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: [redacted]

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

Comments coordinated by [redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- 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?

The current standard treatment for advanced, inoperable gastric cancer within the NHS is palliative chemotherapy. Accepted standard first line regimens are ECF: epirubicin, cisplatin and infused 5-Fluorouracil (5-FU), ECX: epirubicin cisplatin and capecitabine and EOX: epirubicin, oxaliplatin and capecitabine. In patients with contraindications to these regimens (for example due to pre-existing peripheral neuropathy, renal impairment or impaired left-ventricular cardiac function), a combination of carboplatin and infused 5-FU or capecitabine (Carbo-F or Carbo-X) may be used. The ECF regimen was established as a standard therapy by the REAL study (Ross *et al.,* 2002). The REAL-2 study demonstrated non-inferiority of oxaliplatin to cisplatin and capecitabine to infused 5-FU. Additionally, the longest median overall survival was seen in patients treated with EOX (Cunningham *et al.,* 2008). The majority of oncologists within the UK are now using EOX as first line therapy. However, availability of funding for oxaliplatin and capecitabine prevents some clinicians from adopting this regimen.
The main alternative to capecitabine is infused 5-FU, delivered via a pump connected to a central venous access device (CVAD) continuously throughout treatment. 5-FU within ECF is associated with a slightly lower frequency of diarrhoea than EOX and hand foot syndrome than ECX (Cunningham *et al.,* 2008). However, the requirement for a CVAD is associated with an increased risk of thromboembolic (Starling *et al.,* 2009) and infective complications (Cunningham *et al.,* 2008). Additionally, patients prefer oral treatments (Pfeiffer *et al.,* 2006; Twelves *et al.,* 2006). Another important advantage of capecitabine compared to infused 5-FU is a moderate improvement in overall survival in advanced oesophago-gastric cancer demonstrated by a meta-analysis (Okines *et al.,* 2009).

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?

Whilst several prognostic factors including poor performance status, raised serum alkaline phosphatase and the presence of liver and peritoneal metastases have been identified (Chau *et al.,* 2004), there are no data to suggest that these patients do not benefit from capecitabine compared to infused 5-FU. In a randomised trial comparing cisplatin/5-FU with cisplatin/capecitabine in advanced gastric cancer, no significant differences in treatment effect were seen for any sub-group (Kang *et al.,* 2009).

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)?

Capecitabine should be prescribed by trained oncologists, but taken by patients in the community. No additional input is required. Patients need to be counselled regarding how and when to take their capecitabine tablets, but compared to the specialist nursing input previously needed to train patients to manage their CVAD/5-FU pump, this is a reduction in input.
In January 2008 the National Patient Safety Agency issued a rapid alert concerning incorrect dosing of oral chemotherapy (National Patient Safety Agency Rapid

Response Report, January 2008). As a consequence specialist units have already set up robust prescribing and dispensing processes for oral chemotherapy (including capecitabine) so there would be no further need for additional professional input.

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?

Capecitabine is also widely used in patients with advanced cancers of the oesophago-gastric junction (OGJ) and oesophagus as these patients were also included in the REAL-2 study (Cunningham et al., 2008). This is outside the licensed indication but evidence-based from this large multicentre randomised phase III study. Of note, EOX is the standard arm in the current NCRI REAL3 study.
Capecitabine is also used in the localised disease setting as part of peri-operative ECX chemotherapy. The MRC MAGIC study demonstrated that peri-operative ECF chemotherapy improves overall survival in localised gastric cancer compared to surgery alone (Cunningham *et al.,* 2006). The non-inferiority of capecitabine to infused 5-FU demonstrated by the REAL-2 (Cunningham *et al.,* 2008) and ML17032 (Kang *et al.,* 2009) studies has been extrapolated to the localised disease setting due to the convenience of the oral medication and reduced risk of CVAD-associated complications. ECX is the standard arm of the current MRC ST03 study.

*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.*

The European Society of Medical Oncology (ESMO) Clinical Recommendations for gastric cancer (Jackson *et al.,* 2009) advise the use of palliative chemotherapy regimens including a platinum and fluoropyrimidine with options including ECF, EOX and ECX for advanced gastric cancer. The REAL-2 trial (Cunningham *et al.,* 2008), ML17032 study (Kang *et al.,* 2009) and meta-analysis of the REAL-2 and ML17032 studies (Okines *et al.,* 2009) are appropriately used to underpin these recommendations.

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?

Capecitabine is easier to use than infused 5-FU; in particular because no CVAD is required. Another advantage of oral dosing is the ease of interrupting dosing and make dose adjustments to manage any fluoropyrimidine-related toxicity that occurs.
Concomitant warfarin with capecitabine has to be carefully managed with more intense INR monitoring in patients requiring formal anticoagulation. This is due to a known interaction. Alternatively, patients can have their anticoagulation changed to daily low molecular weight heparin injections.
No additional tests are required for patients to receive capecitabine compared to infused 5-FU. Capecitabine cannot be used in patients with severe renal impairment although infused 5-FU can be used in these patients with appropriate dose adjustments.

Patient acceptability of capecitabine is good and two of the three studies assessing patient acceptability of oral compared with intravenous fluoropyrimidines in colorectal cancer have been in favour of the oral comparator.

The recent National Chemotherapy Advisory Group Report established that the use of chemotherapy has expanded rapidly in the last few years and is creating significant capacity issues in both Cancer Centres and Units (Report of the National Chemotherapy Advisory Group, 2009) As a consequence specialist units are being encouraged to review and streamline their chemotherapy service provision. The use of capecitabine in this indication would potentially have a positive effect on chemotherapy provision. Patients receiving infused 5-FU through a CVAD (ECF) require weekly trips to the chemotherapy suite. Patients receiving capecitabine (ECX/EOX) only have one trip every 3 weeks. Therefore the number of hospital visits for patients with gastric cancer receiving a course of capecitabine-based rather than infused 5-FU-based treatment would reduce from 24 to 8.

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.

This is no different for capecitabine compared to infused 5-FU.

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?

The use of capecitabine in advanced oesophago-gastric cancer in clinical practice is entirely reflective of that reported from the REAL-2 study. This is largely because this was a UK-based multicentre study, conducted at small as well as large oncology units throughout the UK.
The most important outcomes of overall survival, progression free survival, response rate, toxicity and quality of life were all measured in the REAL-2 trial. These reflect outcomes which are important both to the clinician and patient.

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?

A slight increase in grade 3-4 diarrhoea, lethargy and hand-foot syndrome were reported with EOX compared to ECF in the REAL-2 study, but these can be managed easily with interruption +/- dose reduction. Additional peripheral neuropathy was also reported, but this is associated with the substitution of oxaliplatin for cisplatin rather than capecitabine for 5-FU. These increased toxicities were balanced by a reduction in neutropenia and thromboembolism.
No new side effects have been discovered in clinical practice as capecitabine is now a widely used drug in clinical trials in colorectal and breast as well as oesophagogastric cancer trials and clinical practice. Additionally, 461 patients treated with capecitabine within REAL-2 were evaluable for toxicity, therefore this large study is representative of practice.

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.

No, the relevant data are published.

References:

Chau I,,Norman, A. R, Cunningham, D et al. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer--pooled analysis from three multicenter, randomized, controlled trials using individual patient data. J Clin Oncol 2004; 22 (12): 2395-403

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Jackson C, Cunningham D & Oliveira J On behalf of the ESMO Guidelines Working Group. Gastric cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009; 20 (Supplement 4): iv34–iv36.

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Okines AFC, Norman AR, McCloud P et al. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol 2009 Sept; 20 (9): 1529-34

Pfeiffer, P., Mortensen, J.P., Bjerregaard, B. et al. Patient preference for oral or intravenous chemotherapy: A randomised cross-over trial comparing capecitabine and Nordic fluorouracil/leucovorin in patients with colorectal cancer. Eur J Cancer 2006, 42(16): 2738-43.

Starling, N, Rao, S, Cunningham, D et al. Thromboembolism in patients with advanced gastroesophageal cancer treated with anthracycline, platinum, and fluoropyrimidine combination chemotherapy: a report from the UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group. J Clin Oncol 2009; 27 (23); 3786-93

Twelves, C., Gollins, S., Grieve, R., Samuel, L. A randomised cross-over trial comparing patient preference for oral capecitabine and 5-fluorouracil/leucovorin regimens in patients with advanced colorectal cancer. Ann Oncol 2006, 17(2): 239-45.

Risks of incorrect dosing of oral anti-cancer medicines, National Patient Safety Agency Rapid Response Report, 22 January 2008

Chemotherapy Services in England: Ensuring Quality and Safety. Report of the National Chemotherapy Advisory Group August 2009

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)?

NICE guidance on this technology will allow uniform availability of capecitabine for patients with advanced gastric cancer across the UK. NHS staff are very unlikely to need any additional education or training due to current NICE-guided use of capecitabine in colorectal cancer. No additional facilities or equipment will be needed.