Evidence Review Group's Report

Title: Capecitabine for the treatment of advanced gastric cancer.

Produced by CRD and CHE Technology Assessment Group

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Mark Sculpher has a minority shareholding in a consulting company which has undertaken work for Roche during the last three years but not in the clinical area of gastric cancer. Mark Sculpher did not participate personally in this consultancy.

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Gill Norman wrote the clinical effectiveness sections of the report; Marta Soares, Piia Peura, Steven Rice and Dong Suh and Mark Sculpher wrote the cost effectiveness sections of the report and performed the economic analyses; Kath Wright wrote the sections on the search strategies; Alison Eastwood and Mark Sculpher commented on and revised the report.

Conflicts of interest

Mark Sculpher has a minority shareholding in a consulting company which has undertaken work for Roche during the last three years but not in the clinical area of gastric cancer. Mark Sculpher did not participate personally in this consultancy.

Matthew Seymour is a co-investigator in a trial ("321GO") which includes capecitabine as treatment for patients with advanced gastroesophageal cancer. The trial is peer-reviewed and funded by Cancer Research UK, but also receives some supplementary financial support from Roche (£50k over 2 years). He also attended the ASCO Oncology Conference last year as a guest of Roche.

Daniel Swinson is also a co-investigator on the “321GO” study. Roche have also offered to sponsor his trip to ASCO this year.

Stephen Kelly accepted financial support from Roche in 2008 and 2009 to attend the British Oncology Pharmacists Association Annual Symposium on behalf of the Leeds Teaching Hospitals NHS Trust Pharmacy Department.

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List of abbreviations

AE	Adverse events
aGC	Advanced gastric cancer
BSA	Body surface area
C	Cisplatin
CEA	Cost-effectiveness analysis
CF	Cisplatin plus 5-Fluorouracil
CI	Confidence interval
CMA	Cost-minimisation analysis
CX	Cisplatin plus capecitabine
ECF	Epirubicin plus cisplatin plus 5-Fluorouracil
ECX	Epirubicin plus cisplatin plus capecitabine
EORTC-30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30
EOF	Epirubicin plus oxaliplatin plus 5-Fluorouracil
EOX	Epirubicin plus oxaliplatin plus capecitabine
EQ-5D	EurQol 5 Dimensions
ERG	Evidence Review Group
F or 5-FU	5-Fluorouracil
HR	Hazard ratio
HRQL	Health related quality of life
IPD	Individual patient data
ITT	Intention-to-treat
LYG	Life years gained
MS	Manufacturer's submission
NHS	National Health Service
O	Oxaliplatin
OR	Odds Ratio
PFS	Progression-free survival
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality-adjusted life years
QoL	Quality of Life
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
RR	Relative risk
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
X	Capecitabine

1 Summary

1.1 Scope of the submission

This report presents the ERG's assessment of the manufacturer's (Roche) submission (MS) to NICE on the use of capecitabine (Xeloda®) for the first-line treatment, in combination with a platinum-based chemotherapy regimen, of advanced gastric cancer (aGC). The MS included a cost-minimisation analysis (CMA).

The MS adhered to the scope for the appraisal issued by NICE in that it considered the use of capecitabine, compared with 5-fluorouracil (5-FU), in combination with cisplatin or oxaliplatin, with or without epirubicin, within the licensed indication of patients with metastatic or locally advanced inoperable gastric cancer. One of the two studies contained in the MS included patients outside the licensed population, with advanced oesophageal cancer or cancer of the oesophogastric junction; such patients were considered to be indistinguishable from the licensed population in terms of treatment pathway and subgroup analyses were not presented.

1.2 Summary of submitted clinical effectiveness evidence

The MS focused on direct evidence from two phase III randomised controlled trials (RCTs).[1 2] Efficacy outcomes from these trials were pooled in an individual patient data (IPD) meta-analysis.[3] REAL-2 was a 2 x 2 factorial trial which compared 5-FU with capecitabine and cisplatin with oxaliplatin. The following regimens were used: 5-FU plus cisplatin plus epirubicin (ECF); capecitabine plus cisplatin plus epirubicin (ECX); 5-FU plus oxaliplatin plus epirubicin (EOF); capecitabine plus oxaliplatin plus epirubicin (EOX). A second trial ML-17032, compared capecitabine plus cisplatin (CX) with 5-FU plus cisplatin (CF). Both trials were designed to show non-inferiority of capecitabine compared with 5-FU.

1.2.1 Pooled analysis

The IPD meta-analysis of the ITT populations of the REAL-2 and ML-17032 trials found a statistically significant benefit in overall survival for capecitabine

compared with 5-FU (unadjusted HR: 0.87; 95% CI 0.77, 0.98, p=0.027).[3] There was no statistically significant difference between capecitabine and 5-FU groups in progression-free survival (PFS) (unadjusted HR: 0.91; 95% CI: 0.81 to 1.02, p=0.093), but response rates were statistically significantly higher in the capecitabine groups (unadjusted OR: 1.38; 95% CI: 1.10, 1.73, p=0.006). The ERG was unable to assess the validity of this meta-analysis due to minimal reporting of the methods employed; further details of these were requested but were not available.

1.2.2 Individual trials: efficacy

REAL-2 found statistically significant non-inferiority of capecitabine on the primary outcome of overall survival assessed in the per-protocol population (adjusted HR: 0.89; 95% CI: 0.77, 1.02). ML17032 found statistically significant non-inferiority of capecitabine on the primary outcome of PFS in the per-protocol population (adjusted HR: 0.85; 95% CI: 0.65, 1.11). Statistically significant non-inferiority on the outcome of overall survival (unadjusted HR: 0.85, 95% CI: 0.64, 1.13) was also demonstrated in the trial.

There was minimal health related quality of life (QoL) data reported in the MS. In the REAL-2 trial scores on the General Health Status subscale of the EORTC-30 questionnaire[4] were reported not to differ significantly at baseline or three months. The ERG requested additional data; the manufacturer subsequently supplied the baseline data for all subscales and the changes from baseline for 12 and 24 weeks for each subscale. This showed few statistically significant differences between the groups (Appendix 2, pp43-44; Appendix 4).

1.2.3 Individual trials: safety

Safety analyses showed some significant differences in adverse events profiles between capecitabine and 5-FU regimens. However, in the REAL-2 trial, all statistical analyses were pairwise comparisons with the ECF arm, which the trial was not powered to assess. Of particular note were grade 3 or 4 neutropenia which occurred significantly more often in the ECX arm ($p<0.05$) and significantly less often in the EOX and EOF arms ($p<0.01$) compared to the ECF arm; grade 3 or 4 diarrhoea which occurred significantly

more often in the EOX and EOF arms compared to the ECF arm ($p<0.05$); and grade 3 or 4 hand-foot syndrome which occurred significantly more often in the ECX arm compared to the ECF arm ($p<0.05$). In the ML17032 trial stomatitis occurred more often and with greater severity in the CF arm, while hand-foot syndrome was more common in the CX arm.

1.3 Summary of submitted cost effectiveness evidence

The manufacturer's literature search identified one economic evaluation relevant to this decision problem (MS, pp55-56). The methods and results of the identified study are consistent with the manufacturer's *de novo* economic evaluation.

Based on the evidence derived from the clinical trials, the manufacturer conducted a CMA. The costs of capecitabine based regimens (ECX, EOX, CX) were compared to their equivalent 5-FU based regimens (ECF, EOF, CF, respectively) in the treatment of aGC. The cost calculations considered costs relating to drug acquisition and to drug administration. It was assumed that there were no significant differences in the incidence or severity of adverse events between capecitabine and 5-FU based regimens, and therefore the costs of treatment related adverse events were not included in the analysis. A time horizon of 5.5 cycles (each lasting for 21 days) for all regimens was used in the base case analysis; this represented the mean number of cycles administered in the REAL-2 study.

The results of the manufacturer's base case analysis indicated that capecitabine regimens are cost-saving compared to the equivalent 5-FU based regimens. The total net cost savings for capecitabine based regimens were £1,620 (ECX vs. ECF), £1,572 (EOX vs. EOF) and £4,210 (CX vs. CF). Capecitabine remained cost saving in the manufacturer's one-way sensitivity analysis, scenario analysis and worst case analysis. In response to the ERG's points of clarification regarding the initial submission, the manufacturer provided additional evidence on the costs of adverse events, drug acquisition inputs and costs of additional survival (see Appendix 2).

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

1.4.1.1 Completeness

The MS appears to include all relevant evidence from completed RCTs with respect to the question of efficacy; the ERG's search revealed no additional completed RCTs.

1.4.1.2 Included trials

The REAL-2 trial was large (N = 1,002), adequately powered, and closely reflective of UK standard practice, using triplet therapies comprising epirubicin, a platinum-based chemotherapy (cisplatin or oxaliplatin) and a fluoropyrimidine (5-FU or capecitabine). The patient population is also representative of those UK patients who are considered fit enough for standard chemotherapy, although these patients are not representative of the UK aGC patient population as a whole (see Sections 1.4.2 and 3.1).

The ML17032 trial assessed doublets which the ERG's clinical advisors indicated would be used in patients considered unable to tolerate triplet therapy. However, such doublets would be given at a lower dose than was employed in the trial. It should also be noted that the trial population was not representative of the UK (see section 1.4.2 and 3.1).

1.4.1.3 Cost effectiveness

The submission included a review of the literature of the cost-effectiveness of capecitabine for aGC. The manufacturer undertook a *de novo* economic evaluation in order to compare capecitabine based regimens with the equivalent 5-FU based regimens. In the context of the current assessment the ERG deems CMA to be an appropriate framework with which to analyse the decision problem. Cost estimates have been generated appropriately and are robust to uncertainties regarding assumptions and sources.

1.4.2 Weaknesses

1.4.2.1 Quality of Life

The primary weakness of the initial MS was the limited QoL data. The REAL-2 trial was reported as assessing QoL using the EORTC-30 version 3 questionnaire administered at baseline, and after three, six, nine and 12 months. However, reporting of this assessment was limited to the statement that there were high levels of compliance at baseline and three months and no significant differences between the groups on the Global Health Status subscale at either of these time points. The ERG requested that the full results of the QoL assessment for all time points be made available. No QoL data were presented for the ML17032 trial; the ERG requested that the manufacturer provide any such data. In response to these requests the manufacturer provided the levels of compliance at 24 weeks, data on the baseline scores for all subscales, and changes from baseline at 12 weeks and 24 weeks for the REAL-2 trial (Appendix 2, pp43-44; Appendix 4) and stated that QoL was not assessed in ML17032 (Appendix 2, p2)

1.4.2.2 Completeness

The MS did not include any data from non-randomised trials. It was unclear whether inclusion of such trials would have provided additional information for the assessment of safety. The ERG requested that any such data be supplied. It was also unclear whether the inclusion of trials of capecitabine conducted in other indications would have provided additional information for the safety analysis, despite differences in the regimens used. The ERG therefore requested that any such data be supplied. In response to both these requests the manufacturer stated that they regarded the safety data from the two RCTs, in conjunction with the Summary of Product Characteristics (SPC), as sufficient evidence.

1.4.2.3 Review process

There were a number of issues identified with the search strategy, including two apparent errors which the manufacturer was invited to comment on or clarify. These were acknowledged and corrected in the manufacturer's

response to the letter of clarification but these corrections did not materially affect the review as no additional studies relevant to the scope were identified.

The systematic review process was vulnerable to bias and error because a single reviewer was responsible for its execution. The inclusion criteria were poorly defined with respect to interventions, comparators, population and outcomes. Those criteria which were stated also posed potential problems; although they did not impact on studies actually included they had the potential to exclude relevant studies. No separate review process was conducted for the safety analysis.

1.4.2.4 Included trials:

Both trials were open-label non-inferiority trials and REAL-2 was unblinded for all outcomes while for ML1703 the MS reported blinded outcome assessment only for the primary outcome of PFS. The ERG requested these data for the outcomes of tumour response and adverse events. The manufacturer subsequently supplied these data for response rates and related outcomes (see Appendix 2, pp21-23).

The ML17032 trial was unrepresentative of UK practice in the schedules and doses employed and in the population treated. When the non-inferiority analyses of efficacy outcomes were performed using a margin of 1.25 relative to the efficacy of 5-FU, rather than 1.40 as the protocol had specified, the trial had only 50% power to detect statistically significant non-inferiority.

The REAL-2 trial included a majority of patients who are outside the licensed indication, having advanced inoperable cancer of the oesophagus or gastroesophageal junction. However, the ERG's clinical experts confirmed that treatment for each of these cancers would follow the same course as that for advanced inoperable gastric cancer. While REAL-2's population was representative of patients considered fit for standard therapy, the median age was significantly lower than that of the total UK population of patients with aGC (see Section 3.1).

1.4.2.5 Cost effectiveness

The appropriateness of using a cost-minimisation approach to evaluate the cost-effectiveness of capecitabine is dependent not only on clinical evidence from the REAL-2 and ML17032 trials, but also on evidence relating to QoL and adverse events. The shortcomings in QoL and safety identified above are therefore relevant when evaluating the limitations of the adopted approach. There are also several shortcomings identified in the costing procedures. However, these were considered minor and further evaluations by the ERG showed no impact in overall conclusions.

In addition, the manufacturer failed to consider uncertainty when justifying the use of CMA. Also, a probabilistic sensitivity analysis was not conducted by the manufacturer.

1.4.3 Areas of uncertainty

The MS stated that second-line therapy is rarely used in aGC. However, in the REAL-2 trial, 14% of patients were reported to receive such therapy and the ERG's clinical experts confirmed that a proportion of patients seen in UK practice would be given second-line treatment following platinum and fluoropyrimidine therapy. The ERG requested details of second-line treatment and also efficacy data broken down by receipt of this therapy. The manufacturer reported that they were unable to supply these data.

Other areas of uncertainty related to the prognostic implications of the presence in the included studies of patients from outside the licensed indication, and the relevance of the ML17032 trial to UK practice.

With respect to the economic evaluation, areas of uncertainty relate to the assumptions of equal incidence and severity of adverse events, the QoL associated with aGC patients, the costs of additional survival and the handling of parameter uncertainty. This is because the appropriateness of the economic evaluation method, CMA, is based on these assumptions.

1.5 Key issues

The ERG identified some shortcomings in the assumptions and methods of the MS for both clinical and cost-effectiveness. However, after clarification and further analyses these did not alter the overall conclusions.

A large proportion of the patients in REAL-2 did not have aGC, but rather advanced cancer of the oesophagus or the gastroesophageal junction. These patients (62% of the trial population) were therefore outside the licensed indication. The ERG's clinical advisors considered it appropriate to consider these patient groups alongside aGC since, regardless of the specific terms of the licence, UK patients are usually treated with the same regimens irrespective of whether the primary tumour is sited in the stomach or oesophagus.[Chau, 2009 #15]

Due to a lack of clarity in the search process, it is unclear whether relevant data on adverse events from non-randomised trials have been excluded from the analysis. The MS did not identify any such trials; the ERG therefore requested that details of any non-randomised trial in aGC, together with relevant safety data be provided. The manufacturer declined to provide further data.

2 Background

2.1 Critique of manufacturer's description of underlying health problem

The MS provides a clear summary of the incidence of gastric cancer, and the proportion of patients presenting with advanced inoperable disease.

2.2 Critique of manufacturer's overview of current service provision

The MS accurately reports the development of chemotherapeutic practice in the UK. However, it states that single-agent fluoropyrimidines may still have a

role in the treatment of aGC. This does not reflect the views of the ERG's clinical experts, nor are such single agent regimens included in the subsequent reporting of research on the use of different regimens in UK practice.

The diagram illustrating the use of different regimens in the UK (Figure 2, MS p17) is unclear and does not give information on the number (range) of cycles given for each regimen. The ERG requested clarification and further information. The manufacturer supplied a correctly labelled diagram and further information on the source of the information and the numbers of cycles employed in UK practice (Appendix 2, pp9-10).

3 Critique of manufacturer's definition of decision problem

3.1 Population

The MS states that the population of interest is patients with aGC. This is in accordance with the licensed population although NICE's scope defines the population more narrowly as patients with advanced inoperable gastric cancer. The characteristics of the trial populations are shown in Table 1.

Table 1: Characteristics of trial populations based on Tables 3 and 5 of the MS, Table 1 in Cunningham et al. (2008)[1] and Table 1 in Kang et al. (2009).[2]

	REAL-2 (per protocol population)				**ML17032** (ITT population)	
Trial Arm	ECF	ECX	EOF	EOX	CF	CX
N (ITT)	263	250	245	244	156	160
N (PP)	249	241	235	239	137	139
N (safety analysis: nonhaematological)	234	234	225	227	155*	156*
N (safety analysis: haematological)	236	229	231	232	155*	156*
Median age: years (range)	65 (22-83)	64 (25-82)	61 (33-78)	62 (25–80)	56 (22-73)	56 (26-74)
% Male	81.1	80.5	81.3	82.8	69	64
Performance status	ECOG: 0 or 1: 88.4% 2: 11.6%	ECOG: 0 or 1: 87.6% 2: 12.4%	ECOG: 0 or 1: 91.5% 2: 8.5%	ECOG: 0 or 1: 90.0% 2: 10.0%	Karnofsky Performance Status Median (range): 80 (70-100)	Karnofsky Performance Status Median (range): 80 (70-100)
Gastric cancer (%)	36.1	42.3	37.0	43.5	100	100
Metastatic (%)	79.5	76.8	77.0	75.7	100**	100**
Ethnicity	NR	NR	NR	NR	67% Asian; 19% Caucasian; 10% Hispanic	66% Asian; 19% Caucasian; 11% Hispanic
Previous treatment	7.6% surgery	7.5% surgery	7.7% surgery	8.8% surgery	22% surgery; 10% adjuvant therapy	25% surgery; 11% adjuvant therapy

* A single population was defined for the safety analyses in ML17032 ** All patients appeared to have >1 metastatic site, although a small proportion were classified as “Not reported” in Kang et al. (2009)

The larger of the two trials, REAL-2, included a large number of patients outside the licensed indication of gastric cancer. The proportions of patients with gastric cancer ranged from 36.1% in the ECF group to 43.5% in the EOX group (Table 2). Other patients had oesophageal cancer or cancer of the gastroesophageal junction.

Table 2: Representation of cancer sites in the REAL-2 trial based on Table 5 in the MS and Table 1 in Cunningham et al. (2008).[1]

Cancer Site	ECF (%)	ECX (%)	EOF (%)	EOX (%)
Gastric	36.1	42.3	37.0	43.5
Oesophageal	34.9	29.5	39.6	34.3
Gastroesophageal junction	28.9	28.2	23.4	22.2

The presence of large numbers of patients outside the licensed population was not considered to be of significance in the MS, because the treatment pathway for patients with advanced inoperable cancer of the oesophagus or gastroesophageal junction is regarded as identical to that for patients with advanced inoperable gastric cancer. Therefore no analysis of the impact of cancer site on efficacy outcomes was presented. The ERG's clinical advisors confirmed that the assumption of treatment equivalence was reasonable. However, cancer site is linked to carcinoma histology which may have prognostic significance, as squamous cell carcinoma of the oesophagus and gastroesophageal junction shows a trend toward poorer overall survival than adenocarcinoma.[8] In light of this, the ERG requested efficacy data broken down by cancer site. The manufacturer supplied a forest plot showing these data which indicated no statistically significant difference between the sites for the outcome of overall survival (Appendix 2, p20).

Of more significance is the fact that, while REAL-2's population is representative of patients considered fit for standard therapy in the UK, it was not representative of the age and fitness of the total UK population of patients with aGC. The median age of patients in REAL-2 was 63 years, while the ERG's clinical advisors stated that the median age at death for patients who die from aGC in the UK is 80 years; only 17% of aGC deaths are in patients under the age of 65 years.

Other factors known to have prognostic significance are the following: performance status, presence of liver metastases, presence of peritoneal metastases and alkaline phosphatase levels.[5 6] In view of this the ERG requested data broken down by these factors. The manufacturer supplied forest plots which showed data for overall survival broken down by the following additional variables: performance status, disease extent, age, gender, histology and differentiation (Appendix 2, p20). They stated that they were unable to supply data on any additional subgroups. The ERG also requested data broken down by whether patients were recruited into the dose escalation phase of the trial. The manufacturer responded by referring the ERG to the published interim report;[9] and supplying brief safety data which indicated acceptable toxicity for the 625mg/m^2 dose of capecitabine (Appendix 2, pp18-19).

The MS referred to a multivariate analysis of the REAL-2 data including the factors of age, performance status and disease extent; this was not presented and the ERG requested that it be provided. The manufacturer subsequently supplied additional information on variables which were included and excluded from the model, and the outputs for these variables (see Appendix 2, pp15-18). On the basis of this information the analysis appeared appropriate.

REAL-2 included both patients with locally advanced inoperable cancer and those with metastatic cancer. Although such patients are both included in the licensed indication there are differences in prognosis, particularly with respect to response rates. Accordingly the ERG requested that the manufacturer provide the efficacy data broken down by disease stage (M0 versus M1). As noted above a forest plot illustrating this was supplied for the outcome of overall survival. A minority of patients (approximately 7%) had undergone prior surgery and the ERG requested that the manufacturer provide efficacy data broken down by receipt of surgical treatment. The manufacturer reported that they were unable to supply this information.

The ML17032 trial appeared to include only patients with metastatic gastric cancer, although a small number of patients were classified as having an unreported number of metastatic sites.[2] However, the trial had an upper age

limit of 75 years (in contrast to REAL-2 which had no age limit) and patients had a median age at least 5 years younger than that of REAL-2. The UK clinical population has a median age of 80 years at death from aGC (see above). The ethnicity of the patients was also unrepresentative of the UK population, with only 19% of patients described as Caucasian (67% of patients were Asian, 11% Hispanic and the remainder classified as Other). A substantial minority (22-25%) of patients had undergone prior full or partial gastrectomy, and a proportion of these (11% of the trial population) had received prior adjuvant chemotherapy.[2]

3.2 Intervention

The NICE final scope indicates that the relevant intervention is capecitabine in combination with a platinum-based regimen.

The MS recommends that capecitabine is administered in combination with cisplatin plus epirubicin, with oxaliplatin plus epirubicin, or with cisplatin alone.

Both the MS and the SPC state that, when given continuously, the recommended dose of capecitabine is 625mg/m^2 taken orally twice daily for the duration of the 21 day cycle. When given for 14 days followed by a seven day rest period, the recommended dose of capecitabine is 800-1000mg/m^2 twice daily. The MS states that continuous administration is in combination with cisplatin/oxaliplatin plus epirubicin while 14 day treatment followed by a seven day rest period is in combination with cisplatin alone.

The MS states that treatment cycles are repeated until disease progression or unacceptable toxicity. The REAL-2 trial administered up to eight cycles although the median number of cycles received was six. The mean numbers of cycles were as follows: ECF 5.24; ECX 5.76; EOF 5.44, and EOX 5.42. The ML17032 trial did not specify a maximum number of cycles; 45% of patients in the CX arm received six cycles and 20% received eight (figures for CF were 34% and 13% respectively). The manufacturer stated that mean numbers of cycles were 4.43 for the CF group and 5.14 for the CX group (see Appendix 2, p11).

The SPC states that, for patients receiving treatment in combination with cisplatin, appropriate premedication to maintain hydration and anti-emesis should be started prior to beginning cisplatin therapy, in accordance with the SPC for cisplatin.

The ERG's clinical advisors confirmed that capecitabine in combination with cisplatin or oxaliplatin is regularly used in clinical practice. They stated that standard therapy would also include epirubicin, but that this would be omitted in older or less fit patients. They also stated that in UK practice the chemotherapy would be administered for a maximum of between six and eight cycles, with the consequence that the median number of cycles would likely be lower than the six documented in the REAL-2 trial. The manufacturer stated that clinicians responding to market research carried out on their behalf perceived that 4.6 cycles of ECX were typically delivered (see Appendix 2, p14).

The manufacturer's recommendations on doses and scheduling of the different regimens reflect the two trials included in the MS, as well as the SPC. In the case of the triplet regimes assessed in REAL-2, the ERG's clinical experts confirmed that these doses and schedules were reflective of UK clinical practice. However, in the case of the doublet regimes assessed in ML17032, the doses and schedules were not representative of current UK practice, which would typically involve administering 5-FU/capecitabine for the duration of the 21 day cycle, rather than for five days and 14 days respectively (as in ML17032); and which would employ lower doses of both agents as they would typically be given to less fit patients.

3.3 Comparators

The manufacturer stated that the comparator was 5-FU in combination with a platinum-based regimen; the MS addressed the following regimens as comparators: 5-FU in combination with cisplatin alone, 5-FU in combination with cisplatin plus epirubicin, 5-FU in combination with oxaliplatin plus epirubicin. The multivariate analysis reported by the REAL-2 trial also included a comparison between capecitabine in combination with cisplatin and

capecitabine in combination with oxaliplatin, which was also included in the MS.

The manufacturer had conducted market research which indicated that these represented the chemotherapy regimes used in the UK, with the exception of a small proportion of patients treated with other regimes. The ERG's clinical experts indicated that 5-FU in combination with a platinum-based therapy, with or without epirubicin, would constitute the great majority of UK practice where capecitabine was not used and patients were sufficiently fit. They indicated that the use of doublet regimens was not standard practice, but would be considered where a patient was not felt to be fit enough to receive triplet therapy with an epirubicin component. However, the doublet regimen would be administered at a reduced dose in these circumstances. The manufacturer's response to the letter of clarification (Appendix 2, p10) indicated that there may be some use of carboplatin, which would be included in the category of "other regimes".

3.4 Outcomes

The MS focused on the outcomes used in the included trials and published meta-analysis.

The primary outcome of the meta-analysis was overall survival, and this was also the primary focus of the MS. Secondary outcomes were PFS and response rate. The primary outcome of the REAL-2 trial was also overall survival, with PFS as a secondary outcome. The primary outcome of the ML-17032 trial was PFS; overall survival was a secondary outcome. Both trials reported complete and partial response rates. Duration of response and time to response were also reported in the MS. Both studies also reported adverse events; no statistical pooling of the safety data was attempted. The adverse events reported were clinically relevant, and included hand-foot syndrome (palmar-plantar erythrodesia), neutropenia, stomatitis and diarrhoea.

There was extremely limited assessment of QoL in the MS, which may reflect the limited reporting in the journal publications of the trial. The REAL-2 study did assess QoL, but reporting of the results of this assessment was very

limited in the MS, being limited to a statement of equivalence on one subscale at baseline and 12 weeks. Given the nature of the comparison, this lack of supporting evidence was considered to represent a serious weakness. Further data on this outcome was requested by the ERG. Data supplied in response to this request comprised median baseline scores (N, mean, median and standard deviation) on each of the subscales (Physical, Role, Cognitive, Emotional, Social and Global QoL), symptom scores and mean changes from baseline at 12 and 24 weeks on each of these subscales (Appendix 2, pp43-44; Appendix 4). However, no details of the statistical analyses were provided. The ML17032 trial did not assess QoL.

3.5 Time frame

Median follow-up times were a median of 17.1 months in REAL-2, and 21.4 months (CF) or 21.5 months (CX) in ML17032 (Table 3). The duration of follow-up for individual trial arms was not reported in the MS; Table 3 shows this data as reported in the published trial reports. The median numbers of 21 day cycles administered was six in the REAL-2 trial and a median of 5.5 was employed in the MS.

Table 3: Duration of follow up and survival in included trials taken from Cunningham et al. (2008) and Kang et al. (2009)

Trial / Arm	Follow-up (median): months
REAL-2	
ECF	17.5
ECX	17.6
EOF	19.3
EOX	18.9
ML17032	
CF	21.4
CX	21.5

3.6 Other relevant factors

The ERG's clinical advisors highlighted the importance of the patient's age and fitness in determining treatment. In particular, they noted that older patients do not withstand the toxicity of the standard dose triplet therapies considered in the MS.

4 Clinical effectiveness

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturer's search strategy and comment on whether the search strategy was appropriate.

The MS lists the databases searched, reports the date that the searches were carried out (12th October 2009) and states the period covered by each of the database searches. Additional searches of web resources are described and the overall aim of the strategy is described as being to identify "citations referring to human clinical trials, gastric cancer (and variants thereof) and capecitabine (and variants thereof)".

The databases specified by NICE as a minimum are: Medline, Embase, Medline in Process and the Cochrane Library while the databases searched by the manufacturer were: Medline, Embase, Medline in Process, Embase Alert and Biosis. It appears that one of the key resources, the Cochrane Library, has not been used.

The database searches were conducted using the Datastar search interface and this is not accessible to the ERG. Consequently the ERG is not able to reproduce and run the strategies to confirm that all potential studies have been identified.

Critique of the strategies used has highlighted a number of issues. The searches appear to have been carried out across all databases at once so there is one strategy that covers all the databases. The search statements given are all numbered but the numbering is not consecutive e.g. lines given are 1, 2, 7, 11, 12, 14 and so on. There is no explanation given for the missing lines 3, 4, 5, 6 and so on.

The manufacturers state that the search covered the period 1993 onwards but there is no search statement given that demonstrates this limit being applied.

The search of Embase used the EMTREE terms stomach cancer and capecitabine. No synonyms were used (e.g. gastric cancer, xeloda) although

the description of the strategy refers to variants being used. Similarly, the search of Medline uses MeSH term stomach neoplasms but no synonyms (e.g. gastric cancer) although the description of the strategy refers to variants being used.

In the section of the strategy (lines 52, 53, 56, 57, 84) that relates to the Biosis database there is an error in the Boolean logic applied. Line 57 combines lines 52 and 53 (xeloda and capecitabine) using the Boolean AND whereas the Boolean OR should have been used. The effect of doing this is that 143 records were identified by line 57, whereas a minimum of 1680 records should have been identified at line 57. The manufacturer was asked to comment on this, and their response to the letter of clarification acknowledged the error. They therefore provided a report arising from re-running the searches using the correct Boolean logic. This identified four relevant additional records. Of these, three were publications relating to the ML17032 trial and one related to a phase III trial which would have been excluded under the terms of the scope (Van Cutsem et al., 2009).

Lines 80 and 81 aim to limit the results of the Medline and Embase searches to clinical trials. This has been done using the publication type in MEDLINE (pt=clinical-trial) and the EMTREE term (clinical-trial$) in EMBASE. In the description of the strategy the manufacturers state that “individual studies and meta-analyses were sought” but the effect of limiting to “clinical trial” will have been to remove any records that were tagged with meta-analysis but not clinical trial. Meta-analysis terms are available in both Medline and Embase and these could have been included in the search strategies.

The MS describes how the abstracts of the American Society of Clinical Oncology (ASCO) annual meeting for the years 2004 to 2009 were searched using the Journal of Clinical Oncology website. The website search and strategy used was summarised appropriately. Further searches using an internal Roche database were conducted.

There is no description of a search for ongoing studies in the MS and the ERG requested that the manufacturer supply details of any such search. In

response the manufacturer stated that the Roche trial management system and Current Controlled Trials (http://www.controlled-trials.com) were searched. The MS states that the manufacturer is not aware of any ongoing trials.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

Trials were included in the MS if they randomised patients to two different treatments available in the UK. Trials were excluded if they were phase II studies or if neither study arm would be considered relevant to UK practice.

The inclusion criteria did not specify the intervention or comparators of interest beyond the requirement that they be available in the UK, nor did they specify the population of interest. Outcomes were not defined. The failure to specify the inclusion criteria in accordance with the scope may have increased the potential for bias and error in the selection process. This is of particular concern as the process was conducted by a single reviewer, which also increases these risks.

The decision to exclude phase II RCTs is not adequately justified in the MS: randomised phase II trials can contribute useful data to a pooled analysis. This is can be particularly important with respect to the safety analysis. Additional data relevant to the safety analyses could also potentially be available from non-randomised trials of capecitabine in gastric cancer; the exclusion of such trials from all analyses may have resulted in the omission of such data. The ERG requested additional safety evidence from any non-randomised trials from the manufacturer; the manufacturer responded that the two large RCTs presented were the most relevant data. The limitation of the safety analysis to data from aGC trials appeared appropriate given that in other indications capecitabine is used at higher doses as monotherapy or in combination with docetaxel; the manufacturer did not supply any additional data from such indications. An additional requirement for “relevance to UK practice” was used as further justification to exclude trials which include comparisons between capecitabine and 5-FU in the licensed indication, but which also include therapies such as docetaxel; this is not clearly justified.

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded.

Two studies were included in the MS: REAL-2[1] and ML17032[2]. Also included was a meta-analysis of the efficacy data from these trials.[3]

Table 4: Studies included in the MS

Study	Comparison
REAL-2 [1]	ECF versus ECX versus EOF versus EOX
ML17032 [2]	CF versus CX
IPD meta-analysis of REAL-2 and ML17032 [3]	X combinations versus F combinations

A flow diagram of the number of studies included and excluded at each stage of the review process was presented but it was unclear how the numbers related to the identified studies. Clarification was requested but the manufacturer's response failed to resolve the lack of clarity. The MS identified the following excluded studies:

Table 5: Studies identified and excluded in the MS.

Study	Comparison	Reason for exclusion
Capecitabine versus S-1 Study[10] [11]	Capecitabine 1250mg/m2 b.i.d. versus S-1 40-60mg b.i.d. in 96 patients aged ≥65 years with aGC.	Did not include a randomisation between two treatments available in the UK. Lies outside the scope as neither arm includes a platinum-based therapy.
ATTAX study [12] [13]	Weekly docetaxel 30mg/m2/ d1, cisplatin 8 x 60mg/m2 d1, 5-FU 200mg/m2/d continuously versus docetaxel 30mg/m2/ d130mg/m2/w plus capecitabine 1,600mg/m2/d d1-14.	Phase II study not designed to produce robust comparison of efficacy and toxicity. Inclusion of docetaxel also reduces relevance to UK practice. Lies outside the scope as capecitabine arm does not include a platinum-based therapy.

One additional excluded study was identified in the response to the letter of clarification; this did not assess a randomised comparison between capecitabine and 5-FU (Appendix 2, p39).[14]

4.1.4 Details of any relevant studies that were not included in the submission ?

No additional completed studies directly relevant to the efficacy question were identified in a search by the ERG. The manufacturer stated that they were not aware of any ongoing studies. A search of ClinicalTrials.gov by the ERG

retrieved one study which would have been eligible for inclusion based on the scope:

> Docetaxel and Oxaliplatin in Gastric Cancer: Docetaxel plus oxaliplatin versus docetaxel plus oxaliplatin plus 5-FU versus docetaxel plus oxaliplatin plus capecitabine. Ongoing but not recruiting patients; NCT00382720 [Estimated completion date: March 2010]

This would be excluded if the manufacturer's exclusion criteria were applied, as it was a randomised phase II trial and docetaxel was given in all arms.

There were also a number of ongoing studies which we would have expected a search by the manufacturer to identify as they involved capecitabine in the treatment of aGC, even though they would subsequently be excluded from consideration because they did not assess a relevant comparison. These are listed in Appendix 3.

4.1.5 Description and critique of manufacturer's approach to validity assessment

Validity assessment appears to have been undertaken as part of the data extraction process by a single reviewer. This increases the chances of bias and error within the assessment process. The assessment used appropriate criteria, comprising allocation concealment, sample size justification, length of follow-up, use of blinded outcome assessment, parallel/cross-over design, whether conducted in the UK or comparable with UK, consistency of dosing regimens with the SPC, comparability of study groups, appropriateness of statistical analysis, and use of an intention–to-treat (ITT) analysis.

Allocation concealment, which is the masking of the randomisation sequence from those enrolling patients, though listed as a criterion, is not in fact assessed. Instead a discussion of blinding, and reasons for the use of an open-label design are presented. The ERG's validity assessment (see Table 6) found that allocation concealment was adequate in REAL-2 and unclear in ML17032.

The manufacturer's validity assessment of comparability between groups at baseline stated that the REAL-2 trial showed comparability. However, it

appears that the proportion of patients within the licensed indication of gastric cancer (rather than cancer of the oesophagus or the gastroesophageal junction) was not balanced across the arms. From the forest plot of overall survival data subsequently provided by the manufacturer (Appendix 2, p20) this does not appear to be critical, as site did not appear to be associated with statistically significant differences in outcome for the fluoropyrimidine therapies.

The MS correctly identified the lack of blinding in both trials and the fact that ML17032 was underpowered when the analyses were altered to use a non-inferiority margin of 1.25, rather than 1.40 as originally planned. The ERG acknowledges the difficulties associated with blinding of such trials, due to ethical and scheduling considerations, but the potential for bias from open-label designs remains. REAL-2 in particular did not employ independent outcome assessment, and in the MS such assessment was reported only for the primary outcome of PFS in ML17032. In response to a request from the ERG, the manufacturer provided the results of the independent assessment for response rate and some related outcomes. These data differed significantly from those of the non-independent assessors in a number of respects and were more conservative with respect to capecitabine (Appendix 2, p22).

Whilst the primary outcome of overall survival is unlikely to be impacted, the lack of independent assessment in the REAL-2 trial remains a concern for PFS, response rate and occurrence and grading of adverse events. This is of particular concern with non-inferiority trials, as it is possible for an assessor to bias the results towards equivalence even without knowing the group to which a patient has been allocated.[15]

In the case of non-inferiority trials an ITT analysis for the primary end-points may be inappropriate and a per-protocol analysis is correctly identified as the valid approach. The criteria for entry into the safety analyses in the REAL-2 trial are not clearly specified in the MS; however the manufacturer responded to a request for clarification from the ERG with an explanation of the numbers

of patients assessed in the safety analyses and the statement that no additional criteria were used.

Table 6: ERG's validity assessment of trials included in the MS based on information in the published trial reports.[1 2]

	REAL-2	ML17032
Was the method used to generate random allocations adequate?	Yes	Unclear
Was the allocation adequately concealed?	Yes	Unclear
Were the groups similar at baseline?	Some differences in % patients with gastric cancer	Yes
Were patients blind to treatment allocation?	No	No
Were care providers blind to treatment allocation?	No	No
Were outcome assessors blind to treatment allocation?	No	Yes, but blinded assessments reported only for some outcomes*
Were there any unexpected imbalances in dropouts between the groups? (If so were they explained/adjusted for?)	No	No
Is there any evidence to suggest that more outcomes were assessed than were reported?	No	No
Did the analysis use an ITT analysis appropriately?	Yes, as secondary analyses following per-protocol primary analyses (non-inferiority trial).	Yes, as secondary analyses following per-protocol primary analyses (non-inferiority trial).

*Independent assessments reported only for PFS in the MS; data relating to response rates provided in response to request by ERG.

No attempt to assess the validity of the IPD meta-analysis was reported in the MS, and the ERG were unable to assess this due to inadequate reporting of methods in the publication,[3] which the manufacturer confirmed was the only information available to them (Appendix 2, pp6-9)

4.1.6 Description and critique of manufacturer's outcome selection

The primary outcome of the published IPD meta-analysis was overall survival, and this was also the primary focus of the MS. Secondary outcomes were PFS and response rate. The primary outcome of the REAL-2 trial was also overall survival, with PFS as a secondary outcome. The primary outcome of the ML-17032 trial was PFS; overall survival was a secondary outcome. Both trials reported complete and partial response rates. The REAL-2 study stated

that RECIST criteria[16] which are widely adopted were employed to determine response rates. The ML17032 trial did not state that RECIST criteria were used, but it appeared from the description of the criteria that this was in fact the case. Duration of response and time to response were also reported in the MS for ML17032.

Both studies also reported adverse events; no statistical pooling of the safety data was attempted. The adverse events reported were clinically relevant and included hand-foot syndrome (palmar-plantar erythrodesia), neutropenia, stomatitis and diarrhoea. The ERG's clinical advisors regarded febrile neutropenia and diarrhoea of grade two and above (if prolonged) as having the greatest implications for clinical management. The MS also reported the percentage of patients with treatment delays for both trials and the mean days of treatment delay per patient for the REAL-2 trial. As discussed in section 1.4.2 no additional safety data was included in the submission and the manufacturer responded to a request for data from non-randomised trials or trials in other indications with a statement that they had provided sufficient data.

There was extremely limited assessment of QoL in the MS, which may reflect the limited reporting in the journal publications of the trial. The ML17032 trial did not assess QoL; the REAL-2 study did assess QoL using the EORTC-30.[4] This is an appropriate instrument, designed and validated for the assessment of QoL in clinical oncology trials, but reporting of the results of this assessment is limited in the MS, being restricted to a statement of equivalence of one subscale at baseline and 12 weeks. Given the nature of the comparison, this lack of supporting evidence was considered to represent a serious weakness in the MS. Further data on this outcome was requested by the ERG. In response to this request the manufacturer supplied the number of patients assessed, mean, median and standard deviation of scores for each of the subscales; together with the changes from baseline in these scores at 12 and 24 weeks (Appendix 2, pp43-44).

4.1.7 Describe and critique the statistical approach used

The MS focuses on the statistical analyses reported in the published trial reports[1 2] and the IPD meta-analysis,[3] although additional analyses are reported in some instances (see below). In the case of the trial reports this means that non-inferiority per-protocol analyses are presented for the efficacy outcomes for both trials, while the meta-analysis presented ITT superiority analyses.

The REAL-2 trial had 80% power to detect non-inferiority with a margin of 1.23 based on preservation of the effect of 5-FU. The estimate of efficacy of 5-FU was derived from the REAL trial which indicated a one-year survival rate of 35%.[17] Secondary analysis to test the hypothesis that capecitabine was superior to 5-FU was also undertaken. The safety data presented were pairwise comparisons between ECF and the other individual arms, although the trial was powered to assess the fluoropyrimidine [F versus X] and platinum [C versus O] comparisons.

The ML17032 trial was powered to detect non-inferiority with a margin of 1.40 based on preservation of 57% of the effect of 5-FU. This was later revised to a margin of 1.25 based on preservation of 72% of the effect of 5-FU. This revised margin reduced the power of the trial to detect significant non-inferiority to 50%. The estimate of efficacy of 5-FU was derived from two trials in aGC (Kang et al., 2009) which assessed the following comparisons:

i) 5-FU alone versus 5-FU plus cisplatin versus 5-FU plus doxorubicin plus mitomycin C[18]

ii) 5-FU versus 5-FU plus cisplatin versus uracil and tegafur plus mitomycin[19]

Secondary analysis to test the hypothesis that capecitabine was superior to 5-FU was also undertaken.

Hazard ratios were calculated and Kaplan-Meier survival curves presented for the outcomes of overall survival and PFS, while odds ratios were calculated

for response rates. These methods were appropriate for analyses of survival outcomes.

For the REAL-2 trial a multivariate analysis was conducted which included performance status, extent of disease and age, and excluded primary tumour site, gender and histology. No further details of this analysis were reported and they were requested by the ERG. The manufacturer subsequently supplied additional information on variables which were included and excluded from the model, and the outputs for these variables (see Appendix 2, pp15-18). On the basis of this information the analysis appeared appropriate.

In some instances data were presented based on the ITT rather than the per-protocol population, and no rationale was presented for this. The ERG requested clarification and correction of populations in these instances. These analyses were subsequently supplied but in most instances did not materially affect the outcomes. In some instances the MS presented analyses which were not reported in the published trial reports; for example the adjusted analysis for PFS in the ML17032 trial; in other instances published analyses were omitted from the MS (e.g. the unadjusted analysis of overall survival from REAL-2). The analyses presented in the MS gave a more conservative estimate of the efficacy of capecitabine; however their source was unclear. In response to the points of clarification, the manufacturer indicated that they had access to the clinical study report (CSR) (Appendix 2). This was not included in the MS and the ERG subsequently requested that it be provided. The manufacturer did not provide a copy of the full CSR, but did provide additional selected tables (Appendix 2, pp43-44; Appendix 4).

The published meta-analysis used an IPD analysis of ITT data from the REAL-2 and ML17032 trials to test the hypothesis that capecitabine in combination with platinum-based chemotherapy with or without epirubicin was superior to 5-FU in combination with platinum-based chemotherapy with or without epirubicin.[3] Such an analysis based on non-inferiority trials was not inappropriate, although the particular issues of validity pertaining to non-inferiority trials should have been considered. As the meta-analysis did not include a validity assessment of included trials, it is not clear if this was the

case. The details of the statistical analysis were not reported in the published report which is the only information available, therefore the ERG were unable to critique the methods. However, it did not appear that there was any attempt to include the trial as a variable in the analyses; given the clinical differences between the trials this may be a potentially significant omission.

4.1.8 Summary statement

The decision problem is defined in the MS as capecitabine combined with a platinum based chemotherapy compared with 5-FU combined with a platinum based chemotherapy for the first line treatment of aGC. The MS includes all the completed studies relevant to the assessment of efficacy; although the exclusion criteria had the potential to exclude relevant evidence the ERG did not identify any additional relevant studies. One ongoing randomised phase II trial which assessed a comparison within the terms of the scope was identified by the ERG (NCT00382720). The manufacturer's exclusion criteria would have excluded this from consideration, both because it is a phase II trial, and because it includes docetaxel in all trial arms, which is not widely used in UK practice.

Relevant outcomes were reported for both trials, with overall survival, PFS, response rates and adverse events being reported. Appropriate criteria were used to assess response rates. However in some instances the per-protocol data were unavailable, despite the primary analyses being based on the per-protocol population as appropriate for a non-inferiority trial. This was partially rectified in the manufacturer's response to the letter of clarification.

Incomplete data were presented for the assessment of QoL. No data were presented for the ML17032 and only limited data on compliance and scores on one subscale of the EORTC-30 were provided. The ERG requested that full data be provided for this outcome. The manufacturer supplied more complete data for the REAL-2 trial (Appendix 2, pp43-44) but reported that ML17032 did not include an assessment of QoL.

4.2 Summary of submitted evidence

4.2.1 Summary of results

4.2.1.1 Pooled analysis

The published IPD meta-analysis of the REAL-2 and ML-17032 trials found a statistically significant benefit in overall survival for capecitabine compared with 5-FU in the ITT population (unadjusted HR: 0.87; 95% CI 0.77, 0.98, p=0.027). This finding was maintained in a multivariate analysis which included performance status, age, and presence of metastatic disease (adjusted HR: 0.87; 95% CI: 0.77, 0.98, p=0.02). Gender and histology were thrown out of the analysis for lack of effect.[3] There was no statistically significant difference between capecitabine and 5-FU groups in PFS (unadjusted HR 0.91; 95% CI: 0.81, 1.02, p=0.093); treatment with 5-FU or capecitabine was thrown out of the multivariate analysis for lack of effect (p=0.052). Logistic regression analysis showed response rates to be statistically significantly higher in the capecitabine groups (OR: 1.38; 95% CI: 1.10, 1.73, p=0.006), a result confirmed in the multivariate analysis. The ERG was unable to assess the validity of this meta-analysis due to limited reporting of the methods employed.

4.2.1.2 Individual trials: efficacy

REAL-2

The MS reported that REAL-2 found statistically significant non-inferiority of capecitabine on the primary outcome of overall survival using a hazard ratio adjusted for performance status, extent of disease and age (HR: 0.89; 95% CI: 0.77, 1,02) in the per-protocol population. This was based on the comparison: [ECF +EOF] versus [ECX + EOX]. The unadjusted hazard ratio for the per-protocol population was 0.86 (95% CI: 0.80, 0.99).[1] Statistically significant non-inferiority of oxaliplatin to cisplatin was also demonstrated in the per-protocol population (adjusted HR: 0.95; 95% CI: 0.82, 1.09). This was based on the comparison: [ECF + ECX] versus [EOF + EOX]. Interaction testing found no interaction between fluoropyrimidine and platinum groups (p=0.36).

Four-way comparisons were conducted in the ITT population. These indicated non-inferiority of each of the three comparators to ECF. Overall survival in the EOX arm was also found to be statistically significantly superior to the ECF arm (HR 0.80; 95% CI: 0.66, 0.97, p=0.02).

The MS states (Table 9) that in the per-protocol population the analysis of PFS showed non-inferiority (HR 0.90; 95% CI: 0.80, 1.03). However, this was not reported in Cunningham et al.;[1] which reported only the results of analysis in the ITT population (HR 0.92; 95% CI: 0.81 to 1.05). Four-way comparisons in the ITT population also showed no differences in response rates.

There was minimal QoL data reported in the MS. In the REAL-2 trial scores on the General Health Status subscale of the EORTC-30 questionnaire were reported not to differ significantly at baseline or three months. The ERG requested additional data. The additional data supplied in response to this request indicated that there were few statistically significant differences between trial groups at baseline or in changes from baseline at 12 or 24 weeks (Appendix 2, pp43-44; Appendix 4). However given the lack of details of the analyses undertaken the ERG cannot be certain that the statistical significance related to pairwise comparisons with the ECF group; as was reported briefly in the published report.[Cunningham 2008, #54] At baseline the median scores on the Social subscale were statistically significantly higher in the ECX and EOF groups compared to the ECF group. The EOF group also scored significantly higher on the Role subscale compared to the ECF group. The tables indicated that there were statistically significant differences at baseline on two symptom domains between the EOF and ECF groups; as in one instance the values appeared identical it was not clear that this was in fact the case. The only differences in change from baseline scores were reported in the Social subscale at 12 weeks, with a more marked reduction in the EOF group compared to the ECF group, and in the appetite symptom domain where there was a smaller reduction in the ECX group compared to the ECF group. These analyses were all pairwise comparisons which the trial was not powered to assess.

ML17032

The MS reports that ML17032 found statistically significant non-inferiority of capecitabine on the primary outcome of PFS in the per-protocol population (adjusted HR: 0.85; 95% CI: 0.65, 1.11). This was not reported in the published trial report.[2] The unadjusted per-protocol analysis, reported in both the trial report and the MS found a similar result (HR: 0.81; 95% CI: 0.63, 1.04). Statistically significant non-inferiority on the outcomes of overall survival (unadjusted HR: 0.85; 95% CI: 0.64, 1.13) and response rate in the per-protocol population (unadjusted OR: 1.80; 95% CI: 1.11 to 2.94) were also reported in both the MS and the trial report. As noted in section 4.1.5, independent assessment of response rate supplied in response to the letter of clarification was conservative to capecitabine (see Appendix 2, p22). No QoL assessment was reported.

4.2.1.3 Individual trials: safety

Safety analyses showed some significant differences in adverse events profiles between capecitabine and 5-FU regimens.

REAL-2

All comparisons are relative to ECF; other between-group comparisons were not reported in either the MS or the published report.[1] The trial was not powered to assess pairwise comparisons between the study arms, however data for [F versus X] and [C versus O] comparisons were not reported. Some but not all of these differences were noted in the MS. In REAL-2 grade 3 or 4 neutropenia occurred significantly more often in the ECX arm ($p<0.05$) and significantly less often in the EOF and EOX arms ($p<0.01$ in both cases). Of particular clinical significance, grade 3 or 4 diarrhoea occurred significantly more often in the EOF and EOX arms ($p<0.01$ in both cases); there was no statistically significant difference between the ECF and ECX arms which may indicate a differential effect related to the platinum agents rather than a difference in the fluoropyrimidines. Grade 3 or 4 hand-foot syndrome was more common in the ECX arm ($p<0.05$). There were significantly fewer days of treatment delay in the EOF compared to the ECF arm ($p<0.01$), although the proportion of patients with treatment delay was not reported to differ. The

ERG requested information on reasons for treatment delays; the manufacturer reported that they did not have access to this data (Appendix 2, p5). Other statistically significant differences appeared to relate to the [C versus O] comparison, and not to reflect the impact of capecitabine.

Grade 3 or 4 stomatitis was significantly more common in the EOF arm than the ECF arm ($p<0.05$) which was a surprising finding since it is usually more problematic in regimes using 5-FU (cf the ML17032 trial below). Also surprising was the significantly lower incidence of thromboembolism in both oxaliplatin arms compared to ECF ($p<0.01$), whilst ECX was statistically significantly different from ECF.

ML17032

Stomatitis was reported to have occurred more often and with greater severity in the CF arm, while vomiting was also reported to be more frequent in this group. Hand-foot syndrome was more common in the CX arm although it led to treatment discontinuation in only one case. Treatment modifications for anaemia, vomiting, nausea, diarrhoea and hand-foot syndrome were more frequent in the CX arm compared to the CF arm.

Additional data

No further safety data were provided in response to the ERG's request; the manufacturer stated that the two RCTs (REAL-2 and ML17032) and the RCTs in other indications identified in the Xeloda (Capecitabine) SPC provided relevant information. The ERG's clinical advisors stated that data from trials of capecitabine in indications other than aGC may be of limited relevance, as these single-agent regimens involve higher doses of capecitabine than the polychemotherapy regimens used in aGC.

Table 7: Efficacy outcomes for trials included in the MS based on Tables 6-9 in the MS, Table 2 in Cunningham et al. (2008)[1] and Table 2 in Kang et al. (2009)[2]

Trial	**REAL-2**				**ML17032**	
Trial Arm	ECF	ECX	EOF	EOX	CF	CX
Overall survival (months)	9.9	9.9	9.3	11.2	9.3	10.5
Overall survival (% at 1 yr)	37.7	40.9	40.4	46.8	NR	NR
Progression-free survival (months)	6.2	6.7	6.5	7.0	5.0	5.6
Overall response rate (%)	40.7	46.4	42.4	47.9	32*	46*
Full response (%)	4.1	4.2	2.6	3.9	3	2
Partial Response (%)	36.6	42.2	39.8	44.0	29	44
Duration of Response (months)	NR	NR	NR	NR	6.2	7.6
Time to response (months)	NR	NR	NR	NR	3.8	3.7

*Assessment reported in MS; for independently assessed figures see Appendix 2, p22

Table 8: Safety outcomes for trials included in the MS based on Tables 10-12 in the MS, Table 3 in Cunningham et al. (2008)[1] and Table 3 in Kang et al. (2009)[2]

Trial	**REAL-2**[a]				**ML17032**	
Trial Arm	**ECF** % all grades (% grade 3/4)	**ECX** % all grades (% grade 3/4)	**EOF** % all grades (% grade 3/4)	**EOX** % all grades (% grade 3/4)	**CF** % all grades (% grade 3/4)	**CX** % all grades (% grade 3/4)
Anaemia*	78 (13)	80 (11)	66 (7)	64 (9)	NR	NR
Thrombocytopenia*	15 (5)	17 (5)	13 (4)	21 (5)	NR	NR
Neutropenia*	74 (42)	86 (51)	68 (30)	63 (28)	30 (19)	32 (16)
Febrile Neutropenia*	13 (9)	11 (7)	12 (9)	9 (8)	NR	NR
Leucopenia	NR	NR	NR	NR	17 (4)	15 (3)
Diarrhoea	39 (3)	42 (5)	63 (11)	62 (12)	15 (4)	19 (4)
Stomatitis	51 (1)	39 (2)	44 (4)	38 (2)	26 (6)	12 (2)
Hand-foot syndrome	30 (4)	46 (10)	29 (3)	39 (3)	3 (0)	22 (4)
Nausea and vomiting	79 (10)	82 (8)	83 (14)	79 (11)	Nausea: 57 (3) Vomiting: 58 (13)	Nausea: 55 (2) Vomiting: 48 (6)
Peripheral neuropathy	30 (0)	36 (2)	80 (8)	84 (4)	NR	NR
Lethargy	90 (17)	93 (16)	90 (13)	96 (25)	NR	NR
Fatigue/asthenia	NR	NR	NR	NR	26 (1)	29 (3)
Anorexia	NR	NR	NR	NR	27 (<1)	29 (2)
Alopecia	82 (44)[c]	83 (47)[c]	75 (28)	74 (29)	NR	NR
Thromboembolism[d]	17 (NA)	13 (NA)	8 (NA)	8 (NA)	NR	NR
Death within 60 days	7 (NA)	6 (NA)	6 (NA)	6 (NA)	3 (NA)	5 (NA)
Treatment delay	59	60	48	50	48[b]	62[b]

* Outcomes are assessed using haematological safety population for REAL-2

[a] Figures for REAL-2 are rounded to nearest whole % [b] Percentage of patients with treatment modification resulting from adverse events

[c] Figures are for grade 2 which was the highest reported grade [d] Only assessed in per protocol population [e] Only assessed in ITT population

4.2.2 Critique of submitted evidence syntheses

The MS included a published IPD meta-analysis of the efficacy data from the REAL-2 and ML17032 trials.[3] This analysis was based on the ITT populations and assessed the hypothesis that capecitabine was superior to 5-FU in combination with a platinum chemotherapy with or without epirubicin. The manufacturer did not present a validity assessment of this analysis but did note that the authors did not state how the studies in the analysis were selected for inclusion. There is no documented search for studies, and inclusion criteria were not defined in the published report of the meta-analysis. The meta-analysis included both the studies identified in the MS, and the ERG did not identify any additional completed studies which fell within the scope. Data checking and verification with the trial investigators were not reported.

There was limited description of the methods used in the statistical analysis; the type of model used and stratification by trial were not reported. A subgroup analysis based on the following variables was included in MS: performance status (0 or 1 versus 2), age (greater than versus less than 60 years), and disease spread (locally advanced versus metastatic disease). The ERG requested information from the manufacturer on the methods used in the meta-analysis but they were unable to supply any further details. The ERG is unable to comment further on the reliability of the findings of the meta-analysis.

No statistical synthesis of safety data was presented. The narrative synthesis of safety data was not always consistent with the information in the evidence tables, or with the approach taken in the economic analysis. In particular statements such as “there was little impact on the overall number of adverse events experienced” (MS, p50) did not reflect the statistically significant differences observed for grade 3 or 4 neutropenia, anaemia, diarrhoea, hand-foot syndrome, lethargy and stomatitis in one or both of the capecitabine arms (ECX or EOX) in pairwise comparisons with ECF. There were also a few instances where statistically significant results from Cunningham et al. (2008)[1] were not indicated in the MS (MS, p50, Table 11).

4.3 Summary

The ERG has documented a number of potential problems with the systematic review processes employed in the MS. However, in practice, these potentials for bias do not appear to have impacted on the identification of those completed studies relevant to the efficacy outcomes of the scope. It is possible that data from nonrandomised studies relevant to the assessment of safety may have been excluded from the MS.

There are some issues with the design of the included trials, not least the potential for bias with unblinded assessment of outcomes other than overall survival. This may be particularly problematic with non-inferiority trials even when assessors are blinded to group identity. The included meta-analysis included IPD data from the two studies relevant to the scope, although its validity could not be assessed.[3]

The included trials were in relevant populations, although REAL-2 included a large proportion of patients outside the licensed population. These patients, with advanced oesophogastric junction or oesophageal cancer were regarded as having identical treatment requirements to the licensed population of patients with aGC, and no subgroup or stratified analysis was presented. The forest plot supplied in response to a request for further information indicated no statistically significant differences in responses related to the site of the primary tumour. The REAL-2 population was representative of those seen in UK clinical practice who are considered fit for standard therapy, although not of the aGC population as a whole. However, the population in ML17032 did not reflect that seen in UK practice in terms of age or ethnicity; a substantial proportion of patients had also received prior full or partial gastrectomy.

Both trials used comparator regimes relevant to the scope, although it should be noted that oxaliplatin in combination with epirubicin and either 5-FU or capecitabine was used outside of its licensed indication. The REAL-2 trial was relevant to, and reflective of, UK practice in terms of the intervention and comparator regimens assessed. The ML17032 trial did not reflect UK practice in the doses and schedules used for both the capecitabine and 5-FU arms.

The included studies used appropriate outcomes, in that overall survival, PFS, response rate and adverse events were assessed by both trials. The very limited QoL data available was a weakness in the MS which was partially addressed in the response to the letter of clarification (Appendix 2, p43-44). There was no reported data for ML17032, and reporting for REAL-2 remained limited to reporting of baseline scores and changes from baseline at 12 and 24 weeks.

The per-protocol data from the REAL-2 study indicated non-inferiority on the primary outcome of overall survival for the comparison of capecitabine in combination with epirubicin and cisplatin or oxaliplatin versus 5-FU in combination with epirubicin and cisplatin or oxaliplatin (adjusted HR: 0.89; 95% CI: 0.77, 1.02).

The per-protocol data from ML17032 indicated non-inferiority on the primary outcome of PFS for capecitabine in combination with cisplatin alone versus 5-FU in combination with cisplatin alone (adjusted HR: 0.85; 95% CI: 0.65, 1.11).

An IPD meta-analysis found that capecitabine was statistically significantly more effective that 5-FU when given in combination with a platinum-based regime with or without epirubicin on the outcome of overall survival (unadjusted HR: 0.87; 95% CI: 0.77, 0.98).

The safety analysis indicated the following clinically important differences between study arms in the REAL-2 study: grade 3 or 4 neutropenia occurred significantly more often in the ECX ($p<0.05$) and significantly less often in the EOX and EOF ($p<0.01$) arms compared to the ECF arm; grade 3 or 4 diarrhoea ($p<0.05$) occurred significantly more in the EOX and EOF arms; and grade 3 or 4 hand-foot syndrome occurred significantly more often in the ECX arm ($p<0.05$). The ML17032 study found the following differences: stomatitis occurred more often and with greater severity in the CF arm, while hand-foot syndrome was more common in the CX arm.

5 Economic evaluation

This section focuses on the economic evidence submitted by the manufacturer in their initial report and in their response to points of clarification from the ERG. The submission is subject to a critical review on the basis of the MS and by direct examination of the electronic version of the economic model. The critical appraisal is conducted with the aid of a checklist to assess the quality of economic evaluations and a narrative review to highlight key assumptions and possible limitations. Section 6 presents a description of the additional information provided by the manufacturer following ERG points of clarification and a critique of this by the ERG, alongside additional work undertaken by the ERG to address any remaining uncertainties.

5.1 Overview of manufacturer's economic evaluation

The manufacturer's initial economic submission to NICE included:

1. A description of the databases and websites searched in the literature review (MS, p.55). A description of the systematic search strategy used to identify existing cost-effectiveness studies for capecitabine in gastric cancer with full details in a separate Appendix (MS, p118–122, Appendix 10). A description of the identified studies (MS, p55-56).

2. A report of the CMA conducted by the manufacturer. This was accompanied by an explanation for the choice of a CMA rather than a full economic evaluation. The report described the technology; comparators and patient population; the categories of resource use costed; the resource use and unit cost assumptions and sources; the base-case results; and sensitivity analysis (MS, p56-100; Figures 12-15; Tables 14-54).

3. An electronic Excel file of the costing assumptions and calculations.

Following a number of points of clarification raised by the ERG, additional information and analyses were contained in the manufacturer's response (see

Appendix 2). A summary of the manufacturer's approach and signposts to the relevant sections in the MS are reported in Table 9.

The MS evaluated whether the use of capecitabine is cost-saving compared to IV 5-FU. No sub groups were evaluated; this was justified by the manufacturer in terms of there being no sub groups identified in the NICE scope. The manufacturer argued that a CMA was adopted instead of a conventional cost-effectiveness analysis because the two non-inferiority trials, upon which this analysis is based, showed that oral capecitabine is at least, if not more, safe, efficacious and convenient than IV 5-FU. As reported in Section 4.2.1.2.1, the REAL-2 trial reported that the unadjusted hazard ratio for mortality for capecitabine combinations (ECX and EOX) versus IV 5-FU combinations (ECF and EOF) was 0.86 (95% CI: 0.80, 0.99) for the per protocol population.[1] The ML17032 trial reported that the hazard ratio for PFS for capecitabine and cisplatin compared to IV 5-FU and cisplatin was 0.81 (95% CI: 0.63, 1.04) for the per protocol population.[2] No sub-group clinical results were reported.

The costs and health effects of adverse events were also excluded from the analysis. The manufacturer stated that the overall tolerability of capecitabine was considered at least as good as that of IV 5-FU. As reported in Section 4.2.1.3**,** the adverse event associated more with capecitabine was hand-foot syndrome in the REAL-2 and ML17032 trial. The adverse event associated more with IV 5-FU was stomatitis in the ML17032 trial. The manufacturer assumed that the health outcomes are as least as good for the capecitabine complications compared to the IV 5-FU complications, and that the IV 5-FU complications would cost at least as much as the complications for capecitabine.

Table 9: Summary of the manufacturer's economic evaluation (and signposts to MS)

	Approach	Source / Justification	Signpost (location in MS)
Model	Three cost-minimisation analyses (CMA) were conducted, combining capecitabine and 5-FU with different drugs. These are detailed below under comparators.	Two non-inferiority RCTs and a meta-analysis reported that oral capecitabine is at least, if not more, as safe, efficacious and convenient than 5-FU.	Section 7.2.6.2, p.63 Table 18, p. 62
States and events	The CMA approach did not require health states. Health states were only considered in a simple QALY threshold analysis. The only health state included in this analysis was progression free survival (PFS).		
Comparators	One CMA compared ECX with ECF. A second CMA compared EOX EOF. A third CMA compared CX with CF.	These 6 regimens appear to represent the vast majority of current practice in the NHS.	Section 7.2.3.1, p. 58-59
Sub groups	No sub groups were analysed.	No sub groups were identified in the final NICE scope.	Section 7.2.2.2, p. 58
Natural History	No natural history modelling was undertaken.		Section 1.8, p.8.
Treatment effectiveness	The non-inferiority of capecitabine compared to 5-FU for survival was assumed.	This assumption was based on the REAL-2 and ML17032 non-inferiority trials, and meta-analysis of these studies.	Section 7.2.7.6.1, Table 18, p.59-62
Health related QoL	The CMA did not require health related QoL evidence. Health related QoL was only considered in a simple QALY threshold analysis. EQ-5D data for progression free survival were used for this analysis.	The utility evidence for the QALY threshold analysis was obtained from the BO18255 trial. The patients actually had aGC and were HER 2- positive, but this was considered the best available estimate.	Section 7.2.10.1, page 87
Adverse events	No adverse events were included on the assumption of no difference in adverse events between the regimens being compared. The costs associated with adverse events due to 5-FU were assumed to be at least as great as those associated with the adverse events due to capecitabine.	This was based on the REAL 2 and ML17032 non-inferiority trials.	Section 7.2.7.4, p.66
Resource utilisation and costs	Resource utilisation and costs were presented for each of the 6 regimens. The cost categories included drug acquisition costs and drug administration costs. Drug administration costs included installation and replacement of the central venous access device for 5-FU, outpatient hospital visits, inpatient hospital visits, nurse time, the acquisition cost of ambulatory pumps, hospital pharmacy time and NHS transport cost.	This was based on the REAL 2 and ML17032 non-inferiority trials. Expert nurse opinion was used to verify resource use assumptions.	Section 7.2.8, p.67-81
Discount rates	No discounting was performed.	The time horizon was less than one year.	Section 7.2.5, p.59
Sensitivity analysis	One-way sensitivity analysis, scenario analysis and a threshold analysis were conducted.	Parameter ranges were based on published ranges and standard deviations, nurse expert opinion or assumptions.	Section 7.2.10.2, p.83-84

ECX = capecitabine combined with epirubicin and cisplatin, ECF = 5-FU combined with epirubicin and cisplatin, EOX = capecitabine combined with epirubicin and oxaliplatin, EOF = 5-FU combined with epirubicin and oxaliplatin, CX = capecitabine combined with cisplatin, CF = 5-FU combined with cisplatin

Three CMAs were conducted reflecting the alternative 5-FU based regimens.

- A comparison of capecitabine combined with epirubicin and cisplatin (ECX) with IV 5-FU combined with epirubicin and cisplatin (ECF).
- A comparison of capecitabine combined with epirubicin and oxaliplatin (EOX) with IV 5-FU combined with epirubicin and oxaliplatin (EOF).
- A comparison of capecitabine combined with cisplatin (CX) with IV 5-FU combined with cisplatin (CF).

The three CMAs were undertaken in order to ensure that the cost differences identified were due to the alternatives of IV 5-FU and capecitabine alone rather than to differences in other elements of the regimens, which addresses the decision problem in the scope.

A brief overview of the key assumptions used in the CMAs is reported below. This is followed by a more detailed critique of the economic evaluation and its assumptions.

- Oral administered capecitabine-based chemotherapy has equivalent clinical efficacy to IV administered 5-FU based chemotherapy regimens.
- There are no differences in treatment-related adverse events between the oral administered capecitabine and the IV administered 5-FU based chemotherapy regimens.
- No drug wastage was taken into account.
- The NHS supplies transport for 20% of patients attending hospital visits.

Other specific assumptions related to resource use quoted by the manufacturer in Table 18, (MS, p62-63), all favour the IV 5-FU regimens (i.e. they are conservative with respect to capecitabine).

5.1.1 Published cost-effectiveness studies

The search strategy was described in the MS to identify published cost-effectiveness studies for capecitabine in the treatment of aGC. The manufacturer searched a variety of electronic databases including Medline, Medline (R) In Process, Embase, Health Economic Evaluation Database (HEED), the NHS Economic Evaluation Database (NHS EED) and ISPOR Research Digest. The manufacturer also searched the websites of the National Institute of Health and Clinical Excellence (NICE) and the Scottish Medicines Consortium (SMC). Detailed search strategies for Medline, Embase and NHS EED are presented separately in Appendix 3 of the MS.

One economic evaluation relevant to this decision problem was identified. This was Roche's 2007 submission to the SMC for capecitabine in this indication. The results reported are consistent with this submission.

5.1.2 Natural history

Given the use of CMA, natural history was not formally modelled.

5.1.3 Treatment effectiveness within the submission

The manufacturer argues that capecitabine is at least as effective as IV 5-FU, based on evidence from the clinical trials available. Because of this, a CMA was undertaken and thus effectiveness data were not explicitly included in an economic evaluation.

5.1.4 Adverse events

The manufacturer assumed no difference in treatment-related adverse events based on the evidence from the two non-inferiority trials, REAL-2[1] and ML17032.[2] The authors argued that, although capecitabine is associated with more hand-foot syndrome than 5-FU, it is easily treated at little cost with moisturizing cream. The manufacturer also highlighted that there may be risk of infection and thrombus formation with infusion of 5-FU, which could have significant health and cost implications, though they did not base this on statistically significant evidence from the trials. Excluding such considerations favours capecitabine.

5.1.5 Health related QoL

Evidence on health related QoL was not included in the base case economic evaluation as the manufacturer conducted a CMA. A simple QALY threshold analysis was conducted. See Section 5.1.6 for details.

5.1.6 Resources and costs

Resource utilisation and costs were presented for each of the 6 regimens.

The cost categories included were drug acquisition costs and drug administration costs which are discussed in more detail below.

5.1.6.1 Drug acquisition costs

The calculation of drug acquisition costs was based on the recommended adult dose and an assumption of no drug wastage in the use of vials. The drug utilisation was determined using assumptions about the dosing schedule, body surface area, dose intensity and the number of cycles. The dosing schedules were based on those used in the REAL-2[1] and ML17032[2] trials. The schedules are detailed in Table 10 and Table 11.

Table 10: Dosing schedules for the drug regimens in the REAL-2[1] and ML17032[2] trials. Adapted from Tables 20-22, (MS pp69-70).

Regimen	Epirubicin dose and frequency	Cisplatin dose and frequency	Oxaliplatin 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
EOF	50mg/m^2 Day 1 of each 21 day-cycle		130mg/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
EOX				Day 1-21. Oral capecitabine 625mg/m^2 twice per day for all 21 days of each cycle
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

The ERG sought clarification from the manufacturer about how drug utilisation was calculated. The manufacturer clarified that the dose intensity was

calculated on the basis of the actual drug utilisation figures from the REAL-2 trial as a percentage of protocol doses. The same number of cycles was applied for each treatment regimen based on the mean number of 21 day cycles in the REAL-2 trial across all regimens. Average patient body surface area (BSA) was assumed to be 1.7m^2 which was justified by its use in other submissions to NICE.

The total drug utilisation calculations per regimen are presented in Table 11. The recommended dose and doses per cycle come from Table 10 and Table 11.

The drug unit costs were based on the average price per mg across all generic products available for a specific drug, as listed in the British National Formulary (BNF),[20] except for capecitabine, which was discounted by 10% due to Pharmaceutical Pricing Regulation Scheme (PPRS) price adjustments. The prices are listed in Table 12.

Table 11: Calculation of drug utilisation. Copied from Table 25 (MS, p71).

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**

Table 12: Unit cost price of evaluated drugs. Copied from Table 26 (MS, p72)

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

5.1.6.2 Drug administration costs

The drug administration schedules were based on the schedules in the REAL-2 and ML17032 trials. The activities and components costed are listed for each regimen in Table 13 along with the days from the start of treatment during which the costs are incurred. Significant assumptions are as follows:

- *Line insertion*. For treatment regimens that include IV 5-FU, a central venous access line is inserted before treatment begins. This central line remains in place until all cycles of this treatment have finished or until failure of the central line. The line insertion at the start of treatment was costed and patients were assumed not to stay overnight. The cost of replacement of any line insertion that has failed was not costed. This assumption favours IV 5-FU and is, therefore, conservative with respect to capecitabine.

- *Line extraction.* It was assumed that the central line extraction at the end of treatment would coincide with a routine visit, and was therefore not costed. This assumption favours IV 5-FU and is therefore conservative with respect to capecitabine.

- *Pharmacy preparation costs.* Only the preparation costs for 5-FU and capecitabine were included as the other preparations were considered to cost the same for both regimens in each CMA. The 5-FU preparation costs were assumed to be more than those for capecitabine based on an earlier publication that distinguished ‘complex’ and ‘simple’ preparations.[21]

- *Pump.* The pump for IV 5-FU was assumed to be replaced every 7 days and replaced and flushed by a nurse in outpatient care for the ECF and EOF regimens.

- *Drug delivery and hospital attendance*s. For all regimens it was assumed that all attendances were outpatient visits, even though for the CF regimen a proportion of patients are likely to have inpatient visits. This assumption favours IV 5-FU and is therefore conservative with respect to capecitabine.

Table 13: The activities costed for each treatment regimen and the days in each cycle during which the activity takes place. Based on Tables 32-35, (MS, pp79-81).

	Regimen Days at which the activity takes place from start of treatment in every cycle				
Activity/ component	**ECF & EOF**	**ECX & EOX**		**CF**	**CX**
Line insertion	D1[3]			D1[3]	
Drug delivery. 1st attendance. Output/day case	D1	D1		D1[1]	D1
Drug delivery. Subsequent attendances. Nurse cost to flush central line a change pump	D7,14				
Drug delivery. Subsequent attendances. Outpatient/day case				D2-4[1]	
Drug delivery. Inpatient stay 5 days				D1-5[2]	
Pump cost	D1,7,14				
Transport cost (20% of patients)	D1,7,14	D1		D1-5	
Pharmacy preparation:	D7,14 "Complex" (IV)	D1 "Simple" (oral)		D1-5 "Complex" (IV)	D1 "Simple" (oral)

Shaded cells indicate the activity was not costed for the regimen
[1] Base case activity; [2] Activity in scenario analysis, which replaces the other drug delivery activities; [3] Line insertion was only done at the start of the first cycle.

For all regimens, some visits were considered outpatient activity and some visits were considered day-case activity. An average cost was derived with weights based on patient numbers obtained from The National Schedule of Reference Costs 2007-08

(http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098945).

The costs of X-rays and minor disposables are assumed to be included in the average cost of a visit.

- *NHS Transport costs.* It was assumed that no transport costs were incurred for the CX regimen. The manufacturer did not provide an explanation for this. For the other regimens, it was assumed that 20% of patients in England and Wales were likely to require hospital transport.

- *Unit costs.* Unit costs were mostly taken from The National Schedule of Reference Costs 2007-08 (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098945). Exceptions were the pharmacy preparation costs quoted above and the cost of an ambulatory pump, which was obtained from a manufacturer's UK website (Baxter). The price year appeared to be 2007-08, although there was some inconsistency here. The total cost of each activity for each treatment regimen was calculated by multiplying the number of visits with the number of cycles with the relevant cost shown in Table 14.

Table 14: The activity cost, the number of times the activity takes place each cycle (number of visits to hospital), and the number of cycles. Based on Tables 32-35, pages 79-81, in the MS.

	Regimen Visits to hospital per cycle and the number of cycles					
Activity/ component	**ECF & EOF**	**ECX & EOX**		**CF**	**CX**	**Activity cost (£)**
Line insertion	Visits=1 Cycles=1			Visits=1 Cycles=1		445.77
Drug delivery. 1st attendance. Output/day case	Visits=1 Cycles=5.5	Visits=1 Cycles=5.5		Visits=1[1] Cycles=5.5	Visits=1 Cycles=5.5	281.45
Drug delivery. Subsequent attendances. Nurse cost to flush central line a change pump	Visits=2 Cycles=5.5					36.83
Drug delivery. Subsequent attendances. Outpatient/day case				Visits=3[1] Cycles=5.5		198.72
Drug delivery. Inpatient stay 5 days				Visits=1[2] Cycles=5.5		1,435.64
Pump cost	Visits=3 Cycles=5.5					38.50
Transport cost (20% of patients)	Visits=3 Cycles=5.5	Visits=1 Cycles=5.5		Visits=5 Cycles=5.5		28.43*20%
Pharmacy preparation:	Visits=3 Cycles=5.5 "Complex"	Visits=1 Cycles=5.5 "Simple"		Visits=5 Cycles=5.5 "Complex"	Visits=1 Cycles=5.5 "Simple"	Complex 41.87 Simple 25.34

Shaded cells indicate the activity was not costed for the regimen
[1] Base case activity; [2] Activity in scenario analysis, which replaces the other drug delivery activities

5.1.7 Discounting

No discounting was performed as the time horizon was less than one year.

5.1.8 Sensitivity analyses

Four types of sensitivity analyses were conducted.

- *One-way sensitivity analysis.* This varied each base case parameter value individually across ranges obtained from either published sources

or standard errors, based on nurse expert opinion or an assumption. A range of +/-20% was assumed for NHS Reference Costs.

- *Scenario analysis.* This was conducted to represent an alternative way to administer CF in clinical practice in England and Wales. In the base case, all patients were assumed to be treated as outpatients. In this scenario analysis, all 5 days of visits are inpatient visits. The increased costs are presented in Table 14.

- *Worst case analysis.* A worst case analysis was performed where the extreme values of the ranges for each parameter that favoured IV 5-FU were combined to assess the cost differences between 5-FU and capecitabine under this scenario.

- *QALY threshold analysis.* As a simple alternative to the CMA, a threshold analysis was conducted to explore the estimated incremental survival that would be necessary for IV 5-FU to be considered cost-effective at specified cost-effectiveness thresholds given its incremental cost. A utility value was multiplied with the additional PFS assumed for 5-FU to calculate additional QALYs. A utility value for the health state of PFS in aGC was taken from earlier publications.[14 22 23]

The manufacturer conducted the threshold analysis using formulas 1 and 2 below.

Formula 1. $\Delta E\ (QALYs) = \frac{\Delta C}{\lambda}$

Formula 2. $\Delta E\ (LYGs) = \frac{\Delta E\ (QALYs)}{0.73}$

Where:

ΔE = change in effectiveness, ΔC = change in cost
LYG = life years gained
$\Delta E(QALYs)$ = E(5-FU regimen) - E(Capecitabine regimen)
ΔC = C(5-FU regimen) - C(Capecitabine regimen) in the base case

λ = Cost-effectiveness threshold, £20,000/QALY or £30,000/QALY

0.73 = PFS health state utility value

5.1.9 Model validation

The MS states that the Excel model was checked by a Roche health economic modeller not previously employed in its development. This involved checking the completeness and feasibility of reported results compared to other published economic evaluations of the same indication; execution of selected extreme tests to check the plausibility of the model outcomes; and a review and confirmation of all the formulas in the model.

5.2 Critique of approach used

The ERG has assessed the manufacturer's economic evaluation using Drummond et al.'s checklist.[24] This is shown in Appendix 1. In Table 15, the methods used in the manufacturer's submission are compared to those detailed in the NICE reference case.[25]

Table 15: A consideration of the MS using a checklist based on NICE's reference case and other methodological recommendations.

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de-novo evaluation meets requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Yes	The comparisons ECF vs. ECX and EOF vs. EOX meet the requirements of the reference case. It is, however, unclear whether the comparison CF vs. CX represents current practice in the UK.
Type of economic evaluation	Cost-effectiveness analysis (CEA)	No	The reference case obliges the use of conventional CEA; nevertheless in the context of the current assessment the ERG deems cost-minimisation analysis (CMA) to be an appropriate framework with which to analyse the decision problem. CMA may be considered a form of CEA as long as the effects of the alternative treatments can reasonably be assumed to be equal.
Perspective on costs	NHS and PSS	Yes	NHS and PSS costs have been taken into account.
Perspective on outcomes	All health effects on individuals	NA	Although this item is not applicable for cost-minimisation studies, the decision to choose this method was based on all health effects on individuals (clinical effects and adverse events). The ERG thus considers the perspective on outcomes to comply with the reference case.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	The economic model has a time horizon of 5.5 chemotherapy cycles of 21 days per cycle. Given the use of CMA, all long term costs are assumed equivalent. The ERG thus considers this element to comply with the reference case.
Synthesis of evidence on outcomes	Systematic review	NA	Not applicable since CMA was used. However, the decision to conduct CMA was based on a systematic review of clinical evidence for effectiveness (see Section 4.1). Although data on adverse events were not based on a separate systematic review (see Section 4.1.2), the ERG considers the analyses to comply with the requirements established by the reference case.
Measure of health effects	QALYs	NA	Not applicable since CMA was used in the base case. A QALY threshold analysis was, however, conducted in sensitivity analysis.
Source of data for measurement of HRQL	Reported directly by patients and/or carers	NA	Not applicable since CMA was used. The value of utilities used in the threshold analysis could not be validated by the ERG from the references provided by the manufacturer.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	NA	Not applicable since CMA was used. The source of preference data used in the threshold analysis was, however, unclear.
Discount rate	Annual rate of 3.5% on both costs and health effects	No	Costs have not been discounted since the time horizon of the analysis is less than one year.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	NA	Not applicable since CMA was used.
Sensitivity analysis	Probabilistic sensitivity analysis	No	Probabilistic sensitivity analysis was not undertaken despite the fact that this is entirely feasible with CMA. Instead, a range of analyses was conducted, including one-way sensitivity analysis, scenario analyses, worst case analysis and incremental QALY threshold analysis.

Abbreviations: HRQL, health related QoL; NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years, NA, not applicable

5.2.1 Published cost-effectiveness studies

A systematic review was undertaken to identify published cost-effectiveness studies. The databases specified by NICE as a minimum for cost-effectiveness are: Medline, Embase, Medline in Process, EconLIT and NHS EED. The databases searched by the manufacturer were: Medline, Embase, Medline in Process, NHS EED, and Health Economic Evaluation Database. It appears that the manufacturer used an earlier version of the report template and hence one of the required resources, EconLIT, was not used. The database searches were conducted using the Datastar search interface and this is not accessible to the ERG. Consequently the ERG has not been able to reproduce and run the strategies to confirm that all potential studies have been identified.

A review of the strategies used highlighted an error in line 14 In the Medline search strategy where all the terms for gastric/stomach cancer have been combined. In line 1 stomach-neoplasms.de. has not been included in this combination and is not used at any other point in the strategy. The manufacturer was asked to clarify the impact of this omission. In their response they provided a report of the search with this omission rectified and reported that no additional studies were identified (see Appendix 2, p40). The search strategies used for NHS EED and HEED are briefly described and the results identified listed. The website searches of the NICE web pages, the Scottish Medicines Consortium and the International Society of Pharmacoeconomics & Outcomes Research are all summarised appropriately.

5.2.2 Comparators

Capecitabine is indicated for first-line treatment of aGC in combination with a platinum based regimen. The ERG's clinical advisors indicate that ECF/ECX, and EOF/EOX regimens reflect current clinical practice in NHS. In addition, the guidelines from European Society for Medical Oncology support the use of these regimens, in the above mentioned indication.[26]

As stated in Section 3.2, the comparison between CF and CX reflects the chemotherapy regimens used in the multinational ML17032 trial.[2] Clinical experts consulted by the ERG do not consider the doses and scheduling of the CF and CX regimens to represent current treatment patterns in the UK.

NICE's scope for this appraisal was set to compare capecitabine with 5-FU in combination with platinum based chemotherapy regimens. The ERG considers the pairwise comparisons between specific regimens including either capecitabine or 5-FU (ECF vs. ECX, EOF vs. EOX and CF vs. CX) to be appropriate.

5.2.3 Type of economic evaluation

5.2.3.1 Dealing with uncertainty

In the submission, the manufacturer undertakes a CMA. In CMA it is assumed that the effectiveness of the therapies under comparison is the same, and thus the choice between treatments depends only on their costs – the least costly being the most cost effective. However, conducting CMA is often inappropriate because expected (mean) effectiveness is estimated with uncertainty which has to be allowed for in the economic analysis.[27] When expected effectiveness is uncertain, it is important to assess whether this uncertainty impacts on decision uncertainty – and this is only achieved by performing a full cost-effectiveness analysis (including probabilistic sensitivity analysis). As argued by Claxton,[28] statistical significance is not relevant in economic evaluation. When the efficacy of a treatment is not statistically significantly different from alternative treatment(s), we can only state that there is not enough evidence to demonstrate the potential differences. Briggs and O'Brien,[27] however, suggest there is an exceptional situation where CMA may be appropriate: when effectiveness data are drawn from a non-inferiority or equivalence trial. This is the case for the manufacturer's evaluation of capecitabine, where a CMA approach was justified based on two non-inferiority trials, REAL-2[1] and ML17032.[2] As discussed in section 4.2 the clinical analysis of these trials, together with the meta-analysis that combines them,[3] suggests that capecitabine is at least as efficacious (in terms of overall survival) and as well tolerated as 5-FU based regimens.

The use of CMA may, therefore, be considered appropriate given the results of the two trials and of the meta-analysis. However, the manufacturer fails to comment explicitly on the uncertainty found around the estimates of efficacy despite the fact that treatments cannot be considered exactly equivalent given the uncertainty in estimating their effectiveness. In the two capecitabine trials, the null hypotheses of non-inferiority of the capecitabine regimen was considered rejected if the upper limit of the 95% CI was more than 1.25 for the PFS hazard ratio (ML17032) (revised analysis with reduced power, see Section 4.1.7), and more than 1.23 for the OS hazard ratio (REAL-2). In both studies the non-inferiority of capecitabine was considered proven. However, the adjusted 95% confidence intervals for the hazard ratios crossed 1.0 which means that there is a small but non-zero probability of capecitabine being less effective than 5-FU-based regimens. A full cost-effectiveness analysis and probabilistic sensitivity analysis would have quantified the probability that capecitabine was less effective and less cost-effective than its comparators.

Although there is a small probability that capecitabine is clinically inferior to 5-FU based regimens (in terms of overall survival), there is a greater probability that it is superior. The manufacturer presented the results of an IPD meta-analysis on the efficacy of capecitabine in prolonging overall survival, combining the results of these two trials.[3] Results of this analysis suggest that capecitabine is superior to 5-FU (Section 4.2.1). It should be noted, however, that the ERG was unable to assess the validity of the meta-analysis (see Section 4.1.7). Hence, although a CMA assumes *identical* effectiveness between the therapies under comparison, the meta-analysis suggests that capecitabine may actually be more effective on average. When uncertainty is considered, there is non-zero probability that capecitabine is less effective but a greater probability that it is more effective.

It should be noted that the above arguments are based on the assumption that there is no difference in the incidence or severity of adverse events between capecitabine and 5-FU regimens. This will be further discussed in this Section 5.2.6.

In relation to costs, a full probabilistic sensitivity analysis was not performed so the probabilities that capecitabine is less and more costly than its comparators have not been formally quantified. However, the mean estimates, sensitivity analyses and worst case scenario suggest capecitabine has a lower mean cost than 5-FU-based regimens.

The issues related to the uncertainty over the expected incremental costs and effects of capecitabine are illustrated in the four cost-effectiveness planes (scenarios A to D) shown in Figure 1. The cost-effectiveness plane is divided in four quadrants:

Quadrant I. Capecitabine is more effective ($\Delta E>0$), and more costly ($\Delta C>0$) than 5-FU.

Quadrant II. Capecitabine is more effective ($\Delta E>0$), and less costly ($\Delta C<0$) than 5-FU. Capecitabine dominates 5-FU.

Quadrant III. Capecitabine is less effective ($\Delta E<0$), and less costly ($\Delta C<0$) than 5-FU.

Quadrant IV. Capecitabine is less effective ($\Delta E<0$), more costly ($\Delta C>0$) than 5-FU. 5-FU dominates capecitabine.

In Figure 1, scenario A represents the distribution of incremental effects reported in the meta-analysis and incremental costs reported in the manufacturer's submission. An ellipse represents the joint uncertainty of expected incremental costs and effects (effectively the uncertainty in cost-effectiveness). This scenario is based on the assumption that not only are mean costs lower and mean effects higher with capecitabine (i.e. based in quadrant II), but also that the 95% confidence intervals are located entirely in that quadrant. This is consistent with the results of the meta-analysis and, despite the absence of a probabilistic sensitivity analysis, of the cost analysis presented in the MS.

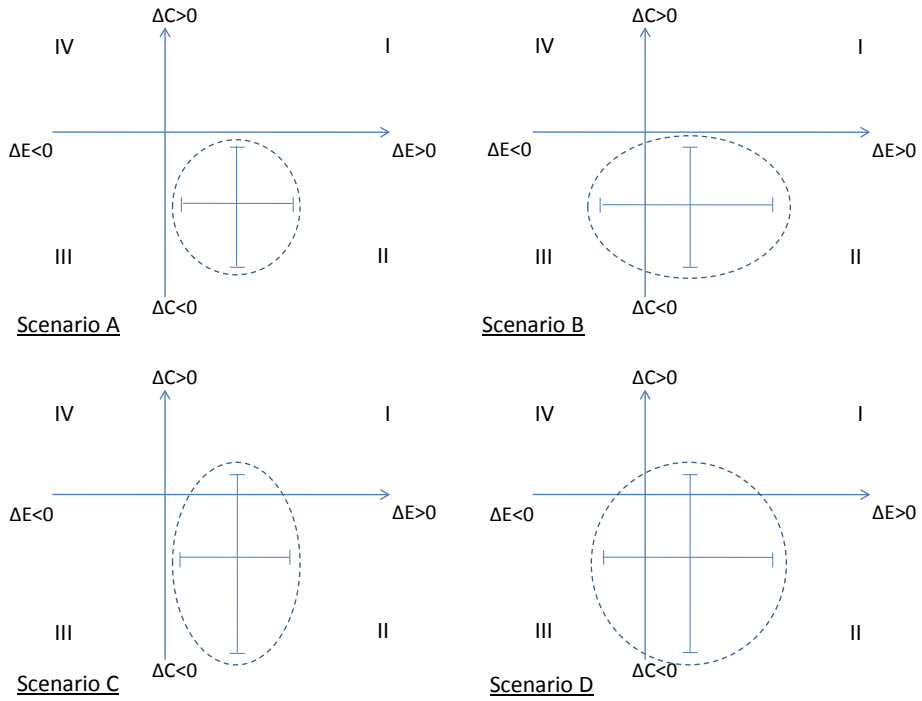

Figure 1: Hypothetical scenarios over the cost-effectiveness of capecitabine. Cost-effectiveness planes. Horizontal bars represent the confidence intervals for the effect difference between capecitabine and 5-FU. Vertical bars indicate hypothetical confidence intervals for incremental costs. The ellipses represent the 95% confidence ellipse for incremental cost and effectiveness estimates. The confidence ellipse is the two dimensional analogue of a confidence interval, used when considering two parameters simultaneously (costs and benefits in this case). Thus a 95% confidence ellipse may be defined as the joint 95% confidence region for two potentially correlated parameters.

However, three additional scenarios may also represent the uncertainty around costs and effects of capecitabine. These are depicted in Figure 1 (scenarios B to D).

Scenarios B and D represent a situation where there is some uncertainty in the superior effectiveness of capecitabine in relation to 5-FU. This situation may be consistent with the individual efficacy estimates from the two equivalence trials, rather than the meta-analysis. The 95% CI regarding the incremental efficacy of capecitabine crosses the y-axis, indicating there is some non-zero probability (higher than 5%) that capecitabine is less effective than 5-FU.

Scenarios C and D represent a situation where, there is more uncertainty over the fact that capecitabine is cost saving, meaning that that there is a non-zero probability that capecitabine is more costly than 5-FU (costs cross the x-axis).

The ERG presents this scenario because a full probabilistic analysis of the costs was not submitted by the manufacturer.

The aim of presenting these four scenarios (Figure 1) is to demonstrate that the appropriateness of CMA in a given situation does not solely rely on establishing whether a treatment has lower *mean* costs and equal or higher *mean* effects; the uncertainty in those mean estimates also matters. In using CMA, the MS interprets the evidence on capecitabine to establish the treatment in quadrant II. This interpretation presumes that capecitabine has a lower mean cost and higher mean effect than its comparators, and that there is a negligible probability that the opposite situations are true. This seems a reasonable interpretation if it is felt that the meta-analysis of the two trials represents the best characterisation of the clinical evidence, and that the sensitivity analyses and worst case scenario undertaken by the manufacturer reasonably demonstrate that the probability of capecitabine being a more costly intervention is negligible.

5.2.3.1 Costs of added survival with capecitabine

The conclusion from the meta-analysis that capecitabine has a greater mean survival duration (with a small probability of being inferior on this outcome) raises another consideration regarding the appropriateness of CMA. By prolonging survival, cost savings associated to capecitabine use may be offset (at least partially) by costs arising from the management of gastric cancer during the extension of survival duration. Such costs could include those of additional treatments and palliative care. In this case, scenario C in Figure 1 may be plausible. A full cost-effectiveness analysis would be expected to include the costs associated with additional life expectancy and to relate these to gains in QALYs, but the manufacturer fails to address this issue in the submission. The simple threshold analysis using QALYs included in the MS (p.87 of MS) addresses a quite different issue: if 5-FU based regimens are more costly than those using capecitabine, what would the additional effectiveness (in terms of QALYs) need to be for 5-FU to be cost-effective? Hence a full cost-effectiveness analysis may have been justified. However, if the inclusion of the costs of capecitabine associated with additional survival

duration resulted in a higher cost per QALY gained, this would be the result of further lines of treatment or later-stage palliative care having a high cost per QALY. Ethical issues are likely to be raised by the possible determination that capecitabine may not be cost-effective on the basis that treatments and care provided later in the course of aGC have costs per QALY gained above conventional thresholds.

The ERG asked the manufacturer for information on the costs associated with additional life expectancy. The additional analyses provided by the manufacturer are reported in Section 6.1.

Overall, therefore, the ERG considers the use of CMA in this submission to be reasonable. Although issues are raised about the implications of uncertainty in mean costs and effects of capecitabine, and about the additional costs incurred by the NHS resulting from additional survival duration, these are unlikely to have a material effect on decision making regarding the product.

5.2.4 Efficacy

As described in Sections 4.2.1 and 5.1.3, the manufacturer provides sufficient information on the non-inferiority of oral capecitabine compared to IV 5-FU to justify the use of CMA. Results of a meta-analysis were also appropriately considered. Issues regarding uncertainty over the efficacy estimates are discussed in Section 5.2.3.

5.2.5 Adverse events

The manufacturer assumes no differences in treatment-related adverse events between oral capecitabine and IV 5-FU. This assumption is based on the results of the two non-inferiority trials.[1 2] Since large sample sizes are needed to detect rare adverse effects, further relevant information about the safety profile of capecitabine (in the relevant dose) was requested from the manufacturer. However, no further information was provided (see Sections 3.4 and 4.2.1.3).

In Section 5.2.3 and in the MS it was assumed that all health effects (clinical efficacy and treatment-related adverse events) of the compared therapies are

equivalent. The manufacturer also assumed 5-FU related adverse events are at least as costly as capecitabine related adverse events making the analysis conservative for capecitabine. Based on discussions with clinical experts, this ERG considers this a reasonable assumption. However, following the ERG's request for additional information on adverse events, further analysis was presented by the manufacturer (see Section 6.1).

5.2.6 Health related QoL

Evidence on QoL from the REAL-2 trial is described in Sections 4.1.6 and 4.2.1.2 (Appendix 2 and MS, p44). This evidence was not used in the base case economic evaluation as the manufacturer conducted CMA. However, an incremental QALY threshold analysis was conducted (MS, p87), where a single utility estimate for PFS was used. The estimate was reported to have been derived from a BO18255 trial in aGC using the EQ-5D utility instrument, and assumes the value of 0.73.[14 22 23]

The value of utilities used in the threshold analysis could not be validated by the ERG from the references provided by the manufacturer. However, the manufacturer states this utility value to be the best available evidence although no systematic review of the literature seems to have been undertaken to support this. In addition, little information is provided on the methods used to derive the utility estimate, and no uncertainty around the single point estimate is reported. The appropriateness of QALY threshold analysis is further discussed in Section 5.2.9.

5.2.7 Resource utilisation and costs

In general, the ERG considers that the manufacturer has identified all the relevant cost categories: drug acquisition inputs and drug administration inputs. Routine monitoring costs were considered a part of the administration costs (MS, p63). This assumption was considered appropriate by the ERG's clinical advisors.

Regarding costing procedures, the following sections outline identified shortcomings, although the ERG does not expect these to significantly alter the conclusions of the analysis.

5.2.7.1 Drug acquisition inputs

Dosing of capecitabine. In the MS capecitabine was costed on a per milligram basis. The recommended dose for capecitabine in aGC is 625 mg/m^2. Assuming a body surface area of 1.7 m^2, a 1062.5 mg dose per administration is recommended. The manufacturer has used this recommended dose (1062.5 mg) when calculating costs. However, in practice, capecitabine is only available as 150 mg and 500 mg tablets, thus the dispensable dose would need to be rounded to match the available tablets. In this example, the dispensable dose per administration would be 1000 mg (2 x 500 mg tablet). The effects of costing on a per tablet basis are further explored by the ERG in Section 6.2.1.

Dosing of 5-FU. In the MS 5-FU was costed on a per milligram basis. This does not take into account possible wastage in vials. If wastage had been considered when costing 5-FU, the total costs of 5-FU regimens would be higher than currently reported in MS. This approach is conservative with respect to capecitabine.

According to the ML17032 trial, patients in the control arm (CF regimen) received 800 mg/m^2 per day of 5-FU as a continuous infusion. However, in the base case the cost calculations assumed that 1000 mg/m^2 of 5-FU were received. This assumption is not conservative and is further explored by the ERG in section 6.2.1.

Drug unit costs. In the MS, the unit costs for epirubicin, cisplatin and oxaliplatin were calculated by averaging the NHS list prices for available non-proprietary products (e.g. epirubicin 2 mg/ml, available vial sizes are 5 ml, 25 ml, 50 ml, and 100 ml). This was considered by the ERG not to be conservative with respect to capecitabine because it does not consider that the NHS is likely to prefer the cheapest product. This assumption affects the incremental analysis because, in the MS, intensities were assumed to differ between the alternative regimens. This assumption is further explored by the ERG in Section 6.2.1.

Dose intensity. In the MS, dose intensities are reported to be less than 100% in accordance with the REAL-2 trial. The ERG considers the possibility that, despite this, a full dose of capecitabine might have been dispensed and thus the cost of the full dose has been incurred. The manufacturer has clarified that intensities reported for capecitabine consider the actual amount utilised by the patients and argues that, despite this, no drug wastage occurs (Appendix 2). However, the ERG considers that there is a possibility of existing wastage in which case the manufacturer's cost analysis may underestimate the costs of capecitabine, thus being non conservative.

The ERG also notes that the number of treatment cycles was assumed common for each regimen and no significant differences in frequency and severity of adverse events are assumed. It would then seem to be consistent to assume common dose intensities between the regimens rather than to use the regimen specific estimates from REAL-2.

The ERG further explores these issues in Section 6.2.2.

Number of cycles. A mean number of 5.5 cycles was assumed in the CMA. This reflects the average number of cycles across all regimes in the REAL-2 trial. However, the ERG's clinical advisors suggest that, in the UK, the mean number of cycles is likely to be smaller than 5.5. This is because the maximum number of cycles patients received in the REAL-2 study was eight, but current practice in most centres in the UK is likely to consist of a maximum of six cycles. However, in the one-way sensitivity analysis (MS, pp83-85) the manufacturer varied the number of treatment cycles from 2.75 to 8.25 with limited implications for cost results. The ERG considers that this shows the conclusions to be robust to the number of cycles used.

In further information provided by the manufacturer, there is a consideration of the possibility of using the observed numbers of cycles for each arm as reported in the REAL-2 and ML17032 trials instead of the average across arms as used in their base case (Section 6.2.2). Further data on the uncertainty surrounding the mean number of cycles observed in each arm of the REAL 2 and ML17032 trials were not provided by the manufacturer.

Body surface area. Clinical advisors to the ERG considered the use of an average body surface area of 1.7m^2 to be appropriate. The effects of alternative estimates for body surface area have been appropriately evaluated in the manufacturer's sensitivity analysis (MS, pp83-85).

5.2.7.2 Drug Administration Inputs

Pharmacy costs. The pharmacy costs were assumed to be higher when dispensing IV 5-FU (defined as a "complex" preparation) than when dispensing oral capecitabine (defined as "simple" preparation). However, because of the risk of incorrect dosing, current NHS recommendations state that prescribing, dispensing and administering oral anti-cancer medicines should be carried out and monitored to the same standard as injected therapy.[29] The ERG considers it more plausible for pharmacy costs to be equivalent between 5-FU and capecitabine regimens.

Transport costs. As stated in Section 0, the drug administration cost for CX regimens do not include transport costs (MS, p92; Table 47). However, the transport costs are included in the drug administration costs for CF regimens (MS, p92; Table 46), and thus these should also be included for the first drug delivery attendance of the CX treatment cycle. The ERG considers this exclusion of transport costs for CX regimen to be non-conservative.

Hospital visits costs. The manufacturer has derived a weighted average cost of day case and outpatient based hospital visits for drug delivery by averaging national average cost figures by national data on the level of use of these two forms of hospitalisation (i.e. weighted average). The ERG's clinical advisors deem that, for infusion-based treatments, drug delivery is typically undertaken on a day case. Since drug delivery as a day case is more expensive than as an outpatient, the manufacturer's assumption is conservative.

5.2.8 Subgroup analysis

The ERG accepts the assumption that the capacity to benefit clinically from treatment will not differ for patients with different characteristics. However, patient characteristics may differentially affect incremental costs. The ERG considers that the number of delivered chemotherapy cycles may be affected

by different patient characteristics (e.g. severity of illness, or frailty of patients). Although clarifications on this were sought, no further information has been provided by the manufacturer.

In a one-way sensitivity analysis, the manufacturer varied the number of treatment cycles (MS, pp83-85) showing the cost savings with capecitabine to be robust. The ERG feels that this is likely to be adequate, but notes that it would have been informative to match the number of delivered treatment cycles to specific patient characteristics.

5.2.9 Sensitivity analysis

One-way sensitivity analysis. The ERG considers that, in isolation, one way sensitivity analysis is not an adequate method of handling parameter uncertainty. The appropriate method to handle parameter uncertainty would have been probabilistic sensitivity analysis (PSA), where the overall uncertainty in the results depends on jointly varying the uncertain parameters. However, one-way sensitivity analysis may be useful in identifying which parameters most substantially impact the results.

The manufacturer specified the ranges used in sensitivity analysis (MS, p84; Table 36) and in worst case analysis by either consulting nurse experts or by using assumptions. The ERG deems resource utilisation ranges to be appropriate. It is the ERG's opinion that the ranges regarding unit costs would more appropriately have followed those reported in the NHS reference costs. The consequences of altering the ranges of unit costs are assessed in a revised worst case scenario analysis (Section 6.2).

Worst-case scenario analysis. The manufacturer justified the exclusion of PSA by citing the results of worst case sensitivity analysis where all the assumptions and estimates were set at their least favourable for capecitabine.

The ERG has not been able to reproduce the results of the worst case analysis (MS, p96; Table 52). Since the manufacturer did not include the worst case scenario analysis in their submitted electronic Excel file, the ERG was unable to revise the manufacturer's calculations. The ERG suspects that values reported in Table 38 (MS, p86) do not describe all of the parameter

estimates that were changed for the worst case analysis. However, the results of manufacturer's worst case scenario analysis are conservative with respect to capecitabine compared to those in the ERG's recalculation.

Scenario analysis. A scenario analysis representing an alternative way to administer the regimen CF was conducted by the manufacturer. However, clinical advisors to the ERG have suggested that the use of CF does not reflect the current practice patterns in the UK, in which case this analysis may be considered irrelevant.

Threshold analysis. The manufacturer's base case analysis was a CMA but a threshold analysis was also presented (see Section 5.1.8). In view of the efficacy evidence detailed in the manufacturer's submission, the ERG considers that the use of this simple threshold analysis cannot be justified. As discussed in Sections 1.2, 4.2 and 5.2.3, there is no evidence that mean effects are superior with 5-FU based regimens and the probability of such a result is likely to be small. In which case modelling a scenario where 5-FU is more effective is unlikely to be relevant to the determination of capecitabine's cost-effectiveness. As discussed in Section 5.2.3, a more meaningful sensitivity analysis using a full cost-effectiveness framework would have been to explore the implications of the costs of managing patients during the additional period of survival that the meta-analysis suggests would be generated by capecitabine. The ERG asked the manufacturer for information on the costs associated with additional life expectancy (see Section 6.1.3).

5.3 Results included in manufacturer's submission

The results of the CMA are presented in the MS (pp88-98). Table 16 summarises the results from the base case and worst case scenario analysis. The results of the base case show that capecitabine regimens are cost-saving compared to their equivalent IV 5-FU based regimens. In addition, capecitabine remains cost saving in the worst case scenario analysis (MS, p86; Table 38).

Table 16: Summary results of the base case and worst case scenario analysis based on the manufacturer's submission. Estimates are expected costs per patient.

Regimen	*Costs of capecitabine based regimen*	*Costs of 5-FU based regimen*	*Incremental costs*
Base case			
ECX vs. ECF	£3,645.86	£5,265.72	-£1,619.86
EOX vs. EOF	£6,728.74	£8,300.57	-£1,571.84
CX vs. CF	£3,242.08	£7,452.36	-£4,210.29
Worst case scenario			
ECX vs. ECF	£2,299.85	£2,373.63	-£73.78
EOX vs. EOF	£4,611.76	£4,652.30	-£40.54
CX vs. CF	£1,942.02	£3,116.56	-£1,174.53

The manufacturer reports a range of one-way sensitivity analyses (MS, p94; Tables 36 and 49), which suggest that the conclusions of the analysis are not sensitive to changes in any particular parameter.

The results of the threshold analysis (MS, p97) indicate that, given the incremental costs of 5-FU based regimens (ECF, EOF, and CF) reported in the base case analysis (£1,620-£4,210), these regimens would have to provide incremental QALYs of 0.081 - 0.211 and 0.054 – 0.140, to be considered cost-effective at thresholds of £20,000, and £30,000 respectively. Assuming a constant utility value of 0.73 for the PFS period, this translates to 0.111-0.288 and 0.074-0.192 incremental life years, respectively.

In addition, the manufacturer reports scenario analyses which replace the costs of outpatient visits with those of inpatient visits for the CF regimen administration (MS, p96; Tables 50-51). In this scenario the cost savings per patient realised by using CX rather than CF is £6,708.63.

5.4 Comment on validity of results presented with reference to methodology used

The manufacturer's results indicate that the use of oral capecitabine instead of IV 5-FU results in overall savings to the NHS. The validity of the methodology adopted by the manufacturer, a CMA, is subject to a number of considerations, outlined in Section 5.2.2. The reference case obliges the use of cost effectiveness analysis; nevertheless in the context of the current

assessment the ERG considers CMA to be an appropriate framework with which to analyse the decision problem.

5.5 Summary of uncertainties and issues

A number of potential uncertainties are identified and described in Section 5.2, and summarised in Table 17. However, the results in the MS seem broadly valid. The ERG expects the remaining uncertainties and shortcomings of the analysis to have little impact on the results, but further explores these in Section 6. Further validation of the analysis did not change the conclusion of the analysis.

Table 17: Summary of uncertainties and issues identified in Section 5.2

Topic, uncertainty or issue	*Likely consequences for the results and conclusions*	*Additional analysis by manufacturer*	*Additional analysis by ERG*
5.2.2 Comparators			
Clinical experts consulted by the ERG do not consider CF and CX regimens to represent current practice in UK.	None	None	None
5.2.3 Type of economic evaluation			
Although the reference case defines the need for cost-effectiveness analysis, the manufacturer presented a CMA.	None, the ERG agrees that CMA is applicable	Yes (Section 6.1.3)	Yes (Section 6.2.3)
5.2.4 Efficacy			
No issues identified	-	-	-
5.2.5 Adverse events Treatment-related adverse events for 5-FU were assumed at least as costly as for capecitabine. The overall incidence and severity of adverse events was also assumed equal.	Unknown	Yes (Section 6.2.1)	None
5.2.6 Health related QoL Source of utility estimate and preference weights could not be validated.	None for CMA, but unknown for threshold analyses	No	Yes (Section 6.2.3)
5.2.7 Resource utilisation and costs			
5.2.7.1 Drug acquisition inputs			
*Dosing of capecit*abine: capecitabine was costed on a per mg basis	Minor	None	Yes (Section 6.2.1)
Drug unit costs: The cost/mg for epirubicin, cisplatin and oxaliplatin was calculated by averaging the NHS list prices of non-proprietary products	Minor, not conservative to capecitabine	None	Yes (Section 6.2.1)
Dose intensity: Dose intensity of 100% was not considered for capecitabine	Minor, not conservative to capecitabine	Yes (Section 6.1.2)	Yes (Section 6.2.2)
Dose intensities were assumed to vary between regimens	Minor	None	Yes (Section 6.2.2)
Number of cycles: Number of treatment cycles was assumed common for each regimen	Minor	Yes (Section 6.1.2)	Yes (Section 6.2.2)
The average number of treatment cycles is likely to be smaller than 5.5	Minor, see manufacturer's sensitivity analysis	None	None
5.2.7.2 Drug administration inputs			
Pharmacy costs: Pharmacy costs with capecitabine were considered a "simple" preparation	Minor, not conservative to capecitabine	None	Yes (Section 6.2.1)
Transport costs: The drug administration cost for CX regimens do not include transport costs	Minor, not conservative to capecitabine	None	Yes (Section 6.2.2)
Hospital visits costs: Infusion-based drugs are more likely to be delivered as a day-case than as an outpatient visit.	Minor, conservative to capecitabine	None	None
5.2.9 Sensitivity analysis			
Worst-case scenario analysis: ERG was not able to reproduce the results from the worst-case scenario analysis	Unknown	None	Yes (Section 6.2.2)
Threshold analysis: The usefulness of the QALY threshold analysis is limited	Not relevant	Yes (Section 6.1.3)	Yes (Section 6.2.3)

6 Additional work undertaken by the manufacturer and by the ERG

In response to the ERG's request for clarifications, the manufacturer presented a new set of scenario analyses. These are described in Section 6.1.

However, there are some possible limitations to the analyses and, for this reason, the ERG has explored several revisions to the base case. Also, additional scenario analyses and a worst case analysis were carried out, expanding on the revised base case. Furthermore, although the ERG accepts that a CMA is an appropriate format of analysis for this decision problem, we have also assessed the implications of any additional costs associated with capecitabine extending patients' expected survival duration (Section 6.2).

6.1 Additional analysis undertaken by the manufacturer

As reported in Section 5.1, the ERG requested clarification on a number of points related to the manufacturer's economic evaluation. The replies from the manufacturer are presented in Appendix 2. Additional economic analyses undertaken by the manufacturer are summarised below.

6.1.1 Adverse events

The manufacturer identified the main grade 3 and 4 adverse events with higher incremental frequency than 3% between capecitabine and 5-FU regimens (Appendix 2, pp33-35). The ML17032 and REAL-2 studies only reported incremental frequencies higher than 3% for stomatitis, neutropenia and hand-foot syndrome. However, these differences are only statistically significant for neutropenia and hand-foot syndrome (see Section 4.2.1.3).

The manufacturer states that the difference in the costs of treating these adverse events are minimal (ranging from £0.84 to £9.36) between capecitabine and 5-FU regimens (Appendix 2, p35), and do not affect the conclusion of the economic analysis.

However, as stated in Section 4.1.6 and in Section 5.2.5, the manufacturer has not provided additional safety data, as requested by the ERG, and thus rare adverse events may not have been identified due to the large sample sizes needed to detect these. Thus the ERG believes that some uncertainty remains in the treatment-related adverse events between capecitabine and 5-FU regimens.

6.1.2 Drug acquisition inputs

Dose intensity. The manufacturer provided additional analyses where dose intensity of 100% is assumed for all regimens (Appendix 2, p31). However, as stated in Section 5.2.7.1, the ERG feels that a more conservative approach would have been to consider the dose intensity of 100% just for capecitabine. Further analysis conducted by the ERG is reported in Section 6.2.2.

Number of cycles. Table 18 reports the results of the additional analysis (Appendix 2, pp12-13) using the observed number of cycles for each arm as reported in REAL-2 and ML17032 studies (ECF: 5.24, ECX: 5.76, EOF: 5.44, EOX: 5.42, CF: 4.43, CX: 5.14) instead of the average 5.5 cycles across arms. In Table 18 the results of the manufacturer's additional analysis are compared to the results of the manufacturer's base case (reported in Section 5.3). The table indicates that base case finding of cost savings for capecitabine is robust to this change of assumption.

Table 18: Summary of results of the manufacturer's additional analysis using observed number of cycles compared to manufacturer's base case analysis using mean number of cycles

	Additional analysis (observed number of cycles)			*Base case (mean number of cycles)*
Regimen	*Costs of capecitabine based regimen*	*Costs of 5-FU based regimen*	*Incremental costs*	*Incremental costs*
ECX vs. ECF	£3,712	£5,038	-£1,326	-£1,619.86
EOX vs. EOF	£6,631	£8,092	-£1,461	-£1,571.84
CX vs. CF	£3,030	£6,089	-£3,059	-£4,210.29

6.1.3 Cost of additional survival

In the additional analysis presented, the manufacturer acknowledged that costs are likely to be incurred during the additional survival period for patients on capecitabine-based therapies.

Based on the results reported in the meta-analysis,[3] the manufacturer has estimated that capecitabine based regimens provide an additional 0.141 years (1.69 months) of survival time compared to 5-FU based regimens (Appendix 2, pp25-28). Since the result of the meta-analysis indicates that there is no significant difference in PFS between capecitabine and 5-FU based regimens, the manufacturer assumes that additional survival is spent in a progressed health state.

In order to calculate the cost of additional survival in a progressed health state, the manufacturer reports a range of values from recent advanced cancer publications (Appendix 2, p29). A progressive disease cost estimate of £542/month (calculated based on advanced breast cancer guidelines) is used to calculate the cost of additional survival (£524/month x 1.69 months = £917). Given that this estimated cost of additional survival with capecitabine is less than the estimated cost savings from using the drug rather than 5-FU based regimes, the manufacturers conclude that this sensitivity analysis shows the base case conclusions to be robust.

6.2 Additional analysis undertaken by the ERG

6.2.1 Revised base case

Limitations to the costing methods in the manufacturer's base case were identified above (Section 5.2.5). Although the ERG expects such limitations to have little impact on the main conclusions of the analysis, the base case was revisited according to drug use and unit costs of treatments, and pharmacy drug preparation costs. The changes undertaken by the ERG to the manufacturer's base case are itemised below. The impact of these individual changes is evaluated within each item. The overall results, obtained when implementing all the changes listed, are also presented.

6.2.1.1 Dosing of capecitabine

As explained in Section 5.2.5.1, the manufacturer has costed capecitabine on a per mg basis. The ERG considers it more appropriate to calculate the acquisition cost of this drug on a per tablet basis.

In Table 19 the ERG has thus calculated the costs per administration of capecitabine for the recommended dose in each regimen (full dose). Considering a BSA of 1.7 m^2, a patient should receive 1062.5 mg of capecitabine per administration (ECX and EOX regimen). However, because capecitabine is only available in tablets of 500 and 150 mg, it has been assumed that the dose of capecitabine dispensed was the recommended dose per administration rounded to the nearest possible combination of 500 and 150 mg tablets (the available doses of capecitabine). In this case, patients would receive 1000 mg of capecitabine per administration (2 tablets of 500 mg) and this would cost £4.43. Calculations of costs were based on the least costly combination of tablets.

However, clinical advisors to the ERG indicated that, in practice, the capecitabine dose may be reduced due to, for example, toxicity related to the treatment. In this case, fixed reductions to 75 or 50% of the full dose are recommended (MS, Appendix 1). The cost per administration of capecitabine for patients receiving a 75% and 50% reduced dose is, £3.55 and £2.21, respectively (relating to a dispensable dose of 800 mg and 500 mg in ECX and EOX regimens, see Table 19). These costs were calculated in the same way as for a full dose.

Table 19: Administered doses and related costs of capecitabine tablets (costing conducted on a per tablet basis). Scenarios where patients are receiving the recommended dose per regimen (full dose), or reduced doses of capecitabine were considered in the calculations. Two possibilities of dose reduction are considered: 75% and 50% reduction of the recommended dose (per m^2).

	Regimen		
	ECX	**EOX**	**CX**
Full dose			
Dose in mg per m^2	625	625	1000
Dose in mg per administration*	1062.5	1062.5	1700
Dispensable dose in mg per administration +	1000	1000	1650
Number of 500 mg tablets‡	2	2	3
Number of 150 mg tablets¥	0	0	1
Cost per administration of capecitabine	£4.43	£4.43	£7.31
Reduced dose (75% of the full dose)			
Dose in mg per m^2	468.8	468.8	750
Dose in mg per administration *	796.9	796.9	1275
Dispensable dose in mg per administration	800	800	1300
Number of 500 mg tablets	1	1	2
Number of 150 mg tablets	2	2	2
Cost per administration of capecitabine	£3.55	£3.55	£5.76
Reduced dose (50% of the full dose)			
Dose in mg per m^2	312.5	312.5	500
Dose in mg per administration *	531.25	531.25	850
Dispensable dose in mg per administration	500	500	800
Number of 500 mg tablets	1	1	1
Number of 150 mg tablets	0	0	2
Cost per administration of capecitabine	£2.21	£2.21	£3.55

* Calculated assuming 1.7 m^3 of body surface area,
+ Rounded up to the nearest possible dose
‡Unit cost capecitabine 500mg: £40.02/120 tablets = £2.2129/tablet
¥Unit cost capecitabine 150mg: £40.02/60 tablets = £0.667/tablet

Because some patients may receive a full dose and others a reduced dose, the average dose of capecitabine received (across all patients) is smaller than the recommended dose. The dose intensities (the amount of drug delivered per unit of time) reported in the REAL-2 trial reflect this fact. The ERG has therefore used these intensities to estimate the proportion of patients receiving a reduced dose, *p,* by using the formulas below.

$$\text{Intensity} = \frac{\text{Average dose}}{\text{Full dose}}$$

$$\text{Average dose} = \text{Full dose} \times (1 - p) + \text{Reduced dose} \times p$$

With the available data, this analysis needs to assume that the dose is reduced to either 75% or 50% of the full dose, although in practice there may be patients with a 75% dose reduction and others with a 50% dose reduction.

The estimated proportion of patients receiving a reduced dose is shown in Table 20. The proportion of patients to have had the capecitabine dose reduced by 25% (in relation to the full dose) is estimated to be 58% for patients receiving the ECX regimen and 59.5% for patients receiving the EOX regimen. If doses were reduced by 50%, to observe the intensities expressed in the table, approximately 23% of patients would have had a dose reduction.

In the REAL-2 trial, the proportion of patients undergoing at least one dose reduction of one of the drugs in the regimen was observed to be between 35 and 42% across the arms of the trial (ECF: 35%; ECX: 40%; EOF:, 39%; EOX: 42%).[1]

By knowing the proportion of patients with a dose reduction, the calculation of an average cost per administration (see formula below) and the costs of capecitabine for 5.5 cycles can be performed as follows:

Average cost per adminstration

$$= \text{cost per administration}_{\text{Full dose}} \times (1 - p)$$

$$+ \text{Cost per administration}_{\text{Reduced dose}} \times p$$

When comparing these re-estimated total costs per cycle with those presented in the manufacturer's base case, the differences are not significant. The costs of capecitabine (used within the ECX regimen) are estimated to be £962.56 when costings are per mg (Table 19). When instead a per tablet calculation is performed, the estimated costs of capecitabine are lower (£903.79, Table 19). This is mainly because the dose per administration dispensed in tablets is, in most occasions, rounded downwards in relation to the dose in mg (Table 19).

Table 20: Total costs of capecitabine per regimen of 5.5 cycles. Calculations undertaken by the ERG were attained by costing capecitabine on a per tablet basis. These calculations are based on an average cost per administration, considering the possibility that a proportion of patients may receive a reduced dose of either 75% or 50% (in relation to the full dose). The proportion of patients receiving a reduced dose was estimated from the intensities observed in the REAL-2 trial. Calculations undertaken by the manufacturer were on a per mg basis, and considered directly the intensities observed in the REAL-2 trial.

		Regimen		
		ECX	EOX	CX
Costing per tablet	**Costing per tablet (ERG revised calculations)**			
	Based on the recommended dose			
	Intensity	100.00 %	100.00 %	100.00 %
	Estimated proportion of patients receiving reduced dose, *p* *	0.00%	0.00%	0.00%
	Average cost per administration	£4.43	£4.43	£7.31
	Cost of capecitabine for 5.5 cycles	£1,022.38	£1,022.38	£1,125.11
	Based on the possibility of having a 25% dose reduction			
	Intensity	88.40%	88.10%	100.00%
	Estimated proportion of patients receiving reduced dose , *p* *	58.00%	59.50%	0.00%
	Average cost per administration	£3.92	£3.90	£7.31
	Cost of capecitabine for 5.5 cycles	£904.63	£901.59	£1,125.11
	Based on the possibility of having a 50% dose reduction			
	Intensity	88.40%	88.10%	100.00%
	Estimated proportion of patients receiving reduced dose , *p* *	23.20%	23.80%	0.00%
	Average cost per administration	£3.91	£3.90	£7.31
	Cost of capecitabine for 5.5 cycles	£903.79	£900.72	£1,125.11
Costing per mg	**Costing per mg (MS calculations)**			
	Intensity	88.40%	88.10%	100.00%
	Cost of capecitabine for 5.5 cycles	£962.56	£959.30	£1,161.46

* Proportion of patients using a reduced dose were estimated from the intensities observed in the REAL 2 trial

6.2.1.2 Dosing of 5-FU in the CF regimen

As stated in Section 5.1.7.1, the dose of 5-FU in the CF regimen was not correctly calculated. When the dose assumed in the calculations was changed from 1000 to 800 mg/m^2 the costs per cycle associated to the CF regimen

changed from £871.97 to £776.22. Consequently, the incremental drug acquisition cost of CX compared to CF changes from £682.74 to £778.49.

6.2.1.3 Drug unit costs

The ERG has costed each individual treatment by assuming the costs (£/mg) of the product that has the minimum price per mg. This is not relevant for 5-FU as all products have the same price per mg.

Table 21: Manufacturer and ERG revised unit acquisition costs assumed in the base case regarding treatments other than capecitabine. Calculations were undertaken by the ERG by costing these treatments using the minimum cost for non-proprietary products and by the manufacturer using the average cost for non-proprietary products.

	Base case		
	Manufacturer	*ERG's revised*	*Description of products with minimum price*
Drug Name	*£/mg*	*£/mg*	
Fluorouracil	£0.0128	£0.0128	Non-proprietary, Injection, any product *
Cisplatin	£0.5257	£0.4900	Non-proprietary, Solution for injection, 1 mg/mL, 50 mL/vial, price £24.50
Epirubicin	£1.6605	£1.5447	Non-proprietary, Solution for injection, 2 mg/mL, 100 mL/vial, price £308.93
Oxaliplatin	£2.9975	£2.9950	Non-proprietary, Solution for injection, 1 mg/mL, 100 mL/vial, price £299.50

* All fluorouracil formulations have the same price per mg

In Table 22, we evaluate the impact of the changes made to the manufacturer's estimates by comparing total acquisition costs of 5-FU based regimens in the MS and the ERG's revised calculations. The total costs do not vary significantly.

Table 22: Total acquisition costs assumed for regimens excluding capecitabine. Calculations undertaken by the ERG by costing treatments other than capecitabine using the minimum cost for non-proprietary products and by the manufacturer using the average cost for non-proprietary products.

	Acquisition costs	
regimen	*MS*	*ERG's revised*
ECF	£1,446.84	£1,378.14
EOF	£4,481.69	£4,428.56
CF	£871.97	£845.24

6.2.1.4 Pharmacy costs

Current NHS recommendations mean that the pharmacy costs of dispensing oral capecitabine are equivalent to those of dispensing an IV solution, such as 5-FU (see Section 5.2.7.2). In the revised base case the distinction between

simple and complex preparations was eliminated. The pharmacy costs regarding "complex" preparations were assumed for both 5-FU and capecitabine.

Table 23: Total administration costs assumed for regimens. Calculations undertaken by the manufacturer considering pharmacy costs for IV products as 'complex' and capecitabine as 'simple' costs and by the ERG by considering costs with both as 'complex'.

	Administration costs	
regimen	*MS*	*ERG's revised*
ECF and ECX		
ECF	£3,818.88	£3,818.88
ECX	£1,718.64	£1,809.56
EOF and EOX		
EOF	£3,818.88	£3,818.88
EOX	£1,718.64	£1,809.56
CF and CX		
CF	£6,580.39	£6,580.39
CX	£1,687.36	£1,778.28

6.2.1.5 Overall results of the ERG's base case

A summary of the overall changes undertaken by the ERG to the base case is shown in Table 24.

Table 24: Comparison of the values used in the base cases produced by the manufacturer and by the ERG. The base case produced by the ERG revised the dosing of capecitabine and 5-FU, drug unit costs and pharmacy costings.

Model variable	*Manufacturer's base case*	*ERG's revised base case*
Drug costs		
ECF and ECX		
ECF per cycle	£263.06	£250.57
ECX per cycle	£350.40	£327.73
EOF and EOX		
EOF per cycle	£814.85	£805.19
EOX per cycle	£910.93	£890.88
CF and CX		
CF per cycle	£158.54	£136.27
CX per cycle	£282.67	£271.21
Drug administration costs		
Pharmacy costs for capecitabine	£25.34	£41.87

The revised results for the base case (Table 25) suggest only slight reductions in cost savings when 5-FU is replaced by capecitabine in chemotherapy regimens.

Table 25: Results regarding acquisition costs, administration costs and total costs (acquisition plus administration costs) for each of the relevant regimens. Results are as reported in the MS and as obtained from the ERG's revision of the base case. The results produced by the ERG revised the dosing of capecitabine and 5-FU, drug unit costs and pharmacy costings.

	MS			*ERG revised analysis*		
Regimen	**Acquisition cost**	**Administration cost**	**Total cost**	**Acquisition cost**	**Administration cost**	**Total cost**
ECF	£1,446.84	£3,818.88	£5,265.72	£1,378.14	£3,818.88	£5,197.02
ECX	£1,927.22	£1,718.64	£3,645.86	£1,802.49	£1,809.56	£3,612.05
ECX vs. ECF	**£480.38**	**-£2,100.24**	**-£1,619.86**	**£424.35**	**-£2,009.32**	**-£1,584.97**
EOF	£4,481.69	£3,818.88	£8,300.57	£4,428.56	£3,818.88	£8,247.43
EOX	£5,010.09	£1,718.64	£6,728.74	£4,899.85	£1,809.56	£6,709.41
EOX vs. EOF	**£528.40**	**-£2,100.24**	**-£1,571.84**	**£471.29**	**-£2,009.32**	**-£1,538.03**
CF	£871.97	£6,580.39	£7,452.36	£749.50	£6,580.39	£7,329.89
CX	£1,554.71	£1,687.36	£3,242.08	£1,491.63	£1,778.28	£3,269.91
CX vs. CF	**£682.74**	**-£4,893.03**	**-£4,210.29**	**£742.13**	**-£4,802.11**	**-£4,059.98**

6.2.2 Revised sensitivity analysis

The ERG undertook additional sensitivity analyses based on the revised base case. In Table 26 a brief description of each of the additional analyses performed is shown. Note that, for each scenario, only the parameters described are changed. The remaining parameters were set to the values assumed in the revised base case (results in Section 6.2.1.5).

Table 26: Specification of additional sensitivity analysis undertaken. Note that for each scenario, only the parameters described are changed. The remaining parameters were set up to the values assumed in the revised base case (results in section 6.2.1.5).

Scenario	*Parameter*	*Parameter value (changed in relation to the ERG's revisited base case)*	*Description*
1	Intensity for capecitabine	100%	Intensities may refer to administered instead of dispensed capecitabine. Dispensed capecitabine is assumed to correspond to the full dose (maximum wastage)
2	Intensity for all regimens assumed to be equal to average	90.24%	If the number of cycles was assumed constant for every regimen, and if no significant differences in AE are assumed, then the intensities should also have been assumed constant throughout the regimens (excludes CX and CF regimens)
3	Number of cycles	ECF: 5.24; ECX: 5.76; EOF: 5.45; EOX: 5.42; CF: 4.43; and CX: 5.14	Allowed to differ between three drug regimens, as reported in REAL-2 and ML17032 trials
4	Transport costs assumed for the first delivery of capecitabine in CX regimen	Reflects an increase of £5.69 (20% of £28.43) in administration costs for the CX regimen	Transport costs assumed for 20% of patients receiving a first delivery of capecitabine in CX regimen, as patients need to pick up their prescribed pills.

The results expressed in incremental costs obtained from these distinct analyses (Table 28) do not differ significantly from the revised base case. Additional analysis undertaken by the manufacturer included an analysis similar to scenario 3 (see Section 6.1.2 and Appendix 2, pp.12-14), but this was based on the manufacturer's base case and not the base case revised by the ERG.

The ERG has also conducted a worst case scenario based on the revised base case. This analysis was conducted according to Table 38 of the MS (MS p.86), but updating the values used for unit costs, as specified in Table 27.

Table 27: Differences regarding the values assumed in worst case analysis conducted by the manufacturer and ERG. Note that the worst case scenario analysis was specified in Table 38 of the MS (p 86). Parameters represented in the current table are only parameters for which the ERG has attributed different values.

Worst case scenario analysis	***MS***		***ERG revised analysis***	
	Value assumed	Source of data	Value assumed	Source of data
Central line insertion	£356.62	- 20%	£259.75	National Schedule of Reference Costs 2007-08 *
Drug delivery. Subsequent attendance. Outpatient or day care visit	£158.97	- 20%	£120.28	
Transport to hospital visit (return trip)	£22.75	- 20%	£20	

* The value assumed in ERG's revised analysis reflects the 25% percentile of between hospital variability in the costs of the relevant DRG.

Results regarding the revised worst case scenario analysis are also shown in Table 28.

Table 28: Results of the base case, additional scenario analysis (as specified in Table 26) and worst case scenario analysis. Results are as reported in the MS and as obtained from the ERG's revision.

	Incremental cost		
Analysis	*ECX vs. ECF*	*EOX vs. EOF*	*CX vs. CF*
ERG revised results			
Base case	-£1,584.97	-£1,538.03	-£4,059.98
Additional scenario 1	-£1,467.22	-£1,417.24	-£4,059.98
Additional scenario 2	-£1,538.62	-£1,538.62	-£4,059.98
Additional scenario 3	-£1,434.61	-£1,560.99	-£4,011.80
Additional scenario 4	-£1,584.97	-£1,538.03	-£4,048.61
Worst case scenario*	-£212.52	-£180.34	-£964.59
MS results			
Base case	-£1,619.86	-£1,571.84	-£4,210.29
Worst case scenario*	-£73.78	-£40.54	-£1,174.53

* The ERG was not able to replicate the worst case scenario analysis presented by the manufacturer, thus care must be taken when comparing results produced by the ERG's and manufacturer

6.2.3 Costs of extending survival

In the additional analysis presented, the manufacturer acknowledged that costs are likely to be incurred during the additional survival period for patients on capecitabine-based therapies. In the absence of costs of the extended survival in aGC, the manufacturer used estimates from other cancers which are thus uncertain. The ERG has therefore undertaken a threshold analysis, evaluating the maximum costs the NHS should be willing to pay for the extension of survival time given specified cost effectiveness thresholds.

Assume incremental costs can be split in two components, incremental costs associated with the treatment period, $\Delta C_{treatment\ period}$, and incremental costs related to extended survival, $\Delta C_{treatment\ survival}$. Costs associated with extended survival can be formulated as a function of known variables: incremental benefits,ΔE , incremental costs of the treatment period, and different levels of the cost-effectiveness threshold,λ

$$\Delta C_{treatment\ survival} < \Delta E \cdot \lambda - \Delta C_{treatment\ period}$$

By evaluating the above as an equality, the analysis estimates how high the costs of treatment and care in the extended survival period with capecitabine have to be to generate a cost per QALY gained at the threshold.

The values assumed and assumptions made to perform this analysis are listed in Table 29.

Table 29: Threshold analysis evaluating the costs of extending survival: input parameter values assumed

	Assumed values	*Description*
Cost effectiveness threshold, λ	£20,000 or £30,000	Assumption
Median survival	285 days	Meta analysis [3]
Hazard ratio capecitabine vs. 5-FU	0.87	Hazard ratio (overall survival) for the comparison of capecitabine and 5-FU in combination therapy of aGC [3]
ΔE	0.168 years	Calculations described in text. Calculations assume an exponential distribution to describe time to death.
Utility value for progression free survival	0.73	Manufacturer's assumption
$\Delta C_{treatment\ period}$		
ECX vs. ECF	-£1,584.97	Incremental costs for each regimen as calculated by the ERG (Table 25)
EOX vs. EOF	-£1,538.03	
CX vs. CF	-£4,059.98	

The effectiveness benefits were calculated by assuming the median overall survival time (285 days) for the comparator (5-FU based regimens) to inform the parameter of an exponential distribution describing time to death. The estimated mean survival time for 5-FU under such an assumption was 411 days (the parameter of the exponential distribution representing the daily hazard assumes the value of 0.002432). By applying directly the hazard ratio

for capecitabine (0.002432 x 0.87) we evaluate the parameter of another exponential distribution, now describing the time to death under capecitabine based regimens. By using these calculations, the mean time to death for capecitabine based regimens was estimated to be 473 days, and the incremental expected survival was estimated to be 0.168 years, 61.4 days. Total gains in QALYs associated with capecitabine regimens were estimated to be 0.123 QALY (assuming a utility value of 0.73).

The gains in life expectancy estimated by the ERG are similar to the ones estimated by the manufacturer (0.141 years, see Section 6.1.3)

The results of the threshold analysis are shown in Table 30. The costs of prolonging survival by 61.4 days must be below £3,996 (the minimum value in Table 30) for the treatment to be considered cost-effective, when assuming the cost-effectiveness threshold is £20,000 per QALY gained.

Table 30: Maximum values of costs associated with the extended survival (threshold analysis) to take the cost per QALY gained of capecitabine up to the specified cost effectiveness thresholds

	Maximum costs of extended survival, where effects are measured in QALY gains	
	$\lambda =$ **£20,000**	$\lambda =$ **£30,000**
ECX vs. ECF	£4,042.53	£5,271.30
EOX vs. EOF	£3,995.59	£5,224.36
CX vs. CF	£6,613.28	£7,842.05

There are, however, uncertainties regarding the adequacy of the utility value assumed (see Section 5.2.6). How the maximum costs associated with extended survival vary with the utility value (considering a threshold of £20,000 per QALY and the regimen EOX vs. EOF) is shown in Figure 2.

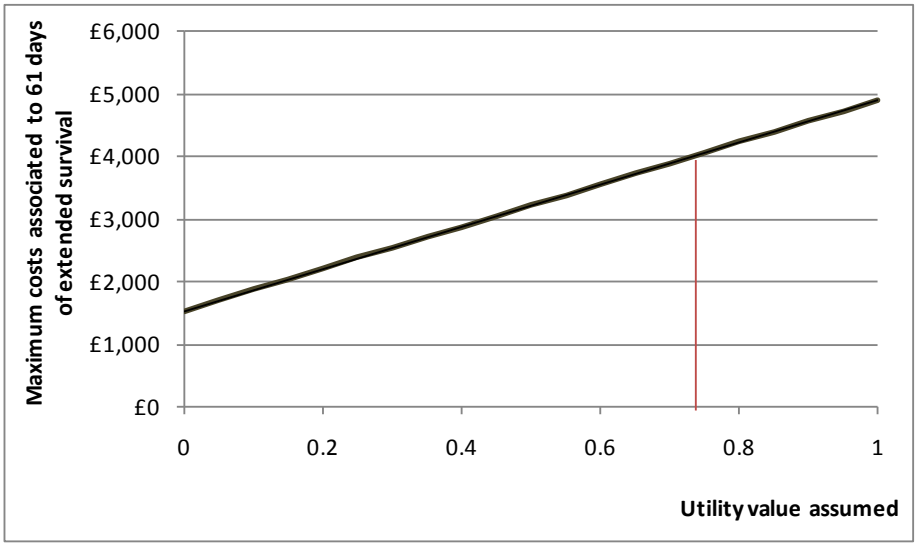

Figure 2: Maximum costs associated with extended survival as a function of the utility value assumed in the threshold analysis. The analysis regards the comparison EOX vs. EOF and considers a willingness to pay (WTP) of £20,000 per QALY gained

The highest estimate of costs associated with extension of survival (as presented by the manufacturer (Appendix 2, p.29; Table 9) is £600 per month. By having the life of a patient extended by 0.168 years, £1,212 is estimated to be incurred (0.168 x £600 x 12). The estimated costs of additional survival are much lower than any of the threshold costs in Table 29. However, the manufacturers' estimates of the cost of the additional survival period are not based on gastric cancer patients and may be under-estimates. The threshold costs in Table 29 are higher than the costs of receiving a capecitabine regimen during the additional survival period. The ERG's clinical advisors suggest that no more expensive pharmaceutical regimens are likely to be used after those considered in the main analysis. It would, therefore, seem unlikely that these threshold costs would ever actually be reached, suggesting that the manufacturers' analysis is robust to this area of uncertainty.

7 Discussion

7.1 Summary of clinical effectiveness issues

The MS presents the results of a systematic review of the literature. The methodology of the process was unclear and the procedures used had the

potential to increase bias and error. The inclusion criteria used had the potential to exclude relevant trials, but in practice did not appear to do so. The ERG has not identified any additional evidence relevant to the assessment of efficacy from completed trials, but has identified an ongoing study which meets the criteria of the scope; this trial would have been excluded by the manufacturer's inclusion criteria. It is unclear whether there is additional unrandomised evidence which would be relevant to the assessment of safety; the ERG requested that any such data be supplied but the manufacturer stated that they regarded the safety data from the two RCTs, in conjunction with the SPC as sufficient evidence.

The MS included two non-inferiority trials which compared capecitabine in combination with a platinum-based chemotherapy to 5-FU in combination with a platinum-based chemotherapy. It also included an IPD meta-analysis of the two trials.

The REAL-2 used the fluoropyrimidine and platinum agents in combination with epirubicin in schedules which are highly relevant to UK clinical practice. It should be noted that one of the platinum-based agents, oxaliplatin, was used outside of its licensed indication. This trial also included a majority of patients who were outside the licensed indication, and thus the scope. These patients, with advanced oesophageal or gastroesophageal junction cancer, were considered by the manufacturer to be identical to the licensed population in terms of clinical pathway, and no stratification of the analysis was undertaken. Whilst the ERG's clinical advisors agreed that these patients would receive identical treatment to those within the licensed indication, potential prognostic implications led the ERG to request that the efficacy data be broken down by cancer site. The forest plot supplied in response to this request did not indicate statistically significant differences in response associated with primary tumour site.

The ML17032 trial assessed capecitabine in combination with cisplatin. The regimens used in this trial were of limited relevance to UK clinical practice, and the population differed substantially from that seen in UK practice, being younger and of differing ethnic composition. This trial was also underpowered

when a non-inferiority margin of 1.25 was employed for the analyses rather than 1.40 as per protocol.

Both trials demonstrated non-inferiority of capecitabine to 5-FU on survival outcomes within the licensed indication and there was evidence from the pooled analysis that capecitabine has superior efficacy in terms of overall survival. The safety analyses indicated that there were some differences between the regimens; the significance of these was inconsistently reported. The ERG's clinical advisors considered that the most clinically significant difference was the statistically significantly higher incidence of diarrhoea in the EOX group compared to the ECF group in the REAL-2 trial. It should be noted that the analyses reported were pairwise comparisons which the trial was not powered to assess.

The MS provides convincing evidence of the non-inferiority of capecitabine, and some indication of potential superiority, in terms of survival and response outcomes. The safety analyses also indicated that the adverse event profiles were broadly comparable.

However, the nature of the technology is such that it would be expected to result in improvements in QoL relative to the existing treatment (5-FU). While the MS assessed appropriate outcomes, almost no QoL data were presented. This reflected the paucity of information in the published trial reports. The absence of data which convincingly demonstrate even non-inferiority was considered to constitute a serious weakness in the MS. This was partially addressed by the provision of further data from REAL-2 in response to the ERG's request that full details of the assessment conducted in REAL-2 be supplied, and that any extant data relating to ML17032 also be provided. This data showed few statistically significant differences between the groups at baseline or in changes from baseline scores at 12 and 24 week assessments (Appendix 2, pp43-44). The manufacturer clarified that ML17032 did not assess QoL (Appendix 2, p2).

7.2 Summary of cost effectiveness issues

Based on evidence regarding the efficacy and safety of capecitabine, the manufacturer conducted a CMA. The costs of capecitabine based regimens (ECX, EOX, CX) were compared to their equivalent 5-FU based regimens (ECF, EOF, CF, respectively) in the treatment of aGC, and the results of this analysis suggest that capecitabine regimens are cost-saving. Capecitabine remained cost saving in the manufacturer's one-way sensitivity analysis, scenario analysis and worst case analysis.

Areas of uncertainty relate to the assumptions of equal incidence and severity of adverse events, the utility associated with aGC patients, the costs of additional survival and the handling of parameter uncertainty. This is because the appropriateness of the economic evaluation method, CMA, is based on these assumptions.

7.3 Implications for research

There is clearly scope for more research on the impact of capecitabine compared with 5-FU on QoL. Lack of information about this outcome meant that the ERG was unable to assess whether the patient preference and QoL improvements associated with oral chemotherapy can be applied in this specific setting.

References

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Appendix 1: Drummond's check list for assessing economic evaluations

	Question	Response	Comment
1	**Was a well-defined question posed in answerable form?**	**Yes**	An overview of the decision problem is reported in manufacturer's submission (MS, p9, Table 1).
1.1	Did the study examine both costs and effects of the service(s) or programme(s)?	No	Although this item is not applicable for CMA, the decision to choose this method was based both on clinical effects and adverse events. The ERG thus considers the analyses to comply with the reference case.
1.2	Did the study involve a comparison of alternatives?	Yes	The study focussed on the following pair wise comparisons: ECF vs. ECX; EOF vs. EOX and CF vs.CX.
1.3	Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?	Yes	NHS and PSS costs have been taken into account
2	**Was a comprehensive description of the competing alternatives given (i.e. can you tell who did what to whom, where, and how often)?**	Yes	Further details in Sections 5.1 and 5.2.2.
2.1	Were there any important alternatives omitted?	No	Clinical experts contacted by the ERG validated the adequacy of the alternatives included.
2.2	Was (should) a do-nothing alternative be considered?	No	Clinical experts contacted by the ERG validated the inadequacy of a do-nothing alternative.
3	**Was the effectiveness of the programme or services established?**	Yes	The justification for the use of CMA was based on all evidence available for the clinical effectiveness of the interventions (see Sections 5.1.3, and 5.2.4).
3.1	Was this done through a randomised, controlled clinical trial? If so, did the trial protocol reflect what would happen in regular practice?	Yes	Evidence on effectiveness was drawn from two Phase III studies: the REAL-2 and the ML17032 trials. The REAL-2 trial was conducted in the UK and was designed to reflect clinical practice.
3.2	Was effectiveness established through an overview of clinical studies?	Yes	The manufacturer conducted a systematic review to retrieve relevant clinical evidence. The safety data was derived from the two phase studies REAL-2 and ML17032.
3.3	Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	No	
4	**Were all the important and relevant costs and consequences for each alternative identified?**	Yes	In general, the ERG considers that the manufacturer has identified all the relevant cost categories. Because a CMA was conducted, effects were not explicitly included in the base case analysis. However, the justification for the use of CMA was based on all evidence available for the clinical effectiveness, and on trial evidence for what regards adverse events. For further details see Sections 5.1.4 - 5.1.6, and 5.2.5 – 5.2.7.
4.1	Was the range wide enough for the research question at hand?	Yes	
4.2	Did it cover all relevant viewpoints? (Possible viewpoints include the community or social viewpoint, and those of patients and third-party payers. Other viewpoints may also be relevant depending upon the particular analysis.)	Yes	NHS and PSS costs have been taken into account
4.3	Were the capital costs, as well as operating costs, included?	Yes	The main source of unit costs used was the NHS reference costs, and these reflect capital and

			operating costs.
5	**Were costs and consequences measured accurately in appropriate physical units (e.g. hours of nursing time, number of physician visits, lost work-days, gained life years)?**	Yes	For further details see Section 5.1.6.
5.1	Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?	No	Efficacy and adverse events were assumed to be equivalent between capecitabine and 5-FU based regimens. The ERG considers all relevant cost categories to have been included in the evaluation. However, the cost consequences related to the possibility of capecitabine extending lifetime were not considered in this analysis. In response to the ERG's request the manufacturer provided an additional analysis on the expected costs of additional survival (see Section 6.1.3).
5.2	Were there any special circumstances (e.g., joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	No	
6	**Were the cost and consequences valued credibly?**	Yes	For further details see Section 5.1.6 and 5.2.7.
6.1	Were the sources of all values clearly identified? (Possible sources include market values, patient or client preferences and views, policy-makers' views and health professionals' judgements)	No	Drug unit costs and drug administration unit costs were clearly identified. The value of utilities used in the threshold analysis could not be validated by the ERG from the references provided by the manufacturer.
6.2	Were market values employed for changes involving resources gained or depleted?	Yes	
6.3	Where market values were absent (e.g. volunteer labour), or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?	NA	
6.4	Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type or types of analysis – cost-effectiveness, cost-benefit, cost-utility – been selected)?	Yes	Manufacturer provides sufficient data to justify the use of CMA (see Section 5.2.3).
7	**Were costs and consequences adjusted for differential timing?**	**No**	Costs and consequences have not been discounted since the time horizon of the analysis was less than one year. For further details see Section 5.1.7.
7.1	Were costs and consequences that occur in the future 'discounted' to their present values?	No	
7.2	Was there any justification given for the discount rate used?	NA	
8	**Was an incremental analysis of costs and consequences of alternatives performed?**	No	Since a cost-minimisation approach was used, incremental analyses were performed only on costs
8.1	Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits, or utilities generated?	No	Since a cost-minimisation approach was used, only incremental costs were of interest.

9	**Was allowance made for uncertainty in the estimates of costs and consequences?**	Yes	For further details see Section 5.1.8 and 5.2.9.
9.1	If data on costs and consequences were stochastic (randomly determined sequence of observations), were appropriate statistical analyses performed?	No	Neither an analysis of individual patient level data nor probabilistic sensitivity analysis was conducted.
9.2	If a sensitivity analysis was employed, was justification provided for the range of values (or for key study parameters)?	Yes	Justification for the ranges used in sensitivity analysis is provided. However, the manufacturer fails to state which ranges are based on expert opinion and which are assumptions.
9.3	Were the study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the confidence interval around the ratio of costs to consequences)?	No	
10	**Did the presentation and discussion of study results include all issues of concern to users?**	Yes	
10.1	Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?	No	Because CMA was used, only incremental costs were of interest.
10.2	Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?	Yes	One economic evaluation relevant to this decision problem was identified. This was Roche's 2007 submission to the SMC for capecitabine in this indication. The results reported are consistent with this submission of Roche.
10.3	Did the study discuss the generalisability of the results to other settings and patient/client groups?	No	The results apply to UK setting and patients with advanced inoperable gastric cancer. No subgroups of patients were considered.
10.4	Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or relevant ethical issues)?	Yes	In response to ERG's request the manufacturer provided analysis on costs of additional survival.
10.5	Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	Yes	The manufacturer reports an overview of the factors relevant to NHS and other parties (MS, p101-108)

ECF: 5-FU combined with epirubicin and cisplatin

ECX: Capecitabine combined with epirubicin and cisplatin

EOF: 5-FU combined with epirubicin and oxaliplatin

EOX: Capecitabine combined with epirubicin and oxaliplatin

CF: 5-FU combined with cisplatin

CX: capecitabine combined with cisplatin

MS: Manufacturer's submission

NHS: National Health Service

CMA – Cost minimisation analysis

PSS: Personal Social Services

SMC: Scottish Medicines Consortium

ERG: Evidence Review Group

Appendix 2: Manufacturer's response to letter of clarification

MS Bijal Joshi
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21 January 2010

Capecitabine for the treatment of advanced gastric cancer. **Clarification questions**

Dear Bijal,

Thank you very much for your Email dated 8th January 2010.

Please find below answers to the clarification questions raised regarding the use of capecitabine in advanced gastric cancer. Roche welcomes the opportunity to provide further clarification around our submission and would be pleased to answer any additional questions which might arise.

Best wishes.

Yours sincerely,

Section A: Clinical Effectiveness:

General comment

The REAL-2 study though supported by Roche is not a Roche sponsored study. The only data available to Roche from this study are those in the Clinical Study Report (CSR) which -typically of an investigator-led, non-commercial study - is fairly brief, plus the peer-reviewed study publication and conference presentations. These do not contain all the information requested by the ERG and we cannot, therefore, fully answer all of the questions relating to REAL-2.

Similarly, although ML17032 is a Roche study it was completed some time ago and the project team disbanded. As such it is very difficult, at short notice to find additional information about the study not obvious from either the peer-reviewed publication or the CSR.

Quality-of Life

A1. In the REAL-2 trial, the submission refers to a single subscale of the questionnaire at baseline and at 12 weeks (page 44). Please provide detailed data for the whole of the EORTC questionnaire at all time points (that is baseline, three months, six months, nine months and 12 months). Please include any measure of variability or uncertainty recorded such as standard deviation, or standard error.

The subscale reported on page 44 of the Roche submission was that reported in the peer-reviewed publication from REAL-2 and, it is assumed, depicts what the investigators considered to be the key QoL data from the study. The CSR for REAL 2 gives more information, but this is still restricted to baseline, 12 and 24 weeks. Appendix 1 gives all of the QoL information provided in the CSR.

A2. Please provide, if available, any quality-of-life data for ML17032

Quality of life data was not collected in study ML 17032.

Safety

A3. Please provide any further relevant information on the safety profile of capecitabine (with the relevant dose). If relevant, please provide safety information from Phase II studies or studies outside gastric cancer.

Safety information from two large RCTs using capecitabine at the relevant dose in the relevant condition was presented in the original Manucturer's Submission for this Appraisal. It is difficult to see what further information could be more relevant than this. Information on the safety of capecitabine at other doses in other conditions (colorectal and breast cancer) obtained from large RCTs can be found in the Xeloda ® SPC (already supplied) and the relevant submissions made by Roche as part of TA's 61, 62 and 100. If NICE has any more specific concerns around safety that are not answered by our original submission, these additional data sources or the answers below, Roche will be happy to try and answer them.

A4. Please clarify the definition of "one dose" as used in the eligibility for safety analyses in both REAL-2 and ML17032. Please clarify, particularly for capecitabine, if this refers to one cycle or a component of a cycle.

One dose means a single administration i.e. a single oral or IV dose NOT a treatment cycle.

A5. Please clarify if there were any further criteria for entry into safety analysis for REAL-2 beyond the one stated in page 37 (that is, "one dose"). Page 48 provides an additional criterion for ML17032 (that is, one post-baseline safety assessment).

None

A6. Please provide the appropriate numbers (N) for haematological and non-haematological safety outcomes for all arms in table 11. The

numbers (N) as currently given appear to be a mixture of the two across all the arms rather than for each arm/outcome. Please confirm that the percentages given for each outcome have been calculated using the appropriate numbers (N). Please clarify why the numbers included in the haematological and non-haematological safety analyses differ; please explain how the numbers were derived

The numbers (N) for Table 11 are as stated in our original submission. For all non-haematological toxicities the percentages are percentages of the numbers treated with the each regimen as shown in the column headings. For haematological toxicities the percentages are percentages of the numbers treated with each regimen and assessable for haematological toxicity as shown in footnote 1 beneath the table. This is consistent with the data presentation in the peer-reviewed and published report of the study by Cunningham *et al.* (2008).

Therefore, it can be confirmed that percentages have been calculated using the appropriate N numbers.

The REAL-2 study report states above a table of non-haematological toxicity that "*These data relate to the per protocol population of 964 patients. There were also 44 patients with no toxicity recorded. The denominator for the toxicity assessments was therefore 920 patients".*

It is reasonable to assume that 928 patients had some recording of haematological toxicity making up the haematological toxicity population, and that the difference in N numbers arose through differences in data reporting rather than any protocol specified difference in definition of "haematological" and "non-haematological" safety populations, though as has already been explained Roche has limited access to REAL-2 study data and so this explanation cannot be verified.

A7. Please provide details for the reasons for treatment delays documented in table 12.

This information was not included in the CSR prepared by the investigators nor in the their study publications. As such it is unavailable to Roche.

A8. Please provide data on the treatment exposure for ML17032 comparable to that provided for REAL-2 in table 12.

Exactly comparable data to that shown in Table 12 of Roche's original submission for REAL-2 are not available for ML17032 without further data analysis, which cannot be conducted in the timescale allowed. However, similar data are available as shown in Table 1

Table 1.Treatment exposure by study arm in the ML17032 study (Safety Population)

	CF n=155	**CX n=156**
Total number of cycles delivered	686	802
Mean number of cycles*	4.43	5.14
% fluoropyrimidine dose delivered	97	92
% cisplatin dose delivered	95	96
% patients with fluoropyrimidine treatment delay	38.7	46.2
% patients with cisplatin treatment delay	37.4	35.3

* Median not available

Table 1 shows that as in REAL-2, most patients in both experimental and control arms of ML 17032 received close to 100% of the intended doses of both fluoropyrimidines and cisplatin. Treatment durations were somewhat longer on CX than CF and this, rather than reduced tolerability may explain the higher incidence of patients with a fluoropyrimidine dose delay in the CX

compared to the CF arm of the study, since the time to first fluoropyrimidine dose reduction for adverse events was similar in both study arms – CX median 46 days, mean 64 days; CF median 50 days, mean 57 days.

A9. Please clarify why safety outcomes are not listed under secondary outcomes for the ML17032 trial.

This was an oversight during writing of the NICE submission. Safety outcomes were a secondary end-point in ML 17032.

A10. Please clarify the criteria for entry into the safety analysis for ML17032. Those listed in page 37 differ from those in page 48.

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. The Safety Population in this study consisted of 311 patients from a randomized population of 316. Four patients were excluded from the Safety Population having had no study treatment, and 1 because no post-baseline safety assessment was carried out.

<u>Individual patient data meta-analysis</u>

A11. Please provide details of the statistical methodology used in the individual patient data meta-analysis.

As explained in the Roche's original submission, the individual patient data meta-analysis was produced by collaborators independent of Roche (the investigators responsible for the REAL-2 in collaboration with those who conducted the ML 17032 study) and Roche have no access to information beyond that in the peer-reviewed publication by Okines *et al.* (2009) cited in the submission, a copy of which has been supplied. This paper states:-

*"**Hypothesis***

Capecitabine is superior to 5-FU within doublet and triplet combination chemotherapy for patients with advanced oesophago-gastric cancer. Primary and secondary end points are OS and PFS and RR, respectively.

patients

Individual patient data were collected on the 1002 patients randomised within REAL-2 and 316 patients randomised within ML17032 on patient study number, gender, age and performance status (PS) at randomisation [Eastern Cooperative Oncology Group (ECOG) PS for REAL-2, Karnofsky PS for ML17032], dates of disease progression, death and last follow-up, histopathology (adenocarcinoma/squamous/undifferentiated), site of primary tumour (oesophagus/oesophago-gastric junction/stomach), extent of disease (locally advanced/metastatic) and chemotherapy arm randomised (CF/CX for ML17032 or EOX/EOF/ECX/ECF for REAL-2).

Statistical methods

All calculations used a two-sided P value and a threshold of 0.05 to indicate statistical significance. Statistical analyses were carried out using SPSS.

analysis population

OS and PFS were analysed strictly on an intention-to-treat (ITT) basis; the ITT population being defined as all patients randomised in the REAL-2 and ML17032 studies (total n = 1318). RR was analysed in patients with measurable disease only (n = 1264).

Primary end point

OS was calculated from the date of randomisation to the date of death from any cause. Patients lost to follow-up or those with no date of death recorded were censored on the date of last follow-up. Kaplan–Meier survival curves were generated and median OS calculated for the ITT population with 95% CI. Comparison between patients treated with 5-FU combinations and

those treated with capecitabine combinations were made using the log-rank test and the HR and its 95% CI were calculated for the comparison. Stepwise multivariate Cox regression analysis was 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% which have been validated as equivalent , histology (adenocarcinoma versus squamous cell versus undifferentiated), extent of disease (locally advanced versus metastatic) and gender. Forest plots with tests of heterogeneity were created to show the treatment effects in each group.

Secondary end points

PFS was calculated from the date of randomisation to the date of disease progression or death from any cause. Patients without a date of progression recorded were censored on the date of last follow-up. As per the analysis of OS, Kaplan–Meier survival curves were generated and median PFS calculated for the ITT population with 95% CI. Comparison between patients treated with 5-FU combinations and those treated with capecitabine combinations was again made using the log-rank test and HR and 95% CIs calculated. Stepwise multivariate Cox regression analysis was used to calculate the corrected HR and 95% CI, incorporating factors as previously described.

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 the REAL-2 trial, the unconfirmed RR and its 95% CI was calculated. Comparison was made using the chi-squared test and multivariate logistic regression analysis used to

control for demographic factors on patients with complete data (n = 1231)".

Roche cannot add further to this description of the methodology employed by the authors.

Current UK practice and treatment pathway

A12. Please provide details of the methods used in the research conducted by First Line Research (summarised in figure 2). Please include, for example, how many hospitals were included, how the information was collected and any other relevant information.

First of all it should be explained that due to a transcription error Roche's submission indicates that the research was conducted for Roche by First Line Research. In fact the research on *first-line chemotherapy usage* was carried out for Roche by Synovate Ltd. As part of an on-going project to track changes in the gastric chemotherapy market.

During each wave of the study 50 oncologists were approached and asked if they treated gastric cancer. Those that confirmed that they did so were asked about what chemotherapy regimens they used. This was done by providing them with a grid containing the regimens shown in Figure 2 and asking them what percentage of patients that they treat with first-line palliative chemotherapy receive each of the regimens listed. They were instructed that that percentages had add up to 100%. Earlier waves of the research were carried out by telephone interview but in 2009 a change was made to self-completion using an on-line questionnaire.

The number of clinicians answering the gastric chemotherapy question was 40, 39 and 32 in 2007, 2008 and 2009, respectively. Roche does not have a specific breakdown of the clinicians answering the gastric question, but in 2009 of the 50 clinicians approached 28 were clinical oncologists, 22 medical oncologists, 40 were consultants and 10 specialist registrars.

A13. Please include labels for all treatment options in figure 2. One option is currently missing and one is incomplete. Please also provide the actual patient numbers for each regimen per calendar year.

The incompletely labelled option (yellow 20%, 32%, 30% in 2009, 2008 and 2007, respectively) is ECF; the pink option (2007 and 2008 only) is “others” and the dark blue option (3% shown in 2009 only is EOF)

A14. In a statement by one of the clinical experts (Dr Rodney Burnham), reference is made to patients with contraindications to the standard first line regimens ECF, ECX and EOX (for example due to pre-existing peripheral neuropathy, renal impairment or impaired left-ventricular cardiac function). These patients may instead receive a combination of carboplatin and infused 5-FU or capecitabine (Carbo-F or Carbo-X combinations). Please clarify if these regimens were identified in the market research conducted by First line Research.

No, though they may be a component of the “other” regimens which make up a small part of the total in years 2007 and 2009. It is agreed that some substitution of carboplatin for cisplatin occurs but it is probably relatively uncommon. In designing our market research questionnaire, it was not felt to be a sufficiently widespread practice to merit listing in the grid of treatment options. As a result any usage may have been picked up under “other regimens”.

Chemotherapy cycles

A15. Please provide the mean number of chemotherapy cycles for each trial arm in the REAL-2 trial. Please provide any details of the variability or uncertainty, such as standard deviations.

The published Appendix of supplementary information to the main peer-reviewed publication of the REAL-2 study (Cunningham *et al* 2008) reports the total number of patients and treatment cycles by study arm. From these figures, mean treatment duration by study arm can be calculated. Using this approach the mean number of cycles was, respectively, as stated in Section 7.2.1.2 of the Roche original submission. This however includes a typo for the ECF regimen. To clarify the numbers are as follows:

5.24, 5.76, 5.44 and 5.42 cycles, for ECF, ECX, EOF and EOX

A16. Please provide an estimate of the average number of chemotherapy cycles for the alternative chemotherapy regimens identified in the submission used in routine clinical practice in the UK. Please state how the average number of cycles might vary.

As stated in response to question A15, in the REAL-2 study, the mean number of cycles was 5.24, 5.76, 5.44 and 5.42 cycles, for ECF, ECX, EOF and EOX, respectively. Although clinical trial populations are seldom completely representative of patients in clinical practice, REAL-2 was an investigator-led study with pragmatic entry criteria and disease assessments reflecting those in clinical practice.

In the ML17032 study, where the two-drug regimens CF and CX were used and the target was 8 cycles, 45% of CX patients reached 6 cycles compared with 34% of CF recipients.

Contrary to that reported on page 57 of the original Roche submission, the mean number of cycles for ML17032 are indeed available and are 4.43 and 5.14 for CF and CX, respectively (as reported in question 8 above). Roche apologises for this oversight The impact of utilising the actual mean treatment durations upon the subsequent costing exercise is provided below:

Taking into account the mean number of cycles for all regimes, the replacement of ECF by ECX, EOF by EOX and CF by CX will result in an additional drug acquisition cost of £640, £504 and £751 respectively, but a saving of £1,966, £1966 and £3,810 in drug administration costs.

Therefore, the use of oral capecitabine instead of IV 5-FU provides direct overall savings to the NHS per patient per course of £1,326; £1,461 and £3,059 in the ECF vs ECX, EOF vs EOX and CF vs CX regimens respectively, as shown in Table 2, Table 3 and Table 4.

Table 2. Overall NHS cost of ECF and ECX regimens*

07-08 Ref costs	ECF Cost	ECX Cost	Incremental cost ECF vs ECX
Drug acquisition cost	£1,378	£2,018	-£640
Drug administration	£3,659	£1,694	£1,966
Total	£5,038	£3,712	
Savings			**£1,326**

* Rounded to the nearest £

Table 3. Overall NHS cost of EOF and EOX regimens*

07-08 Ref costs	EOF Cost	EOX Cost	Incremental cost EOF vs EOX
Drug acquisition cost	£4,433	£4,937	-£504
Drug administration	£3,659	£1,694	£1,966
Total	£8,092	£6,631	
Savings			**£1,461**

* Rounded to the nearest £

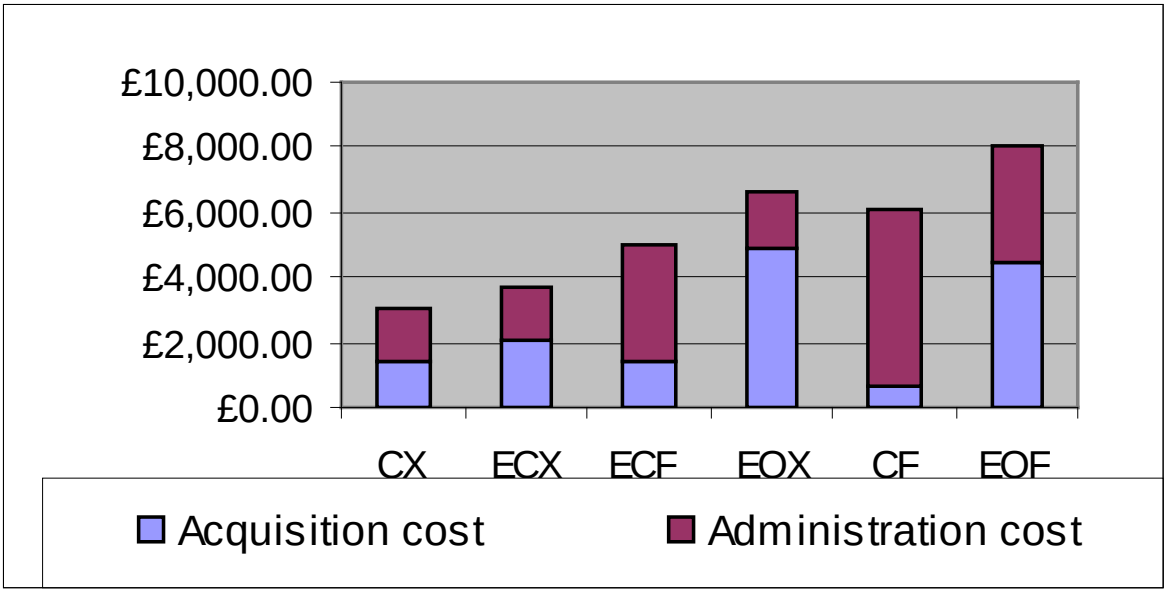
Table 4. Overall NHS Cost of CF and CX*

07-08 Ref costs	CF	CX	Incremental cost CF vs CX
Drug acquisition cost	£702	£1,453	-£751
Drug administration	£5,387	£1,577	£3,810
Total	£6,089	£3,030	
Savings			**£3,059**

* Rounded to the nearest £

In summary, as shown in Table 2, Table 3 and Table 4 above 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 1.

Figure 3. Overall Total Direct NHS cost for advanced gastric cancer regimens



True “clinical practice” treatment durations are hard to establish, though Roche has attempted to do this through market research for the two regimens that predominate in the UK. In the most recent wave of the Synovate market research described in response to question A12, above, the following question was asked: *“Of those patients who are given ECX / ECF for the what is the average number of cycles of capecitabine monotherapy / ECX / ECF received versus the actual number of cycles given?”* There were 25 responders to this question for both regimens. Clinicians using ECF planned, on average to deliver 6.0 cycles, and *perceived* that 4.9 cycles were typically delivered. For ECX the corresponding figures were 5.9 and 4.6 cycles. Given the small sample size and the fact that this research was based on perception rather than patient records, it is difficult to conclude much except that clinicians using ECF and ECX plan to deliver the same duration of treatment and that they perceive them to be similar in efficacy and tolerability (assuming these to be the factors that drive treatment duration).

In summary, it is our belief, backed by evidence from 2 recent RCTs utilising 6 quite distinct platinum-based chemotherapy regimens plus UK market research that treatment duration does not differ much between regimens,

though it may be somewhat shorter in clinical practice than in clinical trials (regardless of whether 5-FU or capecitabine is used as the fluoropyrimidine element of treatment).

A17. In table 12 page 51, please provide the number (N) for the median number of cycles in the EOX group in the REAL-2 trial. Please explain what the figures in the brackets for this line represent.

As stated in the appendix to the trial publication by Cunningham et al (2008) the median number of cycles for all treatment arms in REAL-2, including EOX, was 6. The figures in brackets in Table 12 are p-values compared to the control arm of ECF

Patient population and efficacy data

A18. For the REAL-2 trial, please provide details of the multivariate analysis by performance status, age and disease that is referred to in page 42.

The REAL-2 CSR states that the following prognostic factors were entered into the multivariate analysis of overall survival: PS, extent of disease, age +/- 63 years, primary disease site, gender and histology. Differentiation was not included as it was removed by the model in the per protocol comparisons and reduced power because of missing values.

Outputs from the model are presented as follows.

Fluoropyrimidine delivery per protocol

Variables included in final model

Factor	Group	N	p-value	HR	95% CI
5-FU delivery	5-FU Capecitabine	484 480	 0.096	1 0.889	 0.774-1.021
Performance Status	0 1 2	312 549 103	 <0.001 <0.001	1 1.358 2.410	 1.162-1.586 1.899-3.058
Extent of disease	Locally advanced Metastatic	219 785	 <0.01	1 1.563	 1.318-1.853
Age	</=63 >63	495 469	 0.028	1 0.856	 0.746-0.983

Variables not included in final model

Factor	Group	N	p-value
Primary site	Oesophagus	333	0.325

	Oesophago-gastric junction Gastric	248 383	
Gender	Female Male	179 785	0.072
Histology	Adenocarcinoma Squamous carcinom	847 117	0.088

Platinum delivery per protocol

Variables included in final model

Factor	Group	N	p-value	HR	95% CI
Platinum delivery	Cisplatin Oxaliplatin	490 474	 0.425	1 0.945	 0.822-1.086
Performance Status	0 1 2	312 549 103	 <0.001 <0.001	1 1.376 2.401	 1.180-1.606 1.890-3.050
Extent of disease	Locally advanced Metastatic	219 785	 <0.001	1 1.560	 1.316-1.850
Age	</= 63 >63	495 469	 0.021	1 0.849	 0.739-0.976

Variables not included in final model

Factor	Group	N	p-value
Primary site	Oesophagus	333	0.325

	Oesophago-gastric junction Gastric	248 383	
Gender	Female Male	179 785	0.072
Histology	Adenocarcinoma Squamous carcinom	847 117	0.088

A19. Please provide further information on the patients involved in the dose escalation phase of the REAL-2 trial documented in Cunningham et al, 2008. Please provide details of the exact treatment received and the outcomes.

The dose escalation portion of REAL-2 is described in detail by Sumpter *et al* (2005). Because the three drug combinations that included capecitabine (ECX and EOX) had not been formally evaluated prior to the study, the REAL-2 prototocol utilised what was considered to be a conservative daily dose of capecitabine (500mg/m^2 -75% of the monotherapy dose for continuous use) with a protocol specified plan to dose escalate by 25% (to 625 mg/m^2) if an interim analysis after the recruitment of the first 80 patients showed acceptable tolerability. Acceptable tolerability was protocol defined as Grade 3 and 4 fluororopyrimidine-associated toxicity (defined as stomatitis, hand-foot syndrome and diarrhoea) in less than 10% of patients. The observed rate of fluoropyrimidine-associated toxicity was 5.1% and dose escalation was carried out.

As also reported by Sumpter *et a*l (2005) the REAL-2 protocol specified a further safety analysis after the recruitment of the first 200 patients. This was carried out on the first 204 patients and revealed that at the higher dose of 625 mg/m^2 the rate of fluoropyrimidine-related toxicity was 14.7% (95% CI; 4.9-31%) compared with 13.7% (95% CI; 7.4-22%) for 5-FU and within the 11-29% range specified by the protocol for continuing treatment without further alteration of the capecitabine dose, which remained at 625 mg/m^2 for the rest of the study.

A20. Please provide details of the second-line treatment for the 14% of the patients in the REAL-2 trial.

Roche does not have access to this information which appears neither in the investigator-prepared CSR or the publications arising from the study

A21. Please provide efficacy data broken down according to the following subgroups from the REAL-2 trial:

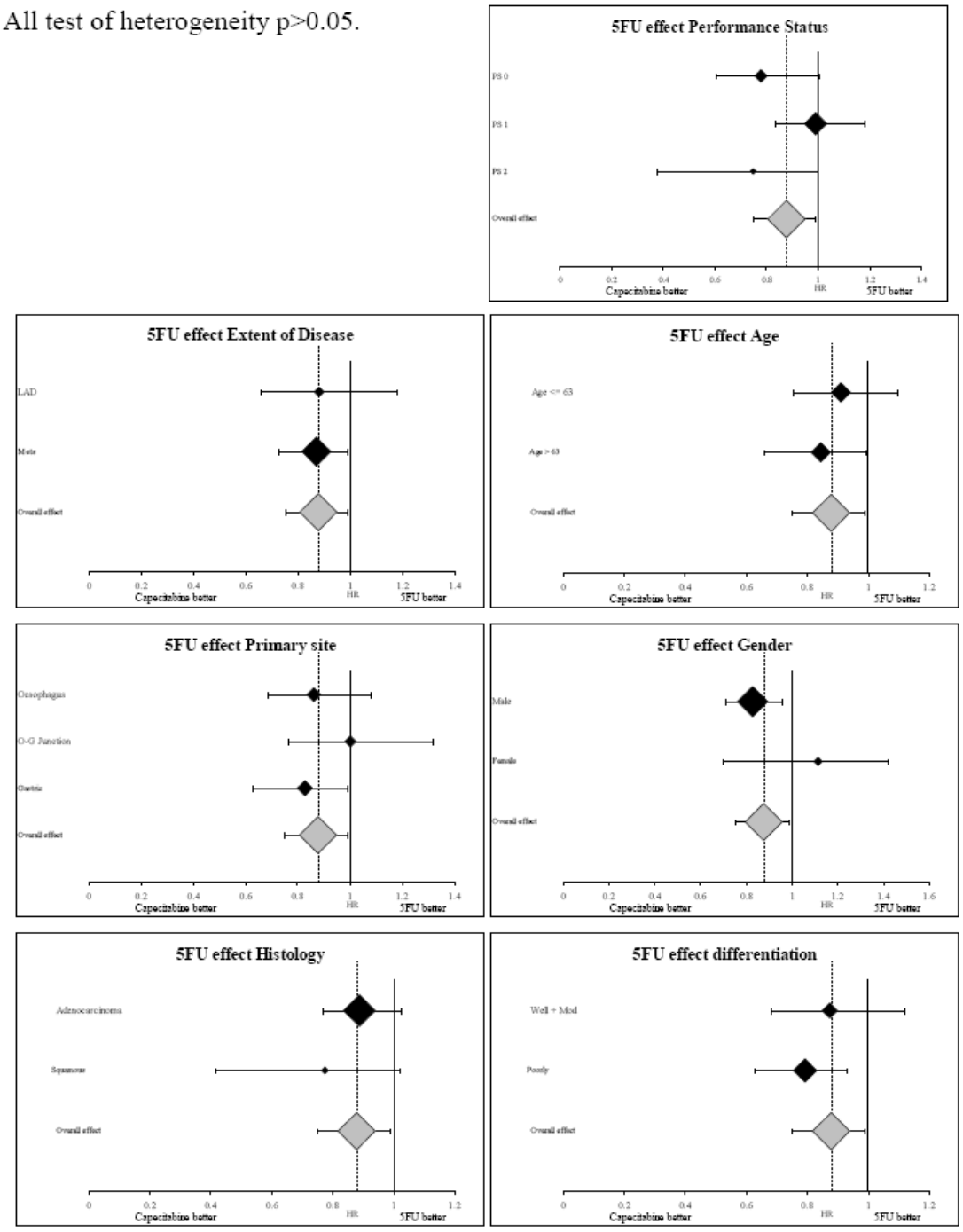
- **cancer site (gastric, oesophogastric junction and oesophageal)**
- **performance status**
- **whether previous treatment was received**
- **receipt of second-line treatment (14% of patients)**
- **other prognostic factors eg liver and peritoneal metastases, alkaline phosphatase etc.**

Only limited information on efficacy by sub-group are included in the REAL-2 CSR and has already been explained Roche do not have access to patient level data to conduct further analyses.

The following Forest plots taken from the CSR show the OS HR and 95% CI for capecitabine compared with 5-FU for a series of prognostic groups within the REAL-2 study

Figure 2. Relative overall survival by fluoropyrimidine received in different patient sub-groups in the REAL-2 study

All test of heterogeneity p>0.05.



These Forest plots show that in all but one sub-group examined the HR for OS indicates at least equivalent OS with capecitabine compared to the standard 5-FU regimen. The only group where the HR exceeds 1 (indicating 5-FU better than capecitabione) was female patients but this was a small group and the 95% CI for the HR is wide, with the lower boundary easily incorporating both unity and the HR for whole study population.

A similar analysis is presented in the CSR for outcome according to platinum agent used for a range of patient subgroups. As this appraisal is not concerned with choice of platinum agent this analysis is not presented in detail, but it shows that the OS for most sub-groups is at least as good on oxaliplatin as cisplatin, with no group obviously having their outcome prejudiced by receiving the newer agent.

A22. For the ML17032 trial, please provide the following:

- **independently assessed results for all outcomes in addition to the per-protocol PFS**

The CSR does not report independently assessed results for all of the study outcomes for which investigator observed outcomes are reported. Investigator observed outcomes were protocol defined as those on which the primary efficacy analysis would be conducted and the purpose of independently observed outcome measures was to provide a measure of the sensitivity of outcomes to observer bias. Table 6 of Roche's original submission gives investigator assessed and independently assessed results for PFS (the primary study end-point).

Table 5, below, expands Table 7 from Roche's original submission to include independently assessed as well as investigator assessed end-points where available. Clearly, OS does not require independent assessment. Typically, for an oncology study, independent assessors were less likely to observe a treatment response than investigators. However, for both investigator and independently assessed end-points dependent on determination of response a consistent pattern of at least equal activity was seen in the experimental arm compared with the CX control arm.

Table 5. Secondary end-points in study ML 17032 (unadjusted analyses)

End point	CX N=156 (ITT) N=139 (PP)	CF N=155 (ITT) N=137 (PP)	HR/OR (95% CI)	P value
Median OS (ITT; months)	5.6 (4.8, 6.9)	5.0 (3.9, 5.7)	HR (0.63, 1.03)	0.003 *vs.* non-inferiority margin 1.25
Median OS (PP; months)	10.5	9.3	HR 0.85 (0.64-0.13)	0.008 *vs.* non-inferiority margin 1.25
ORR (Investigator PP; %) 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
ORR (Investigator ITT; %) Complete response rate (%) Partial response rate (%)	40.6 (32.9, 48.7) 1.9 (0.4, 5.4) 38.8 (31.2, 46.8)	28.8 (21.9, 36.6) 2.6 (0.7, 6.4) 26.3 (19.6, 33.9)	OR 1.69 (1.06, 2.70) OR 0.73 (0.16, 3.30) OR 1.77 (1.10, 2.86)	0.0335 0.7205 0.0244
ORR (Independent PP; %) Complete response rate (%) Partial response rate (%)	31.7 (24.0, 40.1) NA NA	25.5 (18.5, 33.7) NA NA	OR 1.24 (0.85, 1.80)	0.2672
ORR (Independent ITT; %) Complete response rate (%) Partial response rate (%)	27.5 (20.7,35.1) 0 27.5	23.1 (16.7, 30.5) 0 23.1	OR 1.28 (0.82, 1.75)	0.3493
Mean time to response (Investigator PP; months)	NA	NA	HR 1.66 (1.13, 2.43)	0.01
Mean time to response (Investigator ITT; months)	3.7	3.8	HR 1.61 (1.10,2.35)	0.015
Mean time to response (Independent PP; months)	Not available in main body of CSR available in the time-scale of this response but reported as “similar” to ITT population			
Mean time to response (Independent ITT; months)	NA	NA	HR 1.23 (0.79,1.90)	0.3644
Median response duration (Investigator PP; months)	NA	NA	NA	NA
Median response duration (Investigator ITT; months)	7.6	6.2	HR 0.88 (0.56,1.36)	0.554
Median response duration (Independent PP; months)	NA	NA	HR 1.05 (0.60,1.81)	0.8728
Median response duration (Independent ITT; months)	NA	NA	NA	NA

*ITT population

Abbreviations: HR, hazard ratio; ITT, intent-to-treat population; NA, not reported in the documentation available ;OR, odds ratio; ORR, overall response rate; OS, overall survival; PP, per protocol population.

- **Clarification as to why ITT data are reported for mean time to response and median response duration but ORR is reported per protocol. Please provide per protocol and ITT data appropriately**

As PP and ITT data for time to response and median response duration were similar, only the ITT data (which are more completely reported in the CSR) were presented in the interests of brevity. In compliance with NICE’s request PP data are, where possible, included in Table 5, above.

Similarly, in the interests of brevity and in the absence of clear differences between ITT and PP data, for response rates only PP data were presented in Roche's original submission. On consideration, since these have been subjected to a test of superiority the ITT data are more appropriate and both are now included in Table 5, above.

- **Clarification whether the p-values are one-sided or two-sided α's**

Reported tests of non-inferiority of PFS were two-sided but the CSR states that similar results were obtained with one-sided tests

- **Data broken down by whether previous treatment was received.**

The ML 17032 CSR includes information on outcomes according to whether or not patients had received prior chemotherapy. However, only 33 patients in the ITT population had received such treatment limiting the power of the analysis. In as much as the limited results (see Table 6 and Table 7) from this analysis permit any conclusions to be made, it appears that capecitabine is as effective as 5-FU regardless of prior chemotherapy exposure.

Table 6. Survival outcomes in study ML 17032 according to prior chemotherapy exposure

Efficacy parameter	Prior chemotherapy	CX		CF		HR (95% CI)
		n	Median (months)	N	Median (months)	
PFS (PP)	Yes	17	8.4	11	6.5	0.71 (0.30, 1.67)

	No	122	5.4	126	5.0	0.83 (0.63, 1.88)
OS (ITT)	Yes	18	12.9	15	8.8	0.63 (0.26, 1.50)
	No	142	9.7	141	9.2	0.90 (0.68, 1.20)

Table 7. Response rates in study ML 17032 according to prior chemotherapy exposure (ITT)

Prior chemotherapy	CX		CF		OR (95% CI)
	n	Responders (ORR)	N	Responders (ORR)	
Yes	18	10 (55.6%)	15	4 (26.7%)	3.44 (0.79, 15.02)
No	142	55 (38.7%)	141	41 (29.1%)	1.54 (0.94, 2.53)

Section B: Cost Effectiveness

B1. The meta-analysis suggests statistically significant survival benefits for capecitabine in advanced gastric cancer compared with 5-FU. Please provide details of the expected costs associated with a patients' care during the additional survival period for patients on capecitabine-based therapy.

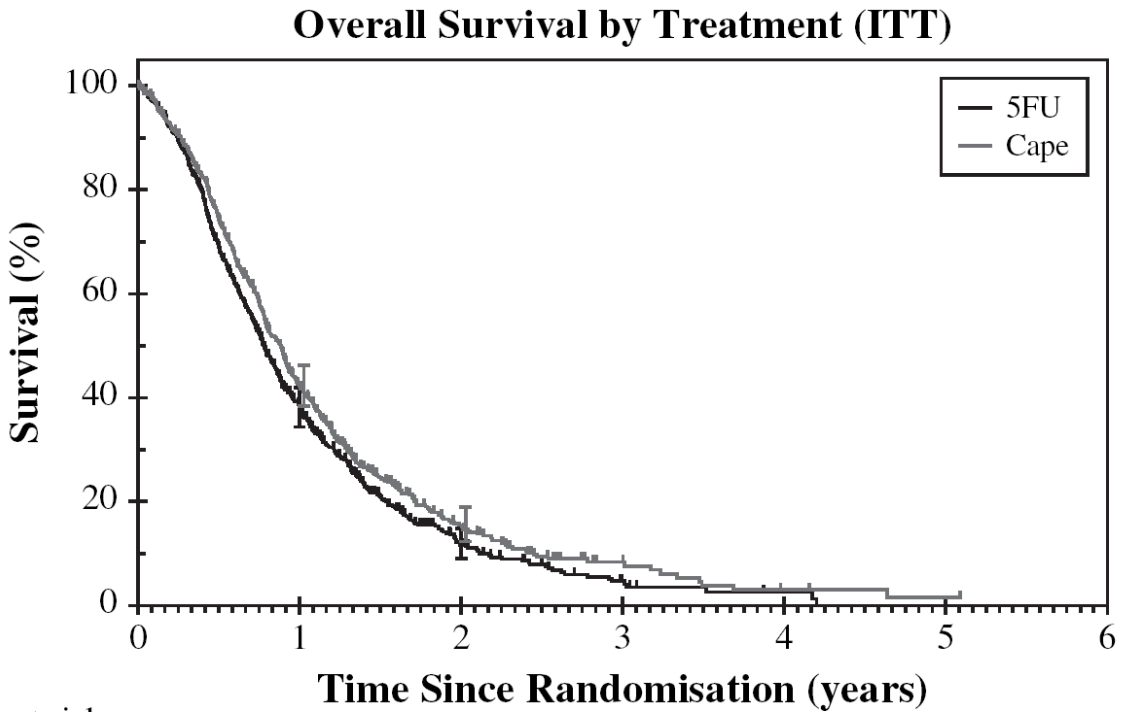
Results from the meta-analysis indicate that there was not significant difference in PFS between the capecitabine and the 5FU arms, therefore for the purposes of costing, the additional OS benefit is assumed to be generated from time spent within the progressed health state. As the progressed disease health state generally represents higher costs compared to a PFS health state in oncology modeling, Roche considers this a conservative assumption.

The following steps were taken to calculate the expected costs associated with a patients' care during the additional survival period for patients on capecitabine-based therapy.

Step 1. Estimate the OS of patients treated with capecitabine based on the meta-analysis conducted by Okines et al, 2009

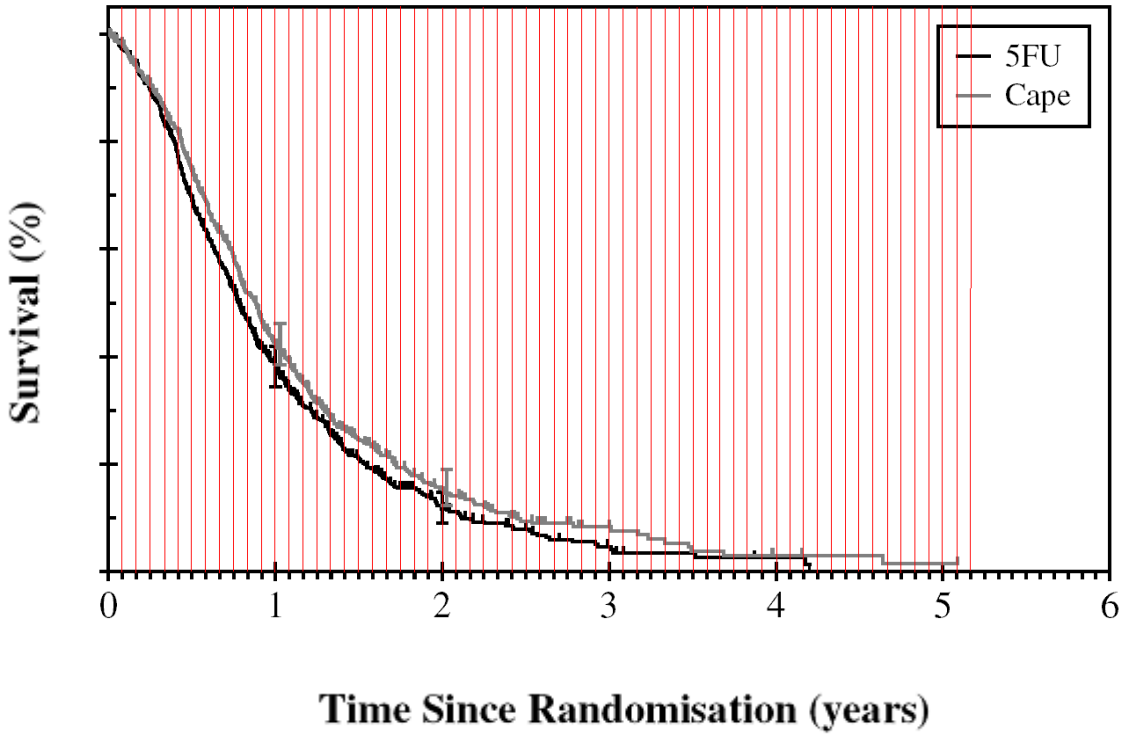
The Kaplan–Meier curves published by Okines et al 2009 (See Figure 3) below were used to estimate the mean overall survival in patients treated with capecitabine-based chemotherapy and 5-fluorouracil (5-FU)-based chemotherapy using an area under the curve procedure.

Figure 3. OS Kaplan Meiers from Okines et al.



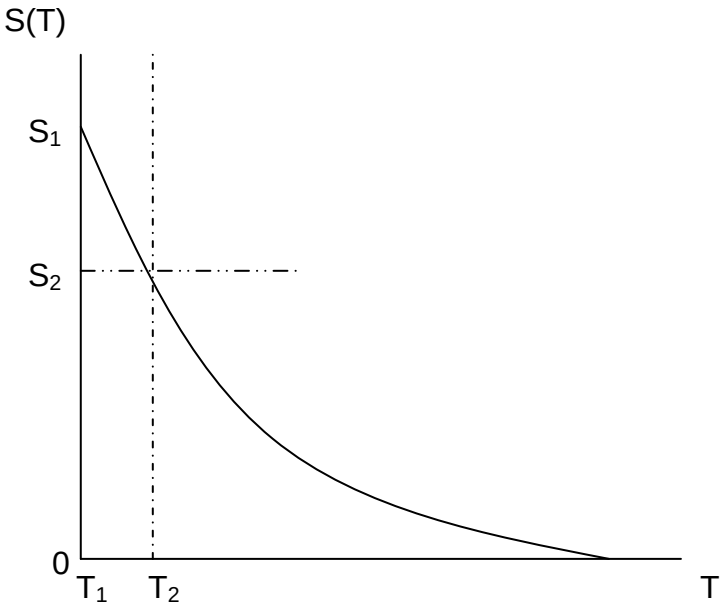
Microsoft Paint was utilised to divide each curve into monthly segments to ensure data point sampling was equivalent for both curves. (See Figure 4 below).

Figure 4. Segmented OS curves:



The above graph was placed in TechDig and the S(t) and T values at each sample point (as close to one month as possible with by hand data extraction) recorded. The resultant data was exported into Excel and used to determine the area under each segment. Each month long segment was split into a rectangle and triangle to allow estimation of each segment's area. See Figure 5.

Figure 5. Segment AUC methodology:



$$AUC_{SEMGMENT(T2-T1)} = ((T_2 - T_1) \times (S_2 - 0)) + ((\frac{T_2 - T_1}{2}) \times (S_1 - S_2))$$

The individual segments were then summed together to determine the area under each curve.

Mean OS estimates produced by AUC analysis based on Okines et al. (2009) KM curves are shown in Table 8.

Table 8. Mean OS estimate. Meta-analysis of the Real-2 and ML17032 trial (Okines et al , 2009)

	Mean OS estimate (years)
Capecitabine	1.186
5FU	1.046
Incremental	0.141

Therefore the meta-analysis conducted by Okines et al 2009 suggest that capecitabine based regimens provide an additional 0.141 years (1.69 months) of survival time in the 'progressed' disease state.

Step 2. Identify the BSC cost for the PD health state

Given that no explicit PD cost for advanced gastric cancer was found in the literature, a range of recent values from related advanced cancer were identified (see Table 9).

Table 9. List of progressive disease costs from a selection of advanced cancer publications

Source	Progressive Disease cost	Comments/Reference
NICE submission. Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer, July 2009	£600 per month	Tappenden 2007, Tappenden P et al. Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. Health Technology Assessment. 2007; 11 (12). http://www.hta.ac.uk/execsumm/summ1112.htm
CG81: Advanced breast cancer guideline: diagnosis and treatment, February 2009	£542 per month (calculated based on 4.33 weeks per month)	Resource source: NICE CG81. Costing source: PSSRU (2009). Community nurse: home visit 20 min., once a week. £65 per hour = £21.67 per week Clinical nurse specialist: 1hr contact time, once a week. £55 per hour = £55 per week per week GP contact: 1 home visit, every fortnight £57 per visit including direct care staff costs Therapist: 1 hour, every fortnight. £40 per visit for NHS therapist. TOTAL= (£24*4.33) + (£55*4.33) + (£28.5*4.33) + (£20*4.33) = £541.99
Bevacizumab, sorafenib, tosylate, sunitinib and temsirolimus for renal cell carcinoma. A systematic review ad economic evaluation, May 2008	£435 per 6 week model cycle (equivalent to £314 per month)	Peninsula Technology Assessment Group (PenTAG), May 2008

A range of suitable values have been identified in Table 9. In the absence of explicit PD cost for advanced gastric cancer, we have selected the NICE guideline GC81 (as this guideline provides a broader scope than a technology appraisal review) to calculate the PD cost and assumed that the resources required for the progressed disease in the breast cancer setting are comparable to that of the advanced gastric cancer. Therefore we used the calculated progressed disease monthly cost of £542 to inform our analysis.

Step 3. Calculate the expected cost associated with the additional survival period for patients on capecitabine based therapies

The additional expected costs associated with a patients' care during the 1.41 month additional survival period for patients on capecitabine-based therapy was therefore calculated at £917 (£542 per month X 1.69 months).

Given that in the base case the cost savings of switching from 5FU to capecitabine are £1,620, £1,572 and £4,210 for the ECF vs ECX, EOF vs EOX and CF vs CX respectively, the additional £917 cost (that provides an extra 1.69 months of overall survival benefit) would not alter, the conclusion that capecitabine is a cost saving technology compared to 5FU.

These analyses do not account for the additional QALYs generated by capecitabine from the assumed additional survival. This would suggest a cost premium could even be tolerated in this scenario and capcitabine remain cost effective.

B2. Please clarify whether the calculations of dose intensity reported for capecitabine in the cost minimisation analysis considered the dispensed amounts or the amounts actually utilised by the patients.

The calculations on dose intensity reported for capecitabine, in the cost minimisation analysis, considered the actual amount utilised by the patients.

The capecitabine SmPC states that treatment of capecitabine is to be continued until disease progression or unacceptable toxicity. Since confirmation of disease progression takes place at routine monitoring visits, it is unlikely for patients to stop treatment in between routine monitoring visits. In addition, as stated in the capecitabine submission, nurse expert opinion confirmed that drug wastage is minimal, as patients are given the required amount of capecitabine until the next planned visit. Therefore the actual amount utilised by patients is assumed to be similar to that dispensed.

However, a scenario has been considered below which assumes 100% dose intensity for all regimens to account for any potential difference between the

amount of drug dispensed and amount actually utilised by patients. The cost savings of switching 5FU with capecitabine within this scenario can be seen in Table 10.

Table 10. Total cost considering 100% dose intensity for all regimens. REAL-2 and ML17032

Cohort	Acquisition cost	Administration cost	Total cost
ECF	£1,573.86	£3,818.88	£5,392.74
ECX	£2,160.07	£1,718.64	£3,878.72
Incremental cost (savings) per patient when switching from ECF to ECX	£586.22	-£2,100.24	**-£1,514.02**
EOF	£4,922.38	£3,818.88	£8,741.26
EOX	£5,508.60	£1,718.64	£7,227.24
Incremental cost (savings) per patient when switching from EOF to EOX	£586.22	-£2,100.24	**-£1,514.02**
CF	£871.97	£6,580.39	£7,452.36
CX	£1,554.71	£1,687.36	£3,242.08
Incremental cost (savings) per patient when switching from CF to CX	£682.74	-£4,893.03	**-£4,210.29**

Results in Table 10 confirms that even taken into account any potential wastage across all regimens, switching 5FU with capecitabine offers savings in all regimens.

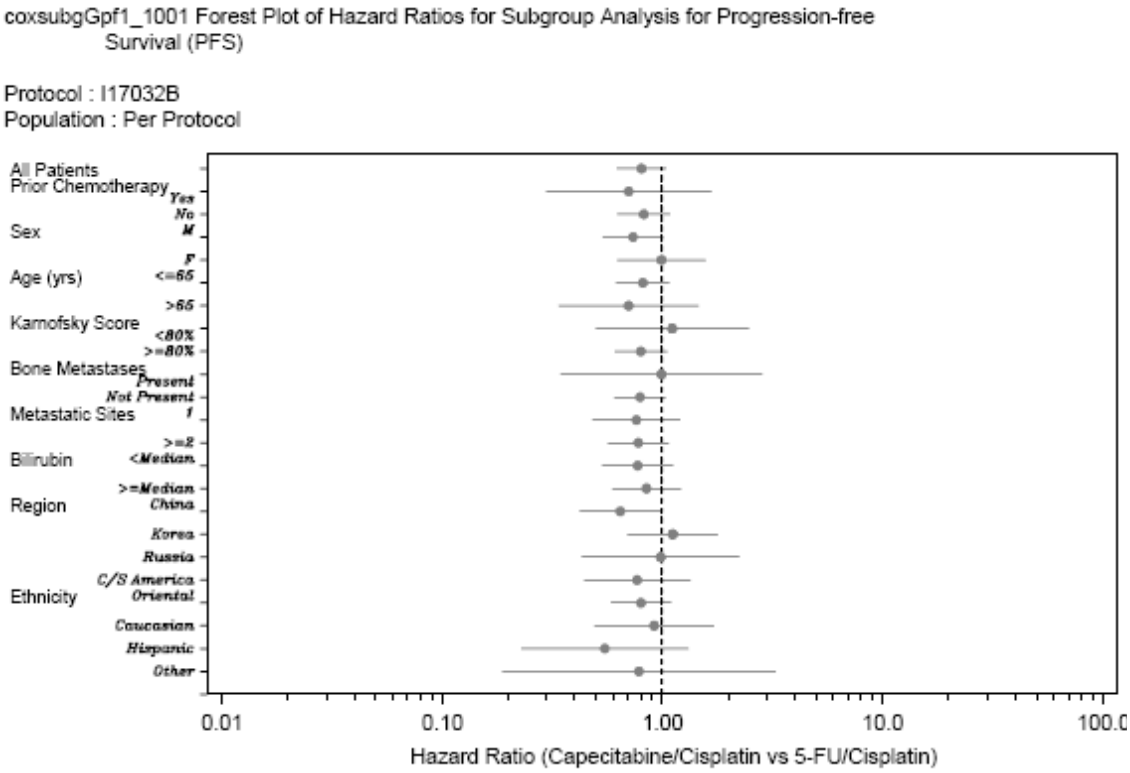
B3. Please state how the mean number of cycles vary between different subgroups of patients, such as by tumour histology, performance status, locally advanced vs metastatic disease. Please provide a sensitivity analysis informed by these data.

Breakdown of treatment duration by patient subgroup is not included in the documentation of the REAL-2 study accessible to Roche, neither is it included in the CSR for ML 17032.

As explained in response to question A21, in REAL-2, capecitabine and 5-FU reported similar efficacy regardless of the patient subgroup examined.

The same was found in ML 17032, as shown in Figure 6

Figure 6 Forest plot of Hazard ratios for PFS by patient subgroup in study ML 17032.



† China includes patients from China, Hong Kong and Malaysia.

Program : $PROD/cdp10283/ml17032/coxsubg.sas / Output : $PROD/cd10283b/i17032b/reports/coxsubgGpf1_1001.cgm
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Logically, even if treatment durations differ across sub-groups, it appears clinically plausible they will differ to a similar extent for both 5-FU and capecitabine. Table 49 (p.94) of the original Roche submission illustrated the impact of varying the assumed treatment duration across a range of 2.75 to 8.25 cycles. Capecitabine was cost savings across this range of treatment duration. Indeed even restricting treatment duration to 1 cycle, capecitabine is

cost saving. Longer treatment durations only increase the margin fo this cost saving outcome.

B4. Please provide details of the evaluation of adverse events costs referred to in page 100 point 4.

Results from the ML17032 trial show that most treatment-related adverse events occurred with a similar frequency in both study arms. 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. Please, refer to table 10 of the original Roche's capecitabine submission (Section 6.7.2)

The REAL2 reported few differences between ECF and EOF and the corresponding capecitabine arms (ECX and EOX). Such differences generally reflect 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 (which can be treated with a moisturizer cream). There are no striking differences between EOF and EOX. Please, refer to table 11 of the capecitbine submission (Section 6.7.3).

Therefore, based on these findings adverse events cost were not included in the submission.

It should be noted that the REAL-2 investigators were familiar with both capecitabine and 5-FU at the time of designing the trial. They recognized that both gave rise to qualitatively similar toxicities and defined fluoropyrimidine toxicities as diarrhoea, mucositis and han-foot syndrome. The initial dose-escalation part of the study was designed to ensure that the collective burden of these amongst capecitabine recipients did not exceed that amongst 5-FU recipients. At the second interim safety analysis of REAL-2 after dose escalation to the final study dosing the rates of grade 3 and fluoropyrimidine toxicity were 14.7% (95% CI; 4.9-31%) and 13.7% (95% CI; 7.4-22%) in the

capecitabine and 5-FU arms respectively (see response to A 19). In short, the dose of capecitabine in REAL-2 was titrated to produce treatment arms roughly equitoxic from a fluoropyrimidine perspective and no great differences between the study arms were expected or seen in this regard.

Below are the costings related to the main adverse events reported in the ML17032 and REAL-2 trials where differences between study arms can be attributed to the switch from 5-FU to capecitabine (and with a higher incremental frequency than 3%). See Table 11, Table 12 and Table 13 below.

Table 11. Treatment-related adverse events grade 3 and 4 in the safety population. REAL-2 and ML17032

Adverse event	ECF (%) (N=234)	ECX (%) (N=234)	Δ (%)	EOF (%) (N=225)	EOX (%) (N=227)	Δ (%).	CF (%) (N=155)	CX (%) (N=156)	Δ (%)
Neutropenia	41.7	51.1	-9.4	29.9	27.6	2.3	19	16	3
Febrile neutropenia	9.3	6.7	2.6	8.5	7.8	0.7	No recorded	No recorded	N/A
Diarrhoea	2.6	5.1	-2.5	10.7	11.9	-1.2	4	4	0
Stomatitis	1.3	1.7	-0.4	4.4	2.2	2.2	6	2	4
Hand-foot syndrome	4.3	10.3	-6	2.7	3.1	-0.4	0	4	-4
Nausea and vomiting	10.2	7.7	2.5	13.8	11.4	2.4	11	8	3

Table 12. Unit costs for treatment-related adverse events grade 3 and 4 in the safety population with incremental frequency >3%. REAL-2, ML17032

Grade 3 and 4 AE Treatment-related	Cost per episode (£)	Reference / comment	Uplifted cost (£)
Stomatitis	£188	TA162 erlotinib	£209
Neutropenia	N/A	A laboratory measure with no direct impact on patients. Thus, patients were not treated for neutropenia	N/A
Hand and foot syndrome	£137	York CRD September 2004 (cited in the Bevacizumab in combination with fluoropyrimidine-based chemotherapy for	£156

		the first-line treatment of metastatic colorectal cancer)	

Table 13. Cost of grade 3 and 4 treatment related adverse events with incremental frequency >3%

Adverse event (grade 3 & 4)	Cost per episode	Δ(% pts) ECF vs ECX	Δ cost ECF vs ECX	Δ (% pts) EOF vs EOX	Δ cost EOF vs EOX	Δ(% pts) CF vs CX	Δ cost CF vs CX
Stomatitis	£209	-0.4 %	-£0.84	2.2%	£4.6	4%	£8.4
Hand-foot syndrome	£156	-6%	-£9.36	-0.4%	-£0.62	-4%	-£6.24
Total:			-£10.2		£3.98		£2.16

Table 13 illustrates that the difference in cost of treating adverse events related to the switch of 5FU to capecitabine are minimal and will not affect the economic analysis substantially.

Section C: Search strategy and textual errors

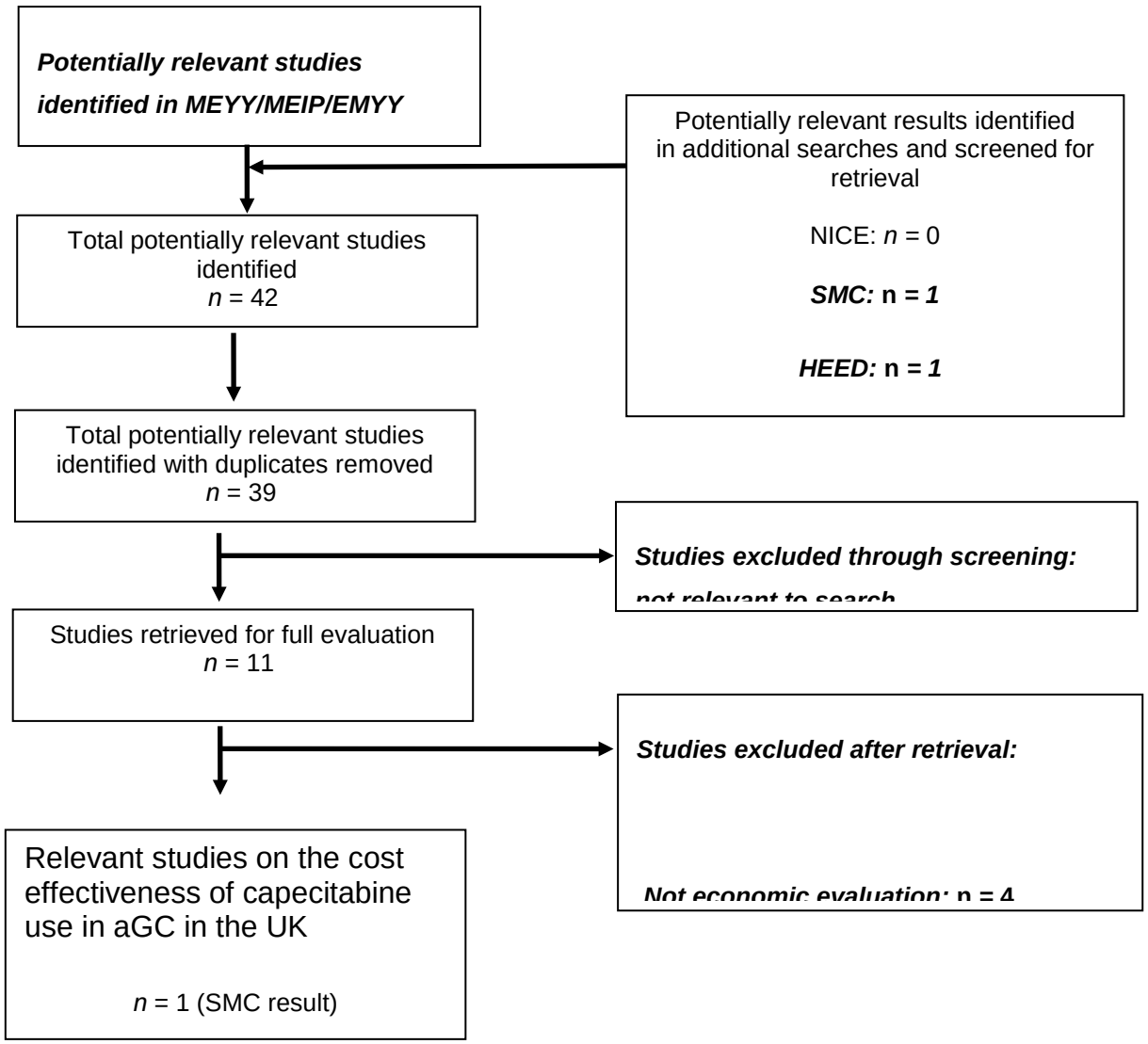
C1. In the QUORUM flow diagram in figure 4, please clarify how the 11 records covering the 4 RCTs are identified from the initial 179 records.

NICE is referred the last paragraph of 6.1 of Roche's original submission. Section 6.2.1 of the STA template requests that the manufacturer *"Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group"* The intervention is defined by the Scope as capecitabine and the relevant patient group as patients with advanced/metastatic gastric cancer. The reviewer (as described in Section 6.1

of Roche's original submission) scrutinised each of the 179 records starting with the title, progressing if required to the abstract or full text until it was clear that the record should be included or excluded i.e. when it had been determined that the record referred to an RCT of capecitabine in advanced gastric cancer. The number of studies excluded on the basis of title, abstract and full text is included in Figure 4 of Roche's original submission, but no formal record was kept of reasons for exclusion which were varied (non-comparative study, animal study, review article etc)

C2. Please include a QUORUM flow diagram for the cost effectiveness review process.

The below QUORUM details the economic evaluation search carried out in section 7.1.



Upon reviewing the search notes the reasons for exclusion have been clarified. The disparity between the exclusion break-down provided in the appendix to the submission and the below QUORUM is due to this re-assessment and clarification of reasoning behind exclusion.

C3. Please clarify the source of the other economic evaluation of capecitabine in gastric cancer conducted in the UK (London Cancer New

drugs Group APC/DTC briefing). It is not mentioned in the search process in page 122

The economic evaluation of capecitabine in gastric cancer conducted in the UK (London Cancer New drugs Group APC/DTC briefing) was obtained via Roche internal colleagues.

C4. Please clarify if there was a search for ongoing studies. This was not mentioned in the search strategy.

This was not formalised or required within the template. However a check was made of Roche's own trial management system for Roche sponsored/supported studies and on the Current Controlled Trials database (http://www.controlled-trials.com/)

C5. Please clarify the following issues identified in the search strategies provided in the submission (appendices 2 and 3):

- **In the clinical effectiveness search strategy (lines 52, 53, 56, 57, 84) that relates to the Biosis database, there appears to be an error in the Boolean logic applied. Line 57 combines lines 52 and 53 (xeloda and capecitabine) using the Boolean AND whereas the Boolean OR should have been used. This results in 143 records being identified in line 57 whereas a minimum of 1680 should have been identified.**

Roche is obliged to NICE for spotting this error in the search strategy (the assumption that the Boolean AND on line 57 should have been the Boolean OR is correct). Rerunning the search on 15.01.10 yields a total of 1769 records at line 57 which increases the yield at the end of the search to 172 records (from 83). Review of these records reveals 4 additional records that refer to RCTs of capecitabine in gastric cancer which should have been included in the list of **all** RCTs. These are as follows:

Hee RM, Kang YK. ML17032 trial: capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in advanced gastric cancer. *Expert Rev Anticancer Ther.* 2009; **9**: 1745-1751

Kang Y, Kang W, Shin D B *et al.* Similar safety results of capecitabine/cisplatin (XP) vs. continuous infusion of 5-FU/cisplatin (FP) from a phase III trial in patients (pts) with previously untreated advanced gastric cancer (AGC). *Eur J Cancer Suppl.* 2005; **3** (2) Suppl S: 205

Kang Y, Kang W, Shin D B *et al.* Capecitabine/cisplatin vs. continuous infusion of 5-FU/cisplatin as first-line therapy for patients (pts.) with advanced gastric cancer (AGC): a randomised phase III trial. *Eur J Cancer Suppl.* 2007; **5** (4): 259

Van Cutsem E, Kang YK, Shen L *et al.* Trastuzumab added to standard chemotherapy (CT) as first-line treatment in human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC): efficacy and safety results from the Phase III ToGA trial. *Eur J Cancer Suppl.* 2009; **7** (3): 7

However, of these 4 additional records, 2 (Kang *et al.* 2005; Kang *et al.* 2007) relate to additional conference presentations of data from, and one (Hee *et al* 2009) to a commentary on the ML 17032 study. These add no additional information to that contained in the original Roche submission. The remaining record (Van Cutsem *et al.* 2009) reports on an RCT that includes capecitabine and in both arms and provides no information on the efficacy or tolerability of capecitabine compared with 5-FU.

Thus correcting the error in the search strategy identified by NICE makes no difference to the evidence base for this appraisal and has no impact on Roche's original submission.

- **In the cost effectiveness Medline search strategy, there appears to be an error in line 14 where all the terms for gastric/stomach cancer have been combined. Line 1 stomach neoplasms.de has not been included in this combination and has not been used at any other point in the strategy. The effect of omitting the one MeSH term for**

gastric/stomach cancer could be that potential studies were not identified; this may have been compensated for in other lines of the strategy but this cannot be confirmed without reproducing and re-running the search.

The amended MEDLINE search strategy is provided below. The search was conducted on 20/01/2010. No additional results were identified by the addition of the previously erroneously omitted STOMACH-NEOPLASMS.DE term into search term 14.

No.	Database	Search term	Info added since	Results
1	MEYY	STOMACH-NEOPLASMS.DE.	unrestricted	30926
2	MEYY	GASTRIC NEAR NEOPLA$5	unrestricted	979
3	MEYY	GASTRIC NEAR CANCER$5	unrestricted	21136
4	MEYY	GASTRIC NEAR CARCIN$5	unrestricted	8147
5	MEYY	GASTRIC NEAR TUMO$5	unrestricted	4751
6	MEYY	GASTRIC NEAR METASTA$5	unrestricted	3047
7	MEYY	GASTRIC NEAR MALIG$5	unrestricted	1416
8	MEYY	STOMACH NEAR NEOPLASM$5	unrestricted	31007
9	MEYY	STOMACH NEAR CANCER$5	unrestricted	4482
10	MEYY	STOMACH NEAR CARCIN$5	unrestricted	1567
11	MEYY	STOMACH NEAR TUMO$5	unrestricted	1872
12	MEYY	STOMACH NEAR METASTA$5	unrestricted	541
13	MEYY	STOMACH NEAR MALIG$5	unrestricted	431
14	MEYY	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	41138
15	MEYY	COST ADJ EFFECTIVENESS ADJ ANALYSIS	unrestricted	4165
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	69529
17	MEYY	ECONOMIC ADJ EVALUATION	unrestricted	4075
18	MEYY	Cost ADJ Minimi$7	unrestricted	728
19	MEYY	15 OR 16 OR 17 OR 18	unrestricted	71922
20	MEYY	Xeloda	unrestricted	195
21	MEYY	CAPECITABINE	unrestricted	2185

22	MEYY	ANTINEOPLASTIC-COMBINED-CHEMOTHERAPY-PROTOCOLS.DE.	unrestricted	60820
23	MEYY	20 OR 21 OR 22	unrestricted	61949
24	MEYY	14 AND 19 AND 23	unrestricted	8

C6. In the data extraction of ML17032 (page 37) it is reported that 'patients were excluded from the per protocol population if they received less than 6 weeks treatment for reasons of PD or death'. Please clarify if this was intended to read 'for reasons other than PD or death'.

NICE's assumption is correct the text on page 37 should read "for reasons other than PD or death"

C7. Page 39 of the submission states that there were 63 centres which were all in the UK. In Cunningham et al. (2008), it is stated that there were 61 centres, 59 of which were in the UK while 2 were in Australia. Please clarify.

The CSR states that patients were recruited at 63 sites in the UK and Australia. It then lists these. The list contains 61 entries. Of these two- "Poole/Bournmouth" and "Salisbury/Southampton" are the subject of a footnote stating that these both represent two centres (it is unclear why they are connected – possibly because a single investigator recruited at both sites?) This would appear to account for discrepancy in site numbers. The claim that the two Australian sites are in the UK was an error on the part of the writer of the Roche submission.

C8. In figure 8 (page 42), the title reads 'Kaplan-Meier curves of PFS'. Please clarify if this should be 'Kaplan-Meier curves of OS' (as per the caption).

It can be confirmed that the title of Figure 8 should refer to OS not PFS

C9. Section 6.5.2 (page 45) reads "Although the authors of the meta-analysis do specify…" please clarify if this was this intended to read "do not specify…."

It can be confirmed that text in question should read "do **not** specify…"

C10. Please confirm that the last paragraph on page 45 should read '5-FU combinations and those treated with capecitabine combinations' rather than '5-FU combinations and those treated with 5-FU combinations'.

It can be confirmed that text in question should read "5-FU combinations and those treated with **capecitabine** combinations"

C11. In table 25 (page 71), 5-FU is given for 21 days in the CF regimen. Please confirm that this should be **5 days.**

C12. In table 39 (page 89), the cost of epirubicin in the ECX regimen is given as £792. The calculations used appear to be £692. Please confirm that this should be £**692.**

Appendix 1. QoL data from REAL 2 CSR

10.1 Quality of Life

Table 10-1 gives a brief breakdown of the QOL compliance. Quality of life is part of the randomisation/eligibility criteria. The compliance in this study is remarkably good considering the multi-centre nature and the poor prognosis of the patients. 70.1% and 61.9% of patients expected to complete the QOL form completed 12 and 24 weeks respectively. However, this is only for patients who are expected to complete the forms (dead and withdrawn, refused patients excluded).

Table 10-1 Quality of life compliance (% of patients expected to complete a form)

	ECF	ECX	EEF	EEX	Total
Baseline					
QOL complete	240	227	228	236	931
	96.0%	94.2%	97.0%	98.7%	96.5%
Reasons for no QOL					
Refused		1			1
Reason Unknown	8	10	5	2	25
Administrative error	2	3	2	1	8
12 week assessment					
Died before 12 weeks	35	27	25	29	116
Refused QOL	3	4	1	2	10
Withdrawn	1		1	2	4
QOL complete	142	146	152	145	585
% of those expected	67.3%	69.5%	73.1%	70.4%	70.1%
Too ill to complete QOL	9	4	2	3	18
Administrative error	34	33	24	35	125
Reason unknown		27	30		106
24 week assessment	82			66	
Died before 24 weeks	3	62	67	3	277
Refused QOL	104	7		111	13
QOL complete	61.9%	105	106	64.2%	426
% of those expected	5	58.7%	63.1%	4	61.9%
Too ill to complete QOL	19	3	3	24	15
Administrative error	37	23	23	31	89
Reason Unknown		41	36		145

Baseline levels Functional domains

Report

		ECF REGIMEN	ECX REGIMEN	EEF REGIMEN	EEX REGIMEN	Total
Mean	PhysBase	81.50	83.24	83.42	82.45	82.63
	RoleBase	68.76	71.37	73.21	70.72	70.97
	EmotBase	72.28	73.48	71.04	71.20	72.00
	CogBase	86.70	85.99	86.28	86.14	86.29
	SocBase	68.55	73.80	72.46	71.06	71.41
	GlobBase	60.54	63.90	63.43	61.79	62.38
N	PhysBase	238	221	225	232	916
	RoleBase	239	222	222	230	913
	EmotBase	239	220	220	226	905
	CogBase	240	222	224	228	914
	SocBase	237	221	221	228	907
	GlobBase	240	223	224	230	917
Median	PhysBase	87.00	87.00	87.00	87.00	87.00
	RoleBase	67.00	83.00	♪ 83.00	83.00	83.00
	EmotBase	75.00	75.00	75.00	75.00	75.00
	CogBase	100.00	100.00	100.00	100.00	100.00
	SocBase	67.00	♪ 83.00	♪ 83.00	83.00	83.00
	GlobBase	67.00	67.00	67.00	67.00	67.00
Std. Deviation	PhysBase	18.309	18.399	18.897	20.041	18.911
	RoleBase	30.833	31.023	31.511	31.704	31.255
	EmotBase	23.339	22.314	23.087	23.810	23.134
	CogBase	19.775	18.461	19.648	19.289	19.280
	SocBase	28.597	28.163	30.472	30.761	29.530
	GlobBase	22.322	21.832	23.841	23.651	22.925

♪ p<0.05 ♫ p<0.01

Mean changes from baseline at time point 1 (12 weeks) and time point 2 (24 weeks)

	armcd				
	ECF REGIMEN	ECX REGIMEN	EEF REGIMEN	EEX REGIMEN	Total
Physdif2	-8.9264	-11.0222	-9.9185	-12.3813	-10.5783
Physdif3	-9.9200	-10.5361	-9.6300	-10.9048	-10.2537
Roledif2	-5.8000	-5.4863	-11.5108	-12.9275	-8.9653
Roledif3	-9.1600	-8.9293	-14.9167	-9.0865	-10.4687
emotdif2	8.1154	5.7956	6.2000	3.7185	5.9367
emotdif3	3.8163	3.8061	6.3736	4.2286	4.5179
cogdif2	-4.1756	-3.5182	-3.7007	-4.1022	-3.8708
cogdif3	-6.5500	-2.6939	-8.3750	-6.5849	-6.5525
socdif2	-4.0462	-4.4527	♪ -12.0000	-9.1739	-7.4842
socdif3	-4.0510	-11.7368	-8.1684	-5.7048	-7.3461
globdif2	-.1567	-2.3750	-4.2993	-2.0511	-2.2316
globdif3	-3.9293	-1.6354	-3.2917	-1.3714	-2.5404
fatdif2	8.5038	10.0385	6.1504	11.1304	8.9718
fatdif3	11.3960	14.3474	12.9149	7.8190	11.5165
nvdif2	-2.0511	-3.5177	-1.2590	-2.0839	-2.2321
nvdif3	-1.6733	-.8218	-3.5100	-4.8991	-2.7654
paindif2	-11.1504	-12.9323	-8.1159	-8.5870	-10.1624
paindif3	-5.9388	-11.3918	-7.9053	-4.8411	-7.4458
dyspdif2	4.1022	1.6338	1.6383	-.4653	1.6986
dyspdif3	9.7255	6.8725	6.6238	.8991	5.9420
slpdif2	-6.7826	-7.5248	-7.0211	-3.2535	-6.1385
slpdif3	-6.2059	-10.1881	-11.2079	-4.2685	-7.9005
appdif2	-19.9927	♪ -9.4638	-12.5745	-8.5694	-12.5929
appdif3	-14.0784	-6.9505	-12.7800	-11.9174	-11.4442
condif2	-11.7744	-3.1752	-8.1439	-8.4493	-7.8692
condif3	-9.9604	-3.0306	-4.4948	-3.7264	-5.3085
clardif2	2.7727	2.6912	6.1103	8.6594	5.0886
clardif3	4.6600	-.3571	.3646	1.2453	1.4950
findif2	1.7405	.5000	7.2086	3.3597	3.2385
findif3	3.9900	1.0722	9.4316	1.5327	3.9173

♪ p<0.05 ♫ p<0.01

We subsequently asked for a clearer version of these (pp43-44) and were provided with the tables given in Appendix 4.

Appendix 3: Ongoing studies identified by the ERG from a search of ClinicalTrials.gov

Title	Comparison(s)	Status	ClinicalTrials.gov identifier
Paclitaxel plus capecitabine	CX versus X plus Paclitaxel	Recruiting	NCT01015339
Avastin in combination with Xeloda and Cisplatin	CX versus CX plus bevacizumab	Recruiting	NCT00887822
Phase II study of ECX versus CX	ECX versus CX	Recruiting	NCT00743964
EXPAND	CX versus CX plus cetuximab	Recruiting	NCT00678535
Oxaliplatin and S-1 or oxaliplatin and capecitabine	OX versus O + S-1	Recruiting	NCT00985556
REAL-3	EOX versus EOX plus panitumumab	Recruiting	NCT00824785
Epirubicin, oxaliplatin and capecitabine or docetaxel and oxaliplatin	EOX versus oxaliplatin plus docetaxel	Recruiting	NCT00806949
AMG 102 plus ECX	ECX versus ECX plus AMG 102 *	Recruiting	NCT00719550
AVGAST	CX versus CX plus bevacizumab	Ongoing but not recruiting	NCT00548548
LOGIC	OX versus OX + lapatinib	Recruiting	NCT00680901
Phase 2 study of AMG 386 (20060439)	CX versus CX + AMG386	Ongoing but not recruiting	NCT00583674
Metastatic Gastric cancer FFCD 03-07	ECX versus FOLFIRI (5-FU plus irinotecan plus folinic acid)	Ongoing but not recruiting	NCT00374036
MATRIX EG	ECX versus ECX plus matuzumab	Completed	NCT00215644

*Study employed several doses of experimental agent.

Appendix 4: QoL data from REAL-2 CSR (page numbers refer to CSR)

10 Other endpoints

10.1 Quality of Life

Table 10-1 gives a brief breakdown of the QOL compliance. Quality of life is part of the randomisation/eligibility criteria. The compliance in this study is remarkably good considering the multi-centre nature and the poor prognosis of the patients. 70.1% and 61.9% of patients expected to complete the QOL form completed 12 and 24 weeks respectively. However, this is only for patients who are expected to complete the forms (dead and withdrawn, refused patients excluded).

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Refused QOL	104	7		111	13
QOL complete	61.9%	105	106	64.2%	426
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Reason Unknown		41	36		145

Baseline levels Functional domains

Report

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	CogBase	86.70	85.99	86.28	86.14	86.29
	SocBase	68.55	73.80	72.46	71.06	71.41
	GlobBase	60.54	63.90	63.43	61.79	62.38
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	SocBase	237	221	221	228	907
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	EmotBase	75.00	75.00	75.00	75.00	75.00
	CogBase	100.00	100.00	100.00	100.00	100.00
	SocBase	67.00	♪ 83.00	♪ 83.00	83.00	83.00
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	SocBase	28.597	28.163	30.472	30.761	29.530
	GlobBase	22.322	21.832	23.841	23.651	22.925

♪ $p<0.05$ ♫ $p<0.01$

Baseline Symptom domains

		ECF REGIMEN	ECX REGIMEN	EEF REGIMEN	EEX REGIMEN	Total
Mean	FatBase	35.68	34.32	33.18	35.83	34.78
	NVbase	22.76	19.06	19.97	21.03	20.74
	PainBase	28.21	27.43	24.98	25.66	26.59
	DyspBase	16.60	16.15	13.26	15.82	15.48
	SlpBase	32.03	32.24	31.48	31.56	31.83
	AppBase	47.11	42.51	42.00	41.40	43.29
	ConBase	31.47	26.19	23.52	26.46	26.98
	DiarBase	6.51	7.47	10.27	8.23	8.09
	FinBase	15.66	16.10	15.20	16.34	15.83
Std. Deviation	FatBase	24.143	25.177	26.051	25.644	25.227
	NVbase	25.247	22.992	24.400	26.391	24.811
	PainBase	25.650	26.898	23.945	27.449	26.013
	DyspBase	25.133	23.125	21.090	24.888	23.651
	SlpBase	31.132	32.543	31.656	30.119	31.310
	AppBase	36.868	35.917	36.079	35.563	36.128
	ConBase	33.607	30.935	29.648	32.946	31.944
	DiarBase	16.366	18.277	19.692	19.782	18.575
	FinBase	29.235	27.913	28.422	29.351	28.708
Median	FatBase	33.00	33.00	33.00	33.00	33.00
	NVbase	17.00	17.00	17.00	17.00	17.00
	PainBase	17.00	17.00	17.00	17.00	17.00
	DyspBase	.00	.00	.00	.00	.00
	SlpBase	33.00	33.00	33.00	33.00	33.00
	AppBase	33.00	33.00	33.00	33.00	33.00
	ConBase	33.00	33.00	♫ .00	.00	33.00
	DiarBase	.00	.00	♪ .00	.00	.00
	FinBase	.00	.00	.00	.00	.00

♪ $p<0.05$ ♫ $p<0.01$

Mean changes from baseline at time point 1 (12 weeks) and time point 2 (24 weeks)

	armcd				
	ECF REGIMEN	ECX REGIMEN	EEF REGIMEN	EEX REGIMEN	Total
Physdif2	-8.9254	-11.0222	-9.9185	-12.3813	-10.5783
Physdif3	-9.9200	-10.5361	-9.6300	-10.9048	-10.2537
Roledif2	-5.8000	-5.4853	-11.5108	-12.9275	-8.9653
Roledif3	-9.1600	-8.9293	-14.9167	-9.0865	-10.4687
emotdif2	8.1154	5.7956	6.2000	3.7185	5.9367
emotdif3	3.8163	3.8061	6.3736	4.2286	4.5179
cogdif2	-4.1756	-3.5182	-3.7007	-4.1022	-3.8708
cogdif3	-8.5500	-2.6939	-8.3750	-6.5849	-6.5525
socdif2	-4.0462	-4.4627	♪ -12.0000	-9.1739	-7.4842
socdif3	-4.0510	-11.7368	-8.1684	-5.7048	-7.3461
globdif2	-.1567	-2.3750	-4.2993	-2.0511	-2.2316
globdif3	-3.9293	-1.6354	-3.2917	-1.3714	-2.5404
fatdif2	8.5038	10.0385	6.1504	11.1304	8.9718
fatdif3	11.3960	14.3474	12.9149	7.8190	11.5165
nvdif2	-2.0511	-3.5177	-1.2590	-2.0839	-2.2321
nvdif3	-1.6733	-.8218	-3.5100	-4.8991	-2.7664
paindif2	-11.1504	-12.9323	-8.1159	-8.5870	-10.1624
paindif3	-5.9388	-11.3918	-7.9053	-4.8411	-7.4458
dyspdif2	4.1022	1.6338	1.6383	-.4653	1.6986
dyspdif3	9.7255	6.8725	6.6238	.8991	5.9420
slpdif2	-6.7826	-7.5248	-7.0211	-3.2535	-6.1385
slpdif3	-6.2059	-10.1881	-11.2079	-4.2685	-7.9005
appdif2	-19.9927	♪ -9.4638	-12.5745	-8.5694	-12.5929
appdif3	-14.0784	-6.9505	-12.7800	-11.9174	-11.4442
condif2	-11.7744	-3.1752	-8.1439	-8.4493	-7.8592
condif3	-9.9604	-3.0306	-4.4948	-3.7264	-5.3085
diardif2	2.7727	2.6912	6.1103	8.6594	5.0886
diardif3	4.6600	-.3571	.3646	1.2453	1.4950
findif2	1.7405	.5000	7.2086	3.3597	3.2385
findif3	3.9900	1.0722	9.4316	1.5327	3.9173

♪ $p<0.05$ ♫ $p<0.01$