patients per week. While not a massive burden on case load compared to some other treatments there is a risk that this treatment is seen as an easy oral tablet and is squeezed into already over-capacity nursing and pharmacy services.

Local experience with introduction of similar technologies for Renal Cell Cancer in some areas has highlighted that a sudden surge in usage associated with new funding can result in short term supply problems within the wholesaler network. NICE should confirm with Bayer if there will be

sufficient stock available and if this can be carefully distributed to relevant wholesalers throughout the UK in adequate time.