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:

Submitted by [redacted]

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

Comments coordinated by Professor David R. Ferry PhD FRCP [redacted]

Are you (tick all that apply):

X a specialist in the treatment of people with the condition for which NICE is considering this technology?

X a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

X 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)

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.

First line advanced non-small cell lung NSCLC) cancer treatment 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.

Pemetrexed, early 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 (Shih et al 1997, Cancer Res 57, 1116-23). Phase I trials identified that a 10 minute infusion given 3-weekly was the optimal schedule for tumour activity and toxicity (Thodtmann et al, 1999, J Clin Oncol 17, 3009-3016). At doses of 500 mg/m^2 peak serum concentrations are in the range 150-200 ng/mL well in excess of the IC_{50} 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/m^2 there is linearity of AUC and C_{max}. Protein binding is 81%. Excretion of pemetrexed is 80% renal. 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 B_{12} deficiency respectively (Niyikiza et al, 2002, Mol Cancer Thera, 1, 545-552). 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/m^2 3-weekly with oral folic acid daily 350-1000 ug and B_{12} 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).

Randomised trials of pemetrexed in advanced lung cancer.
After the introduction of pemetrexed into the second line setting (Hanna et al 2004, 22, 1589-1597), a first line clinical trial was designed. This trial (Scagliotti et al, 2008, 26, 3543-3550) was a noninferiority study using the fixed margin method. Patients of good performance status with any NSCLC histology were randomised to receive either cisplatin 75 mg/m^2 plus gemcitabine 1250 mg/m^2 (day 1) and gemcitabine 1250 mg/m^2 day 8 on a 3week cycle versus cisplatin 75 mg/m^2 plus pemetrexed 500 mg/m^2 day 1 only of a 3-week cycle. After learning from the previous pemtrexed trials in mesothelioma all patients had B_{12} and folic acid supplementation. The trial protocol requested tissue samples for biomarker analysis. The noninferiority design assumed a HR of 1.0 when 1190 deaths occurred giving an 80% power to reject H_0. Using the Cox proportional hazards model and two tailed 95% confidence intervals rejection of the H0 occurred when the upper limit of the HR was < 1.176. There was pre planned analysis between treatment arms and histology.

The first patient was randomised in July 2004 and the total accrual of 1725 achieved in December 2005. To give an idea of scale the RCT of MIC chemotherapy versus no chemotherapy which demonstrated an improved survival from 4.5 to 6 months randomised only 400 patients. Only 103 patient failed screening. By March 2007 1270/1725 patients had died.

The median number of cycles on each arm was 5. The numbers of delays for cisplatin related toxicity were small and equal between the arms at 1.8% pemetrexed arm versus 4.2% gemcitabine arm, leading to dose-intensity for cisplatin of 95% (pemetrexed arm) versus 93.5% (gemcitabine arm). There were less dose delays due to pemetrexed (1.5%) versus gemcitabine (10%). Along with better delivery of chemotherapy, patients in the pemetrexed arm had less febrile neutropaenia (1.3 versus 3.7%, p = 0.002), less severe anaemia (5.6 versus 9.9%, p= 0.001), less severe thrombocytopaenia (4.1 versus 12.7%, p < 0.001). There were less red cell transfusions in the pemetrexed arm, 16.1% versus 27.3%, p < 0.001) and less platelet transfusions (1.8 versus 4.5%, p= 0.02). Not surprisingly there was a lower rate of erythropoietin and GCSF use in the pemetrexed arm. Deaths considered due to study medication was <1 % in both arms of the trial.

The median survival in the cisplatin/pemetrexed and cisplatin/gemcitabine arms were identical at 10.3 months, thus the trial had a HR = 0.94 (0.84-1.05) and the primary end point of noninferiority was met. As is often the case with Kaplan-Meier survival curves the median isn't the whole story. At 12 months the survival in the pemetrexed arm was 43.5% and at 24 months was 18.9%, the corresponding figures for the gemcitabine arms were 41.9% and 14.0%. Clearly something was going on.

Subgroups of patients in the Scagliotti trial

Group	Number of patients	Median survival (months)		HR (95% CI)	P
		CP	CG		
All patients	1725	10.3	10.3	0.94 (0.84-1.05)	
Adenocarcinoma	847	12.6	10.9	0.84 (0.71-0.99)	0.03
Large cell	153	10.4	6.7	0.67 (0.48-0.96)	0.03
Squamous	473	9.4	10.8	1.23 (1.00-1.51)	0.05
Nonsquamous*	1000	11.8	10.4	0.81 (0.70-0.94)	0.005
Not classified	252	8.6	9.2	1.08 (0.81-1.45)	0.586

* adenocarcinoma + large cell

In terms of overall survival how confident can we be that the result from this clinical trial is reliable? There is little doubt this trial was run to the highest standards and the end point of

death is entirely reliable. Perhaps the superior results in adenocarcinoma and large cell cancer was due to a statistical freak and somehow patients with better outcomes were erroneously assigned this histology instead of squamous cell cancer by mistake. This mistake would have to have occurred in over 100 centres across Europe and the USA. Consistent and uniform errors would have to made. The probability of this happening is remote in the extreme. Perhaps if there had been central review of pathology the result would have changed. For this analysis not having central review could be regarded as a strength. In this study working pathologists *independently* came to these diagnoses in their daily work. This is what will happen in practice. Are the subgroups are too small to provide a reliable answer? Trials can always be larger, this always reduces the size of the confidence intervals, but there is trade off with costs and ethics of randomising too many patients to inferior treatments. The effect of pemetrexed in this trail are large by the standards on NSCLC and certainly if this interim analysis had been available to a Data Monitoring Committee it is highly unlikely they would have allowed more nonsquamous patients to be entered.

In this trial there was a prespecified analysis based on histology. In recent years clinical and biological differences between histological subtypes of NSCLC have been emerging. At the chromosome level chromosome 3 deletions are much more common in squamous cell cancers (Wistuba et al 2002, Oncogene, 21, 7298-306). At the oncogene level KRAS mutation is very rare in squamous cell cancers, but occurs in 10-30% of adenocarcinoma (Herbst et al NEJM 359, 1367-1380). EGFR kinase domain mutations are very rare in squamous cell cancers, but occur in 10-40% of adenocarcinomas. In addition early methylation of p16 is seen in squamous cell cancers and very rarely in adenocarcinomas (Lichesi et al, 2008, Cancer Res 2570-78). Recently bronchioalveolar stem cells have been isolated where KRAS, Pten and PI3kinase have been implicated in evolution to adenocarcinomas (Yangi, et al 2007, J Clin Invest, 117, 2929-40). All these genetic changes are commoner in adenocarcinoma, but in squamous cell cancers amplification of PIK3CA (PIK3 catalytic domain) occurs in 33% of cases versus 6% in adenocarcinoma (Yamamoto et al, Cancer Res, in press).

There is little doubt that biologically adenocarcinoma and squamous cell cancer of the lung are very different. Clinically the peripheral location of adenocarcinomas has been recognised for decades. One of the first therapy related observations of differences between adenocarcinoma and squamous cell cancers was the increased risk of haemoptysis with VEGF binding antibody bevacicumab, which led to the exclusion of these patients from clinical trails with this class of agent (Johnson et al J Clin Oncol 22, 2184-91). There is also emerging data on the expression of thymidylate synthase levels and effectiveness of pemetrexed. TS expression is higher in squamous cell cancers (Einhorn 2008 JCO, 21, 3485-6) and we know from preclinical models that high TS expression correlates with decreased efficacy of pemetrexed (Giovannetti et al 2005, Mol Pharmacol 68, 110-118). In addition we are learning more about the expression of the reduced folate carrier, which could lead to differential biological effects.

Are there other data which from other clinical trials which provides independent confirmation of the finding of superiority of pemetrexed in adenocarcinomas versus squamous cell cancers? The main plank in this data comes from a clinical trial of pemetrexed versus placebo in patients who had stable disease or response after first line platin based chemotherapy but had not received pemetrexed (Ciuleanu et al 2008 Proc Am Soc Clin Oncol 26, 426s). This trial randomised 663 patients with NSCLC with a 2:1 randomisation to pemetrexed 500 mg/m^2 3-weekly till progression or placebo. The very low toxicity of pemetrexed allowed this. The median age of the patients entered was 60, with 72% being PS0 and 28% PS1. 50 % had adenocarcinoma, 27% squamous cell cancer and 20% couldn't be classified. The median number of cycles in the pemetrexed arm was 4 and in the placebo arm was 3.

	Median PFS (months)			Median OS (months)		
Histology	Pem	Control	P value	Pem	Control	P value
Adenocarcinoma (n = 482)	4.60	2.66	< 0.00001	16.4	11.7	0.005
Large cell (n=20)	4.53	1.45	0.999	9.1	5.5	0.091
Squamous (n = 181)	2.43	2.50	0.986	9.6	11.9	0.231
Other	4.11	1.58	0.0001	11.3	7.0	0.005

The post second line treatment was more extensive in placebo patients with 50% having further anticancer drugs, versus 37% in the pemetrexed arm. The effect in adenocarcinoma patients is striking and illustrates the same phenomenology as in the first line trial of Sagliotti. It must be remembered that these patients did not have pemetrexed first line. This approach is being explored in a randomised clinical trial where pemetrexed is being given in the first line setting and then randomisation to sequential immediate pemetrexed or placebo is occurring.

Are there other examples of differential effects of chemotherapy in adenocarcinomas versus squamous cell cancers? In squamous oesophageal cancer the combination of mitomycin, ifosfamide and cisplatin has a pathological CR rate of 16% in the neoadjuvant before surgery context. In adenocarcinoma the pathological CR rate is 0% and survival much worse (Darnton et al, 2003, JCO,.4009-4015).

The results of the Scagliotti trial are robust and certainly did not occur by chance. The superior survival outcome associated with decreased toxicity and hospital attendances for chemotherapy is a rare double win for patients.

Setting for technology delivery
Pemetrexed is given as 10 minute infusion intravenously. It will reduce the duration of the chemotherapy in combination with cisplatin by 20 minutes on day 1 of each cycle. It has the major advantage that no blood tests are needed before day 8 as is the case with gemcitiabine because there is no day 8 treatment. This chemotherapy will be given in the outpatient setting, but we still have some oncology departments where they have not yet reached that level of development and still admit patients for chemotherapy. The decreases in febrile neutropaenia rates, decreased blood transfusions and decreased requirement for platelets are also major advantages.

Variation of use in the NHS
Because of the improved survival and toxicity some centres have already approved pemetexed in combination with cisplatin ahead of NICE assessment. This is a minority of centres, but momentum is building.

Clinical guidelines
No guidelines have to my knowledge have been issued.

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?

Ease of use
Pemetrexed is easier to deliver than gemcitabine, the infusion is shorter and there is no day 8 treatment.

Rules for starting and stopping treatment
Starting treatment would be dependent upon a diagnosis of adenocarcinoma, or large cell cancer of the lung, in a good PS patient with good renal function. Stopping would occur after 2 cycles if CT showed PD or SD and no symptom improvement. After 4 cycles of cisplatin/pemetrexed no further chemotherapy would be planned and patients would enter follow up.

Applicability of trial evidence to standard UK oncology practice
The trail data would translate easily into UK clinical practice with a wide spread shift of patients from cisplatin/gemcitabine to cisplatin/pemetrexed.

Impact of side-effects
Switching to cisplatin/pemetrexed will substantially reduce admissions for infections, neutropaenic fevers, blood transfusions and platelet transfusion. Patients will also enjoy a better tolerance of treatment and less hospital visits.

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)?

If pemetrexed is adopted first line for the treatment of advanced nonsquamous NSCLC then this will ease the delivery in chemotherapy suites because of the lack of need for day 8 treatments.

No new equipment of facilities will be needed.

There would need to be some staff education around the delivery of im B_{12} and folate supplementation.