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?

Patients usually present with a pleural effusion. This is usually treated by drainage, a surgical pleuradesis is the most efficient way of gaining control. After this, patients can remain well for on average 5 months but this can vary.

Patients are now considered for the MARS trial in the UK. If eligible, all patients are offered chemotherapy and then randomised to either radical surgery and radiotherapy or randomised not to received radical surgery and radiotherapy . This accounts for about 30% of patients being worked up for this approach but only 5% randomised.

I do not offer treatment to all patients and did take part in the MESO1 trial in which patients were offered no chemotherapy or chemotherapy. This was hard to do but I felt it was necessary so that all patients in the future could be offered treatment and we would know the true value of it – in general I selected asymptomatic patients for this or those patients who questioned the potential value of chemotherapy.

In general, symptomic patients with a good performance status (0,1,2) in my practice are offered chemotherapy with MVP (mitomycin, vinblastine and cisplatin) or vinorelbine (oral or intravenously). A gemcitabine combination with either cisplatin or carboplatin is also active. The average number of courses given is 4. I have used quite a bit of pemetrexed alone and in combination. I have found this an active and well tolerated regimen and the results of an audit of this experience were present at BCRM, Birmingham 2006 and have been submitted to BJC for publication.

Is there significant geographical variation in current practice?

Yes, I think so, as not all lung oncologists have experience in treating this disease and therefore in the absence of evidence showing that treatment prolongs life estime that the symptom gain in not worth it.

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?

As above

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?

There are well described prognostic subgroups. Sarcomatoid pathology is a particularly bad subgroup – but no subgroup that potentially could not benefit from treatment.

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)?

Specialist oncology centres used to treating this disease. No extra input should be needed.

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?

Currently not available in the NHS – in general turned down by the PCTs.

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.

Patients must be performance status 0,1 and fit to receive a moderate dose of cisplatin (75mg/sq.m) from the Vogelgang randomised phase III trial.

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?

The results first reported in 2002 demonstrated a statistically significant advantage in median survival (12.1 months versus 9.3 months, p=0.02) in the combination treatment arm (Vogelzang et al., 2003). A long term update of this trial has reported a further increment in the median survival advantage of the combination arm (12.8 months versus 9.0 months, p=0.003)(Vogelzang et al., 2005). A second phase III trial of similar design, substituting raltitrexed for pemetrexed has been published and also shows a statistically significant improvement in median survival (11.4 months versus 8.8 months, p=0.048) compared to cisplatin alone (van Meerbeeck et al., 2005) – This also included PS 2 patients

I think these phase III study reflects the real clinical situation. I think the control arm of single agent cisplatin was a reasonable comparator – it was also the choice of the EORTC doing a similar trial at that time (van Meerbeck et al). Both of these trials have given very similar results for both control and investigational arm.

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?

For me the most important issue is the fact that the median survival was 12 months with pemetrexed and cisplatin, and this was better than the control arm, we have a similar trend in out smaller audit and therefore I think there is a survival gain for these patients. If this trial needs to be repeated then this will take up to 4 years to show results and will cost around 0.5 million pounds – meanwhile our patients will be dying quicker than in other countries.

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?

The toxicity profile is typical for most chemotherapy and is dictacted by the cisplatin drug and not the pemetrexed.

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?

There is very little change in the treatment being given in practically terms – the difference is the new technology appears to work better in terms of better survival.

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.

As in the trial this treatment should be restricted to patients who are PS 0/1 and who will receive cisplatin with the pemetrexed with the cisplatin dose being 75mg/sq.m

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.

We have analysed the use of (AP) pemetrexed and cisplatin (75 mg/sq/m), n=21, in an expanded access program (EAP) and will focus only on the patients with PS 0/1 like in the Vogelgang paper. We have compared them to a historic group of patients with PS 0/1 who we have treated with MVP (50 mg/sq.m), n=85, (published by Andrepoulou et al). Patients had pathologically confirmed MM. The median number of cycles of chemotherapy was 4 for AP and 3 for MVP.

There was a trend towards increased time to symptom progression with AP (30 vs 19 weeks, p=0.3) and median survival (52 vs 34 weeks, p=0.6) but no difference in progression free survival (PFS 23 vs 20 weeks, p=0.7). There was reduced overall toxicity with the pemetrexed regimens for alopecia (p=0.01) but no differences in grade 3-4 toxicity. The median survival at 52 months is as in the Vogelgang paper.

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)?

No extra resources

Please note: 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.