Clinical Expert Submission Template

Thank you for agreeing to give us a personal statement on your 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. Your statement can be as brief as you like, but we suggest a maximum of 8 pages.

If there are special reasons for exceeding this 8-page limit please attach an Executive Summary to your statement.

What is the 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?

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.

Non-small cell lung cancer treatment in the NHS
First line treatment of advanced NSCLC is primarily with cisplatin based chemotherapy. The clinically significant benefits have been accepted sine 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.

Erlotinib and petered in the treatment of non small cell lung cancer
With regard to first line therapy, there is little data in the public domain. There is a trial INSTEP of gefitinib for poor performance and elderly patients which will report in 2007. There are two randomised trials of cisplatin/penetrated versus cisplatin gemcitabine which should shortly be in the public domain.

Second and third line treatments
Although first line chemotherapy produces survival benefits large enough to make this standard treatment world wide, the limitations of this treatment and familiar to medical oncologists treating this condition. Response rates are in the range 25-40% and median survival in good performance status patients (PS 0/1) is 9-11 months. Eventually all patients relapse and with a median duration of response being 3-4 months re-exposure to platins is rarely effective.

That is why second line trials were undertaken and the success of taxotere in 2000 (Shepherd et al, J Clin Oncol, 2000, 18, 2095-2103) led this to becoming a world wide standard of care. The remainder of this review will focus on second/third line use of erlotinib and pemetrexed in NSCLC.

Erlotinib, clinical trials background
Erlotinib is a selective EGFR tyrosine kinase inhibitor. It has good bioavailability and the dose limiting toxicity in phase I trials was diarrhoea. In phase II trials erlotinib showed good activity against non small cell lung cancer which led to the testing of erlotinib added to first line chemotherapy in two randomised trials where erlotinib failed to improve the survival of stage IIIIB/Iv patients in combination with cisplatin/gemcitabine (Herbst et al, 2005, J Clin Oncol, 23, 5892-5899) or carboplatin/taxol. Not only were the trials of erlotinib negative, but also the trials with a similar EGFR inhibitor gefitinib were also negative (Herbst et al, 2004, J Clin Oncol, 22, 785-794), this effectively ended interest in combining oral EGFR inhibitors with chemotherapy in NSCLC. Attention then switched to the use of erlotinib in the second and third line settings as a single agent. The pivotal trial, BR21 (Shepherd et al, 2005, NEJM, 353, 123-132), was published in 2005 and bears detailed assessment.

Pemetrexed, clinical trails background
Pemetrexed is a cytotoxic. It is an antifolate antimetabolite which inhibits the folate dependent enzymes thymidylate synthesase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase. Phase I trials identified that a 10 minute infusion given 3-weekly was the optimal schedule for tumour activity and toxicity. At doses of 500 mg/m^2 peak serum concentrations are in the range 150-200 ng/mL well in excess of the IC50 to inhibit target enzymes (5-10 ng/mL). The pharmacokinetics is well described by a two compartment model. The total systemic clearance is ~95

mL/min with a Vss of 16.1 L . Over the dose range 0.2 to 1400 mg/m2 there is linearity of AUC and Cmax. Protein binding is 81%. Excretion of pemetrexed is mainly renal, 80% being renal eliminated. During phase III trials in malignant mesothelioma toxicity such as diarrhoea and febrile neutropaenia was associated with elevated homocysteine and methylmalonic acid, associated with folic acid and B12 deficiency respectively. The supplementation of patients in this randomised trial dramatically reduced life-threatening toxicity which led to the recommendation that single agent pemetrexed doses should be 500 mg/m2 3-weekly with oral folic acid daily 350-1000 ug and B12 1 mg 9-weekly. The trial H3E-MC-JMEI compared pemetrexed to single agent taxotere in NSCLC the second line setting and randomised 571 patients (Hanna et al, 2004, J Clin Oncol, 22, 1589-1597).

There are 3 pivotal clinical trials in second-line NSCLC to consider and compare.

	TAX317 (Shepherd et al 2000)	BR21 (Shepherd et al 2005)	H3E-MC-JMEI (Hanna et al, 2004)
Design	RCT	RCT	RCT
Control arm	Best supportive care	Best supportive care	Taxotere 75 mg/m2
Experimental arm	Taxotere 75 mg/m2	Erlotinib 150 mg daily	Pemetrexed 500 mg/m2 3w
Patients	204	731	571
Median age	61	61	58
PS 0/1/2	17/62/25	13/53/24	88/12/0 %
Response to prior therapy	35%	38%	36%

	Response	TTP*	Survival
TAX317 control	0 %	2.1	4.6
TAX317 taxotere	5.5%	2.7	7.5
BR21 control	<1%	2.0	4.7
BR21 erlotinib	8.9%	2.1	6.7
H3- taxotere	8.8%	2.1	7.9
H3 petered	9.1%	2.3	8.3

What is remarkable about the three pivotal trials is the consistency of outcome. BR21 and TAX317 have placebo control arms and the median survival of the patients in these arms of the trials were 4.7 and 4.6 months respectively. In the treatment arms of the three trials the median survival was 6.7-8.3 months. The age of patients recruited in all three trials was 58-61 years, or 10 years younger than the median of patients diagnosed with lung cancer. The other consistency which stands out is that across the trials 35-38% of patients had responded to their prior treatment. For the trials of chemotherapy patients who had PD on last chemotherapy had a much lower chance of response, 0/19 in TAX317 and in H3E was 4.6% (versus 11% in patients who had responded). In BR21 response to prior therapy was significant in the univaraite survival analysis (HR 0.7, P = 0.004).

The main difference in patients between trials is the exclusion of PS2 patients from the pemetrexed v taxotere trial. Thus we have no RCT data to guide treatment of PS2 patients with pemetrexed.

The three second line treatments have markedly different toxicity profiles. These are summarised in table 3 below.

	G3/4 neutropaenia	G3/4 diarrhoea	Nausea (all grades)	fatigue
TAX317 control	0%	0%	26%	28%
TAX317 taxotere	76%	4%	36%	22%
BR21 control	0%	<1%	34%	23%
BR21 erlotinib	0%	6%	40%	19%
H3- taxotere	40%	0.4%	17%	5.4%
H3 petered	5%	2.5%	31%	5.3%

Quality of life is always regarded as a supplementary reason to give second-line chemotherapy in NSCLC. In TAX317 there was some evidence that QoL did not deteriorate on taxotere compared to BSC and some evidence of less weight loss and significant decreases in he use of opiates for pain (49 v 32%, p = 0.01). In the taxotere versus pemetrexed trial a much larger number of patients had QoL assessed, 474. There were no clear differences between taxotere and pemetrexed. The data for BR21 has been published in a separate paper (Bezjak et al, 2006 J Clin Oncol, 24, 3831-3837). What is most notable is what medical oncologists have appreciated for some time, response correlates closely with improved QoL. Thus for patients with response to erlotinib 72% had improvement in cough, but only 21% of PD patients had cough improvement (P < 0.01). This underlines the need to identify patients likely to respond to erlotinib.

Subgroups of patients

Subgroup analysis of RCTs should almost always be discouraged, but provides a more robust answer than ad hoc phase II trials and selective opinion. The erlotinib versus placebo trial BR21 does provide some information on subgroups, but whilst the conclusions confirm previous data with EGFR inhibitors, it was also in part contradictory.

What BR21 confirmed was that the best subgroups in the univariate analysis were never smokers (HR 0.40), and being adenocarcinoma versus squamous cell cancer. What this paper controversially did not confirm is that mutations in the kinase domain correlated with survival benefit, but EGFR expression did. Thus the conclusion of the authors was that ALL groups benefited and therefore ALL patients could be offered erlotinib. The reason this is controversial or at least challenging is because of the data demonstrating that patients with mutations in the kinase domain of the EGFR have very high response rates (60-90%) and apparently good survival (Lynch et al 2004, NEJM, 350, 2129-39). Amplification by FISH analysis of EGFR may be the best predictor at the molecular level, but validation of these methods in standard clinical practice is lacking.

For taxotere and pemetrexed the subgroups most likely to benefit are those of good performance status who responded to previous treatment. For erlotinib the additional factors of never smoker ,female, brochioalveolar histology and possibly expression amplification and mutation in the kinase domain of the receptor and additional factors to take into account. However the only level 1 evidence we have from the only published placebo controlled trial (BR21) indicates all groups of patients benefit. This area needs further research.

Setting for technology delivery
Erlotinib is taken as a tablet. Patients need assessment with CT scanning and evaluation of serum biochemistry before considering prescribing erlotinib. The need for CT scanning is because it is essential to evaluate and define relapse before commencing treatment. A medical oncologist familiar with NSCLC needs to assess the symptoms of the patient because symptom palliation is an important part of the rationale. After one month patients can be reassessed. If symptoms improvement is occurring then it usually occurs within the first month of treatment. Those patients without symptomatic improvement should have early CT scanning so if there is progression erlotinib can be stopped. Many patients will be difficult to assess and CT scanning offers the best means of making objective decisions to prevent unwarranted continuation of ineffective treatment

Variation of use in the NHS
There is very little NHS use of erlotinib. Pacts have no money to fund medicines which are not NICE approved and no matter how clear the case is for use they will use lack of NICE appraisal as a blanket reason to reject appeals for treatment. For that reason most NHS use is clinical trial related and access for eligible patients is thus very low.

Clinical guidelines
The use of erlotinib and pemetrexed has to my knowledge not been incorporated into high level UK guidelines which have been published in peer review journals.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, if already available, compares with current alternatives used in the UK. Is the technology 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 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 in clinical practice reflects that observed under clinical trial conditions. 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?

Ease of use
Erlotinib is easier to use than taxotere or pemetrexed, because it is an oral medication with a good toxicity profile. Both taxotere and pemetexed require high doses of corticosteroids to prevent allergic reactions and rashes. These chemotherapy drugs should only be given in oncology centres or satellite clinics where trained staff work with chemotherapy pharmacists.

Rules for starting and stopping treatment
All three drugs should be stopped if there is no objective evidence of radiological benefit after 6 weeks. For all agents this is best done with CT scanning.

Applicability of trial evidence to standard UK oncology practice
The evidence for pemetrexed and erlotinib translates well into UK oncology practice. What should be noted is that evidence for pemetrexed is limited to PS0/1 patients. For both pemetrexed and erlotinib the patients entered were 10 years younger than the median age of patients with the disease. Therefore only in exceptional circumstances should elderly patients over the age of 70 be considered for treatment because evidence of tolerability and benefit is lacking.

Impact of side-effects
The side effects of chemotherapy can be devastating and this can be the case for pemetrexed. In my experience careful selection of patients with good renal function and careful folate/B12 supplementation means most patients avoid G3/4 toxicity . For erlotinib data also is limited to those < 70 years, however PS2 patients were included in the BR21 trial. The majority of patients will be able to tolerate treatment with erlotinib or pemetrexed without dose reduction, and the reason to discontinue both of these drugs in relapsed NSCLC will be disease progression

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

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)?

The NHS is required by the Department of Health and 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 Welsh Assembly Government to vary this direction.

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

Delivery of care
The use of pemetrexed would require the use of chemotherapy outpatient chairs. It would also be advisable to develop proforma prescriptions which included the necessary premedication and folate/B21 supplementation needed to avoid errors in drug delivery.

Erlotinib could be given in the outpatient oncology clinic. Oral drugs are often more difficult to supervise than IV medicines. Good patient education by physicians familiar with erlotinib will improve compliance and reduce the risks patients continue with medication when it is causing harm.

All new drugs require training of the extended teams which oncologists work with to treat patients, especially chemotherapy nurses.

In reality the introduction of pemetrexed and erlotinib would be relatively easy for most oncology departments. The critical decisions would fall on oncologists to select the patients likely to benefit. Also it would be ideal to give patients a choice of which treatment they preferred to explore. There is no doubt fitter younger patients may want to have taxotere or pemetrexed before erlotinib, and that there would be some tendency for patients to receive more than one treatment after failure of first line therapy. This is of course speculation, but it would be important to audit the changes in practice should NHS patients get the opportunities to receive these medicines already widely available in the rest of the developed world.