Clinical Specialist 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: Professor David R. Ferry PhD FRCP

Name of your organisation Royal Wolverhampton NHS Trust

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.)? **NHS consultant treating patioents**
- 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.

How is the condition currently treated in the NHS?

First line treatment of advanced NSCLC is primarily with cisplatin based chemotherapy. The clinically significant benefits, of prolonged survival and improved quality of life, have been accepted since the 1995 meta analysis (Chemotherapy in NSCLC, 1999, BMJ 311 899-909). A number of chemotherapy drugs can be added to cisplatin to improve response rate and survival, including older drugs such as mitomycin/vinblastine (in MVP), or more recently introduced drugs such as gemcitabine (GC), taxotere (TC), or navelbine (NP). There was a tendency to replace cisplatin with carboplatin, but the efficacy of carboplatin regimens is in doubt and currently under investigation in the randomised trial BTOG-2 in the UK. Currently the vast majority of patients having first line chemotherapy have gemcitabine as the partner drug for platins, and increasingly those patients with adenocarcinoma have cisplatin combined with pemetrexed because of the superior efficacy of this regimen (Scagliotti et al, 2008, 26, 3543-3550).

In general 4 cycles of first line platin based chemotherapy is delivered and in the UK is widely considered to be the optimal duration of therapy. In the USA often more prolonged first line platin based therapy is delivered and a meta analysis lends some support to this conjecture (Soon et al, 2009, JCO, 27, 3277-3283). Needless to say meta analysis is not as reliable as well constructed large enough randomised trials and until these have been conducted those proposing more prolonged platin therapy beyond 4 cycles should be considered to be expressing an opinion not strongly supported by evidence.

Erlotinib is an inhibitor of EGFR tyrosine kinase. It is taken orally at a dose of 150 mg per day and compared to placebo prolongs life in the second/third line setting in NSCLC (Shepherd et al , 2005, NEJM, 353, 123-132). The main toxicity of erlotinib is skin rash and diarrhoea which causes discontinuation of drug in around 5% of patients and dose modification in around 20% of patients. It was therefore a natural development to advance the second line use of erlotinib into the immediate post platin therapy window, known as maintenance therapy. The one large published pivotal trial is known as SATURN, and has been presented in part at ASCO 2009 (without survival outcomes, Cappuzzo et al, Proc ASCO 2009, 8001) and at World Lung 2009 (Cappuzzo et al J Thoracic Oncology 2009, Ab A2.1) where survival data were presented for the first time.

Although early RCTs of maintenance treatment of NSCLC with navelbine (Westeel et al 2005, JNCI, 97, 499-506) or gemcitabine (Brodowicz et al 2006 Lung Cancer 52, 155-163) failed to show benefit, in the last 2 years three pivotal large RCTs of maintenance therapy have been undertaken in advanced NSCLC. Maintenance therapy (MT) is best regarded as switching chemotherapy to a treatment other than that used for induction of response, with the objective of prolonging remission and hopefully overall survival. Three strategies have been deployed in NSCLC using different drugs after platin induced remission: (1) The tubulin binding drug taxotere; (2) the multi targeted antifolate pemetrexed (Ciuleanu et al 2009, Lancet 374, 1432-1440); (3) the EGFR inhibitor erlotinib (Cappuzzo et al 2009). All three trials used the the paradigm illustrated in Fig 1 below. In all three trials, those patients who progressed on first line treatment were not considered for maintenance therapy. Other patients were not considered for maintenance therapy if their PS fell or for other medical reasons.

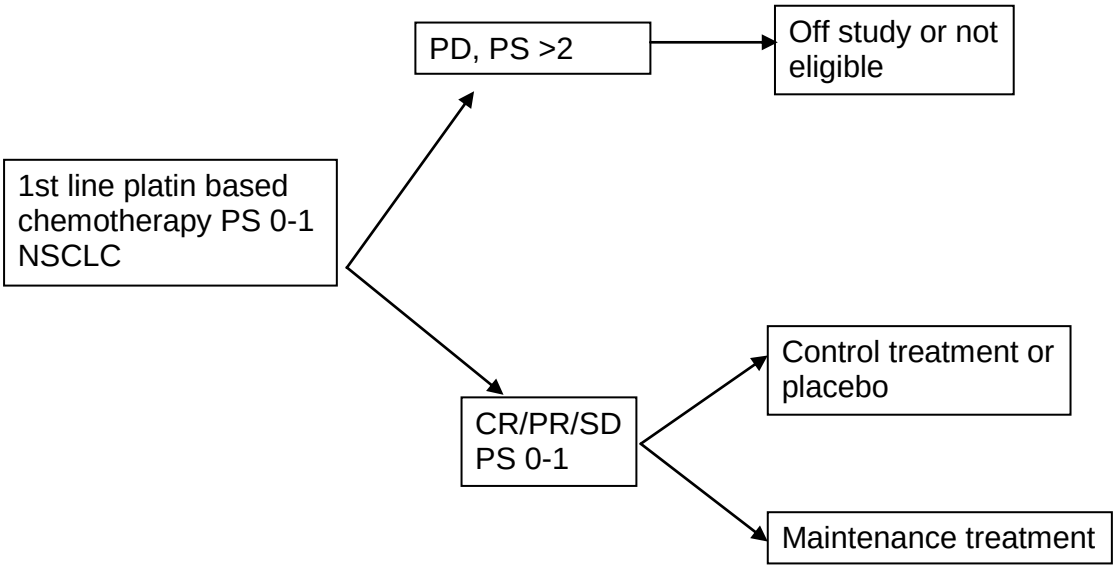

Figure 1 Trial design for maintenance therapy in NSCLC.

The three trials differ little in eligibility criteria and duration of planned maintenance therapy. Table 1 outlines the basic details of the three key trials.

Table 1

Maintenance therapy	Median age all	Number of patients given platin	Median number of platin treatments	Number randomised to MT (months)	Median age MT patients	Histology
Taxotere	65	566	3.4	309	65	All
Pemetrexed	NR	NR	4	663[a]	60	All
Erlotinib	NR	1949	4	889	60	All

(a) Randomised 2:1 pemetrexed: placebo infusion; NR not reported

The characteristics of the patients randomised to the maintenance therapy question varied little between the three trials. In Table 2 the % of patients with CR/PR versus SD is listed and is very similar between the trials.

Table 2

Maintenance therapy	% patients CR/PR to platin	% patients SD to platin	% of patients given first line platin
Taxotere	45	55	55
Pemetrexed	50	50	Unknown
Erlotinib	45	55	45

The response to maintenance therapy was measured in each of the trials and was found to be 11.9% immediate v 5.4% plabebo, 11.7% immediate v 11.2 % for delayed taxotere and for pemetrexed was 3.4% pemetrexed versus 0.5% placebo.

Table 3

Maintenance therapy	Number of patients treated	Median duration of randomised treatment	PFS (months)	OS (months)
Taxotere (I)	145	4.4 cycles	5.7	12.3
Taxotere (D)	98[a]	3.8 cycles	2.7[c]	9.7d
Pemetrexed	441	5.0 cycles	4.0	13.4
Placebo	222[b]	3.5 cycles	2.0[d]	10.6[e]
Erlotinib	438	NR	3.2	12.0
Placebo	451	NR	3.0	11.0[f]

a 98/156 patients received delayed taxotere because some patients were not sufficiently well to have delayed taxotere as judged by their physicians. B less placebo patients because of 2:1 randomisation. c $P < 0.0001$ compared to immediate taxotere. D $P < 0.0001$ compared to pemetrexed. d $P= 0.0853$ versus taxotere, e $P = 0.012$; f $P = 0.0088$ versus erlotinib.

Off study treatment after progression in maintenance trials.

The trial of maintenance versus delayed taxotere did not report on treatment after progression which is likely to have been substantial. For the pemetrexed and erlotinib trials this data was reported in detail (Table 4). This data is important because significant imbalances could theoretically affect the survival. Within the pemetrexed trial the only imbalance was to use more antimetabolites (pemeterexed and gemcitabine) in the control arm, if anything likely to dilute the effect of active

treatment arm. In a parallel way, in the erlotinib trial the only imbalance was the higher rate of tyrosine kinase inhibitors in the placebo arm. Thus from the data available it is very unlikely that these positive trials obtained their results from further active treatment inducing bias. If anything the use of further treatments may have diluted survival benefits in the experimental arms.

Table 4

Further treatment	Ciuleanu et al 2009		Cappuzzo et al 2009	
	Pemetrexed arm	Placebo arm	Erlotinib arm	Placebo arm
Taxanes	26	35	30	31
Antimetabolites	10	32	24	23
Antineoplastics	13	17	16	18
TKIs	35	31	11	21
Platins	12	15	9	12

All numbers are % of patients randomised to active of placebo arms of respective trials.

Subgroup analysis

It can be considered that all the maintenance trials selected a subgroup to study, namely those patients with response or stable disease and excluded those patients with PD. The Ciuleanu et al trial because of its design does not allow us to know the number of patients treated with platins to find the patients with response or stable disease for the trial. In both the taxotere and erlotinib trials around half of the patients given first line treatment did not get randomised, yet PD rates in first line trials are generally around 20-25% of patients (Fidias et al 2009), probably mostly with SD did not get randomised to the maintenance therapy. The reasons for this are unclear but could relate to drops in PS, patient choice or physician bias.

The main subgroup analysis in the erlotinib trial related to EGFR biology. Thus for the erlotinib trial the HR for all randomised patients (N = 889) for OS was 0.81 (0.70-0.95). The HR for IHC + patients (N = 621) versus 0.91 (0.59-1.38) for IHC-negative patients. For EGFR wild type, N = 388, (WT) the HR was 0.77 (0.61-0.97). For EGFR mutant patients (N = 49) there was no obvious benefit for maintenance erlotinib versus placebo (HR 0.83 (0.34-2.02).

More data was presented for PFS, the HR for adenocarcinoma , N = 401, was 0.6 (0.48-0.75) and squamous cell cancer, N = 259 was 0.76 (0.60-0.95). For smoking history all groups benefited, but never smokers (N = 152) had a HR of 0.56, former smokers (N = 242) an HR of 0.66 and current smokers (N = 480) an HR of 0.80.

The main subgroup analysis for the pemetrexed trial relates to histology. Thus maintenance pemetrexed did not benefit squamous cell patients, but did benefit adenocarcinoma or other non-squamous histology. Thus in the analysis of the non-squamous group (N = 481) the HR favouring pemetrexed maintenance was 0.7 (0.56-0.88), $p < 0.001$. This equates to 15.5 versus 10.3 months ($p < 0.0001$).

Setting in which technology would be used

Whilst maintenance erlotinib is an oral treatment, the assessment of the complex symptoms caused by NSCLC, combined with the nature of toxicity and need for a significant number of dose reductions means a physician extensively trained in cancer systemic therapies should manage these patients. Ideally a cancer physician who also understands the alternatives including when to refer for radiotherapy, will make the key decisions in management. By ensuring safety monitoring those 15-20%

who develop severe diarrhoea will be intercepted before they become acute admissions. In addition proper monitoring with CT scanning will save money by stopping treatment once patients begin to progress.

Use of erlotinib in the NHS
Erlotinib is being used as a second line treatment after failure of platin therapy. My impression from speaking to physicians across the country and from questions put to me at invited lectures is that some doctors are already using 'early second line' erlotinib in some case. This is very difficult to police.

Clinical guidelines
A profusion of guidelines are and have been written. It is now necessary for clinical governance purposes for every NHS Trust to have local guidelines, and often Networks have so called site specialised groups who will write overlapping guidelines. In addition various professional societies and groups have guideline writing committees. This business is then replicated at European levels. NICE is currently re-writing their version of Lung Cancer Guidelines and will finish this task in 2010. It is probably not the right time to complete this task in this area because so much data is new and difficult to place into a coherent non-contradictory whole. My own feeling is this is not the time write guidance, it is the time to design some trials to address the uncertainties thrown up by the new data.

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?

Comparison to other technologies
The use of maintenance erlotinib arrives at a time of flux in the therapy of advanced NSCLC. It is very likely that those patients with EGFR mutations (~ 10% of NSCLC) will be treated first line with a better tolerated EGFR inhibitor, gefitinib (Mok et al 2009, NEJM, 361:947-957). This will not undermine the use of erlotinib in the maintenance setting because it is active in patients with WT EGFR. It is also active in

squamous cell cases where pemetrexed is inactive. The choice therefore for squamous cell cases is to have erlotinib or taxotere maintenanace therapy. On the face of it the benefit for taxotere seems larger than with erlotinib, but caution about cross trial comparisons is needed. Whilst the patients enrolled in the two trials are similar only a head to head comparioson could provide definitive data.

For non-squamous NSCLC erlotinib can be compared to taxotere and pemetrexed. Again the benefit for pemetrexed versus erlotinib seems large (5 months versus 1 month). This difference is probably too large to allow investigators to feel comfortable to participate in an RCT of maintenance pemetrexed versus erlotinib. Thus for patients with non-squamous NSCLC after induction therapy erlotinib is unlikely to be a dominant strategy over pemetrexed.

The complication we have not considered is that for non-squamous NSCLC first line pemetrexed/cisplatin is now by consensus considered to be the first line treatment of choice. We don't yet know if following first line cisplatin/pemetrexed further maintenance pemetrexed (NCT00789373) will add anything and this is being addressed by a 900 patient RCT due to report in 2012. We also don't know if the data obtained with erlotinib after platin/other drug doublets but not involving pemetrexed will produce the same result as SATURN.

We also don't know if serial exhibition of erlotinib after taxotere (squamous cell cases) or pemetrexed (non squamous cases) produces benefits similar to those found in the first line maintenance.

Everyday use versus clinical trial conditions
The everyday use in the NHS will be very similar to those in the clinical trial. These patients will need a monthly outpatient assessment, ideally with availability of their blood test results checking renal and liver function. These patients should have a 2-monthly CT scan because when PD is defined as in the trial treatment should be stopped. There is probably no value in monthly chest X-ray unless there is gross clinical progression.

Side effects and significance
A small number of patients, around 1 in 20 will stop because of diarrhoea or intolerable skin rash and around 20% will need a permanent dose reduction to 100 mg/day or lower. Having said this it should not be forgotten that overall SATURN defined a definite QoL and symptom improvement in the whole population of patients.

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.

None

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)?

Everyday application in the NHS

If erlotinib maintenance therapy were recommended then all the equipment and personnel are there to deliver this therapy already. We would probably need more resource to CT monitor patients on treatment and radiologists would need education so as they could report according to RECIST criteria. This would be important because it would prevent continuation of treatment of patients progressing on therapy.