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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Capecitabine for the Treatment of Advanced Gastric Cancer

Roche Submission to the
National Institute for Health and Clinical Excellence
Submitted: 2nd December 2009

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Section A

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Brand Name: Xeloda

Approved Name: Capecitabine

Therapeutic class: Cytotoxic anti-cancer agent (fluoropyrimidine antimetabolite)

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yes. EMEA approval was granted on 28th March 2007.

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

The indication under consideration in this appraisal is “First line treatment of advanced gastric cancer (aGC) in combination with a platinum based [chemotherapy] regimen”.

Capecitabine has four other EMEA approved indications:

- the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer.
- the treatment of metastatic colorectal cancer
- in combination with docetaxel for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy [that has included] an anthracycline.

- monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

A fluoropyrimidine, in the form of intravenous (IV) 5-FU or oral capecitabine is viewed as an essential element of chemotherapy for aGC. Roche market research indicates that the majority of UK patients currently receive capecitabine as their fluoropyrimidine.

Capecitabine has been available to UK clinicians since it first regulatory approval in aGC in 2007. As well as its use in aGC, it is also widely used for the treatment of colorectal and breast cancers and Roche estimates that thousands of patients are treated with capecitabine each year in the UK. Overall there is very wide experience of the use of capecitabine amongst clinicians and nurses involved in treating solid cancers in the UK.

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

Yes. Capecitabine is approved by regulatory agencies throughout the world including the USA and the whole of Europe (through the EMEA). Further details can be provided on request.

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

The Scottish Medicines Consortium reviewed this indication for capecitabine in 2007 and issued guidance indicating that capecitabine should be available for the treatment of aGC under the NHS in Scotland on 10th September 2007.

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Oral tablets in strengths of 150 mg (packs of 60 tablets) and 500mg (packs of 120 tablets).

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

Roche anticipates that, in the UK, the majority of aGC patients receiving capecitabine will do so as part of the ECX regimen of epirubicin, cisplatin and capecitabine (Xeloda). In this regimen the dose of capecitabine is 625 mg/m^2, twice daily. The planned duration of treatment is usually 24 weeks (as per clinical trials) but early cessation of treatment for lack of efficacy or toxicity reduces the average treatment duration to about 5.5 cycles (16.5 weeks).

Some patients will also receive the CX regimen of cisplatin and capecitabine, where capecitabine is given on an intermittent schedule at a dose of 1,000 mg/m^2 twice daily for 14 days in every 21 days with treatment continued until disease progression or intolerable toxicity (typically around 5 cycles). Another group will receive EOX (the same as ECX but with cisplatin replaced by the alternative platinum drug, oxaliplatin). Again, the treatment duration would typically be around 16.5 weeks/5.5 cycles.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

As of the 1st January 2010 (following an agreed 10% reduction in the list price of Xeloda) the acquisition cost of capecitabine (excluding VAT) will be:

150mg tablets, 60 = £40.02

500mg tablets, 120 = £265.55

1.10 What is the setting for the use of the technology?

Capecitabine is an oral treatment self-administered by patients in their own home. The treatment of aGC is overseen by hospital-based oncologists, and the other (IV administered) chemotherapy drugs given with it are administered in the hospital, normally in a chemotherapy day-unit.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations

needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

None that Roche is aware of beyond the patient's ability to swallow tablets (capecitabine as proposed here is being used to replace IV 5-FU). By removing the need for protracted IV infusions of 5-FU, adoption of capecitabine will simplify treatment by removing the need for central venous access to be obtained and maintained and the procurement, replenishment and maintenance of the portable infusion pumps used to deliver 5-FU

2 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

Table 1. Overview of Decision Problem

	Final scope issued by NICE	Decision problem addressed in the submission.
Population	People with advanced, inoperable gastric cancer.	As scope
Intervention	Capecitabine in combination with platinum-based chemotherapy regimens.	As scope
Comparator(s)	Fluorouracil in combination with platinum chemotherapy regimens.	As scope, specifically the ECF, EOF and CF regimens
Outcomes	Overall survival Progression-free survival	As scope, though the importance of response rates is questionable

	Response rates Adverse effects Health-related quality of life.	
Economic Analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs and outcomes between the technologies being compared. Costs will be considered from an NHS and personal social services perspective	Both of the major studies comparing 5-FU and capecitabine in advanced gastric cancer were based on the assumption that if oral capecitabine proved as effective and well tolerated as IV 5-FU, then it would be the preferred treatment – the studies looked for non-inferiority of clinical outcomes. The studies were successful in demonstrating non-inferiority (indeed they showed a trend towards superior outcomes with capecitabine) Against this background a cost-minimisation approach to economic analysis is considered more appropriate and will be utilised in the submission.
Subgroups to be considered	None specified	None
Special considerations, including issues related to equity or equality	None specified	None identified

Section B

3 Executive summary

Background

Gastric cancer is the tenth most commonly diagnosed cancer in the UK. Just under 7,000 new cases are diagnosed each year in England and Wales and these account for around 4,200 deaths. The mortality rate is high because most patients present with disease too advanced for curative surgical removal of their tumor (see section 4.1). For the 80% of patients unsuitable for curative surgery (Bachman, 2002), palliative chemotherapy is an option and it is estimated that, in England and Wales, just over half (around 2,900) of the patients with advanced gastric cancer (aGC) receive such treatment (see section 8). Palliative chemotherapy modestly improves survival as well as relieving disease symptoms.

The chemotherapy for aGC conventionally comprised protracted infusions of 5-FU plus cisplatin, sometimes with the addition of an anthracycline drug (epirubicin or doxorubicin). Until recently the most widely used regimen in the UK was ECF. This consists of IV cisplatin and epirubicin administered once every 3 weeks plus the fluoropyrimidine 5-FU, administered by continuous IV infusion delivered via a permanently implanted venous access device and portable infusion pump. Although this provides good palliative benefits the requirement for patients to be permanently attached to a 5-FU pump has significant drawbacks. These include:

Negative impact of implanted venous access and pump on body image
Inconvenience of permanent attachment to a pump and line which interferes with activities of work, leisure and daily living
Need to visit hospital, typically weekly, for pump replenishment and line maintenance
Anxiety and inconvenience of pump (mechanical failure) and line (dislodgement, blockage, thrombosis, infection).

The insertion and maintenance of lines, the filling, maintenance and replenishment of pumps and dealing with line complications also place a significant burden on the NHS both in terms of cost and occupation of valuable spaces in chemotherapy clinics.

There has also been some use of the CF combination (cisplatin plus 5 days infusion of 5-FU), typically for patients not wanting or unsuitable for an ambulatory 5-FU pump, though this too has drawbacks since patients need either to be admitted to hospital for their chemotherapy or discharged with an ambulatory pump attached to a permanent venous access, attending the hospital delay for pump replenishment.

Capecitabine

Given the disadvantages of infused 5-FU regimens for aGC, the possibility of replacing them with oral flouropyrimidines, like capecitabine, is attractive. Capecitabine (Xeloda®) is an orally administered pro-drug of 5-FU which has already been shown to be as effective and well tolerated as IV 5-FU in the treatment of early and advanced colorectal cancer. It has received positive reimbursement

endorsements from both NICE and the SMC for all existing indications (including aGC in the case of the SMC), where its use has consistently been demonstrated to result in significant cost savings to the NHS as well as having patient benefits in these settings; it also addresses national healthcare policies that support the use of oral cancer treatments and the delivery of care closer to home.

This submission will therefore present the clinical and economic evidence supporting the use of capecitabine as an alternative to IV 5-FU for aGC.

Table 2. Capecitabine key information

Approved Name	Capecitabine
Brand Name	Xeloda
Marketing Status	Capecitabine was granted marketing authorisation on the 28th March 2007.
Indication	"Capecitabine is indicated for the first line treatment of patients with advanced gastric cancer (aGC) in combination with a platinum based chemotherapy regimen".
Pharmacological Action	Capecitabine is a non-cytotoxic pro-drug of 5-FU which is reliably absorbed from the gut and is well tolerated when given by mouth, facilitating oral treatment. It is converted, within the body, to 5-FU in a three step process with each step facilitated by a different enzyme (Miwa et al. 1998). The last of the three enzymes involved, thymidine phosphorylase - also known as tumour associated angiogenic factor - is found in particularly high concentrations in many solid tumours (Miwa et al. 1998), leading to the preferential accumulation of 5-FU in tumour tissues.
Formulation	Oral tablets containing 150mg and 500mg of capecitabine
Pack Sizes	The 150mg tablets come in packs of 60 tablets while the 500mg tablets come in packs of 120 tablets
Acquisition Cost	From January 2010 the cost of a 150mg (60 tablets) of capecitabine (minus VAT) will be £40.02 and a 500 mg (120 tablets) vial (minus VAT) will be £265.55.
Frequency of treatment	In combination treatment, capecitabine's recommended dose is the continuous administration of 625mg/m2 taken orally twice daily during the 21 day cycle (ECX and EOX regimens) or 800-1000mg/m2 when administered twice daily for 14 days followed by a 7-day rest period (CX regimen), with each 21-day 'cycle' being repeated until disease progression or unacceptable toxicity.

Comparators

The base case choice of comparators within the economic evaluation is ECF, EOF and CF regimens, in line with current standard chemotherapy for aGC in England and Wales. ECF and EOF were also the comparators used in the REAL-2 clinical trial (Cunningham et al. 2006) and CF was used in the ML17032 trial (Kang et al, 2006) Even though ECF is much more widely used than CF and EOF, all combination

regimens can be considered an adequate representation of the standard of care in the UK for the first line treatment of aGC, as reflected in the NICE final scope.

Table 3. Decision Problem Overview

Disease setting	Current standards of care in England	Relevant license indication	Questions for this appraisal
Patients with advanced, inoperable gastric cancer.	Both oral capecitabine and IV Fluorouracil in combination with platinum base chemotherapy regimens	"Capecitabine is indicated for the first line treatment of patients with advanced gastric cancer (aGC) in combination with a platinum based chemotherapy regimen".	Is oral capecitabine, when given in combination with platinum base chemotherapy to patients with advanced gastric cancer clinically and cost effective?

Clinical Effectiveness Evidence

Capecitabine in aGC has demonstrated equivalent clinical efficacy and safety to infused 5-FU in two randomised phase III clinical trials (REAL 2 and ML 17032). In the first trial it replaced continuous IV 5-FU in the ECF (the current standard chemotherapy for aGC in Scotland) and EOF (a variant of ECF in which cisplatin is replaced by the less nephrotoxic platinum drug, oxaliplatin) regimens. In the second it was substituted for 5-day IV infusion of 5-FU in the CF combination. These two studies were, primarily, designed to demonstrate non-inferiority of the capecitabine containing regimen versus the control 5-FU-based treatment with regard to overall survival and progression-free survival respectively. The underlying assumption in both cases being that the advantages of oral therapy are such that this would be the preferred option as long as it did not produce worse outcomes than 5-FU). In both cases this primary end-point was met and in a clear trend could be seen towards superior outcomes (both primary and secondary) in the capecitabine arm. In terms of primary study end-points, replacing continuous 5-FU in the ECF/EOF regimens with oral capecitabine produced a hazard ratio for risk of death (capecitabine vs. 5-FU) of 0.89 (95% confidence interval 0.77-1.02, well below the protocol-defined non-inferiority boundary of 1.23), whilst switching from 5-FU to capecitabine in the CF regimen reduced produced a hazard ratio for progression-free survival cisplatin plus capecitabine versus CF of 0.85 (95% confidence interval 0.65, 1.11; p=0.005).

A meta-analysis of these two studies demonstrated a significant improvement in overall survival when capecitabine was used in place of 5-FU – hazard ratio 0.87 (95% confidence interval 0.77-0.98; p=0.027)

These two studies also demonstrated not only that moving from infused IV 5-FU to oral capecitabine, as a minimum, maintained efficacy with regard to important clinical end-points, but also that this could be done without compromising on treatment toxicity, which in both studies was very similar in the 5-FU and capecitabine groups.

The only adverse event that was consistently more frequent in patients receiving capecitabine was hand-foot syndrome. Hand-foot syndrome is characterised by redness and soreness of the palms of the hands and soles of the feet. It is generally of only mild-moderate intensity and does not presage any more serious event. It is primarily dealt with by dose reduction or treatment interruption, which result in rapid resolution. As such, it is generally perceived as an inconvenience rather than something which has great implications for the patient or NHS resources. Conversely, capecitabine was consistently associated with a trend towards reduced stomatitis compared with 5-FU and, because, oral capecitabine does not require the placement of a permanent venous access, it is not associated with the need to resolve unpleasant, often costly and occasionally life-threatening access complications such as thrombosis or infection.

Overall, given the well-established patient preference for effective oral treatments and the NHS burden associated with IV administration of chemotherapy, data from the ML17032 and REAL-2 provide a compelling clinical case for the adoption of capecitabine as the fluoropyrimidine element of platinum-containing chemotherapy for aGC.

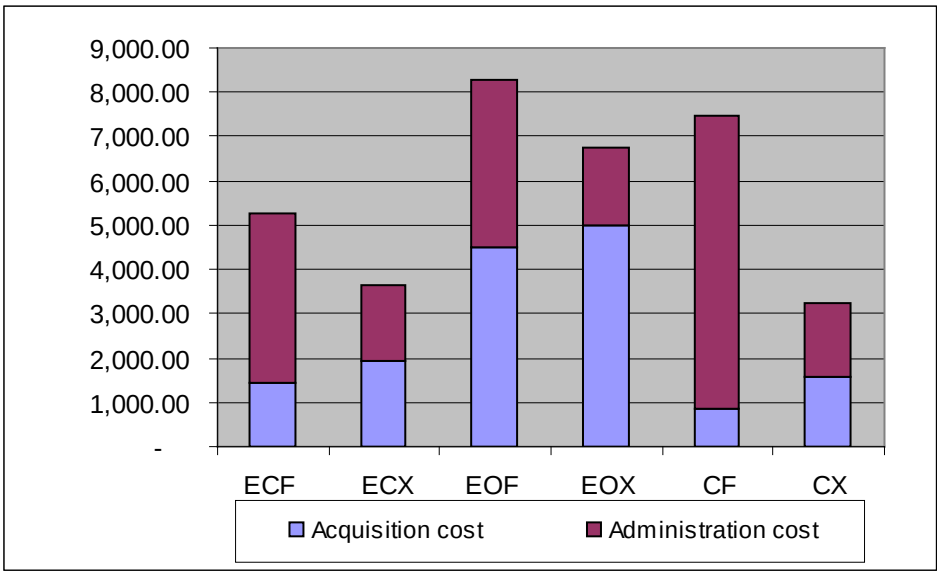
Cost Effectiveness Evidence

Based on the phase III clinical trial evidence that demonstrates oral capecitabine is at least as clinically effective as IV 5-FU, with a comparable side effect profile, a cost-minimisation analysis constructed in excel has been undertaken comparing the direct NHS costs associated with alternative advanced gastric cancer regimens (ECF and ECX; EOF and EOX and CF and CX). Direct costs included, drug acquisition costs, pharmacy preparation time, monitoring costs, drug administration, medical supply cost and staff costs.

Costs associated with the management of adverse events were not included as the treatment related adverse events demonstrated in the phase III trials were comparable with no significant variation in the associated cost of management anticipated.

The additional drug acquisition costs for capecitabine are: £480 (ECX), £528 (EOX) and £683 (CX) per patient course compared to the equivalent 5-FU based regimens. Through the avoidance of 5-FU drug administrations, these additional drug costs are more than offset by drug administration savings of £2,100 (ECX and EOX) and £4,893 (CX). Consequently the net cost savings for capecitabine based regimens are £1,620, £1,572 and £4,210 per patient respectively. Figure 1 below shows the total cost for each of the regimens evaluated.

Figure 1. Overall Total Direct NHS cost for alternative advanced gastric cancer regimens



Sensitivty analysis which varied model assumptions across a wide range of values to to reflect parameter uncertainty demonstrated that capecitabine remained cost saving, despite extreme changes in assumptions.

4 Context

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage

Epidemiology

There were 6,706 new cases of gastric cancer reported in England and Wales in 2006 and 4,255 deaths in 2007 (CRUK, 2009a). Compared with historic data these figures demonstrate that in the UK – as in most developed countries- the incidence of gastric cancer and the associated mortality are in steady and dramatic decline, with a 70% reduction in mortality over the last 30 years (CRUK, 2009b). However, they also demonstrate that gastric cancer still represents a significant source of morbidity and mortality. This is both because it is still a relatively common cancer and because the prognosis after diagnosis is, generally, poor. In the UK, it is the seventh most common cancer in men and the fourteenth most common in women. Although one year survival has increased from 14% in the early 1970's to 35% now (in parallel with a decline in post-operative mortality), 5 year survival is still very low, at 15% (CRUK, 2009c). The poor long-term outcomes seen in the UK reflect the fact that diagnosis is usually made late at a point when spread of the tumor either locally or by metastasis precludes complete surgical excision, the only potentially curative treatment.

Treatment and outcomes

Surgery forms the primary form of treatment for gastric cancer and UK Cancer Registry data together with a survey of gastric cancer surgery in 23 NHS hospitals suggest that around 37% of patients have some sort of surgery for their cancer (CRUK, 2009d), though only in about 20% is it viewed as curative (Bachman *et al.* 2002) and for the rest it is carried out with palliative intent. Despite the acknowledged importance of surgery, around two-thirds of UK patients present with inoperable disease. For such patients, palliative chemotherapy is the only treatment option that offers an improvement in survival.

There is no internationally accepted gold-standard for the palliative chemotherapy of gastric cancer and many regimens have been tested in randomised controlled trials. This prompted Wagner *et al*. (2006, 2007) to conduct a systematic review and meta-analysis of chemotherapy for aGC. They concluded that the case for palliative chemotherapy in aGC is strong and that it provides a convincing benefit in terms of overall survival compared with Best Supportive Care (BSC) alone. They estimated that the overall survival hazard ratio (HR) of 0.39 (95% CI, 0.28-0.52) in favour of chemotherapy translates into a mean survival increase of about 6 months – a very substantial benefit given the very poor prognosis in aGC. 5-FU has historically formed the foundation of chemotherapy in aGC and was included in all regimens in the meta-analysis and the authors concluded that further gain can be achieved by

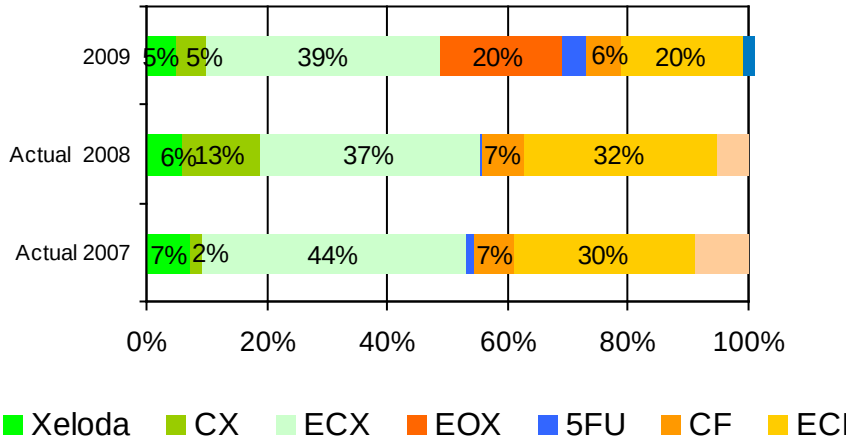
adding in second- and third-agents, most commonly an anthracycline (epirubicin or doxorubicin) and cisplatin, though they note that the benefits of combination chemotherapy over single-agent fluoropyrimidines are modest so that single-agent infusional 5-FU or two drug combinations incorporating 5-FU still have a role.
Of the three drug combinations available, Wagner *et al* considered ECF (epirubicin, cisplatin and continuously infused IV 5-FU) to have the best tolerability.

Chemotherapy for aGC in the UK

Until recently, ECF was the dominant chemotherapy for aGC in the UK. ECF was devised by clinicians working at the Royal Marsden Hospital in London at a time when the role of palliative chemotherapy for aGC was still gaining acceptance in the UK and many key UK treatment centers gained experience of it during a large investigator-initiated study comparing ECF versus FAMTX (a North American regimen of doxorubicin, 5-FU and high-dose methotrexate). This study, published by Webb *et al* in 1997, established ECF as the UK standard of care, a position that it maintained following completion of the REAL study (Ross *et al* 2002) in which epirubicin was substituted by mitomycin-c and until the publication of the REAL-2 study. REAL-2 (which is described in more detail later in this submission) attempted to improve on ECF by making two changes – replacement of continuously infused 5-FU with oral capecitabine in the interests of greater convenience and patient acceptability and the replacement of cisplatin with oxaliplatin. This second change was intended to further improve on the convenience of ECF by using a less toxic platinum derivative that does not require extensive patient hydration with large volumes of IV fluid around the time of administration.

Since, REAL-2 met its co-primary end-point of demonstrating that continuously infused 5-FU could be replaced with oral capecitabine without compromising tolerability or efficacy there has been widespread adoption of ECX (and in a smaller number of centres, EOX) in the UK, where, as shown in Figure 2, it now represents the most widely used chemotherapy regimen for aGC. This rapid uptake is explained by the advantages to both patients and the NHS of oral over IV fluoropyrimidine therapy.

Figure 2. Usage of chemotherapy regimens for advanced gastric cancer in the UK (based on market research conducted for Roche by First Line Research)

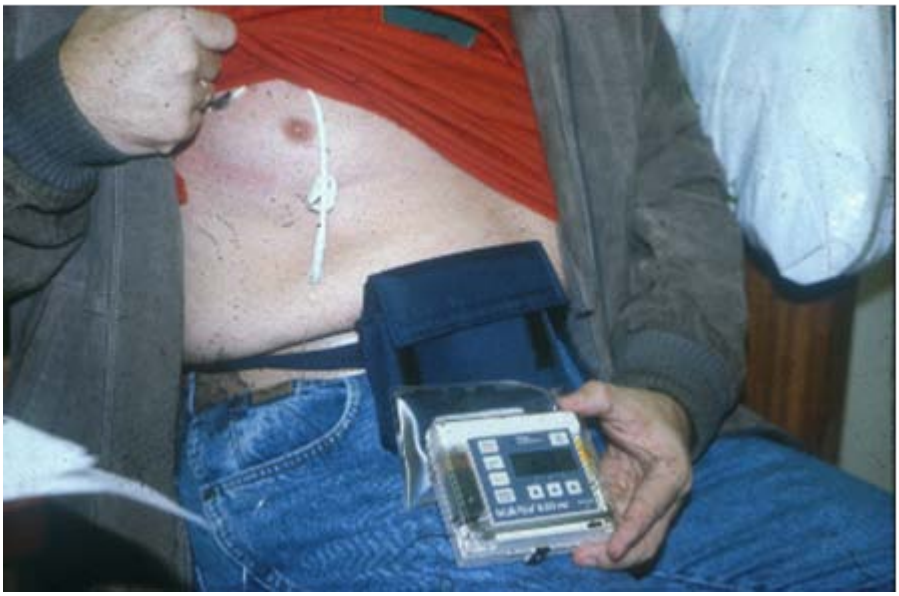


Abbreviations and synonyms: C, cisplatin; E, epirubicin; 5FU/ F, 5-fluorouracil X/Xeloda, capecitabine.

Why capecitabine is already widely used in place of 5-FU

Continuous IV infusion requires the establishment and maintenance of a permanent IV access. These are costly to place and maintain and are a frequent cause of complications both on insertion and in long-term management (Frank et al. 2001; Kuter, 2004; Schwartz et al. 2000; Verso & Agnelli 2003). The device its and associated pump (see Figure 3) also act as a constant reminder to patients of their diagnosis and treatment, as do the hospital visits required to maintain them - patients receiving capecitabine are, potentially, only required to attend hospital once every 3 weeks to receive the IV components of their combination chemotherapy, rather than at least weekly for pump and venous access care as is the case for most patients receiving continuously infused 5-FU. As well as helping them to spend less time thinking about their disease, fewer hospital visits will result in less inconvenience for patients and lower transport costs for both the patients and the NHS. In other settings, patients have demonstrated a clear preference for oral over IV chemotherapies (Liu et al. 1997; Twelves et al. 2006; Kopec et al. 2007; Borner et al. 2002; Twelves et al. 2006) including a preference for capecitabine over 5-FU (5-FU itself cannot be administered orally because of its poor and erratic absorption from the gut).

Figure 3. Ambulatory infusion pump and central line used for continuous infusion of 5-FU



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The future

Apart from the move to oral fluoropyrimidines, the treatment of aGC has remained almost unchanged for a decade despite the clear need for improvement. This looks set to change as the biology of the disease is better understood and non-specific cytotoxic therapy is augmented by targeted therapies set to interact with the specific abnormalities of gastric cancer cells. The first of these to be tested successfully in a large randomised trial was trastuzumab the anti-HER2 antibody already widely used in breast cancer. In the recently reported TOGA study (Van Cutsem et al. 2009) reduced the risk of death by 35% and increased median survival by 4.2 months in patients with high levels of HER2 overexpression or gene amplification when added to a combination of cisplatin plus capecitabine or 5-FU– substantially more than the impact reported by Wagner et al (2006, 2007) for adding in additional conventional cytotoxic drugs to aGC chemotherapy regimens.

4.2 What was the rationale for the development of the new technology?

As discussed in Section 4.1, the fluoropyrimidine drug 5-fluorouracil (5-FU) has long formed the backbone of chemotherapy regimens for gastrointestinal cancers, including aGC. However it has several disadvantages. Notably, its poor and erratic absorption precludes oral administration (Kummar et al. 2005) and its antitumour activity is also modest unless its activity is optimised by protracted intravenous (IV) infusion (over days or weeks) or co-administration with folinic acid (FA) (reviewed by Kummar et al. 2005).

Capecitabine has been developed as a well-tolerated, efficacious and cost-effective orally administered fluoropyrimidine to replace 5-FU. It was first approved by the EMEA for the treatment of metastatic colorectal cancer on the basis of evidence that it was at least as effective, better tolerated, more convenient and more cost-effective than IV bolus 5-FU plus FA (Cassidy et al. 2002; Cassidy et al. 2008; Scheithauer et al. 2003; Twelves et al. 2001; Twelves et al. 2005; Van Cutsem et al. 2004).

The equivalence of capecitabine in this situation prompted interest in its use as an alternative to other 5-FU regimens including the protracted infusions of 5-FU used as part of the combination chemotherapy of aGC such as the ECF regimen that dominated treatment in the UK and the CF (cisplatin and 5-FU) combination that is also used.

As has already been explained in Section 4.1, protracted infusions of 5-FU are less than ideal for both the patient and the healthcare system, so that the possibility of replacing them with an oral treatment is an attractive one and provided a strong impetus for trials comparing these two approaches to fluoropyrimidine therapy.

4.3 What is the principal mechanism of action of the technology?

Capecitabine is a non-cytotoxic pro-drug of 5-FU which is reliably absorbed from the gut and is well tolerated when given by mouth, facilitating oral treatment. It is converted, within the body, to 5-FU in a three step process with each step facilitated by a different enzyme (Miwa et al. 1998). The last of the three enzymes involved, thymidine phosphorylase - also known as tumour associated angiogenic factor - is found in particularly high concentrations in many solid tumours (Miwa et al. 1998), leading to the preferential accumulation of 5-FU in tumour tissues.

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

As explained in Section 4.1 the current standard treatment for aGC includes cytotoxic chemotherapy incorporating a fluoropyrimidine, conventionally IV 5-FU. In the UK this is most commonly administered by protracted infusion via an ambulatory pump. It is suggested that oral capecitabine be substituted for IV 5-FU resulting in more convenient and tolerable treatment for patients and resource savings for the NHS.

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice

Optimum chemotherapy regimen

As has been explained above there is little global consensus on the optimum chemotherapy regimen in aGC, particularly on whether the addition of an anthracycline offers a good balance of toxicity and benefit. However, it is recognised globally that a fluoropyrimidine (conventionally prolonged IV infusion of 5-FU) is the foundation of aGC chemotherapy regimens, so that the uncertainty around optimum chemotherapy does not impact on the change proposed here – the substitution of capecitabine for 5-FU.

In the UK (until the advent of the ECX regimen where 5-FU is replaced by capecitabine), the ECF regimen (epirubicin, cisplatin, 5-FU) was, by some margin, the preferred regimen amongst UK clinicians.

Management of 5-FU infusion pumps

When using ECF (and other regimens incorporating protracted 5-FU infusions) centres differ in their approach to managing 5-FU infusions. Typically a 5-FU pump (which can be a disposable device or an electromechanical one with a disposable reservoir) lasts 7 days before it needs replenishment. In some centres, in others a District Nurse may perform this service, whilst in others patients are expected to

return to the hospital on a weekly basis. All of these have advantages and disadvantages to patients and the NHS and none is ideal.

Diagnosis of aGC

In diagnosing aGC it can be difficult to distinguish tumours of the distal oesophagus from those of the gastro-oesophageal junction (Wagner et al, 2006). Although, some clinical trials exclude doubtful cases, this issue is not particularly important in clinical practice as both cancers receive the same palliative chemotherapy.

4.6 Provide details of any relevant guidelines or protocols.

Most relevant is guidance from the Scottish Medicines Consortium (SMC) which reviewed the use of capecitabine in combination with a platinum based chemotherapy regimen for first-line treatment of aGC in 2007 and issued guidance 401/07 on 10th September of that year which states that **capecitabine (Xeloda®)** is accepted for use within NHS Scotland for first line treatment of patients with advanced gastric cancer in combination with a platinum-based chemotherapy regimen.

In the USA the National Comprehensive Cancer Network, **"Clinical practice guidelines in oncology – gastric cancer, version 2"** (2009) recommend a variety of acceptable chemotherapy regimens for the palliative treatment of locally advanced and metastatic gastric cancer. These include:

Fluoropyrimidine (5-FU or capecitabine)
DCF (Docetaxel, cisplatin and 5-FU)
ECF
ECF modifications (referenced to the REAL-2 study so implicitly including EOX, ECX and EOF)
Oxaliplatin plus fluoropyrimidine (5-FU or capecitabine)
Irinotecan plus fluoropyrimidine (5-FU or capecitabine)

Most other guidance pre-dates the availability of Phase III data on capecitabine, so that although they support the use of fluoropyrimidine-based chemotherapy they often make no reference to the role of oral fluoropyrimidines:

Scottish Intercollegiate Guidelines Network (SIGN)

The SIGN "Quick reference guide to management of oesophageal and gastric cancer" (SIGN 2006) which states that:

- there is evidence showing that, in patients with locally advanced or metastatic cancer of the oesophagus or stomach with good performance status, combination chemotherapy including cisplatin and infusional 5-FU (such as ECF or MCF) should be considered and thus establishes the relevance of ECF as a current standard of care in Scotland.

European Society for Medical Oncology (ESMO) "Minimum clinical recommendations for diagnosis, treatment and follow-up of gastric cancer" (Cunningham *et al.* 2005)

These state that:

- in treatment of metastatic disease, combination regimens incorporating cisplatin and 5-FU with or without anthracyclines are generally used
- ECF is one among the most active and well tolerated combination regimens
- alternative regimens including oxaliplatin, irinotecan, docetaxel, and oral fluoropyrimidines can be considered.

Japanese Gastric Cancer Association guidelines (Kakajima, 2002)

These state that “in patients with unresectable tumour, but good performance status, combination chemotherapy with cisplatin and 5-FU or its derivatives may be the regimen of preference and recommendation”

5 Equity and equality

5.1 Identification of equity and equalities issues

Are there any issues relating to equity or equalities (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?
No issues relating to equity or equalities have been identified.

How has the analysis addressed these issues?

Not applicable.

6 Clinical evidence.

6.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in appendix 2, section 9.2.

Search strategy

Literature searching was carried out by an experienced information scientist working in the Medical Information Department of Roche Products Ltd as a capecitabine product specialist. The following electronic databases were interrogated on 12th October 2009: Embase (1993 to date), Medline (1993 to date), Medline in Process (latest eight weeks), Embase Alert (latest eight weeks), Biosis (1993 to date and most recent update). A broad strategy was used to identify citations referring to human clinical trials, gastric cancer (and variants thereof) and capecitabine (and variants thereof). Individual studies and meta-analyses were sought. The full search strategy is included in Appendix 2, Section 9.2.

In addition the abstracts of the American Society of Clinical Oncology (ASCO) Annual Meeting for the years 2004-2009 were interrogated through the Journal of Clinical Oncology website on 15th October 2009. Again a broad search strategy was used with a search carried out for any abstract containing the words “gastric” and “capecitabine” in the title or abstract body.

The Roche internal “Publication Planning” database for Xeloda (capecitabine) was also interrogated for citations relating to gastric cancer (though this did not identify any publications not already found using the external sources just described).

Clinical sections of the application to the EMEA for the extension of the Xeloda (capecitabine) Marketing Authorisation to include aGC were reviewed for additional studies of relevance.

The outputs of literature searches were scrutinised by a single reviewer (Associate Head of Medical Affairs at Roche Products Ltd, with 10 years experience of working with capecitabine) to determine whether citations should be accepted or rejected and whether additional information was needed to do this (i.e. abstract or full text publication if not provided by the search). Where studies were selected for inclusion in this submission data extraction was done by the same individual responsible for scrutinising literature search outputs.

6.2 Study selection

6.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.

ML 17032 Study

Kang Y, Kang WK, Shin DB *et al*. Randomized phase III trial of capecitabine/cisplatin (XP) *vs.* continuous infusion of 5-FU/cisplatin (FP) as first-line therapy in patients (pts) with advanced gastric cancer (AGC): efficacy and safety results. *American Society of Clinical Oncology Annual Meting* 2006; Abstract and oral presentation. Available from: www.asco.org

Kang YK, Kang WK, Shin DB *et al.* Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: A randomised phase III noninferiority trial. *Annals Oncol.* 2009; **20**: 666-673.

REAL-2 Study

Chong G, Cunningham D. Can cisplatin and infused 5-fluorouracil be replaced by oxaliplatin and capecitabine in the treatment of advanced oesophagogastric cancer? The REAL 2 trial. *Clinical Oncol.* 2005; **17**; 79-80.

Sumpter K, Harper-Wynne C, Cunningham D *et a*l. Report of two protocol planned interim analyses in a randomized multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. *Br J Cancer* 2005; 92: 1976-1983

Cunningham D, Rao S, Starling N *et al.* Randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer: The REAL 2 trial. *American Society of Clinical Oncology Annual Meeting* 2006; Abstract and oral presentation LBA4017. Available from: www.asco.org

Cunningham D, Starling N, Rao S *et al.* Capecitabine and oxaliplatin for advanced esophagogastric cancer. *New Engl J Med* 2008; **358**: 36-46.

Capecitabine versus S-1 Study

Kang Y, Lee J, Min Y *et al* A randomised multi-center phase II trial of capecitabine (X) versus S-1 (S) as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. American Society of Clinical Oncology annual meeting 2007; Abstract 4546 Available from: www.asco.org

Lee JL, Kang YK, Lee HJ *et al.* A randomised multicentre phase II trial of capecitabine vs S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. *Br J Cancer* 2008 **99**: 584-590.

ATTAX Study

Tebbutt N, Gebski V, Strickland A *et al.* Randomised phase II study evaluating weekly docetaxel in combination with cisplatin and 5FU or capecitabine in metastatic oesophago-gastric cancer. *American Society of Clinical Oncology Annual Meeting* 2006; Abstract 4067 Available from: www.asco.org.

Tebbutt N, Sourjina T, Strickland A *et al.* ATTAX: Randomised phase II study evaluating weekly docetaxel-based chemotherapy combinations in advanced esophago-gastric cancer, final results of an AGITG trial. American Society of Clinical Oncology annual meeting 2007; Abstract 4528 Available from: www.asco.org.

Meta-analysis

Okines AFC, Norman AR, McCloud P *et al.* Meta-analysis of the REAL-2 and ML 17032 trials: Evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. *Annals Oncol.* 2009; **20**: 1529-1534.

6.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

Trials listed in Section 6.2.1 were excluded from the review if:-

1. They did not include a randomisation between two treatment available in the UK

2. They were phase II studies not designed to produce robust comparisons of efficacy and toxicity

3. Neither study arm would be considered as a standard relevant to UK practice.

6.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this.

Applying the 3 rules outlined in Section 6.2.2 had the following impact on the "Complete list of studies" identified in Section 6.2.1:

ML17032 study – no impact, so included in systematic review

REAL-2 study – no impact, so included in systematic review

Capecitabine versus S-1 – excluded from systematic review based on rule 1. S-1 is another oral fluoropyrimidine agent not licensed in Europe and, as far as Roche is aware, there is no plan for making it available in the UK. As such a comparison between S-1 and capecitabine and S-1 is not informative with regard to the current appraisal.

ATTAX- excluded from systematic review based on rule 2. This study was hypothesis generating only. It is also of limited relevance to UK practice (rule 3) where docetaxel containing combinations are little used.

For list of publications see Section 6.2.1. Unless otherwise stated data on the two remaining studies of relevance will be drawn from the peer reviewed full publications (Cunningham et al 2008; Kang et al 2009) with supporting information from trial protocols.

6.2.4 List of relevant non-randomised controlled trials

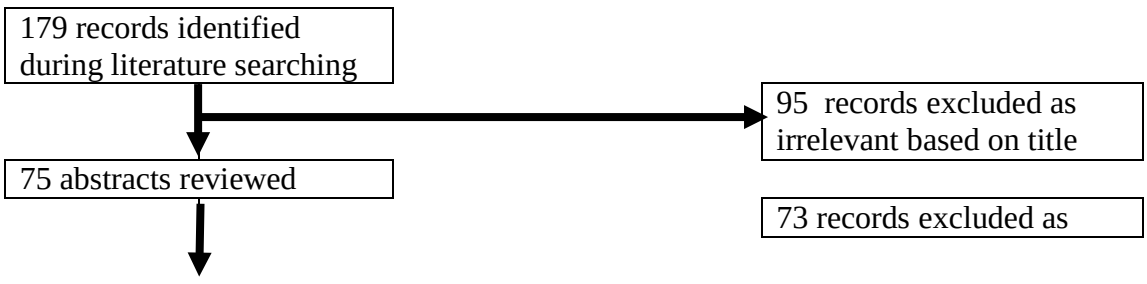
Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.
None included.

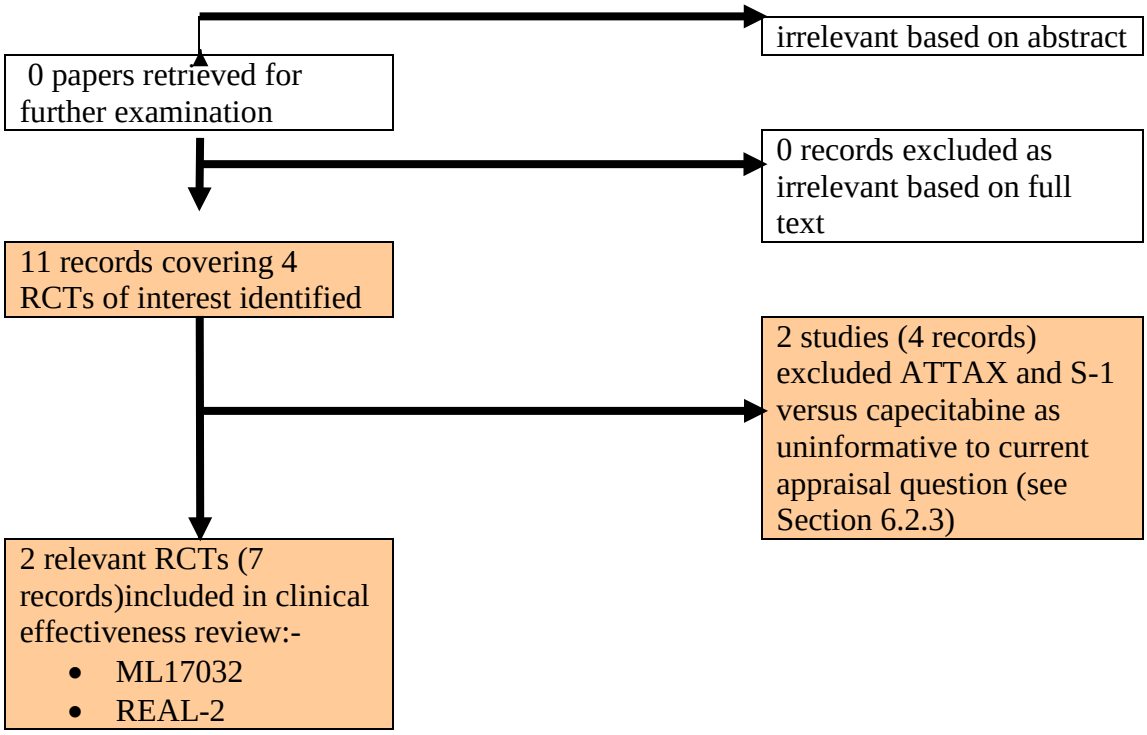
6.2.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

None known.

Figure 4. QUORUM flow diagram of study selection process used in Roche's submission*





*Includes all records identified during literature searching except Roche internal documents (regulatory documents, trial protocols, DRAMs and CSRs) whose existence was already known and which were requested directly from the appropriate Roche personnel

6.3 Summary of methodology of relevant RCTs

6.3.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.

CONSORT ITEM	ML 17032	REAL -2
Scientific Background .	Literature review shows that combination chemotherapy with cisplatin and 5-FU has good activity in aGC which is better than certain other fluoropyrimidine-based combinations. In 5-FU/cisplatin regimens, 5-FU is usually administered for 5 days as a continuous infusion, requiring hospital admission, frequent outpatient visits, or central-line insertion. In clinical trials in colorectal cancer the orally active fluoropyrimidine, capecitabine, has been shown to be as effective as 5-FU potentiated by folinic acid. In animal studies the combination of capecitabine and cisplatin has been shown to have additive activity against human gastric cancer xenografts. In phase II studies, capecitabine has been shown to have useful activity and good tolerability against aGC when used as monotherapy or in combination with cisplatin. The aim of the present study was to compare oral capecitabine in combination with cisplatin to IV 5-FU/cisplatin with regard to efficacy and safety in previously untreated patients with aGC	Combination chemotherapy with the ECF regimen of epirubicin, cisplatin and continuously infused 5-FU was at the time of study design the predominant chemotherapy regimen used in the UK for the palliation of aGC (now ECX as a consequence of this study). Although effective within the limits of what conventional chemotherapy can achieve in this disease, it has significant drawbacks:- The requirement for patients to receive 5-FU as a continuous IV infusion delivered using a portable pump via a permanent venous access. This poses a significant burden on patients and has significant cost implications to the healthcare system Cisplatin requires extensive IV pre-hydration and post-hydration to prevent cisplatin-induced kidney damage. This usually requires patients to spend a whole day every three weeks in the chemotherapy suite receiving cisplatin (or else receive it overnight as an inpatient). Again this is inconvenient and unpopular with patients and resource intensive for the health service. These drawbacks led the developers of the ECF regimen to ask whether the regimen could be improved by the use of newer fluoropyrimidine and platinum drugs. They hypothesized that the oral fluoropyrimidine, capecitabine, would obviate the need for infusional 5-FU whilst the less nephrotoxic platinum drug, oxaliplatin, would require less hydration and so could be administered more rapidly and without the same level of gastrointestinal side-effects. An existing body of evidence showed that capecitabine was at least as effective and better tolerated than 5-FU in colorectal cancer whilst oxaliplatin was known to have good activity against a range of gastrointestinal malignancies. Furthermore, early phase studies indicated that substitution of capecitabine for 5-FU and oxaliplatin for cisplatin did not dramatically alter the activity of ECF. Against this background the investigators' hypothesis was that replacement of either 5-FU with capecitabine or cisplatin with oxaliplatin would be advantageous provided antitumour outcomes were not compromised. This was the hypothesis that they set out to test in this study which was an open-label 2 x 2 randomised, phase III study comparing continuously infused IV 5-FU with oral capecitabine and cisplatin with oxaliplatin

Continued…

CONSORT ITEM	ML 17032	REAL -2
Objectives	The overall purpose of this study was to compare capecitabine plus cisplatin (CX) with 5-FU and cisplatin (CF) in the treatment of aGC The primary objective of this study was to confirm non-inferiority of PFS with CX compared to CF in the treatment of aGC	The overall purpose this study was to test the hypothesis that substituting capecitabine for 5-FU or oxaliplatin for cisplatin in the ECF regimen for oesophagogastric cancer does not compromise its efficacy or safety. The primary study objective was to determine Non-inferiority of overall survival of: -Capecitabine compared to 5-FU -Oxaliplatin compared to cisplatin when these substitutions are made within the ECF regimen
Interventions	Patients were randomly allocated on a 1:1 basis to one of the following chemotherapy regimens CF (Control arm) Cisplatin 80 mg/m2 IV Day 1 5-FU 800 mg/m2 IV Days 1-5 as a continuous infusion CX Cisplatin 80 mg/m^2 IV Day 1 Capecitabine 1000 mg/m^2 orally, twice daily Days 1-14 In both cases treatment was repeated every 3 weeks until disease progression or unacceptable toxicity	Patients were randomly allocated on a 1:1:1:1 basis to one of the following four chemotherapy regimens ECF (Control arm) Epirubicin 50 mg/m2 IV Day 1 Cisplatin 60 mg/m2 IV Day 1 5-FU 200 mg/m2 IV Days 1-21 as a continuous infusion via central line. ECX Epirubicin 50 mg/m2 IV Day 1 Cisplatin 60 mg/m2 IV Day 1 Capecitabine 625 mg/m2 orally twice daily Days 1-21*. EOF Epirubicin 50 mg/m2 IV Day 1 Oxaliplatin 130 mg/m2 IV Day 1 5-FU 200 mg/m2 IV Days 1-21 as a continuous infusion via central line. EOX Epirubicin 50 mg/m2 IV Day 1 Oxaliplatin 130 mg/m2 IV Day 1 Capecitabine 625 mg/m2 orally twice daily Days 1-21. Dual lumen Hickman lines were inserted in patients randomised to either of the infused 5-FU-containing combinations. In all cases treatment was repeated every 3 weeks for 8 cycles in the absence of progressive disease or unacceptable toxicity
Randomisation-generation	Roche, as sponsor produced the randomisation list, which was stratified by country. A random permuted block design was used within each country; the block size was 4.	Not stated in publication
Randomisation – concealment	This was an open-label study, neither investigators nor patients were blind to treatment allocation, though tumour response assessments were repeated by independent assessors blind to treatment allocation	This was an open-label study, neither investigators nor patients were blind to treatment allocation

Continued…

CONSORT ITEM	ML 17032	REAL -2
Randomisation-implementation	Clinphone (Nottingham, England) administered the randomization through a telephone calling system using secure access codes. Roche sent the access codes in tamper-evident security envelopes to the principal investigator at each site. After entry of the accesscode and a personal identification number (PIN), an authorized person at a study site entered the center's number and the patient's Case Report Form (CRF) number and date of birth. The call system then provided a randomization number and identified the treatment to be given to the patient. That information was recorded in the patient's CRF.	Patients were randomised by telephone at the Institute of Cancer Research (ICR) randomisation office with randomization stratified by Centre, Metastatic disease vs Locally advanced disease and performance status (0-1 vs 2).
Blinding	This was an open label study – it would have been unethical to subject capecitabine-treated patients to prolonged infusion of placebo 5-FU.	This was an open label study – it would have been unethical to subject capecitabine-treated patients to continuous infusion of placebo 5-FU or to subject oxaliplatin recipients to the extensive hydration required for cisplatin administration.

6.3.2 Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

CONSORT ITEM	ML 17032	REAL-2
Eligibility criteria	Patient population Patients with advanced gastric adenocarcinoma. **Inclusion criteria** To be eligible for inclusion in the study, each patient had to fulfil all the following criteria: • Provided written informed • Histological confirmed gastric adenocarcinoma with advanced and/or metastatic disease • At least one measurable lesion according to the RECIST that had not been irradiated • Age between 18 and 75 years of age • Creatinine clearance >60ml/min • Ambulatory and having a Karnofsky performance status ≥70% • Having a life expectancy of at least 3 months **Exclusion criteria** Patient who met any of the following criteria were excluded from the study: • Pregnant or lactating women, women of childbearing potential unless using a reliable and appropriate contraceptive method • Sexually active males unwilling to practice contraception during the study • Previous cytotoxic chemotherapy (except adjuvant or neoadjuvant treatment completed at least 6 months prior to enrolment) • Organ allografts (kidney and liver) • Clinically significant cardiac disease or myocardial infarction within the previous 12 months • Evidence of central nervous system metastases • History of another malignancy within the last 5 years, except cured basal cell carcinoma of the skin and cured carcinoma *in situ* of the uterine cervix • The following laboratory values: o Neutrophil count ≤1.5 x 10^9, platelet count <100x10^9/l o Serum bilirubin ≥1.5 x upper limit of normal range (ULN) o ALAT or AST >2.5 x ULN, or >5 x ULN in the case of liver metastases o Alkaline phosphatise >2.5 x ULN, or >5 x ULN in the case of liver metastases, or >10 x ULN in the case of bone disease • Radiotherapy within 4 weeks before the start of study treatment or prior radiotherapy to the indicator lesion(s) measured in the study • Major surgery within 4 weeks before the start of study treatment, without complete recovery • Treatment with any investigational study drug within 4 weeks before the start of treatment • Serious, uncontrolled intercurrent infections • Lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome • Abnormal audiogram or auditory abnormality • Active (significant or uncontrolled) gastrointestinal bleeding The above inclusion and exclusion criteria plus the randomisation process used produced two well-balanced patient treatment groups as shown in Table 4	Patient population Patients with inoperable advanced carcinoma of the oesophagus, oesophageal-gastric junction or stomach. **Inclusion criteria** To be eligible for inclusion in the study, each patient had to fulfil all the following criteria: • Histologically verified locally advanced or metastatic adenocarcinoma, squamous cell or undifferentiated carcinoma of the oesophagus, oesophagogastric junction or stomach • Primary tumour classified as inoperable on the basis of either findings at laparotomy or CT scan and endoscopic ultrasound results • Uni-dimensionally measurable disease • Age ≥18 years • No prior chemotherapy or radiotherapy unless the latter was adjuvant treatment with relapse outside the radiotherapy field • Adequate bone marrow function : Platelets >100x109/l; White blood cell count >3x109/l) • Adequate renal function: Glomerular filtration rate ≥60 ml/min and serum creatinine within normal range • Adequate hepatic function: Bilirubin <2 x ULN • Eastern Cooperative Oncology Group (ECOG) performance status 0-2 • Life expectancy of at least 3 months • No concurrent uncontrolled medical illness • On suspicion of left ventricular dysfunction, a multigated cardiac scan was performed and patients were excluded if this was below the reference range for the institution • Written informed consent **Exclusion criteria** Patient who met any of the following criteria were excluded from the study: • Uncontrolled angina pectoris, heart failure, clinically significant uncontrolled cardiac arrhythmias or any patient with a clinically significant abnormal ECG or cardiac history having a LVEF of lower limit of normal range for institution as determined by MUGA scan or echocardiogram • Any other serious uncontrolled medical conditions • Clinically significant hearing loss/persistent tinnitus • Any pregnant or lactating woman (any woman of child-bearing potential required to have a pregnancy test prior to randomisation and must take adequate precautions to prevent pregnancy during treatment) The above inclusion and exclusion criteria plus the randomisation process used produced two well-balanced patient treatment groups as shown in Table 5.

Table 4. Summary of baseline characteristics of patients enrolled in the ML 17032 study.

Variable		Capecitabine/ cisplatin (N=160)	5-FU/ cisplatin (N=156)
Sex	Male Female	103 (64%) 57 (36%)	108 (69%) 48 (31%)
Age (years)	Median Range	56 26-74	56 22-73
Prior cancer-related therapy	 Adjuvant chemotherapy Gastrectomy (full/partial)	 18 (11%) 40 (25%)	 15 (10%) 34 (22%)
Karnofsky score at baseline	Median Range	80 70-100	80 70-100
Metastatic sites	Skin Lung Pleura Soft tissue Peritoneum Bone Liver	1 (<1%) 13 (7%) 6 (4%) 5 (3%) 30 (19%) 11 (6.9%) 81 (51%)	1 (<1%) 12 (8%) 4 (3%) 7 (4%) 29 (19%) 9 (6%) 72 (46%)
Number of metastatic sites at baseline	1 2 3 >3	46 (29%) 81 (51%) 25 (16%) 7 (4%)	63 (40%) 63 (40%) 21 (14%) 6 (4%)
Ethnicity	Oriental Caucasian Hispanic Other	105 (66%) 31 (19%) 17 (11%) 7 (4%)	104 (67%) 29 (19%) 15 (10%) 8 (4%)

Table 5. Baseline characteristics of patients enrolled into the REAL-2 study

	ECF n=249	ECX n=241	EOF N=235	EOX n=239
Median age (range)	65 22-83	64 25-82	61 33-78	62 25-80
Male (%) Female (%)	81.1 18.9	80.5 19.5	81.3 18.7	82.8 17.2
Oesophagus (%) O-G junction (%) Gastric (%)	34.9 28.9 36.1	29.5 28.2 42.3	39.6 23.4 37.0	34.3 22.2 43.5
PS 0/1 (%) PS 2 (%)	88.4 11.6	87.6 12.4	91.5 8.5	90.0 10.0
Metastatic (%) Locally advanced (%)	79.5 20.5	76.8 23.2	77.0 23.0	75.7 24.3
Adenocarcinoma (%) Squamous (%) Other/undifferentiated (%)	90.0 7.6 2.4	89.6 9.5 0.8	86.0 12.8 1.3	87.4 12.1 0.4
Number of metastatic sites: 0/1 (%) >/=2 (%)	 63.5 36.5	 59.3 40.7	 60.9 39.1	 64.4 35.6
Prior surgery (%)	7.6	7.5	7.7	8.8

Abbreviations: O-G, oesophageal-gastric; PS, Eastern Co-operative Oncology Group Performance Status

6.3.3 Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

CONSORT ITEM	ML 17032	REAL- 2
Sample Size	The sample size for the study was derived from the statistical hypothesis under test. For determination of the sample size, two assumptions were made: first, that the median PFS would be 5 months for both treatment groups, and second, that the test for non-inferiority of the PFS rate of the CX group compared with CF, as measured by the hazard ratio, would be with a one-sided 95% confidence interval (CI). If the upper limit of the one-sided 95% CI of the hazard ratio was less than the limit of non-inferiority, then the alternative hypothesis of non-inferiority would be accepted. With the limit of non-inferiority set to 1.40, a sample size of 135 patients in each treatment group and 220 events in total provide a power of 80% that the upper limit of the one-sided 95% CI of the hazard ratio will be less than 1.40. At the same time, the point estimate of the hazard ratio will be less than 1.12 with a probability of 80%. The sample size was increased by 10% and rounded to 150 per treatment group to allow for patient withdrawals. For the hierarchical test of non-inferiority with the limit set to 1.25, a sample size of 135 patients in each treatment group would provide statistical power of 50% at the 0.05 level of significance with a one-sided test.	The sample size for the study was derived from the statistical hypothesis under test. Patient numbers were based on a one year survival of 35% with the reference ECF regimen (based on its performance in the preceding REAL study; Ross et al 2002). It was estimated that the recruitment of 1000 patients (250 per arm) would allow equivalence to be demonstrated around the 1-year survival of 35% with a maximum allowable difference of 7.5% with at least 80% power (1-sided, alpha=5%), comparing 5-FU vs capecitabine and cisplatin vs oxaliplatin.
Participant flow	See Figure 5 below	See Figure 6 below
Recruitment	316 patients were recruited from 42 sites in 12 countries between 30th April 2003 and 18th May 2005	1002 patients were recruited from 63 UK centres between 27th June 2000 and 11th May 2005.

Figure 5. Patient disposition in the ML17032 study

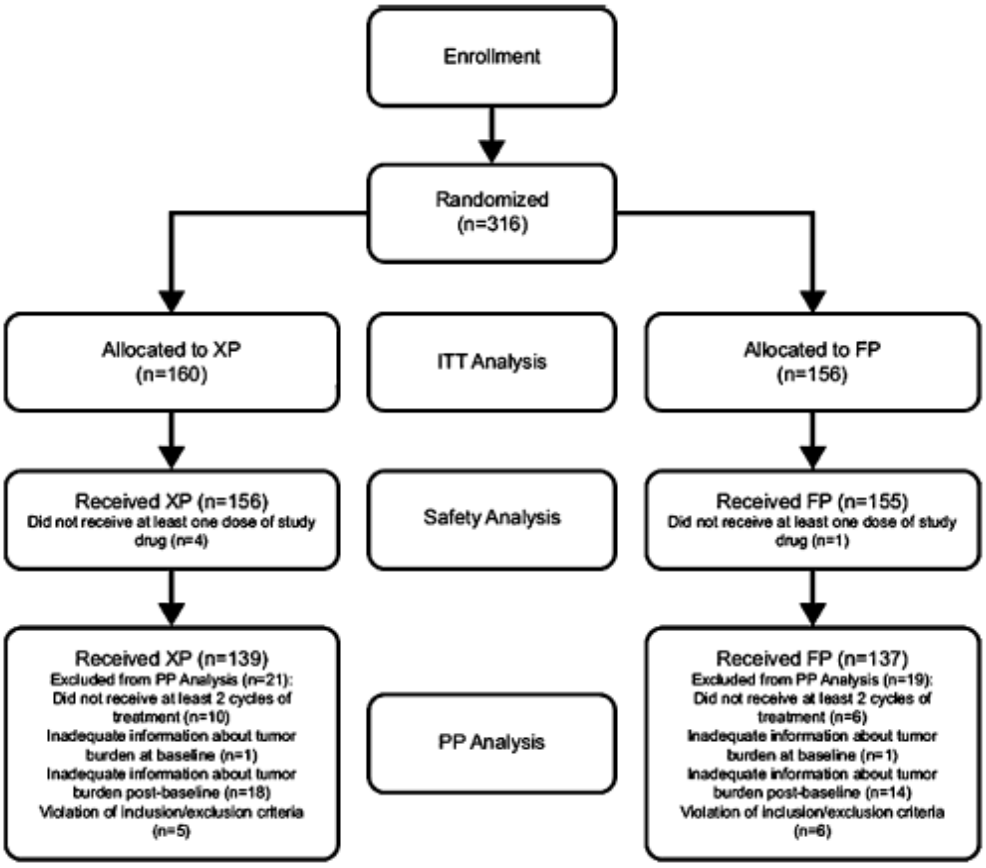
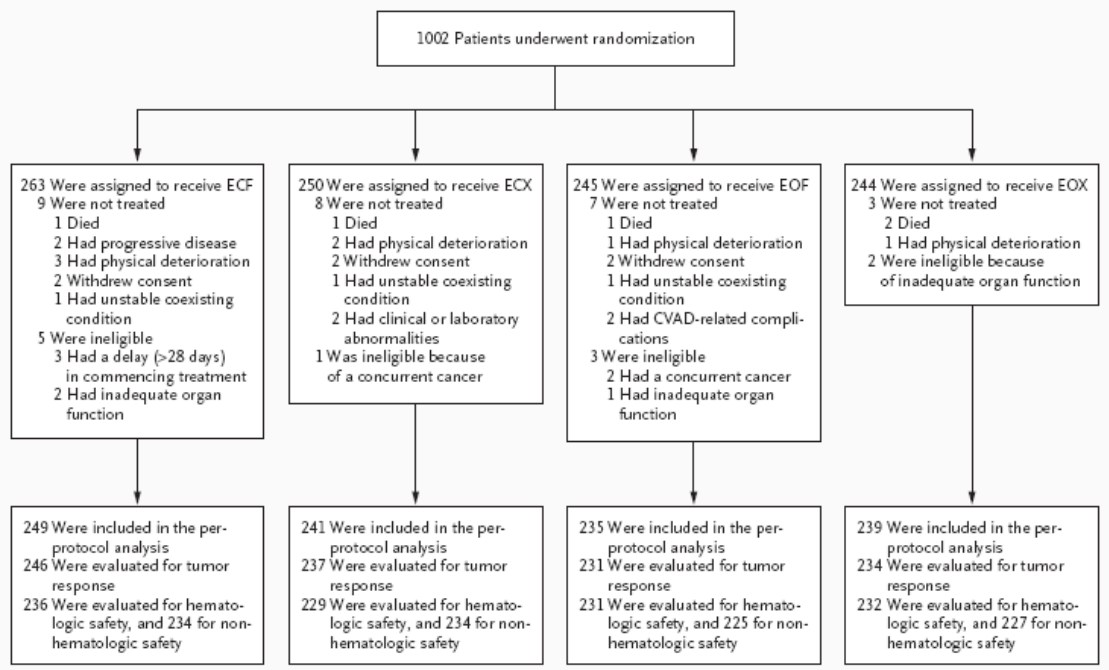


Figure 6. Patient disposition in the REAL-2 study



Abbreviation: CVAD, central venous access device

6.3.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from prespecified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

CONSORT ITEM	ML17032	REAL 2
Outcomes	**Primary study end-point** Non-inferiority of progression-free survival (from randomisation to disease progression or death from any cause, whichever occurred first) in patients receiving CX compared with those receiving CF. **Secondary** • Non-inferiority of overall survival (from randomization to death from any cause) in patients receiving CX compared to those receiving CF. • Time to disease progression • Duration of response • Time to response • Overall RR • Complete RR	**Primary study end-point** Non-inferiority of overall survival (from randomization to death from any cause) in patients receiving capecitabine compared with those receiving continuously infused 5-FU and in patients receiving cisplatin versus those receiving oxaliplatin **Secondary** • Non-inferiority of progression-free survival (from randomization to first evidence of progression or death) in patients receiving capecitabine compared with those receiving continuously infused 5-FU and in patients receiving cisplatin versus those receiving oxaliplatin • Response rates using the internationally recognized RECIST criteria • Duration of response and time to progression • Toxicity (classified according to Common Toxicity Criteria V2) and its reversibility with these regimens. • Quality of life using EORTC QOL QLQ-C30

6.3.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were preplanned or post-hoc.

CONSORT ITEM	ML 17032	REAL- 2
Statistical methods	**Hypothesis to be tested** The primary hypothesis to be tested was that PFS for patients receiving CX was not inferior to PFS for those receiving CF. The null hypothesis Ho to be rejected if the upper limit of the 95% confidence interval (CI) for the PFS hazard ratio HRCX/CF was less than 1.40. If Ho was rejected versus a non-inferiority margin of 1.40, a prespecified sequence of hierarchical tests were to be conducted. Firstly, non-inferiority using a margin of 1.25 and, secondly, superiority of CX over CF. **Statistical methodology applied** The primary analysis carried out on the Per Protocol population (see definition below) used Cox regression stratified by geographic region and adjusted for prespecified prognostic factors. A secondary analysis was an unadjusted Cox regression stratified by geographic region. Equality of treatment effect, measured by HRCX/CF across subgroups of prespecified prognostic factors was tested using Cox regression. Survival functions were plotted using the Kaplan-Meier method. Overall response rates (ORRs) for CX and CF were compared with the Cochran Mantel Haenszel test stratified by geographic region. **Analysis populations** **Intent-to-treat (ITT**) All randomized patients. **Per protocol population (PP)** Randomised Patients were excluded from the PP if they received <6 weeks of treatment for reasons of PD or death or <50% of the anticipated treatment during the first 6 weeks of the trial, if there were major inclusion/exclusion criteria violations or if there was inadequate information on tumour burden. **Safety**. All randomized patients receiving at least one dose of study drug.	**Hypothesis to be tested** The co-primary hypotheses to be tested were that OS for patients receiving capecitabine was not inferior to those receiving 5-FU and that OS for patients receiving oxaliplatin was non-inferior to those receiving cisplatin. For each comparison the null hypothesis Ho was to be rejected if the upper limit of the 95% confidence interval (CI) for the OS hazard ratio HRCX/CF was less than 1.23. **Statistical methodology applied** The primary analysis carried out on the Per Protocol population (see definition below) compared unadjusted hazard ratios for death from a Cox regression model for the experimental regimens with the standard regimens. **Analysis populations** **Intent-to-treat (ITT**) All randomised patients **Per protocol population (PP)** Randomised Patients were excluded from the PP if they did not receive any protocol treatment or if they represented major protocol inclusion/exclusion violations. **Safety**. All randomised patients receiving at least one dose of study drug

6.3.6 Critical appraisal of relevant RCTs

The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study meeting the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The critical appraisal will be validated by the Evidence Review Group. The following are suggested criteria for critical appraisal, but the list is not exhaustive.

	ML 17032	REAL 2
How was allocation concealed?	This was an open-label study. As already discussed placebo control would have been unethical as it would have required pts allocated to capecitabine to receive large amounts of placebo IV infusional therapy with resultant discomfort and risk of harm.	This was an open-label study. As already discussed placebo control would have been unethical as it would have required pts allocated to capecitabine to receive large amounts of placebo IV infusional therapy with resultant discomfort and risk of harm
What randomisation technique was used?	Robust – using a central IVRS system	Robust- using a centralised telephone based system
Was justification of sample size given?	The sample size was set through computer simulation, based on a statistical assessment of what would be required to demonstrate non-inferiority, based on a reasonable assumption of outcomes in the control arm. One possible criticism of the study design is that the statistical plan for the study originally stated that a Hazard Ratio of up to 1.4 for the comparison of OS would be deemed to demonstrate non-inferiority consistent with retention by CX of at least 57% of the treatment effect of CF. A non-inferiority margin of 1.25, was added for regulatory purposes, consistent with retention by CX of at least 72% of the treatment effect of CF. However, the power of the study with the lower non-inferiority margin was only 50%	Yes. Sample size was based on a statistical assessment of likely and meaningful outcomes and assumptions on control outcomes based on recent experience by the same investigators.
Was follow-up adequate?	Yes. The mean duration of follow-up for progression and survival was 22 months in both arms. This is more than double the median OS in the study and approximately 4 times the median PFS	Yes. Median follow-up at time of final analysis was 17.1 months, with only 29 patients followed up for less than 1 year. This is more than adequate given the median survival in the patient group in question
Were the individuals undertaking assessment aware of allocation?	Assessments of tumour response were carried out by both the investigators who were not blind to response (see comments above on the impossibility of blinding) and also by independent assessors blind to treatment allocation. Both are reported	Yes – see comment above on impossibility of blinding. However, the primary end-point in this study – OS- is not amenable to observer bias and with little second-line therapy the only significant variable influence is trial treatment allocation
Was the design parallel group or cross-over?	Parallel-group. Minimal cross-over/carry-over is likely. Second-line treatment is uncommon in this condition and even if given would be unlikely to be with treatment from the other study arm (the working hypothesis at the start of the study was that all study treatments represented alternative means of delivering the same therapy).	Parallel-group. Minimal cross-over/carry-over is likely. Second-line treatment is uncommon in this condition and even if given would be unlikely to be with treatment from another study arm (the working hypothesis at the start of the study was that all study treatments represented alternative means of delivering the same therapy).

Was the study conducted in the UK?	No – it was a multinational study carried out in China, Korea, Russia and Central and South America.	Entirely – at 63 different treatment centres.
How do the patients in the study reflect those seen in clinical practice?	The most obvious difference is in their ethnicity – because of the countries where the study was conducted, just under 20% of patients were Caucasian, whereas Caucasians clearly make up the majority of UK patients. Trial patients were also younger by 5-10 years than those treated in the REAL-2 study. (because REAL-2 was a pragmatic UK based study, it can be assumed that these more closely represent typical patients receiving chemotherapy for aGC in the UK). This study also excluded the small group of patients with tumours of non-adenocarcinomatous histology who, in clinical practice, receive the same treatment as those with adenocarcinomas. However, it should be noted that despite these differences, outcomes in this study were very similar to those in the REAL and REAL-2 studies where the study recruits can be assumed to be fairly representative of the UK population of patients receiving chemotherapy for aGC.	This study was investigator initiated (with Roche financial support) and designed to be pragmatic – entry criteria were designed to allow entry to the sort of patients that UK clinicians see and treat in routine clinical practice
Do dosage regimens used reflect those in the product SPC?	Yes. The SPC is not restrictive on acceptable dosage regimens for the use of capecitabine with cisplatin-based chemotherapy. However, data from this study are cited as clinical evidence within the SPC so that use of this regimen was clearly anticipated by those drafting and approving the SPC	Yes. The SPC is not restrictive on acceptable dosage regimens for the use of capecitabine with cisplatin-based chemotherapy. However, data from REAL-2 are cited as clinical evidence within the SPC so that use of this regimen was clearly anticipated by those drafting and approving the SPC
Were the study groups comparable?	Largely (see Table 1) The biggest imbalance between the study arms was in the percentage of patients having only a single site of metastatic disease – 40.4% in the control arm and 28.8% in the CX arm. More limited disease is likely to be a favourable prognostic characteristic, as such, any bias introduced by this imbalance is likely to favour the control treatment.	Yes. See Table 2
Were the statistical analyses appropriate?	Yes. They were carried out according to a prospective statistical plan prepared with statistician input.	Yes. They were carried out according to a prospective statistical plan prepared with statistician input.
Was an ITT approach taken to efficacy analysis?	Not for the primary non-inferiority end-point where a per protocol analysis is the correct approach. In a non-inferiority comparison the aim is to demonstrate a lack of difference. In patients randomised but not treated the trial treatment received (i.e. none) is the same, inclusion of these patients in a non-inferiority comparison increases the chances of showing no difference between two treatment that are, in reality, different in efficacy.	Not for the primary non-inferiority end-points where a per protocol analysis is the correct approach. In a non-inferiority comparison the aim is to demonstrate a lack of difference. In patients randomised but not treated the trial treatment received (i.e. none) is the same, inclusion of these patients in a non-inferiority comparison increases the chances of showing no difference between

		two treatment that are, in reality, different in efficacy.
Were there other confounding factors?	None identified	This study included not only patients with aGC but also those with oesophageal cancers and those of the oesophageal-gastric junction. As such it does not show results specific to aGC. However, in practice clinicians view advanced tumours of the stomach and oesophagus as a single entity with regard to chemotherapy treatment and would expect similar outcomes (excepting any differences in underlying prognosis) from studies conducted in pure aGC, oesophageal and mixed populations.

6.4 Results of the relevant comparative RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

6.4.1 Results of study ML 17032

6.4.1.1 Primary end-point: non-inferiority of PFS

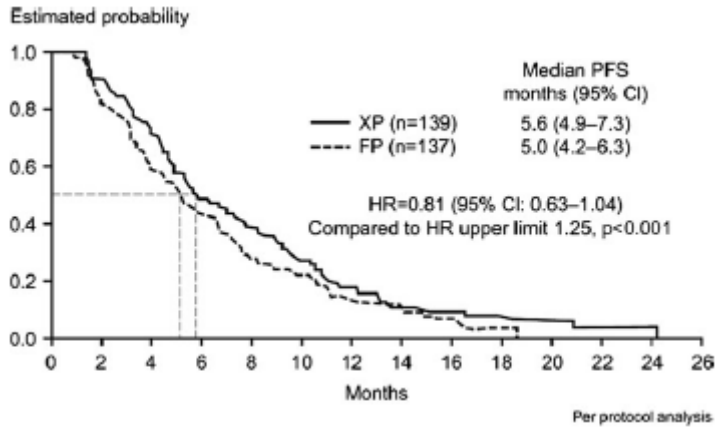
This study met its primary end-point of demonstrating the non-inferiority of PFS in patients receiving CX compared with those receiving the standard treatment CF using an adjusted Cox proportional hazards model. In the PP population the Hazard Ratio for CX versus CF was 0.85 (95% CI 0.65, 1.11) – this result showed that CX was significantly non-inferior (P=0.005 versus the prespecified non-inferiority margin of 1.25). As shown in Table 6. PFS was also found to be non-inferior in the unadjusted analysis, regardless of whether the PP or ITT population was examined and regardless of whether disease progression was assessed by investigators or by blinded, independent assessors. In each case there was a trend towards prolonged PFS in the CX group. The non-inferiority of PFS (and trend towards improved PFS) in patients receiving CX compared to CF is shown graphically in Figure 7.

Table 6. Progression-free survival in ML 17032 (unadjusted analysis)

Population	Median (months) (95% CI)		Hazard ratio PFS (95% CI)	P (versus non-inferiority margin 1.25)
	CX (N=139)	CF (N=137)		
PP investigator assessed	5.6 (4.9, 7.3)	5.0 (4.2, 6.3)	0.81 (0.63, 1.04)	P<0.001
ITT investigator	5.6 (4.8, 6.9)	5.0 (3.9, 5.7)	0.80 (0.63, 1.03)	P<0.001

assessed				
PP independently assessed	6.6 (5.4, 8.4)	6.1 (5.0, 7.1)	0.90 (0.69, 1.18)	P=0.0169

Figure 7. Kaplan-Meier curves of PFS in the per protocol population of patients treated with CX and CF in study ML 17032.



6.4.1.2 Secondary efficacy endpoints

As shown in Table 7, as well as reaching its primary goal of demonstrating that CX is non-inferior to CF in terms of PFS, secondary efficacy end-points in this study all favoured CX.

Table 7. Secondary end-points in study ML 17032 (per protocol population; unadjusted analysis)

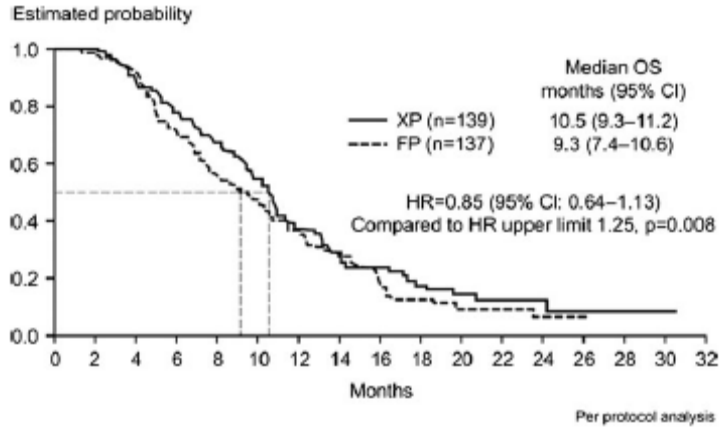
End point	(N=139)	(N=137)	HR/OR (95% CI)	P value
Median OS (months)	10.5	9.3	HR 0.85 (0.64-1.13)	0.008 *vs.* non-inferiority margin 1.25
ORR (%) Complete response rate (%) Partial response rate (%)	46 (38-55) 2 44	32 (24-41) 3 29	OR 1.8 (1.11-2.94)	0.020
Mean time to response (months)*	3.7	3.8	HR 1.61 (1.10-2.35)	0.015
Median response duration (months)*	7.6	6.2	HR 0.88 (0.56-1.36)	0.554

*ITT population

Abbreviations: HR, hazard ratio; OR, odds ratio; ORR, overall response rate; OS, overall survival.

The non-inferiority of OS (and trend towards improved OS) in patients receiving CX compared to CF is shown graphically in Figure 8.

Figure 8. Kaplan-Meier curves of PFS in the per protocol population of patients treated with CX and CF in study ML 17032.



6.4.2 The REAL-2 study

6.4.2.1 Primary end-point: non-inferiority of overall survival

As shown in Table 8, the co-primary endpoints of the study were met. Capecitabine was shown to be non-inferior to 5-FU and oxaliplatin was shown to be non-inferior to cisplatin in terms of overall survival. Indeed, the hazard ratios for the comparisons of capecitabine with 5-FU and oxaliplatin with cisplatin are both below 1 indicating a trend towards improved survival with capecitabine and oxaliplatin over 5-FU and cisplatin, respectively. Interaction testing revealed no interaction between the fluoropyrimidine and platinum groups (P=0.36).

Substitution of 5-FU for capecitabine resulted in a trend towards improved survival whichever of the two platinum drugs was used – so that ECX outperformed ECF and EOX outperformed EOF.

Non-inferiority for the comparisons of fluoropyrimidines and platinum agents was maintained in the multivariate analysis which included the following factors in the model: PS, extent of disease, age and excluded: primary tumour site, gender and histology. The adjusted hazard ratio for death in the capecitabine groups as compared with the fluorouracil groups, was 0.89 (95% CI, 0.77-1.02) and for the oxaliplatin, as compared with the cisplatin groups, it was 0.95 (95% CI, 0.82-1.09).

Table 8. Overall survival results in the REAL-2 study (unadjusted).

OS results for Non-Inferiority (2x2 comparisons) and individual Regimens			
2x2 comparisons Per Protocol	**1 year OS (95% CI)**	**Median OS (months)**	**HR (95% CI)**
5FU: ECF + EOF	39.4% (35.0-44.0)	9.6	Reference regimen
Capecitabine: ECX + EOX	44.6% (40.1-49.0)	10.9	0.86 (0.80-0.99)*
Cisplatin: ECF + ECX	40.1% (35.7-44.4)	10.0	Reference regimen
Oxaliplatin: EOX + EOF	43.9% (39.4-48.4)	10.4	0.92 (0.80-1.10)*
Regimens ITT			

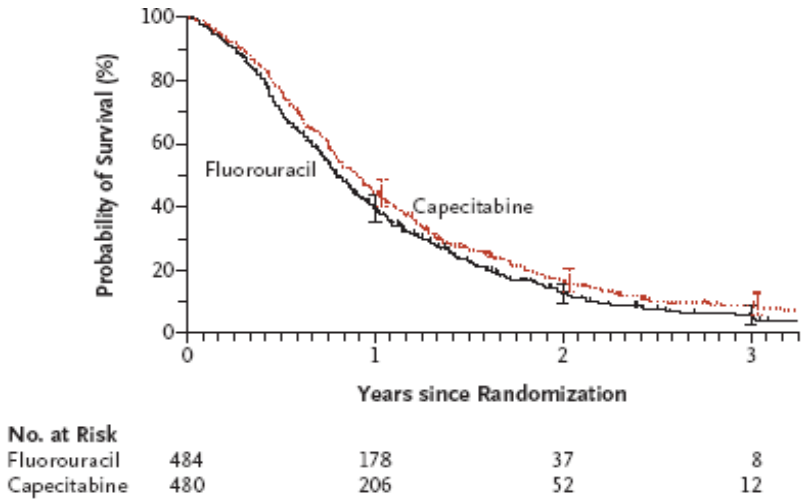
ECF n=263	37.7% (31.8-43.6)	9.9	Reference regimen
EOF n=245	40.4% (34.2-46.5)	9.3	0.95 (0.79-1.15)
ECX n=250	40.8% (34.7-46.9)	9.9	0.92 (0.76-1.11)
EOX n=244	46.8% (40.4-52.9)	11.2	0.80 (0.66-0.97) ‡

*The Upper limit of the 95% CI excludes 1.23 we can therefore conclude non-inferiority ‡ p=0.02 comparison with ECF..

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival

The trend towards improved survival amongst capecitabine recipients over 5-FU treated patients is illustrated graphically in Figure 9.

Figure 9. Kaplan-Meier survival curves for patients treated with capecitabine and 5-FU in REAL-2 (per protocol population)



Overall the most effective regimen was EOX which produced a significant improvement in OS compared with the standard regimen ECF. The hazard ratio for EOX versus ECF was 0.80 (95% CI, 0.66-0.97; p=0.02).

6.4.2.2 Secondary efficacy end-points in REAL-2

Progression-free survival did not differ significantly in the two-by-two comparison of 5-FU and capecitabine (see Figure 10) or in the comparison of oxaliplatin and cisplatin (hazard ratio 0.92; 95% CI 0.80-1.04; P=0.19)or in the comparisons between each study group and the ECF group (see Table 9), though again all comparisons showed a non-significant trend favouring capecitabine over 5-FU and oxaliplatin over cisplatin.

Figure 10. Kaplan-Meier progression-free survival curves for patients treated with capecitabine and 5-FU in REAL-2 (ITT population)

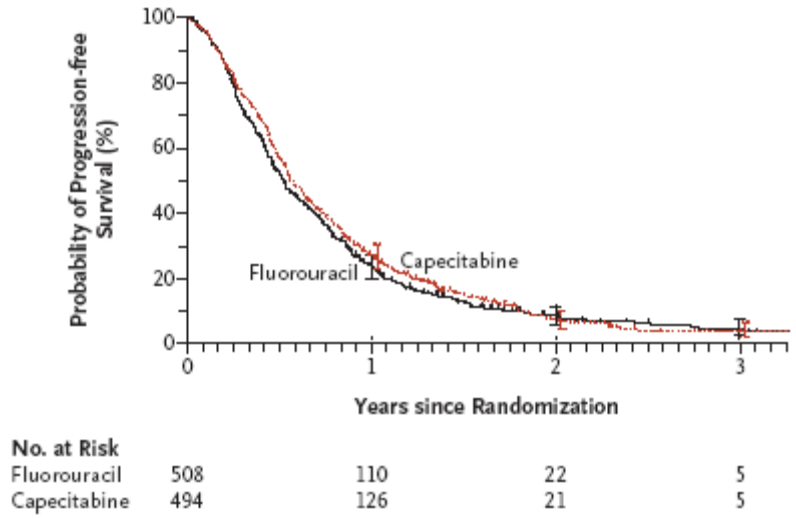


Table 9. Secondary end-points in REAL-2

Progression-free survival				
2x2 comparisons Per Protocol	**Median (months)**	**Hazard ratio (95% CI)**		**P value**
5FU: ECF + EOF n=484	6.3	Reference regimen		
Capecitabine: ECX + EOX n=480	7.0	0.9 (0.8-1.03)		0.2176
Cisplatin: ECF + ECX n=490	6.5	Reference regimen		
Oxaliplatin: EOX + EOF n=474	6.8	0.93 (0.8-1.06)		0.1897
Regimens ITT				
ECF n=263	6.2	Reference regimen		
EOF n=245	6.5	0.97 (0.81-1.17)		0.77
ECX n=250	6.7	0.98 (0.82-1.17)		0.80
EOX n=244	7.0	0.85 (0.70-1.02)		0.07
Response rates				
	Overall % (95% CI)	**Complete %**	**Partial %**	
Regimens ITT				
ECF n=263	40.7 (34.5-46.8)	4.1	36.6	Reference
EOF n=245	42.4 (36.1-48.8)	2.6	39.8	0.69
ECX n=250	46.4 (40.0-52.8)	4.2	42.2	0.20
EOX n=244	47.9 (41.5-54.3)	3.9	44.0	0.11

Abbreviations: CI, confidence interval

6.4.2.3 Quality of life (QoL) in REAL-2

Compliance in completing QoL questionnaires was high, with 96% and 70% completion at baseline and 12 weeks, respectively. Mean scores on the questionnaire's Global Health Status subscale at baseline and at 12 weeks showed no significant differences between the ECF group and the other groups.

6.5 Meta-analysis

Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. If a meta-analysis is not considered appropriate, the rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal. If any of the relevant RCTs listed in response to section 6.2.3 are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored. The following steps should be used as a minimum.

6.5.1 Identification of meta-analysis

The search strategy described in Section 6.1 and used for the identification of randomised controlled trials also identified a meta-analysis of the ML17032 and REAL-2 studies (Okines et al. 2009).

6.5.2 Criteria for inclusion of studies within meta-analysis

Although the authors of the meta-analysis do specify how they selected trials for inclusion, their approach identified the two randomised, controlled trials identified during the systematic literature search conducted for this submission and described in Section 6.1.

6.5.3 Hypothesis tested

This study combined patient level data from 1318 patients entered into these two studies in order to test the hypothesis that “capecitabine is superior to 5-FU within doublet and triplet combination chemotherapy for patients with advanced oesophago-gastric cancer”

6.5.4 End-points examined

Progression-free and overall survival

Primary and secondary endpoints were OS and PFS and RR, respectively, with OS measured from date of randomisation to death from any cause (patients lost to follow-up or no date of death censored at date of last follow-up) and PFS calculated from date of randomisation to the date of progression or death from any cause (patients without a date of progression recorded were censored on the date of last follow-up).

For both OS and PFS Kaplan-Meier curves were generated and median values calculated for the ITT population with 95% CI. Comparisons between patients treated with 5-FU combinations and those treated with 5-FU combinations were made using the log-rank test and the HRs and 95% CI were calculated for the comparison. Stepwise multivariate Cox regression analyses were used to calculate the corrected HR and 95% CI, incorporating the factors: age (<60 versus >/=60), PS (ECOG PS 0-1 or Karnofsky PS>/=80% versus ECOG PS>1 or Karnofsky <80%), histology (adenocarcinoma versus squamous histology versus undifferentiated), extent of disease (locally advanced versus metastatic) and gender. Forest plots with tests of heterogeneity wee created to show the treatment effects in each group.

Response rates

RR, defined as best response evaluated by RECIST criteria was calculated for all patients with measurable disease at randomisation (n=1264). As additional confirmatory scans were not required in the REAL-2 trial, the unconfirmed RR and its 95% CI was calculated. Comparison was made using chi-squared test and multivariate logistic regression analysis used to control for demographic factors on patients with complete data (n=1231).

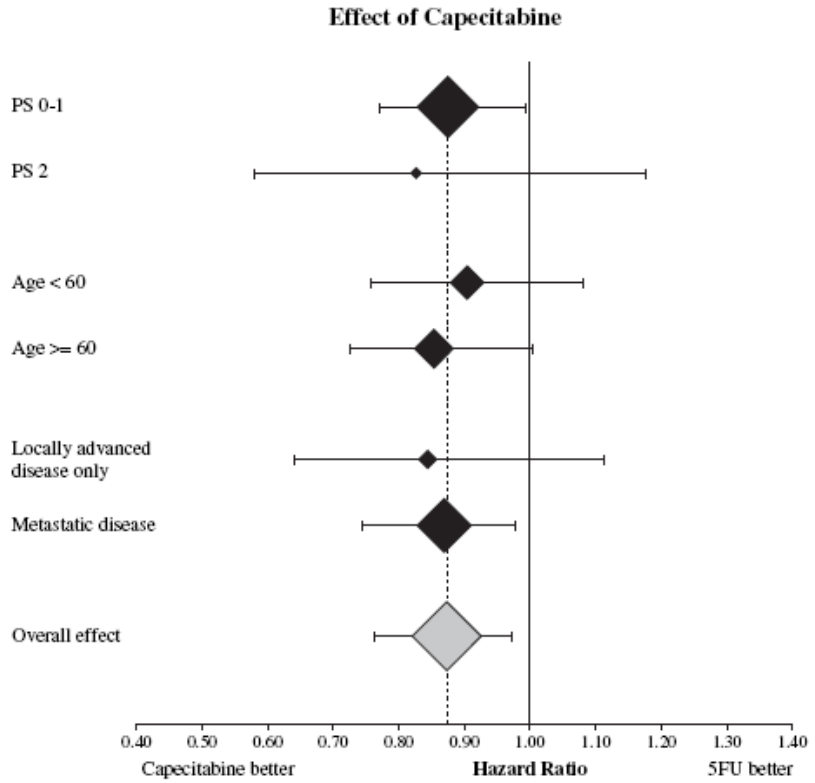
6.5.5 Results

6.5.5.1 Primary end-point overall survival

OS was compared for 664 patients treated with 5-FU combinations and 654 treated with capecitabine combinations. The median OS was 285 days (95% CI 265-305 days) for patients treated with 5-FU and 322 days (95% CI 300-343 days) for patients treated with capecitabine, giving an unadjusted HR of 0.87 (95% CI 0.77-0.98) favouring capecitabine (P=0.027). There was no evidence of any significant heterogeneity of treatment effect according to baseline patient characteristics (see Figure 11).

Superiority of capecitabine over 5-FU was maintained on multivariate analysis; adjusted HR 0.87 (95% CI 0.77-0.98, P=0.02).

Figure 11. Superiority of OS with capecitabine compared to 5-FU in the combination chemotherapy of advanced gastric cancer (from Okines *et al.* 2009)



6.5.5.2 Secondary end-points

There was an insignificant trend towards improved PFS in capecitabine recipients (unadjusted HR 0.91; 95% CI 0.81-1.02, P=0.093) and treatment with 5-FU or capecitabine was thrown out of the Cox regression model for lack of significant effect on PFS (P=0.052).

Overall RR was 45.6% in the 631 patients treated with capecitabine compared with 38.4% in the 633 patients treated with infused 5-FU. Logistic regression analysis (confirmed in multivariate analysis) demonstrated a statistically significant higher objective RR in patients with capecitabine compared with those treated with 5-FU – odds ratio 1.38 (95% CI 1.10-1.73, P=0.006).

6.5.6 Summary of efficacy

There is evidence from two large, well designed, randomised controlled clinical trials that protracted IV infusion of 5-FU can be replaced with oral capecitabine in aGC without compromising response rate, progression-free survival or overall survival. All of these parameters show a trend towards improvement after switching to capecitabine and when the two studies were meta-analysed the improvements in overall survival and disease response rate became statistically significant.
The (at least) non-inferiority of capecitabine compared to 5-FU was unaffected by the exact regimen of 5-FU used (continuous or intermittent), the partner platinum agent (oxaliplatin or cisplatin), whether the fluoropyrimidine was part of a two drug (CX/F) or three drug (ECF/X, EOX/F) cytotoxic regimen (ECX/F, EOX/F) and the

region in which the study was conducted (ML 17032 predominantly in Asia; REAL-2 in the UK).

6.6 Indirect/mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. An 'indirect comparison' refers to the synthesis of data from trials in which the technologies of interest have not been compared in head-to-head trials, but have been compared indirectly using data from a network of trials that compare the technologies with other interventions.

No indirect comparisons required or conducted.

6.7 Safety

Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.

6.7.1 Trials of relevance to this review

The largest body of safety data relating to the indication in this appraisal comes from the two phase III studies discussed in the description of comparative efficacy (REAL-2 and ML 17032).

6.7.2 Safety analyses from study ML17032

Comparison of the safety profiles of the 2 treatment groups constituted a secondary objective of the study. The safety population included all patients who received at least one dose of study medication and who had at least one post-baseline safety assessment. Within the safety population, 156 patients were randomised to receive capecitabine/cisplatin, and 155 were allocated to receive 5-FU/cisplatin.

As shown in Table 10, most treatment-related adverse events occurred with a similar frequency in both study arms and there were few differences in safety clearly attributable to the switch from 5-FU to capecitabine. The only clear exceptions are stomatitis which occurred more often and with greater severity in 5-FU patients and hand-foot syndrome which was more common in capecitabine patients.

Table 10. Treatment-related adverse events occurring in more than 15% of patients in study ML17032.

Safety parameter	Frequency n (%)	
	Capecitabine/cisplatin	5-FU/cisplatin

	(N=156)		(N=155)	
	Any grade	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Nausea	87 (55)	3 (2)	85 (57)	4 (3)
Vomiting	66 (48)	11 (6)	91 (58)	13 (8)
Diarrhoea	31 (19)	8 (4)	23 (15)	7 (4)
Stomatitis	18 (12)	3 (2)	41 (26)	10 (6)
Neutropenia	51 (32)	25 (16)	46 (30)	29 (19)
Leucopenia	22 (15)	4 (3)	26 (17)	6 (4)
Anorexia	44 (29)	3 (2)	43 (27)	1 (<1)
Fatigue/asthenia	46(29)	4 (3)	42 (26)	2 (1)
Hand-foot syndrome	34 (22)	6 (4)	6 (3)	-
Death within 60 days of treatment start	8 (5)		5 (3)	

6.7.3 Safety information from REAL-2 study

Comparison of the safety profiles of the 4 study treatments constituted a secondary objective of REAL-2. Within the safety population, 461 patients were randomised to receive capecitabine and 459 were allocated to receive 5-FU.

As shown in Table 11 there are few differences between ECF and EOF and the corresponding capecitabine-containing arms, ECX and EOX. Such differences as were seen generally reflected those seen in the ML 17032 study. In the ECX arm, the only statistically significant differences compared with ECF are modest increases in Grade 3 and 4 neutropenia (a laboratory measure with no direct impact on patients) and Grade 3 and 4 hand-foot syndrome, with clear but not significant trends towards increased all-grade hand-foot syndrome and reduced stomatitis with capecitabine compared with 5-FU. There are no striking differences between EOF and EOX except for an increased level of fatigue in the EOF arm.

Table 11. Most common treatment-related adverse events (safety population)

Adverse event	**ECF (N=234)**		**ECX (N=234)**		**EOF (N=225)**		**EOX (N=227)**	
	All	**Grade**	**All**	**Grade**	**All**	**Grade**	**All**	**Grade**

	grade	3 or 4	grade	3 or 4	grade	3 or 4	grade	3 or 4
	Percent							
Anaemia[1]	78.4	13.1	79.5	10.5	65.8	6.5	64.2	8.6
Thrombocytopenia[1]	14.5	4.7	17.0	4.8	13.4	4.3	21.1	5.2
Neutropenia[1]	73.6	41.7	85.6	51.1*	68.4	29.9	62.9	27.6**
Febrile neutropenia[1]	13.2	9.3	10.5	6.7	11.5	8.5	9.8	7.8
Diarrhoea	39.3	2.6	41.9	5.1	62.7	10.7	61.7	11.9**
Stomatitis	50.9	1.3	39.3	1.7	44.4	4.4*	38.1	2.2
Hand-foot syndrome	29.8	4.3	45.9	10.3*	28.9	2.7	39.3	3.1
Nausea and vomiting	79.1	10.2	82.1	7.7	83.1	13.8	78.9	11.4
Peripheral neuropathy	30.0	0.4	36.3	1.7	79.6	8.4	83.7	4.4
Lethargy	89.7	16.6	92.7	15.5	90.2	12.9	96.1	24.9*
Alopecia[2]	81.5	44.2	82.5	47.4	75.4	27.7	74.2	28.8
Thromboembolism[3]	16.9	NA	13.3	NA	7.7	NA	7.5	NA
Death within 60 days % (95% CI)[3]	7.2 (4.7-11.l)		5.6 (3.4-9.3)		5.7 (3.4-9.5)		6.1 (3.8-10.0)	

1. This side-effect of treatment was measured in the haematological safety population, consisting of 236 patients in the ECF group, 229 patients in the ECX group, 231 patients in the EOF group and 232 patients in the EOX group.

2. The highest grade of alopecia was grade 2, which is listed in the grade 3 or 4 column

3. The diagnosis of thromboembolism was made only in the per-protocol population

4. Death within 60 days after randomization was evaluated only in the intent-to-treat population

* P<0.01 to P<0.05 for comparison with ECF group

** P<0.001 to P<0.01 for the comparison with the ECF group.

6.7.4 Clinical impact of treatment toxicity

As demonstrated above a move from infused 5-FU to oral capecitabine has little impact on the overall number of adverse events experienced by patients or on the frequency of severe and life-threatening events.

One measure of the impact of treatment toxicity on patients is the extent to which it interferes with the ability to deliver treatment because it causes treatment delays, treatment interruptions or dose reductions. In this respect there is little to choose between 5-FU and capecitabine.

In study ML17032 slightly more CX than CF patients (45% *versus* 34%) completed 6 cycles and 8 cycles of treatment (20% *versus* 13%) whilst the median overall ratio of the dose received to the dose planned was 1.00 for cisplatin in both arms, 0.99 (range 0.14-1.06) for capecitabine and 1.00 (range 0.60-1.12) for 5-FU. Adverse events leading to dose modification were rather more common amongst CX than CF recipients (62% *versus* 48%), though it is plausible that this is a consequence of dosing schedule – the protracted administration of capecitabine compared to 5-FU in this study meant that by the time fluoropyrimidine toxicity emerged in CF patients modification of doses for that cycle would, be impossible, whilst tailoring the capecitabine dose to patient tolerance towards the end of CX cycles is feasible. In any event dose modification, where carried out was clearly a successful strategy as the rates of treatment discontinuation for safety reasons was the same in both study arms (18%).

Similarly, as shown in Table 12, choice of fluoropyrimidine had little effect on treatment delivery in the REAL-2 study.

Table 12. Treatment exposure by study arm in the REAL-2 study

	ECF n=250	**ECX n=243**	**EOF n=236**	**EOX n=239**
Total number of cycles delivered	1310	1400	1285	1295
Median number of cycles	6	6 (0.021)	6 (0.323)	(0.426)
% fluoropyrimidine dose delivered	90.5	88.4 (p=0.185)	88.3 (p=0.242)	88.1 (p=0.116)
% platinum dose delivered	92.6	92.3 (p=0.836)	91.7 (p=0.261)	91.6 (p=0.163)
% epirubicin dose delivered	92.6	89.2 (p=0.003)	93.0 (p=0.571)	91.9 (p=0.372)
% patients with treatment delay	58.8	60.1	47.9	50.2
Mean days treatment delay per patient	7.7	11.2 (p=0.121)	5.8 (p=0.01)	7.4 (p=0.072)

All p-values relative to ECF

As shown in Tables 7 and 8 the rates of death within 60 days of starting study treatment were not obviously impacted by choice of fluoropyrimidine.

6.7.5 Hand-foot syndrome

Hand-foot syndrome

This is the only common toxicity more frequently seen in capecitabine treated patients than those receiving 5-FU, it is therefore worthy of separate comment. Hand-

foot syndrome (also known as palmar-plantar erythrodysasthesia or PPE) involves drying and reddening of the palms of the hands and the soles of the feet, which can become sore especially if it is not managed and it proceeds to cracking of the skin along flexure lines. Fortunately, although common, it generally has limited impact on patients being of Grade 1 (discomfort which does not disrupt normal activities) or Grade 2 (discomfort which affects the activities of daily living) severity. This is partly because it can readily be identified in its early stages facilitating prompt treatment interruption/dose reduction, something which clinicians are now very experienced in doing, given the large number of patients that they have now treated with capecitabine. Hand-foot syndrome is not a precursor of more serious problems - there is no definition of Grade 4 – life-threatening- hand-foot syndrome, underscoring the point that this side-effect is uncomfortable and inconvenient rather than dangerous. Moreover the management of hand-foot syndrome is simple and cheap – it is managed primarily by capecitabine dose adjustment and the use of simple emollient creams to keep the hands and feet hydrated and supple.

a) ***Provide details of any additional safety issues for the drug in the indication(s) under review compared to relevant active comparator(s), which were not identified in the trials described previously.***

The delivery of 5-FU by prolonged IV infusion requires the insertion of a permanent venous access (central line). Even with careful handling such devices represent a possible entry point and focus for infection and thrombus formation, particularly in patients who may be immunosuppressed as a result of chemotherapy or who have coagulopathies related to their cancer. These complications – along with other catheter-related complications- are common. In a recent review by Kuter (2004) it is reported that central venous catheters become infected in 4-33% of cases and a focus of thrombosis in 12-74%.

Management of catheter-related complications may be local e.g. removal or unblocking using a thrombolytic agent. However, systemic therapy may be required either to deal with the local problem or because it has become systemic.

At best, dealing with line complications is resource intensive and inconvenient for the health service and the patient. At worst, they can result is life-threatening medical problems, like neutropenic sepsis. However, by replacing infused 5-FU with oral capecitabine they can be entirely avoided except in the group of patients whose venous access is so poor that they require a central catheter for other parts of their treatment.

6.8 Non-RCT evidence

6.8.1 Details of how the relevant non-RCTs have been identified and selected

None relevant

6.8.2 Summary of methodology of relevant non-RCTs

6.8.3 Critical appraisal of relevant non-RCTs

6.8.4 Results of the relevant non- RCTs

6.9 Interpretation of clinical evidence

6.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

In the palliative chemotherapy of aGC overall survival and preventing symptomatic deterioration are the twin aims. These must be achieved without excessive toxicity that might offset prolonged life or reduced disease symptoms.

Both of the phase III studies described measured overall survival and this was at least as good with capecitabine as infused 5-FU.

Both studies also measured PFS which, again, was at least as good with capecitabine as 5-FU. Patients free of progression can reasonably be expected to be free of worsening disease symptoms and the psychological benefit to patients of knowing that their cancer is not growing is important. As such, PFS is also a clinically important end-point.

Both phase III studies collected comprehensive safety data demonstrating that capecitabine and 5-FU have broadly similar safety and tolerability. REAL-2 also demonstrated that a move to capecitabine does not compromise quality of life.

In short, the phase III studies described above have assessed the outcomes of greatest relevance to clinical practice, and shown capecitabine to be as effective and safe as 5-FU as the fluoropyrimidine component of combination regimens in aGC.

In addition, capecitabine is an oral treatment which will free patients from the need to be attached to a cumbersome 5-FU pump for the treatment duration. In many cases it will also free them from the requirement for a permanent venous access with its attendant complications and of regular visits to the hospital for 5-FU pump care. As has already been discussed (see Section 4.1) there is already ample evidence that most patients prefer oral chemotherapy regimens provided, as is the case of capecitabine in aGC, they do not compromise antitumour efficacy.

6.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the

technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

The combined results of REAL-2 and ML17032 provide robust evidence that replacing infused 5-FU with capecitabine in the platinum-based chemotherapy of aGC does not compromise safety efficacy or quality of life regardless of chemotherapy regimen used or patient or disease characteristics, current or present treatment.

The results obtained in REAL-2 are particularly relevant to the UK since this trial was conducted solely in this country and its entry criteria were such that the trial would be expected to recruit the sort of patients who routinely receive combination chemotherapy for aGC in this country. In addition, this study used as a control what was, prior to its completion, the dominant chemotherapy regimen for aGC in this country.

Study ML 17032 is also relevant to the minority group of UK patients who currently receive intermittent CF chemotherapy, possibly because they do not want, or are considered unable to cope with a portable pump and central venous access. Because ML 17032 was conducted in Asia, Europe and Central and South America, the ethnicities of the patients recruited could raise concerns that its results may not be fully applicable to a country like the UK, with a mainly Caucasian population. However, pre-planned subgroup analyses of this study demonstrated that ethnicity had no bearing on the primary endpoint of non-inferiority of PFS with CX relative to CF.

Both the ML 17032 and REAL-2 studies used dosage regimens that are described within the SmPc for Xeloda (capecitabine).

Overall, there seems to be no reason to suspect that if approved by NICE for this indication the use of capecitabine to treat aGC in routine clinical practice in the UK would differ significantly from that described in the two key trials described in this submission. Moreover, there is no reason to suppose that the efficacy or safety of capecitabine as a substitute for infused 5-FU would be different in UK clinical practice from what has been reported in clinical trials.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

The search strategy was designed to retrieve studies on the cost-effectiveness of capecitabine in the treatment of advanced gastric cancer (as per the decision problem). Keyword strategies were developed using key references retrieved through initial scoping searches. Search strategies did not include search terms or filters that would limit results to specific publication types or study design. In addition to broad medical databases, health economic databases and websites of health technology assessment (HTA) agencies were searched. All databases and websites searched are listed in Table 13. The search strategy is provided in Appendix 3.

Table 13. Literature review Databases

General Databases
Medline (MEYY)
EMBASE (EMYY)
Medline (MEIP)
Health economic databases and websites
NHS Economic Evaluation Database (NHS EED)
Health Economic Evaluation Database (HEED)
International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Research Digest
Health Technology Assessment Agency websites
National Institute of Health and Clinical Excellence (NICE)
Scottish Medicines Consortium (SMC)

7.1.2 Description of identified studies

The literature search identified one evaluation relevant to this decision problem; Roche's 2007 SMC submission for capecitabine for the first line treatment of advanced gastric cancer in combination with a platinum-based chemotherapy regimen.

In this study a cost-minimisation exercise was conducted on the basis of the equivalent efficacy of capecitabine and 5-FU demonstrated in the clinical trials. An extensive range of relevant resource requirements were considered.

The analysis demonstrated that capecitabine combination therapies could produce equivalent health outcomes to those of 5-FU combination therapies at lower cost to the NHS in Scotland. Whilst capecitabine drug acquisition costs were higher than 5-FU, the lower administration costs associated with capecitabine based regimens compensated for these costs. The estimated net saving per patient comparing a 5-FU based regimen to an equivalent capecitabine based regimen was over £1,500 per patient. The SMC granted positive advice on the basis of this appraisal in 2007. As

the price of capecitabine will be reduced by 10% from 1 January 2010, the drug acquisition of capecitabine will reduce further.

The remaining search results were excluded for the reasons detailed in Appendix 3.

7.2 De novo economic evaluation(s)

Manufacturer economic model described in detail below.

7.2.1 Technology

7.2.1.1 How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.

Capecitabine is indicated for the first-line treatment of advanced gastric cancer in combination with a platinum-based regimen. Throughout this evaluation it is assumed that capecitabine is used according to its licensed indication.

In combination treatment, capecitabine's recommended dose is the continuous administration of 625mg/m^2 taken orally twice daily during a 21 day cycle (ECX regimen) or 800-1000mg/m^2 when administered twice daily for 14 days followed by a 7-day rest period (CX regimen), with each 21-day 'cycle' being repeated until disease progression or unacceptable toxicity.

Drug dose and dose frequency of all regimens included in the economic model are taken from the two key phase III randomised controlled trials relevant to this appraisal: the REAL-2 trial (Cunningham et al. 2006) and the ML17032 trial (Kang et al, 2006). Both these trials utilised the dosing regimens described in each relevant products SPC. (as detailed in Table 14,Table 15 and Table 16 below).

Table 14. ECF and ECX drug dose and dose frequency (as per the REAL-2 trial)

Regimen	Epirubicin dose and frequency	Cisplatin dose and frequency	Fluoropyrimidine dose and frequency
ECF	50mg/m^2 Day 1 of each 21 day-cycle	60mg/m^2 Day 1 of each 21 day-cycle	Day 1-21. IV 5-FU 200mg/m^2 per day for all 21 days of each cycle, as a continuous infusion
ECX			Day 1-21. Oral capecitabine 625mg/m^2 twice per day for all 21 days of each cycle

Table 15. EOF and EOX drug dose and dose frequency (as per the REAL-2 trial)

Regimen	Epirubicin dose and frequency	Oxaliplatin dose and frequency	Fluoropyrimidine dose and frequency
EOF	50mg/m^2 Day 1 of each	130mg/m^2 Day 1 of each	Day 1-21. IV 5-FU 200mg/m^2 per day for all 21 days of each cycle, as a continuous infusion

EOX	21 day-cycle	21 day-cycle	Day 1-21. Oral capecitabine 625mg/m^2 twice per day for all 21 days of each cycle

Table 16. CF and CX drug dose and dose frequency (as per the ML17032 trial)

Regimen	Cisplatin dose and frequency	Fluoropyrimidine dose and frequency
CF	80mg/m^2 Days 1-5 as a continuous infusion	Days 1-5. IV 5-FU 800mg/m^2 as a continuous infusion
CX		Days 1-14. Oral capecitabine 1000mg/m^2 twice daily

7.2.1.2 Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators.

The license indication states treatment should be until disease progression. The base case evaluation assumes all patients have an average time on treatment of 5.5 cycles which was also the assumed time horizon of the model. 5.5 cycles (5290 cycles / 968 patients) represented the mean no of cycles observed in the REAL2 study for ECF (5.4 cycles), ECX (5.76), EOF (5.45) and EOX (5.42).

Calculation of the drug costs also accounted for the level of dose intensity observed in the REAL2 studyu and is described in further detail below.

As the mean treatment duration was not reported in the ML17032 trial, it was assumed the same mean treatment duration of 5.5 cycles was applied to the CF and CX regimens, as observed in the REAL 2 trial.

7.2.2 Patients

7.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

The patient cohort within the economic evaluation are assumed to have the same baseline characteristics as those observed in the REAL II trial (Cunningham at al, 2006) for the comparisons involving EOX, EOF, ECF and ECX and and the ML17032 trial (Kang et al, 2006) for the comparison of CF and CX. Two separate models have been designed in this evaluation. The baseline characteristics of the trials are described in greater detail in Section 6.

7.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

No sub-group cost effectiveness analysis was conducted as no subgroups were identified in the final NICE scope or were apparent from the clinical trials.

7.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

Please see section 7.2.2.2 above.

7.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

Patients enter the economic evaluation at the start of treatment receiving either oral capecitabine or IV 5-FU combination based regimens. The model assumes that patients exit the evaluation after 5.5 cycles, consistent with the observed mean treatment duration in the RCT Phase III registration studies (Cunningham at al, 2006) and (Kang et al, 2006). Due to the assumption of equivalent efficacy no differences in incremental costs and effect are assumed to occur post treatment cessation and therefore were excluded from the economic analysis.

The assumed points of entry and exit within the evaluation are the same for all treatments.

7.2.3 Comparator technology

7.2.3.1 What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

In the base case, capecitabine based regimens (ECX, EOX and CX) were compared to their equivalent 5-FU based regimens (ECF, EOF and CF). These six regimens represent the vast majority of current chemotherapy utilised for the treatment of aGC in England and Wales. ECF and EOF were the comparators used in the REAL-2

clinical trial (Cunningham et al. 2006) and CF was used in the ML17032 trial (Kang et al, 2006). Even though ECF is much more widely used than CF and EOF, all combination regimens can be considered an adequate representation of the standard of care in the UK for the first line treatment of aGC, as reflected in the NICE final scope, and are therefore valid comparators (as explain in section 6, above).

The base-case therefore presents the cost-comparison of ECX versus ECF; EOF versus EOX and CX versus CF. Market research conducted for Roche by First Line Research in 2009 on the usage of chemotherapy regimens for advanced gastric cancer in the UK confirmed the validity of the comparators, see Figure 2.

7.2.4 Study perspective

The economic analysis reflects the perspective of the NHS and Personal Social Services.

7.2.5 Time horizon

What time horizon was used in the analysis, and what was the justification for this choice?

The cost-minimisation approach includes the period during which patients receive chemotherapy, since this is the time when relative costs under this analytic framework are assumed to differ. As explained above, a mean of 5.5 cycles of 21 days per cycle has been assumed in this analysis. As this period is less than one year, no discounting of future costs or benefits was carried out.

7.2.6 Framework

a) Model-based evaluations

7.2.6.1 Please provide the following.

- **A description of the model type**

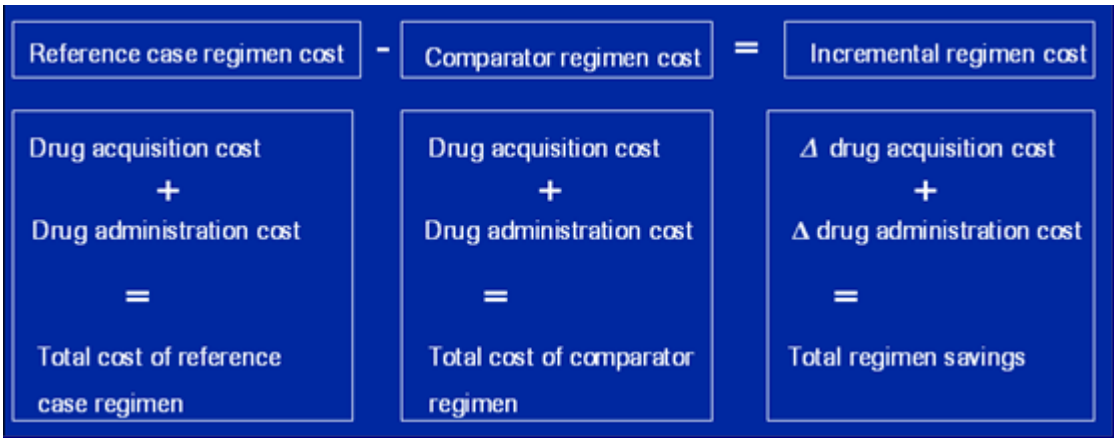
As described within the clinical section, on the basis of at least equivalent clinical effectiveness, similar safety and improved patient convenience, a cost-minimisation model was developed in Excel™ to allow the comparison of costs for each regimen within the NHS in England and Wales.

This analysis captures all significant incremental (and decremental) direct NHS costs relating to the switch from IV 5-FU based chemotherapy to oral capecitabine regimens. Healthcare resource use was examined to identify differential resource components/activities associated with drug acquisition and administration of each regimen; costs were then calculated by multiplying the quantity of these components/activities by their respective unit costs.

- **A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.**

The cost minimization model considers both drug acquisition and drug administration costs for all regimens evaluated, as shown in Figure 12 below.

Figure 12. Schematic of the cost minimization model



The drug utilisation of each regimen was calculated by accounting for the licensed dose, dose intensity, mean number of cycles as observed in the clinical trial and body surface area.

The drug administration for each regime was calculated by takening into account staff costs, medical supply costs, pharmacy costs, NHS transport costs and hospitalisation (outpatient visits and inpatient stays).

A breakdown of the elements of drug administration and drug utilization are detailed in section 7.2.7.2 below.

- **A list of all variables that includes their value, range (distribution) and source.**

Table 17. Model Parameters and Values

Model Variable	Value	Source
Costs		
Drug costs		
ECF per cycle	£263.06	BNF 58, SPC, REAL 2 (Cunningham et al. 2006
ECX per cycle	£350.40	BNF 58, 2010 Xeloda Price, SPC, REAL 2 (Cunningham et al. 2006
EOF per cycle	£814.85	BNF 58, SPC, REAL 2 (Cunningham et al. 2006
EOX per cycle	£910.93	BNF 58, 2010 Xeloda price, SPC, REAL 2 (Cunningham et al. 2006
CF per cycle	£158.54	BNF 58; SPC, (Kang et al, 2006)

CX per cycle	£282.67	BNF 58; 2010 Xeloda price, SPC, (Kang et al, 2006)
Drug administration costs†		
Central line insertion	£445.77	National Schedule of Reference Costs 2007-08
Drug delivery first attendance	£281.45	National Schedule of Reference Costs 2007-08
Drug delivery by nurse. Subsequent attendance	£36.83	National Schedule of Reference Costs 2007-08
Drug delivery. Subsequent attendance. Outpatient/daycare visit	£198.72	National Schedule of Reference Costs 2007-08
Pump	£38.50	Baxter Healthcare
Transport to hospital visit (returned trip)	£28.43	National Schedule of Reference Costs 2007-08
Pharmacy preparation "Complex" (IV)	£41.87	Tappenden, P et al 2007
Pharmacy preparation "Complex" (oral)	£25.34	Tappenden, P et al 2007
In patient stay for drug delivery	£1,435.64	National Schedule of Reference Costs 2007-08
Treatment days per cycle (21 days in each cycle)		
For ECF, ECX, EOF and EOX regimens		
Epirubicin (IV)	Day 1 of each cycle	REAL 2 (Cunningham et al. 2006)
Fluorouracil (IV)	Every day of each cycle	REAL 2 (Cunningham et al. 2006), SPC)
Capecitabine (oral)	Every day of each cycle (administered twice daily)	REAL 2 (Cunningham et al. 2006), SPC
Cisplatin (IV)	Day 1 of each cycle	REAL 2 (Cunningham et al. 2006), SPC
Oxaliplatin (IV)	Day 1 of each cycle	REAL 2 (Cunningham et al. 2006), SPC
For CF and CX regimens		
Fluorouracil (IV)	Days 1-5, administered at a higher dose of 800mg/m2	ML17032 (Kang et al, 2006), SPC
Capecitabine (oral)	Days 1-14, administered twice daily at a higher dose of 1000mg/m2	ML17032 (Kang et al, 2006), SPC
Cisplatin (IV)	Day 1 of each cycle	ML17032 (Kang et al, 2006), SPC

†Drug administration costs include any resources, activities or charges needed for the administration of the regimen and are costed per unit

The assumed ranges for each model parameter are listed in Section 7.2.11 (sensitivity analysis). Further detail on the calculation of costs is provided in Section 7.2.9.

- **A separate list of all assumptions and a justification for each assumption.**

Table 18. Economic evaluation assumptions

Assumption	Comments/Source
1. Oral administered capecitabine based chemotherapy is assumed to have equivalent clinical efficacy as IV administered 5-FU based chemotherapy regimens, as shown in section 6.	Both the REAL 2 (Cunningham et al. 2006) and the ML17032 (Kang et al, 2006) met their primary non-inferiority end points and both trials demonstrated a clear trend towards superior outcomes (both primary and secondary) in the capecitabine arm. Replacing continuous 5-FU in the ECF/EOF regimens with oral capecitabine produced a hazard ratio for risk of death (capecitabine vs. 5-FU) of 0.86 (95% confidence interval 0.75-0.99; p=0.025), whilst switching from 5-FU to capecitabine in the CF regimen reduced produced a hazard ratio for progression-free survival cisplatin plus capecitabine versus CF of 0.85 (95% confidence interval 0.63, 1.04; p=0.005).
2. No differences in treatment-related adverse events are assumed between the oral administered capecitabine and the IV administered 5-FU based chemotherapy regimens. Costs associated with the management of adverse events are not included in this analysis as the net costs associated with adverse event management are unlikely to be higher for oral administered capecitabine than IV administered 5-FU regimens.	The overall tolerability profile of capecitabine is considered similar and at least as good as that of 5FU. (See Section 6). The grade 3 and 4 adverse events commonly associated with IV 5-FU (ie; central-line related complications such as infection and thromboembolism) can be very expensive to manage. In contrast, the adverse events more commonly associated with oral capecitabine (ie; diarrhoea and hand-foot syndrome) are inexpensive to manage, (see section 7.2.7.4)
3. Patients treated with CF regimen attend hospital on outpatient visits every day for 5 consecutive days rather than on an inpatient basis	Patients attend hospital either as an outpatient visit every day for 5 consecutive days or as an inpatient basis and stay in hospital for 5 days. Since we do not have information on the proportions held by each of these options in actual clinical practise in the NHS in England and Wales, the less expensive approach was assumed, that is all CF patients are treated as an outpatient visit. This assumption will be tested in sensitivity analysis (section 7.2.11).
4. No drug wastage has been taken into account.	Nurse expert opinion confirmed that drug wastage is minimal, as patients are given the required amount of capecitabine until next planned visit and vial shares occurred where large volume of patients are treated with 5FU.
5. It assumed that the NHS supplies transport for 20% of patients attending hospital visits	A Roche Advisory Board on colorectal cancer (2008) advised that 30% of patients use NHS paid transport. However, nurse opinion confirmed that a minority of patients (and as little as 14% in some hospitals) are supplied with NHS transport. In the

	absence of more information, we assumed that NHS supplies transport to 20% of the patients. This assumption is tested in sensitivity analysis.
6. Central line removal costs for regimens containing IV 5FU have not been included	Some patients may come to hospital as an additional visit to have the line insertion removed. However, nurse expert advice suggests that most patients get the line removed as part of a routine visit. This assumption favours 5FU regimens.
7. This analysis does not take into account the cost of replacement of any line insertion what may fail: blocked, rejected or get infected This will be tested in sensitivity analysis	Some lines inserted for 5-FU regimens may fail through blockage, infections etc. This assumption favours 5FU regimens.
8. This analysis assumes that x-rays and other minor disposables used to insert the central line are included in the cost of the visit and therefore no separate cost for this activity has been included	Some hospitals may charge a separate cost for the x-ray, as per nurse expert advice. This assumption favours 5FU regimens.
9. The pharmacy cost is assumed to be higher when dispensing a “complex” preparation than when dispensing a “simple” preparation	SeeTappenden P et al, 2007
10. Patients taking ECF do not stay in hospital overnight on day one of their treatment	Feedback from nurse experts confirmed that some patients may need to be hospitalised overnight on day one of ECF treatment. This assumption favours 5FU regimens.
11. A nurse charge of £36.83 has been used for the care required on days 7 and 14 of each ECF and EOF cycles (flush line and change pump)	Some patients attend hospital to receive this care and their attendance may be classed as: “Deliver subsequent elements of a chemotherapy cycle (Currency code: SB15Z)”, which is £198.72 rather than £36.83. This will be tested in sensitivity analysis (section 7.2.11).
12. Routine monitoring cost are carried out as part of the drug administration visits	REAL 2 (Cunningham et al. 2006) and the ML17032 (Kang et al, 2006), Nurse expert opinion

7.2.6.2 Why was this particular type of model used?

As per section 6, the two non-inferiority randomised clinical trials considered in this analysis: REAL 2 (Cunningham et al. 2006) and ML17032 (Kang et al, 2006) reported that oral capecitabine is at least, if not more, safe, efficacious and convenient that IV 5FU, in the treatment of advanced gastric cancer.

In addition, a meta-analysis of these two studies demonstrated a significant improvement in overall survival when capecitabine was used in place of 5-FU – hazard ratio 0.87 (95% confidence interval 0.77-0.98; p=0.027).

This allows us to simplify our economic evaluation without compromising its ability to inform the decision problem by simply concentrating on calculating the differential cost of drug acquisition and drug administration that result from substituting 5FU with oral capecitabine across the treatment regimens currently used in the NHS.
This type of economic evaluation is also consistent with all the previous economic evaluations that have been positively appraised by both the SMC and NICE, on capecitabine within this and other existing indications.

7.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

In line with a cost minimisation analysis, the structure is to consider the differential costs associated with drug acquisition and administration. This approach is common practice when carrying out a cost minimisation analysis and therefore, no alternative structures were considered.

As the point estimate for the overall survival hazard ratios favoured capectabine compared to 5FU, the construction of a full cost utility model would was assumed to add unecessary complication to the evaluation without modifying the final decision or reducing uncertainty as to the likely cost effectiveness of capectabine in aGC.

The course of the disease was represented in section 7.2.6.1, above.

7.2.6.4 What were the sources of information used to develop and inform the structure of the model?

The main sources that informed the model structure (in terms of drug used and administration patterns) was the REAL 2 (Cunningham et al. 2006) and the ML17032 (Kang et al, 2006) randomised clinical trials. Clinical opinion helped define the typical treatment pathway and likely direct NHS costs incurred.

7.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The cost model structure captures all essential features of the conditions relevant to the decision problem. Those elements of direct cost excluded from the analysis are justified in the assumptions table above.

7.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a

minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

No applicable, as there are no discrete time intervals in the model.

7.2.6.7 Was a half-cycle correction used in the model? If not, why not?

No applicable. A half cycle correction was not relevant to the model structure.

7.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

No applicable. Cost and clinical outcomes were not extrapolated beyond the trial period.

b) Non-model-based economic evaluations

Not Applicable. Only model-based economic evaluations were performed for this submission.

7.2.7 Clinical evidence

7.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

N/A

7.2.7.2 How were the relative risks of disease progression estimated?

N/A

7.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

N/A

7.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

Evidence from the Phase III studies REAL-2 and ML17032 shows that a move from IV 5-FU to oral capecitabine in the platinum-based chemotherapy of advanced gastric cancer does not result in major changes in treatment tolerability. Although oral capecitabine is associated with more hand-foot syndrome than IV 5-FU (<5% frequency for grade 3 and never life threatening), this side-effect usually has limited impact on patients, can be easily managed by dose reduction and incur little or no expense to the NHS (perhaps a small use of moisturizing cream). By contrast, IV treatment with 5FU requires prolonged IV infusions via a central line which is a possible entry point and focus for infection and thrombus formation which can be life-threatening and difficult (and potentially expensive in some cases) to treat as some patients may require hospitalisation), particularly in patients who may be immunosuppressed as a result of chemotherapy or who have coagulopathies related to their cancer. These complications – along with other catheter-related complications- are common. In a review by Kuter (2004) it is reported that central venous catheters become infected in 4-33% of cases and cause thrombosis in 12-74%.

Based on this, the net costs associated with adverse event management appear highly unlikely to be higher for oral administered capecitabine and their inclusion would only further increase the direct NHS cost savings fromcapectabine.

7.2.7.5 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

N/A

7.2.7.6 Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

N/A

7.2.7.7 How were health effects measured and valued?

N/A

7.2.7.8 Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis.

No

7.2.7.9 Were any health effects excluded from the analysis? If so, why were they excluded?

N/A

7.2.8 Resource identification, measurement and valuation

7.2.8.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

The following resources were included in the evaluation:
1) Drug acquisition inputs (drug utilisation and drug unit cost) for the following regimens:

a) ECF
b) ECX
c) EOF
d) EOX
e) CF
f) CX

2) Drug administration inputs (resource utilisation and their unit costs)
- a) Installation and replacement of central venous access device (CVADs)
- b) Outpatients hospital visits for treatment administration
- c) Inpatient hospital visits for treatment administration
- d) Nurse time treatments
- e) Acquisition cost of ambulatory pumps
- f) Hospital pharmacist time and cost for drug preparation
- g) NHS Transport cost

The following section describes each component in more detail.

7.2.8.2 How were the resources measured?

This section explains the methodology used to identify and measure the key components/activities of health care resources and costs required to administer the 5-FU and capecitabine regimens for the treatment of advanced gastric cancer. Total costs are calculated by multiplying the quantity of these components/activities by their respective unit costs.

This section is divided into the following subsections:

7.2.8.2.1 Evidence sources

7.2.8.2.2 Drug acquisition inputs

7.2.9.2.2.1 Drug Utilisation
7.2.9.2.2.2 Drug Unit Cost

7.2.8.2.3 Drug administration inputs

7.2.9.2.3.1 Drug Administration Resource Utilisation
7.2.9.2.3.2 Drug Administration Unit Cost
7.2.9.2.3.3 Drug Administration Inputs Summary

7.2.9.2.1 Evidence sources

Healthcare resource utilisation was estimated using a combination of sources, including: clinical trial information (drug utilisation), nurse expert opinion (drug administration requirements expected within England and Wales clinical practice) and literature sources (unit costs).

Expert opinion was sought to validate the regimens' administration requirements in England and Wales clinical practice. This advice was provided primarily by five specialist nurses experienced in administering regimens to advanced gastric cancer patients from the following trusts: Southampton General Hospital, Christie Hospital NHS Trust, Mount Vernon Hospital, Broomfield Hospital and Newcastle upon Tyne NHS Foundation Trust.

Telephone conversations were carried out with the nurse experts of above Trusts during October 2009. Experts were informed that the purpose of obtaining their views was to inform the analysis of capecitabine within aGC for a NICE submission and gave consent for their views to be used in this way. The experts were asked questions which described the administration of the regimens used in their hospitals to treat advanced gastric cancer. Their views are based on first-hand clinical experience of advanced gastric cancer regimens' administration.

Nurse's advice showed that there is some variation in the way patients are treated in different trusts. For example, some hospitals encourage patients on CF regimens to come to hospital as outpatients (every day for the 5 days of the treatment) rather than stay in the hospital as inpatients, in line with the cancer reform strategy, while in other trusts patients usually receive CF as inpatients.

Table 19 below summarises the input data from various evidence sources:

Table 19. Data input. Evidence sources

Data	Source
Eligible patients/condition Recommended regimen drug dosing	Capecitabine regulatory label, SmPC

Recommended regimens dosing Drug administration method Healthcare setting involved in drug administration Dosing intensity observed Dosing duration	Clinical trials REAL 2 (Cunningham et al. 2006) and ML17032 (Kang et al, 2006)
Patient body surface area	Assumption used in other NICE submissions
Available drug formulations Drug acquisition cost	BNF 58, 2010 Xeloda price
Schedule of visits to hospital and other NHS care Drug administration method Healthcare setting involved in drug administration Use of hospital transport	SmPC and Expert opinion to inform on the typical clinical practice pattern expected within England and Wales
Cost of outpatient and inpatient visits to hospital Cost of hospital transport	National Schedule of Reference Costs 2007-08
Costing of ambulatory pump	Baxter Healthcare
Costing of pharmacy preparation	Tappenden, P et al 2007

7.2.9.2.2 Drug acquisition inputs

Drugs costs were calculated according to the recommended adult dose and no wastage was assumed for any therapies, as wastage was considered to be minimal, by nurse expert opinion.

Two components have been considered in this section: drug utilisation and drug unit cost, and are described below. Total drug costs were then calculated by multiplying the drug utilisation by their respective unit costs.

7.2.9.2.2.1. Drug Utilisation

The total drug utilisation of each regimen was calculated by taking the following items into account: dosing schedule, dose intensity, number of cycles and body surface area.

Dosing schedule

Dosing schedules were taken from the REAL-2 trial (Cunningham et al. 2006) are shown in Table 20 and Table 21 and from the ML17032 trial (Kang et al, 2006) shown in Table 22 below. Each regimen has a 21-day 'cycle' being repeated for 24 weeks or until disease progression. These dosing is also recommended within the capecitabine label.

Table 20. REAL-2 trial. Dose regimens for ECF and ECX drug regimens

Regimen	Epirubicin	Cisplatin	Fluoropyrimidine
ECF	50mg/m^2	60mg/m^2	IV 5-FU 200mg/m^2 per day for 21 days as

			a continuous infusion
ECX			Oral capecitabine 625mg/m^2 twice per day for 21 days

Table 21. REAL-2 trial. Dose regimens for EOF and EOX drug regimens

Regimen	Epirubicin	Oxaliplatin	Fluoropyrimidine
EOF	50mg/m^2	130mg/m^2	IV 5-FU 200mg/m^2 per day for 21 days as a continuous infusion
EOX			Oral capecitabine 625mg/m^2 twice per day for 21 days

Table 22. ML17032 trial. Dose regimens for CF and CX drug regimens

Regimen	Cisplatin	Fluoropyrimidine
CF	80mg/m^2	IV 5-FU 800mg/m^2 Days 1-5 as a continuous infusion
CX		Oral capecitabine 1000mg/m^2 twice daily. Days 1-14

Dose intensity

The dose intensity captures the degree of dose titration and any missed/additional doses, in relation to the recommended (per protocol) dosing schedule.

The REAL 2 trial (Cunningham et al. 2006) reports that drug utilisation typically varies from recommended/ per protocol initial doses, due to drug titration. Therefore, since significant differences between recommended and actual doses may be observed, the actual drug utilisation figures from the clinical trial are used within the economic analysis. These figures provide a more accurate estimate of the likely drug utilisation levels in England and Wales clinical practice. However, dose intensity will be tested in sensitivity analysis (section 7.2.11). The percentages of drug doses actually observed relative to the scheduled dosing requirements, or dose 'intensities' within the REAL-2 trial (Cunningham et al, 2006) are as shown in Table 23 and Table 24 below:

Table 23. REAL-2 trial dose intensities for ECF and ECX

Regimen	Epirubicin	Cisplatin	Fluoropyrimidine
ECF	92.6%	92.6%	90.5%
ECX	89.2%	92.3%	88.4%

Table 24. REAL-2 trial dose intensities for EOF and EOX

Regimen	Epirubicin	Cisplatin	Fluoropyrimidine
EOF	93%	91.7%	83.3%
EOX	91.9%	91.6%	88.1%

Note that dose intensities do not apply to the CF and CX regimens, due to the nature of dosing schedule, as per results from the ML12032 trial (Kang et al, 2006).

Number of cycles

The mean number of 21 day 'cycles' within the REAL 2 trial (Cunningham et al. 2006) was 5.5. Sensitivity analysis will evaluate uncertainty in this parameter.

Body surface

The average patient body surface area (BSA) was assumed to be 1.7m^2, as per other UK NICE submissions, like Herceptin in breast cancer and SMC submissions like capecitabine in advanced gastric cancer.

Total drug utilisation

Based on the above parameters, the estimated drug utilisation figures per patient course of chemotherapy are shown in Table 25 below:

Table 25. Drug utilisation

Drug	Recommended Dose (per m^2)	Dose intensity	Doses per cycle	Cycles	BSA	Total drug usage
ECF						
Epirubicin	50mg	x 92.6%	x 1	x 5.5	x 1.7m^2	433mg
Cisplatin	60mg	x 92.6%				519mg
IV 5-FU	200mg	x 90.5%	x 21			35,540mg
ECX						
Epirubicin	50mg	x 89.2%	x 1	X 5.5	x 1.7m^2	417mg
Cisplatin	60mg	x 92.3%				518mg
Capecitabine	625mg	x 88.4%	x 42			216,967mg
EOF						
Epirubicin	50mg	x 93.0%	x 1	x 5.5	x 1.7m^2	435mg
Oxaliplatin	130mg	x 91.7%				1,115mg
IV 5-FU	200mg	x 83.3%	x 21			32,712mg
EOX						
Epirubicin	50mg	x 91.9%	x 1	X 5.5	x 1.7m^2	430mg
Oxaliplatin	130mg	x 91.6%				1,113mg
Capecitabine	625mg	x 88.1%	x 42			216,230mg
CF						
Cisplatin	80mg	x 1	x1	x 5.5	x 1.7m^2	748mg
IV 5-FU	800mg	x 1	x 21			37,400mg
CX						
Cisplatin	80mg	x 1	x 1	x 5.5	x 1.7m^2	748mg
Capecitabine	1000mg	x 1	x 28			261,800mg

7.2.9.2.2.2. Drug Unit Costs

Individual drug costs were taken from the British National Formulary (BNF-58, Sep 2009) with the exception of capecitabine (as the list price of capecitabine will drop 10% below the BNF 58 value from 01/01/10, as part of the PPRS price adjustments).

Epirubicin is available as a branded product (Pharmorubicin®), in powder or solution formulation, and as a generic product in solution form. The NHS list price of generic epirubicin (ex VAT) is: 5 mL vial = £16.99, 25 mL vial = £84.95, 50 mL vial = £169.92 and 100 mL = £308.93 (2 mg/mL solution). The average price per mg of generic epirubicin listed in BNF 58 is approximately £1.6605.

Cisplatin is available in a generic powder or solution formulation. The NHS list price of generic cisplatin solution (ex VAT) is: 10 mL vial = £ 5.85, 50 mL vial = £24.50 and 100 mL vial = £50.22 (1 mg/mL solution). The average price per mg of cisplatin in the generic solutions listed in BNF 58 is approximately £0.5257.

Oxaliplatin is available as generic powder for reconstitution and as a branded (Eloxatin®) concentrate for intravenous infusion. The NHS list price of generic oxaliplatin for reconstitution (ex VAT) is: 50 mg = £150, 100 mg = £299.50. The average price per mg of oxaliplatin in the generic forms listed in BNF 58 is approximately £2.9975.

There is a range of generic fluorouracil injection preparations listed in the BNF. The NHS list price of 25 mg/mL fluorouracil (ex VAT) is: 10 mL vial = £3.20, 20 mL vial = £6.40 and 100 mL vial = £32.00. The NHS list price of 50 mg/mL fluorouracil (ex VAT) is: 10 mL vial = £6.40, 20 mL vial = £12.80, 50 mL vial = £ 32.00 and 100 mL vial = £ 64.00. The average price per mg of fluorouracil for the generic products listed in BNF 58 is approximately £0.0128.

Capecitabine is only available as a branded product (Xeloda®). From 01/01/10 the NHS list price of oral Capecitabine (ex VAT) will be: 150mg (60 tablets) = £40.02 and 500mg (120 tablets) = £265.55. This equates to a pricing of £0.0044/mg.

The prices per mg for each drug used in the economic analysis are as shown in Table 26 below:

Table 26. Unit cost price of evaluated drugs (BNF58, September 2009 and 2010 Xeloda new pricing)

Resource	Price/mg
Epirubicin	£1.6605
Cisplatin	£0.5257
5-FU	£0.0128
Capecitabine*	£0.0044
Oxaliplatin	£2.9975

Please, note that from 1 January 2010 the price of Xeloda will be 10% less than the list price published in BNF No. 58, subject to DoH approval.

The total NHS costs of drug acquisition were then calculated by multiplying the total dose usage (Table 25) by the unit cost price (Table 26). Results can be seen in section 7.3.1.1.1.

7.2.9.2.3 Drug Administration Inputs

Following the same methodology as in section 7.2.9.2.2, two components have been considered in this section: drug administration resource utilisation and drug administration unit cost. Total administration costs are then calculated by multiplying the quantity of each drug administration components by their respective unit costs.

This section has been divided into three sub-sections:
7.2.9.2.3.1 Drug Administration Resource Utilisation
7.2.9.2.3.2 Drug Administration Unit Cost

7.2.9.2.3. Drug Administration Inputs Summary

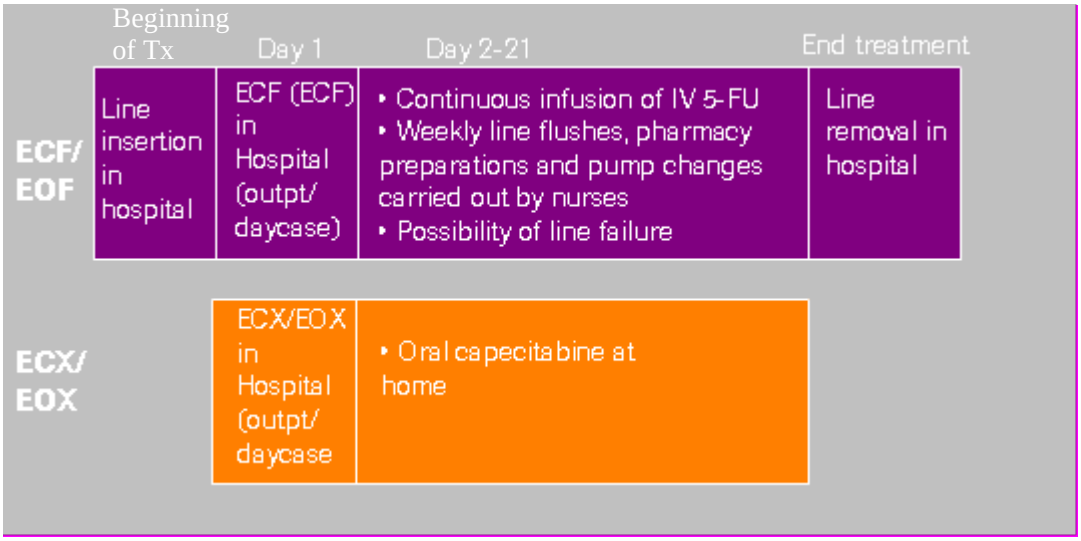
7.2.9.2.3.1 Drug Administration Resource Utilisation

The treatment administration schedule for each regimen provided the framework to analyse the administration resources used. Triple therapy (ECF, ECX, EOF and ECX) and double therapy (CF and CX) regimens schedules are explained separately below.

ECF, ECX, EOF and EOX regimen schedules

The REAL 2 trial (Cunningham et al. 2006) was utilised as a starting point from which to investigate the likely requirements of each treatment regimen. Cunningham et al. 2006 describe the sequence of drugs to be administered in each regimen and their route of administration. Nurse experts consulted confirmed these regimen details were relevant within the context of the NHS in England and Wales. The treatment administration schedules for IV 5FU and oral capecitabine regimens are described separately and shown in Figure 13 below.

Figure 13. Schema of treatment schedule for ECF/EOF and ECX/EOX



ECF/EOF:

STEP 1. Insertion of the central line.
Before treatment can start, a central line is inserted, as IV 5-FU infusions require central venous access line. This procedure is carried out in hospital typically a day before the treatment is administered. The line remains in place throughout all remaining cycles of treatment (except in cases of line failure, when it would have to be replaced).

STEP 2: On day 1 of the cycle the following medication:

- epirubicin bolus injection,
- cisplatin (or oxaliplatin) infusion and
- commencement of the IV 5-FU continuous infusion via the central venous access line.

This treatment is administered in hospital in an outpatient/day case visit, even though some patients are required to stay overnight, as confirmed by nurse expert opinion.

STEP 3: On days 2-21 patients require IV 5-FU continuous infusion with further weekly care on days 7 and 14, as follows:

- weekly pharmacy preparations of the IV 5-FU
- weekly pump replacements to deliver the continuous IV 5-FU
- weekly central line flushes

The last two activities are typically carried out by a nurse in hospital, even though in some cases district nurses visit the patient at home to carry out the treatment, as confirmed by nurse expert opinion. For the base case, it is assumed that all patients visit hospital, as nurse expert opinion confirmed that this is the most common way to carry out these activities. This parameter was tested in sensitivity analysis.

STEP 4: At the end of the chemotherapy treatment, the pump is disconnected and the central line is removed by a nurse. Even though this may take another hospital outpatient visit, we have taken the assumption least favourable to capecitabine and decided not to include this potential separate final visit in our analysis, as the central line removal could be carried out at a scheduled routine visit.

ECX/EOX:

STEP 1: On day 1 the following medication is administered in hospital on an outpatient/day case basis:

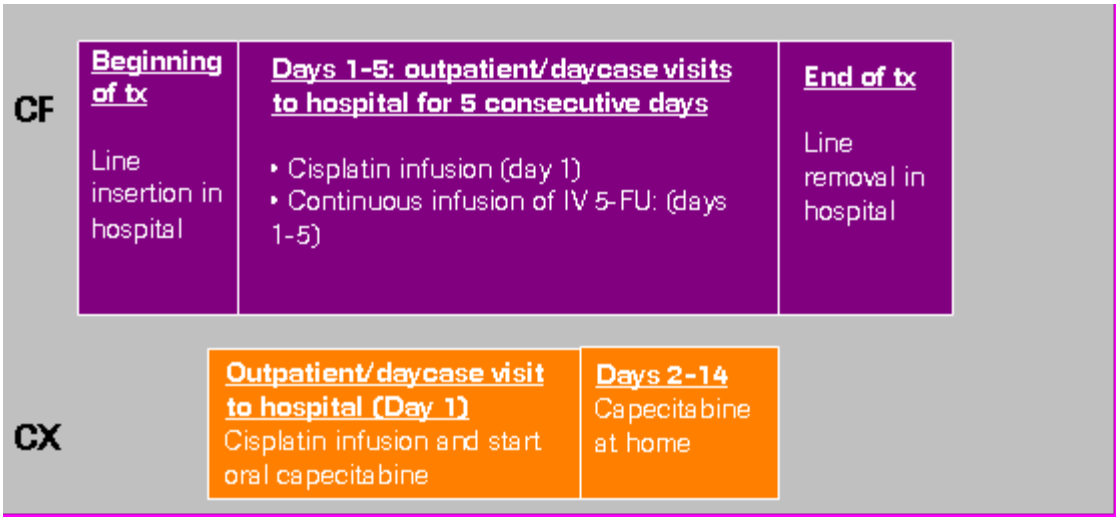
- epirubicin bolus injection,
- cisplatin (or oxaliplatin) infusion, and
- commencement of oral capecitabine therapy.

Unlike patients treated with a 5-FU regimen, patients receiving capecitabine treatment are discharged after day 1 of their chemotherapy and there is typically no further care associated with their drug administration until the start of their next cycle.

STEP 2: Oral capecitabine therapy at home on days 2-21 of each cycle

Treatments are repeated every 3 weeks until disease progression or unacceptable toxicity.

Figure 14. Schema of treatment schedule for regimens CF and CX



CF and CX schedules

The ML17032 trial (Kang et al, 2006) provided the basis for investigating the likely requirements of the treatment administration schedule for CF and CX regimens. They indicate the sequence of drugs to be administered and their route of administration. These regimen details did not differ significantly from the NHS England and Wales clinical practice as described by the nurse experts. The treatment administration schedules for IV 5FU and oral capecitabine regimens are outlined separately and shown in Figure 14 above.

CF:

Patients attend hospital either on an outpatient/daycase visit every day for 5 consecutive days or on an inpatient basis and stay in hospital for about 5 days, whilst the regimen is administered. Since we do not have information as to what is the split of these two options in England and Wales NHS clinical practice, a conservative approach regarding the likely incremental or cost of capecitabine was taken and it was assumed that all patients are treated within an outpatient setting.. However, this assumption will be tested in sensitivity analysis (section 7.2.11).

STEP 1: Before treatment starts, the central line is inserted in hospital, (as explained above).

STEP 2: On day 1, patients receive in hospital (outpatient/daycase visit) cisplatin infusion and commence the IV 5-FU continuous infusion via the central line for days 1 to 5.

STEP 3: On Days 2-5, patients continue receiving IV 5-FU continuous infusion via the central line in hospital (outpatient/daycase visit).

STEP 4: At the end of treatment: the central line is removed in hospital.

CX:

STEP 1: On day 1, patients receive in hospital (outpatient/daycase visit) cisplatin infusion, and commence of oral capecitabine therapy.

STEP 2: On days 2-14, patients take oral capecitabine therapy at home. Treatments are repeated every 3 weeks until disease progression or unacceptable toxicity.

In conclusion, the fundamental difference between these regimens is the replacement of IV 5-FU therapy by oral capecitabine.

Unlike patients treated with a 5-FU regimen, patients receiving capecitabine treatment are discharged after day 1 of their chemotherapy and there is typically no further care associated with their drug administration until the start of their next cycle.

7.2.9.2.3.2 Drug Administration Unit Cost

The following section describes the estimated unit costs for NHS resources required to administer the regimens considered in this analysis. These costs are based on published data.

Hospital visits

The unit costing of the visits required to administer the advanced gastric cancer regimens was based on The National Schedule of Reference Costs 2007-08. They are outline below and shown in Table 27.

Table 27.Cost of hospital visits (NHS Reference Cost 07-08)

Visit type	Activity	Cost
Day case outpatient visit, coded as: "Vascular Access except for Renal Replacement Therapy without Complications (Currency code QZ14B)	Insertion of central line	£445.77
1st attendance outpatient/daycase visit, coded as: "Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance (Currency code: SB14Z)".	Outpatient/daycase visit to administer either ECF, EOF, ECX, EOX, CF or CX, at day 1 of each cycle	£218.45 per visit. (A weighted average of day case and outpatient)
Subsequent care by a nurse on days 7th and 14th of ECF and EOF cycles	Flush central line and change pump on days 7 and 14 of each ECF and EOF cycles	£36.83
Subsequent attendance outpatient/daycase visit on days 3 to 5 to administer CF was coded as "Deliver subsequent elements of a chemotherapy cycle (Currency code: SB15Z)".	Outpatient/daycase visit to administer CF regimens on days 3 to 5	£198.72 per visit. (A weighted average of day case and outpatient)

- The daycase outpatient visit to insert the central line was coded as "Vascular Access except for Renal Replacement Therapy" (Currency code QZ14).

As this activity may have some complications associated with it, a weighted average unit cost of this activity with complications (currency code QZ14A) and without complication (currency code QZ14B) was carried out. The weighted average cost for this visit is £445.77, as calculated in Table 28.

Table 28. Weighted average unit cost of the central line insertion

Currency Code	Currency Description	Activity	National Average Unit Cost	Weighted Average Unit Cost
QZ14A	Vascular Access except for Renal Replacement Therapy with CC	6,058	£486	£445.77
QZ14B	Vascular Access except for Renal Replacement Therapy without CC	18,191	£432	

- The 1st attendance outpatient visit to administer ECF, EOF, ECX, EOX, CF and CX, was coded as: "Deliver complex chemotherapy, including prolonged infusional treatment at first attendance (Currency code: SB14Z)".

  A weighted average of day case and outpatient national average unit costs was calculated because hospitals may code these visits as either outpatient or day case visits. The weighted average is £218.45 per visit, as calculated in Table 29.

Table 29. Weighted average unit cost of 1st attendance daycase and outpatient visit

Currency Code	Currency Description	Outpatient Activity	Outpatient National Average Unit Cost	Daycare Activity	Daycare National Average Unit Cost	Weighted Average OP and D/C
SB14Z	Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance	28,173	£208	80,426	£307	**281.45**

- Subsequent nurse treatment on days 7 and 14 of ECF and EOF cycles (to flush the central line and change the pump) was coded as NHS Trusts and PCTs combined Community Nursing Services: District Nursing Services. Adult face to face. Code: CN301AF.

  The cost for each visit on days 7 and 14 of ECF and EOF cycles is £36.83

  As explained above, this may be a conservative assumption, as the attendance of some patients to hospital may be classed as: "Deliver subsequent elements of a chemotherapy cycle (Currency code: SB15Z)", which average cost is £198.72 rather than £36.83. This assumption will be tested in sensitivity analysis (section 7.2.11).

- Subsequent outpatient visits on days 3 to 5 to administer the CF regime was coded as "Deliver subsequent elements of a chemotherapy cycle (Currency code: SB15Z)".

A weighted average of day case and outpatient national average unit costs was calculated because hospitals may code these visits as either outpatient or day case visit. The weighted average is £198.72, as calculated in Table 30.

Table 30. Weighted average unit cost of 1st attendant daycase and outpatient visit

Currency Code	Currency Description	Outpatient Activity	Outpatient National Average Unit Cost	Daycare Activity	Daycare National Average Unit Cost	Weighted Average OP and D/C
SB15Z	Deliver subsequent elements of a chemotherapy cycle	28,814	£154	60,602	£220	**198.72**

Pharmacy Drug Preparation cost

Pharmacy drug preparation costs are not included within the 2007-2008 National reference costs and therefore need to be costed separately.

Only the pharmacy preparation cost for 5-FU and capecitabine have been included in this analysis, as the time to prepare epirubicin, cisplatin and oxaliplatin is the same for all of the regimens being compared.

Pharmacy drug preparation costs were estimated using the same classification employed by the SCHARR evaluation of bevacizumab (Tappenden P et al, 2007). Each infusion preparation was classed as being a “complex” pharmacy preparation and each bolus preparation or oral medication classed as a “simple” pharmacy preparation. Unit cost for complex and simple preparations were taken from the SCHARR analysis and uplifted from 2005 to 2009 costs using the healthcare inflation index published within the PSSRU report 2009 and are shown in Table 31 below.

Table 31. Pharmacy Unit preparation costs

Pharmacy preparation type	2005 SCHARR	Inflated to 2009
Complex	£39.74	£41.87
Simple	£24.05	£25.34

Drug Ambulatory Pumps

Typically a 5-FU ambulatory pump lasts 7 days before it needs replenishment.

The cost of the ambulatory pump was estimated to be £38.50, based on a pump provided by a large medical supplier (Baxter UK website, Folfusor SV2 (product code: 2C4702K). http://www.ecomm.baxter.com/ecatalog/browseCatalog.do?lid=10011&hid=10000&cid=10001&key=bf61f5fe7228a1d177d07ee7eb8398a&pid=442402).

Transport cost

The transport cost for one trip, based on the National Schedule of Reference Costs 2007-08 (NHS Trusts Patient Transport Services: Outpatient) is £28.43.
Previous submissions to NICE have considered that 30% of patients use NHS paid transport in England and Wales and nurse expert advice confirmed that a minority of patients use NHS paid transport (and in some areas may be as low as 14%). Based on these sources, we have estimated that in England and Wales 20% of patients are likely to require hospital transport (paid by the National Health Service) to attend hospital visits related to the administration of treatment for advanced gastric cancer. It is assumed that these journeys are provided by hospital transport services (rather than ambulance or paramedic services), and that each patient round-journey to and from hospital equates to one 'trip'. This parameter was tested in sensitivity analysis.

7.2.9.2.3.3 Drug Administration Inputs Summary

To aid clarity, the drug administration inputs detailed in the two previous sub-sections are summarised in the next four tables:

Table 32. Summary of drug administration inputs for ECF and EOF regimens

Day	Activity/ component	Source	Visits	Cycles	Activity cost
D0/D1	Line insertion	NHS 07-08 Ref. costs. Ref code: L911/HRGQZ14B	1	1	£445.77
D1	Drug delivery. 1st attendance. Outpt/day case	NHS 07-08 Ref. costs. Ref code:SB14Z	1	5.5	£281.45
D7&14	Drug deliver. subsequent attendances. Nurse cost	National Schedule of Reference Costs 2007-08 - NHS Trusts and PCTs combined Community Nursing Services: District Nursing Services. Code: CN301AF	2	5.5	£36.83
D1,7&14	Pump cost	Baxter UK website, Folfusor SV2 (product code: 2C4702K)	3	5.5	£38.50
D1,7&14	Transport cost (20% of patients)	NHS 07-08 Ref cost- Patient Transport Services: Outpatient (PTS)	3	5.5	£28.43
D7&14	Pharmacy preparation: "Complex" (IV)	SCHARR/Tappenden, P et al 2007	3	5.5	£41.87

Table 33. Summary of drug administration inputs for ECX and EOX regimens

Day	Activity	Source	Visits	Cycles	Activity cost
D1/cycle	Drug delivery. 1st attendance	NHS 07-08 Ref. costs. Ref code:SB14Z	1	5.5	£281.45
D1/cycle	Transport cost (20% of patients)	NHS 07-08 Ref cost-Patient Transport Services: Outpatient (PTS)	1	5.5	£28.43
D1/cycle	Pharmacy preparation: "Simple" (oral)	SCHARR/Tappenden, P et al 2007	1	5.5	£25.34

Table 34. Summary of drug administration inputs for the CF regimen

Day	Activity	Source	Visits	Cycles	Activity cost
D0-1	Line insertion	NHS 07-08 Ref. costs. Ref code: L911/HRGQZ14B	1	1	£445.77
D1/cycle	Drug delivery. 1st attendance. Outpatient/day case	NHS 07-08 Ref. costs. Weighted average. Ref code:SB14Z	1	5.5	£281.45
D2-4/cycle	Drug delivery. Subsequent attendances. Outpatient/day case	NHS 07-08 Ref. costs. Weighted average. Ref code: SB15Z	3	5.5	£198.72
D1-5/cycle	Drug delivery. Inpatient stay 5 days	07-08 Ref cost. Code:QZ14B	1	5.5	£1,435.64
D1-5/cycle	Pharmacy preparation: "Complex" (IV)	SCHARR/Tappenden, P et al 2007	5	5.5	£41.87
D1-5/cycle	Transport cost (20% of patients)	NHS 07-08 Ref cost-Patient Transport Services: Outpatient (PTS)	5	5.5	£28.43

Table 35. Summary of drug administration inputs for the CX regimen

Day	Activity	Source	Visits	Cycles	Activity cost
D1/cycle	Drug delivery. 1st attendance. Outpatient/daycase	07-08 Ref. costs. Ref code:SB14Z	1	5.56	£281.45

	Pharmacy preparation: "Simple" (oral)	SCHARR/Tappenden, P et al 2007	1	5.5	£25.34

The total NHS costs of drug administration are calculated by multiplying the total drug administration resource utilisation (activities/components types and frequency) by their unit cost price above and then adding the costs for each regimen. Results can be seen in section 7.3.1.1.1.

7.2.8.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

The resources measured were in line with the REAL 2 (Cunningham et al. 2006) and the ML17032 (Kang et al, 2006) treatment protocols and dosing intensity. In addition, some assumptions relating to drug administration were estimated outside the trial setting (as described above 7.2.9.2) and validated with nurse experts to ensure that these resources were a reflection of the NHS England and Wales current clinical practice.

7.2.8.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment)

Only resources for the average number of medication cycles were included as per the REAL 2 (Cunningham et al. 2006) and the ML17032 (Kang et al, 2006) trials and as per nurse expert advice. No subsequent treatments were included. This is justified as no further incremental costs or benefits will occur following this time point for the treatments under evaluation.

7.2.8.5 What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives

National reference costs (2007-2008) were the preferred means of valuing resources. Prices were taken from National reference costs 2007/2008, BNF 58 and PSSRU 2008. Only when costs could not be identified from these sources were alternative sources, such as literature review or expert opinion, utilised to inform the model. Drug preparation costs, which were assumed to differ between the oral capecitabine and the IV 5 FU regimens, are not captured in the national reference costs. These costs were estimated using the same classification employed by the SCHARR evaluation of bevacizumab (Tappenden P et al, 2007).

Finally, a large medical supplier (Baxter UK) was used to obtain UK cost for the pump required for the administration of 5-FU. This source has also been used in

other 5FU submissions like SMC capecitabine for advanced gastric cancer appraisals.

7.2.8.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales

As described in Section 7.2.9.2, from 01/10/20 the NHS list price of oral capecitabine (ex VAT) will be: 150mg (60 tablets) = £40.02 and 500mg (120 tablets) = £265.55.

7.2.8.7 Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

No additional infrastructure would be required for the administration of oral capecitabine. In fact, one of the key features of the adoption of capecitabine is the replacement of IV 5FU and associated administration requirements and costs.

7.2.8.8 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

The way the resources were measured and valued is consistent with the reference case. Only NHS and PSS resources and costs were included. Emphasis was placed on identifying areas where differential resources usage and costs between the oral capecitabine and the IV 5 FU regimens were applicable.

The 2010 price of Xeloda was used throughout. Only when costs could not be identified from these sources were alternative sources, such as literature review or expert opinion, utilised to inform the model. See section 7.2.9.5

7.2.8.9 Were resource values indexed to the current price year?

Those costs obtained from sources prior to 2009 (i.e. pharmacist preparation costs) were inflated to 2009 levels using the PSSRU 2008 cost index.

7.2.8.10 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

All assumptions regarding estimation of resources are detailed in sections 7.2.6.1 and 7.2.9.2.

7.2.9 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

No discount was applied as the evaluation time is less than 1 year.

7.2.10 Sensitivity analysis

7.2.10.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

The uncertainty around appropriate parameter values used in the analysis has been addressed through one way sensitivity analysis, varying each base case input individually.

Scenario analysis representing an alternative way to administer CF in clinical practice in England and Wales was also investigated.

Probabilistic sensitivity analysis was considered but not undertaken because even in the worse case scenario (where parameters values were simultaneously assumed to be the least favourable upper or lower bound values to capecitabine regimes), all capecitabine regimes remained cost saving compared to the equivalent IV 5FU regimens.

Finally a threshold analysis to explore the estimated incremental survival necessary for IV 5FU to be considered cost effective, given its estimated incremental cost, was performed.

7.2.10.2 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

One Way Analyses (on Base-case scenario)

One way sensitivity analyses were conducted on key parameters that may potentially change in clinical practice.

The more certain parameters, such as BNF drug list prices have not been subjected to sensitivity analysis. In addition, parameters unlikely to affect the incremental cost-comparison analysis, such as utilisation or administration requirements associated with cisplatin, oxaliplatin and epirubicin (as resources associated with these drugs are the same for both oral capecitabine and IV 5FU regimens) have not been subjected to sensitivity analysis either.

Parameters in Table 36 below were varied across their appropriate ranges. Where no published information regarding probable ranges or standard errors were available, either a range based on nurse expert opinion or an assumed range was applied. A 20% range was applied to NHS reference costs, as whilst subject to local variation, this does not necessarily represent uncertainty in the parameter estimate. One could actually argue that there is a high degree of certainty as to the cost incurred to the NHS with respect to the activies in question.

Table 36. One Way Sensitivity Analysis Parameter Ranges

Parameter	Base case Point estimate, (range/alternative)	Source of range data
Resource utilisation		
Body surface area (m^2)	1.7 (0.85 – 2.55)	+/- 50%
5-FU dose intensity. ECF regimen	90.5% (81.5% - 99.6%)	+/- 10% (range limited, to avoid exceeding 100%)
5-FU dose intensity. EOF regimen	83.3% (74.97% - 91.63%)	+/- 10% (range limited, to avoid exceeding 100%)
Capecitabine dose intensity. ECX regimen	88.4% (79.56% - 97.24%)	+/- 10% (range limited, to avoid exceeding 100%)
Capecitabine dose intensity. EOX regimen	88.1% (79.3% - 96.91%)	+/- 10% (range limited, to avoid exceeding 100%)
No. of cycles	5.5 (2.75 – 8.25)	+/- 50%
% line replacement due to failures	0% (50%)	+50%
Proportion patients whose ECF and EOF care (line flush and pump change) on day 7 and 14 is charged at £36.83 (Nursing Services. Code: CN301AF) vs £198.72 (Drug delivery. Subsequent attendances. Outpatient/day case. Ref code: SB15Z)	100% (0%-50%)	Dichotomous scenarios, mutually exclusive Scenarios where 0%, 50% and 100% of the patients treated on days 7 and 14 of ECF and EOF cycles incurred a nurse charge (£36.83) or a subsequent attendance outpatient/day case charge (£198.72)
Proportion patients/visits requiring hospital transport	20% (10% - 30%)	+/- 50%
Unit Costs		
National Schedule of Reference Costs 2007-08. Line insertion	£445.77 (£356.62 - £534.92)	+/- 20%
National Schedule of Reference	£281.45	+/- 20%

Costs 2007-08. Drug Delivery. 1st attendance. Outpt/day case visit. Weighted average.	(£225.16 - £337.74)	
National Schedule of Reference Costs 2007-08. Drug delivery. Subsequent attendance. Nurse cost	£36.83 (£29.47 - £44.20)	+/- 20%
National Schedule of Reference Costs 2007-08. Drug delivery. Subsequent attendances. Outpt/day case visit. Weighted average	£198.72 (£158.97 - £238.46)	+/- 20%
National Schedule of Reference Costs 2007-08. Transport cost Services Outpatient/Daycare	£28.43 (£22.75 - £34.12)	+/- 20%
Pharmacy "complex" preparation IV 5-FU	£41.87 (£20.94- £62.81)	+/- 50%
Pharmacy "simple" preparation capecitabine	£25.34 (£12.67 – £38.01)	+/- 50%
Pump cost	£38.50 (£19.25 - £57.75)	+/- 50%

Scenario analysis. Inpatients visits for CF regimen administration

Some patients treated with CF stay in hospital as inpatients rather that attending daily outpatient visits for five consecutive days per cycle. These arrangements are particularly common for those patients travelling from remote areas.

Inpatient visit cost is coded in the National Schedule of Reference Costs 2007-08 as "- NHS Trusts Elective Inpatient HRG Data. Currency Code:QZ14B" . Each inpatient visit cost is £1,436. The drug administration inputs for this scenario are shown in Table 37. Note that line insertion has not been included as it is assumed to be part of the 5 day inpatient charge.

Table 37. Summary of drug administration inputs for the CF inpatient regimen

Day	Activity	Source	Visits	Cycles	Activity cost
D1-5/cycle	Drug delivery. Inpatient stay 5 days	07-08 Ref cost. Code:QZ14B	1	5.5	£1,435.64
D1-5/cycle	Pharmacy preparation: "Complex" (IV)	SCHARR/Tappenden, P et al 2007	5	5.5	£41.87
D1-5/cycle	Transport cost (20% of patients)	NHS 07-08 Ref cost- Patient Transport Services: Outpatient (PTS)	1	5.5	£28.43

Drug acquisition inputs for these patients are the same as for those who attend hospital in an outpatient basis; as shown in section 7.2.9.2.2.

Worse case analysis

A worse case scenario was performed, as described above and shown in Table 38.

Table 38. Worse case scenario parameter ranges

Parameter	Base case Point estimate, (less favourable range value for capecitabine)	Source of range data
Resource utilisation		
Body surface area (m^2)	1.7 (2.55)	+ 50%
5-FU dose intensity. ECF regimen	90.5% (81.5%)	- 10%
5-FU dose intensity. EOF regimen	83.3% (74.97%)	- 10%
Capecitabine dose intensity. ECX regimen	88.4% (97.24%)	+ 10%
Capecitabine dose intensity. EOX regimen	88.1% (96.91%)	+ 10%
No. of cycles	5.5 (2.75)	- 50%
% line replacement due to failures	0% (0%)	0%
Proportion patients whose ECF and EOF care (line flush and pump change) on day 7 and 14 is charged at £36.83 (Nursing Services. Code: CN301AF) vs £198.72 (Drug delivery. Subsequent attendances. Outpatient/day case. Ref code: SB15Z)	100% (100%)	100%
Proportion patients/visits requiring hospital transport	20% (10%)	- 50%
Unit Costs		
National Schedule of Reference Costs 2007-08. Line insertion	£445.77 (£356.62)	- 20%
National Schedule of Reference Costs 2007-08. Drug delivery. Subsequent attendance. Nurse cost	£36.83 (£29.47)	- 20%
National Schedule of Reference Costs 2007-08. Drug delivery. Subsequent attendances. Outpt/day case visit. Weighted average	£198.72 (£158.97)	- 20%
National Schedule of Reference Costs 2007-08. Transport cost Services Outpatient/Daycare	£28.43 (£22.75)	- 20%
Pharmacy “complex” preparation IV 5-FU	£41.87 (£20.94)	- 50%
Pharmacy “simple” preparation IV 5-FU	£25.34 (£38.01)	+ 50%
Pump cost	£38.50 (£19.25)	- 50%

Incremental QALY threshold analysis

Even though a cost minimisation analysis was decided to be the most appropriate and efficient analysis for this decision making, as explained in section 7.2.6.2; for completeness, we have carried out a QALY threshold analysis. We have estimated how much better the incremental QALY for IV 5-FU regimes would have to be, in order for the cost effectiveness decision to change. Given the hazard ratios observed in the pivotal phase III studies, this scenario seems highly unlikely, but may be of curiosity to the decision maker in light of a cost minimisation analysis being presented.

Given that no utility data was collected in the trials informing this evaluation and that no utilities were found in the literature for this exact population, the utility value for aGC patients in PFS was taken from the BO18255 trial (Van Cutsem et al: 2009, Bang et al, 2009), using the EQ-5D data available until progression. Even though only HER 2- positive patients with advanced gastric cancer were enrolled in the BO18255 trial; the PFS health state utility value reported in this trial (0.73) was considered the best available for the purposes of this analysis. Incremental cost effectiveness ratio (ICER) thresholds of £20,000 and £30,000 were considered in this analysis.

7.2.10.3 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

As explained in section 7.2.10.1., probabilistic sensitivity analysis was considered but not undertaken because even in the worse case scenario, all capecitabine regimes still offer cost saving compared to the equivalent IV 5-FU regimes.

7.2.11 Statistical analysis

How were rates or probabilities based on interval

7.2.11.1 s transformed into (transition) probabilities?

N/A

7.2.11.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

N/A

7.2.12 Validity

7.2.12.1 Describe the measures that have been undertaken in order to validate and check the model.

An internal validation of the Excel™ model was carried out by a Roche health economic modeler not previously involved in the development of the model.
The following validation procedures were performed:

- Check of completeness and feasibility of reported results (drug cost acquisition and drug administration cost) as compared to other published economic evaluations targeting the same indication
- Execution of selected extreme tests to check the plausibility of model outcomes. Extreme testing was applied to cost of study drugs and drug administration
- Review and confirmation of all formulas in the model

Due to the simplicity of the model structure, no further validation was considered necessary.

7.3 Results

7.3.1 Base-case analysis

7.3.1.1 What were the results of the base-case analysis?

The model base-case results are presented below for the following regimes:

7.3.1.1.1 Total cost of ECF vs ECX and EOF vs EOX

a) Drug acquisition cost
b) Drug administration cost
c) Overall NHS cost

7.3.1.1.2 Total cost of CF vs CX

a) Drug acquisition cost
b) Drug administration cost
c) Overall NHS cost

7.3.1.1.1 Total cost of ECF vs ECX and EOF vs EOX

a) Drug acquisition cost

The estimated drug acquisition costs per patient course of chemotherapy for each regimen are calculated by multiplying drug utilisation (shown in Table 25) by drug unit cost (shown in Table 26), and are presented in Table 39 and Table 40 below:

Table 39. Total drug Acquisition Cost Results for ECF and ECX

Regimen	Total dose (mg)	Drug unit cost (£/mg)	Total acquisition cost (£)
ECF			
Epirubicin	432.91mg	£1.6605/mg	£718.82
Cisplatin	519.49mg	£0.5257/mg	£273.11
Fluorouracil	35,539.35mg	£0.0128/mg	£454.90
Total			**£1,446.84**
ECX			
Epirubicin	417.01mg	£1.6605/mg	£792.43
Cisplatin	517.80mg	£0.5257/mg	£272.23
Capecitabine	216,966.75mg	£0.0044/mg	£962.56.60
			£1,927.11

The incremental drug acquisition cost for ECX vs ECF per patient is therefore (£1,927.22 - £1,446.84 =) **£480.38.**

Table 40. Total drug Acquisition Cost Results for EOF and EOX

Regimen	Total dose (mg)	Drug unit cost (£/mg)	Total acquisition cost (£)
EOF			
Epirubicin	434.78	£1.6605/mg	£721.93
Oxaliplatin	1,114.61	£2.9975/mg	£3,341.05
Fluorouracil	32,711.91	£0.0128/mg	£418.70
Total			**£4,481.69**
EOX			
Epirubicin	429.63	£1.6605/mg	£713.39
Oxaliplatin	1,113.40	£2.9975/mg	£3,337.41
Capecitabine	216,230.44	£0.0044/mg	£959.30
			£5,5010.09

The incremental drug acquisition cost for EOX vs EOF is therefore (£5,5010.09 - £4,481.69 =) **£528.40.**

b) Drug administration cost

The incremental drug administration costs per patient chemotherapy course for each regimen are calculated by multiplying administration activities/components by their unit cost, and are shown in Table 41 below

Table 41. Drug administration cost for ECF and EOF regimens

Day	Activity/ component	Source	Visits	Cycles	Activity cost	Total Cost

D0/D1	Line insertion	NHS 07-08 Ref. costs. Weighted average Code: L911/HRGQZ14B.	1	1	£445.77	£445.77
D1/cycle	Drug Delivery. 1st attendance. Outpt/daycase	NHS 07-08 Ref. costs. Weighted average Code:SB14Z.	1	5.5	£281.45	£1,547.99
D7&14x6cycles	Drug deliver. subsequent attendances. Nurse cost	07-08 Ref. costs -. Code: CN301AF.	2	5.5	£36.83	£405.18
D1,7&14x6cycles	Pump cost	Baxter UK website, Folfusor SV2 (product code: 2C4702K)	3	5.5	£38.50	£635.25
D1,7&14x6cycles	Transport cost (20% of pts)	NHS 07-08 Ref cost- Patient Transport Services: Outpatient (PTS)	3	5.5	£28.43	£93.84
D7&14x6cycles	Pharmacy preparation: "Complex" (IV)	SCHARR/Tappenden, P et al 2007	3	5.5	£41.87	£690.86
Total						**£3,818.88**

Table 42. Drug administration cost for ECX and EOX regimens

Day	Activity	Source	Visits	Cycles	Activity cost	Total Cost
D1/cycle	Drug Delivery.1st attendance	NHS 07-08 Ref. costs. Weighted average. Ref code:SB14Z.	1	5.5	£281.45	£1,547.99
D1/cycle	Transport cost (20% of patients	NHS 07-08 Ref cost- Patient Transport Services: Outpatient	1	5.5	£28.43	£31.28
D1/cycle	Pharmacy preparation: "Simple" (oral)	SCHARR/Tappenden, P et al 2007	1	5.5	£25.34	£139.37
Total						**£1,718.64**

The incremental drug administration cost for both ECX compared to ECF and EOX compared to EOF for a typical mean of 5.5 cycles per patient is therefore £2,100 (£3,818.88 - £1,718.64).

c) Overall NHS cost

The replacement of ECF by ECX or EOF by EOX will result in an additional drug acquisition cost of £480.38 or £528.40 respectively, but a saving of £2,100.24 in drug administration costs in both cases.

Therefore, the use of oral capecitabine instead of IV 5-FU provides direct overall savings to the NHS per patient per course of £1,619.86 (£2,100.24 – £480.38) in the ECF vs ECX regimens and an overall saving of £1,571.84 (£2,100.24 - £528.40) in the EOF vs EOX regimens, as shown in Table 43 and Table 44.

The resource savings provided by the elimination of the need to purchase the ambulatory pump required for the IV 5FU regimens alone appears enough to offset the extra drug cost incurred by the oral capecitabine regimen. When the other administration resource savings associated with the transfer of 5-FU based to equivalent capecitabine based are considered, the cost advantage of capecitabine based regimens becomes greater.

Table 43. Overall NHS cost of ECF and ECX regimens

07-08 Ref costs	ECX Cost	ECF Cost	Incremental cost ECF vs ECX
Drug acquisition cost	£1,927.22	£1,446.84	-£480.38
Drug administration	£1,718.64	£3,818.88	£2,100.24
Total	£3,645.86	£5,265.72	
Savings			**£1,619.86**

Table 44. Overall NHS cost of EOF and EOX regimens

07-08 Ref costs	EOX Cost	EOF Cost	Incremental cost EOF vs EOX
Drug acquisition cost	£5,010.09	£4,481.69	-£528.40
Drug administration	£1,718.64	£3,818.88	£2,100.24
Total	£6,728.74	£8,300.57	
Savings			**£1,571.84**

7.3.1.1.2 Cost of CF versus CX

a) Drug acquisition cost

The estimated drug acquisition costs per patient course of chemotherapy for each regimen are calculated by multiplying drug usage (from Table 25) by the drug unit cost (from Table 26), and are presented in Table 45 below:

Table 45. Drug acquisition Cost Results for CF and CX

Regimen	Total dose (mg)	Drug price (£/mg)	Total acquisition cost (£)
CF			
Cisplatin	748.00 mg	£0.5257/mg	£393.25
Fluorouracil	37,400.00 mg	£0.0128/mg	£478.72
Total			**£871.97**
CX			
Cisplatin	748.00 mg	£0.5257/mg	£393.25
Capecitabine	261,800.00 mg	£0.0044/mg	£1,161.46

Total	**£1,554.71**

The incremental drug acquisition cost of CX compared to CF per patient is £799.75 (£1,554.71 - £871.97).

b) Drug administration cost

The incremental drug administration costs per patient chemotherapy course for CF and CX are calculated by multiplying administration activities/components by their unit cost, and are shown in Table 46 and Table 47 below

Table 46. Drug Administration Cost for CF regimen

Day	Activity	Source	Visits	Cycles	Activity cost	Total Cost
D0-1	Line insertion	NHS 07-08 Ref. costs. Ref code: L911/HRGQZ14B.	1	1	£445.77	£445.77
D1/cycle	Drug Delivery. 1st attendance. Outpatient/day case	NHS 07-08 Ref. costs. Weighted average. Ref code:SB14Z.	1	5.5	£281.45	£1,547.99
D2-4/cycle	Drug delivery. Subsequent attendances. Outpatient/day case	NHS 07-08 Ref. costs. Weighted average. Ref code: SB15Z.	3	5.5	£198.72	£3,278.81
D1-5/cycle	Pharmacy preparation: "Complex" (IV)	SCHARR/Tappenden, P et al 2007	5	5.5	£41.87	£1,151.43
D1-5/cycle	Transport cost (20% of patients)	NHS 07-08 Ref cost- Patient Transport Services: Outpatient (PTS)	5	5.5	£28.43	£156.39
Total						**£6,580.39**

Table 47. Drug Administration Cost for CX Regimen

Day	Activity	Source	Visits	Cycles	Activity cost	Total Cost
D1/cycle	Drug Delivery. 1st attendance	07-08 Ref. costs. Ref code:SB14Z.	1	5.5	£281.45	£1,547.99
D1/cycle	Pharmacy preparation: "Simple" (oral)	SCHARR	1	5.5	£25.34	£139.37
Total						**£1,687.36**

The incremental drug administration cost for CX vs CF is therefore £ 4,893.03 (£6,580.39 - £1,687.36)

c) Overall NHS cost

The replacement of CF by CX results in an additional £682.74 in drug acquisition costs, but a saving of £4,893.03 in drug administration costs.

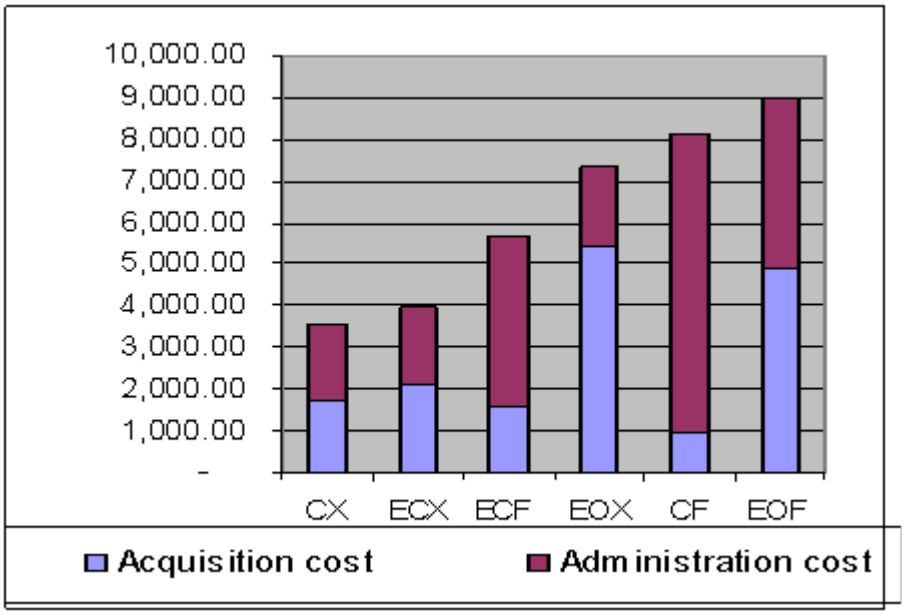
Therefore, the use of oral capecitabine instead of IV 5-FU provides direct overall healthcare savings to the NHS of £4,210.29 (£4,893.03 – £682.74) per patient per course, in the base-case analysis, as shown in Table 48.

Table 48. Overall NHS Cost of CF and CX

07-08 Ref costs	CX	CF	Incremental cost CF vs CX
Drug acquisition cost	£1,554.71	£871.97	£682.74
Drug administration	£1,687.36	£6,580.39	-£4,893.03
Total	£3,242.08	£7,452.36	
Savings			**£4,210.29**

In summary, oral capecitabine regimes are less costly for the NHS than IV 5-FU regimens, this is mainly due to the fact that oral capecitabine is administered at home with limited cost to the NHS and IV 5FU requires further administration care with substantial drug administration cost to the NHS. See Figure 15.

Figure 15. Overall Total Direct NHS cost for advanced gastric cancer regimens



7.3.2 Subgroup analysis

7.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

N/A. No sub-group analysis was performed

7.3.3 Sensitivity analyses

7.3.3.1 What were the main findings of the sensitivity analyses?

One Way Analyses (on Base-case scenario)

The one-way parameter sensitivity analysis results are shown in Table 49 below:

Table 49. One-way Sensitivity Analysis Results

Parameter	Point estimate, (range/alternative)	Cost comparison result (ECX savings)	Cost comparison result (EOX savings)	Cost comparison result (CX savings)
Base case		Cost Savings: £1,619.86	Cost Savings: £1,571.84	Cost Savings: £4,210.29
Resource utilisation				
Body surface area (m^2)	1.7 (0.85 - 2.55)	No change ((£1,860.05 - £1,379.67)	No change (£1,836.04 - £1,307.64)	No change (£4,551.66 - £3,868.01)
5-FU dose intensity in ECF regimen	90.5% (81.5% - 99.6%)	No change (£1,574.62 - £1,665.60)	N/A	N/A
5-FU dose intensity in EOF regimen	83.3% (74.97% - 91.63%)	N/A	No change (£1,529.97 - £1,613.71)	N/A
Capecitabine dose intensity in ECX	88.4% (79.56% - 97.24%)	No change (£1,716.11 - £1,523.60)	N/A	N/A
Capecitabine dose intensity in EOX	88.1% (79.29% - 96.91%)	N/A	No change (£1,667.77- £1,475.91)	N/A
No. of cycles	5.5 (2.75 – 8.25)	No change (£1,032.81 - £2,206.90)	No change (£1,008.80 - £2,134.87)	No change (£2,328.03 - £6,092.54)
% line replacement due to line failures	0% 50%	No change (£1,842.74)	No change (£1,794.72)	No change (£4,433.17)
Proportion of patients whose ECF and EOF care on day 7 and 14 is charged at £36.83 (nursing cost) rather than £198.72 (subsequent attendance Outpatient/ day case)	100% (0%-50%)	No change (£3,400.56- £2,510.21)	No change (£3,352.54- £2,462.19)	No change (N/A)
Proportion of patients/visits requiring hospital transport	20% (10% - 30%)	No change (£1,588.58 - £1,651.14)	No change (£1,540.56- £1,603.11)	No change (£4,132.09 - £4,288.48)
Unit Costs				

National Schedule of Reference Costs 2007-08. Line insertion	£445.77 (£356.62 - £534.92)	No change (£1,530.70-£1,709.01)	No change (£1,482.68-£1,660.99)	No change (£4,121.13-£4,299.44)
National Schedule of Reference Costs 2007-08. Drug Delivery.1st attendance. Outpt/day case visit. Weighted average.	£281.45 (£225.16 - £337.74)	No change (No change-No change)	No change (No change-No change)	No change (No change-No change)
National Schedule of Reference Costs 2007-08. Drug delivery. Subsequent attendance. Nurse cost	£36.83 (£29.47 - £44.20)	No change (£1,538.82-£1700.89)	No change (£1,490.80 - £1,652.87)	No change (N/A)
National Schedule of Reference Costs 2007-08. Drug delivery. Subsequent attendances. Outpt/day case visit. Weighted average	£198.72 (£158.97 - £238.46)	No change (N/A)	No change (N/A)	No change (£3,554.52 - £4,866.05)
National Schedule of Reference Costs 2007-08. Transport cost Services Outpatient/Daycare	£28.43 (£22.75 - £34.12)	No change (£1,607.35-£1,632.37)	No change (£1,559.33-£1,584.35)	No change (£4,179.01-£4,241.56)
Pharmacy "complex" preparation IV 5-FU	£41.87 (£20.94 - £62.81)	No change (£1,274.43-£1,965.28)	No change (£1,226.41-£1,917.26)	No change (£3,634.57-£4,786.00)
Pharmacy "simple" preparation capecitabine	£25.34 (£12.67 – 38.01)	No change (£1,689.54-£1,550.17)	No change (£1,641.52-£1,502.15)	No change (£4,279.97 - £4,140.60)
Pump cost	£38.50 (£19.25 - £57.75)	No change (£1,302.23-£1,937.48)	No change (£1,254.21 - £1,889.46)	No change N/A

The results of this one-way sensitivity analysis show that all oral capecitabine regimens (ECX, EOX and CX) remain cost saving when compared to their equivalent IV 5FU regimes (ECF, EOF and CF).

This analysis indicates that the results are most sensitive to hospital visits cost on days 7 and 14 for ECF and EOF (i.e. nurse charge vs outpatient subsequent attendance) and the number of cycle's of treatment patients received. The analysis is less sensitive to uncertainty around the type of pharmacy preparation or the transportation costs.

Furthermore, as explained above, the cost of providing the ambulatory pump alone for the ECF and EOF regimens (without taken into account any administration costs) is enough to offset the extra drug cost incurred by corresponding oral capecitabine regimen. That is:

- Total pump cost for ECF/EOF: £38.5 x 3 pumps x 5.5 cycles = £635.25
- Extra drug cost in the ECX regimens for 5.5 cycles: £480.38
- Extra drug cost for the EOX regimens for 5.5 cycles: £528.40

Therefore, when the equivalent clinical effectiveness and improved convenience of oral capecitabine are considered alongside cost-savings, it can be surmised that oral capecitabine may dominate IV 5FU.

Scenario analysis. Inpatients visits for CF regimen administration

The drug acquisition cost for CF is £871.97, as per Table 45 above (section 7.3.1.1.2) and the drug administration cost is £9,078.74, as shown in Table 50 below:

Table 50. Drug administration cost for patients treated with CF that stays in hospital on an inpatient basis

Day	Activity	Source	Tasks	Cycles	Activity cost	Total Cost
D1-5/cycle	Drug delivery. Inpatient stay 5 days	07-08 Ref cost. Code:QZ14B	1	5.5	£1,435.64	£7,896.04
D1-5/cycle	Pharmacy preparation: "Complex" (IV)	SCHARR/Tappenden, P et al 2007	5	5.5	£41.87	£1,151.43
D1-5/cycle	Transport cost (20% of patients)	NHS 07-08 Ref cost- Patient Transport Services: Outpatient (PTS)	1	5.5	£28.43	£31.28
Total						**£9,078.74**

Based on above calculation, the total NHS cost for inpatients treated with CF is £9,950.71. Therefore, for patients in this scenario, the cost savings per patient the NHS can realise by using CX rather than CF is £6,708.63 shown in Table 51 below.

Table 51. Overall NHS Cost of CF (inpatient) and CX

07-08 Ref costs	CX	CF inpatients	CX vs CF
Drug acquisition cost	£1,554.71	£871.97	-£682.74
Drug administration	£1,687.36	£9,078.74	£7,391.37
Total	£3,242.08	£9,950.71	
Savings			**£6,708.63**

Worse case scenario analysis

The results from the worse case scenario are shown in Table 52

Table 52. Worse case scenario. Overall NHS Cost of CF and CX

Cohort	Acquisition cost	Administration cost	Total cost
ECF	1,051.20	1,322.43	£2,373.63
ECX	1,517.61	782.24	£2,299.85

Incremental cost per patient when switching from ECF to ECX	466.41	-£540.19	**-£73.78**
EOF	3,329.87	1,322.43	£4,652.30
EOX	3,829.52	782.24	£4,611.76
Incremental cost per patient when switching from EOF to EOX	499.65	-£592.45	**-£40.54**
CF	653.98	2,462.58	£3,116.56
CX	1,166.03	775.99	£1,942.02
Incremental cost per patient when switching from CF to CX	512.06	-£1,686.59	**-£1,174.53**

Therefore, even in the worse case analysis, all capecitabine regimes still offer cost saving compared to the equivalent IV 5FU regimes.

Threshold analysis

Table 53 and Table 54 below show the incremental benefits that IV 5FU regimes would have to provide at an ICER threshold of £20,000 and £30,000 assuming a utility of 0.73; in order to for IV 5FU regimens to be considered cost effective compared to oral capecitabine regimens.

Table 53. £20,000 Threshold. Incremental QALY and Life year gains required for non capecitabine regimens to be considered cost effective

Regimen	Incremental Cost	Incremental QALY	Life Year Gain	Life Month Gain	Life Day Gain
ECF vs ECX	£1,620	0.081	0.111	1.331	40.5
EOF vs EOX	£1,572	0.079	0.108	1.292	39.3
CF vs CX	£4,210	0.211	0.288	3.461	105.2

Table 54. £30,000 Threshold. Incremental QALY and Life year gains required for non capecitabine regimens to be considered cost effective

Regimen	Incremental Cost	Incremental QALY	Life Year Gain	Life Month Gain	Life Day Gain
ECF vs ECX	£1,620	0.054	0.074	0.888	27.0
EOF vs EOX	£1,572	0.052	0.072	0.861	26.2
CF vs CX	£4,210	0.140	0.192	2.307	70.1

ECF vs ECX regimens

At an ICER threshold of £20,000 and £30,000 per QALY, FPS utility of 0.73 (Van Cutsem et al, 2009), (Bang et al, 2009) and an incremental cost of £1,620 for ECF vs ECX regimes, (as per section 7.3.1); this IV 5-FU regimen would have to provide an additional 0.081 and 0.054 QALYs respectively to outweigh the extra cost incurred by ECF, compared to ECX. This is an incremental life month gain of 1.33 and 0.89 months respectively. See Table 53 and Table 54 above.

EOF vs EOX regimens

As per above, at an ICER threshold of £20,000 and £30,000 per QALY, utility of 0.73 and an incremental cost of £1,572 for EOF vs EOX regimes, (as per section 7.3.1); this IV 5-FU regime would have to provide an additional 0.079 and 0.052 QALYs respectively to outweigh the extra cost incurred by EOF, compared to ECX. This is an incremental life month gain of 1.29 and 0.86 months respectively. See Table 53 and Table 54 above.

CF vs CX regimens

Finally, at an ICER threshold of £20,000 and £30,000 per QALY, utility of 0.73 and an incremental cost of £4,210 for CF vs CX regimes, (as per section 7.3.1); this IV 5-FU regime would have to provide an additional 0.211 and 0.140 QALYs respectively to outweigh the extra cost incurred by CF, compared to CX . This is an incremental life month gain of 3.5 and 2.3 months respectively. See Table 53 and Table 54 above.

For all regimens, it is not plausible or reasonable to assume that 5-FU increases the survival or QALY of a patient in the region of 1 to 3 months (depending on the ICER threshold and the regimen considered), as this is contrary to the evidence from the REAL 2 (Cunningham et al. 2006) and the ML17032 trial (Kang et al, 2006).

This ICER threshold analysis has been carried out for completeness, however as per section 6 above, the REAL 2 (Cunningham et al. 2006) and the ML17032 trial (Kang et al, 2006) confirmed that both progression-free survival and overall survival results showed non-inferiority and a trend towards improvement when capecitabine is replaced by IV 5-FU, not the other way around. In addition, response rates with oral capecitabine show a statistically significant improvement over IV 5-FU.

Further more, overall safety and tolerability of capecitabine is as good as that of IV 5-FU. Therefore, there is no evidence to suggest that IV 5-FU regimens provide additional benefit over oral capecitabine regimens.

7.3.3.2 What are the key drivers of the cost effectiveness results?

In all cases (base case and sensitivity analysis) oral capecitabine regimens are cost saving compared to their equivalent IV 5FU regimens. The key driver in determining the cost saving status of oral capecitabine based regimens is the substantial resource savings associated with administration of an oral based regimen. Pharmacy preparation type and transport cost to NHS have a marginal impact on cost savings.

7.3.4 Interpretation of economic evidence

7.3.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

To our knowledge, two previous economic evaluations have been conducted in the UK on capectabine use in advanced gastric cancer: SMC capecitabine submission, May 2007 and London Cancer New drugs Group APC/DTC Briefing, February 2009.

Additionally, a similar analysis taking an Italian healthcare system perspective has been published (Garrison et al. 2007). This reported that when replacing IV 5-FU based chemotherapy for aGC, oral capecitabine is cost-saving. Another analysis taking a Japanese perspective (Tanaka et al. 2003) reported that replacement of IV 5-FU for aGC with oral 5-FU is a cost-saving strategy.

Furthermore, a number of publications have reported that when used in other indications, oral capecitabine is a cost-saving replacement for IV 5-FU (Twelves et al. 2001; James et al. 2003; McKendrick et al. 2004; Cassidy et al. 2006).

7.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

The economic evaluation was based upon its licensed indication and aligned with the baseline characteristics of those patients included within the REAL 2 (Cunningham et al. 2006) and the ML17032 (Kang et al, 2006) trials. There is no evidence to suggest that this is not a reasonably representative sample of the likely recipients of capecitabine in England and Wales.

7.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths

1. The clinical effects of oral capecitabine compared to IV 5-FU regimes are based upon 2 large randomised head to head controlled trials demonstrating that both progression-free survival and overall survival results showed non-inferiority and a trend towards improvement when capecitabine is replaced by IV 5-FU. In addition, response rates with oral capecitabine show a statistically significant improvement over IV 5-FU. Further more, overall safety and tolerability of capecitabine is as good as that of IV 5-FU. Therefore the assumption of equivalent efficacy, safety and tolerability is conservative and put oral capecitabine in a strong position in this evaluation.

2. All analysis performed (including sensitivity analysis) confirmed that oral capecitabine regimens are cost saving versus 5FU regimens. This conclusion is supported by the cost effectiveness submission to the SMC in 2007.

3. All plausible uncertainties have been evaluated in one-way sensitivity analysis and in a “worse case” scenario. The results and cost saving conclusion remains very stable to wide variations in model parameters, confirming the strength of the overall result.

4. Key assumptions on drug administration have been validated by NHS nurse experts where possible with experience in the management of advanced gastric cancer patient and use of capecitabine and 5FU. Expert opinion was sought to validate the regimens’ administration requirements in England and Wales’ clinical practice. This advice was provided primarily by a five specialist nurses, with first hand

experience in administering regiments to advanced gastric cancer patients from a variety of trusts.

5. References on costing used in the analysis are based upon NICE reference case of NHS reference costs or other well regarded sources like PSSRU.

6. Conservative assumptions were possible have been made in this analysis, mainly in relation to drug administration. See section 7.2.61. Therefore it can be argued that the cost saving of over capecitabine may be greater than those presented in the base case analysis

Weaknesses

1. Cost minimisation evaluation is not the NICE Guide to Methods' preferred cost effectiveness analysis. However in this evaluation it was considered to be the most appropriate and efficient way to demonstrate cost effectiveness from the perspective of NHS and PSS in England and Wales.

2. This analysis does not take into account the probability that a QALY increment or decrement could occur for capecitabine based regimens in some extreme scenarios. However this was managed via threshold analysis above.

3. No probabilistic sensitivity analysis was presented however PSA was considered but not undertaken because even in the worse case scenarios all capecitabine regimes still offer cost saving compared to the equivalent IV 5FU regimes.

4. No costing of adverse events were included. However upon a detailed evaluation of the likely incremental differences in the management costs associated with the adverse event profiles of the regimens evaluated, it was considered appropriate to exclude it.

Given the evidence presented, it will be extremely unlikely that a cost utility analysis would change the overall conclusion of this evaluation.

7.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

1. The formal estimation of uncertainty around point estimates of the QALYs for capecitabine and non-capecitabine regimens could help more formally validate the conclusions of the threshold analysis.

2. Comprehensive costing of the adverse events associated with each regimen to more formally confirm the assumption of no significant difference in these costs.

3. More detailed prospective micro-costing of aGC resource utilisation.

8 Assessment of factors relevant to the NHS and other parties

8.1 What is the estimated annual budget impact for the NHS in England and Wales?

If it is assumed that the market shares currently held by each regimen remain constant in the absence of NICE approval it is estimated that positive guidance will result in a budget saving of £0.22m in 2010, £0.66m in 2011, £0.92m in 2012, £1.20m in 2013 and £1.38m in 2014.

If it is instead assumed that in the absence of NICE approval all patients who would have received a capecitabine based regimen instead receive an equivalent 5-FU based regimen the impact of positive guidance would be considerably more significant. The more the market share held by capecitabine based regimens is assumed to fall given negative guidance the higher the resource savings enabled by positive guidance.

If the extreme scenario outlined above (the complete replacement of capecitabine based regimens with equivalent 5-FU based regimens given negative guidance) is assumed it is estimated that positive guidance would result in a budget saving of £3.58m in 2010, £4.05m in 2011, £4.33m in 2012, £4.63m in 2013 and 4.84m in 2014.

The true value of the budget savings enabled by positive guidance is likely to be a figure somewhere between these two estimates. The more conservative scenario (in which the market shares held by each regimen remain constant despite NICE approval) is used as a reference case in this analysis. It represents the minimum budget saving enabled by positive guidance in each year of evaluation. The true resource savings enabled by approval of capecitabine in this decision context are likely to be higher than those presented here due to the conservative approach taken towards the decline in capecitabine use given negative guidance.

Table 55. Budget impact of NICE approval (assuming constant market shares given negative guidance)

Year	Impact of approval upon total drug cost	Impact of approval upon total administration cost	Impact of approval upon total cost of all regimens
2010	+ £0.05m	- £0.26m	- £0.22m
2011	+ £0.18m	- £0.84m	- £0.66m
2012	+ £0.26m	- £1.18m	- £0.92m
2013	+ £0.32m	- £1.52m	- £1.20m
2014	+ £0.36m	- £1.74m	- £1.38m

8.2 What number of patients were assumed to be eligible? How was this figure derived?

Capecitabine is indicated for first-line treatment of advanced gastric cancer in combination with a platinum based regimen. The estimated number of patients eligible for treatment under this indication was calculated individually for both England and Wales and then combined to estimate the total number of eligible patients.

England:
The gastric cancer incidence rate in England in 2006 was 0.0122% (Cancer Research UK, February 2006). For the purposes of this evaluation it is assumed that this rate is representative of the incidence rate in 2010-2014. This incidence rate was applied to ONS 2008-based mid-year principal population figures for England in order to determine the number of patients expected to have gastric cancer in the time-period of interest. It was assumed that 80% of patients presenting with gastric cancer would have an advanced form of the disease (Expert opinion). On the basis of market research commissioned by Roche (Synovate Healthcare, 2009) it was assumed that 53% of patients with advanced gastric cancer would receive first line chemotherapy. These remaining patients formed the population eligible to receive capecitabine in this budget impact assessment.

Table 56. Estimated number of patients eligible to receive treatment in England

Assumptions	%	**Value 2010**	**Value 2011**	**Value 2012**	**Value 2013**	**Value 2014**
Local population		52,198,207	52,577,102	52,953,960	53,331,991	53,709,928
Gastric Cancer Incidence	0.0122%	6,368	6,414	6,460	6,507	6,553
Proportion of patients with advanced disease	80%	5,095	5,132	5,168	5,205	5,242
Proportion receiving 1st line chemotherapy	53%	2,700	2,720	2,739	2,759	2,778
Eligible population		2,700	2,720	2,739	2,759	2,778

Wales
The above procedure was repeated for Wales with application of the same data sources and assumptions.

Table 57. Estimated number of patients eligible to receive treatment in Wales

Assumptions	%	Value 2010	Value 2011	Value 2012	Value 2013	Value 2014
Local population		3,010,623	3,024,218	3,039,845	3,055,659	3,071,554
Gastric Cancer Incidence	0.0165%	497	499	502	504	507
Proportion of patients with advanced disease	80%	397	399	401	403	405
Proportion receiving 1st line chemotherapy	53%	211	212	213	214	215
Eligible population		211	212	213	214	215

England and Wales

Predicted eligible population in England and Wales:

2010: 2,700 + 211 = **2,911**
2011: 2,720 + 212 = **2,931**
2012: 2,739 + 213 = **2,952**
2013: 2,759 + 214 = **2,973**
2014: 2,778 + 215 = **2,993**

8.3 What assumption(s) were made about current treatment options and uptake of technologies?

In the absence of NICE approval it was assumed that the market share of first line chemotherapy for advanced gastric cancer currently held by each regimen would remain constant for the period of analysis. These proportions were taken from market research commissioned by Roche (First line research, Xeloda Gastric KPI tracker, August 2009). Capecitabine in combination with a platinum based regimen is currently used in 65% of all chemotherapy for advanced gastric cancer.

Table 58. Assumed proportion of patients receiving each regimen, each year in the absence of NICE approval of capecitabine combination therapy

Treatment Regimen	ECF	ECX	EOF	EOX	CF	CX	Other
Market Share	20%	39%	3%	20%	6%	5%	7%

The above proportions were applied to the eligible population figures calculated in section 8.2 to determine the number of patients likely to receive each treatment regimen each year in the absence of NICE approval.

Table 59. Number of patients receiving each regimen, each year in the absence of NICE approval of capecitabine combination therapy

Treatment Regimen	Value 2010	Value 2011	Value 2012	Value 2013	Value 2014
ECF	582	586	590	595	599
ECX	1,135	1,143	1,151	1,159	1,167
EOF	87	88	89	89	90
EOX	582	586	590	595	599
CF	175	176	177	178	180
CX	146	147	148	149	150
Other	204	205	207	208	210

8.4 What assumption(s) were made about market share (where relevant)?

Table 60. Assumed proportion of patients receiving each regimen, each year given NICE approval of capecitabine combination therapy

Treatment Regimen	Value 2010	Value 2011	Value 2012	Value 2013	Value 2014
ECF	19%	13%	10%	7%	6%
ECX	40%	47%	51%	54%	55%
EOF	2%	1%	1%	1%	1%
EOX	21%	22%	22%	22%	22%
CF	5%	4%	3%	2%	1%
CX	6%	6%	6%	7%	8%
Other	7%	7%	7%	7%	7%

Roche internal forecasting was utilised to predict future market shares for each regimen given NICE approval. It was assumed that the market share held by treatments beyond the scope of this appraisal ('Other' treatments) would remain constant irrespective of NICE's decision. These assumed future market shares were combined with the population figures from section 8.2 to produce Table 61.

Table 61. Number of patients receiving each regimen, each year given NICE approval of capecitabine combination therapy

Treatment Regimen	Value 2010	Value 2011	Value 2012	Value 2013	Value 2014
ECF	553	381	295	208	180
ECX	1,164	1,378	1,505	1,605	1,646
EOF	58	29	30	30	30
EOX	611	645	649	654	659
CF	146	117	89	59	30
CX	175	176	177	208	239
Other	204	205	207	208	210

8.5 What unit costs were assumed? How were these calculated?

The acquisition and administration costs for each regimen were taken from the cost-minimisation exercise carried out in section 7. Drug acquisition costs were from BNF 58 (with the exception of Xeloda as described previously) whilst administration costs were taken from NHS reference costs 2007/2008.

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

Details of all treatment regimens and resource requirements are detailed comprehensively in section 7.

8.7 Were there any estimates of resource savings? If so, what were they?

The switch to oral therapy allows significant resource savings in the administration of each regimen. Section 7 details the source, and extent, of these savings.

Table 62. Acquisition, administration and total costs associated with each regimen

Regimen	Drug Acquisition Costs	Administration Cost	Total Cost
ECF	£1,447	£3,819	£5,266
ECX	£1,927	£1,719	£3,646
EOF	£4,482	£3,819	£8,301
EOX	£5,010	£1,719	£6,729
CF	£872	£6,580	£7,452
CX	£1,555	£1,687	£3,242

Whilst capecitabine based regimens have higher drug acquisition costs than equivalent 5-FU regimens their total costs are lower due to significant administration resource savings enabled by the switch to oral based therapy.

The above costs were applied to the estimated number of patients expected to receive each regimen in the presence and absence of NICE approval to determine the total cost of all regimens (in terms of acquisition and administration costs) in each year of interest.

Table 63. Estimated total cost of all regimens in the absence of NICE approval

Year	Total drug cost	Total administration cost	Total cost of all regimens
2010	£6.72m	£6.90m	£13.62m
2011	£6.76m	£6.95m	£13.72m
2012	£6.81m	£7.00m	£13.81m
2013	£6.86m	£7.05m	£13.91m
2014	£6.91m	£7.10m	£14.01m

Table 64. Estimated total cost of all regimens given NICE approval

Year	Total drug cost	Total administration cost	Total cost of all regimens
2010	£6.77m	£6.64m	£13.40m
2011	£6.94m	£6.11m	£13.06m
2012	£7.07m	£6.83m	£12.89m
2013	£7.18m	£5.53m	£12.71m

2014	£7.26m	£5.36m	£12.63m

The total budget required in the presence and absence of NICE approval were then compared to generate the budget impact of positive guidance.

Table 65. Impact of NICE approval upon budget required for aGC chemotherapy

Year	Budget required given NICE approval minus budget required in the absence of NICE approval
2010	£13.40m - £13.62m = -£0.22m
2011	£13.06m - £13.72m = -£0.66m
2012	£12.89m - £13.81m = -£0.92m
2013	£12.71m - £13.91m = -£1.20m
2014	£12.63m - £14.01m = -£1.38m

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Capacity problems within the IV chemotherapy service have been recognised, and cited as a key reason for the NHS failing to deliver drug therapies recommended by NICE and the Cancer Services Collaborative (DoH, 2004; Richards, 2005). Due to its oral administration, capecitabine may assist in relieving these service pressures and allow redeployment of existing pharmacy (eg; isolator equipment) and nursing staff resources, by reducing the workload involved in intravenous chemotherapy administration. This has been elaborated within a report (Cassidy & Glynne-Jones, 2005) which recommends oral therapies as a potential capacity saving measure. Case studies presented in this report describe how a capecitabine service has been introduced within the Beatson Oncology Centre in Glasgow and that within Grampian an outpatient-based capecitabine service has saved around 2000 bed days each year.

9 References

Bachmann, MO *et al* Cohort study in South and Werst England of the influence of specialzation on the management and outcome of patients with oesophageal and gastric cancers. *Br J Surg*. 2002; **89**: 914-922.

Bang et al: Trastuzumab with Chemotherapy in untreated HER2-positive advanced or metastatic gastric cancer: efficacy results from the ToGA trial. Annals of Oncology (2009);Vol. 20, Suppl. 7 (code O-0015)

Baxter UK website, Folfusor SV2 (product code: 2C4702K. [Accessed online 16 November 2009] http://www.ecomm.baxter.com/ecatalog/browseCatalog.do?lid=10011&hid=10000&cid=10001&key=bf61f5fe7228a1d177d07ee7eb8398a&pid=442402).

Borner M *et al.* Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomized crossover trial in advanced colorectal cancer. *Eur J Cancer*. 2002; **38**: 485-493.

British National Formulary (BNF) No.58, September 2009

Cancer Research UK
http://info.cancerresearchuk.org/cancerstats/types/stomach/incidence/ [Accessed on line 16 November 2009]

Cancer Research UK. CancerStats: Gastric Cancer Incidence – UK, 2006
http://info.cancerresearchuk.org/cancerstats/types/stomach/incidence/index.htm
Cassidy J & Glynne-Jones R. Optimising service capacity to meet demand for cancer drug treatment delivery. Cancer Capacity Coalition 2005

Cassidy J *et al.* First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. *AnnalsOncol.* 2002; **13**: 566-575.

Cassidy J et al. Pharmacoeconomic analysis of adjuvant oral capecitabine versus intravenous 5-FU/LV in Dukes' C colon cancer: the X-ACT trial. British Journal Cancer 2006a; 94: 1122-1129

Cassidy J *et al.* Randomized phase 3 study of capecitabine plus oxaliplatin compared with fluorouracil compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol.* 2008; **26**: 2006-2012.

Cunningham D *et al.* ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of gastric cancer. *Ann Onco*l 2005;**16** (Suppl 1): i22-23

Cunningham D et al. Randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer: The REAL 2 trial. American Society of Clinical Oncology annual meeting 2006; Abstract and oral presentation LBA4017. Available from: www.asco.org [Accessed online 16 November 2009] Journal of Clinical Oncology, 2006; ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement)

CRUK (2009a) *UK stomach cancer incidence statistics*. http://info.cancerresearchuk.org/cancerstats/types/stomach/incidence/index.htm. *Accessed 13.11.909*

CRUK (2009b) *Trends in stomach cancer incidence.* http://info.cancerresearchuk.org/cancerstats/types/stomach/incidence/index.htm#trends. *Accessed 13.11.09*

CRUK (2009c) *Stomach cancer survival statistics*. http://info.cancerresearchuk.org/cancerstats/types/stomach/survival/index.htm. *Accessed 13.11.09*

CRUK 2009d *Symptoms and treatment of stomach cancer.* http://info.cancerresearchuk.org/cancerstats/types/stomach/symptomsandtreatment/index.htm. *Accessed 13.11.09*

Department of Health (DoH): 2004. Variations in usage of cancer drugs approved by NICE. Report of the Review undertaken by the National Cancer Director (NCD) 2004

Expert nurse opinion: Elaine Lennan (Southampton General Hospital), Andrea Burgess (Christie Hospital NHS Trust), Karen Harrold (Mount Vernon Hospital), Matt Riddlestone Broomfield Hospital, Maria Vincent Newcastle upon Tyne NHS

First line research. Advanced Gastric Cancer Xeloda KPI tracker, August 2009

Frank JL *et al.* Ionic implantation of silicone chronic venous access devices does not alter thrombotic complications: a double-blinded, randomized clinical trial. *Surgery.* 2001; **129**: 547-551.

GAD, http://www.gad.gov.uk/Demography%20Data/Population/index.aspx?y=2006&v=Principal [Accessed on line 16 November 2009]

Garrison L et al. Pharmacoeconomic analysis of treating advanced gastric cancer (AGC) with capecitabine/cisplatin (XP) vs 5-FU/cisplatin (FP) regimens in an Italian setting. Abstract ID#14326, accepted for presentation at the ISPOR 12th Annual International Meeting, Virginia, USA, May 19-23, 2007

James R et al. Savings in staff time as a result of switching from De Gramont to oral capecitabine for patients with advanced colorectal cancer. European Journal of Cancer Supplements 2003; 1 (5): S83

Kang YK et al. Randomized phase III trial of capecitabine/cisplatin (XP) *vs.* continuous infusion of 5-FU/cisplatin (FP) as first-line therapy in patients (pts) with advanced gastric cancer (AGC): efficacy and safety results. American Society of Clinical Oncology 2006; Abstract and oral presentation. Available from: www.asco.org [Accessed online 16 November 2009] **ASCO** Edition Journal **of** Clinical Oncology, 2006 **ASCO** Annual Meeting Proceedings Part I. LBA4108.

Kopec JA *et al.* Quality of Life in Operable Colon Cancer Patients Receiving Oral Compared With Intravenous Chemotherapy: Results From National Surgical Adjuvant Breast and Bowel Project Trial C-06. *J Clin Oncol.* 2007; **25**: 424-430.

Kummar S *et al*. Antimetabolites. In: DeVita VT *et al*. editors. *Cancer: Principles and Practice of Oncology*. Philadelphia: Lippincott Williams and Wilkins; 2004. p. 358-374.

Kuter TJ. Thrombotic complications of central venous catheters in cancer patients. *Oncologist* 2004; **9**: 207-216.

Liu G *et al*. Patient preferences for oral vesus intravenous palliative chemotherapy. Journal of Clinical Oncology 1997; **15**: 110-115.

London Cancer New drugs Group APC/DTC Briefing, February 2009

McKendrick J et al. Capecitabine (Xeloda) is resource saving compared to i.v. bolus 5-FU/LV in adjuvant chemotherapy for Dukes' colon cancer patients: medical resource utilisation (MRU) data from a large phase III trial (X-ACT). European Society for Medical Oncology 2004. Poster 276

Miwa M *et al.* Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumors by enzymes concentrated in human liver and cancer tissue. *Eur J Cancer* 1998; **34**: 1274-1281.

National Comprehensive Cancer Centres (2009). NCCN clinical practice guidelines in oncology. Gastric cancer V.2. http://www.nccn.org/professionals/physician_gls/PDF/gastric.pdf. *Accessed 13.11.09.*

National Institute of Clinical Excellence (NICE) Technology Appraisal TA61 - The clinical effectiveness and cost effectiveness of capecitabine and tegafur uracil for colorectal cancer. Date of issue: May 2003. Available from: http://guidance.nice.org.uk/TA61 [Accessed online 16 November 2009]

National Institute of Clinical Excellence (NICE) Technology Appraisal TA62 - The clinical effectiveness and cost effectiveness of capecitabine for the treatment of locally advanced or metastatic breast cancer'. Date of issue: May 2003. Available from: http://guidance.nice.org.uk/TA62 [Accessed online 16 November 2009]

National Institute of Clinical Excellence (NICE) Technology Appraisal TA100 - The clinical effectiveness and cost effectiveness of capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer'. Date of issue: April 2006. Available from: http://guidance.nice.org.uk/TA100 [Accessed online 16 November 2009]

National Institute of Clinical Excellence (NICE).Technology Appraisal TA118. Economic evaluation of bevacizumab for the treatment of metastatic colorectal cancer, 2007; (TA118). Available from: http://guidance.nice.org.uk/TA118 [Accessed online 16 November 2009]

National Institute of Clinical Excellence (NICE) Technology Appraisal TA107 - The clinical effectiveness and cost effectiveness of trastuzumab for the adjuvant treatment of early-stage HER2 positive breast cancer '. Date of issue: Aug 2006. Available from: http://guidance.nice.org.uk/TA107 [Accessed online 16 November 2009]

National Schedule of Reference Costs 2007-08. Department of Health, NHS reference costs 2007-08, published 8 May 2009. [Accessed online 16 November 2009] http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098945

Office of National Statistics (ONS): 2008 – based National Population Projections http://www.statistics.gov.uk/downloads/theme_population/NPP2008/NatPopProj2008.pdf

Office of National Statistics (ONS). Population estimates 2004. Available from: http://www.statistics.gov.uk/CCI/nugget.asp?ID=6 [Accessed on line 16 November 2009]

PSSRU (2008). Need complete ref. Personal Social Services Research Unit (PSSRU): Unit costs of Health and Social Care 2006. Available from:http://www.pssru.ac.uk/uc/uc2008contents.htm [Accessed online 16 November 2009]

Rawlins, M. Response to Sir Ian Kennedy's report. Appraising the Value of Innovation. National Institute for Health and Clinical Excellence, September 2009 [Accessed online 16 November 2009] at http://www.nice.org.uk/media/A43/34/ITEM7KennedyConsultationResponse.pdf

Richards M. Feedback on action plans on uptake of NICE approved cancer drugs. Letter to those involved in implementation of NICE guidance on anticancer drugs 04/04/2005.

Richards M. Feedback on action plans on uptake of NICE approved cancer drugs. Letter to those involved in implementation of NICE guidance on anticancer drugs 04/04/2005.

Rivera et al. (2007) 'Chemotherapy of advanced gastric cancer'. Cancer Treatment Reviews 22, 315-324

Roche Health Economic Modeler: Pierre Ducournau, Health Economic Modeller F. Hoffmann-La Roche, Ltd., Basel, Switzerland,

Roche expert opinion Maxwell Summerhayes, Associate Head of Medical Affairs (Oncology) , Medical Affairs, Roche Products Ltd, Welwyn Garden City, UK

Ross P *et al*. Prospective randomized trial comparing mitomycin,cisplatin, and protracted venous-infusion fluorouracil (PVI 5-FU) with epirubicin, cisplatin, and PVI 5-FU in advanced esophagogastric cancer. *J Clin Oncol.* 2002; **20**: 1996-2004.

Scheithauer W *et al.* Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: safety results of a randomised phase III trial. *Annals Oncol.* 2003; **14**: 1735-1743.

Scottish Intercollegiate Guidelines Network (SIGN). Guideline 87 - Management of gastric and oesophageal cancer. Quick reference Guide. June 2006. Available from: http://www.sign.ac.uk/pdf/qrg87.pdf . *Accessed 13.11.09.*

Schwarz RE *et al.* Transcutaneously tunneled central venous lines in cancer patients: an analysis of device-related morbidity factors based on prospective data collection. *Annals Surgical Oncol.* 2000; **7**: 441–9.

Scottish Medicines Consortium (SMC). 'Capectiabine for first line treatment of patients with advanced gastric cancer in combination with a platinum based chemotherapy based regimen' **SMC ID:** 401/07. **Date of Issue:** September 2007.Available from: http://www.scottishmedicines.org.uk/smc [Accessed online 16 November 2009]

Scottish Medicines Consortium (SMC). 'Capectiabine for metastatic colorectal cancer' **SMC ID: 507/08**. **Date of Issue:** October 2008.Available from: http://www.scottishmedicines.org.uk/smc [Accessed online 16 November 2009]

Scottish Medicines Consortium (SMC). 'Capectiabine for metastatic breast cancer' **SMC ID: 34/03**. **Date of Issue:** March 2003.Available from: http://www.scottishmedicines.org.uk/smc [Accessed online 16 November 2009]

Scottish Medicines Consortium (SMC). Capecitabine following surgery for Stage III (Dukes C stage) colon cancer. August 2005. Available from: http://www.scottishmedicines.org.uk/smc [Accessed online 16 November 2009]

Scottish Medicines Consortium (2007). Capecitabine, 150 mg and 500 mg tablets (Xeloda®). No. 401/07. http://www.scottishmedicines.org.uk/smc/5326.html. *Accessed* 13.11.09.

Synovate Healthcare (2009). Xeloda Gastric Wave 5

Synovate Healthcare, Xeloda GI Wave 5, June 2009

Tanaka K et al. Pharmacoeconomic study of chemotherapy for gastric cancer: analysis of medical costs for oral fluoropyrimidine TS-1 and conventional IV chemotherapy in patients with advanced gastric cancer. Gan To Kagaku Ryoho 2003; 30: 73-80

Tappenden P et al. School of Health and Related Research (ScHARR). The use of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.

Technology Assessment Report (TA118) on behalf of the National Institute for Health and Clinical Excellence (NICE), 2006 [Accessed online 16 November 2009] http://www.nice.org.uk/nicemedia/pdf/colorectal_beva_assessment.pdf

Twelves C et al. Capecitabine (Xeloda) improves medical resource use compared with 5-fluorouracil plus leucovorin in a phase III trial conducted in patients with advanced colorectal carcinoma. European Journal of Cancer 2001; 37: 597-604

Twelves C *et al.* Capecitabine (Xeloda) improves medical resource use compared with 5-fluorouracil plus leucovorin in a phase III trial conducted in patients with advanced colorectal carcinoma. *Eur J Cancer*. 2001; **37**: 597-604.

Twelves C *et al*. Capecitabine as adjuvant treatment for stage III colon cancer. *New Engl J Med.* 2005; **352**: 2696-704.

Van Cutsem et al: J Clin Oncol 27:18s, 2009 (suppl; abstr LBA4509)
(first data presentation at ASCO 2009)

Van Cutsem et al: European Journal of Cancer Supplements, Vol. 7, No 3, September 2009, Page 7 (data presentation at ESMO ECCO 2009)

Van Cutsem E *et al.* Oral capecitabine versus intravenous 5-fluorouracil and leucovrin: integrated efficacy data and novel analyses from two large, randomised, phase III trials. *Br J Cancer.* 2004; **90**: 1190-1197.

Van Cutsem E *et al.* Efficacy results from the ToGA trial. A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC). *J Clin Oncol*. 2009; **27**:18s (suppl; abstr LBA4509 and related presentation).
Abstract and presentation available at:
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=65&abstractID=33044. *Accessed 13.11.09*

Verso M & Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. *J Clin Oncol*. 2003; **21**: 3665-3675.

Wagner AD *et a*l. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol.* 2006; **18**: 2903-2909.

Wagner AD *et al.* Combination chemotherapies in advanced gastric cancer: An updated systematic review and meta-analysis. 2007; *Journal of Clinical Oncology*. **25**, No. 18S (suppl; abstr 4555 and related presentation). Abstract and presentation available at http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=47&abstractID=33949. *Accessed 13.11.09*

Webb A *et al*. Randomised trial comparing epirubicin, cisplatin and fluorouracil versus fluorouracil, doxorubicin and methotrexate in advanced esophagogastric cancer. *J Clin Oncol.* 1997; **15**: 261-267.

Xeloda SmPC 2007. Accessed online November 2008 at http://www.medicines.org.uk access online 16 Nov 09

Xeloda new price from 1 January 2010 will be 10% less than the list price published in BNF No. 58

Appendices

9.1 Appendix 1

Summary of Product Characteristics


Xeloda SPC.pdf

9.2 Appendix 2: search strategy for section 6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9.3 Appendix 3: search strategy for section 7

9.3.1 9.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- Health Economic Evaluation Database (HEED)
- NHS Economic Evaluation Database (NHS EED)
- ISPOR Research Digest

Dialog Datastar was used to search Medline (MEYY), Medline in process (MEIP) and Embase (EMYY). The University of York Centre for Reviews and Dissemination (CRD) website was used to search NHS EED.

9.3.2 9.3.2 The date on which the search was conducted.

All searches were conducted on the 30th of October 2009

9.3.3 9.3.3 The date span of the search.

No restrictions were placed upon the date span of search.

9.3.4 9.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search Strategy for EMYY:

No.	Database	Search term	Info added since	Results
1	EMYY	STOMACH-CANCER.DE. OR STOMACH-CARCINOMA.DE.	unrestricted	26169
2	EMYY	GASTRIC NEAR NEOPLA$5	unrestricted	779
3	EMYY	GASTRIC NEAR CANCER$5	unrestricted	18125
4	EMYY	GASTRIC NEAR CARCIN$5	unrestricted	7376
5	EMYY	GASTRIC NEAR TUMO$5	unrestricted	4126
6	EMYY	GASTRIC NEAR METASTA$5	unrestricted	2538
7	EMYY	GASTRIC NEAR MALIG$5	unrestricted	1230
8	EMYY	STOMACH NEAR NEOPLASM$5	unrestricted	131
9	EMYY	STOMACH NEAR CANCER$5	unrestricted	20561
10	EMYY	STOMACH NEAR CARCIN$5	unrestricted	7757
11	EMYY	STOMACH NEAR TUMO$5	unrestricted	3195
12	EMYY	STOMACH NEAR METASTA$5	unrestricted	464
13	EMYY	STOMACH NEAR MALIG$5	unrestricted	334
14	EMYY	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13	unrestricted	35197
15	EMYY	ECONOMIC-EVALUATION#.DE. OR COST-EFFECTIVENESS-ANALYSIS#.DE. OR HEALTH-ECONOMICS#.DE. OR HEALTH-CARE-COST#.DE. OR COST ADJ MINIMI$7	unrestricted	223156
16	EMYY	CAPECITABINE.W..DE.	unrestricted	6441
17	EMYY	CAPECITABINE	unrestricted	6495
18	EMYY	XELODA	unrestricted	1150
19	EMYY	16 OR 17 OR 18	unrestricted	6495
20	EMYY	14 AND 15 AND 19	unrestricted	31

Search Strategy for MEYY:

No.	Database	Search term	Info added since	Results
1	MEYY	STOMACH-NEOPLASMS.DE.	unrestricted	30385
2	MEYY	GASTRIC NEAR NEOPLA$5	unrestricted	974
3	MEYY	GASTRIC NEAR CANCER$5	unrestricted	20655
4	MEYY	GASTRIC NEAR CARCIN$5	unrestricted	8049
5	MEYY	GASTRIC NEAR TUMO$5	unrestricted	4643
6	MEYY	GASTRIC NEAR METASTA$5	unrestricted	2964
7	MEYY	GASTRIC NEAR MALIG$5	unrestricted	1387
8	MEYY	STOMACH NEAR NEOPLASM$5	unrestricted	30463
9	MEYY	STOMACH NEAR CANCER$5	unrestricted	4389
10	MEYY	STOMACH NEAR CARCIN$5	unrestricted	1531
11	MEYY	STOMACH NEAR TUMO$5	unrestricted	1839
12	MEYY	STOMACH NEAR METASTA$5	unrestricted	532
13	MEYY	STOMACH NEAR MALIG$5	unrestricted	419
14	MEYY	2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13	unrestricted	40292
15	MEYY	Cost ADJ Effectiveness ADJ Analysis	unrestricted	4098
16	MEYY	COST-BENEFIT-ANALYSIS.DE. OR HEALTH-CARE-COSTS.DE. OR MODELS-ECONOMIC.DE. OR COST-OF-ILLNESS.DE. OR DRUG-COSTS.DE.	unrestricted	68495
17	MEYY	Economic ADJ Evaluation	unrestricted	3985
18	MEYY	Cost ADJ Minimi$7	unrestricted	722
19	MEYY	15 OR 16 OR 17 OR 18	unrestricted	70825
20	MEYY	Xeloda	unrestricted	190
21	MEYY	CAPECITABINE	unrestricted	2101
22	MEYY	ANTINEOPLASTIC-COMBINED-CHEMOTHERAPY-PROTOCOLS.DE.	unrestricted	59863
23	MEYY	20 OR 21 OR 22	unrestricted	60937

24	MEYY	14 AND 19 AND 23	unrestricted	8

Search Strategy for MEIP:

No.	Database	Search term	Info added since	Results
1	MEIP	GASTRIC NEAR NEOPLA$5	unrestricted	40
2	MEIP	GASTRIC NEAR CANCER$5	unrestricted	633
3	MEIP	GASTRIC NEAR CARCIN$5	unrestricted	144
4	MEIP	GASTRIC NEAR TUMO$5	unrestricted	145
5	MEIP	GASTRIC NEAR METASTA$5	unrestricted	86
6	MEIP	GASTRIC NEAR MALIG$5	unrestricted	34
7	MEIP	STOMACH NEAR NEOPLASM$5	unrestricted	3
8	MEIP	STOMACH NEAR CANCER$5	unrestricted	98
9	MEIP	STOMACH NEAR CARCIN$5	unrestricted	21
10	MEIP	STOMACH NEAR TUMO$5	unrestricted	40
11	MEIP	STOMACH NEAR METASTA$5	unrestricted	16
12	MEIP	STOMACH NEAR MALIG$5	unrestricted	5
13	MEIP	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12	unrestricted	887
14	MEIP	Cost ADJ Effectiv$5	unrestricted	1488
15	MEIP	Economic ADJ Evaluation	unrestricted	171
16	MEIP	Cost ADJ Minimi$7	unrestricted	21
17	MEIP	Cost ADJ Benefit	unrestricted	176
18	MEIP	14 OR 15 OR 16 OR 17	unrestricted	1716
19	MEIP	XELODA	unrestricted	4
20	MEIP	CAPECITABINE	unrestricted	116
21	MEIP	ANTINEOPLASTIC-COMBINED-CHEMOTHERAPY-PROTOCOLS.DE.	unrestricted	0
22	MEIP	19 OR 20 OR 21	unrestricted	116
23	MEIP	13 AND 18 AND 22	unrestricted	0

Search Strategy for ISPOR Research Digest:
Disorder: Cancer, Topic: All, Keyword: Capecitabine AND Gastric
No results found

Search Strategy for NHS EED:
Capecitabine AND Gastric
1 Result:
Fan L, Liu W C, Zhang Y J, Ren J, Pan B R, Liu D H, Chen Y, Yu Z C. Oral Xeloda plus bi-platinu two-way combined chemotherapy in treatment of advanced gastrointestinal malignancies. World Journal of Gastroenterology 2005; 11(28): 4300-4304

Search Strategy for HEED:
Capecitabine AND Gastric (All data fields)
1 Result: Same study as produced by NHS EED search

Search Strategy for NICE:
The NICE website was searched for 'Capecitabine Gastric'. No relevant studies were identified.

Search Strategy for SMC:
The SMC website was searched for 'Capecitabine Gastric'.
1 Result: SMC advice 401/07. 'Capecitabine for the first line treatment of advanced gastric cancer in combination with a platinum-based chemotherapy regimen'. September 2007.

Assessing findings for relevance:
Three of the 42 records found were identified as being duplicates. The remaining 39 records were assessed for relevance in this decision context. 38 were excluded (as detailed below). The two studies identified as being unrepresentative of the UK were both set in a Chinese context.

Exclusion criteria	Number of articles
Not an economic evaluation	33
Review	1
Not capecitabine	2
Not representative of the UK	2

The remaining evaluation was the 2007 Roche SMC submission for capecitabine for advanced gastric cancer described in Section 7.1.2.

9.3.5 9.3.5 Details of any additional searches, for example searches of company databases (include a description of each database).

No additional searches were performed.