[redacted]
National Institute for Health and Clinical Excellence (NICE)
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London
WC1V 6NA

21 January 2010

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

Dear [redacted]

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,

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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.

Individual patient data meta-analysis

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 £

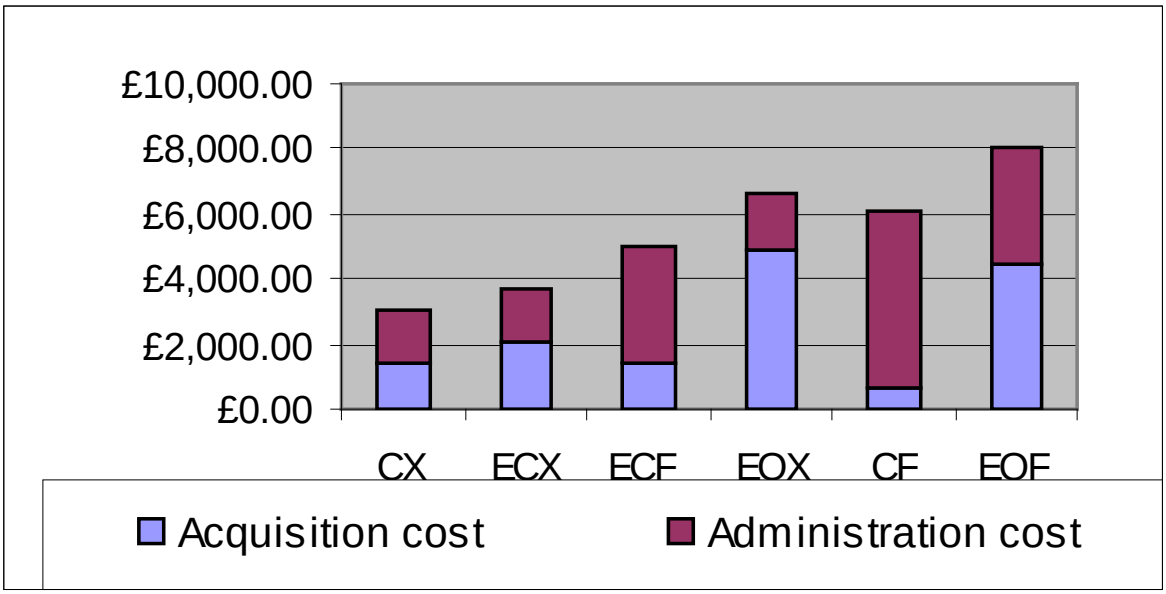
Table 4. Overall NHS Cost of CF and CX*

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 1. 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	484		1	
	Capecitabine	480	0.096	0.889	0.774-1.021
Performance Status	0	312		1	
	1	549	<0.001	1.358	1.162-1.586
	2	103	<0.001	2.410	1.899-3.058
Extent of disease	Locally advanced	219		1	
	Metastatic	785	<0.01	1.563	1.318-1.853
Age	</=63	495		1	
	>63	469	0.028	0.856	0.746-0.983

Variables not included in final model

Factor	Group	N	p-value
Primary site	Oesophagus Oesophago-gastric junction Gastric	333 248 383	0.325
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 Oesophago-gastric junction Gastric	333 248 383	0.325
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

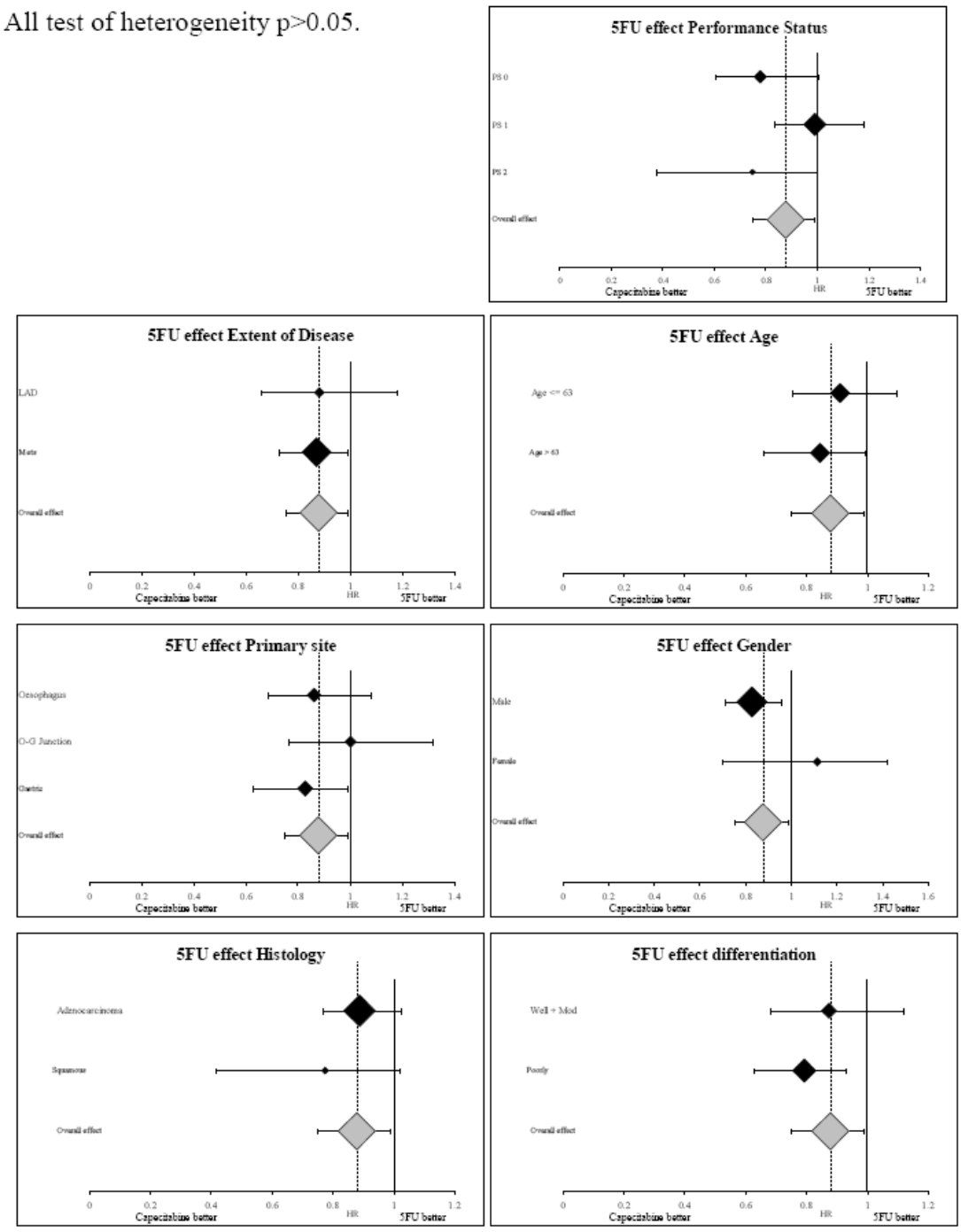
A21. Please provide efficacy data broken down according to the following subgroups from the REAL-2 trial:

- **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



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.

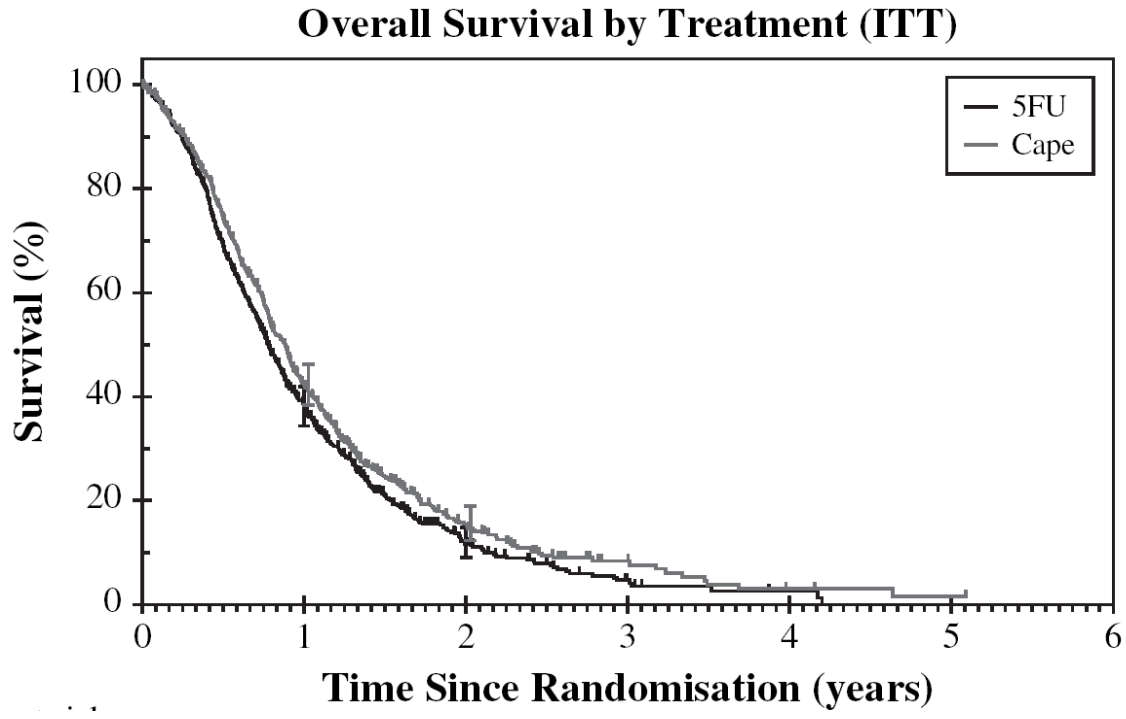
Results from the meta-analysis indicate that there was not significant difference in PFS between the capecitabine and the 5FU arms, therefore for the purposes of costing, the additional OS benefit is assumed to be generated from time spent within the progressed health state. As the progressed disease 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

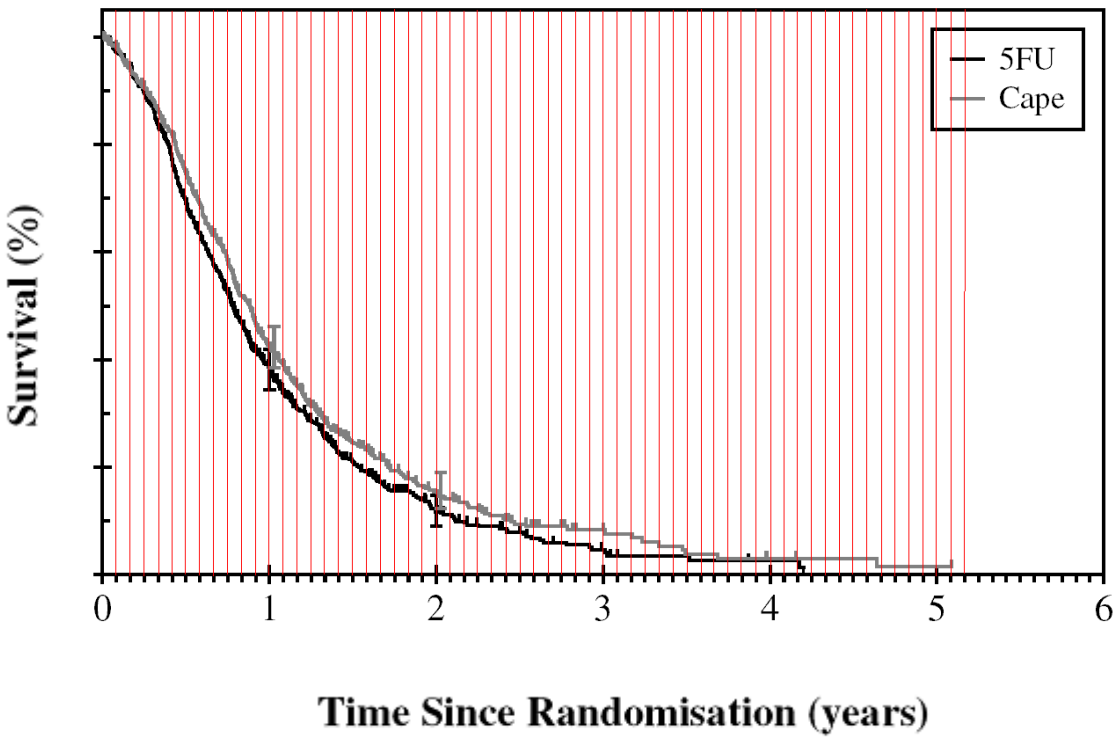
The Kaplan–Meier curves published by Okines et al 2009 (See Figure 3) below were used to estimate the mean overall survival in patients treated with capecitabine-based chemotherapy and 5-fluorouracil (5-FU)-based chemotherapy using an area under the curve procedure.

Figure 3. OS Kaplan Meiers from Okines et al.



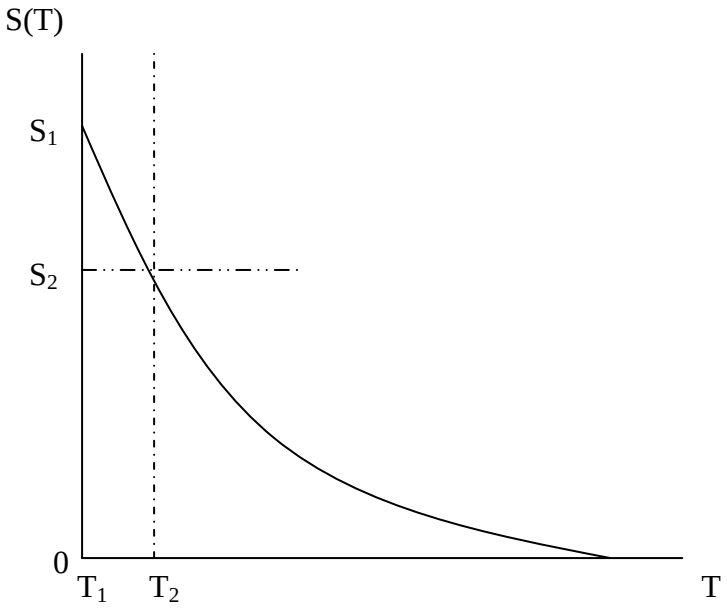
Microsoft Paint was utilised to divide each curve into monthly segments to ensure data point sampling was equivalent for both curves. (See Figure 4 below).

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.

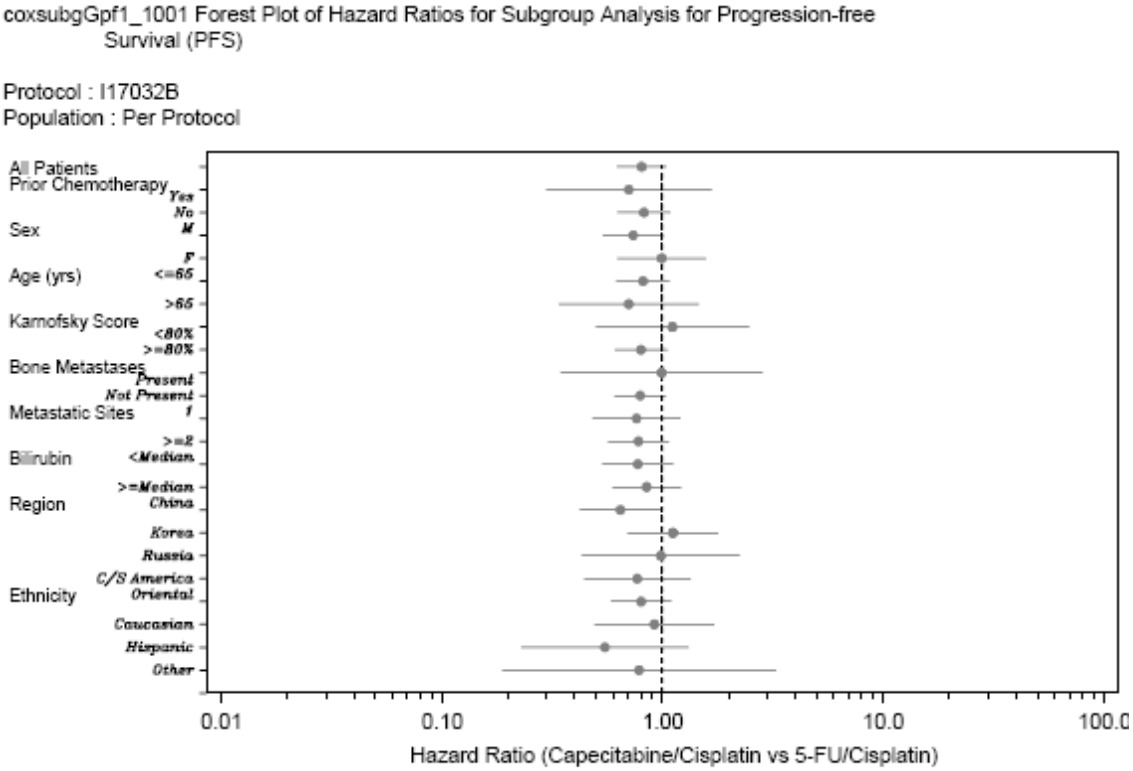
B3. Please state how the mean number of cycles vary between different subgroups of patients, such as by tumour histology, performance status, locally advanced vs metastatic disease. Please provide a sensitivity analysis informed by these data.

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
01MAR2006 10:09

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 the first-line treatment of metastatic colorectal cancer)	£156

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

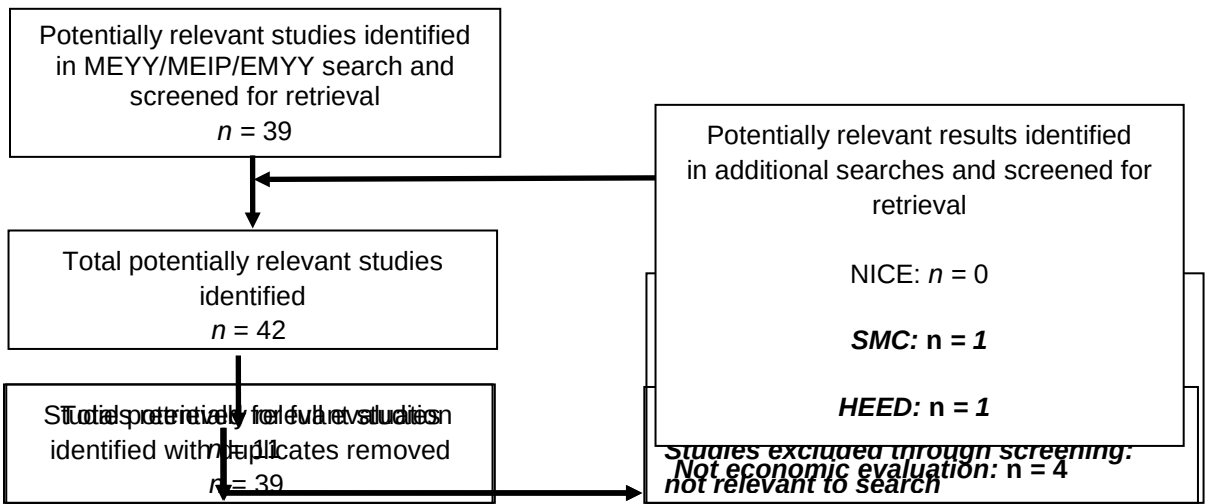
C1. In the QUORUM flow diagram in figure 4, please clarify how the 11 records covering the 4 RCTs are identified from the initial 179 records.

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.



Relevant studies on the cost effectiveness of capecitabine use in aGC in the UK

n = 1 (SMC result)

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

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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	-8.9254	-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	-6.3750	-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	7.8150	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	♪ -9.4538	-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	3.2395
findif3	3.9900	1.0722	9.4316	1.5327	3.9173

♪ p<0.05 ♫ p<0.01