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?.

Treatment is governed by a previously published NICE guidance, in particular:

- No. 30 Breast Cancer – Taxanes (review)
- No. 62 Breast Cancer - Capecitabine

Is there significant geographical variation in current practice?

No, treatment tends to follow the sequence of therapies Anthracycline -> Taxane -> Capecitabine -> Vinorelbine. There is some local variation in the detail of treatment, but the overall strategy appears to be similar across the country.

Are there differences in opinion between professionals as to what current practice should be?

The majority of professionals are happy to follow existing NICE guidance, tailoring treatment to tumour and host biology. The exception is use of the Docetaxel plus Capecitabine regimen which is only used rarely on the basis of associated toxicity.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The alternatives to the technology being appraised are:

- Docetaxel 75 mg/m^2 IV plus Capecitabine 1250 mg/m^2 bd x 14 days, 3 weekly
- Docetaxel IV monotherapy (Dose range 60-100 mg/m^2) 3 weekly.
- Paclitaxel IV Monotherapy (Commonly 175 mg/m^2 3 weekly or 80-90 mg/m^2 weekly in less fit patients)

Docetaxel 75 mg/m^2 IV plus Capecitabine 1250 mg/m^2 bd x 14 days, 3 weekly has been shown to be more **active** but also more **toxic** than Docetaxel 100 mg/m^2 IV monotherapy

Docetaxel 100 mg/m^2 IV monotherapy has been shown to be more **active** but also more **toxic** than Paclitaxel 175 mg/m^2 3 weekly IV monotherapy

Docetaxel 75mg/m^2 is less active than Docetaxel 100 mg/m^2.

There are no comparative data of Docetaxel 75mg/m^2 vs. Paclitaxel 175 mg/m^2 but non-randomised across trial comparisons suggest that they have similar activity.

In practice, many clinicians keep the Docetaxel/Capecitabine in reserve only using it for young and very fit patients with life threatening disease and who are “triple negative” (Oestrogen, progesterone and HER-2 all negative). They use Docetaxel 75-100 mg/m^2 for most patients and weekly paclitaxel for the unfit, elderly and frail.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

There are number of recognised factors affecting outcome and choice of treatment. These include:

- Hormone receptor status
- Her-2 status
- Visceral or CNS disease vs. Soft-tissue & bone disease
- Previous adjuvant therapy
- “Performance Status”
- Organ function

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

This technology would be limited to fitter patients with good organ function but use would be likely to be less restricted than the use of Docetaxel/Capecitabine which is considerably more toxic.

The combination has not been licensed in conjunction with Trastuzumab and so should not be used in HER-2 positive patients.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

Secondary care, specialised cancer units or centres.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

Considerable experience using the Gemcitabine/Paclitaxel regimen has been gained by UK investigators in the NCRN "Tango" trial – half of the >3000 patients included in the trial received Gemcitabine/Paclitaxel as part of the trial treatment. This means cancer teams will be familiar with the regimen and little or no additional input will be required.

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?

Within the Northern Cancer Network, this technology has been approved and is in use within its license.
The Scottish Medicines have turned down an application for use of the technology on the grounds that, although an improvement in efficacy was demonstrated, the economic case was not demonstrated.
The London Cancer New Drugs Group is waiting for NICE guidance

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.

There are no relevant clinical guidelines

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?

The Gemcitabine/Paclitaxel regimen would most likely be used in clinical practice in place of the Docetaxel/Capecitabine combination.

The addition of Gemcitabine to Paclitaxel was tested in a randomised phase III trial interim results of which were presented at the American Society of Clinical Oncology in 2004. Because the analysis was not final, there has been no published report in a peer reviewed Journal. 529 patients from 19 countries were randomised to receive either Paclitaxel 175 mg/m^2 every 3 weeks or the same Paclitaxel schedule with the addition of Gemcitabine 1250 mg/m^2 on the first and 8th day of each treatment cycle. Addition of Gemcitabine improved the response rate from 22% to 41% ($p<0.0001$), median time to documentation of disease progression from 2.9 to 5.2 months (hazard ratio (HR) = 0.65, $p<0.0001$) and overall survival from 15.8 to 18.5 months (HR = 0.78, $p=0.018$). Of note, there was an excess of haematological toxicity (although this was manageable) but very little in the way of additional non-haematological toxicity .

The efficacy results were very similar to those reported from a trial of Docetaxel 100 mg/m^2 IV vs. Docetaxel 75 mg/m^2 IV plus Capecitabine 1250 mg/m^2 bd x 14 days, with both regimens given 3 weekly (O'Shaughnessy, J Clin Oncol, 20:2812, 2002). Note that the Docetaxel dose was reduced to 75mg/m^2 in the combination arm. In this trial the response rate increased from 30 to 42% with the addition of Capecitabine ($p=0.006$), time to progression was increased from 4.2 to 6.1 months (HR=0.65, $p=0.0001$) and survival from 11.5 to 14.5 months (HR=0.775, $p=0.13$). There was, however, a marked increase in toxicity using the combination regimen particularly with respect to non-haematological side effects including diarrhoea, stomatitis and hand-foot syndrome.

What other trials/combinations are relevant?

Chan et al (ASCO 2005) compared the substitution of Gemcitabine 1000 mg/m^2 on the first and 8th day of each treatment cycle (note dose) for Capecitabine 1250 mg/m^2 bd x 14 days, both in combination with Docetaxel 75 mg/m^2 IV. In this trial all efficacy endpoints were similar between the treatment arms. However, there was a trend to longer time to treatment failure in those patients who received Gemcitabine/Docetaxel and this appeared to be due to a reduction in the number of treatment toxicity related chemotherapy discontinuations, principally on the grounds of GI and skin toxicity.

Can these trials be compared?

There are always dangers of cross trial comparisons. However, both Paclitaxel monotherapy and Docetaxel monotherapy have both previously been endorsed by NICE and the addition of Gemcitabine to Paclitaxel appears to produce a similar uplift in activity to that produced by the addition of Capecitabine to Docetaxel. The Paclitaxel/Gemcitabine combination is, however, associated with significantly less toxicity than Docetaxel/Capecitabine.

If data from the Chan trial are considered and it is assumed that Paclitaxel 175 is roughly equivalent to Docetaxel 75, then the Gemcitabine/Paclitaxel regimen under consideration for this appraisal provides similar efficacy to Capecitabine/Docetaxel, which has already been approved by NICE, but with substantial advantages with respect to toxicity.

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.

Use of the technology should be limited to the first line treatment of metastatic or locally advanced breast cancer in those patients who have received an anthracycline but non-taxane containing regimen in the adjuvant setting or who have a contra-indication to anthracyclines. Patients should have adequate performance status and organ function.

Response should be assessed at least every 3 treatment cycles and clinicians should consider the most appropriate method of response assessment at the start of treatment, establishing a baseline against which the assessment will be made.

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?

The clinical trial data accurately reflect “real life”. The trial data accurately reflect UK treatment conditions, in particular the use of adjuvant anthracyclines but not taxanes and so can reasonably be extrapolated to the UK population.

What is the relative significance of any side effects or adverse reactions?

The most significant difference between these trial data and those for Capecitabine/Docetaxel which this might replace is the favourable toxicity profile for Gemcitabine/Paclitaxel.

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?

Treatment with Gemcitabine/Paclitaxel is easily manageable although associated with typical chemotherapy side effects. I am not aware of any toxicity concerns which have arisen since the presentation of the trial data. Gemcitabine/Paclitaxel was used in more than 1500 patients in the UK NCRN “Tango” adjuvant trial and so has been widely used in the UK. A preliminary safety study in “Tango” confirmed the safety of the regimen.

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.

All of the evidence that I believe is relevant to this appraisal has been summarised above.

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)?

Deliverly of Gemcitabine/Paclitaxel requires an additional visit for gemcitabine administration on the 8th day of each treatment cycle. No additional facilities or equipment would be required beyond that for delivery of paclitaxel monotherapy.

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.