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Fluorouracil plasma monitoring: the My5-FU assay for guiding dose adjustment in patients receiving fluorouracil chemotherapy by continuous infusion

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5-FU	5-Fluorouracil
AACR	American Association for Cancer Research
ACCE	Analytic validity, Clinical validity, Clinical utility and Ethical
ACP	Association of Cancer Physicians
ACPGBI	Association of Coloproctology of Great Britain and Ireland
ACRC	Advanced Colorectal Cancer
AE	Adverse Event
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
AS	Age-Standardised
ASCO	American Society of Clinical Oncology
AUC	Area Under the Curve
BIC	Bayesian Information Criterion
BMI	Body Mass Index
BNF	British National Formulary
BSA	Body Surface Area
CapeOx	Capecitabine plus Oxaliplatin
CDDP	Cis-Diamminedichloroplatinum
CEAC	Cost-Effectiveness Acceptability Curve
CENTRAL	Cochrane Central Register of Controlled Trials
CG	Clinical Guideline
CI	Confidence Interval
CHART	Continuous Hyper-Fractionated Accelerated Radiotherapy
CHEERS	Consolidation Health Economic Evaluation Reporting Standards
CLIA	Clinical Laboratory Improvement Amendments
coef	Coefficient
CR	Complete Response
CRC	Colorectal Cancer
CRD	Centre for Reviews and Dissemination
Css	Concentrations at Steady State
CTs	Computerised Tomography Scan
CV	Coefficient of Variation
DALYS	Disability-Adjusted Life Year

DAP	Diagnostics Assessment Programme
DARE	Database of Abstracts of Reviews of Effects
DVT	Deep Vein Thrombosis
DPD	Dihydropyrimidine-Dehydrogenase
EAG	External Assessment Group
ECCO	European Cancer Organisation
EDTA	Ethylenediaminetetraacetic Acid (Anticoagulant)
EGFR	Anti Epidermal Growth Factor Receptor
EMBASE	*Excerpta Medica* Database
ESMO	European Society for Medical Oncology
EONS	European Oncology Nursing Society
EORCT QLQ-C30	The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire
EQ-5D	Euroqol 5 Dimensions
ERG	Evidence Review Group
FA	Folinic Acid
FAP	Familial Adenomatous Polyposis
FOBt	Faecal Occult Blood Test
FOLFIRI	Irinotecan in Combination with 5-Flourouracil and Folinic Acid
FOCUS	Fluorouracil, Oxaliplatin, CPT-11 use and Sequencing
FOLFOX	Oxaliplatin in Combination With 5-Flourouracil and Folinic Acid
FU	Fluorouracil
FUFOL	Folinic acid, 5-Fluorouracil
FUFO	Fluorouracil, Foliniate
G-CSF	Granulocyte Colony-Stimulating Factor
GDG	Guideline Development Group
GI	Gastrointestinal
GISTs	Gastrointestinal Stromal Tumours
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GP	General Practice
h	Hour
HER2	Human Epidermal Growth Factor Receptor 2
H&N	Head and Neck
HNSCCs	Head and Neck Squamous Cell Cancer
HNPCC	Hereditary Non Polyposis Colon Cancer

h/l	Hour per Litre
HPLC	High-Performance Liquid Chromatography
HPLC-UV	High-Performance Liquid Chromatography with Ultraviolet detection
HPV	Human Papilloma Virus
HR	Hazard Ratio
HRG	Health Resource Group
HS	Hospital Stay
HTA	Health Technology Appraisal
HUI	Health Utilities Index
ICER	Incremental Cost-Effectiveness Ratio
INAHTA	International Network of Agencies for Health Technology Assessment
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention to Treat
IPD	Individual Patient Data
Iv	Intravenous
IQR	Interquartile Range
ICU	Intensive Care Unit
KCI	Potassium Chloride
KM	Kaplan-Meier
KRAS-WT	Kirsten Rat Sarcoma-Wild Type
LCI	Lower Confidence Interval
LC-MS	Liquid Chromatography Mass Spectrometry
LOS	Length of Stay
LV5FU2	5-FU + Folinic Acid (leucovorin) regimen
LYG	Life Year Gain
MA	Meta-Analysis
MAb	Monoclonal Antibodies
mCRC	Metastatic Colorectal Cancer
mFOLFOX6	Modified FOLFOX6
MTC	Mixed Treatment Comparison
MD	Mean Difference
MDT	Multi-Disciplinary Team
Mg	Milligrams
MO	Months
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging

MR	Minimal Response
MRS	Magnetic Resonance Spectroscopy
MS	Mass Spectrometer
MTA	Multiple Technology Appraisal
MTD	Maximally Tolerated Dose
N	Number
NR	Not Reported
NA	Not Applicable
NaCl	Sodium Chloride
NMA	Network Meta-analysis
Nc	Total Number of Cycles
nc	Number of Cycles
NCI CTAE	National Cancer Institute Common Terminology for Adverse Event
NCI-CTC	National Cancer Institute-Common Toxicity/Terminology Criteria
NCIN	National Cancer Intelligence Network
NCIN SACT	National Cancer Intelligence Network Systemic Anti-Cancer Therapy Dataset
NCRN	National Cancer Research Network
NIHR	National Institute for Health Research
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NHSBCSP	NHS Bowel Cancer Screening Programme
NICE	National Institute for Health and Care Excellence
NNT	Number Needed to Treat
NR	Not Reported
NS	Not Statistically Significant
ODPM	Onco Drug Personalized Medicine
OHP	Oxaliplatin
ONS	Office for National Statistics
OR	Odds Ratio
OS	Overall Survival
OXA	Oxaliplatin
PASA	Purchasing and Supply Agency
PCM	Personalized Chemotherapy Management
PF	Cisplatin/5-fluorouracil
PD	Progressive Disease

PDAC	Pancreatic Ductal Adenocarcinoma
PICC	Peripherally Inserted Central Catheter
PICO	Patient/Population Intervention Comparison Outcome
PET-CT	Positron-Emission Tomography Fused with Computed Tomography
PFS	Progression Free Survival
PK	Pharmacokinetics
PK-FU	Pharmacokinetic-Guided Fluorouracil
PR	Partial Response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROFUSE	Prospective 5-Fluoouracil Ondose Evaluation
PROMs	Patient Reported Outcome Measures
PROs	Patient Reported Outcomes
PS	Performance Status
PSS	Personal and Social Services
PSSRU	Personal Social Services Research Unit
PTO	Person Trade Off
PVI	Protracted Venous Infusion
QALY	Quality-Adjusted Life Year
QC	Quality Care/Control
QOL	Quality Of Life
QTRAP	Quadrupole Ion Trap Technology
QUADAS	Quality Of Diagnostic Accuracy Studies
RECIST	Response Evaluation Criteria in Solid Tumors
REPEC	Research Papers in Economics
RCT	Randomised Controlled Trial
SCI	Science Citation Index
SCCHN	Squamous Cell Carcinoma of the Head And Neck
SCOT trial	Short Course Oncology Therapy
SCPRT	Short Course Preoperative Radiotherapy
SD	Standard Deviation
SD	Stable Disease
s.e.m	Standard Error of Measurement
SG	Standard Gamble
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic Review
SS	Statistically Significant

SSCI	Social Sciences Citation Index
TA	Technology Appraisal
TNM	Tumour, Node, Metastasis
TPF	Docetaxel, Cisplatin, 5-FU
TTO	Time Trade Off
U/UH2 ratios	Uracil / Dihydrouracil ratio
UICC	Union International Contre Le Cancer/ International Union Against Cancer
UCI	Upper Confidence Interval
UKCRN	UK Clinical Research Network
VAS	Visual Analogue Scale
VEGF	Anti-Vascular Endothelial Growth Factor
Vs.	Versus
WBC	White Blood Cell
WHO	World Health Organisation
WHOICTRP	World Health Organization's International Clinical Trials Registry Platform
WTP	Willingness-To-Pay
XELOX	Oxaliplatin in Combination with Capecitabine
XELIRI	Irinotecan in Combination with Capecitabine
YR(s)	Year(s)

ABSTRACT

Introduction

5-flourouracil (5-FU) is a chemotherapy used in colorectal, head and neck (H&N) and other cancers. Dose adjustment is based on body surface area (BSA) but wide variations occur. Pharmacokinetic (PK) dosing is suggested to bring plasma levels into the therapeutic range to promote fewer side effects and better patient outcomes. We investigated the clinical and cost effectiveness of the My5-FU assay for PK dose adjustment to 5-FU therapy.

Objectives

To systematically review the evidence on:

A. the accuracy of the My5-FU assay compared to gold standard methods (High-Performance Liquid Chromatography [HPLC] and Liquid Chromatography-Mass Spectrometry [LC-MS]).
B. the effectiveness of My5-FU PK dosing compared to BSA
C. the effectiveness of HPLC and/or LC-MS compared with BSA
D. the generalizability of published My5-FU and PK studies
E. costs of using My5-FU

To develop a cost-effectiveness model.

Methods

We searched MEDLINE, EMBASE, Science Citation Index and other databases between January-April 2014. Two reviewers independently screened titles and abstracts with arbitration and consensus agreement. We undertook quality assessment. We reconstructed Kaplan-Meier plots for progression-free survival (PFS) and overall survival (OS) for comparison of BSA and PK dosing.

We developed a cost effectiveness model to compare My5-FU with BSA dosing, using PFS, OS and adverse events and costs with a lifetime horizon, from a Health and Personal Social Services (PSS) with a 3.5% discount rate over a 10 year time horizon with a 2-week cycle length.

Results

8341 records were identified through electronic searches and 35 and 54 studies were included in the clinical and cost effectiveness reviews, respectively. There was a high correlation between My5-FU, HPLC and LC-MS/MS but upper and lower limits of agreement were -18% to +30%. Quality and quantity of evidence were very weak for PK versus BSA dosing for all cancers with no RCTs using

current regimens. Median overall survivals were estimated as 19.6 months (95% CI: 17.0 – 21.0) PK versus 14.6 months (95% CI: 14.1 – 15.3) BSA for 5-FU + FA (folinic acid) and 27.4 months (95% CI: 23.2 – 38.8) PK versus 20.6 months (95% CI: 18.4 – 22.9) BSA for FOLFOX6 in metastatic colorectal cancer. For H&N cancer, two studies of regimens no longer in use were identified. PK versus BSA studies were generalisable to the relevant populations.

We developed cost effectiveness models for mCRC and H&N. The base case assumed a cost per My5-FU assay of £61.03. For mCRC for 12 cycles of a FOLFOX regimen, there was a QALY gain of 0.599 with an ICER of £4,148 per QALY. Probabilistic and scenario analyses gave similar results. The CEAC showed My5-FU to be 100% cost effective at a threshold of £20,000 per QALY. For H&N cancer, again given caveats about the poor evidence base we also estimated that My5-FU is likely to be cost effective at a threshold of £20,000 per QALY.

Conclusions

Using a linked evidence approach My5-FU appears to be cost effective at a willingness to pay of £20,000 per QALY for both mCRC and H&N cancer. Considerable uncertainties remain about evidence quality and practical implementation. RCTs are needed of PK versus BSA dosing in relevant cancers.

1 EXECUTIVE SUMMARY

1.1 Introduction

5-flourouracil is used in a variety of regimens in a variety of cancers including: colorectal cancer, head and neck (H&N) cancer, pancreatic cancer and stomach cancer. This study investigates a method of pharmacokinetic (PK) adjustment of 5-FU levels – My5-FU. Plasma 5-FU levels are measured using My5-FU during a cycle of 5-FU chemotherapy and the dose of 5-FU for the subsequent cycle(s) is estimated. My5-FU testing can be performed on automated clinical chemistry analysers present in standard clinical laboratories.

The rationale for PK dose adjustment is that wide variations have been found between patients in 5-FU concentrations when treated with standard dosing regimens based on body surface area (BSA) calculations and that tighter control of therapeutic 5-FU levels is needed. Commonly reported side effects of 5-FU include anaemia, thrombocytopenia, leukopenia, nausea/vomiting, diarrhoea, mucositis, and hand-foot syndrome. Estimation of plasma 5-FU using PK methods and application of an appropriate algorithm for dose adjustment are required 3-4 times per patient in order to achieve designated target plasma levels. Dosage changes are more common with PK than with BSA methods.

It has been proposed that the assessment of 5-FU with My5-FU will result in dose adjustments which will bring plasma 5-FU more closely into the therapeutic range resulting in will encourage fewer side effects and better patient outcomes.

1.2 Objectives

In the current report we aimed to:

A. Provide a review of the studies which examine the accuracy of the My5-FU assay when tested against gold standard methods of estimation of 5-FU or which develop a treatment algorithm based on plasma 5-FU measures. High performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS) are considered the gold standard for the purpose of assessing the accuracy of 5-FU plasma level measurements.

B. Systematically review the literature on the use of My5-FU to achieve adjusted dose regimen(s) to compare it with BSA-based dose estimation for patients receiving 5-FU-administered by continuous infusion. Variations in current BSA-based dose regimens are considered where appropriate.

C. Systematically review the literature on the use of HPLC and/or LC-MS to achieve dose adjustment to compare it with BSA-based dose regimens for patients receiving 5-FU. This is undertaken for the purpose of performing a linked evidence analysis which incorporates estimates of comparability of assay performance of My5-FU relative to the gold standards (HPLC, LC-MS) as outlined in A.

D. Provide an overview of systematic reviews of clinical outcomes in studies of 5-FU cancer therapies administered by continuous infusion in order to assess the generalizability of outcomes reported in the control arms of studies included in B and C above; outcomes of interest included: incidence of side effects and 5-FU toxicity, treatment response rates, progression-free survival (PFS), overall survival (OS), and health related quality of life.

E. Identify evidence relevant to the costs of using My5-FU. Illustrative clinical pathways have been constructed; for this, we have used information provided by the manufacturer, advice from specialist committee members and other clinical experts, data collected from an identified UK clinical laboratory and analysis of the published literature. We have collected information on the following:
    a. Cost of My5-FU testing
    b. Cost of delivering 5-FU by infusion
       Cost of side effects and 5-FU toxicity and their associated treatment or hospitalisation

1.3 Clinical Effectiveness Summary Methods

We investigated the following decision problem:

- *Population:* Cancer patients (colorectal, head and neck, stomach, pancreatic) receiving 5-FU chemotherapy by continuous venous infusion
- *Intervention:* My5-FU (PK monitoring)
  Including a linked evidence analysis using studies of HPLC and LC-MS to adjust 5-FU dosing
- *Comparator:* BSA
- *Outcome:* Performance of My5-FU (e.g., correlation between My5-FU and "gold standard" in terms of progression free survival, overall survival and adverse events)
- *Setting:* Adjuvant and/or metastatic (the use of My5-FU in patients receiving treatment in the adjuvant or metastatic setting will be considered separately, if evidence permits)

We searched MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; Cochrane Library (including Cochrane Systematic Reviews, DARE, CENTRAL, NHS EED, and

HTA databases); Science Citation Index and Conference Proceedings (Web of Science); NIHR Health Technology Assessment Programme; PROSPERO (International Prospective Register of Systematic Reviews) in January to April 2014. The following trial databases were also searched: Current Controlled Trials; ClinicalTrials.gov; UKCRN Portfolio Database; WHO International Clinical Trials Registry Platform.

Two reviewers independently screened the titles and abstracts of all records identified by the searches and discrepancies were resolved through discussion. Quality assessment was undertaken using the Downs and Black (1998) checklist. Furthermore we adapted the QUADAS-2 checklist for use in assessing the quality of laboratory measurements of analytic validity, and plotted data on key outcomes of interest using Bland-Altman plots.

In the absence of individual participant data (IPD), we used the method of Guyot et al. to reconstruct Kaplan-Meier plots for PFS and OS for comparison of BSA and PK dosing in two regiments. Goodness of fit was judged visually and according to information criteria (Akaike information criterion, Bayesian information criterion). Clinical advisors and a relevant laboratory gave us information on clinical pathways.

1.4 Clinical Effectiveness Summary Results

3,751 records were identified through electronic searches. 203 remained after removal of duplicates and exclusions and 35 papers (representing eight unique studies) were included in the clinical effectiveness review.

1.4.1 Objective A

There is high correlation between My5-FU, HPLC and LC-MS/MS but the Bland-Altman plots show considerable variability. In the comparison of My5-FU with LC-MS/MS even with additional outliers listed as excluded, the validation data provided by the manufacturer shows outliers with a range of variation up to -285ng/mL and +171ng/mL (approx. -25% and +70%). Only one paper reported upper and lower limits of agreement. These were found to be -18% to +30%. These discrepancies between measurements need to be considered carefully. Personal communication with a clinical advisor suggested that this range of values (-18% to +30%) could be considered clinically equivalent; however we remain cautious about outliers.

1.4.2 Objectives B and C

The evidence on PK versus BSA dosing in the treatment of CRC patients is weak in both quantity and quality. This holds to an even greater extent for H&N cancer. Evidence on My5-FU is sparse; we

found only one study of clinical outcomes which compared BSA with PK dose adjustment after application of the My5-FU assay; this study was at risk of selection bias. Of three CRC comparative studies identified, only one was an RCT and unfortunately this study used an unrepresentative 8-h infusion regimen. Single arm studies were heterogeneous, generally of poor design, and were severely limited in ability to deliver useful data for comparison of PK versus BSA dosing. We have been unable to identify any published randomised evidence about the effectiveness of PK-directed dose adjustment for any currently used 5-FU regimen for any cancer type. None of the studies we investigated were of high quality, all had important drawbacks in design, methods, and key outcome coverage; these factors limit their validity and generalizability. From these studies there is therefore limited comparative evidence that can be taken forward for the modelling of the cost-effectiveness of My5-FU dose adjustment vs. BSA-based dose regimens. For example, for overall survival there were no studies of My5-FU. We relied on two studies in relation to PK versus BSA dosing; one using FOLFOX6 was directly relevant to current UK clinical practice. However there were problems with the control arm, not only was it not randomised and somewhat smaller than the pharmacokinetic dose adjustment arm, but only the median overall survival and median progression free survival were reported for it. The other relevant study was an RCT providing an analysis of difference in overall survival using pharmacokinetic dosing as opposed to BSA. However its relevance is questionable since the regimen investigated is not relevant to current UK practice: 5-FU + FA rather than FOLFOX6. There was also no reliable reporting of progression free survival, and we had to infer this using reported durations of response. Parameterised Weibull overall survival curves for these two studies differed noticeably.

We combined reconstructed IPD of single arms from studies from a variety of sources to undertake a comparison of PK dosing with BSA. Overall PK appeared to confer a benefit in both regimens for which any comparative data were available (5-FU + FA [folinic acid] and FOLFOX6 regimens) in both PFS and OS. Kaplan Meier plots resulting from single or combined study arms give approximate median overall survivals for FU + FA of 19.6 months (95% CI: 17.0 – 21.0; three studies) for PK and 14.6 months (95% CI: 14.1 – 15.3; five studies) for BSA, and for FOLFOX6 of 27.4 months (95% CI: 23.2 – 38.8; one study) for PK and 20.6 months (95% CI: 18.4 – 22.9; three studies) for BSA. However these apparent benefits should be viewed with extreme caution because of the quality of the evidence.

For example, the comparison (PK versus BSA) for survival outcomes is greatly weakened by the paucity of evidence for the PK arms: in the case of FOLFOX6 the PK evidence comes from a single non-randomised study which failed to provide full data for the comparator arm, and in the case of 5-FU + FA, the PK evidence for PFS was provided by a lone single arm study in which no comparator data were presented. In terms of adverse events, comparison was hampered by differing and selective

reporting of toxicity outcomes allowing no synthesis of toxicity data. Thus an assessment of the effectiveness of PK for these outcomes relies on the dubious procedure of comparing various arms from different studies with potentially different underlying populations and anticipated outcomes using "derived" data.

For H&N cancer, only two studies comparing BSA and PK were identified. Both studies were more than 15 years old and used regimens no longer in current clinical use.

1.4.3 Objective D

The results for the BSA arms for overall survival and progression free survival in colorectal cancer in the small number of double arm studies available were compared with BSA arms in studies included in the NICE CG 131 systematic review of CRC. These were sufficiently similar to conclude that the BSA arms in the comparison between PK and BSA regimens presented in the two CRC studies were not unrepresentative of CRC patients in general. Likewise, although the paucity of data makes it difficult to draw firm conclusions, the risk of adverse events reported does not appear to be out of line with data from CG131.

1.5 Cost Effectiveness Summary Methods

1.5.1 Search strategy

A comprehensive search of the literature for published economic evaluations, utility studies and cost studies was performed. Several search strategies were required. Searches were undertaken in March and April 2014. Additional searches were undertaken to identify other relevant information to support the development of the economic model (e.g., past NICE assessments in mCRC). No study designs were excluded.

We aimed to develop a model to assess the impact of pharmacokinetic dose adjustment using My5-FU compared to BSA dosing, using the outcomes identified from the clinical effectiveness reviews in terms of PFS and OS with a lifetime horizon, from a Health and Personal Social Services perspective and with a 3.5% discount rate. We incorporated estimates of the impact of My5-FU dose adjustment on test costs, treatment costs, side effect costs and the quality of life impacts of side effects. QALY impact of adverse events was drawn from expert opinion. Costs of grade I/II and grade III/IV adverse events were based on NHS reference costs for those hospitalised and medication costs for those not hospitalised. The model was constructed as a cohort distributed between health states over a 10 year time horizon. A 2 week cycle was employed (in line with the FOLFOX cycle length).

1.5.2 Cost Effectiveness Summary Results

4,578 records were identified through electronic searches. 12 additional records were identified from other sources. After removal of duplicates and exclusions 54 papers were included in the cost effectiveness review.

1.5.2.1 Metastatic colorectal cancer

The base case assumed a cost per completed My5-FU assay of £61.03 and 3.23 assays per patient. Analyses based on FOLFOX studies were hampered by the lack of a proper BSA dosing control arm. We inferred BSA overall and progression free survival curves from reported median survival data suggesting a gain of 0.599 QALYs with PK dosing. The total additional total cost of My5-FU dose adjustment was £2,483, giving a cost effectiveness estimate of £4,148 per QALY. Probabilistic modelling resulted in a similar central estimate. The CEAC showed My5-FU to be 100% likely to be cost effective with a threshold of £20,000 per QALY.

Cost effectiveness estimates were reasonably stable as the source of parameterised curves was varied and in the scenario analysis which used different derivations of the overall survival curves for My5-FU and for BSA dosing.

Sensitivity analyses were undertaken as follows:

- 10% of patients undergoing an additional 12 cycles of FOLFOX treatment after one year
- Outpatient visit required for My5-FU estimation
- Quality of life estimates used from previous NICE guideline CG131

These caused the cost effectiveness estimates to change to £5,272 per QALY, £4,506 per QALY and £6,016 per QALY respectively. These analyses are based on poor quality evidence, are inferred from limited data, and as a consequence are subject to considerable uncertainty.

Cost effectiveness modelling was also undertaken based on 5-FU + FA studies where evidence was derived from an RCT. (Costs of FOLFOX were retained for these analyses because 5-FU + FA is not typically used in the UK). The 5-FU + FA RCT suggests a lower survival gain from My5-FU with a net gain of 0.151 QALYs. Net additional costs of around £883 result in a cost effectiveness estimate of £5,853 per QALY. Changing the method used to infer progression free survival, worsened this cost effectiveness estimate to between £6,965 and £8,615 per QALY.

1.5.2.2 Locally advanced head and neck cancer

We explored the hazard ratios for progression free survival and overall survival required for My5-FU to be cost effective for dose adjustment during induction therapy for locally advanced head and neck cancer. Estimated cost increases associated with My5-FU were not large in the context of costs of current induction therapy followed by chemo-radiotherapy. Given the somewhat longer survival among patients with locally advanced head and neck cancer compared to mCRC patients, hazard ratios required to justify the additional cost at a willingness to pay of £20,000 per QALY were not far from unity and a hazard ratio of 0.95 would be modelled as easily justifying the additional cost. With a hazard ratio of 0.966 for progression free survival and no gain in overall survival there is an estimated net gain of 0.014 QALYs and an estimated cost increase of £285, resulting in a cost-effectiveness estimate of £20,586 per QALY, although this result should be viewed as highly speculative. If there is no impact upon progression free survival, the hazard ratio for overall survival is only required to be 0.990 for the cost effectiveness of My5-FU to be estimated to be £20,601 per QALY.

1.6 Discussion and Conclusions

A cost-effective testing method for 5-FU levels has been considered for some time to be likely to help in replacing body surface area dosing with pharmacokinetically guided 5-FU dose management. Although the clinical and cost effectiveness evidence is extremely limited and is of poor quality, it seems appropriate to conclude that there may be benefits to PK dose adjustment, including benefits in overall survival and progression-free survival and reduction in some adverse events (such as diarrhoea). Although there is a good correlation between different assays measuring 5-FU (i.e., between HPLC-MS for PK dose adjustment and My5-FU), we have some concerns about the clinical significance of the discrepancies found, which may affect the validity of a linked evidence approach.

With the previous caveats in mind we used a linked evidence approach, and the reported benefits of PK dosing to estimate the benefits and costs of use of My5-FU in metastatic colorectal cancer and in H&N cancers. We estimated a base case deterministic ICER for use of My5-FU for a FOLFOX regimen for mCRC given over 12 cycles of £4,148 per QALY compared to the standard BSA-based approach. For H&N cancer, again given the caveats on the available evidence My5-FU is also likely to be cost effective at standard levels of willingness to pay. It should be borne in mind that all of the economic modelling depends upon the assumption of equivalence of My5-FU with HPLC and LC-MS. No data were available to allow investigation of the cost effectiveness of My5-FU in treatment of other cancers.

For the assessment of the effectiveness and cost-effectiveness of PK 5-FU dose adjustment, evidence is required for the comparison of BSA based dosing and PK dosing in the same population (ideally randomised) receiving the same 5-FU regimen. The outcomes from this comparison that are needed for cost effectiveness modelling are ideally: 1) IPD to produce Kaplan Meyer curves for overall survival and progression free survival to infer transition probabilities for model parameters; and 2) adverse events reported as counts per unit time for PK versus BSA treatments. IPD is preferred because it gives the most reliable estimates of clinical effectiveness to inform an economic model. Unfortunately, IPD were not available despite efforts of contacting authors of comparative studies. Therefore, Kaplan Meyer curves were reconstructed to estimate IPD for survival following PK versus BSA dose adjustment of 5-FU.

Practical implementation of My5-FU is a consideration and will require attention to:

- Accurate estimation of plasma 5-FU;
- An appropriate algorithm for dose adaptation;
- Identification of an appropriate target plasma 5-FU level (target range).

1.6.1 Research recommendations

We are conscious that improved data are becoming available with more information on current practice and experiences of colorectal cancer patients in terms of mechanisms of dosing and adverse events etc. (e.g., from the COIN trial). This will help in assessing cost effectiveness of interventions to improve treatment and survival in colorectal cancer. However given the poor quality of the clinical and cost effectiveness evidence available to us, there are a number of research needs including a need for:

- Well conducted RCTs of PK versus BSA dosing in:
    - Metastatic and adjuvant colorectal cancer
    - H&N cancer
    - Other cancers where a 5-FU regimen is used
- Further in depth assessment of the comparability of different methods of current and any newly introduced PK dose adjustment
- Randomised assessment of different algorithms for adjusting 5-FU dosing
- Research on the QALY impact of adverse events of 5-FU which would be of benefit in any further economic assessments.

2 BACKGROUND

2.1 Overview

5-fluorouracil (5-FU) is a chemotherapy drug used to treat several cancers including those of the head and neck (H&N), pancreas, stomach and especially bowel (colorectal) cancer. 5-FU is usually given orally or by continuous intravenous infusion into the blood circulation and is often accompanied by additional chemotherapies. 5-FU is administered in a series of cycles usually over 3 to 6 months. 5-FU is cleared from patients' blood at rates which between patients and the dose that reaches cancer cells can vary between individuals. As a result, some patients may receive doses which are too low to be fully effective, whereas others may experience toxicity because the circulating dose is too high.

The My5-FU test kit is designed to measure the amount of 5-FU circulating in the blood using a small blood sample taken during the 5-FU infusion. Knowing the individual patient's level of 5-FU in the blood allows doctors to adjust the dose to be used at the next cycle of treatment so that it is more appropriate for that individual. The My5-FU assay is manufactured by Saladax Biomedical Inc. and can be used with patients who have various types of cancer. However, thus far most attention has been focussed on colorectal cancer, which is the third most common cancer in the UK, with around 40,000 new cases each year.

The current report was undertaken for the NICE Diagnostics Assessment Programme. We aimed to examine the clinical and cost effectiveness of 5-FU plasma monitoring with the My5-FU assay for guiding dose adjustment in patients receiving 5-FU chemotherapy by continuous infusion in the NHS in England and Wales.

2.2 Conditions and aetiologies

Therapeutic drug monitoring in cancer treatment aims to personalise chemotherapy to improve treatment efficacy, avoid severe toxicity and reduce health care costs by using individual dosing schedules. It takes into account the inter-individual variation in drug metabolism to bring drug exposure into the optimum therapeutic range. This is especially important for cytotoxic anticancer drugs which can have a narrow therapeutic window. 5-Fluorouracil (5-FU or 5-fluoro-2,4-pyrimidinedione) is one of the most widely used cytotoxic drugs.

2.3 Descriptions of the health problem

The following sections will focus on the conditions of most relevance to the current report: colorectal cancer (CRC) and H&N cancer. Additional information less detailed information will be provided for stomach cancer and pancreatic cancer, two other conditions which are also referred to in the report.

2.3.1 Colorectal cancer

Colorectal cancer is the third most common cancer in the Western world and is the second most common cancer-related cause of death in combined male and female populations in the UK.[1] In 2010, there were 15,708 deaths from bowel cancer in the UK (62% from colon cancer, 38% from rectal cancer, including the anus), with 8,574 (55%) in men and 7,134 (45%) in women.[2-4] Around half of people diagnosed with colorectal cancer survive for at least five years after diagnosis.[5]

2.3.1.1 Aetiology, pathology and prognosis

Colorectal cancer (also known as large bowel cancer) can affect both males and females equally at any age, however, it is most common in people over 65 years.[6-8]

Studies have reported that a diet high in fat especially animal fat, red meats and low in fibre to be associated with colorectal cancer. Other possible causes include lack of exercise, smoking and alcohol.[8-10] Two inherited conditions, Familial Adenomatous Polyposis (FAP) and Hereditary Non Polyposis Colon Cancer (HNPCC) account for 1% and 5 % of all colorectal cancer respectively.[11, 12] Those with a history of inflammatory bowel disease (IBD) has a six times greater risk of developing colorectal cancer than the general population.[13]

The majority of colorectal cancers (90%) are adenocarcinomas which originate from epithelial cells of the colorectal mucosa.[14] Adenomas or adenomatous polyps are benign in most cases, but around 10% of adenomas will change into cancer over time.[7, 15] Tumours with a villous histology, larger in size and with severe dysplasia have a higher chance of converting to cancer and these are indicators for progression.[15, 16]

Spread of the disease and diagnosis determines the prognosis of patients. Around half of people diagnosed with colorectal cancer survive for at least five years after diagnosis.[5]

In the UK there are inequalities in cancer survival following a diagnosis of colorectal cancer, in that patients who are more socioeconomically deprived are more likely to have both poorer cancer specific and overall survival.[17] Approximately 80% of patients with colorectal cancer undergo surgical treatment for the cancer with/without adjuvant radiotherapy or chemotherapy (including 5-FU).

Recurrence has been reported in between 11% and 54% of patients.[7] More advanced cancers that have invaded other tissues or progressed to metastatic cancers tend to be treated with multiple chemotherapy drugs.

Advances in treatment and survival are likely to increase lifetime costs of managing colorectal cancer.[18] Cost-of-illness studies are key building blocks in economic evaluations of interventions and comparative effectiveness research. However, the methodological heterogeneity and lack of transparency of studies in this area have made it challenging to compare colorectal cancer costs between studies or over time.[18]

2.3.1.2 Incidence and/or prevalence

In 2010 it was estimated that, 42,747 cases of colorectal cancer were diagnosed in the UK of which 23, 582 and 19,165 cases of colorectal cancer were diagnosed in men and women respectively.[19] Incidence rates of colorectal cancer have increased dramatically in both genders between 1999-2001 and 2008-2010. Between 2001-2003 and 2008-2010, incidence rates increased by 6% in men and 7% in females. The incidence rate of colorectal cancer increases with increasing age i.e. the highest rate is among those aged 85 and over.[5] Around 73% of colorectal cancer cases diagnosed in the UK between 2008 and 2010 were among people aged more than 65 years.

2.3.1.3 Significance for patients in terms of ill-health (burden of disease)

According to one study by Jayatilleke and colleagues,[20] colorectal cancer accounted for approximately 9% and 7% of all cancer DALYs in England and Wales among men and women, respectively.

2.3.1.4 Significance for the NHS

In 2006, the NHS Bowel Cancer Screening Programme (NHSBCSP) introduced faecal occult blood testing (FOBt) for both genders between 60 and 69 years. The test is undertaken by taking small stool sample which is tested for the presence of blood.[21] The benefit of FOBt in terms of reducing mortality was estimated from a systematic review of trials to be 16% and 23% for allocated and screened people respectively.[22] In addition, the test was cost-effective.[22]

Flexible sigmoidoscopy (NHS bowel scope screening) is another programme which has been introduced across England from last year (2013), for the prevention of colorectal cancer in high risk patients by identifying and removing adenomatous polyps in the rectum and colon. This involves one-off flexible sigmoidoscopy around 55 years of age for both men and women.[23]

2.3.1.5 Measurement of disease and/or response to treatment

In the UK, colorectal cancer causes around 16,000 deaths annually. The cancer mortality rates is 16,000 deaths over the time, however it has been estimated that the overall five year relative survival is 50%.[24, 25] A study by Coleman and colleagues reported that in the UK cancer survival rates are low in comparison to other Western countries.[26]

Disease measurements are usually based upon colonoscopy and histology for diagnosis and a range of other investigations including CT scans are undertaken for disease staging. Similarly, response to treatment is assessed by clinical consultation, with a range of tests including CT scans and regular serum antigen tests. Colonoscopy is also undertaken at annual and subsequent 5-yearly follow-up.

2.3.1.6 Diagnosis and management

The symptoms of colorectal cancer include rectal bleeding, a change in bowel habit e.g., diarrhoea or loose stools, abdominal pain and weight loss. These symptoms become more prominent when the disease is in an advanced stage although symptoms depend on location and size of the cancer.[27, 28]

2.3.1.6.1 Staging of colorectal cancer

Treatment options and prognosis depend upon staging of the CRC Staging is defined by how deeply the cancer has grown into the intestinal mucosa and whether it has spread to lymph nodes and other organs and if the tumour, node, metastasis (TNM) classification system is most commonly used (see **Table 1** and Table 2 with modified Dukes's staging with 5 years survival).[29, 30] Dukes's classification of staging is:

- Dukes' A means the cancer is only in the innermost lining of the colon or rectum or slightly growing into the muscle layer.
- Dukes' B means the cancer has grown through the muscle layer of the colon or rectum.
- Dukes' C means the cancer has spread to at least one lymph node in the area close to the bowel.
- Dukes' D means the cancer has spread elsewhere in the body such as the liver or lung.

Table 1. Tumour/node/metastases (TNM) classification of colorectal cancer[29]

Tumour
TX: primary cannot be assessed • T0: no evidence of primary carcinoma in situ (Tis) - intraepithelial or lamina propria only • T1: invades submucosa • T2: invades muscularis propria • T3: invades subserosa or non-peritonealised pericolic tissues • T4: directly invades other tissues and/or penetrates visceral peritoneum
Lymph nodes
NX: regional nodes cannot be assessed • N0: no regional nodes involved • N1: 1-3 regional nodes involved • N2: 4 or more regional nodes involved
Metastasis
MX: distant metastasis cannot be assessed • M0: no distant metastasis • M1: distant metastasis present (may be transcoelomic spread)

Table 2. Stages of colorectal cancer with 5 year survival[30]

Stage (TNM status)	5-year overall survival	Modified Dukes'
Stage 0 (T in situ N0 M0)		-
Stage I (T1 N0 M0)	75%	A
Stage I (T2 N0 M0)	57%	B1
Stage II (T3, N0, M0)	-	B2
Stage II (T4, N0, M0)	-	B3
Stage III (T2, N1, M0/T2 N2 M0)	35%	C1
Stage III (T3, N1, M0/T3 N2 M0)	-	C2
Stage III (T4 N1 M0)	-	C3
Stage IV (any T any N M1)	12%	D

2.3.1.6.2 Diagnosis and management pathway of early and metastatic mCRC

This brief account is based on NICE guideline CG131[7] and advice of clinical experts.

Figure 1, 2 and 3 summarises the clinical pathways for patients with CRC.

There are various options for treatment of early stage colorectal cancer including:

- Surgery i.e. tumour resection if the tumour is resectable;
- Preoperative chemotherapy (this may be considered before surgery in patients with non-resectable primary colorectal tumours or borderline resectable tumours);
- Colonic stent in acute large bowel obstruction;
- Further tumour resection in Stage I colorectal cancer;
- Laparoscopic surgery as an alternative surgery to open resection based on patients' and doctors decision;
- Adjuvant therapy: Monotherapy capecitabine or, combination of oxaliplatin with 5-FU and folinic acid are recommended in most patients with stage III colorectal cancer based on patient's and doctor's decision.

2.3.1.6.3 Advanced colorectal cancer with metastasis

According to NICE guideline CG131[7] one of the following combinations of first and second line chemotherapies is used depending upon side effects experienced and patient's preferences:

- FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first line treatment then single agent irinotecan as second-line treatment or;
- FOLFOX as first line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment or;
- XELOX (capecitabine plus oxaliplatin) as first line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second line treatment.

In standard practice, choice between 5-FU regimens such as FU alone, FU + FA, FOLFOX (FOLFOX4 and FOLFOX6) follows is made with clinician's advice. These regimens are administered for up to 12 cycles, one cycle every two weeks.

FU: Fluorouracil FU + FA: Fluorouracil + Folinic acid FOLFOX4: (oxaliplatin (85 mg/m^2), folinic acid (200 mg/m^2), 5-FU (loading dose of (400 mg/m^2) iv bolus, then (600 mg/m^2) administered via ambulatory for a period of 22 hours[31] FOLFOX6: (oxaliplatin (85-100 mg/m^2), folinic acid (400 mg/m^2), 5-FU (loading dose of (400 mg/m^2) iv bolus, then (2,400-3,00 mg/m^2) administered via ambulatory) for a period of 46 hours[31]

In standard practice the 5-FU dosage administered is based on patient body surface area. BSA is calculated using the Du Bois method[32]: BSA (m^2) = Wt (kg) 0.425 x Ht (cm) 0.725 x 0.007184. Currently FOLFIRI and FOLFOX6 regimens recommend a 5-FU dose of 2,400 mg/m^2 administered by continuous infusion over 46 hours. It remains unclear how to dose cap although dose capping is usually undertaken for large individuals because they may be overdosed using the BSA-based dosage and experience toxicity and adverse events. Adverse events range in severity and include diarrhoea, hand and foot syndrome, mucositis/stomatitis, neutropenia, anaemia, nausea/vomiting, and cardio toxicity. Dose capping is implemented at BSA > $2m^2$ or > $2.25m^2$. In practice larger patients may be capped up to a BSA of $2.4m^2$.[personal communication, ASG NICE committee, 5 June 2014] Dose may be reduced for patients judged at higher risk of toxicity (e.g., those heavily pre-treated with chemotherapy; those with poor performance status particularly 2 and above; those with impaired renal or hepatic function, and those with co-morbidities). In such instances dose of chemotherapy may be started low and cautiously increased while the patient is able to tolerate treatment.

It is well documented that the plasma concentrations of 5-FU vary greatly between individuals who have received "standard" dosage calculated from their BSA.[33] In advanced CRC, treatment focuses on both length and palliation of symptoms (e.g., pain, obstruction). Individualised pharmacokinetic adjustment of 5-FU dosage, which tailors an individual's dosage to achieve the required plasma 5-FU level, might optimise time without toxic effects, while not compromising therapeutic benefit. The potential position of pharmacokinetic dose adjustment in the clinical pathway is illustrated in Figure 3.

In pharmacokinetically adjusted (PK) regimens when the dose at the first cycle is based on patient BSA, a steady state plasma sample is taken (e.g. after 40 hours of a 46 hour infusion). The plasma 5-FU estimate is used to calculate the pharmacokinetic "area under the curve" (AUC = mg * hr /L; where mg / L is the steady state plasma 5-FU concentration and hour the total infusion time in hours). An algorithm that relates AUC to dose adjustment is then used to calculate the dosage required for the next cycle of treatment.[33]

In both "standard" and PK regimes, if toxicity occurs, treatment is stopped and/or the dose is reduced after which treatment is resumed. If there is progression of the disease, it may be reasonable to switch treatment for example from FOLFOX to FOLFIRI. If patients are tolerating treatment even after cycles 12, the treatment is continued until progression, or at the discretion of the medical team, but should be reviewed every 12 weeks.

A recent UK randomised clinical trial has investigated if there is a clinical advantage from treatment holidays between successive 12-week cycles.[34] Figure 1 toFigure 3 illustrate the colorectal cancer diagnosis pathway.

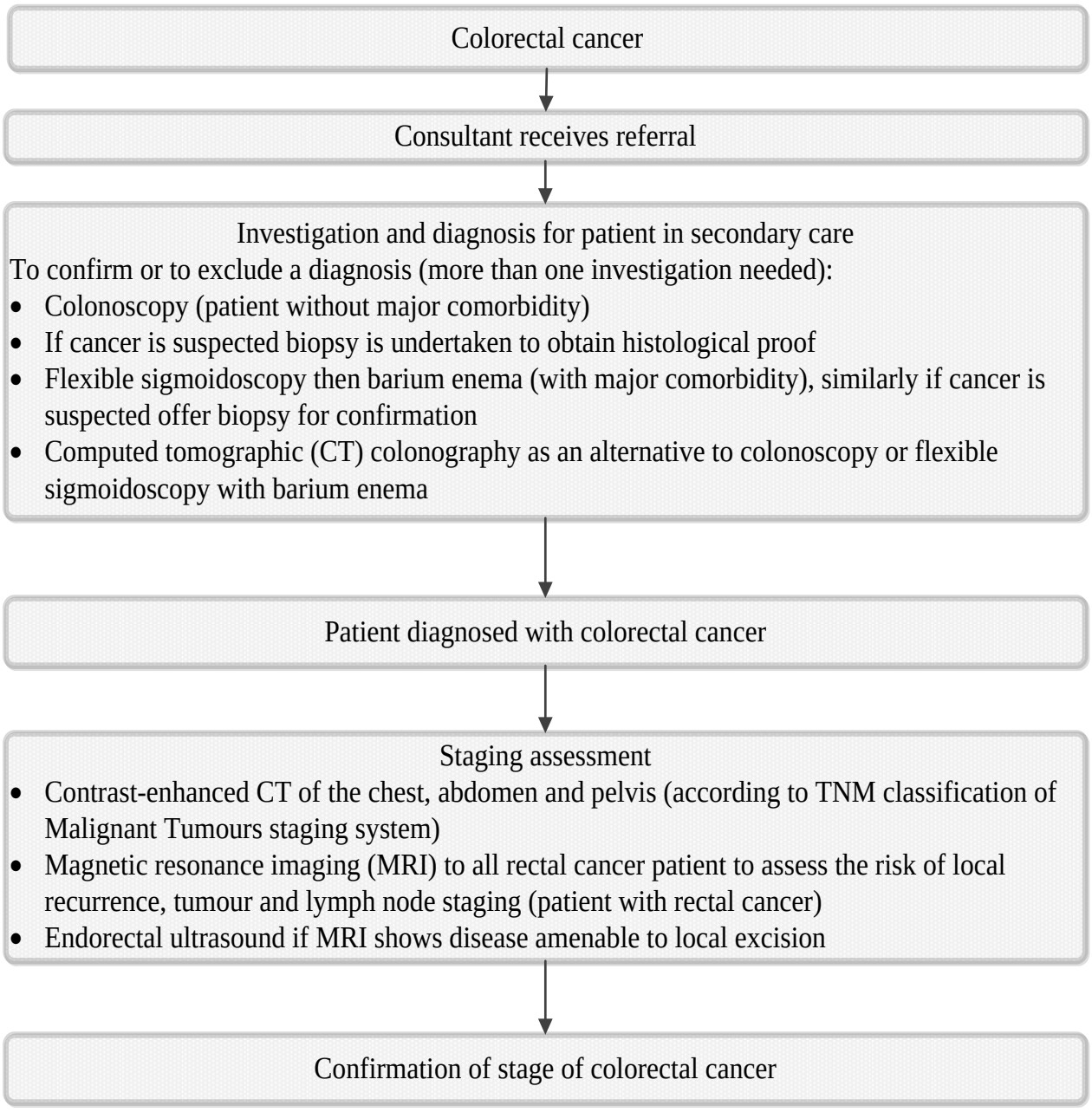

Figure 1. Colorectal cancer diagnosis pathway

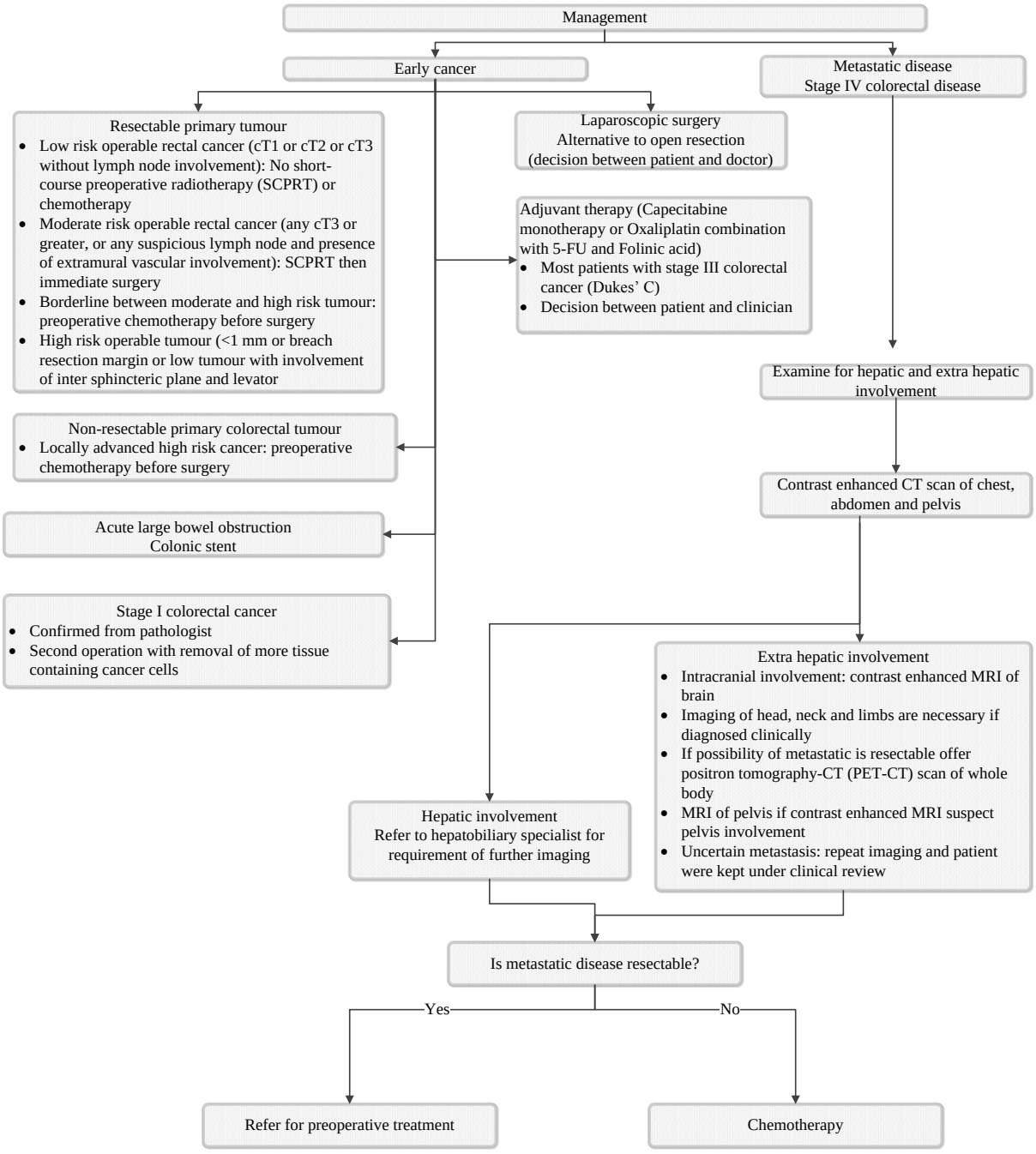

Figure 2. Colorectal cancer management pathway

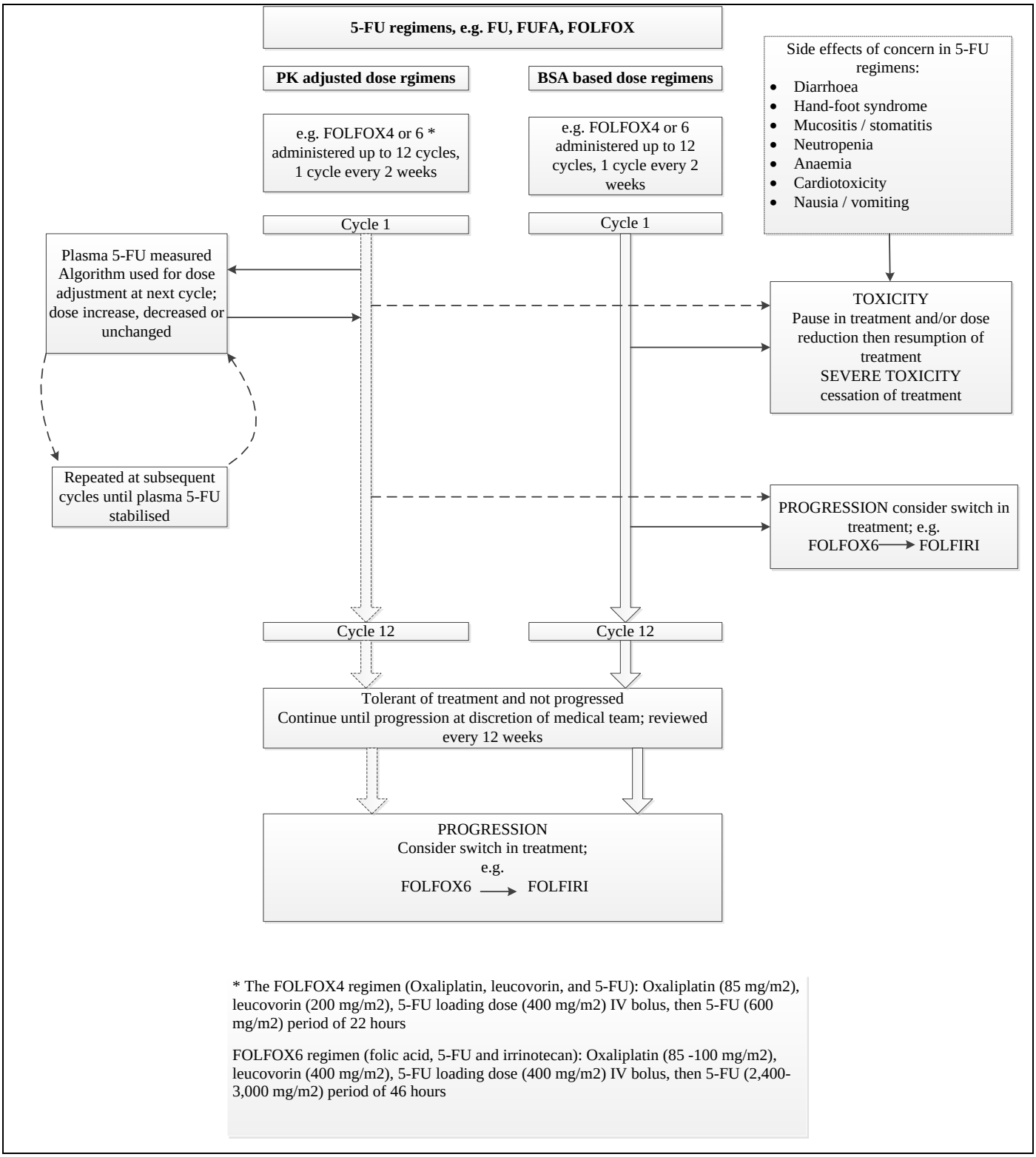

Figure 3. Illustrative role of PK adjustment of 5-FU regimens in treatment of metastatic CRC in standard practice

2.3.1.6.4 The National institute for Health and Care Excellence (NICE) clinical guideline 131

NICE CG131 makes recommendations for diagnosis and management of colorectal cancer and for management of locally advanced and metastatic disease.

An economic evaluation was undertaken using a decision tree. The FOLFOX-irinotecan sequence was taken as a reference for comparisons. All the combinations except FOLFOX-FOLFIRI were found to be dominated by FOLFOX-irinotecan i.e., the latter was less effective and more costly. The ICER of FOLFOX-FOLFIRI was found to be £109,604 per QALY gain. A sensitivity analysis was undertaken discounting the price of drug. The resulting ICER of FOLFOX-FOLFIRI was £47,801 per QALY gain. The probabilistic sensitivity analysis showed that three combination regimens namely FOLFOX-irinotecan, FOLFOX-FOLFIRI and XELOX-FOLFIRI had the highest probability of falling between £20,000-£50,000 per QALY. Based on these findings, the guideline development group (GDG) made the following recommendation:

- If there are no contraindications, then the three combination sequence namely FOLFOX-irinotecan, FOLFOX-FOLFIRI and XELOX-FOLFIRI should be considered as treatment options for treating patients with advanced and metastatic colorectal cancer.

2.3.2 Head and neck cancer

Cancer of the H&N mainly includes cancer of mouth (i.e., oral cancer) and throat and other rare cancers of the nose, sinuses, salivary glands and middle ear. Mouth cancer can be subdivided according to its location such as lip cancer or cancer of the oral cavity. Similarly, throat cancer can be divided into nasopharyngeal cancer (the affected area is at the highest part of the throat behind the nose); oropharyngeal cancer (tonsils and the base of the tongue); cancer of larynx and thyroid cancer (thyroid gland).[35]

The most common type of H&N cancer is squamous cell carcinoma (SCCs), which comprises 90% of all H&N cancers.[36]

H&N cancer begins with a non-invasive lesion in the squamous mucosa that lies in the inner part of the H&N (mouth, the nose and the throat). Following exposure to common carcinogens, a series of changes occurs (i.e., hyperplasia and dysplasia), which causes the cancer to finally become invasive.[36]

The definitive cause for H&N cancer is still unknown; however it has been thought that disease is associated with various factors. Cancer of the H&N occurs in elderly men who actively use tobacco and drink alcohol. Dietary factors thought to be responsible include high intake of red meat, processed meat and fried food and poor diet. Other risk factors include a history of gastro-

oesophageal reflux disease for laryngeal and pharyngeal cancer.[37] Human Papilloma Virus (HPV) infection is also an important risk factor for some H&N cancer (oropharynx and oral cavity).[24, 38]

2.3.2.1 Aetiology, pathology and prognosis

H&N squamous cell cancer (HNSCCs) is the sixth most common cancer and the one of the leading causes of cancer death in the world.[39] In 2011, around 49,260 new cases of H&N cancer were diagnosed in the USA and there were 11,480 cancer deaths in the same year.[40] In England and Wales, around 8100 new H&N cancer cases are diagnosed annually.[41] In the UK in 2010, there were 6,539 new cases of H&N cancer, 66 % in male and 34% in female.[42]

2.3.2.2 Incidence and/or prevalence

The disease incidence increases with age. In the UK, 85% of cases are seen in people who are more than 50 years old. However the incidence has been found to be increasing in younger men and women.[37] In the UK, in the period 2008-2010, approximately 44% of oral cancers were diagnosed in both genders aged over 65 years, and 50% were diagnosed in those aged between 45 and 64 years.[42]

2.3.2.3 Significance for patients in terms of ill-health (burden of disease)

In England and Wales, the age adjusted mortality rate for oral cancer in year was 2.7 per 100,000 in male and 1.05 per 100,000 in female. Likewise in Scotland, the age adjusted mortality rate was 4.6 per 100,000 in male and 1.6 per 100,000 in female between 1995 and 1999. In around 30-40% cases, HNSCCs present at an early stage which is potentially managed by surgery or adjuvant radiotherapy with an intention to cure the disease. In contrast, advanced diseases with unresectable HNSCCs are treated by concurrent chemo-radiotherapy as a palliative therapy mainly to improve survival.[43]

Costs of treatment for (only surgical resection) and caring for HNSCCs after surgery are substantial. Kim and colleagues have reported the total cost of post-operative healthcare utilisation over the five years follow-up. The cost was approximately £255.5 million in 11,403 patients in the UK.[43]

Measurement of disease and/or response to treatment

In the UK, about 7,000 new cases of H&N cancer occur annually. At least 45% of cases survive five years or more.[44] Younger populations have better survival than older populations.[42] Within the UK, there has been an increment of between 5% and 14% in five year survival for most cancers like oral cavity, oropharynx, nasopharynx, and salivary glands. Epidemiologic evidence suggests that in 10% of population in US with H&N cancer shows 55% to 66% of improvement in survival.[44]

Similar to CRC cancer, disease progression and response to treatment are measured by multi-disciplinary team (MDT). After treatment, there are regular examinations in the first two years and

routine follow up after five years. The identification of recurrent tumours or new primary tumours are made by professionals during follow-up visits. Patients are also helped with complications of the disease and adverse events due to treatment. Patients are also given help with functional and psychosocial problems.[45]

2.3.2.4 Diagnosis and management

Sign and symptoms of H&N cancer depend on the location of the primary tumour and also on the extent of the disease. Common signs and symptoms of H&N cancer include hoarseness or change of voice, difficulty in swallowing, lump/swelling in the neck and non-healing mouth ulcers.[46]

2.3.2.4.1 Tumour staging

Tumour staging is necessary to determine the treatment and also to know the prognosis of the condition. Pathological or histological diagnosis is usually done according to the WHO classification from biopsy taken from surgery. Clinical staging of the H&N are done according to American Joint Committee on Cancer (AJCC) and tumour-node-metastasis (TNM). The AJCC classification divides T4 tumours into two categories – T4a for moderately advanced cancer and T4b for very advanced cancer. Stage IV cancers are divided into three categories IVa, IVb and IVc. The latter indicates metastatic disease. The TNM classification of the UICC and AJCC are designed for staging/classifying squamous cell carcinoma and minor salivary cancers.[47-49] See Table 3 and Table 4

According to SIGN guidelines,[37] tumours are broadly subdivided into: a) Early disease (Stage 1 and 1 following the Union International Contre le Cancer (UICC)/TNM classification of malignant tumour); and b) Locally advanced disease stage 3 and 4.

Table 3. TNM staging for head and neck squamous cell cancers (TNM seventh edition 2009) [48]

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IVA	T1, T2, T3	N2	M0
T4a		N0, N1, N2	M0
Stage IVB	Tb	Any N	M0
Any T		N3	M0
Stage IVC	Any T	Any N	M1

Table 4. The International Union Against Cancer (UICC) and American Joint Committee on Cancer (AJCC) staging system for NPC, seventh edition (2010)[49]

Primary tumor (T)	
T1	Tumor confined to the nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal extension
T2	Tumor with parapharyngeal extension
T3	Tumor involves bony structures of skull base and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space
Regional lymph nodes (N)	
N1	Unilateral metastasis in cervical lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, ≤6 cm, in greatest dimension
N2	Bilateral metastasis in cervical lymph node(s), ≤6 cm in greatest dimension, above the supraclavicular fossa
N3	Metastasis in a lymph node(s) >6 cm and/or to supraclavicular fossa
N3a	>6 cm in dimension
N3b	Extension to the supraclavicular fossa
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T1	N1	M0
T2	N0	M0	
T2	N1	M0	
Stage III	T1	N2	M0
T2	N2	M0	
T3	N0	M0	
T3	N1	M0	
T3	N2	M0	
Stage IVA	T4	N0	M0
T4	N1	M0	
T4	N2	M0	
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1

2.3.2.4.2 Diagnosis and management pathway for head and neck cancer

The management of H&N cancer falls into two broad categories: a) management of early stage cancer; and b) management of locally advanced cancer (see Figure 4 and Figure 5).

Most (60-70%) patients present with locally advanced disease. The standard of care for this group is various combinations of surgery, radiotherapy and systemic treatments. Chemotherapy may be used prior to radiotherapy (induction) or combined with definitive or post-operative radiotherapy (synchronous).

TPF regimens (docetaxel + cisplatin + 5-FU) are commonly used in the UK to treat locally advanced cancer (T3/4, N2/3). These regimens are also used as induction chemotherapy (prior to radiotherapy) e.g., to preserve the larynx or, in chemoradiation (concurrent radiation and cisplatin) followed by adjuvant chemotherapy (cistplatin + continuous infusion 5 FU) for nasopharynx cancer. Meta-analysis evidence supports the addition of docetaxel, to cisplatin + 5-FU doublet.[50]

For nasopharyngeal cancer the use of neoadjuvant TPF rather than PF is less well established (clinical expert). The standard synchronous chemotherapy regimen (concurrent radiation + chemotherapy) is single-agent cisplatin 100mg/m2, which is administered three weekly.[51] There are reports of severe side effects from 5-FU including diarrhoea, hand and foot syndrome, mucosities/stomatitis, neutropenia, anaemia, nausea and vomiting and cardiotoxicity.

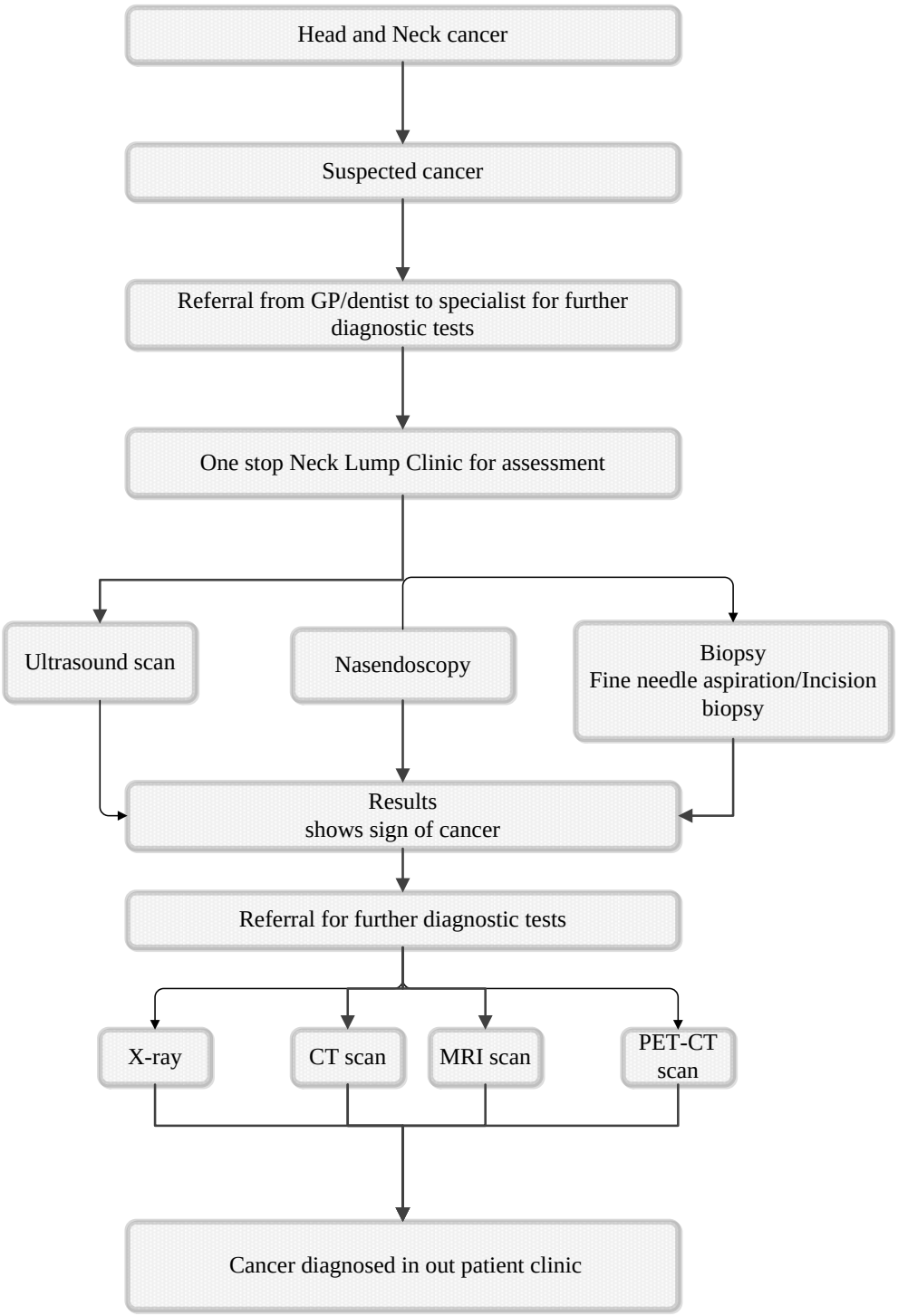

Figure 4. Head and Neck diagnosis pathway

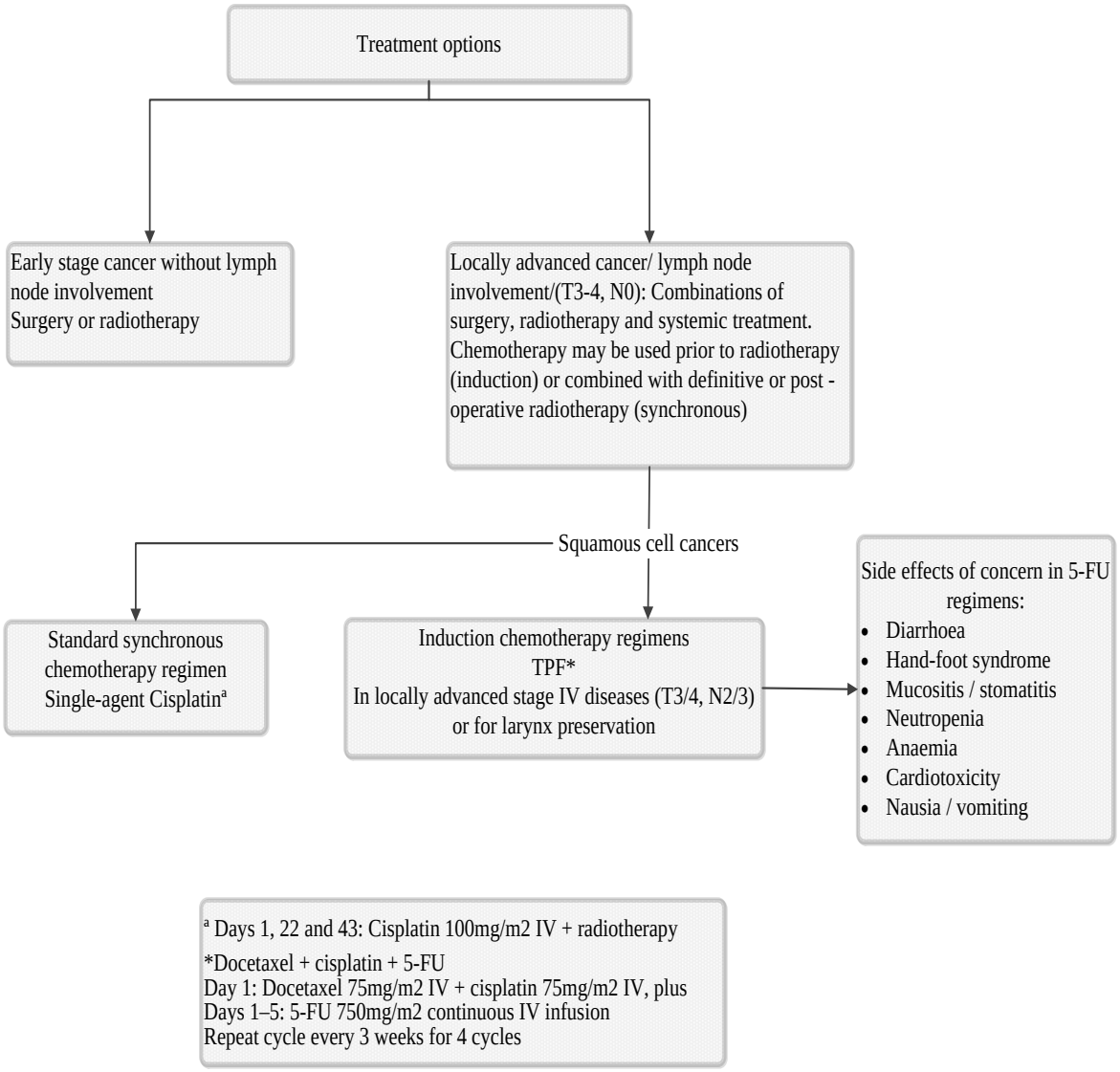

Figure 5. Head and Neck management pathway

2.3.3 Stomach cancer

Stomach cancer refers to any malignant neoplasm occurring in the region between the gastroesophageal junction and the pylorus.[52] Stomach cancer also represents a major cause of cancer mortality worldwide. The most common cancer of the stomach is called adenocarcinoma.[53] This cancer starts in cells which line the innermost layer of the stomach, the mucosa. Stomach cancer spreads locally within the gastric wall and then to adjacent lymph nodes.[54] On reaching the serosa, it might spread into the peritoneal cavity, then distantly.

2.3.3.1 Aetiology, pathology and prognosis

The etiology of gastric cancer is complex, More than 80% of new diagnoses are attributed to Helicobacter pylori infection.[52] Lifestyle, diet, genetics, socioeconomic and a range of other factors appear to contribute to gastric carcinogenesis, despite a decline in the prevalence of Helicobacter pylori infection (a major cause of stomach cancer).[55, 56]

The incidence and mortality rates of stomach cancer appear to increase in socially and economically deprived groups.[57]

The prognosis for patients with stomach cancer appears to depend on age, general health and how far the cancer has spread before it was diagnosed. No general consensus has been reached on the best treatment option.[58]

2.3.3.2 Incidence and/or prevalence

A total of 7,610 new cases of stomach cancer were diagnosed in 2008 in the UK[59] with an estimated five-year survival rate of 18%.[60] Currently, stomach cancer is the 15th most common cancer amongst adults in the UK.[59] In the UK approximately 13,400 people were still alive at the end of 2006, up to ten years after being diagnosed with stomach cancer.[61] In the UK between 2009 and 2011, around 51% of cases were diagnosed in people aged 75 and over and stomach cancer incidence was strongly related to age, with the highest incidence rates in older men and women.[59] Overall, around 15% of people with stomach cancer will live at least five years after diagnosis and about 11% will live at least 10 years. In the UK, around 5,000 people die from stomach cancer each year.[62]

2.3.3.3 Significance for the NHS

Early stage stomach cancer is often treated with surgery, with neo-adjuvant or adjuvant chemotherapy offered where appropriate. The main chemotherapy drugs used to treat stomach cancer include 5-FU, cisplatin, and epirubicin. Advanced stomach cancer is treated with chemotherapy. NICE Technology Appraisal 191 (TA191)[63] recommends capecitabine in conjunction with a platinum-based regimen for the treatment of inoperable advanced gastric cancer.

2.3.3.4 Measurement of disease and/or response to treatment

In 2013, a Cochrane study-level meta-analysis reviewing RCTs of post-surgical chemotherapy vs. surgery alone for gastric cancer, reported a significant improvement in overall survival in 34 studies (HR = 0.85; 95%CI: 0.80-0.90) and in disease-free survival in 15 studies (HR = 0.79; 95%CI: 0.72-0.87) as a result of adjuvant chemotherapy.[64] A recent meta-analysis concluded that D2 lymphadenectomy with spleen and pancreas preservation offers the most survival benefit for patients with gastric cancer when done safety.[65]

2.3.4 Pancreatic cancer

Pancreatic cancer refers to a malignant epithelial neoplasm of the pancreas. Pancreatic cancer, sometimes referred to as pancreatic ductal adenocarcinoma (PDAC), is the eighth and fifth leading cause of cancer-related deaths in the world and Europe, respectively.[66, 67] It has very few symptoms in its early stage so is often diagnosed when the disease is advanced. The primary symptoms of pancreatic cancer include weight loss, stomach pain and jaundice, and these symptoms are associated with a number of conditions.[62]

2.3.4.1 Aetiology, pathology and prognosis

About 65% of pancreatic tumours the cancer starts in the head of the pancreas, 30% in the body and tail, and 5% can involve the whole pancreas.[68] The most common form of cancer occurs in the exocrine cells of the pancreas. These tumours account for over 95% of all pancreatic cancers.

Genetic factors, smoking and previous radiotherapy treatment for another cancer have been associated with an increased risk of developing pancreatic cancer[69-71] Similarly, consumption of red and processed meat increased the risk of pancreatic cancer[72] and patients with chronic Hepatitis B infection have around 20%-60% increased pancreatic risk.[73]

Pancreatic cancer continues to be one of the most aggressive forms of tumour with a five-year survival rate of less than 5% and a median survival of 6 months after diagnosis; as a result it has a poor prognosis of all solid tumours.[74, 75]

2.3.4.2 Incidence and/or prevalence

In 2008, 8,085 people were newly diagnosed with pancreatic cancer in the UK and in 2009, 8,047 people died from pancreatic cancer in the UK.[76] In 2011, approximately 3,600 men (2.6% of all newly diagnosed male cancers) and 3,700 women and (2.7% of all newly diagnosed female cancers) were diagnosed with pancreatic cancer in England.[2] Pancreatic cancer is more common in men than women but this has started to change.

2.3.4.3 Impact of health problem

Pancreatic cancer in England has a crude incidence rate of 13.6 per 100,000 population and similar rates are seen in both sexes. Survival is poor with one-year relative survival estimates of around 19 per cent for both sexes. In many patients, the clinical diagnosis is fairly straightforward, although there are no clear clinical features which identify a patient with curable form of pancreatic cancer.[77]

2.3.4.4 Significance for the NHS

Currently, treatment focuses on palliative surgery to relieve symptoms, resectional surgery with intent to cure, and endoscopic or percutaneous biliary stenting to relieve jaundice. Chemotherapy and radiotherapy are often used, both as palliative treatments as well as in an adjuvant setting in conjunction with surgery.[78]

The main chemotherapy drugs recommended to treat pancreatic cancer are 5-FU, gemcitabine, and capecitabine. If surgery is possible, adjuvant treatment with 5-FU can reduce the risk of recurrence. NICE Technology Appraisal 25 (TA 25)[79] recommends that gemcitabine may be considered as a treatment option for patients with advanced or metastatic adenocarcinoma of the pancreas and a Karnofsky performance score of 50 or more, where first line chemotherapy is to be used. The guidance also states that there was insufficient evidence to support the use of gemcitabine as a second line treatment in patients with pancreatic adenocarcinoma.

2.3.4.5 Measurement of disease and/or response to treatment

The current management of pancreatic cancer is guided by tumour stage, comorbidities and performance status of the patients. In addition to gemcitabine and capecitabine fluorouracil, chemoradiation, and chemoradiation plus fluorouracil or gemcitabine are also used.[80] Surgical resection followed by a 6-month-course of adjuvant gemcitabine-based chemotherapy is considered the standard of care for early-stage disease.[81] Patients with metastatic disease can be considered for systemic palliative chemotherapy. In contrast for patients with locally advanced disease without evidence of metastasis, optimal treatment remains unclear, with chemotherapy alone and chemoradiation both being an option for consideration.[82]

2.4 Description of technology under assessment

2.4.1 5-Fluorouracil

5-Fluorouracil (5-FU or 5-fluoro-2,4-pyrimidinedione) is an antimetabolite of the pyrimidine analogue type, with a broad spectrum of activity against solid tumours (of the gastrointestinal tract, liver, pancreas, ovary, breast, brain, etc.), alone or in combination chemotherapy regimens.[83] 5-FU has been used in daily clinical oncology practice for almost 50 years and continues to be the cornerstone of all major CRC treatment regimens for adjuvant therapy and for advanced metastatic disease.[84] The method of administration of 5-FU varies according to the type, location, and stage of cancer as well as the circumstances and preferences of the individual. 5-FU can be administered by infusion, injection, or orally as a pro-drug (e.g., capecitabine) and prescribed as either a single agent or in conjunction with other chemotherapy drugs.

Approximately 85% or more of administered 5-FU is inactivated and eliminated through the catabolic pathway; the remainder is metabolised through the anabolic pathway.[85] The enzyme dihydropyrimidine-dehydrogenase (DPD) has a major role in clearance of 5-FU and the rate of clearance (inactivation) varies considerably from patient to patient. 5-FU chemotherapy typically lasts 3 to 6 months and usually up to 12 cycles. Each cycle includes a period of 5-FU administration followed by a break to allow for recovery before the next cycle. Administration via continuous infusions usually lasts approximately 22 to 48 hours and requires patients to have a central venous access device such as a Hickman line or PICC line. Some patients have their 5-FU infusion via a portable pump which allows return to home during treatment.

When 5-FU was first developed in the United States, 5-FU monotherapy was usually administered via a bolus schedule, however more recently these have been replaced by infusional regimens based on the work of de Gramont and colleagues.[86, 87]

2.4.2 Intervention technology

2.4.2.1 My5-FU assay

The My5-FU assay (Saladax Biomedical, Inc., PA, USA; previously known as OnDose) is a nanoparticle immunoassay that measures levels of fluorouracil (5-FU) in plasma samples.[88]

As previously reported in the protocol to this work, the My5-FU assay is used with patients receiving 5-FU by continuous infusion to facilitate pharmacokinetic dose adjustment at the next cycle and drug monitoring to achieve an optimal plasma level of the drug. The assay uses two reagents: reagent 1 consists of a "5-FU conjugate" which is a 5-FU-like molecule linked to a long spacer arm; and reagent 2 consists of antibodies covalently bound to nanoparticles, these antibodies are able to bind either 5-FU or the 5-FU conjugate. When reagents 1 and 2 are mixed the nanoparticles aggregate together. In the presence of free 5-FU some of the antibodies bind 5-FU rather than 5-FU conjugate, the amount of aggregation of nanoparticles is reduced and this alters the light absorbing properties of the mixture (that is 5-FU and "5-FU conjugate" compete for nanoparticle-bound antibodies). The light absorbance of the mixture is measured and can be compared against a calibrated standard curve in which light absorbance is compared with known concentrations of free 5-FU in the mixture. In short, photometric detection (changes in absorbance) of nanoparticle aggregation allows for determination of 5-FU concentration in plasma samples.[89] This assay can be performed on automated clinical chemistry analysers present in standard clinical laboratories. The assay requires a peripheral venous blood sample which is taken towards the end of each 5-FU infusion cycle using an EDTA or heparin tube.[90]

Drug monitoring is potentially important for 5-FU because it has a narrow therapeutic index, with doses below the therapeutic window potentially limiting treatment efficacy while doses above the window are more likely to cause side effects and toxicity. Commonly reported side effects of 5-FU chemotherapy include anaemia, thrombocytopenia, leukopenia, nausea/vomiting, diarrhoea, mucositis, and hand-foot syndrome[91] all of which can be dose limiting when severe. Other consequences of 5-FU toxicity can include neuropathy, severe damage to organs, cardiotoxicity, neutropenia, sepsis and septic shock.[92] Patients with DPD deficiency are at significantly increased risk of developing severe and potentially fatal neutropenia, mucositis and diarrhoea when treated with 5-FU.[93, 94]

Results are reported in nanograms 5-FU/millilitre plasma and are converted to an area under the curve (AUC) value by multiplying the concentration of 5-FU in a steady state by the time of the infusion (in hours). This is then compared with a pre-defined optimal therapeutic range and the results, reported as mg·h/L, are used to guide the dose of 5-FU given in the next cycles. Outlier results greater than 50 mg·h/L are assumed to indicate that the blood sample has been taken too close to the infusion port and these results are disregarded. The My5-FU assay has been validated against liquid chromatography-mass spectrometry (LC-MS)[89, 95] and high performance liquid chromatography (HPLC) laboratory techniques commonly used in pharmacokinetic studies.

When using the My5-FU assay in clinical practice, the initial dose of 5-FU is based on a patient's body surface area (BSA). A blood sample is taken towards the end of the infusion cycle. For an infusion greater than 40 hours sampling is recommended at least 18 hours after starting infusion.[96] The sample should also be taken during a steady state period of the infusion which is usually about four hours before the end of the infusion using a non-battery operated device (which is commonly used in the UK). Depending on practice, it may require an additional visit by a district nurse or an additional outpatient attendance. Subsequent doses of 5-FU are calculated using the AUC result, according to a pre-determined dose adjustment algorithm. An example of a dose adjustment algorithm for patients with metastatic colorectal cancer recommends an optimal therapeutic range of 20–30 mg h/L with adjustments of no more than 30% of the dose for each infusion.[96] Patients typically require 3 or 4 pharmacokinetic-directed dose adjustments to reach an optimal therapeutic range.

Dihydropyrimidine Dehydrogenase (DPD) is the rate-limiting enzyme involved in the catabolism of 5-FU. Up to 80% – 85% of an administered dose of 5-FU is broken down by this enzyme to inactive metabolites. DPD converts endogenous uracil into 5,6-dihydrouracil, and analogously, 5-FU into 5-fluoro-5,6-dihydrouracil. The presence of DPD deficiency results in a reduced ability to metabolize and clear 5-FU, and the half-life of the drug, which is normally approximately 10 – 15 minutes, can be

markedly prolonged, to up to 159 minutes.[97-100] Response to 5-FU treatment is inconsistent with approximately 10-30% of patients displaying serious toxicity partly explained by reduced activity of Dihydropyrimidine Dehydrogenase.[95]

In the following section the key principles of the My5-FU assay procedure are provided; the majority of this information has been taken from the Saladax kit instructions.[90]

2.4.2.1.1 Handling and storage instructions:

Store reagents, calibrators and controls should be refrigerated at 2-8° C (35-46° F). Before use, the Nanoparticle Reagent (R2) should be mixed by gently inverting the R2 reagent vial three to five times, avoiding the formation of bubbles.

2.4.2.1.2 Sample collection:

Plasma (EDTA or heparin) specimens may be used with the My5-FU assay. The sample is drawn towards the end of the infusion, preferably two hours before the end, ensuring that the pump still contains solution during the sample draw. The start time of continuous infusion and actual sampling time is recorded. A minimum of 2 mL of blood is collected into an EDTA or heparin tube. The blood sample is collected by venepuncture or through a peripheral IV line to avoid contamination by the infusing drug.

The sample stabiliser is available in Europe which negates the need for ice and immediate access to a centrifuge. The stabilizer maintains 5-FU levels in whole blood for up to 24 hours after collection.

2.4.2.1.3 Calibration:

The My5-FU assay produces a calibration curve with a 0 to 1,800 ng/mL range using the My5-FU Calibrator Kit. The minimum detectable concentration of 5-FU in plasma for the My5-FU assay is 52 ng/mL.

2.4.2.1.4 Quality control:

The My5-FU Control Kit contains three levels of controls at low, medium and high concentrations of 5-FU. A laboratory should establish its own control ranges and frequency. At least two concentrations of quality control should be tested each day as patient samples are assayed and each time calibration is performed. It is important to reassess control targets and ranges following a change of reagent (kit) or control lot.

2.4.2.1.5 Limitations of the procedure:

Performance characteristics for the My5-FU assay have not been established for body fluids other than human plasma containing EDTA or heparin.

2.4.2.2 HPLC / LC-MS

During the last 40 years, several methods for the quantitation of 5-FU levels have been developed and evaluated including: gas chromatography, tachophoresis, HPLC, or thin layer chromatography as separating modalities, and radioactivity, mass spectrometry (MS), fluorescence, ultraviolet absorption, or flame ionization as detection techniques.[101] The majority of these assays have been useful in pre-clinical and clinical pharmacological studies. Drug monitoring combined with early detection of patients at risk enables timely dose adaptation and maintain drug concentrations within a therapeutic window; however, the most effective method to identify such patients is unclear.[102]

HPLC/MS methodology comprises an HPLC column attached, via a suitable interface, to a MS and is capable of analysing a wide range of components. Compounds are separated on the relative interaction with the chemical coating of these particles and the solvent eluting through the column. Components eluting from the chromatographic column are introduced to the mass spectrometer via a specialised interface. Two most common interfaces used for HPLC/MS are the electrospray ionisation and the atmospheric pressure chemical ionisation interfaces.[103] For more details on a HPLC method please refer to a paper by Gamelin and colleagues.[104]

A popular method involves LC-MS/MS.[105-107] Despite LC-MS/MS methods being found to be sensitive and robust, the instrumentation is not in standard use in routine clinical laboratories in the UK. For more details on a LC-MS/MS method please refer to a paper by Kosovec and colleagues.[101]

2.4.3 Current usage of the My5-FU assay in the NHS

The My5-FU assay is currently not in clinical use in the UK, other than for research purposes. Several ongoing clinical trials are taking place. As part of the current report a detailed consultation was made with NICE ASG expert advisors and other clinical experts. The responses to a large range of questions relevant to this work have been used as part of the health economic modelling detailed in Section 6.

2.4.4 Comparators

Currently in most clinical practice in the UK the 5-FU dose administered is calculated according to patients' BSA. As described in previous section of this background chapter, BSA is calculated using the Du Bois method:[32] BSA (m^2) = Wt (kg) 0.425 x Ht (cm) 0.725 x 0.007184. Currently FOLFIRI

and FOLFOX6 regimens recommend a 5-FU dose of 2,500 mg / m^2 administered by continuous infusion over 46 hours.

It is well documented that the plasma concentrations of 5-FU vary greatly between individuals who have received "standard" dosage calculated from their BSA and this dose remains unadjusted at subsequent cycles unless the patient experiences sufficient toxic effects to mandate dose reduction. Such dose reductions are guided by clinical judgment. The dose is not increased above an evidence-based (trial) maximum dose even if there is no toxicity.

Good correlations have been reported between 5-FU plasma levels and the biological effects of 5-FU treatment, both in terms of toxicity and clinical efficacy[108] [109-111] Although this method is commonly used with many anti-cancer drugs, its use has been questioned[112, 113] and clinical investigations have also failed to show a correlation between 5-FU plasma clearance and BSA.[114]

PK guided studies have identified an optimal target therapeutic range for 5-FU and have recommended dose-adjustment algorithms to bring plasma concentrations into the optimal range.[84] However, 5-FU monitoring has not been widely used. Any advances in testing based on LC-MS/MS or nanoparticle antibody-based immunoassay, might facilitate monitoring of 5-FU in routine daily clinical practice.[101, 102]

3 DEFINITION OF DECISION PROBLEM

The current report being undertaken for the NICE Diagnostics Assessment Programme examines the clinical and cost effectiveness of 5-FU plasma monitoring with the My5-FU assay for guiding dose adjustment in patients receiving 5-FU chemotherapy by continuous infusion. The report will allow NICE to make recommendations about how well the My5-FU assay works and whether the benefits are worth the cost of the tests for use in the NHS in England and Wales. The test allows a more tailored dosing of 5-FU which may lead to improved clinical outcomes and less side effects. The assessment will consider both clinical improvement in patients' symptoms and the cost of the test used to measure the amount of 5-FU.

The decision question taken from the NICE scope for this project is shown in the box below:

"What is the clinical and cost effectiveness of the My5-FU assay for the pharmacokinetic dose adjustment of continuous infusion 5-FU chemotherapy?"

3.1 Overall aim of the assessment

The overall aim of this report was to present the evidence on the clinical- and cost-effectiveness of the My5-FU assay for guiding dose adjustment in patients receiving 5-FU chemotherapy by continuous infusion.

3.2 Objectives

In the current report we:

A. *A-1:* Provide a review of the studies which examine the accuracy of the My5-FU assay when tested against gold standard methods of estimation of 5-FU. High performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS) are considered the gold standard for the purpose of assessing the accuracy of 5-FU plasma level measurements.

   A-2: Provide a review of the studies which have developed a treatment algorithm based on plasma 5-FU measures.

B. Systematically review the literature on the use of My5-FU to achieve adjusted dose regimen(s) to compare it with BSA-based dose estimation for patients receiving 5-FU-administered by continuous infusion. Variations in current BSA-based dose regimens are considered where appropriate.

C. Systematically review the literature on the use of HPLC and/or LC-MS to achieve dose adjustment to compare it with BSA-based dose regimens for patients receiving 5-FU. This is undertaken for the purpose of performing a linked evidence analysis which incorporates estimates of comparability of assay performance (in terms of overall survival, progression free survival and adverse events) of My5-FU relative to the gold standards (HPLC, LC-MS) as outlined in A.

D. Provide an overview of systematic reviews of clinical outcomes in studies of 5-FU cancer therapies administered by continuous infusion in order to assess the generalizability of outcomes reported in the control arms of studies included in B and C above; outcomes of interest include: incidence of side effects and 5-FU toxicity, treatment response rates, progression free survival, overall survival, and health related quality of life.

E. Identify evidence relevant to the costs of using My5-FU. Illustrative clinical pathways have been constructed; for this, we have used information provided by the manufacturer, advice from specialist committee members and other clinical experts, data collected from an identified UK clinical laboratory and analysis of the published literature. We have collected information on the following:
    a. Cost of My5-FU testing
    b. Cost of delivering 5-FU by infusion
    c. Cost of side effects and 5-FU toxicity and their associated treatment or hospitalisation

These will be considered from an NHS and Personal Social Services perspective.

4 CLINICAL EFFECTIVENESS METHODS

4.1 Identification and selection of studies

4.1.1 Search strategies for clinical effectiveness

Scoping searches were undertaken to inform the development of the search strategies and to assess the volume and type of literature relating to the assessment questions. An iterative procedure was used, with input from clinical advisors and the NICE Diagnostic Assessment Programme manual.[115] One search strategy was developed for Objectives A, B and C and another two were developed for Objective D (see 4.1.1.2). Search strategies are presented in Appendix 1.

4.1.1.1 Searches for Objectives A, B and C

This search strategy focussed on My5-FU/gold standard technologies, fluorouracil, pharmacokinetics and dose adjustment, with a limit to English language. No study type or date limits were applied. This search strategy developed for EMBASE was adapted as appropriate for other databases. The searches were undertaken in January 2014. All retrieved papers were screened for potential inclusion.

The search strategy comprised the following main elements:

- Searching of electronic bibliographic databases
- Contact with experts in the field
- Scrutiny of references of included studies
- Screening of manufacturer's and other relevant organisations' websites for relevant publications

Bibliographic databases:
MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; Cochrane Library (including Cochrane Systematic Reviews, DARE, CENTRAL, NHS EED, and HTA databases); Science Citation Index and Conference Proceedings (Web of Science); NIHR Health Technology Assessment Programme; PROSPERO (International Prospective Register of Systematic Reviews).

The following trial databases were also searched: Current Controlled Trials; ClinicalTrials.gov; UKCRN Portfolio Database; WHO International Clinical Trials Registry Platform.

The following specific conference proceedings, selected with input from clinical experts, were checked for the last five years:

- ASCO – main and GI ASCO http://meeting.ascopubs.org/site/misc/meetings_archive.xhtml

- AACR http://www.aacr.org/home/scientists/meetings--workshops/aacr-annual-meeting-2014/previous-annual-meetings.aspx
- ESMO Congress http://www.esmo.org/Conferences/Past-Conferences
- ECCO http://www.ecco-org.eu/Events/Past-conferences.aspx
- World GI conference http://annonc.oxfordjournals.org/content/supplemental

The following websites were consulted via the Internet:

- Saladax http://www.saladax.com/
- International Network of Agencies for Health Technology Assessment (INAHTA) Publication http://www.inahta.org/
- The Association of Cancer Physicians (ACP) http://www.cancerphysicians.org.uk/
- Royal College of Physicians: Oncology http://www.rcplondon.ac.uk/specialty/medical-oncology
- UK Oncology Nursing Society www.ukons.org/
- American Society of Clinical Oncology (ASCO) www.asco.org/
- Oncology Nursing Society http://www.ons.org/
- European Society for Medical Oncology (ESMO) www.esmo.org/
- European Oncology Nursing Society (EONS) http://www.cancernurse.eu/
- The Association of Coloproctology of Great Britain and Ireland (ACPGBI) http://www.acpgbi.org.uk/
- British Society of Gastroenterology http://www.bsg.org.uk/

The reference lists of included studies and relevant review articles were checked. Identified references were downloaded into Endnote X7 software.

4.1.1.2 Searches for Objective D

Several UK guidelines and evidence updates based on systematic reviews were identified via searches[7, 37, 116] or personal communication (NICE 2010 Head and Neck Cancer Annual Evidence Update) *[personal communication: NICE 23 April 2014]*. Two search strategies were then developed focussing on finding systematic reviews on the use of fluorouracil in metastatic colorectal cancer (mCRC) and H&N cancer (see Appendix 1). H&N cancer was not considered further in Objective D. The searches were limited to English language and to articles published in or after 2011 (the year the searches were run for the NICE mCRC guideline[7] and most recent H&N evidence update[116]). A focussed search filter for systematic reviews developed in house was used. This search filter will miss less well-reported reviews (e.g., where the terms systematic or meta-analysis are not included in the title or abstract), but recent initiatives, such as PRISMA, mean that this is less of a concern than in the

past.[117] The search strategies developed for Medline were adapted as appropriate for other databases. The searches were undertaken in April 2014.

Bibliographic databases:
MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; Cochrane Library (Cochrane Systematic Reviews, DARE and HTA databases)
The following website was consulted via the Internet.

- Saladax http://www.saladax.com/

Identified references were downloaded into Endnote X7 software.

The searches, inclusion and exclusion criteria for Objective E will be considered separately in section 6.1.

4.1.2 Inclusion and exclusion of relevant studies

4.1.2.1 Objective A - Inclusion criteria

Population:

- Cancer patients (colorectal, head and neck, stomach, pancreatic) receiving 5-FU chemotherapy by continuous venous infusion.

Intervention:

- PK monitoring using My5-FU

Comparator:

- HPLC, LC-MS/MS

Outcome:

- Performance of My5-FU (e.g., correlation between My5-FU and "gold standard")

Setting:

- Metastatic or adjuvant therapy

4.1.2.2 Objective A - Exclusion criteria

Population:

- Animal studies
- No patients, samples or cell lines only
- Patient group unclear
- Studies of cancer patients with cancers other than colorectal, head and neck, stomach, pancreatic

- Studies with less than 80% of included cancers (colorectal, head and neck, pancreatic and gastric cancer)

Treatment:

- Treatment not containing 5-FU
- Non included treatment (e.g., 5-FU + Intα, chemo + radiotherapy)
- Bolus only
- Oral 5-FU

Intervention:

- Method for PK monitoring unclear
- No PK monitoring
- validation of other technology than My5-FU
- Tumour samples analysed

Study type:

- Narrative reviews (but reference lists checked)
- Editorials / letters without original data
- Case studies
- Non-English language papers

4.1.2.3 Objectives B and C - Inclusion criteria

Population:

- Cancer patients (colorectal, head and neck, stomach, pancreatic) receiving 5-FU chemotherapy by continuous venous infusion.

Intervention:

- PK monitoring using HPLC or My5-FU

Comparator:

- BSA or no comparator

Outcome:

Intermediate measures for consideration:

- Proportion of patients with 5-FU plasma levels in the optimal target range
- Area under the curve measurements
- Incidence of over and under dosing
- Frequency of dose adjustment
- Test failure rates

Clinical outcomes related to intermediate measures of 5-FU exposure:

- Treatment response rates
- Progression free survival

- Overall survival
- Health related quality of life
- Incidence of side effects and 5-FU toxicity

Setting:

- Metastatic or adjuvant therapy

4.1.2.4 Objectives B and C - Exclusion criteria

Population:

- Animal studies
- No patients; samples or cell lines only
- Patient group unclear
- population with non-included cancers)
- Studies with less than 80% of included cancers (colorectal, head and neck, pancreatic and gastric cancer)

Treatment:

- Not 5-FU
- Wrong treatment (e.g., 5-FU + Intα, chemo + radiotherapy)
- Bolus only
- Oral 5-FU

Intervention:

- Method for PK monitoring unclear
- No PK monitoring
- Tumour samples analysed

Outcome:

- AUC or 5-FU plasma concentration not related to outcomes

Study type:

- Narrative reviews (but reference lists checked)
- Editorials / letters without original data
- Case studies
- Abstracts without dose adjustment following My5-FU measurement
- Non-English language papers

4.1.2.5 Objective D - Inclusion criteria

Population:

- Colorectal cancer patients receiving 5-FU chemotherapy by continuous venous infusion

Intervention:

- 5-FU therapy as 5-FU + folinic acid (FA) (Gamelin 2008[118]) or FOLFOX6 (Capitain, 2012[119]) regimen

Comparator:

- None or any

Outcome:

- PFS, OS, adverse events/toxicity

Setting:

- Metastatic or adjuvant therapy

Study type:

- Systematic review or meta-analysis

4.1.2.6 Objective D - Exclusion criteria

Population:

- cancers other than CRC

Treatment:

- treatment regimens other than 5-FU + folinic acid (FA) or FOLFOX6

Study type:

- Non-English language papers

4.1.3 Review strategy

The general principles recommended in the PRISMA statement were used.[117] Records rejected at full text stage and reasons for exclusion were documented. Two reviewers independently screened the titles and abstracts of all records identified by the searches and discrepancies were resolved through discussion. Disagreement was resolved by retrieval of the full publication and consensus agreement. Full copies of all studies deemed potentially relevant, were obtained and two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus or discussion with a third reviewer.

4.1.4 Data extraction strategy

Data were extracted by one reviewer, using a piloted, data extraction form (see Appendix 2 toAppendix 4). A second reviewer checked the extracted data and any disagreements were resolved by consensus or discussion with a third reviewer. Further details about data extraction are provided for Objective A-1 below.

4.1.4.1 Data extraction for Objective A-1

A data extraction sheet (Appendix 2) was developed combining basic study information, results, and fields from the data extraction sheets for the other objectives so these data can be linked. The key measure for whether My5-FU can be considered equivalent to LC-MS/MS and HPLC is whether both the upper and lower limits of agreement (mean difference ±2sd) on the Bland-Altman plot are sufficiently small that they can be considered clinically equivalent. Additionally, if the 95% CI of the mean difference (bias) does not intersect zero then an adjustment should be made when converting from one measuring instrument to the other.[120] We also extracted data on the regression between the index test and reference standard, but this can only give information on the correlation between the two measures, and is not informative to the question of whether the two measures can be considered equivalent. Significant correlation cannot be considered evidence for significant equivalence.[120]

4.1.5 Quality assessment strategy

4.1.5.1 Adapting the QUADAS-2 checklist for Objective 1-A

Where appropriate, the quality of diagnostic accuracy studies was assessed using QUADAS-2.[121] For reasons explained below QUADAS-2 was adapted for Objective A-1 (Appendix 5).

QUADAS-2 is a broad tool to assess the quality of primary diagnostic accuracy studies. For this part of the review we were interested in analytic validity of the test only, i.e. its accuracy and reliability in measuring 5-FU plasma levels. Whether the test can accurately predict patients' response to and side effects of treatment (its clinical validity) and be implemented to improve patient outcomes (its clinical utility) are considered in Objectives B, C and D. Therefore we adapted the signalling questions in the QUADAS-2 tool for use with laboratory analytical studies. This was informed by the ACCE guidance for assessing analytic validity for genetic tests.[122]

In domain 1 (patient selection) one signalling question, "was a case-control design avoided?", was removed. In this measure of analytic validity the outcome of interest (5-FU plasma level) is continuous, and therefore by definition there were no cases or controls. The focus of concerns regarding applicability was adapted from relating entirely to patients to also including to plasma sample concentrations.

In domain 2 (index tests) the signalling question "Were the index test results interpreted without knowledge of the results of the reference standard?" was removed because the index test is objective. The signalling question "if a threshold was used, was it pre-specified?" was removed as we were interested in agreement between two continuous measure without a threshold. An additional signalling question was added to account for the potential bias in underreporting or not including failed tests "Were the number of failed results and measurement repeats reported?". Under

applicability was added “Describe the preparation and storage of the sample before the index test was applied:” to check whether sample preparation was similar to potential NHS practice.

In domain 3 (reference standard) the signalling question “Were the reference standard results interpreted without knowledge of the results of the index test?” was removed because the reference standard is objective.

In domain 4 (flow and timing) exclusions from the “2x2 table” and “analysis” were replaced with exclusions from the “Bland-Altman plot” because there will be no thresholds used and therefore no 2x2 tables produced, and the outcome of most interest is the Bland-Altman plot (see data extraction section). Additionally “Did all patients receive a reference standard?” was replaced with “Were both index test and reference standard conducted on all samples?”

4.1.5.2 Quality assessment strategy for Objectives B and C

For Objectives B and C, as a broad range of study designs were identified in the scoping searches, the use of a single checklist, in contrast to individual checklists for each study design, was considered appropriate. The Downs and Black (1998) checklist[123] was therefore used to assess the quality of papers meeting the inclusion criteria (seeAppendix 6). This 27-item checklist enabled an assessment of randomised and non-randomised studies and provides both an overall score for study quality and a profile of scores not only for the quality of reporting, internal validity (bias and confounding) and power, but also for external validity. However, since some questions were not appropriate for single arm studies, the overall score was not considered useful or appropriate and was therefore not used. The results of the quality assessment provide an overall description of the quality of the included studies and provide a transparent method of recommendation for design of any future studies. Quality assessment was undertaken by one reviewer and checked by a second reviewer, any disagreements were resolved by a third reviewer through discussion.

4.1.6 Methods of analysis/synthesis

4.1.6.1 Diagnostic accuracy studies (My5-FU versus HPLC/LC-MS) (Objective A-1)

The My5-FU assay delivers an estimate of plasma 5-FU concentration. For a study population this may potentially allow discrimination of study populations into categories: over-dosed, optimally-dosed and under-dosed. Where results from a gold standard were available, a 2x2 table was constructed allowing diagnostic accuracy to be estimated using standard statistics (e.g., sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values).

Diagnostic accuracy studies (My5-FU versus HPLC/LC-MS) are considered to be those where patient samples are assayed for 5-FU concentration but patient outcomes may not be reported. Those studies

that aimed to test the internal and/or external validity of the My5-FU assay were identified and their findings were summarised and appraised. Studies that do not report test failure rates were noted; where available, test failure rates were tabulated.

4.1.6.2 Patient-based studies (Objectives B and C)

Analyses was stratified according to cancer type, 5-FU delivery mode and cancer stage (e.g., metastatic).

Study, treatment, population, and outcome characteristics were summarised and compared qualitatively and, where possible, quantitatively in text, graphically and in evidence tables. Pooling studies results by meta-analysis was considered. Where meta-analysis was considered unsuitable for some or all of the data identified (e.g., due to the heterogeneity and/or small numbers of studies), we employed a narrative synthesis. This involved the use of text and tables to summarise data allowing reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies were organised by research objective addressed. A commentary on the major methodological problems or biases that affected the studies was included, together with a description of how this may have affected the individual study results.

For Objectives B and C we aimed to identify studies which compared BSA-based dose regimens of 5-FU with continuous infusion in which measures of plasma 5-FU are not undertaken to inform dose changes with dose regimens in which dose adjustment is informed by the My5-FU assay results applied to a stated dose adjustment algorithm. These studies would best report the following outcomes: incidence and severity of side effects of 5-FU; overall survival and progression-free survival as stated in the inclusion criteria. We considered using a linked-evidence approach[124] in which studies report dose adjustment informed by plasma 5-FU measured by other methods (e.g. HPLC, LC-MS); this required evidence of comparable performance of My5-FU with such assay methods.

In studies where My5-FU has been used but there was no comparator arm, or the comparator arm was a convenience sample (retrospective/historical population), outcomes were listed and appraised. Outcomes reported for non-randomised comparator arms (i.e., historical controls) were assessed for their representativeness in the light of information gained from systematic reviews (Objective D). Relevant clinical outcomes from single arm studies were considered for pooling should they be reported in sufficient detail and be considered relevant to the objectives.

4.1.6.2.1 Time to event outcomes

The protocol plan for the current report was to request individual patient data (IPD) from authors of important included papers, so as to inform parameterisation of overall survival and progression-free survival and other relevant outcomes. In practice efforts to obtain IPD were not successful. Therefore the method of Guyot et al. (2012)[125] was used for reconstruction of Kaplan-Meier plots and of IPD. For this the published Kaplan-Meier graphs were scanned using standard software (Digitizelt).[126] Reconstructed KM plots were implemented from the IPD estimates using Stata version 11 software. As a visual test of faithful reconstruction the reconstructed plots were superimposed on the published originals (available on request from authors). Parametric fits using the estimated IPD were obtained for exponential, lognormal, Weibull, loglogistic and Gompertz distributions implemented with the "streg" command with Stata version 11. Goodness of fit was judged visually and according to information criteria (Akaike information criterion, Bayesian information criterion). Simple least squares method, implemented with Microsoft Excel with the "solver" add-in, was used to obtain parameters for distributions when only median survival values were available.

We requested individual patient data (IPD) of key included papers from authors, to enable parameterisation of overall survival and progression-free survival implemented using standard parametric distributions. Goodness of fit to the observed data was judged visually and according to information criteria (Akaike information criterion [AIC], Bayesian information criterion [BIC])). In the absence of IPD becoming available, we digitised published Kaplan Meier (or competing risks) analyses using standard software (e.g., DigitizeIt software).[126] The digitised product was used to construct curve fits using methods developed by Guyot et al. (2012)[125] or Hoyle and Henley (2011).[127]

4.1.6.2.2 Outcomes reported as proportions

Reported percentages were converted to the nearest whole number of patients and the 95% confidence intervals around proportions were estimated using the binomial distribution. Relative risks and associated 95% confidence intervals were estimated in Stata version 11 using the "metan" package. Pooling of relative risks was not undertaken because of differences in treatments and populations between studies.

4.1.6.2.3 Indirect and mixed treatment comparison

The methods outlined in the protocol anticipated the existence of several RCTs or comparative studies that would be appropriate for formal meta-analysis or NMA; the evidence was insufficient to support this approach.

The authors of the NICE guideline for advanced CRC (CG131)[7] undertook network meta--analyses (NMAs) of overall survival and of progression free survival using RCT data for 5-FU treatment

regimens, and this offered a potential template approach for the present project. The CG131 authors were constrained by the lack of full data and their analyses required assumptions of constant hazard (i.e. fitting of exponential survival curves) and of proportional hazards between treatments. CG131[7] preceded publication of the Guyot et al. (2012)[125] procedure to estimate IPD from KM plots. Our use of this method with available PK data revealed that the exponential distribution was the poorest performing of various parametric distributions tried in exploring reported Kaplan-Meier plots. We therefore considered the method described by Ouwens et al. (2010)[128] for NMA of Weibull parametric survival curves since this was reported to avoid proportional hazard assumptions. In practice, because of commercial considerations, the authors' kept the published NMA code incomplete. There was insufficient time available to develop our own code and contact with corresponding author failed to resolve the difficulty. A further problem confronting NMA approaches was the almost total lack of randomised evidence about PK dose adjustment and the heterogeneity of available studies. NMA was therefore not undertaken.

4.1.7 Face-to-face discussions and written questions

Information was extracted from face-to-face discussions and written questions undertaken with a relevant laboratory. Information was used within the model. Expert opinion from Specialist Committee Members and other clinical experts was sought and appropriately cited.

5 CLINICAL EFFECTIVENESS RESULTS

Chapter 5 provides the search results for the clinical effectiveness assessment including results of

- Objective A1 which considers the accurate estimation of plasma 5-FU when using the My5-FU assay; and Objective A2 which considers available information about treatment algorithms based on 5-FU measures.
- Objectives B and C which consider the evidence on PK dosing compared to traditional BSA based dosing.
- Objective D which examines the comparability of BSA comparators used in the PK comparison compared to the generality of BSA regimens.

5.1 Search results for Objectives A, B and C

Figure 6 provides the PRISMA flow diagram for Objectives A, B and C. A total of 3,751 records were identified through electronic searches. One additional record was identified from other sources. The removal of duplicates left 2,565 records to be screened, of which 2,362 were excluded at title/abstract level as these were irrelevant. The remaining 203 records were examined for full-text, of which 35 were included in the clinical effectiveness review (see Appendix 7). The included 35 references represent:

- 4 studies addressing Objective A-1,[89, 95, 129, 130]
- 4 studies for Objective A-2[96, 131-133]
- 29 studies in 30 papers for Objectives B and C,[118, 119, 131-157] of which 3 studies addressed both Objective A-2 and Objectives B and C.[131-133]

Full details on the reasons for excluding studies are full-text can be found in Appendix 8.

10 on-going trials were identified by the manufacturer. The search of on-going trials in Clinical Trials.gov, Current Controlled Trials, UKCRN Portfolio, and WHOICTRP databases (carried out in May 2014) retrieved 3 of these, but we were unable to verify the remaining 7 (seeAppendix 9).

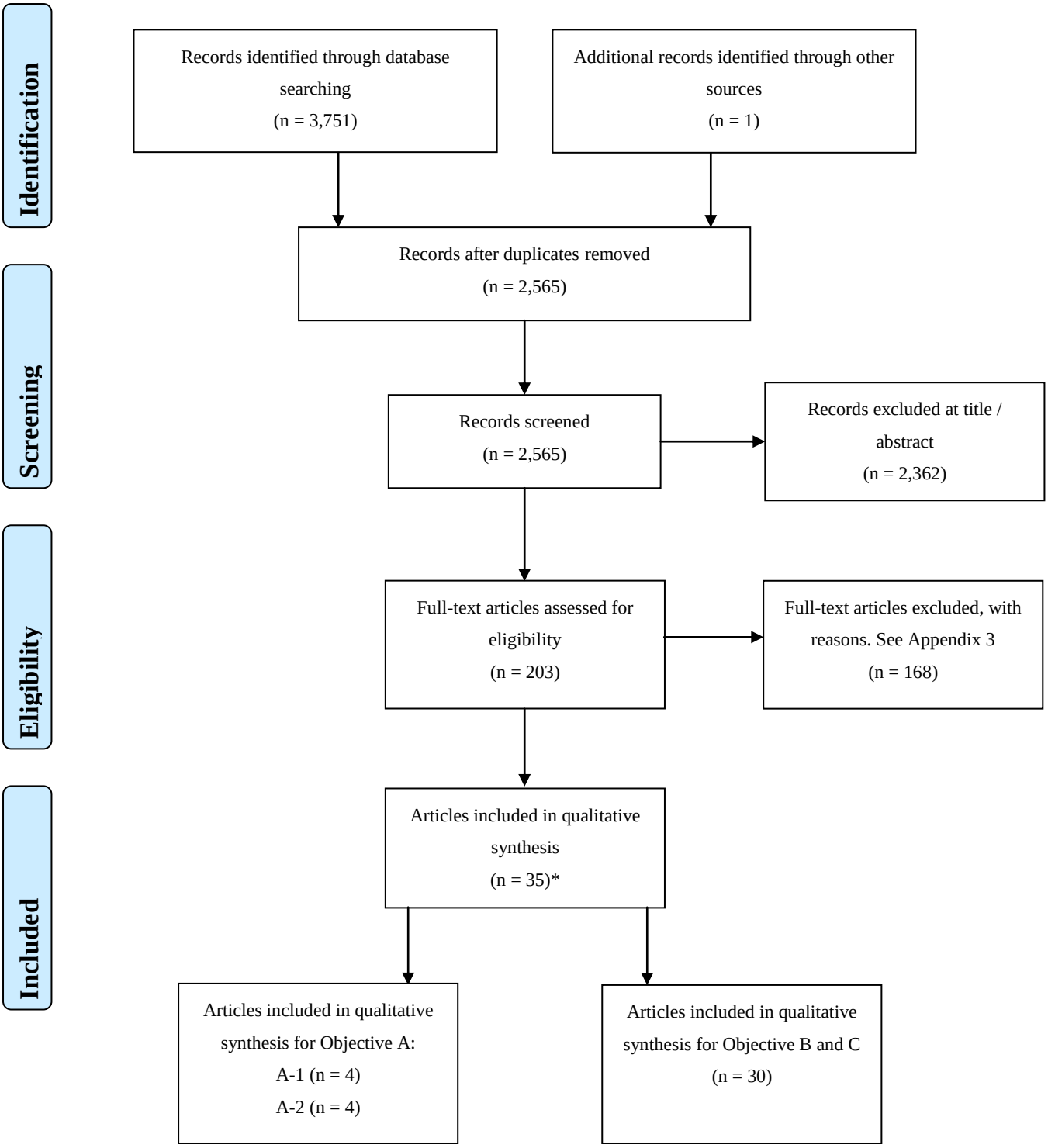

Figure 6. PRISMA Flow Diagram: My5-FU Clinical Effectiveness objectives A, B and C

*3 studies addressed both Objective A-2 and Objectives B and C

5.2 Objective A-1: Provide a review of studies that examine the accuracy of the My5-FU assay when tested against gold standard methods of estimation of 5-FU. High performance liquid chromatography (HPLC) and liquid chromatography–mass spectrometry (LC-MS) will be considered the gold standard for the purpose of assessing the accuracy of 5-FU plasma level measurements.

The first part of Objective A (A-1) aimed to provide a review of the studies that examine the accuracy of the My5-FU assay when tested against gold standard methods of estimation of 5-FU. To achieve this we developed a data extraction template and adapted the QUADAS-2 checklist (seeAppendix 2 andAppendix 5. Please find summaries of the data extraction and quality assessment for Objective A-1 in Table 5 and Table 6. Completed data extraction and quality assessment forms are available from the authors on request.

Two research papers[89, 95] and two abstracts,[129, 130] were found to include information relevant to whether My5-FU can be considered equivalent to LC-MS/MS and HPLC. However, one of the abstracts was considered part of the same study as one of the papers.[95, 129] Therefore, there were three unique studies. Three studies provided Bland-Altman plots, but only one[95] provided the upper and lower limits of agreement and the 95%CI of the mean difference. Validation data provided by the manufacturer included three additional unpublished Bland-Altman plots [Personal communication: S. Salamone, Saladax biomedical, 2014]. These did not include upper and lower limits of agreement, and there may have been some samples in common with one of the papers.[95]

The risk of bias was difficult to judge due to incomplete reporting, particularly in the domain of flow and timing. There was a high risk of bias for patient selection for two out of the four studies, and it was unclear for the other two. This was because there were no assurances given that inappropriate exclusions of patients or samples were made. This could have led to incomplete reporting of both failed samples and outliers, and lead to overly optimistic estimations of bias and limits of agreement. Validation data provided by the manufacturer were judged to have a high risk of bias for flow and timing because in three of the four comparisons made it was stated that outliers were excluded, although how many were excluded or why they were excluded was not stated. Overall there were few concerns about applicability, with the tests considered generally representative of the tests of interest, the only potential concerns involved whether sample collection, preparation and storage matched the proposed NHS method.

Table 5. Data extraction for studies investigating whether My5-FU can be considered clinically equivalent to LC-MS/MS

First author, Year	Index test	Reference Standard	Range of plasma concentrations* (ng/mL)	Bland-Altman Plot			
				Bias (95%CI)	Lower limit of agreement	Upper limit of agreement	Largest outliers
Buchel, 2013[95]	My5-FU	LC-MS/MS	93 to 17881	7.0% (5.5 to 8.5)	-18%‡	30%‡	-50%‡ +95%‡
Beumer, 2009[89]	My5-FU	LC-MS/MS	93-1774	+23ng/mL (NR)	NR	NR	-35%‡ +52%‡
Makihara 2012[130]	My5-FU	LC-MS/MS	41-457	NR	NR	NR	NR
Validation data [S. Salamone, Saladax biomedical, 2014]	My5-FU on 75	LC-MS/MS	100 to 1471	+24.5ng/mL			-285ng/mL to +171ng/mL (approx. -25% to +70%‡)**
Validation data [S. Salamone, Saladax biomedical, 2014]	My5-FU on 75	HPLC	100 to 1471	+1.84ng/mL			-80 to +137ng/mL (approx. -30% to +35%‡) **
Validation data [S. Salamone, Saladax biomedical, 2014]	My5-FU on 117	HPLC	100 to 1471	+5.08ng/mL			-80ng/mL to 150ng/mL (approx.-30% to +35%‡)**
Validation data [S. Salamone, Saladax biomedical, 2014]	HPLC	LC-MS/MS	95 to 1370	22.7ng/mL			-227ng/mL to +166ng/mL (approx.-25% to +60%‡)

*as measured by the index test ** Further outliers were reported as excluded ǂread from plot NR= not reported

Table 6. QUADAS-2 risk of bias for studies investigating whether My5-FU can be considered clinically equivalent to LC-MS/MS

First author, Year	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Buchel, 2013[95]	High	Unclear	Low	Unclear	Low	High	Low
Beumer, 2009[89]	High	Unclear	Low	Unclear	Low	Low	Low
Makihara, 2012[130]	Unclear	Unclear	Low	Unclear	Low	Unclear	Low
Validation data [S. Salamone, Saladax biomedical, 2014]	Unclear	Unclear	Low	High	Low	Unclear	Low

Buchel et al. (2013)[95] took 197 samples from 32 GI cancer patients in one Swiss hospital. They added 50 plasma samples from cancer patients of unspecified type provided by Saladax. Whether there were any participants or plasma samples excluded from the analysis is not stated. They compared the measurements from the Saladax My5-FU immunoassay using the Roche Cobas Integra 800 analyser (index test) to the reference standard Liquid chromatography-tandem mass spectrometry (LC-MS/MS). The range of concentrations for My5-FU was 93 to 17881, and for LC-MS/MS was 102 to 18590. Passing Bablok regression showed strong correlation (Pearson R^2=0.99) with slope 1.08 (95%CI 1.06 to 1.09) indicating that My5-FU measurements increase faster than LC-MS/MS measurements with increasing 5-FU concentrations.[158] The Bland-Altman plot did not appear to show any systematic pattern and therefore the coefficients are interpretable. There was a 7% bias (95%CI 5.5% to 8.5%) indicating that measurements using My5-FU assay were between 5.5% and 8.5% higher than when using LC-MS/MS. The lower and upper limits of agreement are shown on the graph at around -18% and +30%, although the exact figures are not given.

This indicates that the two measurement methods can only be considered equivalent if overestimation of 5-FU concentration by 30% and underestimation of 5-FU concentration by 18% by the My5-FU assay in comparison to LC-MS/MS values are not considered clinically meaningful.

There are nine outliers from the 197 samples including one outlier with over 90% bias. The authors do not propose an explanation for this. Such outliers merit investigation, in particular consideration of the potential impact on clinical care if such outlying measurements occur in practice. The outliers and upper and lower limits of agreement from the Bland-Altman plot are shown in Figure 7. This paper also presented data provided by Saladax giving the performance of the My5-FU assay using four different analysers over the smaller range 102 to 1560ng/mL. The bias that was apparent using the Integra 800 analyser was just 1.4% (95%CI 0.2% to 2.6%) using the smaller subset of 50 samples. The authors propose that this is due to the much higher range of plasma concentrations they have used in the larger samples. This explanation appears reasonable as the regression results indicate that as the 5-FU plasma concentrations increase, the bias towards My5-FU giving higher estimates also increases. These much higher plasma concentrations may be unlikely in clinical practice. No lower and upper limits of agreement are presented for these analyses on the subset of 50 cases so it is difficult to draw any conclusions from them.

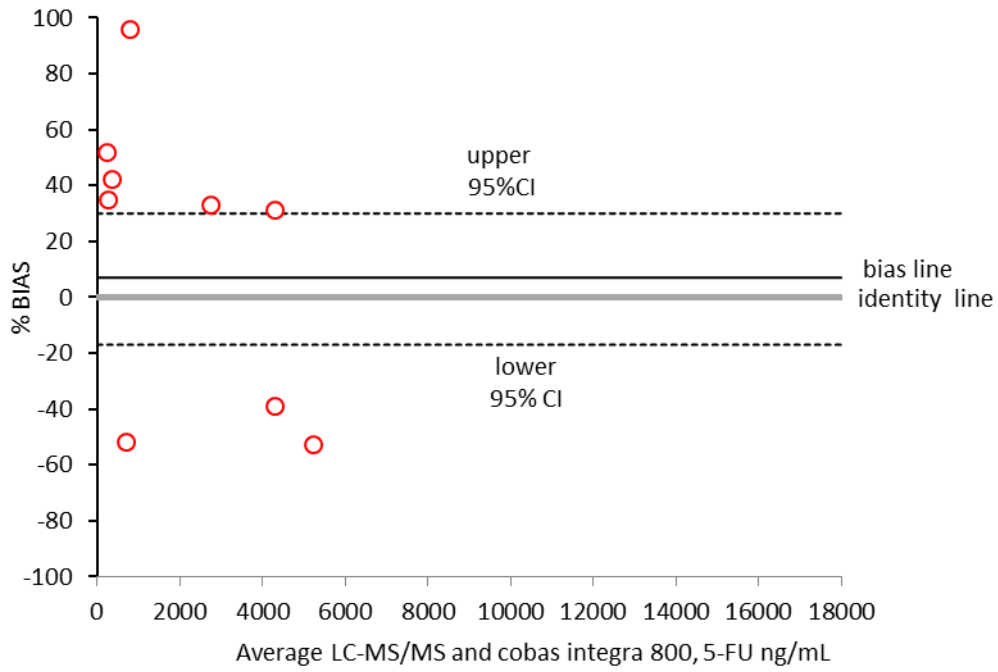

Figure 7. Key elements of the Bland-Altman plot from Buchel et al. (2013).[95] Outliers are indicated by red circles and upper and lower limits of agreement by the dashed lines. Values above 1800 ng/mL may be rare in clinical practice

Beumer et al. (2009)[89] describes part of the development and testing of the My5-FU assay, with the corresponding author (a Saladax employee). They used 156 plasma samples from the blood of 156 H&N cancer and CRC patients. They compared the 5-FU PCM assay using the Olympus AU400 analyser as the index test against LC-MS/MS as the reference standard. They do not state whether there were any exclusions, however there are 156 samples included in the regression analysis so there appear to be no exclusions in that part. The regression showed strong correlation (R^2=0.97), with an

intercept of 10.9ng/mL and gradient of 1.035, indicating a trend towards the My5-FU assay estimating plasma levels as higher than LC-MS/MS, with this effect larger at higher concentrations. However, there are no confidence intervals so we do not know if this is statistically significant. The Bland-Altman plot appears to show a positive bias with no visually detectable pattern of change with increasing average plasma concentration. No mean bias or limits of agreement are reported or shown in the plot and so it is difficult to reach conclusions about the levels of agreement between the two tests from this paper. However, from visual inspection there appears to be one measurement above 50% positive bias and 16 measurements between 25% and 50% positive bias. There appear to be no measurements above 50% negative bias, and three measurements between 25% and 50% negative bias.

The Makihara et al. (2012)[130] conference abstract does not include the key outcomes of interest from a Bland-Altman plot. However this sample of 50 CRC patients whilst showing strong agreement between My5-FU and LC-MS, (R^2=0.8471), agreement was weaker than in other studies. The reasons for this are unclear, but it merits consideration as there are few separate datasets upon which the comparison between tests has been made.

Validation data provided by the manufacturer [personal communication: S. Salamone, Saladax biomedical, 2014] includes a comparison between My5-FU using an AU400 75 analyser and LC-MS/MS 75 for 75 samples (although the methods section appears to only describe 56 samples). An unspecified number of outliers have been excluded. Deming regression shows a gradient of 1.005 that does not significantly differ from unity (95%CI 0.94 to 1.07) and a positive intercept of 22.7ng/mL which is not significantly non-zero (95%CI -4.5 to 50). The Bland-Altman plot shows mean bias +24.5ng/mL, confidence intervals and upper and lower limits of agreement are not given, but values for bias range from -285ng/mL to +171ng/mL, although there will be more extreme values if outliers have been excluded. In percentage terms the range is approximately -25% to +70%. There are also comparisons between the same My5-FU assay with HPLC as the reference standard, with mean bias just +1.84ng/mL and outliers ranging from -80 to +137ng/mL (approx. -30% to +35%). Comparison of the two reference standards used, HPLC and LC-MS/MS is also made with mean bias 22.7ng/mL and range -227ng/mL to +166ng/mL (approx.-25% to +60%) indicating that similar levels of variation in measurements appear to occur between HPLC and LC-MS/MS as do between My5-FU and LC-MS/MS. However it is difficult to draw any conclusions from these data in the absence of knowing which samples were excluded and the reasons for this. Further details from Saladax described excluded samples as those which had no LC-MS/MS result or no HPLC-UV result. However the only plot from the unpublished data where no outliers were reported as excluded was in the comparison of HPLC against LC-MS/MS. And outliers were only excluded in the plots which included My5-FU as index test.

5.2.1 Summary of Objective A-1

Whilst there is high correlation between My5-FU, HPLC and LC-MS/MS, the Bland-Altman plots show considerable variability. In the comparison of My5-FU with LC-MS/MS even with additional outliers detailed as excluded, the validation data provided by the manufacturer shows outliers with a range of variation up to -285ng/mL and +171ng/mL (approx. -25% and +70%). Only one paper reported upper and lower limits of agreement. These were found to be -18% to +30%. These discrepancies between measurements need to be considered carefully from the point of view of clinical significance. If this range of values (-18% to +30%) can be considered clinically equivalent then My5-FU can be considered equivalent to LC-MS/MS, but with careful consideration of the clinical implications of outlier measurements beyond this range.

Buchel et al. (2013)[95] found that the mean difference between LC-MS/MS and My5-FU measurements was 7.0%, with upper and lower limits of agreement as -18% to +30%. This means that the standard deviation of the differences was around 12%. Therefore we would expect that 95% of the measurement differences between LC-MS/MS and My5-FU to lie between -18% and +30%. Also this paper has a positive bias, i.e., +7%, so My5-FU appears to systematically produce higher measurements than LC-MS/MS. The other papers do not share this same bias. It may be simply due to this paper taking measurements well above the clinical range, and these outliers beyond the clinical range are skewing the distribution. No other papers were found to calculate limits of agreement, but several papers reported plot distributions very similar to Buchel. We did not find any data on test-retest reliability. Personal communication with a clinical advisor suggests that -18% to +30% may not be clinically significant; therefore we concluded that the tests may be equivalent, but remain cautious about outliers.

We adapted the QUADAS-2 checklist[121] for use in assessing the quality of laboratory measurements of analytic validity, and developed a data collection sheet with emphasis on the key outcomes of interest from the Bland-Altman plot. We systematically applied these to the research literature. The weaknesses of this analysis lies largely with the evidence base, with missing details of exclusions making interpretation difficult, and only one paper giving upper and lower limits of agreement on the Bland-Altman plot, however it should be noted that these latter limits of agreement are reported for a range of plasma concentrations which are beyond the clinical range.

Overall, there is good correlation between My5-FU and the reference standard of HPLC or LC-MS/MS, however significant variability remains and there was high risk of bias in included studies due to excluded samples and outliers. There may be substantial variability in 5-FU measurement of

between -18% to +30% between the two tests. It is unclear if this is clinically significant. Outliers show even greater variability.

5.3 Objective A-2: Provide a review of studies which have developed a treatment algorithm based on 5-FU measures.

This section provides an overview of published treatment algorithms for 5-FU dose adjustment in cancer patients. Dose adjustment during 5-FU treatment requires knowledge of the plasma concentration of 5-FU following the first cycle of treatment to calculate the AUC (area under the concentration-time-curve) value, which is known to correlate better with outcomes than initial 5-FU dose.[96] Due to the nonlinear pharmacokinetics of 5-FU an algorithm is then needed to calculated the new dose for the second 5-FU treatment cycle if the exposure is not within the desired range. Several algorithms have been reported in the literature for different treatment regimens which are described below. Complete data extraction forms for Objective A-2 are available on request from the authors.

Gamelin et al. (1996)[131] developed a dose adaptation algorithm for the weekly 8h-continous infusion of 1000mg/m^2 5-FU plus 200mg/m^2 bolus folinic acid. In a case series of 40 patients with advanced CRC the 5-FU dose was increased in 250mg/m^2 steps in all patients every 3 - 4 weeks up to 2000mg/m^2 or first signs of toxicity. 5-FU plasma concentrations were measured weekly and the dose adaptation algorithm was based on a regression analysis of the relationship between dose and plasma levels in two groups of patients achieving complete response (CR) or partial response (PR) versus patients with minimal response (MR), stable disease (SD) or progressive disease (PD). The target concentration was set at 2000-3000 µg/l. The adjustment algorithm by Gamelin et al. (1996)[131] is shown in Table 7. This was adapted and used in subsequent studies by the French group[118, 134, 135, 139] (Table 18).

Table 7. Adjustment algorithm developed for 8h 5-FU infusion regimen + FA by Gamelin et al. (1996)[131]

5-FU plasma levels (µg/l)	5-FU dose adjustment (% of previous dose)	In case of toxicity
<500	+50%	Grade 2 toxicity: 200mg dose decrease Grade 3 toxicity: 1 week break than 300mg dose decrease
500-1000	+40%	
1000-1300	+30%	
1300-1500	+20%	
1500-1800	+10%	
1800-2000	+5%	
2000-3000	No modification	
3000-3200	-5%	

3200-3500	-10%	
>3500	-30%	

Kaldate et al. (2012)[96] carried out a retrospective database analysis of pharmacokinetic data from a commercial laboratory setting to define a dose adjustment algorithm for the FOLFOX6 regimen (5-FU + FA + oxaliplatin) with or without bevacizumab. They used a simple regression analysis to model the change in AUC versus the change in dose in 187 CRC patients. The 187 patients produced a total of 307 cycle pair observations, i.e. AUC measurements from two consecutive infusion cycles that included a dose change. The difference in AUC of one cycle pair observation was termed 'change in AUC' (mg*h/l) and the difference in dose of one cycle pair was termed 'change in dose' (mg/m^2). The relationship between 'change in AUC' versus 'change in dose' was investigated using regression analysis. The regression model that described the relationship with an R^2=0.51 was:
'change in AUC' (mg*h/l)=0.02063* change in dose' (mg/m^2).

This relationship was used to establish a dose adjustment algorithm to be used as a practical tool in a clinical setting (Table 8). It is noteworthy that Kaldate et al. (2012)[96] used a revised optimal target AUC range of 20-30 (mg* h/L) rather than the narrower target range of 20-24 (mg* h/L). The lower limit was accepted to be valid based on published efficacy data from Gamelin et al. 1998 and 2008.[118, 139] The upper limit however, was thought to be too low as it was produced using outdated more toxic regimens. The longer infusion time of 46 hours and the combination with other therapies make more recent combination therapies such as FOLFOX6 less toxic and more tolerable. Therefore, the new target range is wider allowing greater 5-FU exposure. This algorithm has not been tested in a prospective study. However, Kaldate et al. (2012)[96] announced that the PROFUSE (PROspective 5-FluoroUracil OnDose Evaluation, NCT014623) study is underway in the US to test the utility of this algorithm.

Table 8. Adjustment algorithm for FOLFOX6 regimen for COC patients by Kaldate et al. (2012)[96]

AUC (mg* h/L) from previous cycle	**Change in dose (mg/m2)**
≥40	↑727
37–39	↑582
34–36	↑436
31–33	↑291
20–30	No change needed
17–19	↓291
14–16	↓436
11–13	↓582
8–10	↓727

Ychou et al. (1999)[132] investigated two different adaptation schedules for the bimonthly LV5FU2 (de Gramont) regimen (FA (200 mg/m^2 per day) by i.v. infusion over 2 h followed by a 5-FU bolus (400 mg/m^2 per day) and immediately after by continuous 5-FU infusion (600 mg/m^2 per day) over 22 h for two consecutive days, i.e. 2000 mg/m^2 per cycle). A prospective cohort of 38 patients with advanced CRC was divided into two groups. Group A received progressive increase of 5-FU between 25 to 50% at every cycle, i.e. 150% maximum at cycle 6 in the absence of ≥ grade 3 toxicity. This steady increase was used to avoid severe toxicities early on. The insights from group A were then used to develop and adaptation algorithm for group B who received a dose increase at cycle 2, which could be extensive, according to the AUC value from cycle 1 in the absence of ≥ grade 3 toxicity. After cycle 2 the dose remained constant during subsequent cycles if toxicity grades remained less than 3. The algorithm is displayed in Table 9. The methods of how the algorithm was developed are unclear. This algorithm was used in subsequent studies by the same group.[137, 148]

Table 9. 5-FU dose adaptation algorithm for the bimonthly LV5FU2 (DeGramont) regimen for CRC patients by Ychou et al. (1999)[132]

AUC in mg*h/l*m^2	**Dose increase**
≤5	150%
5<AUC≤10	100%
10<AUC≤15	50%
15<AUC≤20	25%
>20	No increase

Santini et al. (1989)[133] studied dose adjustment in patients with H&N cancer using 5-FU (1,000mg/m^2*24h) for 5 consecutive days (days 1-5) plus cisplatin (100mg/m^2) on day 0 as first-line chemotherapy treatment. 5-FU pharmacokinetic measurements were taken on day 3 to adjust the dose for the second half of treatment if required. They used a retrospective study group (n=89) to establish the relationship between 5-FU exposure and toxicity in order to identify a threshold AUC_{0-3} value (15,000ng/ml*h) following 3 days of treatment that would be predictable of toxicity. In a prospective study of 81 patients AUC_{0-3} values were determined to decide whether dose reduction was required for the second half of the cycle. It was estimated that a 30% reduction would lead to a subjective decrease in exposure if the AUC_{0-3} reached the threshold value of 15,000ng/ml*h. Furthermore, it was decided to stop treatment at an AUC_{0-3} value of ≥30,000ng/ml*h. Using these two relationships intermediate AUC_{0-3} values (between > 15,000ng/ml*h and < 30,000ng/ml*h) would require a dose decrease following a linear function between % 5-FU dose and 5-FU AUC_{0-3}. Table 10 illustrates the algorithm for four different AUC_{0-3} values. This algorithm was also used by the same group in a later study[153] and was further developed to include dose increases for patients with an $AUC_{1-2\ days}$ value lower than 5760ng/ml*h.[159]

Table 10. Algorithm by Santini et al. (1989)[133] in an example of 4 AUC_{0-3} values

AUC_{0-3} value (ng/ml*h)	5-FU dose adjustment (% of previous 5-FU dose)
<15,000	Same dose
15,000	70%
20,000	45%
≥30,000	Stop treatment

5.3.1 Summary of Objective A-2

Dose adjustment algorithms have been developed by different groups for different regimens. They are based on the observed 5-FU exposure expressed as AUC values or the concentration of plasma 5-FU. [96, 131-133]

Since other factors are involved in the modulation of 5-FU exposure it is advisable to consider additional parameters in the dose adjustment calculation such as genotype, phenotype, physiological, physiopathological and associated treatments.[160] Protocols have been developed known as the ODPM Protocol™ which integrates these additional parameters to optimise previous dose adaptation algorithms.[119] These have been commercialised. Algorithms published for one treatment schedule cannot be extrapolated to other protocols but need to be adapted to different treatment schedules due to the non-linear nature of the 5-FU pharmacokinetics.[160] Therefore, individual algorithms need to be developed for different regimens and adjusted if new combination therapies are developed.

5.4 Conclusions from Objectives A-1 and A-2

Equivalence of My5-FU with HPLC and LC-MS is reasonable; however, the evidence is based on studies which are at high risk of bias due to excluded samples and outliers. Studies developing algorithms have focused on one particular regimen and therefore, algorithms might not be available for all 5-FU containing regimens. Algorithms cannot be simply transferred from one regimen to another but require adjustment to different or more recent regimens and commercialised algorithms may need to be purchased.

5.5 Objective B and C: Systematically review the literature on the use of (B) My5-FU and (C) HPLC and/or LC-MS to achieve adjusted dose regimen(s) to compare it with BSA-based dose estimation (in terms of overall survival, progression free survival and adverse events) for patients receiving 5-FU-administered by continuous infusion. Variations in current BSA-based dose regimens will be considered where appropriate.

The aim of 5-FU chemotherapies is to prolong life and delay disease progression while guarding against deterioration in life quality from toxic side effects. PK dose adjustment may be judged an advance on BSA dosing if it improves on these clinical outcomes in a cost effective way. Therefore, the emphasis here is in studies that compare PFS, OS and toxic events for PK versus BSA treatments; these are crucial for an estimate of clinical effectiveness and for informing an economic model.

The following section provides an overview of the available evidence that was identified and eligible for inclusion to answer objectives B and C. It also provides justification for the evidence which was taken forward to the analysis and modelling stage. The 30 included references represented 29 studies. Of the 29 included studies 24 were single arm studies (i.e., studies that included either a BSA or a PK arm)[131, 132, 134-155] and five were comparative studies.[118, 119, 133, 156, 157] Of these three were in CRC[118, 135, 156] and two in H&N cancer.[133, 157] Comparative studies are defined as those in which patients who received a first line PK adjusted 5-FU dose regimen (the intervention arm) were compared with a similar group who received a BSA based regimen (the control arm), the regimens being identical in all respects other than dose adjustment. It is important to note that Fety et al. (1998)[157] and Fety et al. (1994)[159] both publish results from the same study, where Fety et al. (1994)[159] presented preliminary results. From here on the study is referred to as Fety et al. (1998).[157]

This section provides an overview of the 24 single arm studies, a summary which highlights our concerns with the quality of the studies and discusses evidence that can be taken forward to the analyses and cost-effectiveness modelling. This is followed by an overview of the comparative studies for CRC and H&N separately, including a rational for the studies taken forward to inform the cost-effectiveness modelling. Finally, this section provides more detailed summaries of the studies which inform some of the model parameters.

5.5.1 Overview of single arm studies

The 24 single arm studies included 22 full papers[131, 132, 134-144, 147-155] and two abstracts[145, 146] (further details are provided in Appendix 10 and the full data extraction forms are available on request from the authors). The abstracts describe two investigations of dose adjustment using My5-FU in CRC patients. Of the 22 full papers, 16 investigated CRC patients,[131, 132, 134-144, 147-149] two used a mixed patient population,[150, 151] three studied H&N patients[152-154] and one study included only gastric cancer patients.[155] The major features of these studies are summarised in Table 11.

Table 11. Summary of 24 included single arm studies by cancer type

First author, date, country	Study design	Cancer type	Regimen	5-FU Dose adjustment (algorithm) / PK method	N (cycles)	5-FU related adverse events	Response rate (overall response)	Overall survival (median OS), KM	Progression free survival (median PFS), KM	Relationship between plasma level and outcome (positive, negative, neutral)
Boisdron-Celle, 2002 France[134]	Prospective case series	Advanced CRC	5-FU (8h infusion) + FA (+ oxaliplatin after progression)	Yes (Gamelin 1996)[131] / HPLC	29 (122)	Yes counts (reported extensively but irregularities in numbers reported)	Yes (7/27, 25.9%)	No, No	No, No	Plasma level and toxicity (positive)
Capitain, 2008 France[135]	Case series	Advanced CRC	5-FU + FA (FUFOL 4H and modified deGramont)	Yes (Gamelin 1996)[131] / HPLC	76	Yes risk (time of assessment unclear)	Yes (25/76, 32.9%)	Yes (20 months), Yes	Yes (100 days), No	No
Cattel, 2003 Italy[136]	Prospective case series	Metastatic CRC (Stage IV)	5-FU (14 days) + Oxaliplatin	No / HPLC	13	No	Yes (7/13, 53%)	Yes (9.6 months), No	Yes (7 months) No	No
Duffeur, 2010 France[137]	Retrospective database analysis	Metastatic CRC	deGramont (LV5FU2)	Yes (Ychou 2003)[148] / HPLC	103	Yes risk	Yes (young group: 15/55, 27%;	Yes (young group: 18.7 months;	No, No	AUC and severe toxicity

First author, date, country	Study design	Cancer type	Regimen	5-FU Dose adjustment (algorithm) / PK method	N (cycles)	5-FU related adverse events	Response rate (overall response)	Overall survival (median OS), KM	Progression free survival (median PFS), KM	Relationship between plasma level and outcome (positive, negative, neutral)
							elderly group 17/48, 35%)	elderly group: 13.4 months), No		(neutral)
Findlay, 1996 UK[138]	Case series	CRC (not specified)	5-FU (protracted; not specified)	No / HPLC	19	Yes risk (time of assessment unclear)	Yes (8/19, 42%)	No, No	No, No	Plasma level and response (neutral), Plasma level and toxicity (positive)
Gamelin, 1996 France[131]	Prospective case series (phase II study)	Metastatic CRC	5-FU (8h infusion)	No / Liquid chromatography	40 (2,082)	Yes risk	Yes (18/40, 45%)	Yes (14 months), Yes	Yes (unclear), Yes	Plasma level and toxicity (positive), survival (neutral), response (positive) and quality

First author, date, country	Study design	Cancer type	Regimen	5-FU Dose adjustment (algorithm) / PK method	N (cycles)	5-FU related adverse events	Response rate (overall response)	Overall survival (median OS), KM	Progression free survival (median PFS), KM	Relationship between plasma level and outcome (positive, negative, neutral)
										of response (positive)
Gamelin, 1998 France[139]	Prospective case series (multicentre phase II study)	Metastatic CRC	5-FU (8h infusion)	Yes (Gamelin 1996)[131] / Liquid chromatography	152 (4,096)	Yes counts	Yes (66/117, 56.4%)	Yes (19 months), Yes	Yes (11 months), Yes	Plasma level and toxicity (positive)
Ho, 2011 China[140]	Prospective case series	Metastatic CRC	5-FU (48h infusion) + FA	No / HPLC	16 (80)	Yes counts	Yes (3/16, 18.8%)	Yes (10.5 months), No	Yes (4.1 months), No	Plasma level and toxicity (neutral)
Jodrell, 2001 UK[141]	Prospective case series and simulation study	CRC (relapsed or metastatic)	5-FU (protracted 1-26 weeks)	No / HPLC	61	Yes risk (time of assessment unclear)	Yes (16/61, 26%)	Yes (11 months), No	No, No	Plasma level and toxicity / response (neutral)
Kline, 2011	Case series	CRC (stage	FOLFOX6 +	Yes (NR,	21	No	No	No, No	No, No	NR

First author, date, country	Study design	Cancer type	Regimen	5-FU Dose adjustment (algorithm) / PK method	N (cycles)	5-FU related adverse events	Response rate (overall response)	Overall survival (median OS), KM	Progression free survival (median PFS), KM	Relationship between plasma level and outcome (positive, negative, neutral)
USA[142]		III and IV)	Avastatin, FOLFOX6, FOLFIRI, FOLXOX4	supplied by manufacturer) / My5-FU						
Metzger, 1994 France[143]	Randomised trial*	Metastatic CRC	5-FU (5-day continuous infusion, flat or chronomodulated) + FA + Oxaliplatin	No / HPLC	9	Yes risk (inconsistent grouping of toxicity grades)	No	No, No	No, No	AUC and stomatitis (unclear)
Milano, 1988 France[144]	Prospective case series	Advanced CRC	5-FU (5-day continuous infusion)	No / HPLC	26	Yes counts (grouping grade I+II and III+IV	Yes (3/26, 12%)	No, No	No, No	AUC and toxicity (positive)
Patel, 2012 US[145]	unclear (Abstract	CRC (not specified)	mFOLFOX6 ±	Yes (NR) / My5-FU	58	Yes risk (Grading	No	No, No	No, No	No

First author, date, country	Study design	Cancer type	Regimen	5-FU Dose adjustment (algorithm) / PK method	N (cycles)	5-FU related adverse events	Response rate (overall response)	Overall survival (median OS), KM	Progression free survival (median PFS), KM	Relationship between plasma level and outcome (positive, negative, neutral)
	only)		bevacizumab			tool unclear)				
Patel, 2013 US[146]	unclear (Abstract only)	CRC (not specified)	mFOLFOX6 ± bevacizumab	Yes (NR) / My5-FU	70	Yes risk (Grading tool unclear, total toxicities reported only)	No	No, No	No, No	No
Stremetzne, 1999 Germany[147]	Randomised trial*	Metastatic CRC (unresectable)	5-FU (5-day continuous) + FA	No / Reversed phase ion-pair HPLC	16	Yes risk (time of assessment unclear)	Yes (0/16)	No, No	No, No	AUC and toxicity (neutral)
Ychou, 1999 France[132]	Prospective case series	Advanced CRC	de Gramont (LV5FU2)	Yes (tested 2 different algorithms) / HPLC	38 (204)	Yes risk and counts	Yes (unclear)	No, No	No, No	AUC and response (neutral)
Ychou, 2003	Prospective	Metastatic	de Gramont	Yes (Ychou,	53 (435)	Yes risk	Yes (19/52,	Yes (18.6	Yes (7	AUC and

First author, date, country	Study design	Cancer type	Regimen	5-FU Dose adjustment (algorithm) / PK method	N (cycles)	5-FU related adverse events	Response rate (overall response)	Overall survival (median OS), KM	Progression free survival (median PFS), KM	Relationship between plasma level and outcome (positive, negative, neutral)
France[148]	case series	CRC	(LV5FU2)	1999)[132] / HPLC		(grouping (1) Cutaneous, (2) Haematological III+IV, (3) Digestive and mucositis III+IV)	36.5%)	months), No	months), No	PFS (positive)
Yoshida, 1990 Japan[149]	Prospective case series	Advanced colonic cancer	5-FU	No / HPLC	19	Yes risk (time of assessment unclear, total toxicities reported only)	Yes (10/19, 53%)	No, No	No, No	AUC and toxicity (positive) / response (neutral)
Ciccolini, 2006	Prospective case series	Mixed patient group	5-FU + Carboplatin	No / HPLC-UV	80	Yes risk (grade III	No	No, No	No, No	Relationship between

First author, date, country	Study design	Cancer type	Regimen	5-FU Dose adjustment (algorithm) / PK method	N (cycles)	5-FU related adverse events	Response rate (overall response)	Overall survival (median OS), KM	Progression free survival (median PFS), KM	Relationship between plasma level and outcome (positive, negative, neutral)
France[150]		H&N (46/80, 58%), CRC (30/80, 38%), Breast (4/80, 5%)	5-FU + Cisplatin FOLFIRI FOLFOX			and IV only)				DPD activity and 5-FU plasma levels in patients with severe toxicities
Hendrayana, 2012 Germany[151]	Prospective case series	Mixed patient group (Colon, Gastric, Rectal, H&N)	5-FU plus one or more of the following: bevacizumab, cisplatin, folinate, irinotecan, oxaliplatin, carboplatin, cetuximab	No / My5-FU	33	Yes risk (time of assessment unclear, toxicity grades inconsistent)	No	No, No	No, No	Plasma level and toxicity (positive)

First author, date, country	Study design	Cancer type	Regimen	5-FU Dose adjustment (algorithm) / PK method	N (cycles)	5-FU related adverse events	Response rate (overall response)	Overall survival (median OS), KM	Progression free survival (median PFS), KM	Relationship between plasma level and outcome (positive, negative, neutral)
Etienne, 1994 France[152]	Prospective cohort study	H&N (neo-adjuvant)	Cisplatin + 5-FU	Yes (NR) / HPLC	68 (94)	Yes counts (Haematological and mucositis grade III and IV only)	No	No, No	No, No	AUC and toxicity (positive)
Milano, 1994 France[153]	Prospective case series	H&N	Cisplatin + 5-FU	Yes (Santini, 1989)[133] / HPLC	186	Yes counts (Haematological and digestive Grade II-IV only)	Yes (144/186, 77%)	Yes (33 months), Yes	No, No	AUC and response / survival (positive)
Thyss, 1986 France[154]	Prospective case series	Advanced H&N (no metastasis)	Cisplatin + 5-FU	No / HPLC	29 (63)	Yes counts (Total toxicities reported only)	Yes (24/25, 96%)	No, No	No, No	AUC and toxicity (positive), response (neutral)

First author, date, country	Study design	Cancer type	Regimen	5-FU Dose adjustment (algorithm) / PK method	N (cycles)	5-FU related adverse events	Response rate (overall response)	Overall survival (median OS), KM	Progression free survival (median PFS), KM	Relationship between plasma level and outcome (positive, negative, neutral)
Kim , 2002 Japan[155]	Prospective case series (phase II study)	Advanced gastric cancer	Cisplatin + 5-FU	No / Liquid Chromatography	36	Yes risk	Yes (17/36, 47.2%)	Yes (8 months), No	No, No	Plasma level and response (neutral)

* Random allocation was to two different calcium folate concentrations (Stremetzne et al., 1999)[147] and constant rate versus circadian rate of 5-FU (Metzger et al., 1994)[143] and not PK versus BSA, therefore studies are included in overview of single arm studies. Please note that "mFOLFOX6" refers to Modified FOLFOX6

5.5.2 Summary of single arm studies

The single arm studies included 11 PK[132, 134, 135, 137, 139, 142, 145, 146, 148, 152, 153] and 13 BSA studies.[131, 136, 138, 140, 141, 143, 144, 147, 149-151, 154, 155] Study population (e.g., cancer stage) and treatment regimen varied considerably within the different cancer type studies. Considerable variation was identified for instance for the infusion time of 5-FU amongst CRC patients. The 11 PK studies used 3 different dose adjustment algorithms, while four studies[142, 145, 146, 152] did not specify the algorithm used. The majority of studies[131, 132, 134-141, 143, 144, 147-150, 152-155] used HPLC as the method to determine 5-FU plasma concentration (n=20).

Only four studies[142, 145, 146, 151] (in addition to Kline et al., 2013[156] - see CRC comparative studies below in section 5.5.3) were identified that used the My5-FU assay of which one was an extended abstract and two were meeting abstracts confirming that to date My5-FU has not been investigated extensively.

5.5.2.1.1 Outcomes reported

Generally, the results confirm that higher levels of plasma 5-FU are related to improved outcome in terms of response, progression free survival and overall survival irrespective of the 5-FU regimen used. Furthermore, they appear to suggest that unfortunately the positive relationship between exposure to 5-FU and outcomes is stronger for adverse events/toxicity than for response and survival. Adverse events were generally reported well, however, they were reported as risk (of experiencing at least one event) in 15 studies[131, 132, 135, 137, 138, 141, 143, 145-151, 155] and as counts of events in 7 studies.[134, 139, 140, 144, 152-154] Furthermore, studies used different grading tools to grade severity of toxicity (WHO and NCI CTAE), grouped grades of toxicity differently; some reported toxicity only for broad categories, i.e., haematological and digestive, or reported toxicities only as a total of all toxic events. Response rates varied hugely and median overall survivals from PK and BSA studies overlapped. Survival data in form of KM curves was only reported in three CRC studies[131, 135, 139] and one H&N study.[153]

5.5.2.1.2 Quality concerns

Overall, the evidence from the single arm studies is weak. Study conclusions were mainly based on small study populations. The majority of studies),[131, 132, 134-136, 138-142, 144, 148-151, 153-155] were case series (18/24), which are generally of lower quality because selection bias cannot be assessed.

5.5.2.1.3 Evidence taken forward to the analyses and cost-effectiveness modelling

The emphasis here is in evidence that compares PFS, OS and toxic events for PK versus BSA treatments; these are crucial for an estimate of clinical effectiveness and for informing an economic model. Due to the heterogeneity among the studies, even within cancer types the studies do not lend

themselves to pooling. And while 11 studies[132, 134, 135, 137, 139, 142, 145, 146, 148, 152, 153] were identified that carried out dose adjustment, a comparison with the studies resembling the BSA arm is impossible due to the substantial differences in patient populations, treatment regimens and outcomes assessment (ways in which outcomes were graded, grouped and reported). Therefore, conclusions on the effectiveness of PK dosing cannot be inferred from the single arm studies because of the lack of comparative evidence of PK versus BSA for any of the cancers. Survival data were reported for an obsolete H&N cancer treatment[153] and for three CRC studies.[131, 135, 139] It was unclear whether Gamelin et al. (1996)[131] and Gamelin et al. (1998)[139] used different populations, therefore only the later one was considered. Inferring KM curves from single reported medians would result in endless possibilities of different curves. Furthermore, it would be problematic to infer a curve from single arm studies in the absence of complementary evidence from a comparative arm. Due to the clearly pronounced heterogeneity in reported medians in survival and the lack of confidence intervals meant that no attempt was made at pooling values from single arm studies. As a result, the usable evidence from this section comes from the two CRC studies which reported survival data in the form of KM curves.[135, 139] These supplemented the comparative CRC studies drawn from the following section on comparative studies and are considered further in section 5.5.4.1.[135, 139]

5.5.3 Overview of comparative studies

5.5.3.1 Major features CRC studies

Three comparative CRC studies were identified.[119, 135, 156] These were published by Gamelin et al. (2008),[118] Capitain et al. (2012),[135] and Kline et al. (2013);[156] they were disparate with regard to design, population, treatments, and reported outcomes. The major features of these studies are summarised in Table 12. Full data extraction forms are available from the authors on request.

Table 12. Studies with two groups comparing PK adjusted versus BSA based dose regimens

First author, date, country	Study design	Cancer type	Regimen	PK method	N	Adverse events	Response rate	Overall survival	Progression free survival
Gamelin 2008,[118] France	RCT	mCRC	5-FU + FA	HPLC	104 PK 104 BSA	Yes	Yes	Yes	No
Capitain 2012,[135] France	Retrospective with historical control	mCRC	FOLFOX6	HPLC	118 PK 39 BSA	Yes	Yes	Yes*	Yes*
Kline	Retrospective	stage	FOLFOX6	My5-	19	Yes	No	No	Yes

2013,[156] USA	with two self-selected groups	II/III CRC	or FOLFIRI	FU	PK 16 BSA				
Kline 2013,[156] USA	Retrospective with two self-selected groups	stage IV CRC	FOLFOX6 or FOLFIRI	My5-FU	19 PK 30 BSA	Yes	No	No	Yes
	* Only medians reported for the BSA arm								

5.5.3.2 Summary of comparative CRC studies

Of three comparative studies identified, only Gamelin et al. (2008)[118] was a randomised trial, the other two (Capitain et al., 2012,[135] and Kline et al., 2013[156]) were retrospective studies in which population balance between arms was reasonable on the variables reported. Capitain et al. (2012)[135] and Gamelin et al. (2008)[118] studied only metastatic cancer patients while Kline et al. (2013)[156] included colorectal cancer patients of stages II to IV. The studies used different treatment regimens and different algorithms for 5-FU dose adjustment. None of the studies reported a complete set of outcomes in terms of adverse events, survival and response.

5.5.3.2.1 Outcomes reported

Kaplan-Meier plots were reported variably: by Kline et al. (2013)[156] for PFS, by Capitain et al. (2012)[135] for PFS and OS but only for the PK arm and by Gamelin et al. (2008)[118] for overall survival only. Response was reported by two of the three studies and adverse events were reported as risks of experiencing at least one event.

5.5.3.2.2 Quality concerns

The only RCT did not report methods of randomisation and had perfectly balanced arms. In the other two studies, the absence of randomisation means that true comparability between groups is inevitably compromised. There is a further problem when patients are invited to self-select into PK or BSA dosing. SeeAppendix 11 for Downs and Black (1998)[123] quality assessment.

5.5.3.2.3 Evidence taken forward to the analyses and cost-effectiveness modelling

All three comparative CRC studies had useable information about PFS, OS and adverse events/toxicity for the comparison of PK versus BSA treatment and are considered further in section 5.5.4.3.

5.5.3.3 Major features of H&N studies

Two comparative H&N studies were identified. These were published by Fety (1998)[157, 159] and Santini (1989).[133] These studies were disparate with regard to design, population, treatments, and reported outcomes. The major features of these studies are summarised in Table 13. Full data extraction forms are available on request from the authors.

Table 13. Studies with two groups comparing PK adjusted versus BSA based dose regimens

First author, date, country	Study design	Cancer type	Regimen	PK method	N	Adverse events	Response rate	Overall survival	Progression free survival
Fety, 1998,[157] France	Randomised prospective study	Advanced H&N cancer	Cisplatin + 5-FU (continous 96 h)	HPLC	61 BSA 61 PK	Yes*	Yes	No	No
Santini, 1989,[133] France	Several (group 1 - retrospective study; group 2 - prospective study)	H&N cancer	Cisplatin + 5-FU (5 days 1000mg/m^2/24h)	HPLC	89 Grp 1 (BSA) 81 Grp 2 (PK)#	Yes$	Yes	No	No

* Digestive toxicity (WHO Grade III-IV only) and Haematological toxicity (Neutropenia and Thrombocytopenia WHO Grade III-IV)

Group 1 (89 patients, 228 cycles) corresponded to a retrospective study during which 5-FU blood concentrations were measured for each individual cycle of 77 patients (177 cycles) which allowed comparison of the distribution of AUC values in relation to the response and tolerance to treatment. Group 2 (81 patients, 249 cycles) corresponded to patients entered into a prospective study based on initial data for group 1

$ Haematological and digestive tract toxicities were evaluated according to WHO criteria (grades II, III-IV and II, III, IV)

5.5.3.4 Summary of comparative H&N studies

Only Fety et al. (1998)[157] provided information in a randomised design, while Santini et al. (1989)[133] reported sequential cohorts of patients in whom dose modification was made based on 5-FU exposure. The studies used different treatment regimens and slightly different dose adjustment algorithms and did not report survival data.

5.5.3.4.1 Outcomes reported

Survival data for overall survival and progression free survival was not reported in either of the two studies. Information on response was provided and toxicity was reported as counts of toxic cycles.

5.5.3.4.2 Quality concerns

The only randomised evidence available for H&N cancer was hampered by mismatches between the description of methods undertaken and the reported results. Furthermore, since the patients with protocol violations were removed from the analysis and the induction therapy regimen used only two drugs, the generalisability to dose adjustment methods in current clinical practice remains questionable. See Appendix 11 for Downs and Black (1998)[123] quality assessment.

5.5.3.4.3 Evidence taken forward to the analyses and cost-effectiveness modelling

The studies by Santini and Fety date back to 1989 and 1998, and are the only comparative studies comparing BSA versus PK identified for H&N cancer. The two studies used regimens which are no longer in clinical use and did not provide estimates for OS and PFS. Fety (1998)[157] provided some information on toxicity for the comparison of PK versus BSA dosing in H&N cancer patients and is therefore further considered in section 5.5.4.5. Further detail on the study by Santini (1989)[133] is provided in Appendix 12.

5.5.4 Rationale for taking studies forward for synthesis and modelling of cost-effectiveness

For the assessment of the effectiveness and cost-effectiveness of PK 5-FU dose adjustment, evidence is required for the comparison of BSA based dosing and PK dosing in the same population (ideally randomised) receiving the same 5-FU regimen. The outcomes from this comparison that are needed for cost effectiveness modelling are ideally: 1) IPD to produce Kaplan Meyer curves for overall survival and progression free survival to infer transition probabilities for model parameters; and 2) adverse events reported as counts per unit time for PK versus BSA treatments. IP data is preferred because it gives the most reliable estimates of clinical effectiveness to inform an economic model.

Most included studies had a single arm design (N=24). They mainly reported data about PK adjustment and resulting plasma 5-FU levels, with inferences about DPD activity levels, and occasionally correlations between plasma 5-FU and incidence of adverse events or toxicity. They could not provide between-group comparisons. The disparities between the single-arm studies in treatments, populations, and modes of outcome reporting, precluded synthesis by combining studies. Key outcomes (OS and PFS) were rarely reported and adverse events were reported inconsistently or not at all. Two single arm studies provided survival data in the form of KM curves; these are described below and have been included in the synthesis of evidence for CRC treatment (Section 5.7).

Three CRC comparative studies had useable information about PFS, OS and toxic events for PK versus BSA treatments. Two H&N cancer comparative studies were found, these did not report OS or

PFS. One reported usable information on toxic events. Both H&N cancer studies employed chemotherapies no longer current in use. No comparative evidence was identified on gastric and pancreatic cancer patients.

In summary, the broad search strategy yielded a small volume of studies and these were of disappointingly weak study design; studies mostly failed to report outcomes important for estimating the clinical or cost effectiveness of PK versus BSA.

In the following section first the two single arm CRC studies (Capitain et al., 2008;[135] Gamelin, 1998[139]) and then the three CRC comparative studies (Gamelin et al., 2008;[118] Capitain et al., 2012;[119] and Kline et al. 2013[156]) and the one H&N comparative study (Fety et al., 1998)[157] taken forward for synthesis are described in more detail.

5.5.4.1 Single arm CRC studies taken forward in cost effectiveness analysis

The two single arm CRC studies (Capitain et al., 2008;[135] Gamelin, 1998[139]) are first described in terms of study design and quality, of population, of intervention and outcomes.

5.5.4.1.1 Study design and quality

Capitain et al. (2008)[135] carried out a case series of 76 patients treated with 5-FU for advanced CRC and most had not received previous 5-FU treatment. The study included two regimens weekly or every 2 weeks of 5-FU + FA. Pharmacokinetic dose adjustment was based on plasma 5-FU measurements determined by HPLC and dose adjustment followed Gamelin's (1996)[131] dose algorithm. The median follow up was 3.5 years. The study aimed to determine simple genetic factors that may aid the tailoring of 5-FU administration in first-line chemotherapy of advanced colorectal cancer.

The study was a case series where it was impossible to assess whether the study population was representative of the population from which the participants were recruited. Information on recruitment was minimal. There were weaknesses in the clarity and presentation of data. Overall survival and progression free survival were reported including a KM plot for overall survival but without numbers-at-risk tables. While the study reported adverse events as risks they were not reported separately for the two different regimens included (see Table XX). The study lacks information on plasma measurements, frequency of dose adjustment and outcomes of dose adjustment for the purpose of this review. See Appendix 11 for Downs and Black (1998)[123] quality assessment.

Gamelin et al. (1998)[139] is a prospective case series involving 152 patients with metastatic CRC from 9 different centres. The median length of follow-up was 3 years. 5-FU therapy with individual dose adjustment was investigated in terms of efficacy, tolerance and survival in metastatic CRC patients. The primary and secondary efficacy end points were survival and response rate, respectively. Pharmacokinetic dose adjustment was based on plasma 5-Fu measurements determined by liquid chromatography and dose adjustment followed Gamelin's et al. (1996)[131] dose algorithm.

The study was a case series where again it was impossible to assess whether the study population was representative of the population from which the participants were recruited. Patients lost to follow-up were not accounted for in the analysis which was not stated to follow an intention to treat analysis. The AE rates were reported by cycles (counts), however, the number of total cycles is unknown for the three month period. Response rates, OS and PS were reported extensively including duration of response and KM curves but no numbers-at-risk tables. See Appendix 11 for Downs and Black (1998)[123] quality assessment.

5.5.4.1.2 Population

The reported demographic characteristics of patients are summarised in Table **14**.

Table 14. Baseline characteristics of two single CRC studies

Item	**Capitain et al., 2008[135] Number of patients (%)**	**Gamelin et al., 1998[139] Number of patients (%)**
Patient Number *Total number* *Sample attrition*	 76 0	 152 117 patients assessable for toxicity and response
Age (years) Mean (SD) Median Range	 NR 71.2 39-88	 62 NR 24-75
Sex Men Women	 46 (60.5%) 30 (39.5%)	 84 (55.3%) 68 (44.7%)
Performance status (%) 0-1 2-3	 71 (93.5%) 5 (6.5%)	 95 (62.5%) 57 (37.5%)
Previous 5-FU therapy (%)	13 (17%)	30 (19.7%)
Metastatic sites (%)		

Liver	NR	101 (66%)
Lung	NR	35 (23%)
Lymph nodes	NR	18 (12%)
Others	NR	47 (31%)

5.5.4.1.3 Intervention

The two studies investigated dose adjustment of different 5-FU treatment regimens which are detailed in Table 15.

All patients outside the target plasma concentration of 2,000-3,000 µg/l[139] or an AUC of 25mg*h/l[135] received dose adjustment following a previously published algorithm[131] (see Table 7 in Objective A-2). Patients with grade II toxicity received a dose reduction by 100mg/m^2,[139] or by 10%.[135] In patients with grade III toxicity, treatment was interrupted and once toxicities were resolved, restarted with the dose reduced by 250mg/m^2 [139] or by 25%.[135] Treatment was stopped for patients with grade IV toxicities.

Table 15. Overview of 5-FU treatment regimens (dose at first cycle) used in 2 single arm CRC studies

Item	Capitain et al., 2008[135]		Gamelin, 1998[139]
Regimen	FUFOL 4H	Modified de Gramont	5-FU folinic acid (5-FU + FA) weekly
5-FU	1,200mg/m^2 weekly by 4-h 5-FU continuous infusion	2,500mg/m^2 2-weekly by 46-h continuous infusion	1,300mg/m^2 by 8h continuous infusion
Folinic acid	100mg/m^2 bolus folinic acid	200mg/m^2 bolus folinic acid with 400mg/m^2 5-FU bolus	200mg/m^2 before and 4h after 5-FU infusion
Oxaliplatin / irinotecan	Treatment until progression then considering second line therapy combining 5-FU with oxaliplatin or irinotecan	Treatment until progression then considering second line therapy combining 5-FU with oxaliplatin or irinotecan	NA

5.5.4.1.4 Outcomes

Capitain et al. (2008)[135] reported that nine out of the 76 patients were at high risk of 5-FU toxicity due to abnormally low 5-FU plasma clearance. Of these three had known DPD polumorphisms. The objective response rate was 32.9%, with 6.6% of patients having complete responses. Objective response rate was defined according to the Response Evaluation Criteria in Solid Tumour (RECIST) group. The median OS (see Figure 8) and PFS were 20 months and 3.3 months, respectively. Adverse events were reported as risks of having at least one toxic event. The most common side

effects (all grades) were diarrhoea (22%), hand-foot syndrome (18%) and mucositis (7.5%). 10.5% of all toxicities were grade III and IV toxicities occurred in 10.5% and nine patients were identified to be at high risk of toxicity due to low clearance of 5-FU. Certain genotypes were linked to toxicity and shorter overall survival. The authors presented genetic factors which warrant investigation in future clinical trials to determine patients at risk of 5-FU toxicity or resistance before treatment commences.

In Gamelin et al. (1998)[139] the mean 5-FU dose after 3 months treatment was 1803 ± 386 (950-3,695) mg/m^2. After cycle 1 only 6 (4%) patients had 5-FU measures in the target range. Under- and over-dosing occurred in 124 (82%) and 14 (9%) patients, respectively. After dose adjustment the 5-FU target range was reached in 143 (94.1%) patients. Overall survival for all patients was 19 months and progression free survival 11 months (Figure 9). Overall response rate in patients with measureable disease was 66/117 (56.4%) of which 18 (15.4%) had complete response (as defined according to RECIST). Duration of response from the start of treatment to the time of disease progression was 17 months for complete response and 20 months for partial response (range, 1-36 months). The correlation of optimal therapeutic levels with response was found to be for complete response (CR) plus partial response (PR) versus stable disease (SD) plus progressive disease (PD) p=0.05; and for CR plus PR plus SD versus PD p=0.029. The majority of toxic events (all grades) were diarrhoea (39%) and hand-foot syndrome (30%) which were reported as counts of events.

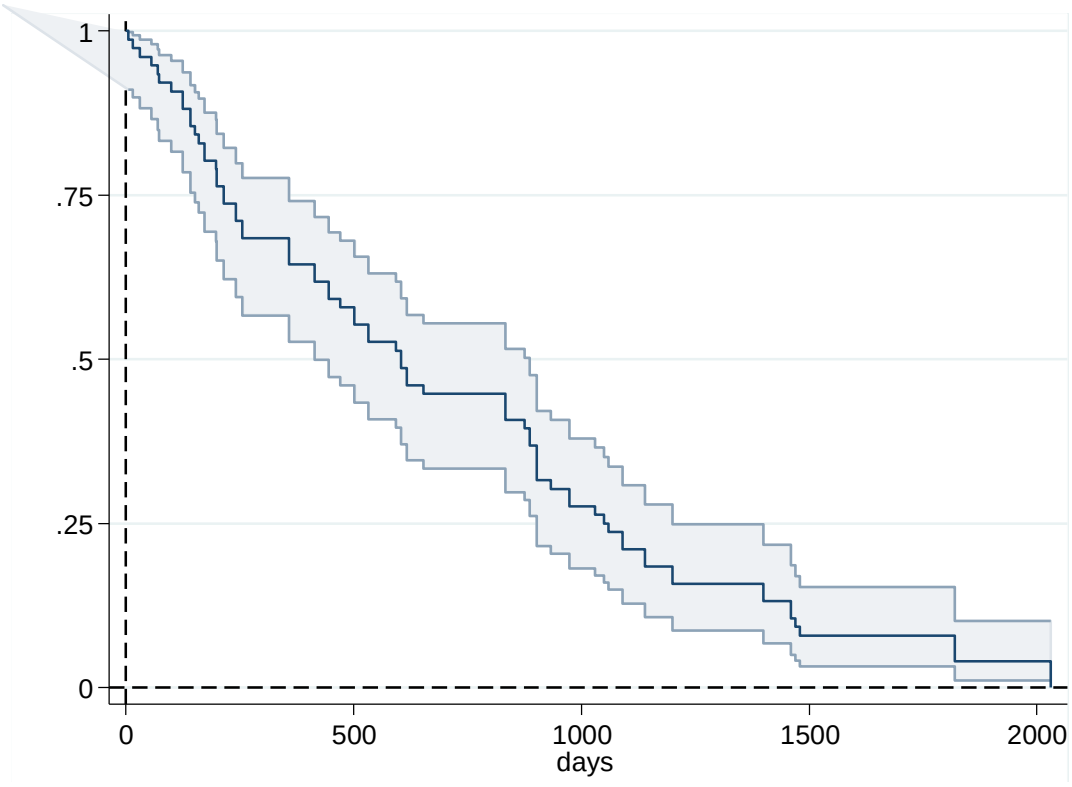

Figure 8. Reconstructed KM plot for overall survival for Capitain (2008)[135]

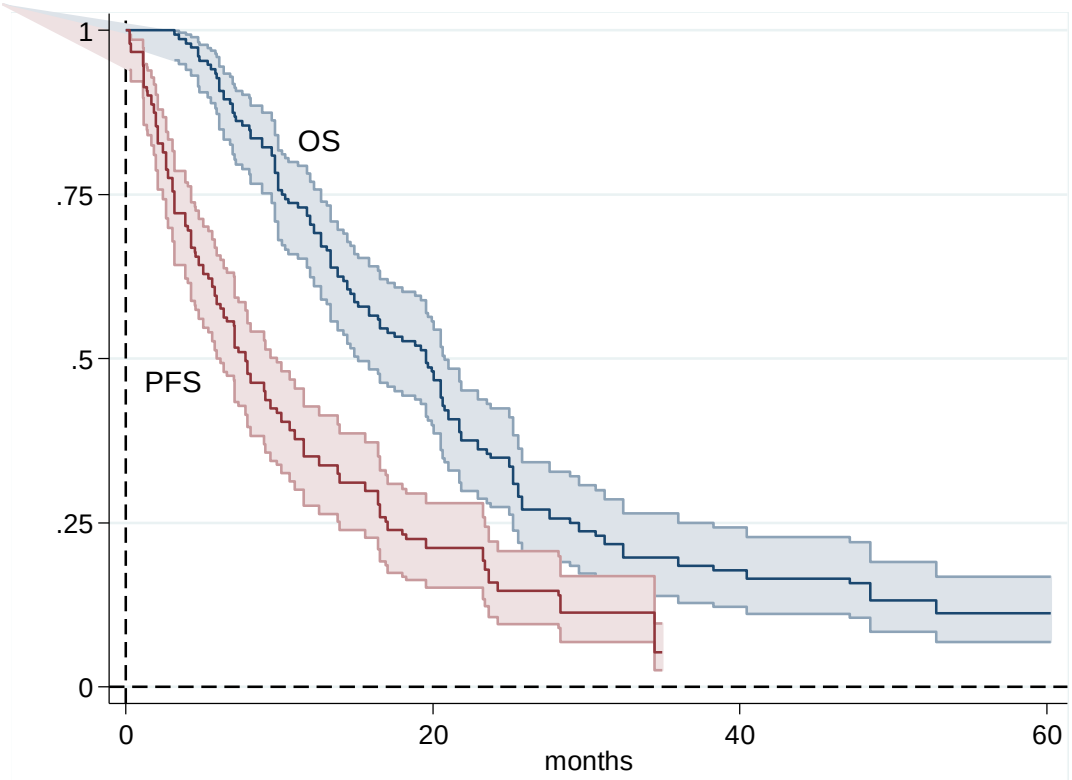

Figure 9. Reconstructed KM plot for overall and progression free survival for Gamelin et al. (1998)[139]

5.5.4.2 Conclusions from single arm CRC studies taken forward in cost effectiveness analysis

Capitain et al. (2008)[135] used dose adjustment to reach a pre-specified target AUC using a previously published algorithm for dose adjustment. In this study, the two regimens of treatment using pharmacokinetic monitoring were well tolerated in an elderly population with a median age of 71 years. While the study reported adverse events as cases, they were not reported separately for the two different regimens included. However, the focus of the study was the identification of single genetic factors predictive for toxicity and effectiveness and therefore linked genetic traits to response. The study lacks information on plasma measurements, frequency of dose adjustment and outcomes of dose adjustment for the purpose of this review.

Gamelin et al. (1998)[139] in his study used dose adjustment to reach a pre-specified target plasma concentration of 5-FU using a previously published algorithm for dose adjustment. The regimen of treatment using pharmacokinetic monitoring was well tolerated in a population with a mean age of 62 years. The study concluded that individual 5-FU dose adjustment with pharmacokinetic monitoring provided a high survival rate with good response and tolerance.

5.5.4.3 Comparative CRC studies taken forward in cost effectiveness analysis

The three comparative CRC studies (Gamelin et al., 2008;[118] Capitain et al., 2012;[119] and Kline et al., 2013[156]) are first described in terms of study design and quality, of population, of intervention / comparator; then according to outcome results described in sequence according to importance (i.e. overall survival, progression free survival, adverse events, dose adjustment and algorithms employed, and other minor outcomes reported). See Appendix 11 for Downs and Black (1998)[123] quality assessment of Gamelin et al. (2008),[118] Capitain et al. (2012)[119] and Kline et al. (2013)[156]

5.5.4.3.1 Study design and quality

Gamelin et al. (2008)[118] was a phase III multicentre RCT which randomised 104 patients to a PK adjusted 5-FU + FA regimen and 104 patients to a BSA based dose regimen. There were 5 centres all located in France. PK adjustment was achieved using HPLC-determined plasma 5-FU estimates coupled with a published dose adjustment algorithm. Median follow up was 3 years. The pre-specified primary outcome was response rate according to RECIST criteria. Methods of randomisation and allocation concealment were not reported. There was no mention of stratification (e.g., according to performance status) or of the use of minimisation methods, yet arms were perfectly balanced for number of patients. Blinding to treatment was not possible; assessment of response rates was assessed by a panel of two independent radiologists and may have been blinded, but this was not specified. There was some mismatch between the description of methods undertaken and the reported results.

Capitain et al. (2012)[119] was a retrospective "proof-of-concept study" comparing 118 patients who received a PK-directed dose adjusted FOLFOX6 regimen with 39 patients who received conventional BSA-directed FOLFOX6 regimen. PK adjustment was by HPLC-determined plasma 5-FU estimates coupled with a commercial adjustment protocol. The intervention patients came from 8 centres and the comparator patients from 2 further and different centres. Median follow-up for PK patients was 1426 days (3.9 years; range 2.2-8.3 years) but was unreported for the BSA arm. The most important weakness in this study was that although the sampling frame for selecting the study populations was described, the proportion of eligible patients that was finally included was not reported; thus the selection method was unclear. To what extent the study was prospective was unclear.

Kline et al. (2013)[156] was a small retrospective single centre analysis of stage II / III and of stage IV CRC patients who self-selected for PK adjusted (N=38) or BSA-based (N=46) FOLFOX6 or FOFIRI regimens. The numbers of patients receiving FOLFOX6 or FOFIRI were not reported. Median follow-up was 14 months (BSA) and 17 months (PK) for stage IV patients, and 23 months (BSA) and

16 months (PK) for stage II/III patients. Lack of randomisation was the major limitation. The allocation of treatments by patient self-selection increases the likelihood of allocation bias.

5.5.4.3.2 Populations

The reported demographic characteristics of patients are summarised in Table 16.

Table 16. Baseline characteristic of patients in 3 comparative CRC studies

Item	**Gamelin 2008[118]**		**Capitain 2012[119]**		**Kline 2013[156] Stage II/III**		**Kline 2013[156] Stage IV**	
	BSA	**PK**	**BSA**	**PK**	**BSA**	**PK**	**BSA**	**PK**
Patient Number	**104**	**104**	**39**	**118**	**16**	**19**	**30**	**19**
Disease stage %								
II	NR	NR	NR	NR	19	5	0	0
III	NR	NR	NR	NR	81	95	0	0
IV	NR	NR	NR	NR	0	0	100	100
Age (years)								
Mean (SD)	71.2 (10.3)	71.5	NR	NR	NR	NR	NR	NR
Median	NR	NR	63	65	66	56	65	58
Range	50-85	52 - 84	32-80	35-	19-77	32-78	46-76	41-81
Sex								
Men (%)	62.5	58.7	62	59	68.7	52.6	60	63.1
Women (%)	37.5	41.3	38	41	31.3	47.4	40	36.9
Performance status %								
0	55	54	NR	NR	NR	NR	NR	NR
0 or 1			77	78	NR	NR	NR	NR
1	40	33	NR	NR	NR	NR	NR	NR
2 or 3	5	13	23	22	NR	NR	NR	NR
Previous therapy %	15.4	10.6	NR	NR	88[¥]	95[¥]	27[¥]	37[¥]
Metastatic sites %								
Liver	74*	81*	60**	56*	NR	NR	NR	NR
Lung	30*	26*	10**	16*	NR	NR	NR	NR
Lymph nodes	11*	19*	4.9	5.0	NR	NR	NR	NR
Others	9*	15*	NR	NR	NR	NR	NR	NR
Different metastatic sites/ patient %								
1	77	68	71	68	NR	NR	53	42
≥ 2	NR	NR	NR	NR	NR	NR	40	47
2	21	24	25	24	NR	NR	NR	NR
3	1	6	6	5	NR	NR	NR	NR
4	0	2	NR	NR	NR	NR	NR	NR
Primary tumor site %								
Colon	NR	NR	NR	NR	75	90	53	79
Rectosigmoid	NR	NR	NR	NR	12.5	0	7	0
Rectum	NR	NR	NR	NR	12.5	10	33	21

* Measurable metastatic sites; ** Unique metastatic sites ¥ surgery BSA = body surface area based dose regimen; NR = not reported; PK = pharmacokinetic dose regimen

5.5.4.3.3 Intervention / comparator

All three studies (Gamelin et al., 2008;[118] Capitain et al., 2012;[119] and Kline et al., 2013[156]) compared BSA-based dosing with PK dose adjustment based on steady state plasma 5-FU levels. Different treatment regimens were used (5-FU + FA, FOLFOX6, FOLFIRI); these are summarised in Table 17 which indicates the dose of 5-FU at the first cycle.

Table 17. Overview of treatment regimens used in three comparative CRC studies

Item	Gamelin et al. (2008)[118]	Capitain et al. (2012)[119]	Kline et al. (2013)[156]
Regimen	5-FU folinic acid (5-FU + FA) weekly	FOLFOX6 every 2 weeks	mFOLFOX6 or mFOLFIRI every 2 weeks
5-FU	5-FU dose of 1,500 mg/m^2 by 8 h infusion	5-FU 2500 mg/m^2 by 46 h infusion	5-FU 2400 mg/m^2 by infusion
Folinic acid	200 mg/m^2 up to a total weekly dose of 400 mg/m^2	200 mg/m^2 bolus with 10 min push 400 mg/m^2 5-FU	Details NR
Platin irinotecan	NA	Oxaliplatin 85 mg/m^2 2h infusion for 2 hours every 2 weeks	Details NR
Before and after oxaliplatin, patients received infusions of magnesium and calcium. NR not reported			

Kline et al. (2013)[156] measured steady state plasma 5-FU with My5-FU the other studies used HPLC. At the start of BSA based therapy the same dose is applied for all patients, dose change only occurs when necessitated by toxicity and dose increases are not undertaken. Only Gamelin et al. (2008)[118] provided details of the PK dose adjustment algorithm; this is summarised in Table 18.

Table 18. Dose adjustment algorithm used for the PK arm patients

In the Absence of Toxicity			**In the Presence of Toxicity**
FU Plasma Concentration (µg/L)	**AUC (mg∗h∗L^{-1})**	**FU Dose Adjustment (± % of previous dose)**	
< 500	< 4	70	Grade II toxicity: dose decreased by 200 mg Grade III toxicity: 1 week break, then dose decreased by 300 mg
500-1,000	4 to < 8	50	
1,000-1,200	8 to < 10	40	
1,200-1,500	10 to < 12	3	
1,500-1,800	12 to < 15	20	
1,800-2,200	15 to < 18	10	
2,200-2,500	18 to < 20	5	
2,500-3,000	20 to < 24	Unchanged	
3,000-3,500	24 to < 28	-5	
3,500-3,700	28 to < 31	-10	

> 3,700	> 31	-15	
The relation between FU plasma concentration and AUC can be illustrated as follows: the infusion was 8 hours; therefore the mid target FU concentration of 2,750 mg / L = 8 * 2,750 µg * hr / L = 22,000 µg * hr / L, which is equivalent to 22 mg * hr / L			

In the PK arm, Capitain et al. (2012)[119] adjusted dose according to an unreported commercial protocol; it is unclear if adjustments were guided by factors additional to plasma 5-FU. Kline et al. (2013)[156] used an algorithm supplied by the My5-FU manufacturer but details were not reported. In the PK arms both dose increases and decreases were implemented.

5.5.4.3.4 Outcomes; overall survival

Gamelin et al. (2008)[118] reported Kaplan-Meier analysis of overall survival; the plots appeared unusual implying that information for time of death was aggregated at spaced time intervals. The reconstructed Kaplan-Meier estimate using the method of Guyot et al. (2012)[125] is shown in Figure 10 and closely overlaps the published figure (available on request from authors).

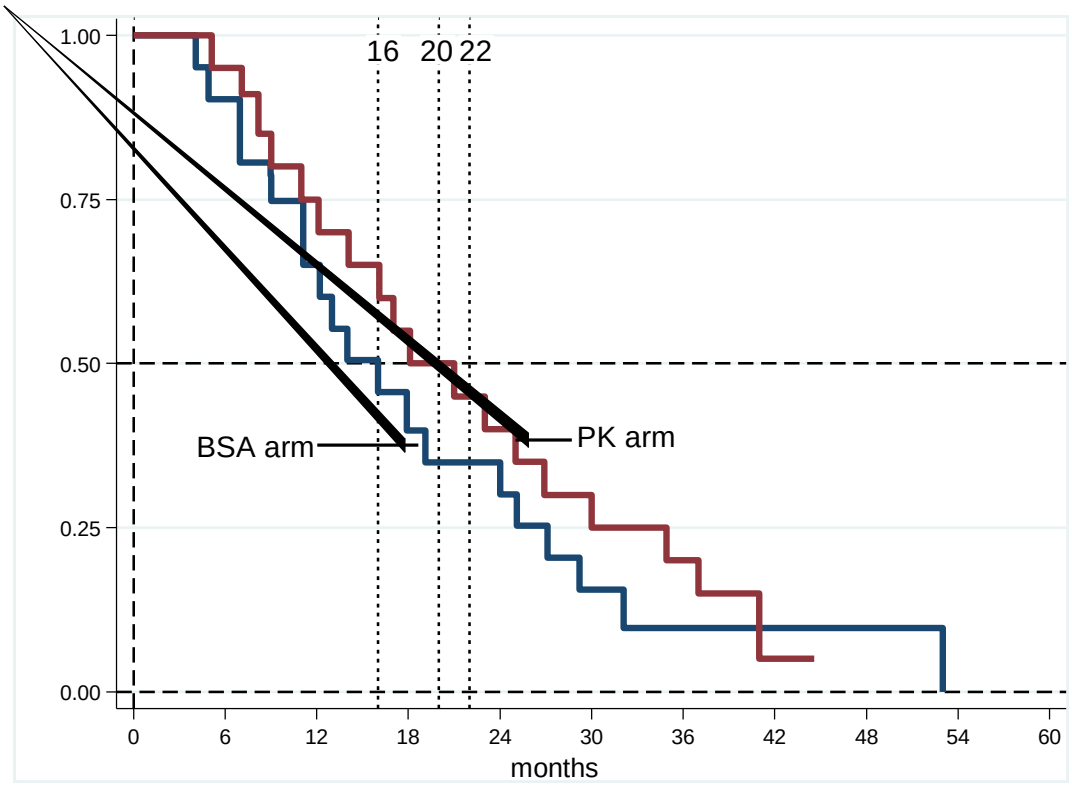

Figure 10. Reconstructed Kaplan-Meier plots for overall survival

Reported median survival was 16 and 22 months for BSA and PK arms respectively and the log-rank test for equivalence was p=0.08. The median estimates appear sensitive to the long horizontal steps that occur at around 0.5 survival; it appears the 22 month estimate reported may be an overestimate.

Weibull, lognormal and log-logistic distributions provided satisfactory models for both arms (Appendix 13). Cox proportional hazards regression for the reconstructed data provided a hazard ratio of 0.82618 (95% CI .6198087 to 1.101265). The log-rank test for equivalence provided a p-value of 0.18. A Weibull model assuming proportional hazards generated a hazard ratio of 0.829255.

Capitain et al. (2012)[119] reported 28 and 22 months median overall survival for PK and BSA arms respectively. No confidence intervals were reported. A Kaplan-Meier plot for only the PK arm was published. The reconstructed plot (using the Guyot et al., 2012[125] method) is shown in Figure 11 and closely overlaps the published figure (available on request from authors).

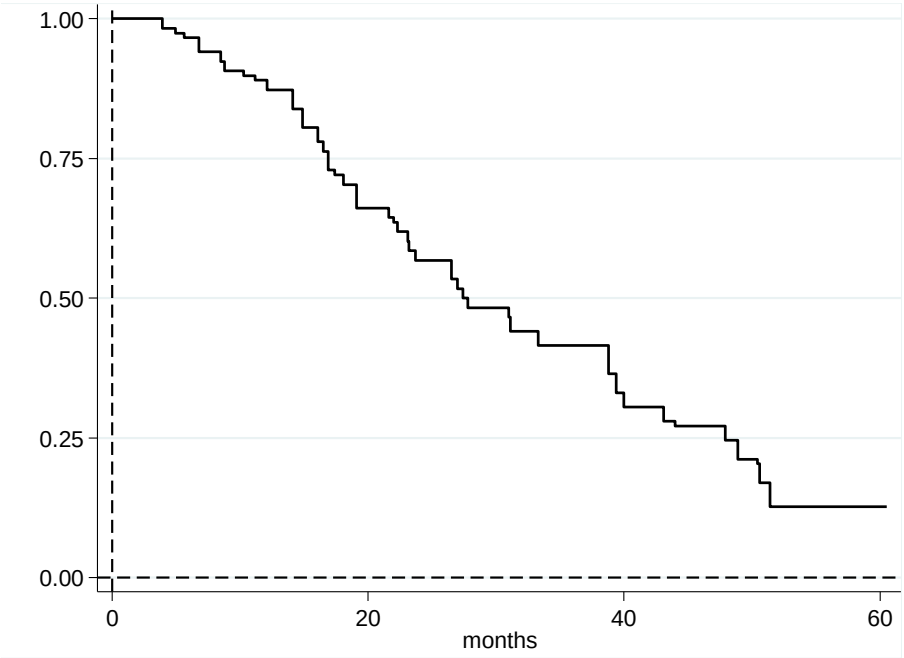

Figure 11. Reconstructed Kaplan-Meier plot for overall survival of the PK group

To investigate the reported OS difference between arms Weibull distributions were used with assumed proportional hazards (i.e. the PK shape parameter was retained for both arms); the median for the BSA arm was used to estimate the BSA scale parameter.

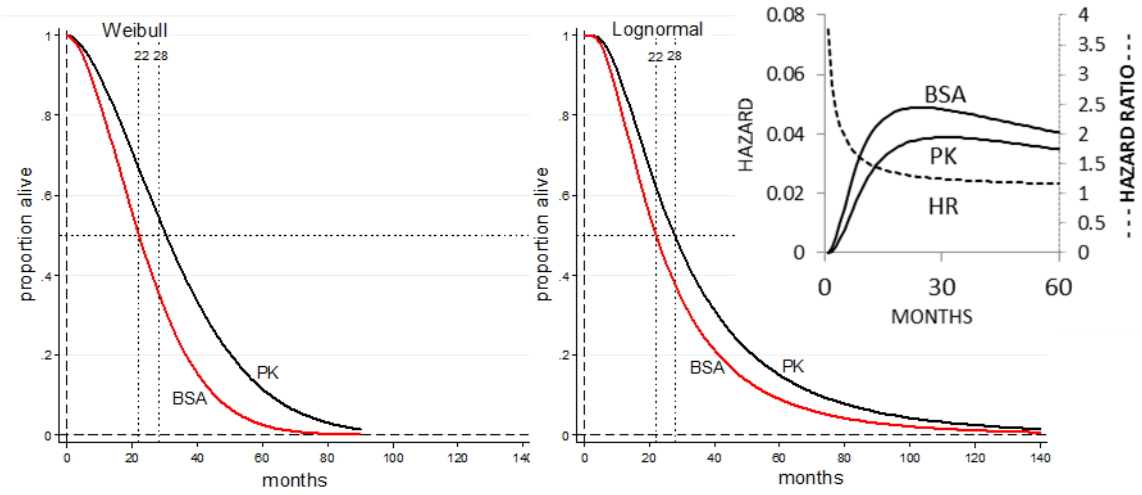

Figure 12. Overall survival modelled on Weibull and lognormal distributions

The resulting curves are shown in Figure 12 (left). The hazard ratio for these was 0.586 (shape parameter 1.6691, scale parameters 0.002333 and 0.0039833 for PK and BSA, respectively). The lognormal distribution also provided a good fit to the reconstructed PK OS data and was used to derive a lognormal estimate of BSA survival that satisfied the reported median of 22 months. Since the mu (μ) parameter defines the median, the PK sigma (σ) parameter was retained for the BSA arm and a new mu parameter found for BSA [here survival is given by: 1- ϕ (ln(t)-μ) / σ ; and median = exp (μ)]. The resulting curves are shown in Figure 12 (right); this also shows the resulting hazard ratio which with this distribution is non-proportional between treatments. Table 19 summarises the model parameters and median and mean survival for the models.

Table 19. Overall survival modelled on Weibull and lognormal distributions (Capitain et al., 2012)[119]

Model	lambda	gamma	median	mean	diff in means
Weibull PK	0.0023328	1.669058	30.31	33.73	
Weibull BSA	0.00398331	1.669058	22	24.48	9.25
	mu	sigma			
Lognormal PK	3.320461	0.745078	27.67	36.53	7.49
Lognormal BSA	3.091042	0.745078	22	27.7	

The study by Kline et al. (2013)[156] did not report overall survival.

5.5.4.3.5 Outcomes; progression free survival

Gamelin et al. (2008)[118]: Although the methods section in Gamelin stated that PFS was analysed, no medians or KM plots were presented. Requests to authors for IPD for PFS failed to illicit any data.

Values were reported for mean time spent in response categories (complete response, partial response, stable disease; as defined according to RECIST) are summarised in Table 20. They infer a benefit from PK for progression free survival (i.e. the mean time for each response category prior to progression was greater for the PK arm than the BSA arm and involved a larger proportion of patients).

Table 20. Mean duration of response categories (Gamelin et al., 2008)[118]

Treatment response	**Mean duration (months)**		**Number of patients**	
Response type	**BSA arm**	**PK arm**	**BSA arm**	**PK arm**
Complete response	NR§	10	1	6
Partial response	6.3	6.8	17	29
Stable disease	5.7	7.6	30	26
§ *assumed the same as in PK arm*				

If it assumed (scenario A) that each patient proceeds from each response category directly to the progressed state then the mean time to progression is 6.0 and 7.5 months in the BSA and PK arms respectively (we assume means, rather than medians were reported because the durations have reasonably normal distributions) An alternative (scenario B) may assume that if patients in each category proceed to the next category (e.g., complete response to partial response and then to stable disease) before reaching the progressive state and the mean durations are as reported, then mean time to progression is 8.27 and 12.48 months in the BSA and PK arms respectively (Scenario B).

Given a mean time to progression under the assumption of normal distribution of duration times for each response type, it is possible to calculate Weibull parameters for a parametric model of time to progression using the following relationship:

$$\text{Mean} = [(\lambda^{-1})^{ (1/\gamma) }] * \Gamma (\gamma^{-1} + 1)$$

Where λ and γ are scale and shape parameters respectively, and Γ represents a gamma distribution. Using the above, and given the mean, there are many solutions for shape and scale parameters unless one is fixed. In order to obtain a single solution, the further assumption is required that the shape parameter for PFS is the same as that for overall survival (these values were 1.827686 for the PK arm and 1.54066 for the BSA arm). With these assumptions the Weibull parameters for PFS in the PK and BSA arms under scenarios A and B are as shown in Table 21.

Table 21. Weibull parameters for PFS under scenarios A and

	A	A	B	B
	λ	γ	λ	γ
PK ARM	0.020467	1.82769	0.00798430047223383	1.82769
BSA ARM	0.05378	1.54066	0.032798314	1.54066

Similarly for a lognormal distribution description of PFS the relationship between mean and median may be used: mean = median * exp ([σ^2] / 2). This has several solutions unless either median or σ is fixed. In order to obtain a single solution the further assumption was made that the σ parameter was the same as that for overall survival for the corresponding study arm (these values were 0.648108 for the PK arm and 0.6944542 for the BSA arm). Median relates to μ parameter according to: median = exp [(σ *(normsinv(0.5)))+(μ)]. Thus the μ parameter for PFS can also be obtained. With these assumptions the lognormal parameters for PFS in the PK and BSA arms under scenarios A and B are as shown in Table 22. Figure 13 summarises the resulting models of PFS.

Table 22. Lognormal parameters for PFS under scenarios A and B

	A	A	B	B
	μ	σ	μ	σ
PK ARM	1.799533	.648108	2.314524667	.648108
BSA ARM	1.550626	.6944542	1.871602091	.6944542

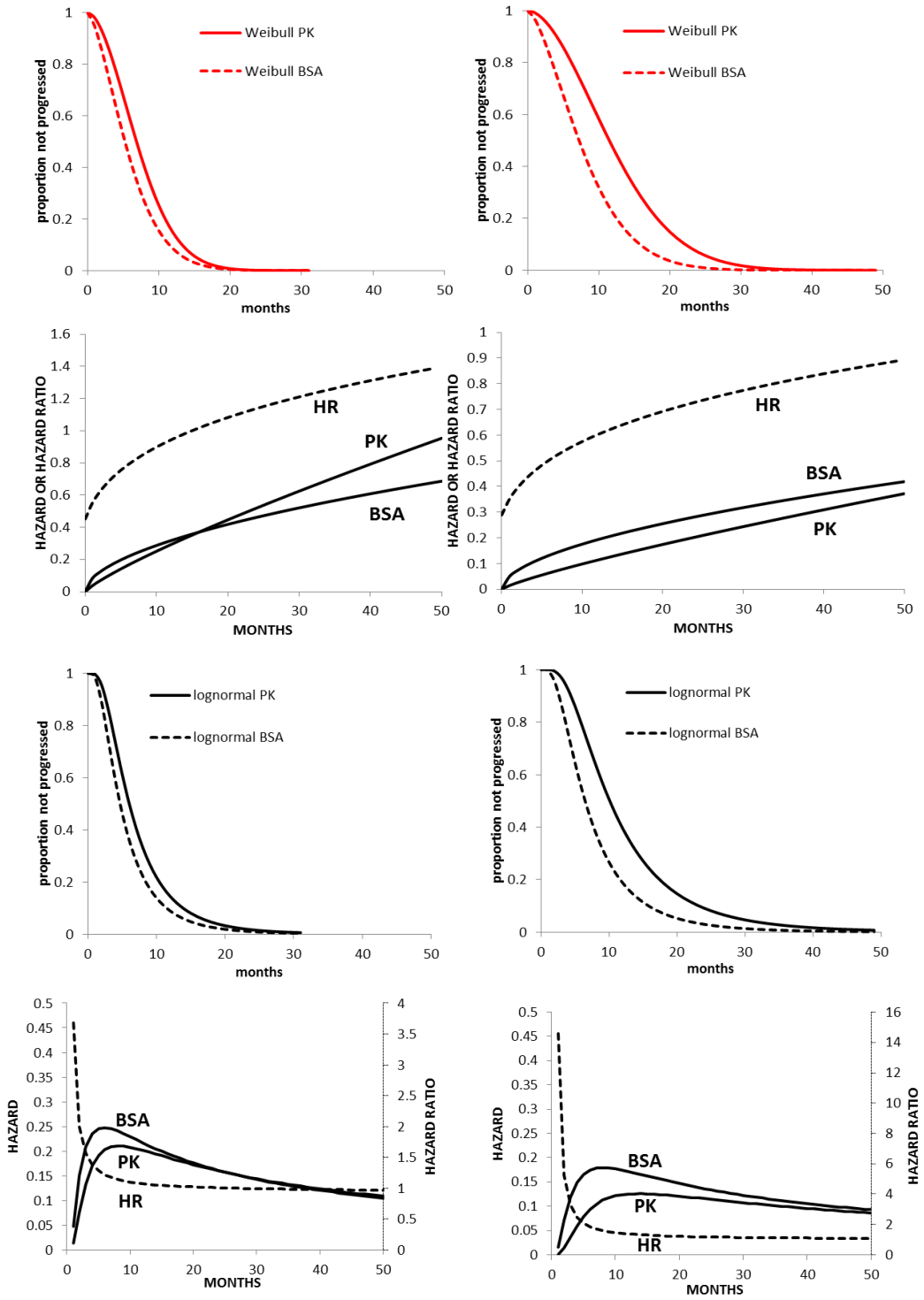

Figure 13. PFS for PK and BSA arms on Weibull (upper) and lognormal (lower) derived parameters under scenarios A (left) and B (right) (Gamelin et al., 2008)[118]

Capitain et al. (2012)[119] reported median PFS of 16 months and 10 months in PK and BSA arms respectively. Confidence intervals were not reported. A Kaplan-Meier plot was provided for only the PK arm. The reconstructed PK Kaplan-Meier (using the Guyot et al., 2012[125] method) is shown in

Figure 14 together with that for overall survival for the PK arm. Both plots closely overlap the published figures (available from authors on request).

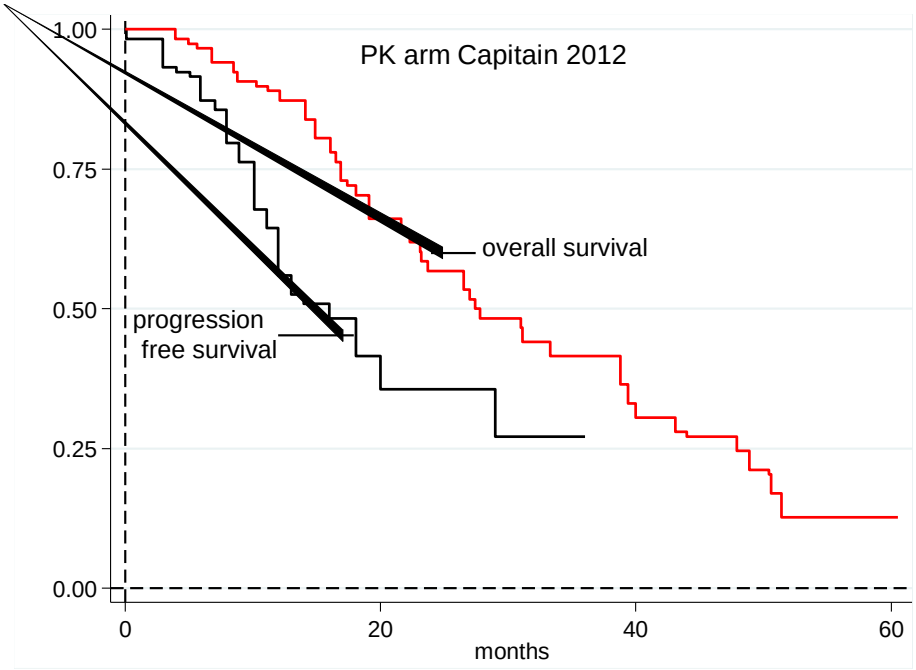

Figure 14. Reconstructed Kaplan-Meier plots for OS & PFS of the PK group (Capitain et al., 2012)[119]

Median PFS from the reconstructed PK arm plot was 16.0 months (95% CI: 12.0 – 20.0) close to the reported value. Weibull, lognormal and log logistic distributions provided moderately well-fitting models to reconstructed data (Appendix 14). To obtain an estimate of PFS for the BSA arm the reported median of 10 months (based on 39 BSA arm patients) was used with the same procedure as described above for OS. For the Weibull model proportional hazard was assumed (HR 0.4817). Table 23 summarises the model parameters for these models.

Table 23. PFS modelled on Weibull, lognormal & log logistic distributions (Capitain et al., 2012)[119]

Model	lambda	gamma	median	mean	diff in means
Weibull PK	0.0243758	1.136683	19.01	25.06	
Weibull BSA	0.050599	1.136683	10	13.18	11.88
	mu	sigma			
Lognormal PK	2.878827	1.244953	17.79	38.62	
Lognormal BSA	2.302588	1.244953	10	21.70	16.92
	P	gamma			
Loglogistic PK	0.057355	0.638179	17.44	38.53	
Loglogistic BSA	0.1	0.638179	10	22.10	16.43

It is noticeable that the mean predicted with the lognormal and log logistic models exceeds the means for overall survival shown in Table 23. This is probably due to the influence of the flatter part of the

PFS KM plot beyond 15 months. Figure 15 illustrates the modelled PFS. Since lognormal and logistic models generate PFS means greater than OS means for the PK arm they appear to be less appropriate than the Weibull. The availability of medians only for the BSA arm limits the reliability of the analysis.

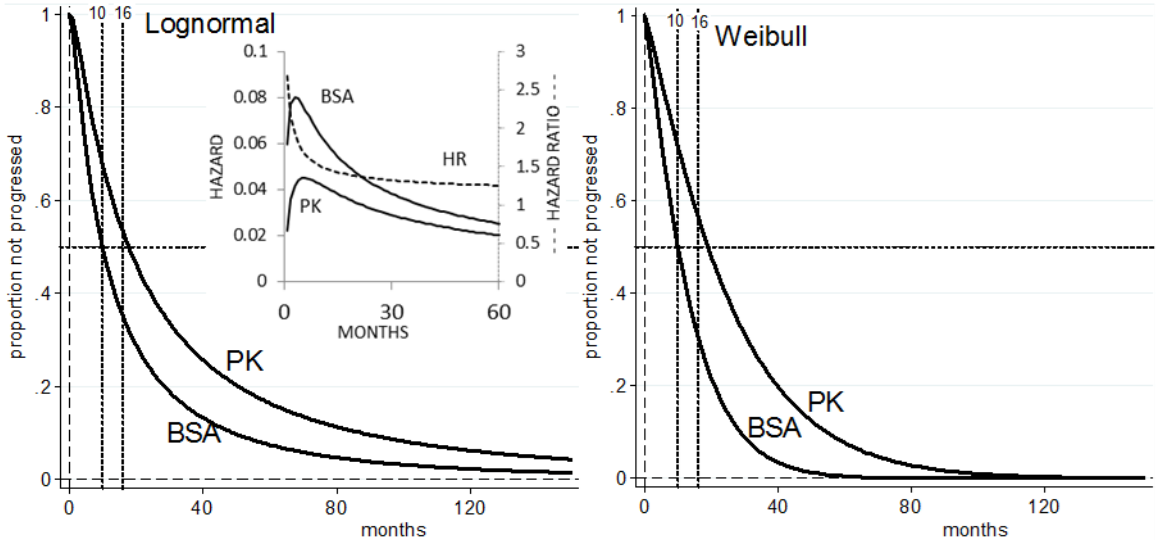

Figure 15. PFS modelled on Weibull and lognormal distributions (Capitain et al., 2012)[119]

Kline et al. (2013)[156] presented Kaplan-Meier analyses of PFS for stage II/III and stage IV patients. Reconstructed plots with the method of Guyot et al. (2012)[125] were discrepant from the published graphs; therefore censoring (tick) and event data were extracted from the plots and used to generate the illustrative graph shown in Figure 16 (left stage II/III patients, right stage IV patients right).

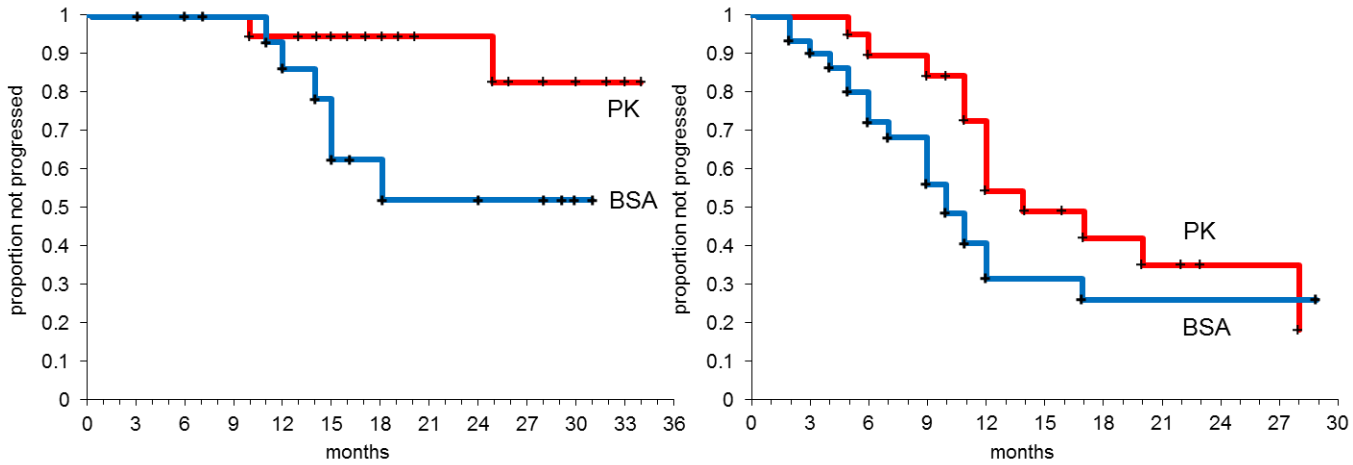

Figure 16. Illustrative graph of PFS. Stage II/III left (NPK= 16, NBSA =19), stage IV right (NPK =19, NBSA=30); upper line PK, lower line BSA

For stage IV the test for equivalence of BSA versus PK (logrank test) yielded P = 0.16. Median PFS was reported to be 14 months and 10 months for PK and BSA groups respectively with median follow-up of 22 months and 20 months in BSA and PK groups respectively.

For stage II/III patients the reported log rank test for equivalence yielded P = 0.0429 suggesting delayed progression for the PK group.

5.5.4.3.6 Outcomes; adverse events

Gamelin et al. (2008)[118] reported the percentage of patients that experienced six categories of adverse event categorised according to four WHO grades of severity. Results for diarrhoea, mucositis, hand and foot syndrome, leukopenia, cardiac toxicity and conjunctivitis at 3 months and at end of treatment of treatment showed little difference; it is therefore assumed the data represents the risk of a patient experiencing the event at least once. Patient risk of diarrhoea, of hand and foot syndrome, and of conjunctivitis was higher than for the other adverse events; the results in each arm at end of treatment are summarised in Table 24.

Table 24. Risk of adverse event according to severity grade and treatment

Adverse event	WHO Grade	BSA; N=96				PK; N=90			
		events	%	LCI (%)	UCI (%)	events	%	LCI (%)	UCI (%)
diarrhoea	IV	3	3.1	0.6	8.9	0	0.0	0.0	4.0
diarrhoea	III	14	14.6	8.2	23.3	4	4.4	1.2	11.0
diarrhoea	II	25	26.0	17.6	36.0	3	3.3	0.7	9.4
diarrhoea	I	13	13.5	7.4	22.0	9	10.0	4.7	18.1
hand & foot	IV	0	0.0	0.0	3.8	1	1.1	0.0	6.0
hand & foot	III	6	6.3	2.3	13.1	10	11.1	5.5	19.5
hand & foot	II	20	20.8	13.2	30.3	20	22.2	14.1	32.2
hand & foot	I	15	15.6	9.0	24.5	29	32.2	22.8	42.9
conjunctivitis	IV	0	0.0	0.0	3.8	0	0.0	0.0	4.0
conjunctivitis	III	0	0.0	0.0	3.8	0	0.0	0.0	4.0
conjunctivitis	II	2	2.1	0.3	7.3	5	5.6	1.8	12.5
conjunctivitis	I	20	20.8	13.2	30.3	10	11.1	5.5	19.5
cardiac	IV	0	0.0	0.0	3.8	0	0.0	0.0	4.0
cardiac	III	1	1.0	0.0	5.7	1	1.1	0.0	6.0
cardiac	II	0	0.0	0.0	3.8	1	1.1	0.0	6.0
cardiac	I	0	0.0	0.0	3.8	1	1.1	0.0	6.0
mucocitis	IV	2	2.1	0.3	7.3	2	2.2	0.3	7.8
mucocitis	III	1	1.0	0.0	5.7	1	1.1	0.0	6.0
mucocitis	II	1	1.0	0.0	5.7	1	1.1	0.0	6.0
mucocitis	I	1	1.0	0.0	5.7	1	1.1	0.0	6.0
leukopenia	IV	1	1.0	0.0	5.7	0	0.0	0.0	4.0
leukopenia	III	1	1.0	0.0	5.7	0	0.0	0.0	4.0
leukopenia	II	2	2.1	0.3	7.3	0	0.0	0.0	4.0
leukopenia	I	0	0.0	0.0	3.8	0	0.0	0.0	4.0

The relative risk (PK versus BSA) of adverse events is summarised in Figure 17. The number of events was sufficiently small for cardiac toxicity and mucositis that any differences between treatments could be attributed to chance. For diarrhoea, and for leukopenia to a lesser extent, the PK regimen appeared to benefit patients. For hand and foot syndrome and for conjunctivitis risk was somewhat greater for patients receiving the PK regimen.

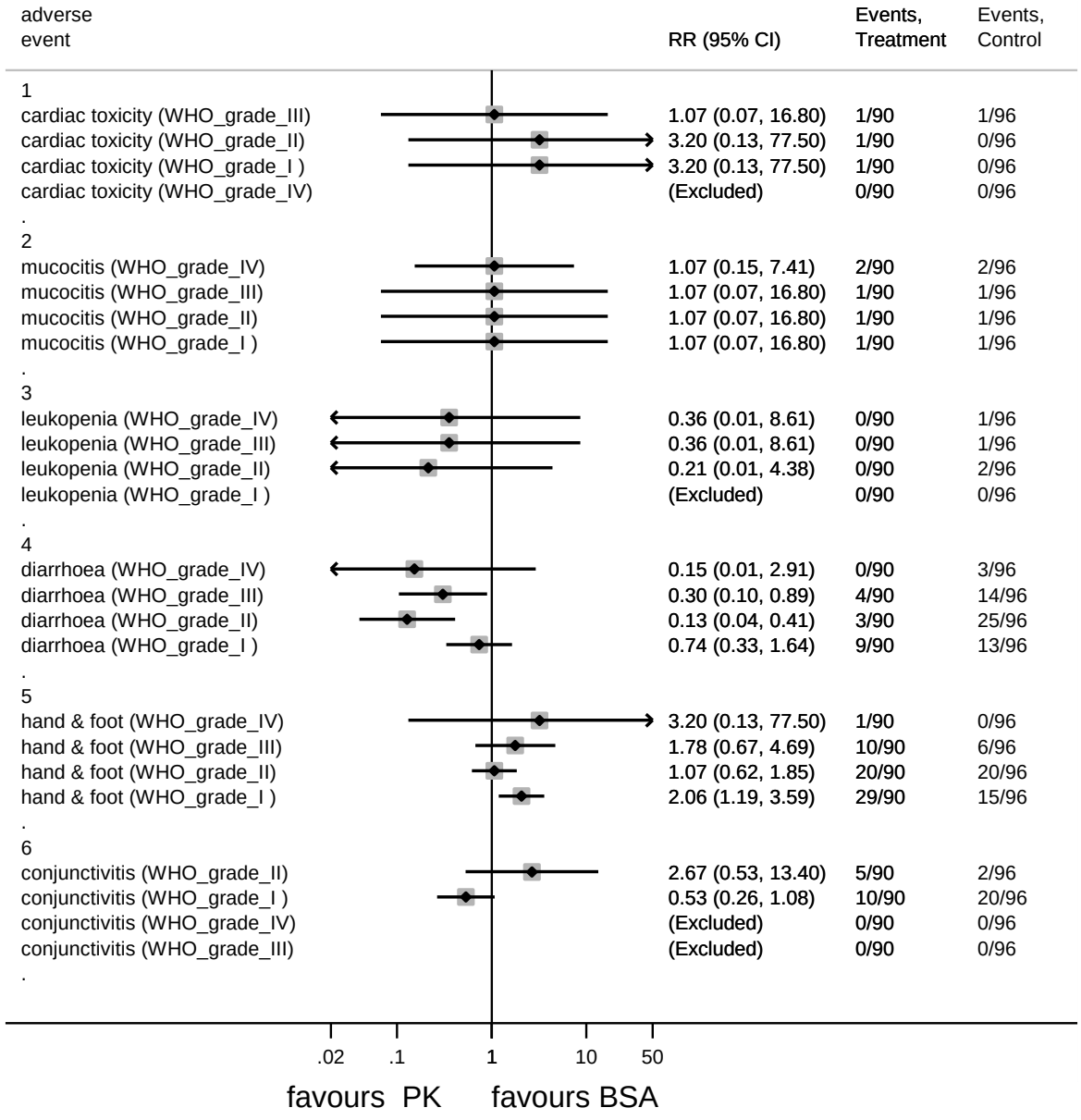

Figure 17. Relative risk of adverse events (PK versus BSA)

Capitain et al. (2012)[119] reported only four types of adverse event which fell within the National Cancer Institute's Common Terminology Criteria scale categories III or IV.[161] Surprisingly hand and foot syndrome was not included. The results are summarised in Table 25.

Table 25. Summary of adverse event results according to treatment regimen

Adverse event	Grade	BSA; N=39	PK; N=118

		events	%	LCI (%)	UCI (%)	events	%	LCI (%)	UCI (%)
diarrhoea	III/IV	5	12	4.30	24.22	2	1.7	0.53	5.99
mucositis	III/IV	6	15	5.86	27.43	1	0.8	0.02	3.08
thrombocytopenia	III/IV	4	10	2.87	20.87	14	12	7.29	19.10
neutropenia	III/IV	10	25	13.04	39.33	18	12.07	25.91	19.5

Published percentages were converted to nearest whole number of patients and point estimates with 95% confidence intervals then derived.

The relative risk (PK versus BSA) of grade III/IV adverse events is summarised in Figure 18. It appears PK reduces risk of diarrhoea and mucositis and also neutropenia (although not significantly).

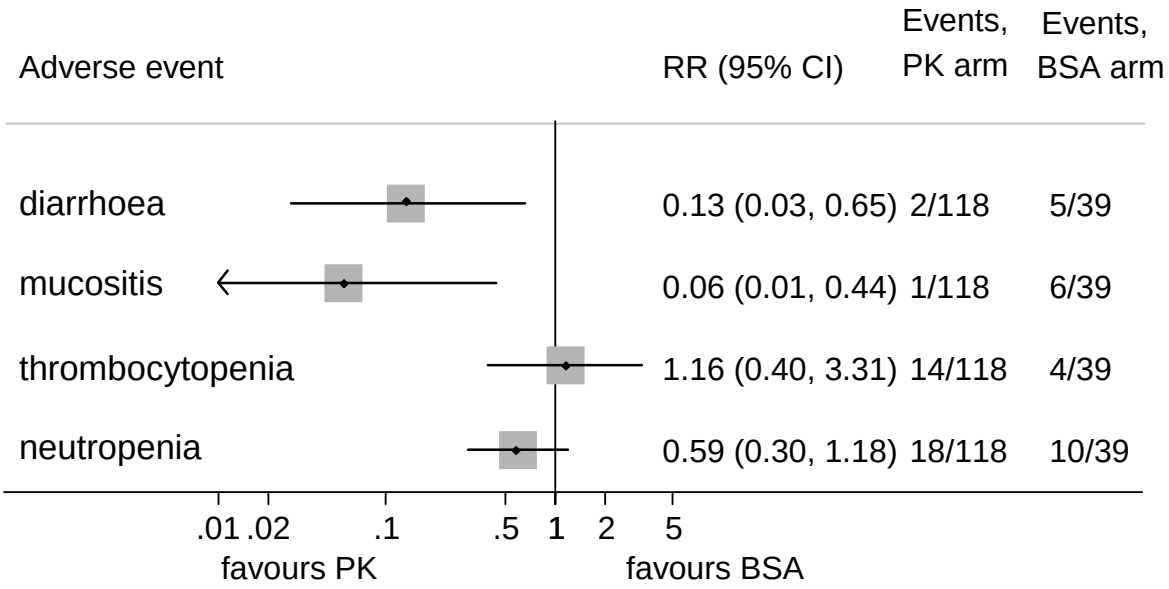

Figure 18. Relative risk of grade III/IV adverse events

The result for diarrhoea is similar to that reported in Gamelin et al. (2008)[118] where the RR for grades III/IV combined was 0.251 95% CI: 0.088 – 0.718. Unlike Capitain et al. (2012),[119] Gamelin et al. (2008)[118] reported a similar risk of mucositis for each arm.

Kline et al. (2013)[156] evaluated toxicity graded according to the National Cancer Institute Common Terminology for Adverse Events version 4.0 (NCI CTAE) scale. Side effects which were considered Grade 3 using the NCI CTAE scale or ere deemed sufficiently serious by the physician to warrant a dose reduction were "designated as adverse effects".

Among stage IV patients, 37% in both BSA and PK groups experienced grade 3 toxicity (Table 26). Among stage II / III patients grade 3 toxicity was more common amongst BSA patients than PK patients (69% versus 32%; P = 0.0437 by Fisher's exact test).

Among all 19 CRC stage II / III receiving a BSA regimen, 3 experienced diarrhoea, vomiting or nausea, side effects associated more with 5-FU than the other components of chemotherapy; eight of all the 16 CRC stage II / III who received PK regimens experienced these side effects (P = 0.0652; Fisher's exact test). Among stage II / III patients grade 3 toxicity was more common amongst BSA patients than PK patients (69% versus 32%; P = 0.0437 by Fisher's exact test). The incidence of different types of dose limiting toxicities for both groups is listed in Table 26 according to stage of disease. Among all 19 CRC stage II / III receiving a BSA regimen 3 experienced diarrhoea, vomiting or nausea, side effects associated more with 5-FU than the other components of chemotherapy; eight of all the 16 CRC stage II / III who received PK regimens experienced these side effects (P = 0.0652; Fisher's exact test).

Table 26. Grade 3 toxicities experienced with BSA and PK based regimens (Kline et al., 2013)[156]

Item	**Stage IV CRC**		**Stage II / III CRC**	
	BSA Method	**PK Monitoring**	**BSA Method**	**PK Monitoring**
Patients with Grade 3 Toxicity; Total n, (%)	11 (37)	7 (37)	11 (69)	6 (32)
Dose-Limiting Toxicity				
Diarrhea, n (%)	4 (13)	4 (21)	8 (50)	3 (16)
Nausea	2	0	1	0
Vomiting	1	0	2	0
Dehydration*	3	0	3	0
Hand-foot syndrome	2	0	0	1
Dehydration*	1	2	0	1
Mouth sore	2	1		
Dysphagia	2	0		
Decreased appetite	0	1		
Malnutrition	1	0	1	0
Weight loss	1	0		
Fatigue	2	0		
Weakness	1	0	1	0
Syncope	1	0	2 (12)	3 (16)
Neutropenia, n (%)	3 (10)	2 (10)	8 (50)	3 (16)
* Dehydration was entered twice in the Grade IV columns				

The number of treatment doses received before adverse side effects were observed was greater for PK-dose adjusted patients than for BSA group patients; this applied for both stage II / III and stage IV patients. The results are summarised in Figure 19.

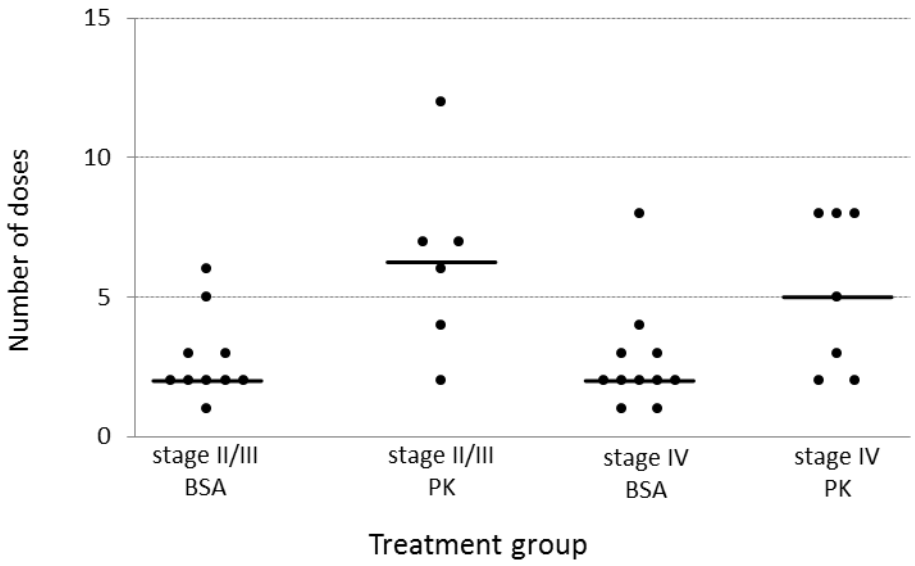

Figure 19. Number of doses received before adverse side effects were observed. The horizontal line represents the median. Numbers of patients were 10, 6, 11 and 7.

5.5.4.3.7 Outcomes; response rates

Gamelin et al. (2008)[118] defined response rates as the primary outcome measure. Response rates are summarised in Table 27.

Table 27. Response rates reported by Gamelin et al. (2008)[118]

Response	**BSA arm (N=104)**	**PK arm (N=104)**
	Number with response	**Number with response**
Complete response	1	6
Partial response	17	29
Stable disease	30	26
Progressive disease	48	39

More patients in the PK arm than the BSA arm experienced complete and partial responses and fewer experienced progression. The relative risk according to response type is summarised in Figure 20.

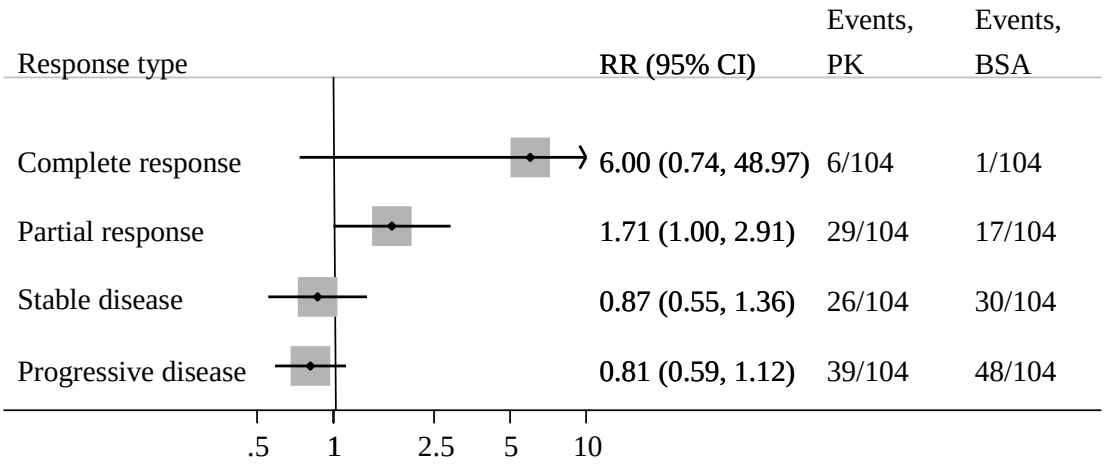

Figure 20. Relative risk of different types of response

Capitain et al. (2012)[119]: Patients' therapeutic response was assessed according to RECIST 1.1 criteria. Reported results are summarised in Table 28.

Table 28. Response rates reported at 3 months and 6 months

Item	**BSA arm (N=39) at 3 months**	**PK arm (N=118) at 3 months**	**PK arm (N=118) at 6 months**
Response type	Number (%) with response	Number (%) with response	Number (%) with response
Complete response	1 (2.6)	3 (2.5)	23 (20.3)
Partial response	17 (44)	80 (67.2)	40 (35.4)
Overall response*	18 (46.6)	83 (69.7)	63 (55.7)
Disease Control**	30 (77)	104 (88.1)	87 (77.0)
Progressive disease	9 (23.0)	14 (11.9)	26 (23.0)
* Overall response = complete response + partial response. ** Disease control = all that have not progressed.			

At 3 months response rates were superior for the PK group. The relative risk (PK versus BSA) of different response categories is shown in Figure 21.

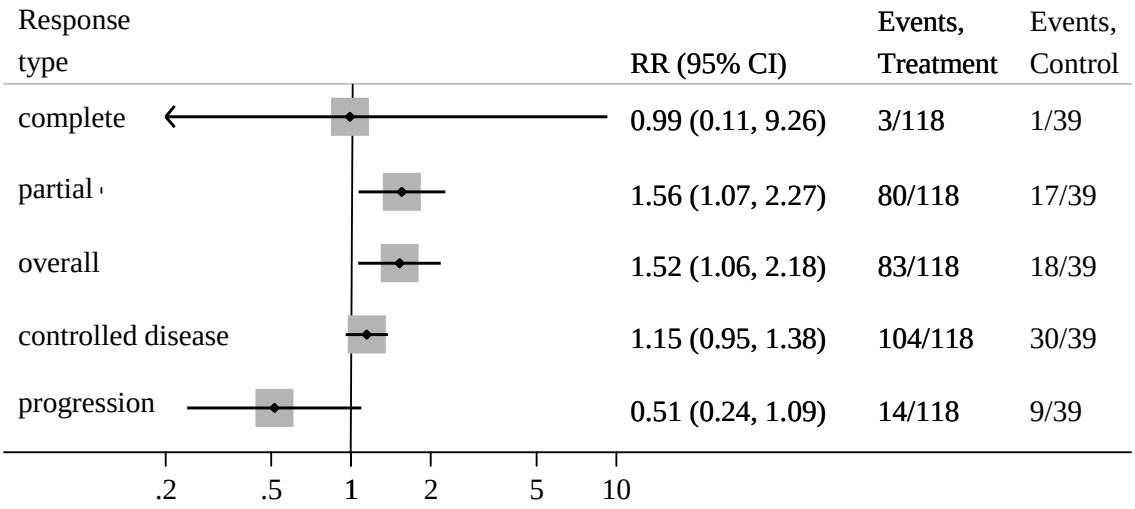

Figure 21. Relative risk of response according response type and treatment

Response rates at six months for the PK arm, but not BSA arm, were also reported. These indicated that a complete response was observed for 23/118 patients. At 3 and 6 months 23% of both BSA and PK patients were classified as progressive disease. This implies a difference of 3 months between arms when 77% remain un-progressed and this fits fairly well with the lognormal and Weibull models for PFS shown in Figure 15.

Kline et al. (2013)[156] did not report response rates.

5.5.4.3.8 Outcomes; dose adjustment and dose received

Gamelin et al. (2008)[118] reported that 94% PK arm patients reached target range plasma 5-FU concentrations (=2,500 to 3,000 µg/L) in a mean of 4 treatment cycles. The dose received when in target range varied greatly between PK regimen patients (see Figure 22).

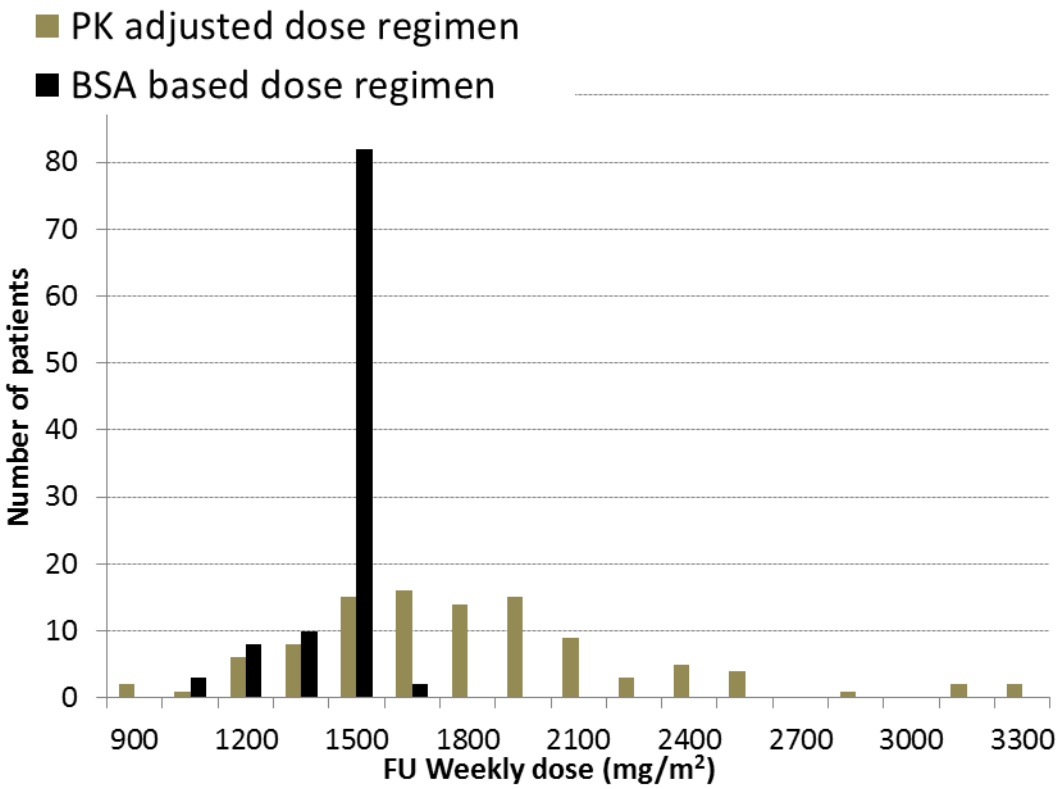

Figure 22. Weekly 5-FU dose received when in target range (PK group) and weekly dose received at 3 months (BSA-based regimen group); data read from graph and graph reconstructed

Most patients (~85%) in the PK group had dose adjustment; the mean dose after three months of treatment was 1,790 mg/m^2 (range: 765 to 3,300 mg/m^2). Of 49 BSA-based regimen patients whose plasma 5-FU concentration was measured only 4 were within target range.

Most PK patients had their dose increased to levels above the starting dose of 1500 mg/m^2; indicating that without dose adjustment these patients' steady state plasma 5-FU concentration was judged to have been less than that desirable for full effect upon cancer cells. The implication of this is that in the BSA arm (where dose was retained at 1500 mg/m^2 or was reduced because of toxicity) a substantial proportion of patients remained under-dosed. According to the rationale of PK adjustment this might be expected to translate into reduced effectiveness in the BSA arm versus PK arm for outcomes such as PFS, OS and response rates. A smaller proportion of the PK group had dose reductions. Under the rational of PK adjustment this might be expected to translate into a more favourable toxicity profile for the PK arm than the BSA arm.

Gamelin et al. (2008)[118] reported that 5-FU plasma levels between 2.5 and 3 mg/L were correlated with grades 1 and 2 diarrhea and grade 1 hand-foot syndrome. Grade 3 diarrhea and hand-foot syndrome were reported to be associated with 5-FU plasma levels > 3 mg/L (3.5 and 3.9 mg/L, respectively; $P = .02$).

In Capitain et al. (2012)[119] the PK group received a mean dose close to 2500 mg/m^2 (mean 94.32% ± 13.7% of theoretical dose) ,by three months most were receiving an adjusted dose and dose increases and reductions of 10 and 20% from 2500 mg/m^2 were common; thus at three months 56 of 118 patients received doses >20% different from their starting dose. Dosage changes reported at three months for the PK group are summarized in Table 29. About 91% of PK patients required dose adjustment. About two thirds of PK patients received dose increases and about 20% had their start dose reduced potentially translating into reduced toxicity compared to BSA patients.

Table 29. Dosage changes at 3 months in the PK group as percentage starting dose

Dosage change from cycle 1 dosage	number of patients	mean % dose change (SD)	% range
>10% increase	75/118	20 (8)	10 - 40
>20% increase	42/118	26 (6)	20 - 40
>10% decrease	22/118	20 (9)	10 - 40
>20% decrease	14/118	26 (5.94)	20 - 40

Within 3 months in the BSA-based dosage group, the 5-FU dose was decreased due to grade 3 toxic adverse effects in 4/39 patients by 15% ± 4% (range, 10% to 25%).

Kline et al. (2013)[156] did not report the proportion of patients that received dose adjustment. A graph was presented illustrating the distribution of doses at each successive cycle. The median dose (horizontal line) remained the same at 2400 mg / m^2 across cycles irrespective of treatment regimen. Whereas BSA patients had dose reductions at increasing frequency with increasing cycles in the PK group both dose increases and dose reductions were undertaken. Based on the published graph it appears that about 25- 30% percent of 19 stage IV PK patients received dose increases by cycles 3 and 4. Some PK patients received dose reductions. Figure 23 summarises this for stage IV patients.

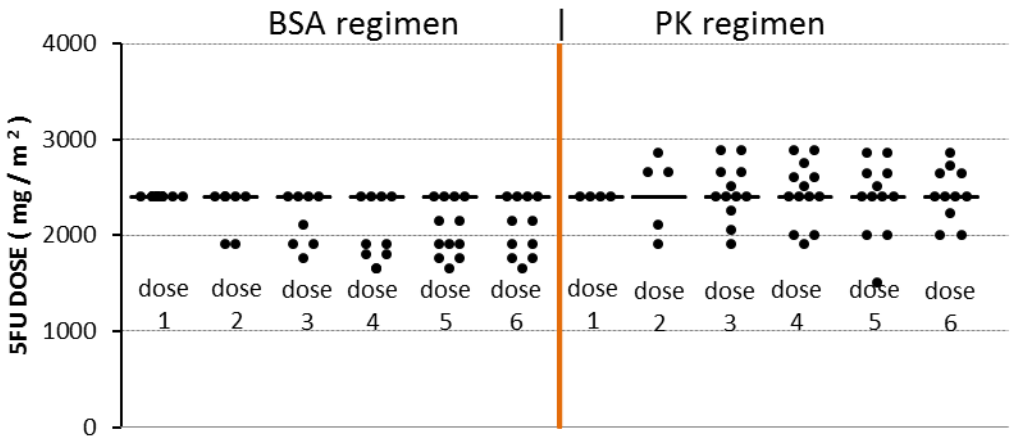

Figure 23. Median dose and distribution of doses at successive cycles for stage IV patients (N = 30 and 19 for BSA and PK groups respectively).

Figure 24 summarises the results for stage II / III patients. In the BSA group dose reductions and median dose decreased with increasing cycles. For the PK group the median dose remained unchanged and patients received dose increases and reductions in about equal proportions.

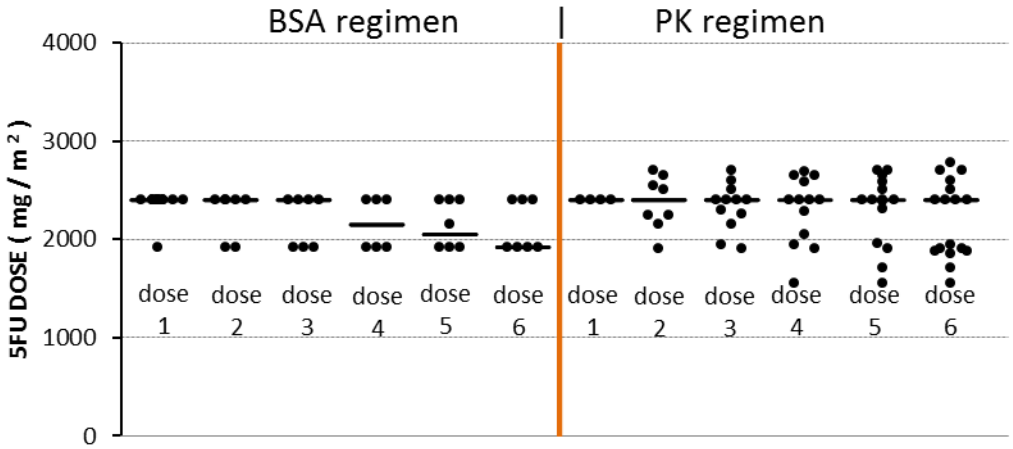

Figure 24. Median dose and distribution of doses at successive cycles for stage II / III patients (N= 16 and 19 for BSA and PK groups respectively).

5.5.4.3.9 Outcomes; performance status

Gamelin et al. (2008)[118] reported the influence of treatment upon patients' performance status in terms of the percentage of patients whose status remained unchanged, worsened or improved relative to baseline. The results are summarised in Table 30. A few patients improved performance status, but for most performance status remained unchanged or worsened.

Table 30. Post-treatment performance status relative to baseline

Performance status	BSA arm	PK arm
Improved	7.6%	11.1%
Stable (no change)	53.8%	61.8%
Worsened	37.6%	26.9%

5.5.4.3.10 Outcomes; plasma 5-FU clearance

Kline et al. (2013)[156] calculated 5-FU clearance by dividing the administered dose by the AUC measure of plasma 5-FU concentration (mg * hr /L). This estimate was interpreted as a measure of patients' ability to metabolise 5-FU. The results indicated that clearance decreased as cycles of treatment accumulated, indicating a reducing ability to metabolise 5-FU. The results are summarised in Figure 25.

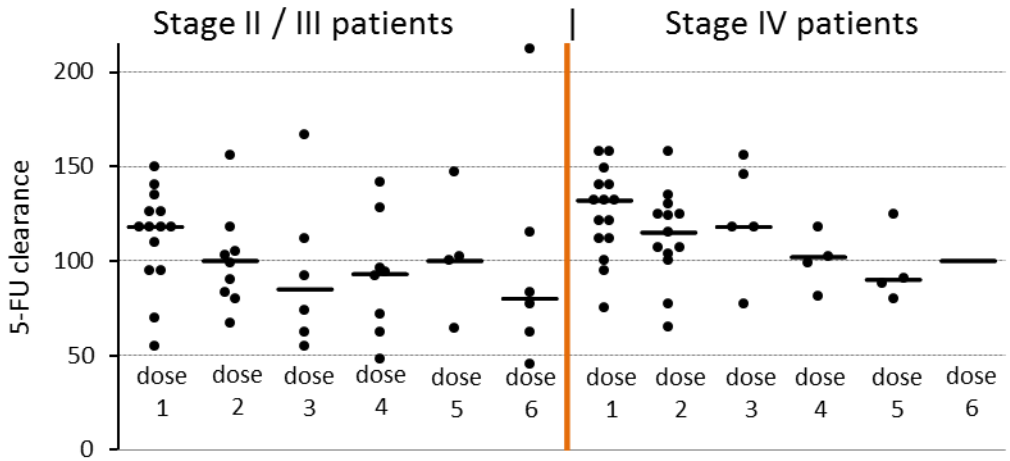

Figure 25. Distribution of 5-FU clearance rates with increasing dose cycles (Kline et al., 2013)[156]

5.5.4.3.11 Outcomes; second, third and fourth line treatments

Capitain et al. (2012)[119] was the only study that documented second, third and fourth line treatments. The distribution of different types of post-first line therapies was reported for the PK group only. These are summarised in Table 31. The proportion of patients that received second, third and fourth line therapies gradually declined; the commonest therapies used were FOLFIRI and targeted therapies.

Table 31. Post first line therapies received by PK regimen patients (Capitain et al., 2012)[119]

Item	Line of therapy			All
	2nd Line	3rd Line	4th Line	N (%)
Type of chemotherapy				
FOLFIRI	58	3	0	61 (51.47)
FOLFOX	0	9	4	13 (11.0)
Targeted-Therapy Regimens	27	29	6	62 (52.5)
Intravenous 5-FU (FUFOL or LV5VU2 Regimen)	8	2	4	14 (11.9)
Oral 5-FU Prodrugs (Capecitabine)	6	5	4	15 (12.7)
Total number of treated Patients (%)	99 (83.9)	48 (40.7)	18 (15.3)	

Abbreviations: 5-FU = fluorouracil; FOLFIRI = folinic acid, fluorouracil, irinotecan; FOLFOX = folinic acid, fluorouracil, oxaliplatin; FUFOL = folinic acid, 5-fluorouracil (weekly 8-hour infusion); LV5VU2 = folinic acid, fluorouracil (biweekly 46-hour infusion).

5.5.4.4 Conclusions from CRC comparative studies

Of three studies identified, only Gamelin et al. (2008)[118] was a randomised trial, the other two (Capitain et al., 2012[119] and Kline et al., 2013)[156] were retrospective studies in which population balance between arms was reasonable on the variables reported. Nevertheless in the absence of high quality randomisation, true comparability between groups is inevitably compromised. There is a further problem when patients are invited to self-select into PK or BSA dosing, in that those who are either healthier or more unwell may self-select to undergo a new method of dose adjustment thus biasing the selection of the sample and reducing validity. It is interesting that in Kline et al. (2013)[156] the proportion of stage IV patients self-selecting for PK adjustment (19 of 49) was noticeably lower than amongst stage II/III patients (19 of 34).

Each study documented considerable inter-patient variation in steady state plasma 5-FU concentration during continuous infusion. The use of dose adjustment algorithms based on these measures resulted in most patients in the PK arm requiring dose changes (in Capitain et al., 2012[119] [91%] and Gamelin et al., 2008[118] [85%]); the proportion was not reported by Kline et al. (2013)[156] but may have been less because of a wider target concentration range for steady state plasma 5-FU (algorithm unreported). In Capitain et al. (2012)[119] and Gamelin et al. (2008)[118] most patients required dose increases; this implied that in the comparator BSA group, patients would have remained under-dosed; according to the rationale for the PK intervention which might result in less effective treatment for cancer cells in this group relative to the PK group albeit potentially with fewer adverse events.

Kaplan-Meier plots reported by Kline et al. (2013)[156] indicated that PK dose adjustment tended to delay disease progression ($p = 0.16$ and $p = 0.043$ for stage IV and stage II / III patients respectively).

Capitain et al. (2012)[119] presented similar evidence, but only median time to progression was provided for the BSA group (medians were 16 and 10 months for PK and comparator groups respectively). Gamelin et al. (2008)[118] did not present time to progression evidence, however data on mean duration of complete and partial responses and of stable disease might possibly allow one to infer that PK dose adjustment prolonged the time to progression.

Gamelin et al. (2008)[118] reported Kaplan-Meier plots showing improvement in overall survival in the PK group relative to BSA group ($p = 0.08$; median survival 22 and 16 months respectively). However Capitain et al. (2012)[119] provided a Kaplan-Meier graph only for the PK group (median survival was 28 and 22 months for PK and comparator group respectively).

Capitain et al. (2012)[119] and Gamelin et al. (2008)[118] found that PK based dose adjustment reduced the risk of grade III and IV diarrhoea (relative risk 0.013 95%CI: 0.03 – 0.65, and 0.251 95%CI: 0.088 – 0.718, respectively). These studies indicated there may be reduced risk of mucositis and of neutropenia / leukopenia but in Gamelin et al. (2008)[118] the risk of hand and foot syndrome increased. Kline et al. (2013)[156] reported that the risk of toxicities was not reduced with PK dose adjustment, but that on average toxicities were delayed and occurred later in the series of treatment cycles. It is difficult to identify reasons for these apparent differences. It would be important to report how adverse events relate to plasma 5-FU concentrations. There was considerable dose variation in both arms, especially in the PK arm, however in the PK arm the target plasma concentration was achieved in most patients for most cycles, it is therefore likely for these patients that the plasma 5-FU concentration was stable. For the BSA arms there was little reporting of plasma 5-FU levels.

Overall the evidence from the three studies tends to support the hypothesis of clinical benefit from PK adjustment, however the evidence is not robust and is compromised by lack of randomisation in two of the studies; furthermore each study failed to present a complete set of comparative data for the major outcomes of clinical importance i.e., progression-free and overall survival and risk of treatment side effects, so that there appears to be appreciable risk of outcome reporting bias.

It should be emphasised that we failed to find any published randomised evidence about the effectiveness of PK-directed dose adjustment for any currently used 5-FU regimen for any cancer type.

5.5.4.5 Comparative H&N study taken forward in cost effectiveness analysis

The study by Fety et al. (1998)[160] is first described in terms of study design and quality, of population, of intervention and outcomes.

5.5.4.5.1 Study design and quality

This multicentre RCT (involving three centres) assigned 61 patients to a PK adjusted 5-FU regimen and 61 patients to a standard based dose regimen. Pharmacokinetic dose adjustment was based on 5-FU measurements determined by HPLC and dose adjustment followed a modified algorithm by Santini et al. (1989).[131] Due to 5-FU-related toxicity, three patients (5.2%) in the BSA arm and three patients in the PK arm (6.1%) left the study before completing chemotherapy. The length of follow up was unclear. The primary end point was the incidence of haematological toxicity and the secondary end point was the equivalence of disease response.

Randomisation was stratified by centre (three centres were involved). Methods of allocation concealment were not reported. Blinding to treatment was not possible; assessment of response rates was assessed by a panel of two independent radiologists and may have been blinded, but this was not specified. There was some mismatch between the description of methods undertaken and the reported results. There were weaknesses in the clarity and presentation of data. It has been previously noted by other authors[85] that the dose adjustment method in this study may have been too complicated, as the 12 protocol violations in the treatment arm (12/61 patients enrolled) were all related to 5-FU dose adjustment miscalculations. Furthermore, since the patients with protocol violations were removed from the analysis and the induction therapy regimen used only two drugs the generalizability to dose adjustment methods in current clinical practice remains questionable. See Appendix 11 for Downs and Black (1998)[123] quality assessment checklist.

5.5.4.5.2 Population

The reported demographic characteristics are summarised in Table 32. Patients had advanced H&N cancer and most had not received previous chemotherapy.

Table 32. Baseline characteristics of Fety et al. (1998)[160]

Item	**Treatment arm**	
	BSA	**PK**
Patient Number *Total number* *Sample attrition/patients not evaluable*	 61/122 (50%) 4/61 (6.6%)	 61/122 (50%) 12/61 (19.7%)
Age (years) Mean (SD) Median Range	 NR 54 29-72	 NR 55 36-69
Sex Men (%) Women (%)	 52/57 (91.2%) 5/57 (8.8%)	 48/49 (98%) 1/49 (2%)
Performance status (%)		

01 2 *3* 4	16/57 (28.1%) 34/57 (59.6%) 7/57 (12.3%) 0 0	11/49 (22.4%) 35/49 (71.4%) 3/49 (6.1%) 0 0
Previous therapy (%)	NR	NR
Metastatic sites (%) Liver Lung Lymph nodes Others	 NA NA NA NA	 NA NA NA NA

5.5.4.5.3 Intervention

Patients were assigned to receive 3 cycles of induction chemotherapy with cisplatin (100 mg/m^2 on day 1) and 5-FU (96-h continuous infusion), either at standard dose (BSA arm; 4 g/m^2) or at a dose adjusted according to the 5-FU AUC (PK arm).

5.5.4.5.4 Outcomes

Quality of life, overall survival and progression free survival were not reported. Adverse event were reported per cycle (counts). Among the 122 patients randomly assigned to one of the two treatment arms, 16 patients (13%) were found to be "unevaluable" for response and toxicity (4 patients in the BSA arm, and 12 patients in the PK arm). Grade II and IV neutropenia and thrombopenia were reduced in the PK arm when compared to the BSA arm (7.6% versus 17.5%; P=0.013). Mucosity (Grade II and IV) was only observed in the BSA arm (5.1%). There was no significant difference in the objective tumour response rate between both arms (77.2% in the BSA arm versus 81.67% in the PK arm).

Conclusions from the H&N study taken forward in cost-effectiveness analysis

The paper by Fety (1998)[157]provides information in a randomised design on 5-FU dose adaptation according to pharmacokinetic parameters versus conventional dosing in patients with advanced head and neck cancer. The overall 5-FU exposure in H&N cancer patients was significantly reduced in the dose adjustment arm compared to the fixed-dose arm. This resulted in reduced toxicity, but no improvement in clinical response. The impact on toxicity and efficacy suggests these patients might benefit from individual PK monitoring. The utility of monitoring 5-FU exposure to reduce toxicity was confirmed. It was noted that no link was found between pharmacokinetics and mucositis. As for tumour response, no difference in 5-FU exposure was observed between patients who achieved a complete response or partial response and patients who had stable disease or progression. This finding was not consistent with previous studies[133, 162] which reported that response and survival were significantly associated with high plasma concentrations in patients with H&N cancer. However, the

findings from the study by Fety (1998)[157, 159] should be treated with caution as the methods and overall results were poorly presented.

5.6 Conclusions for objectives B and C

The evidence on PK versus BSA dosing in the treatment of CRC patients is weak in both quantity and quality. This holds to an even greater extent for H&N cancer. Evidence on My5-FU is sparse; we found only one study of clinical outcomes which compared BSA with PK dose adjustment after application of the My5-FU assay; this study was at risk of selection bias. Of three CRC comparative studies identified, only one was an RCT and unfortunately this study used an unrepresentative 8-h infusion regimen. Single arm studies were heterogeneous, generally of poor design, and were severely limited in ability to deliver useful data for comparison of PK versus BSA dosing. We have been unable to identify any published randomised evidence about the effectiveness of PK-directed dose adjustment for any currently used 5-FU regimen for any cancer type. None of the studies we investigated including the RCT were of high quality, all had important drawbacks in design, methods, and key outcome coverage; these factors limit their validity and generalizability. From these studies there is therefore little evidence that can be taken forward for the modelling of the cost-effectiveness of My5-FU dose adjustment vs. BSA-based dose regimens.

Because of the paucity of evidence from these studies we were concerned that their comparator BSA populations might be unrepresentative, potentially leading to a biased comparison of PK versus BSA. The apparent clinical benefits from PK dose adjustment in the key outcomes of PFS and OS and adverse events could thus represent unrepresentative findings. In the next section we address this issue by comparing PK and BSA outcomes across multiple study arms by including studies retrieved for Objective D which seeks to test if the outcomes reported for the control (BSA) arms of CRC studies included in sections B and C are generalizable. This section provides a synopsis of the available data that links the clinical and cost effectiveness elements of the report.

5.7 Clinical effectiveness synthesis – an overview of PK versus BSA to inform the cost-effectiveness analysis and evidence for Objective D

This section seeks to address Objective D, and then present an overview of evidence assembled for Objectives B, C, and D to compare the clinical effectiveness of PK versus BSA in CRC.

The aim of objective D was to provide an overview of systematic review evidence about BSA based 5-FU regimens in order to assess the generalisability of BSA results from the comparative studies included in the clinical effectiveness Objectives B and C.

5.7.1 Search results for Objective D

Figure 26 provides the PRISMA flow diagram for objective D. Electronic searches identified 67 records; an additional record was identified from other sources. After removal of 12 duplicates, 55 records were screened of which 50 were excluded as irrelevant at title / abstract level. Five records were examined at full text and one was included (NICE Clinical Guideline, CG131, November 2011, entitled "Colorectal cancer: the diagnosis and management of colorectal cancer). The reasons for the exclusion of the four studies are provided in Appendix 8. The focus of the following section will be on CG131 and the included RCTs it reported.

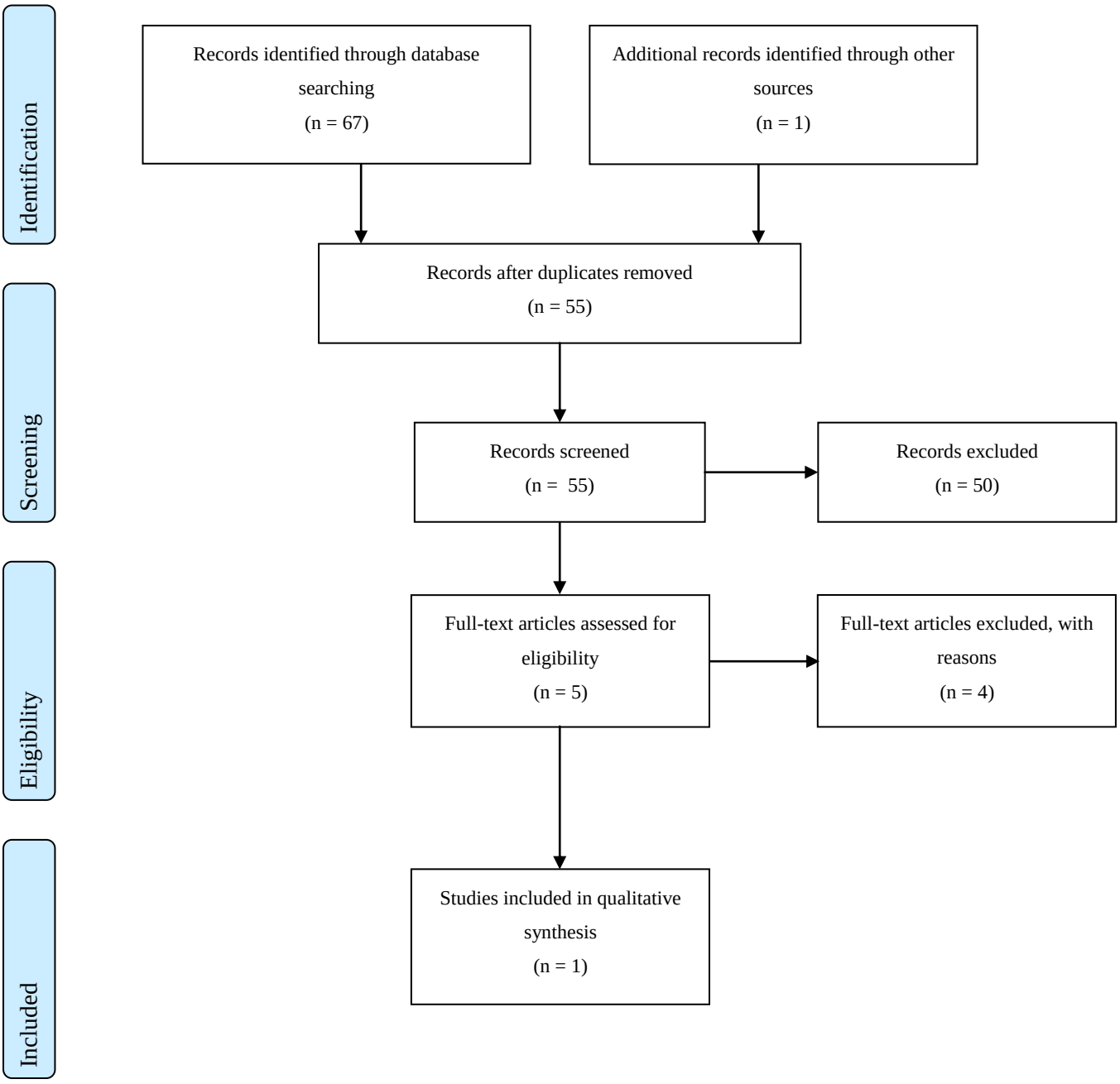

Figure 26. PRISMA Flow Diagram Objective D

5.7.2 Method of selection of RCTs from CG131

CG131 used an extensive NMA of RCTs to compare many 5-FU treatments for CRC with focus on PFS and OS. Evidence was selected from 23 RCTs. Summary survival estimates (HRs) were obtained under assumptions of proportional hazards and of exponential distributions to model survival (these were mainly calculated from median survival values). Analysis of the comparative studies of PK versus BSA and from single arm PK studies (Objectives B and C) indicated that exponential distributions were the least appropriate of those tested for modelling survival data from the reconstructed Kaplan-Meier plots. This, together with a general lack of randomised evidence, meant that a NMA was not considered feasible. Instead for the purposes of this section and for objective D, appropriate primary studies from the CG131 review were identified and PFS and OS Kaplan-Meier plots from these were reconstructed according to the method of Guyot et al. These, supplemented with the evidence from studies in sections B and C, have been used to overview the PFS and OS evidence that can be utilised for a cost effectiveness model. The criteria for selection of studies from CG131 were: the intervention or comparator were either the FOLFOX6 regimen or continuous infusion of a 5-FU + FA regimen, and that the study report included a Kaplan-Meier analysis of OS and or PFS. All CG131 study populations had advanced / metastatic CRC, and according to the CG131 authors all were well conducted RCTs.

The outcomes given emphasis are progression free survival, overall survival and adverse events; this has been dictated by the relevance of these for the cost effectiveness section (Objective E) and by the limiting availability and quality of evidence for other outcomes. The limited evidence in CG131 about adverse events/toxicity is summarised at the end of this section.

Outcomes are considered in turn according to treatment regimens used in the comparative studies; that is: 5-FU + folinate regimens (5-FU + FA) then FOLFOX6. In the comparative study of Kline et al. (2013)[156] patients received either FOLFOX6 or FOLFIRI, results were not separated according to regimen and proportions of patients receiving different treatments was not provided. It was considered impractical to search for published studies or reviews in which patient groups received a mixture of treatments; therefore this section only makes use of the Gamelin, et al. (2008)[118] and Capitain et al. (2012)[119] comparative studies and the single arm studies of Gamelin, et al. (1998)[139] and Capitain, et al. (2008)[135] from Objectives B and C . Because of the uniqueness of the 5-FU + FA used in the Gamelin et al. studies[118, 139] it was necessary to include CG131 studies in which the duration of continuous infusion with 5-FU + FA differed from that in the Gamelin et al. studies.[118, 139]

The studies considered from CG131 were:

a) 5-FU+FA regimen: Kohne et al. (2003),[163] Kohne et al. (2005), [164] Seymour et al. (2007)[165] and Cunningham et al. (2009).[166]

b) FOLFOX6 regimen: Seymour et al. (2007),[165] Hochster et al. (2008),[167] Ducreux et al. (2011)[168] and Tourningand et al. (2004).[169]

In addition, the COIN trial as reported by Adams et al. (2011)[34] was indicated to us by clinical experts as a useful trial that included the FOLFOX6 regimen.

5.7.3 Overview of evidence assembled for Objectives B, C, and D to compare the clinical effectiveness of PK versus BSA in CRC

5.7.3.1 5-FU + FA regimens; overall survival

Four CG131 studies with usable KM plots were identified in which patients with metastatic advanced CRC received a BSA-based 5-FU + FA regimen given by continuous infusion.[163, 164, 165, 166] Reconstructed KM plots are shown in Figure 27 together with the BSA arm for the Gamelin comparative RCT (Gamelin et al., 2008).[118] Note that infusion time used in Gamelin et al. (2008)[118] was different (shorter) than that of the other studies and that the plots are for single arms from different studies. The plots suggest that the control arm in Gamelin et al. (2008)[118] were not substantially different to evidence available in the literature.

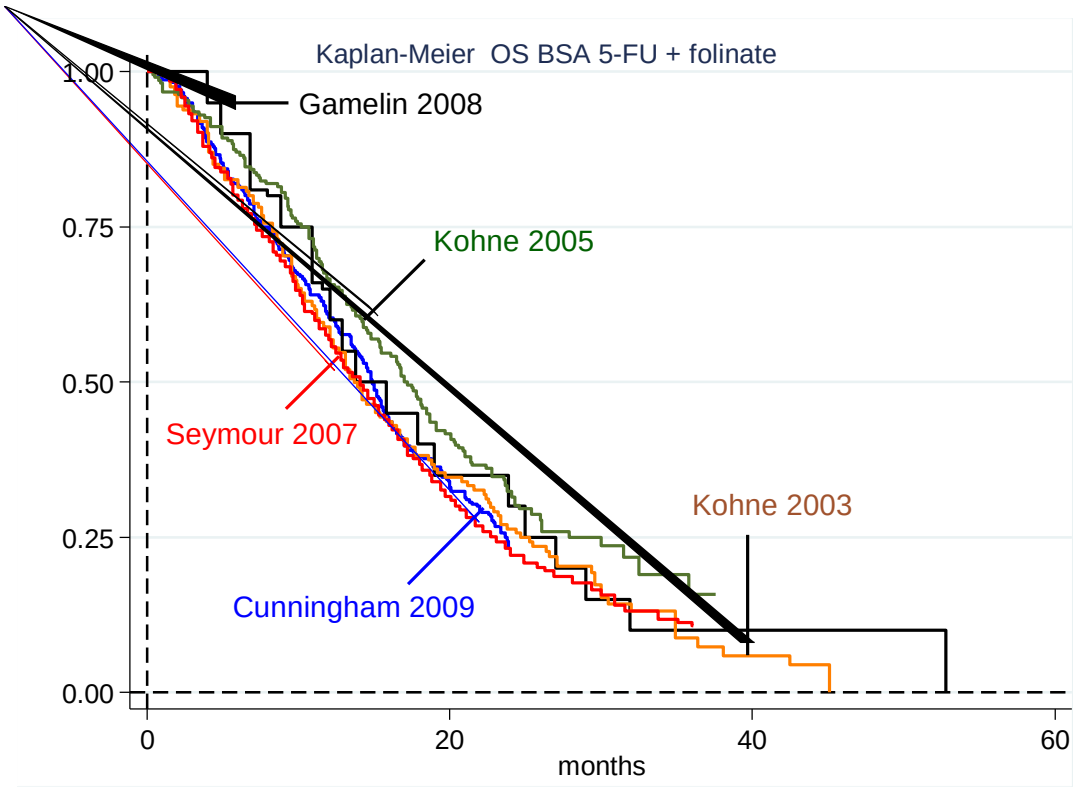

Figure 27. OS for Gamelin et al., 2008[118] 5-FU + FA BSA arm compared with studies from CG131

5.7.3.2 Comparison of overall survival for BSA arms with that for PK arms

Three studies provided KM plots for OS for patients who received continuous infusion 5-FU + FA regimens with PK adjustment of dosage; each was a publication from the same French investigative group.[118, 135, 139] Figure 28 (left) summarises the reconstructed KM plots from these studies. Note that although the treatment regimens were the same in the Gamelin studies (Gamelin et al., 2008[118] and Gamelin, et al., 1998[139]), in Capitain et al. (2008)[135] they involved a much longer infusion time. The plots generate very similar median survivals. When plotted together with the BSA arms (Figure 28 right) there appears to be a small gain in overall survival deriving from PK adjustment. It should be emphasised that except for the contribution from Gamelin et al. (2008)[118] (for both PK and BSA arms) this is a non-randomised comparison of arms from separate studies.

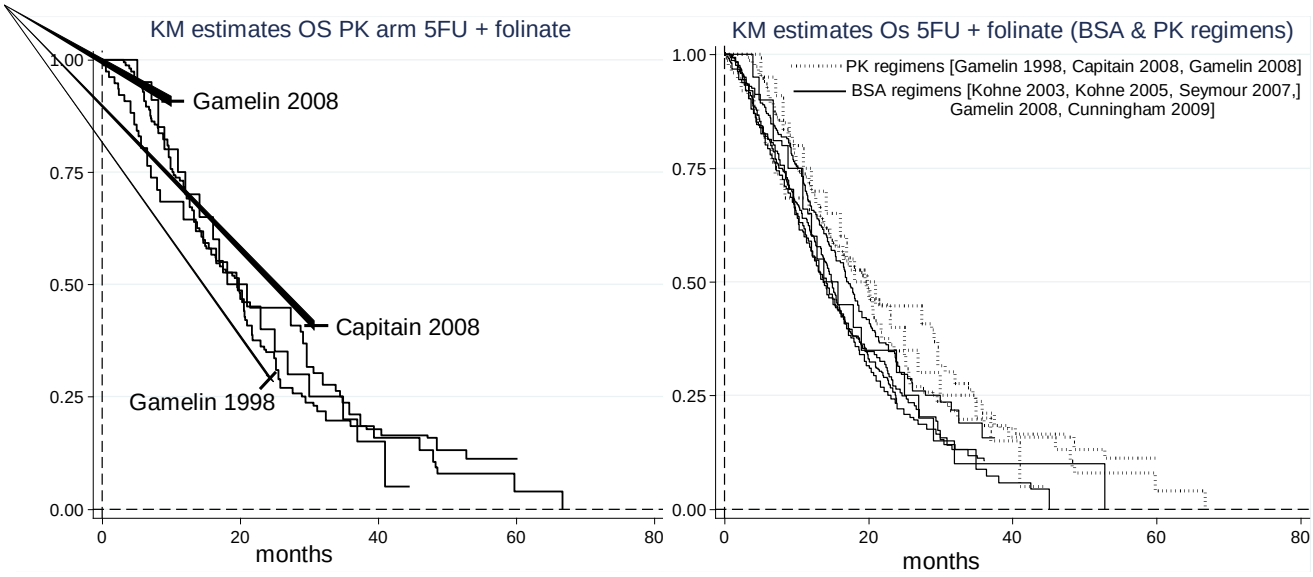

Figure 28. Reconstructed overall survival KM plots for PK regimens (left; inset BSA regimens) and for both PK and BSA regimens (right)

Baseline characteristics of the studies are summarised in Table 33.

Table 33. Baseline characteristics of studies included in the comparison of OS between BSA and PK for 5-FU + FA regimen

Item	5-FU + FA BSA ARMS					5-FU +FA PK ARMS		
	Gamelin 2008[118]	**Kohne 2003[163]**	**Kohne 2005[164]**	**Seymour 2007[165]**	**Cunningham 2009[166]**	**Gamelin 2008[118]**	**Gamelin 1998[139]**	**Capitain 2008[135]**
Number	104	164	216	710	363	104	152	76
Age (years)								
Mean	71.2	NR	NR	NR	NR	71.5	62	NR
Median	NR	62	60.5	63	62	NR	NR	71.2
Range; *(IQR)*	50-85	23-76	24-80	*(56-69)*	29-81	52 - 84	24-75	39-88
Sex								
Men (%)	62.5	62	61.1	70	61	58.7	55.3	60.5
Women (%)	37.5	38	38.9	30	39	41.3	44.7	39.5
Performance status (%)								
0	55	52	58.3	41	50	54	28.3	93.5$^{\infty}$
1	40	41	37.5	50	44	33	34.2	
2 or 3	5	7	4.2	9	6	13	37.5	6.5
Previous therapy (%)	15.4	14	22.7	NR	26	10.6	19.7	17
Metastatic sites (%)								
Liver	74*	NR	NR	76*	29*	81*	97*	58*
Lung	30*	NR	NR	34*	8*	26*	34*	5.3*
Lymph nodes	11*	NR	NR	43*	3*	19*	16*	6.5*
Others	9*	NR	NR	27*	13*	15*	13*	6.5*

(∞ status 0 or 1; * numbers exceed 100% as patients may have multiple sites)

If studies for each treatment arm are simply combined then KM plots for each treatment appear as shown in Figure 29. *It should be strongly cautioned that there are many caveats regarding the validity of this procedure including the assumptions of similar treatments and similar populations; furthermore there is a lack of adjustment for potential patient or study level confounders.* Parametric fits for these and for the individual studies are shown in Appendix 14.

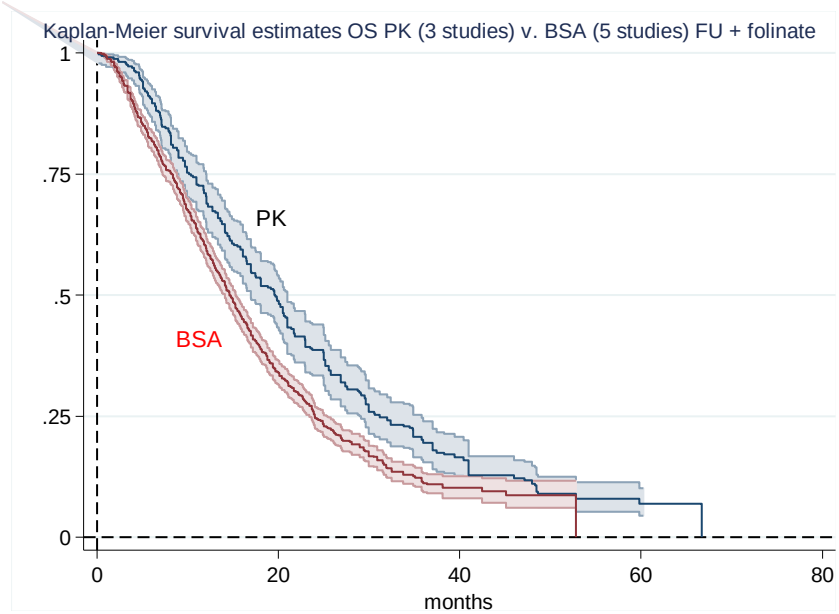

Figure 29. Kaplan Meier plots resulting from combining OS data from studies; the plots and 95% confidence intervals should be viewed with caution

5.7.3.3 5-FU + FA; progression free survival

No PFS data was available for the BSA 5-FU + FA regimen from the studies included in Objectives B and C. Three CG131 studies with usable KM plots were identified[163, 164, 166] (a further study by Giacchetti et al. (2000)[170] was excluded because the 5 day chrono-modulated continuous infusion employed was judged too dissimilar to the relevant regimen).

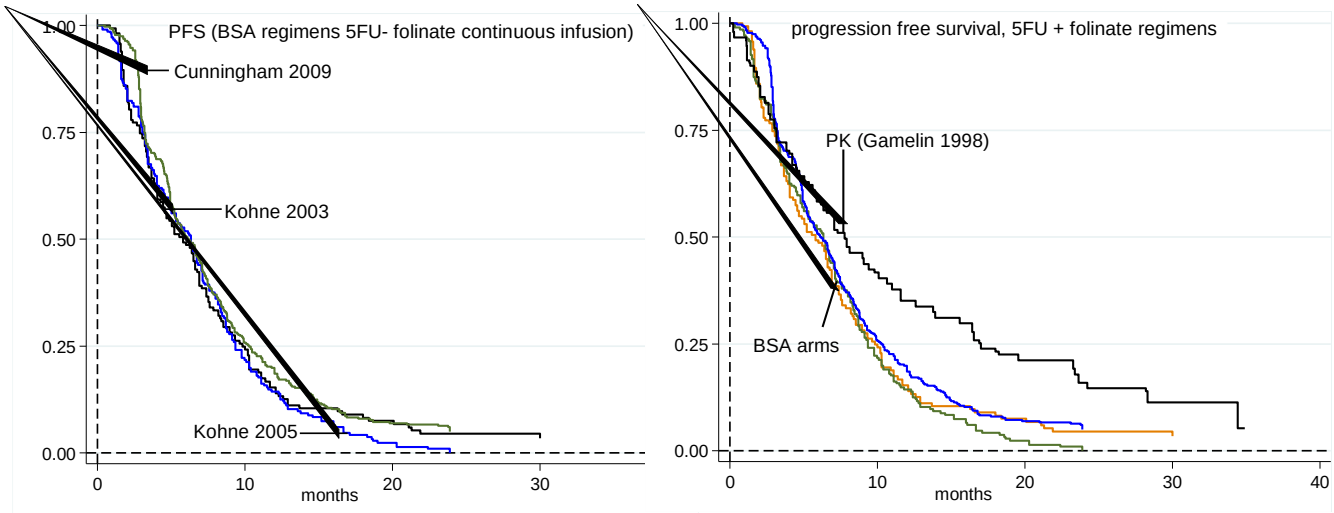

Figure 30. PFS Kaplan Meier plots for three BSA-based FUFO studies (left) compared with that for one PK- based study (right)

Figure 30 (left) shows the reconstructed KM plots for these studies. The plots are similar and generate medians that are very close to those in the published articles. Only one study, (Gamelin, et al., 1998)[139] from Objectives B and C provided evidence about PFS of advanced CRC patients treated

with a 5-FU + FA PK regimen. When plotted with the CG131 studies there is an apparent gain in PFS from the PK regimen. *However caution should be exercised as it should be born in mind that this evidence comes from single arms of independent studies.* Table 34 summarises the baseline characteristics of the populations from these studies.

Table 34. Baseline characteristics of studies included in the comparison of PFS between BSA and PK for 5-FU + FA regimen

Item	**5-FU + FA BSA ARMS**			**5-FU + FA PK ARMS**
	Kohne 2003[163]	**Kohne 2005[164]**	**Cunningham 2009[166]**	**Gamelin 1998[139]**
Number	164	216	363	152
Age (years)				
Mean	NR	NR	NR	62
Median	62	60.5	62	NR
Range	23-76	24-80	29-81	24-75
Sex				
Men (%)	62	61.1	61	55.3
Women (%)	38	38.9	39	44.7
Performance				
0	52	58.3	50	28.3
1	41	37.5	44	34.2
2	7	4.2	6	35.5
3	0	0	0	2
Previous therapy (%)	14	22.7	26	19.7
Metastatic sites (%)				
Liver	NR	NR	29*	97*
Lung	NR	NR	8*	34*
Lymph nodes	NR	NR	3*	16*
Others	NR	NR	13*	13*
Number of metastatic sites (% of patients)				
1	59	40.7	44	72.4
2	28	37.0	56 (≥2)	20.4
≥3	9 Unknown: 5	22.3		7.2
Number of metastases (n)				
1	NR	NR	NR	14
2 or 3	NR	NR	NR	22
>3 to 10	NR	NR	NR	54
>10	NR	NR	NR	61

(* totals exceed 100% as patients may have multiple sites)

5.7.3.4 5-FU + FA regimens; difference between OS and PFS under BSA and PK regimens

Figure 31 summarises the apparent difference between OS and PFS under BSA-based and PK-based 5-FU + FA regimens based on the evidence described above.

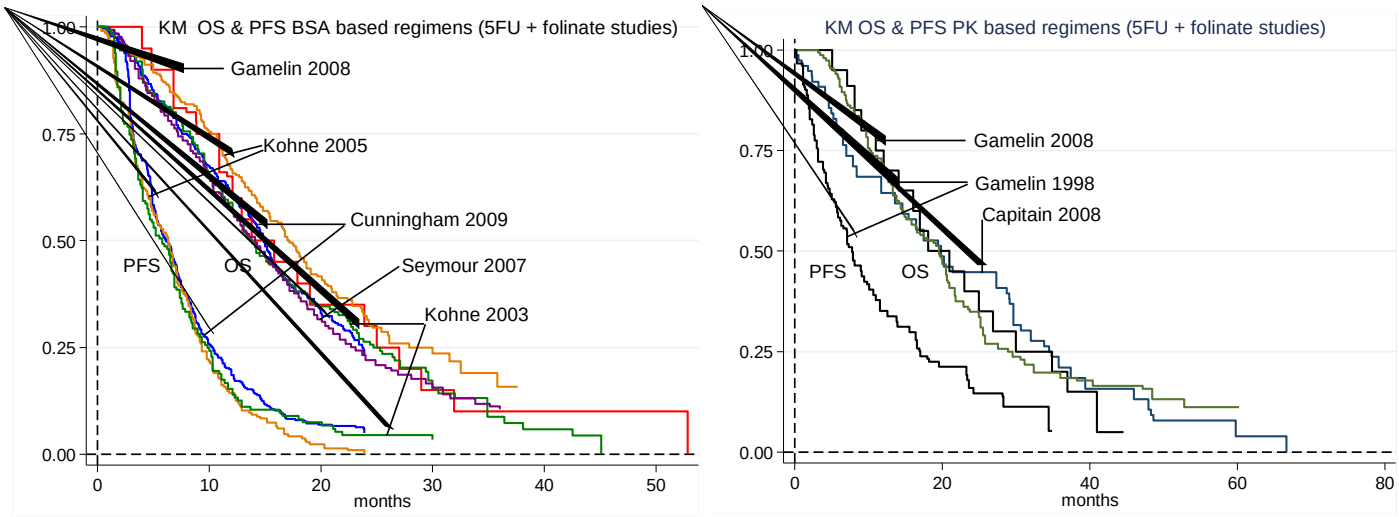

Figure 31. KM plots illustrating the difference between overall survival and progression free survival for FUFO regimens based on BSA dosage and PK-adjusted dosage.

5.7.3.5 FOLFOX6 regimens; comparison of BSA and PK arms overall survival

Four CG131 studies with usable KM plots were identified in which patients with metastatic advanced CRC received a BSA-based FOLFOX6 regimen;[165, 167-169] in addition our clinical advisors pointed to the existence of the UK COIN trial.[34] Reconstructed KM plots for these five studies are shown in Figure 32. The two UK studies (Seymour et al., 2007[165] and COIN 2011[34]) provide very similar OS that is somewhat less than the other three European studies. Also shown is the reconstructed KM plot for the PK arm of the comparative study of Capitain et al. (2012).[119] Unfortunately Capitain et al. (2012)[119] only provided the median overall survival for the BSA arm (22 months). This corresponds closely to the median for the three non UK BSA arms.

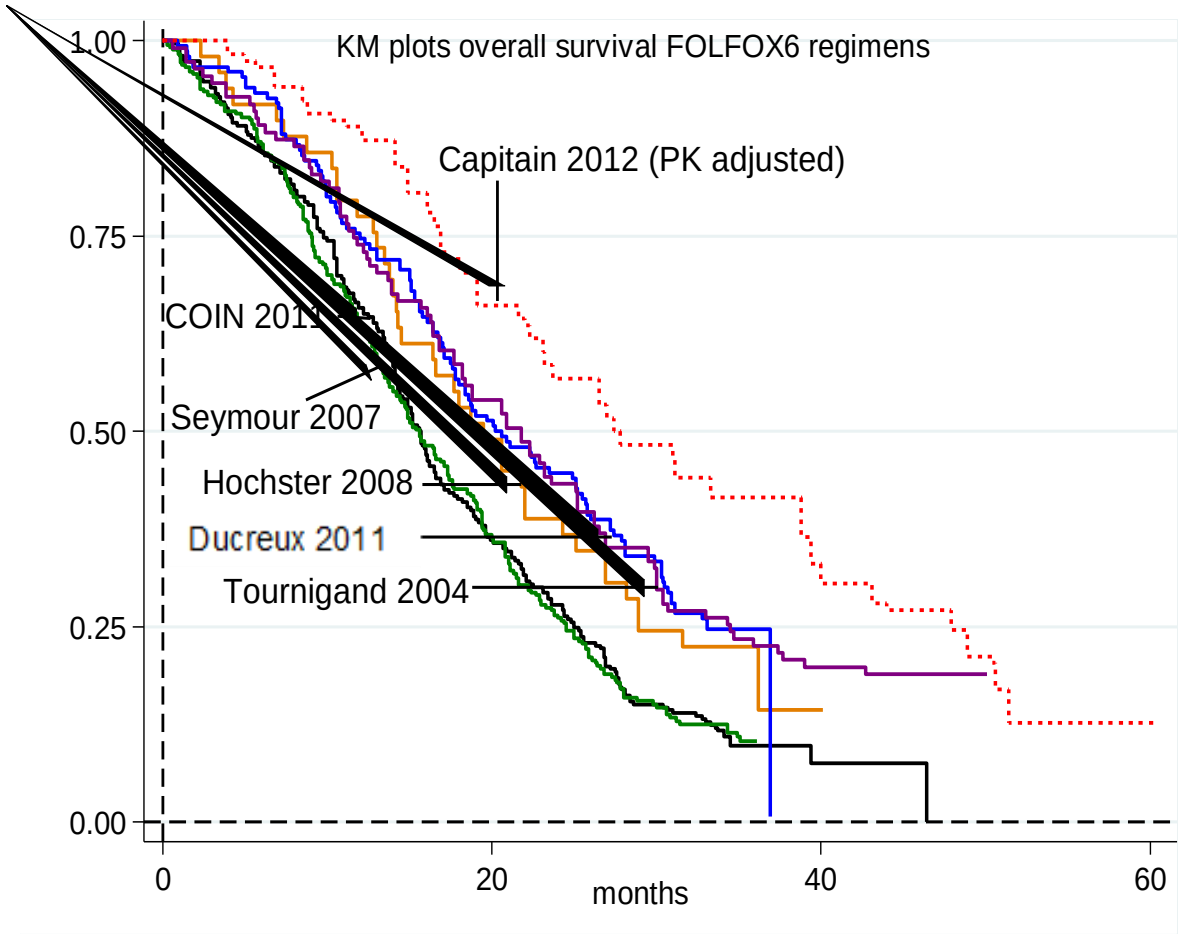

Figure 32. Reconstructed KM plots of overall survival comparing PK and BSA regimens

The difference between the PK and BSA plots implies an OS advantage from PK adjustment of dosage. *It should be emphasised however that the plots are for single arms from different studies and do not represent a randomised comparison*; baseline characteristics for these studies are summarised in Table 35.

Table 35. Baseline characteristics of studies included in the comparison of OS between BSA and PK for FOLFOX6 regimen

Item	BSA arms FOLFOX6						PK arm FOLFOX6
	Capitain 2012 [119]	**Seymour 2007[165]**	**COIN 2011[34]**	**Hochster 2008[167]**	**Ducreux 2011[168]**	**Tournigand 2004[169]**	**Capitain 2012[119]**
Number	39	357	266	49	150	111	118
Age (years)							
Mean (SD)	NR	NR	NR	NR	NR	NR	NR
Median	63	64	63	62	64	65	65
Range *(IQR)*	32-80	(56-69)	(57-69)	35-79	42-84	40-75	35 - 81
Sex							
Men (%)	62	69	64	57	60	72	59
Women (%)	38	31	36	43	40	28	41
Performance status (%)							
0 or 1	77	41	NR	100	93	94	78
2 or 3	23	58	8	0	7	6	22
Previous therapy (%)	NR	26	NR	unclear	19	21	NR
Metastatic sites (%)							
Liver	60*	79*	77*	76*	NR	80*	56*
Lung	10*	39*	43*	47*	NR	30*	16*
Peritoneal or nodes	4.9*	49*	56*	55*	NR	50*	5.0*

(*other or mulitple sites involved therefore does not add up to 100%)

5.7.3.6 FOLFOX6 regimens; progression free survival

Other than a reported median survival (10 months) without confidence intervals no PFS data was available for the BSA FOLFOX6 regimen from the studies included in sections B and C. Two CG131 studies with usable KM plots were identified;[168, 169] in addition the COIN trial[34] was indicated to us by clinical experts. Figure 33 shows the reconstructed KM estimates for these three trials and for the only available PFS data for FOLFOX6 with the PK-adjusted dosage (Capitain et al., 2012).[119] The median of 10 months for the BSA arm in Capitain et al. (2012)[119] is slightly greater than that for the three BSA plots (which were 9.3, 8.9 and 8.1 months in the reconstructed plots for Ducreux 2011, COIN 2011 and Tournigand 2004, respectively)

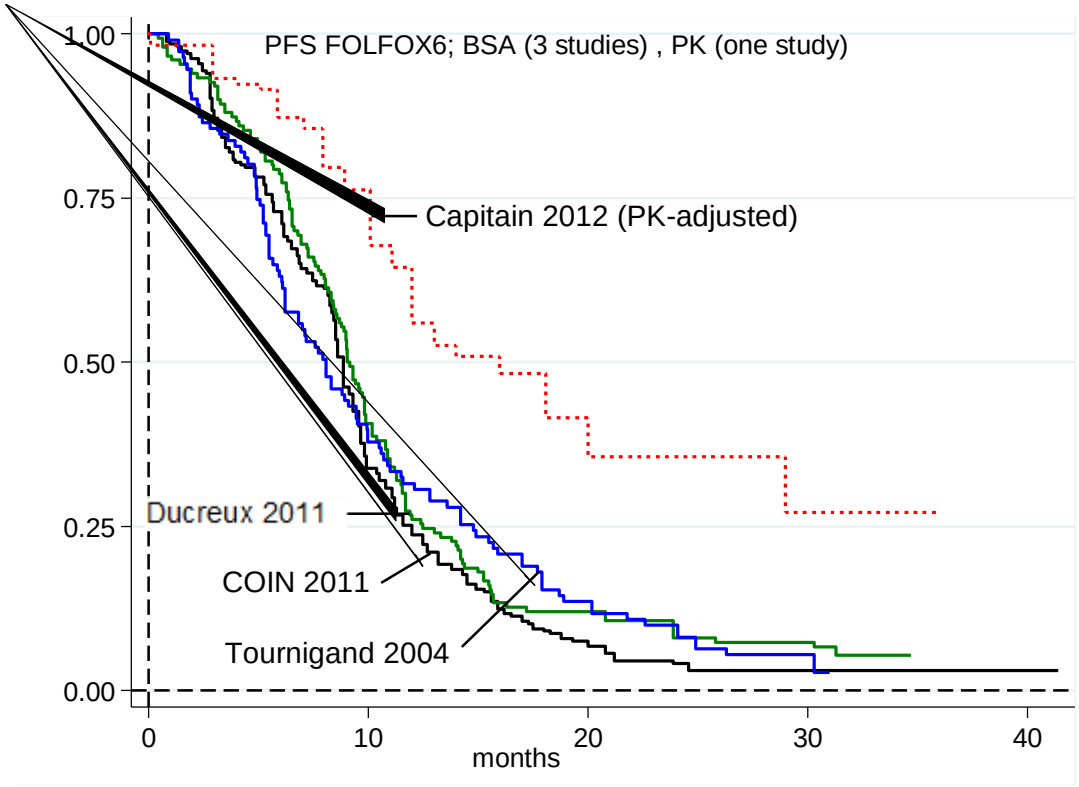

Figure 33. PFS Kaplan Meier plots for three BSA-based FOLFOX6 studies compared with that for one PK-adjusted study

The difference between the PK and BSA plots implies a PFS advantage from PK adjustment of dosage. *It should be noted that the plots are for single arms from different studies and do not represent a randomised comparison and that the PK evidence comes from a single study.* Demographic characteristics of the studies are summarised in Table 36.

Table 36. Baseline characteristics of studies included in the comparison of PFS between BSA and PK for FOLFOX6 regimen

Item	**BSA arms**			**PK arm**
	COIN 2011[34]	**Ducreux 2011**[168]	**Tournigand 2004**[169]	**Capitain 2012**[119]
Number	266	150	111	118
Age (years) Mean (SD) Median Range	 NR 63 57-69 (IQR)	 NR 64 42-84	 NR 65 40-75	 NR 65 35 - 81
Sex Men (%) Women (%)	 64 36	 60 40	 72 28	 59 41
Performance 0 or 1 2 or 3	 NR 8	 93 7	 94 6	 78 22
Previous	NR	19	21	NR

therapy (%)				
Metastatic sites (%) Liver Lung Peritoneal or nodes	 77* 43* 56*	 NR NR NR	 80* 30* 50*	 56* 16* 5.0

(*other or mulitple sites involved therefore does not add up to 100%)

5.7.3.7 FOLFOX6 regimens; difference between OS and PFS under BSA and PK regimens

Figure 34 summarises the apparent difference between OS and PFS under BSA-based and PK-based FOLFOX6 regimens based on the evidence described above. *The evidence for the PK-adjusted regimen comes from a single comparative study which did not provide Kaplan Meier plots for the comparator BSA arm.*

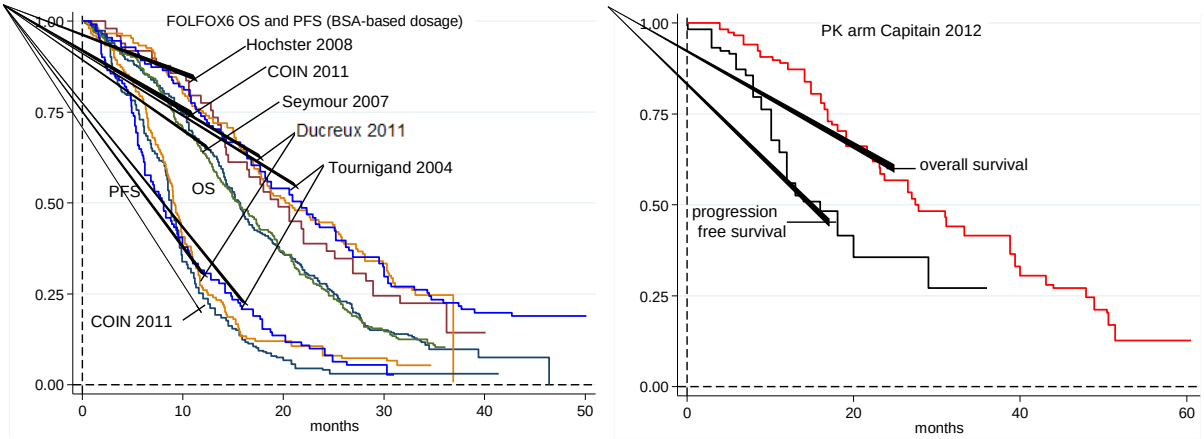

Figure 34. KM plots illustrating the difference between overall survival and progression free survival for FOLFOX6 regimens based on BSA dosage)left) and PK-adjusted dosage (right).

5.7.3.8 Adverse events / toxicity

The authors of the NICE Clinical Guideline for CRC (CG131, November 2011)[7] commented that "mixed treatment methods were not applied to toxicity data as there was insufficient evidence to inform the analysis". For the de novo economic model in CG131 (comparing different treatment strategies) the risk associated with only three potential toxicities were estimated, febrile neutropenia, grade 3/4 diarrhoea and grade 3/4 hand and foot syndrome. They were selected on the basis of data availability and their likely impact upon quality of life. CG131 did not report any toxicity data for a first line 5-FU + FA regimen. Data for first line FOLFOX regimens, taken from the appropriate arms of various studies, was presented and is summarised in Table 37 where data from the Capitain et al. (2012)[119] comparative study is added for comparison.

Table 37. Capitain et al. (2012)[119] and NICE guidance CG 131 toxicities; comparison of the risk of serious toxicity

Item	Capitain 2012[§]	CG 131[§§]	Capitain 2012[§]
Treatment	BSA; N=39	BSA; Multiple studies	PK; N=118
Adverse event			
Diarrhoea Grade III/IV	12 (4.3-24.2)	15.7 (10.7)	1.7 (0.53-5.99)
Hand and foot syndrome Grade III/IV	NR	2.4 (2.7)	NR
Neutropenia[§§§]	25 (13-39)	6.2 (5.6)	12.07 (19.5-25.91)

§ *Published percentages were converted to nearest whole number of patients and point estimates with 95% confidence intervals then derived.* §§ *CG 131 data are means and standard deviation*. §§§ *CG131 referred to "febrile neutropenia" while Capitain referred to "Grade III/IV neutropenia".* NR = not reported

The risk of diarrhoea in the Capitain et al. (2012)[119] BSA arm appeared similar to that estimated by authors of CG131. It should be appreciated that CG131 included FOLFOX4 as well as FOLFOX6 arms in their analysis. The difference between CG131 and Capitain et al. (2012)[119] in the risk of neutropenia may be due to different definitions. The risk of hand and foot syndrome appears to be low, but was not reported by Capitain et al. (2012).[119]

5.8 Conclusions from evidence for Objective D and overview of PK versus BSA

Rigorous assessment of the consistency of the PK comparative study results with the generality of the published literature was hampered by the existence of only a single randomised comparative study, the paucity of comparative studies (n=3 for CRC), their incomplete reporting of important outcomes, the use of an unrepresentative and now obsolete treatment regimen in the randomised CRC study, and the failure by authors to release requested IPD.

Guyot's procedure for constructing an estimate of IPD from published Kaplan-Meier plots provided a platform for comparing survival outcomes and for exploring parametric models. This procedure is best served by existence of good quality published KM plots, risk table information at multiple time points of the plots, and information about the total number of events. In nearly all the survival analyses undertaken for this section most of this information was absent, hence although the reconstructed plots provide a substantially accurate representation of the published plots, the reconstructed IPD could not provide a true representation of censoring times so that parametric fits based on this data should be viewed with some caution.

The results for the BSA arms in Gamelin et al. (2008)[118] (overall survival) and in Capitain et al. (2012)[119] (median values only for overall survival and progression free survival) were compared with BSA arms in studies included in the NICE CG 131 systematic review of CRC. These were

sufficiently similar to conclude that the comparison between PK and BSA regimens presented in the two CRC comparative studies was not biased by non-representative results for the BSA arms.

Nevertheless it is important to appreciate that the comparison (PK versus BSA) for survival outcomes is greatly weakened by the paucity of evidence for the PK arms. In the case of FOLFOX6 the PK evidence comes from a single non-randomised study which failed to provide full data for the comparator arm, and in the case of 5-FU + FA the PK evidence for PFS was provided by a lone single arm study in which no comparator data were presented. Thus, for objective D, an assessment of the effectiveness of PK for these outcomes relies on the dubious procedure of comparing various arms from different studies using "derived" data.

There were similar difficulties in relating published toxicity data to PK comparative study estimates of the risk of 5-FU induced toxicities. These stemmed from paucity of data, differing and selective reporting of toxicity outcomes, and the problems encountered by CG131 authors in synthesising toxicity data from published studies. It is difficult to draw firm conclusions, however with regards to serious diarrhoea both Gamelin et al. (2008)[118] and Capitain et al. (2012)[119] provide evidence supporting a beneficial effect of PK dose adjustment, and for Capitain et al. (2012)[119] at least the risk reported for the BSA arm does not appear to be sufficiently out of line with data from CG131 so as to have biased the non-randomised comparison. On the other hand, although risk of hand and foot syndrome appears low, it may be increased with a PK based regimen.

5.9 Clinical effectiveness results informing the cost-effectiveness model

The clinical effectiveness review provided a range of reported and reconstructed estimates for the survival outcomes for BSA versus PK treatment in metastatic colorectal cancer, and limited data on adverse events from two CRC comparative studies and one H&N RCT which informed the cost-effectiveness analysis of PK 5-FU dosing compared to BSA dosing strategies. These are presented in Table 38 to Table 41. Table 38 and Table 39 give an overview of the reported median of overall or progression free survival (if reported) and the median of the reconstructed KM plots, which were used in the modelling section. Please see Table 45 and Table 46 in 6.2.4 for the combination of these studies in the different base case and scenario analyses undertaken.

Table 38. List of studies from clinical effectiveness review and CG131 that inform the cost-effectiveness analysis of PK dosing of 5-FU in terms of survival outcomes using the 5-FU + FA regimen

Study	BSA – median OS (in months)		BSA – median PFS (in months)		PK – median OS (in months)		PK – median PFS (in months)		Concerns of quality / generalizability
	Reported	Reconstructed	Reported	Reconstructed	Reported	Reconstructed	Reported	Reconstructed	
Gamelin et al. (2008)[118]	16	16	Mean response rate x time till progression	7.2	22	18.1	Mean response rate x time till progression	11.5	Obsolete 5-FU + FA 8h regimen RCT but arms perfectly balanced (BSA N=104, PK N=104) Randomisation and allocation concealment methods not described No PFS reported
Gamelin et al. (1998)[139]	NR	NA	NR	NA	19	19.6	11	7.8	Obsolete 5-FU + FA 8h regimen Case series No ITT analysis Error in reported PFS as not corresponding with the published KM plot
Pooled 3 BSA studies[163, 164, 166]	NA	NA	NA	6.2	NA	NA	NA	NA	RCTs quality assessed see CG131
Pooled 3 PK studies[118, 135, 139]	NA	NA	NA	NA	NA	19.6	NA	NA	In addition to concerns above: Capitain et al. (2008) 2 different non-UK regimens Different infusion times to Gamelin (1998) and Gamelin (2008) Case series Outcomes not reported separately for two different regimens
Pooled 5 BSA studies[118, 163-166]	NA	14.6	NA	NA	NA	NA	NA	NA	RCTs quality assessed see CG131

Table 39. List of studies from the clinical effectiveness review, CG131 and COIN (2011) that inform the cost-effectiveness analysis of PK dosing of 5-FU in terms of survival outcomes using the FOLFOX6 regimen

Study	BSA – median OS (in months)		BSA – median PFS (in months)		PK – median OS (in months)		PK – median PFS (in months)		Concerns of quality / generalisability
	Reported	Reconstructed	Reported	Reconstructed	Reported	Reconstructed	Reported	Reconstructed	
Capitain et al. (2012)[119]	22	Inferred from reported median assuming proportional hazard	10	Inferred from reported median assuming proportional hazard	28	27.4	16	16	Selection method unclear No randomisation Historic control Only median OS and PFS reported for BSA arm Commercial adjustment protocol (likely considered more than pure 5-FU levels)
Pooled 5 BSA studies[34, 165, 167, 168, 169]	NA	17	NA	NA	NA	NA	NA	NA	RCTs quality assessed see CG131 Adams et al. (2011)[34] is an MRC trial with unclear risk of bias (formal quality appraisal available from authors on request)
Pooled 3 BSA studies[34, 168, 169]	NA	NA	NA	8.9	NA	NA	NA	NA	RCTs quality assessed see CG131
Ducreux et al. (2011)[168]	20.5	20.2	9.3	9.0	NA	NA	NA	NA	RCTs quality assessed see CG131
Tournigand et al. (2004)[169]	20.6	21.8	8.0	8.1	NA	NA	NA	NA	RCTs quality assessed see CG131
Non-UK pooled 3 BSA OS[167-169] or 2 BSA PFS[168, 169] studies	NA	20.6	NA	8.98	NA	NA	NA	NA	RCTs quality assessed see CG131 Non-UK trials and UK trials differ in OS, applicability to UK is therefore questioned, Comparative studies are non-UK studies

Table 40. List of studies from clinical effectiveness review that inform the cost-effectiveness analysis of PK dosing of 5-FU in terms of adverse events

Studies		Diarrhoea Grade III/IV N (%, CI)	Nausea/ vomiting N (%)	Hand & Foot Grade III/IV N (%)	Mucositis Grade III/IV N (%)	Neutropenia N (%)	Leukopenia Grade III/IV N (%)	Thrombocytopenia N (%)	Concerns of quality / generalisability
Capitain et al. (2012)[119]	BSA (N=39)	5 (12%, 4.3-24.2)	NR	NR	6 (15%, 5.86-27.43)	10 (25%, 13-39)	NR	4 (10%, 2.87-20.87)	As above in Table 39 Hand & Foot not reported Grade III and IV toxicities only and grouped together
	PK (N=118)	2 (1.7%, 0.53-5.99)	NR	NR	1 (0.8%, 0.02-3.08)	18 (12.07%, 19.5-25.91)	NR	14 (12%, 7.29-19.10)	
Gamelin et al. (2008)[118]	BSA (N=96)	III 14 (14.6%, 8.2-23.3) IV 3 (3.1%, 0.6-8.9)	NR	III 6 (6.3% (2.3-13.1)) IV 0	III 1 (1.0%, 0-5.7) IV 2 (2.1%, 0.3-7.3)	NR	III 1 (1%, 0-5.7) IV1 (1%, 0-5.7)	NR	As above in Table 38
	PK (N=90)	III 4 (4.4%, 1.2-11) IV 0	NR	III 10 (11.1%, 5.5-19.5) IV 1 (1.1%, 0-6.0)	III 1 (1.1%, 0-6.0) IV 2 (2.2%, 0.3-7.8)	NR	III 0 (0%, 0-4.0) IV 0 (0%, 0-4.0)	NR	

Table 41. H&N study informing the cost-effectiveness analysis of PK dosing of 5-FU in terms of adverse events

Study		Digestive toxicity Grade III/IV % of cycles	Mucositis Grade III/IV % of cycles	Neutropenia / Thrombocytopenia % of cycles	Concerns of quality / generalisability
Fety et al. (1998)[157]	BSA (N=61)	17.8	5.1	5.2	Toxicity reported by cycles rather than risk 16 patients (13%) were found to be "unevaluable" for toxicity patients with protocol violations were removed
	PK (N=61)	7.6	0.0	8.1	

6 COST-EFFECTIVENESS AND HEALTH ECONOMICS

6.1 Methods

6.1.1 Search strategy

A comprehensive search of the literature for published economic evaluations, utility studies and cost studies was performed. Several search strategies were required. Searches were undertaken in March and April 2014. Additional searches were undertaken to identify other relevant information to support the development of the economic model (e.g. past NICE assessments in mCRC).

6.1.1.1 Cost search 1: Cost effectiveness of PK dosing and 5-FU

The search strategy developed for objectives A, B and C of the clinical effectiveness review (for methods, see Section 4.1.1 and Appendix 2) was also used to identify any published cost-effectiveness studies. This was considered appropriate because no study type filters were applied. Full copies of all studies deemed potentially relevant by clinical effectiveness reviewers were obtained and assessed by a health economist for inclusion.

6.1.1.2 Cost search 2: Adverse events associated with chemotherapy (all cancers): Quality of life

A series of search strategies was devised to update and expand the literature review of Shabaruddin et al. (2013).[171] The search strategies were developed iteratively and are provided in Appendix 1. Searches were undertaken in Medline and Embase. All records were screened for inclusion by an information specialist and checked by a health economist. Full copies of all studies deemed potentially relevant were obtained and assessed by a health economist for inclusion.

6.1.1.3 Cost search 3: Adverse events associated with chemotherapy (all cancers): Resource use

A scoping search was undertaken to look for existing reviews. Some reviews of interest were identified, but no relevant overarching review was found. Therefore, a search strategy was developed based on the strategies used for Cost search 2. The search strategies were developed iteratively and are provided in Appendix 1. Searches were undertaken in Medline. All records were screened for inclusion by an information specialist and checked by a health economist. Full copies of all studies deemed potentially relevant were obtained and assessed by a health economist for inclusion.

6.1.1.4 Cost search 4: mCRC/H&N cancer: Quality of life and Cost search 5: mCRC/H&N cancer: Resource use

Searches 4 and 5 were developed iteratively, with reference to the search strategies of several published systematic reviews.[172-176] Searches for resource use were limited to English, Humans and the UK perspective (by the addition of several currency and location terms). No date limits were

applied. Searches were undertaken in Medline (See Appendix 1). All records were screened for inclusion by an information specialist and checked by a health economist. Full copies of all studies deemed potentially relevant were obtained and assessed by a health economist for inclusion.

6.1.2 Inclusion criteria for studies to address Objective E

All study designs will be considered for inclusion. Studies will be included that provide information on the following:

- Cost of My5-FU testing
- Cost of delivering 5-FU by infusion
- Cost of side effects and 5-FU toxicity and their associated treatment or hospitalisation costs
- Additional costs associated with changes to continuous infusion protocols

As no full text economic evaluation studies were identified, no studies were assessed using the CHEERS checklist.[177]

6.1.3 Evaluation of costs, quality of life and cost-effectiveness

6.1.3.1 Model structure

Where data allows, the preferred approach will be to model the impact of pharmacokinetic dose adjustment using My5-FU assay compared to BSA dosing, using the clinical outcomes specified in the above and with a lifetime horizon. In the absence of such evidence a linked evidence approach will be adopted, linking My5-FU dose adjustment to other pharmacokinetic dose adjustment studies within the literature. It may assume equivalence between the My5-FU assay and other pharmacokinetic measures of plasma 5-FU (i.e., HPLC and LC-MS) if this appears a reasonable assumption in the light of the clinical review. Model inputs may utilise indirect treatment comparison results or network meta-analysis results to derive estimates of the clinical outcomes for the chemotherapy regimens relevant to current UK clinical practice. It is anticipated that this will be possible for metastatic colorectal cancer, as outlined in more detail in section 5.2.

While it is desirable to try to link evidence through to final survival outcomes, it should be recognised that due to data limitations this may be impossible for some cancers. Where this applies, the assessment will still endeavour to estimate the impact of My5-FU dose adjustment upon test costs, treatment costs, side effect costs and the quality of life impacts of side effects. This truncated analysis will be augmented by threshold analyses that estimate what, if any, additional impacts My5-FU would be required to have upon progression free survival and/or overall survival for it to be cost-effective at conventional NICE willingness to pay thresholds. The estimates of the additional survival will be reported in terms of the absolute additional time required, with this being compared with estimates of

the relevant current mean survival. It will also be reported in the same metric as that used for the estimate of the impact of pharmacokinetic dose adjustment upon overall survival in the mCRC modelling, in order to facilitate a comparison across clinical areas; e.g., as a relative risk or as a hazard ratio.

Necessary choices and definitions regarding the structure of the model will depend on the findings from the literature review and consultation with clinical experts.

6.1.3.2 Issues relevant to analyses

During scoping no end-to-end studies of the My5-FU assay were identified. Evidence was found relating to: the validation of the My5-FU assay with LC-MS, the impact of 5-FU plasma levels on toxicity, pharmacokinetic variability of 5-FU when BSA dosing is used, and the impact of pharmacokinetic dose adjustment of 5-FU on survival. Studies comparing pharmacokinetic dosing with BSA dosing in mCRC were found that reported average 5-FU weekly doses, adverse event rates, progression free survival and overall survival with varying degrees of completeness (Capitain et al., 2012;[119] Gamelin et al., 2008).[118] These, together with other papers that may be identified during the literature searches, may provide sufficient information to enable estimation of the various clinical outcomes for mCRC. The papers' authors will also be approached for the information about the outcomes that were ambiguously, partially or not reported for one or both arms.

Where clinical outcome estimates can be arrived at for My5-FU informed dose adjustment and BSA dosing, these will be the preferred basis of the modelling. The main model structure will be developed to favour these elements over those that may be drawn from a linked evidence approach or from expert opinion. This does not preclude more speculative model structures also being developed.

One way sensitivity analyses will be performed for all key parameters, and for parameters in the models which are based on expert opinion or lie within any more speculative linked evidence modelling. The appropriate model structure may also be subject to some uncertainty. Probabilistic modelling will be performed using parameter distributions instead of fixed values. It may be necessary to perform a number of probabilistic modelling exercises, given the uncertainty around parameter estimates that are based upon expert opinion and the uncertainty around the most appropriate model structure.

Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves or frontiers.

Longer term costs and consequences will be discounted using the UK discount rates of 3.5% for both costs and effects.

6.1.3.3 Health outcomes

Utility values, based on literature or other sources, will be incorporated in the economic model. QALYs will be calculated from the economic modelling.

6.1.3.4 Costs

Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit [PSSRU], British National Formulary [BNF]), discussions with individual hospitals and with the manufacturer.

Costs for consideration will include:

- Cost of My5-FU testing
- Cost of delivering 5-FU by infusion
- Cost of side effects and 5-FU toxicity and their associated treatment or hospitalisation costs
- Additional costs associated with changes to continuous infusion protocols

Other costs for consideration may include:

- Cost of 2nd line therapies
- Palliative care and end of life costs

6.1.3.5 Cost and resource use

Resource use will be estimated in line with the DAP programme manual:

- The perspective will be that of the NHS and PSS
- The cost of the My5-FU assay will be requested from the manufacturer on the basis of this being nationally and publicly available, with additional confirmation of this sought from a UK laboratory currently using My5-FU
- The base case will use list prices for the chemotherapy regimens, but as in the modelling for CG131 the impact of discounted prices available to the NHS may also be explored
- The above two bullets may be augmented with advice from the UK NHS centre currently using the My5-FU assay and possibly bodies such as the NHS Purchasing and Supply Agency (PASA)
- The effect of My5-FU upon resource use in terms of physical units will be presented separately and then coupled with unit costs

6.2 Results

6.2.1 Search results for Objectives E

Figure 35 provides the PRISMA flow diagram for Objectives E. A total of 4,578 records were identified through electronic searches. 12 additional records were identified from other sources. The removal of duplicates left 3,614 records to be screened, of which 3,514 were excluded at title/abstract level as these were irrelevant. The remaining 100 records were examined for full-text, of which 54 were included in the cost-effectiveness review.

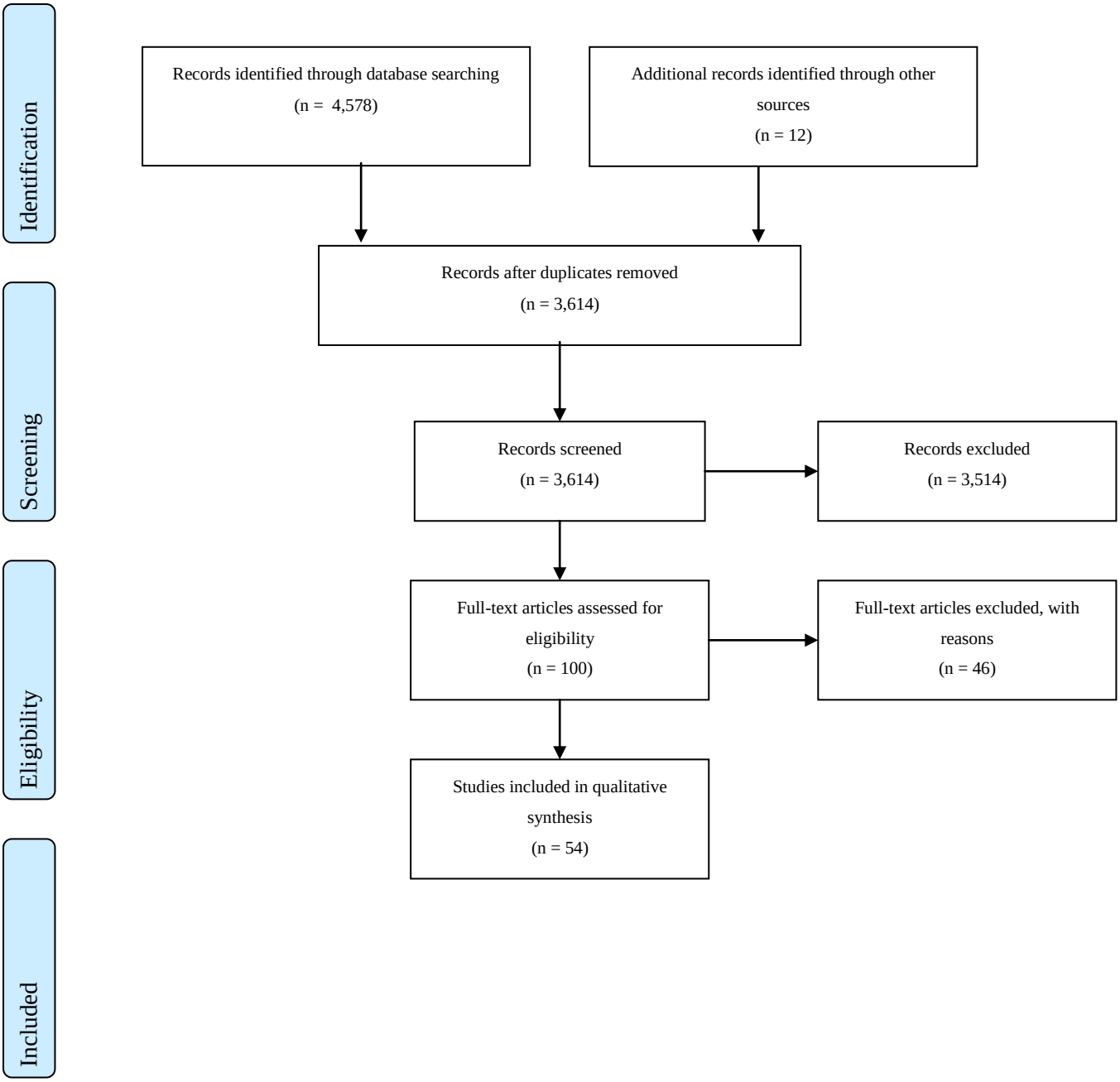

Figure 35. PRISMA Flow Diagram: My5-FU cost effectiveness objective E

6.2.2 Economics of My5-FU dose adjustment

Within the literature review costs are given as stated in the literature, then uprated for inflation using the Hospital and Community Health Services Pay and Prices Index to 2012/13 prices which are

reported in square brackets; e.g. £37. Where costs were reported in foreign currency these are first converted at the then prevailing April exchange rate, and then uprated for inflation using the Hospital and Community Health Services Pay and Prices Index to 2012/13 prices. Where no year is given for prices it is assumed to be the year of publication.

6.2.2.1 Literature review: Economics

The literature review first reviews the only cost effectiveness study of My5-FU for PK dose adjustment. A number of further literature reviews are undertaken and presented in full in the following appendices:

- Appendix 15: previous NICE assessments in mCRC
- Appendix 16: quality of life values for mCRC
- Appendix 17: UK resource use values for mCRC
- Appendix 18: previous NICE assessments in head and neck cancer
- Appendix 19: quality of life values for head and neck cancer
- Appendix 20: UK resource use values for head and neck cancer
- Appendix 21: UK resource use for adverse events
- Appendix 22: adverse events quality of life impacts

These are briefly summarised in what follows. Their contributions to the assumptions and parameter values for this assessment are highlighted but not reviewed in detail within the main body of the report.

6.2.2.2 Cost effectiveness studies of pharmacokinetic 5-FU dosing in mCRC

Becker et al.[1] (2013)[178] in an ISPOR poster presentation summarise the results of a cost utility modelling exercise that compared My5-FU dose adjustment with BSA dosing among patients with mCRC. This adopted a lifetime horizon, and discounted costs and benefits at 3.0%. A range of chemotherapy regimens were analysed, with My5-FU dose adjustment being compared with BSA dosing for:

- 5-FU + folinic acid
- FOLFOX4
- FOLFOX6
- FOLFIRI
- FOLFOX6 + bevacizumab

[1] Funded by Saladax

- FOLFIRI + bevacizumab

The detail of the modelling as presented below is drawn from personal communication and an electronic copy of the model (*R Becker: 2013*).

[redacted]

[redacted]

[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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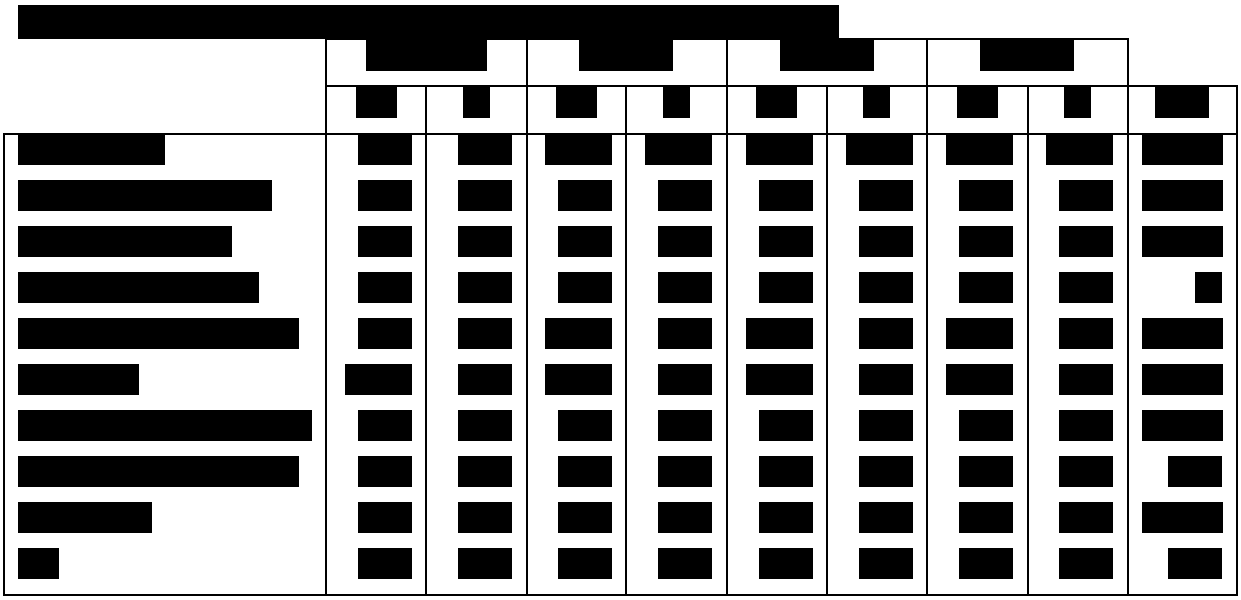

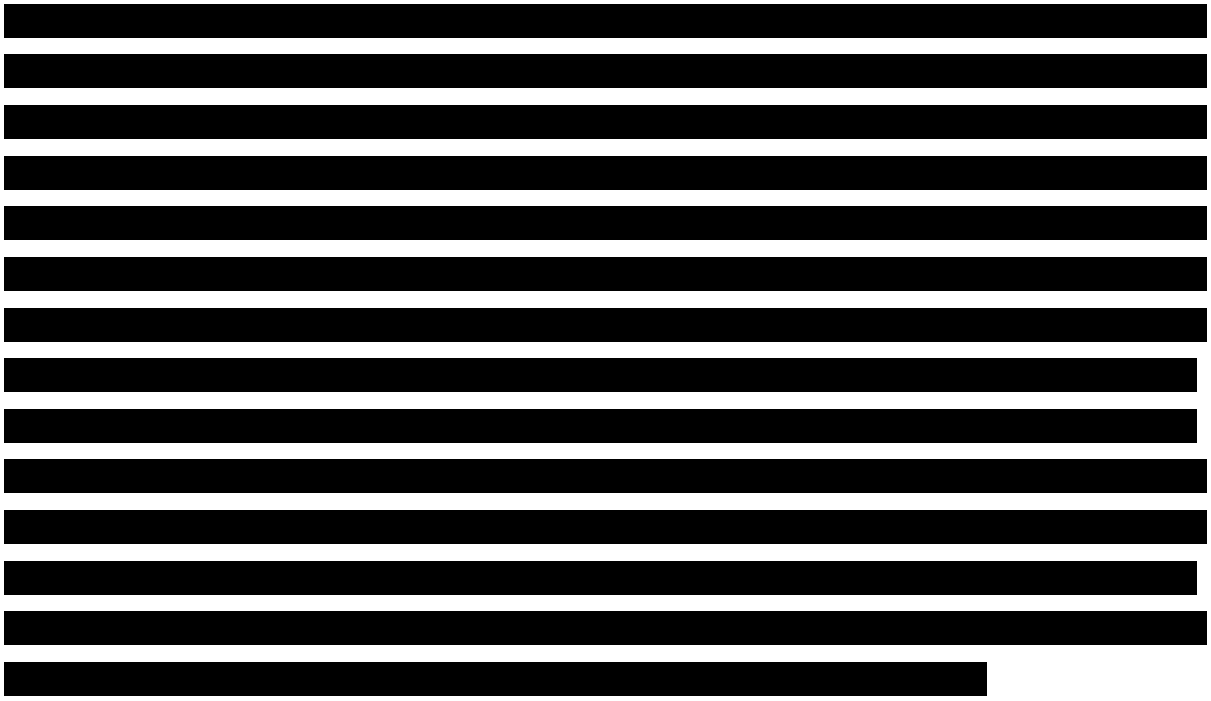

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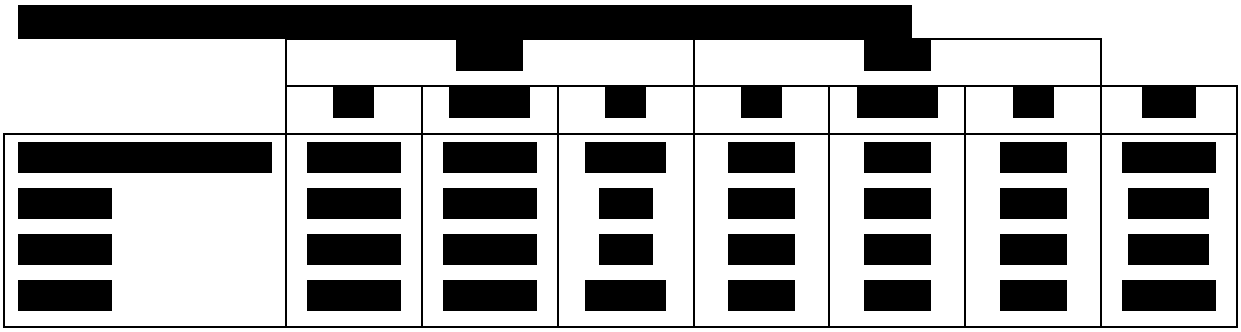

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6.2.3 Previous NICE assessments in mCRC

There have been seven NICE assessments in mCRC: four MTAs (TA61,[181] TA93,[30] TA118[179] and TA242[180]), two STAs (TA176[182] and TA212[183]) and a clinical guideline (CG131).[7] Their methods and data sources are outlined in greater detail in Appendix 15. This can be further summarised, alongside further expert opinion and what it implies for the current assessment, as follows.

6.2.3.1 Chemotherapy administration costs in previous NICE mCRC assessments

For the chemotherapy administration costs the majority of assessments adopted a disaggregate approach, separately costing individual elements such as line insertion, pharmacy preparation, administration and line flushing. The most comprehensive source appears to be the costing of TA93,[30] with these also being used for TA212.[183] CG131 is a slight outlier in terms of only applying the NHS reference cost for the delivery of complex parenteral chemotherapy.[7] The current assessment will adopt the approach of TA93.[30] It will also source some of the inputs, suitably uprated for inflation, such as the cost of pharmacy preparation from TA93[30] and TA212.[183]

6.2.3.2 Duration of treatment in previous NICE mCRC assessments

Assessments have varied between assuming only 12 weeks of treatment or treatment until progression or unacceptable toxicity. Most assumed treatment would be as per the relevant trials, which was in effect until progression or unacceptable toxicity.

But this is complicated by UK clinical practice being now in part informed by the relatively recently reported COIN trial, as reported in Adams et al. (2011).[34] This assessed the impact of intermittent treatment compared to continuous treatment, with patients receiving oxaliplatin plus 5-FU and capecitabine plus 5-FU with some crossing over between the two treatments. Intermittent treatment during COIN consisted of an assessment at 12 weeks. Those with progressive disease moved onto off-protocol treatment, but those with stable or responding disease entered a chemotherapy free treatment period with ongoing monitoring. If progressive disease was found during this ongoing monitoring, patients recommenced their original chemotherapy. This intermittent treatment continued until progressive disease was observed while on therapy or the patient chose to stop.

Expert opinion suggests that a treatment break of between 6 and 12 cycles of FOLFOX would be usual UK practice, with the responses suggesting that 12 cycles would be the more common goal. Given 12 cycles, it is also suggested that very few patients would enter a second course of treatment: at most 20% and more probably less than 10%.

In the light of this, the current assessment will assume for the base case that the goal of treatment is to achieve 12 cycles of treatment. Progression before this point will limit the number of patients that actually achieve this goal.

There remains uncertainty about the actual proportion of progression free survival that UK mCRC patients spend receiving 1st line chemotherapy. The NCIN SACT dataset[184] should in time be able provide information about the chemotherapy regimens being used by tumour type and stage. The NCIN Chemotherapy Intelligence Unit was approached by the EAG about obtaining information about the dosing and durations of 1st line therapy for mCRC. This was with a view to then obtaining information along the lines of the following five bullets for e.g. mCRC patients receiving FOLFOX:

- The distribution between 5-FU doses during patients' first cycles;
- The split between those receiving only one continuous course and those receiving sequenced courses with treatment holidays in between;
- The average course duration and standard error for those receiving only one continuous course;
- The average course duration and standard error for those receiving sequenced courses with treatment holidays; and,
- The average treatment holiday duration and standard error for those receiving sequenced courses with treatment holidays.

But at present the SACT dataset[184] is still in its infancy. While some publications are available, the EAG was informed that the level of granularity and the completeness of the data are not sufficient to enable reliable information about the dosing and durations of 1st line therapy for mCRC to be supplied. The CIU anticipates that the data will become sufficiently robust for analyses such as this in 2014/15.

Data from the COIN trial would have enabled the proportion of progression free survival spent on treatment to have been estimated. Unfortunately, despite the trial steering committee agreeing to its release for this report, it was not possible to arrange an agreement with UCL for this data to be released.

6.2.3.3 Modelling of progression free survival and overall survival in previous NICE mCRC assessments

Buyse et al., (2000)[185] was quoted as concluding that tumour response is a weak predictor of overall response, summarising the results of the main systematic review of this. Pooling patient- level data from 3791 CRC patients enrolled in 25 RCTs suggested that only 38% (9%-69%) of the variation in overall survival was explained by variations in response rates. As a consequence, in common with the previous NICE assessments in mCRC the economics will restrict itself to modelling survival and progression free survival from parameterised curves reported in the clinical effectiveness section.

For the most part, parametric curves have been fitted to Kaplan Meier curves. While not employing the method of Guyot et al. (2012)[125] the Weibull was the most generally used, though CG131[7] adopted the exponential. These curves have quite often been used to calculate the mean survival mathematically, rather than model it. While compact, this method does mean that discounting was not applied. This was justified by the relatively short time mean survival, implying that discounting would have little effect upon net quantities and the resulting cost effectiveness estimates.

But this is not obviously the case. For instance, the Guyot estimated overall survival Weibull for pharmacokinetic dosing as drawn from Capitain et al. (2012)[119] suggests a mean overall survival of 33.73 months. Applying the same shape parameter to the Capitain et al. (2012)[119] median overall survival of 22 months for BSA dosing suggests a mean overall survival of 24.48 months. A net gain from pharmacokinetic dosing of 9.25 months. But discounting at an annual 3.5% reduces this net gain to 8.26 months: a reduction due to discounting of a little over 10%.

In the light of this, the current assessment will model the parameterised curves outlined within the clinical effectiveness section, with a 2 week cycle to reflect the duration of a cycle of FOLFOX.

Continuous discounting, in the sense of each model cycle being associated with a unique discount factor to derive its present values, will be applied at an annual rate of 3.5% for both costs and benefits.

6.2.3.4 Quality of life values in previous NICE mCRC assessments

Previous NICE assessments in mCRC have typically applied two main quality of life values: one for progression free survival and one for survival post progression. The literature underlying these estimates coupled with a systematic review of the literature in order to update these estimates is presented in Appendix 16. This can be briefly summarised as follows:

- TA61[181] performed a cost minimisation analysis so there were no quality of life estimates.
- TA93[30] drew a mean value of 0.76 from EQ-5D data of the FOCUS trial.[186]
- TA118[179] drew a value for progression free survival of 0.80 from the Ramsey et al. (2000)[187] Health Utilities Index study among 173 US colorectal cancer survivors. A multiplier of 0.75 for survival with progression was informed by the standard gamble survey among 30 UK oncology nurses of the Petrou and Campbell (1997) study.[188]
- TA176[182] drew a value of 0.79 for first line treatment from EQ-5D data collected during the pivotal trial. Third line therapy was assigned a value of 0.68 as drawn from Jonker et al. (2007),[189] while second line therapy was assigned a value at the mid-point of 0.73. Survival with progression was assigned 75% of the value for 1st line progression free survival.
- TA212[183] largely relied upon the value of T176.[182]
- CG131[7] drew values of 0.51 for stable disease and 0.21 for progressive disease from the Best et al. (2010)[190] time trade off study among 49 members of the US general public.
- TA242[180] used values of between 0.75 and 0.81 for progression free survival and between 0.69 and 0.79 for survival with progression. These were supplied within the manufacturer submission, these being based upon a reanalysis of the data underlying the Mittman et al. (2009)[191] HUI study of Canadian publicly funded trial of adding cetuximab to the treatment of 575 mCRC patients.

The values used for CG131 are outliers compared to the values used in other NICE mCRC assessments.[7] Note also that Best et al. (2010)[190] also surveyed 49 colorectal patients who reported values of 0.46 and 0.38 for the health states of metastatic stable disease and metastatic progressive disease.

The systematic literature review only identified an additional four references that had not been considered at some point within the previous NICE mCRC assessments. Farkkila et al. (2013)[192] is probably the most interesting, having surveyed Finnish mCRC patients using the EQ-5D valued using the UK social tariff. Those with advanced disease were divided into patients with mCRC who were

still receiving oncological care (n=110) and those only receiving palliative care (n=41). The mean quality of life values were 0.820 (s.e.m. 0.019) and 0.643 (s.e.m. 0.049) respectively.

Shiroiwa et al. (2009)[193] undertook a time trade off study among members of the Japanese general public for mCRC health states that resulted in estimates more in line with those of Best et al. (2010)[190]: 0.59 for treatment with XELOX and no adverse events and 0.53 for treatment with FOLFOX and no adverse events.

Wang et al. (2011)[194] analysed EQ-5D data from an open label trial of panitumumab being added to best supporting care for chemotherapy refractive mCRC patients. The valuation of EQ-5D data is not made clear, but quality of life values for those without adverse events were 0.768 in the panitumumab arm and 0.663 in the best supportive care arm.

There is also an argument that the last few months of survival may be at a somewhat reduced quality of life. Odom et al. (2011)[195] analysed the EQ-5D values from a trial of panitumumab being added to best supportive care for chemotherapy refractive mCRC patients. Unfortunately this used a US valuation for the EQ-5D, but it suggested that there was a reasonably linear decline in quality of life over time among patients at this stage of treatment.

The above suggests that both the results of Farkkila et al. (2013)[192] and those used in the modelling of TA176[182] and TA212[183] are reasonable estimates. They both suggest a similar quality of life decrement of around 0.18 for the move from progression free survival to progressive disease, though it has to be recognised that the Farkkila et al. (2013)[192] 0.643 relates to mCRC patients receiving only palliative care. In the light of this, the current assessment will apply quality of life values of 0.820 for progression free survival and 0.643 for survival with progression as drawn from Farkkila et al. (2013).[192] The values of TA176[182] and TA212[183] will also be applied as a reasonable sensitivity analysis, while the general public values of Best et al. (2010)[190] will be applied as a further sensitivity analysis.

There is a need to model second line treatment for a proportion of patients, and progression free survival from this line of treatment. One approach is to apply the same quality of life value for progression free survival from second line therapy as for progression free survival arising from first line treatment. But it can be argued that progression free survival from second line therapy would tend to be at a lower quality of life than that arising from first line therapy.

Only the modelling of CG131 applied quality of life decrements for adverse events.[7] These were drawn from the Lloyd et al. (2006)[196] standard gamble exercise among 100 members of the UK general public, though related to metastatic breast cancer.

Due to adverse events possibly being more central to the current assessment than to the previous NICE assessments in mCRC, a systematic review of the quality of life impacts of treatment related adverse events has been undertaken. This is presented in Appendix 22 and further summarised below in the section on adverse events and quality of life.

The overall QALY impact of adverse events also depends upon the duration of adverse events. It had been hoped that data from the COIN trial would have informed this for grade III and grade IV events. While the COIN trial steering committee was willing to release patient level data for this report, unfortunately it proved impossible to arrange a data release agreement with the UCL. In the absence of other data, for the current assessment this has been drawn from expert opinion.

6.2.3.5 Adverse event costs in previous NICE mCRC assessments

In general, where adverse events have been costed a single aggregate adverse events cost has been applied within NICE mCRC assessments, though this is at time differentiated by treatment arm. This is usually not sufficiently disaggregated to be applied to particular adverse events as required for the current assessment.

While not entirely transparent, based upon NHS reference costs TA176 estimated a cost per admission for a grade I/II adverse event of £1,050 [£1,216] and for a grade III/IV of £1,170 [£1,354].[182]

TA212 provides a more disaggregate costing of adverse events, but the details of this are not presented and despite the ERG asking for further information none was apparently forthcoming.[183]

CG131 costs grade III/IV diarrhoea at £388 [£420] based upon the NHS reference cost FZ45C short stay NHS reference cost.[7]

In the light of this, for the current assessment the costs of individual grade I/II and grade III/IV adverse events will be based upon:

- The likelihood of hospitalisation
- NHS reference costs for those hospitalised
- Medication costs for those not hospitalised

The values for these are based upon expert opinion as outlined in greater detail in the adverse events sections below.

6.2.4 The cost effectiveness of pharmacokinetic dose adjustment using My5-FU in mCRC

6.2.4.1 The modelling approach

The model has been constructed along the lines of a cohort distributed between health states over a 20 year time horizon. Given the survival curves of the clinical effectiveness section, this is in effect a lifetime horizon. A 2 week cycle has been employed to be in line with the FOLFOX cycle length, with half cycle correction in order to align survival estimates with those of the clinical effectiveness section. 1st line treatment is assumed to be FOLFOX6. The distribution between health states is determined by the parameterised curves, with the 1st line overall survival curve and the 1st line progression free survival curve determining the post progression from 1st line therapy curve. A constant proportion of those progressing from 1st line therapy go on to receive 2nd line therapy which is assumed to be FOLFIRI. This is also associated with a progression free survival curve, as drawn from Tournigand et al. (2004).[169]

The main health states of the model in terms of progression free survival (PFS), survival with progression (SWP) and death and the possible movements between them are outlined below (Figure 36).

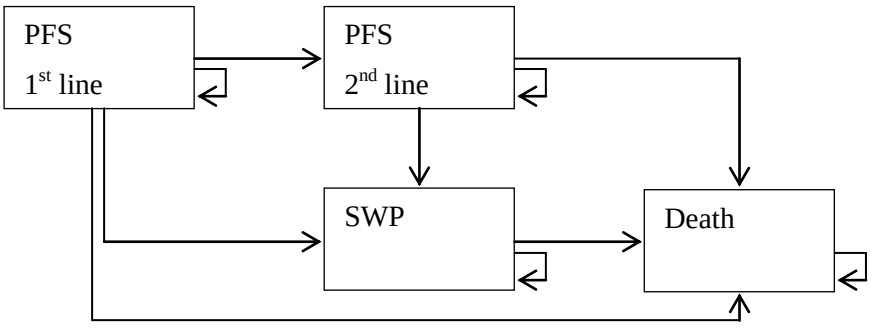


Figure 36. mCRC model structure

In terms of the model structure, for the base case it is assumed that the default is for patients to move from progression free survival into survival with progression and then on to death. Moving directly from progression free survival to death is the exception. This only applies when there is an adding up constraint; i.e. the incident number of deaths implied by the overall survival curve exceeds the number of patients in the survival with progression health state.

The cost and QALY impacts of adverse events associated with 1st line treatment, differentiated by My5-FU dose adjustment and BSA dose adjustment arm, have been included within the modelled, as outlined in greater detail below.

6.2.4.2 1st line therapy: Survival estimates

Capitain et al. (2012)[119] studied pharmacokinetic dose adjustment using FOLFOX6, which is directly relevant to current UK clinical practice. But there are problems with the control arm. Not only was is not randomised and somewhat smaller than the pharmacokinetic dose adjustment arm, only the median overall survival and median progression free survival are reported for it.

Gamelin et al. (2008)[118] provides the clearest analysis of the possible difference in overall survival using pharmacokinetic dosing. But its relevance may be hampered by the regimen being of questionable relevance to current UK practice: 5-FU + FA rather than FOLFOX6. There is also no reliable reporting of progression free survival, though some inference may be made from the reported durations of response.

The parameterised Weibull overall survival curves differ noticeably between Gamelin et al. (2008)[118] and Capitain et al. (2012),[119] as shown below for the first five years (Figure 37).

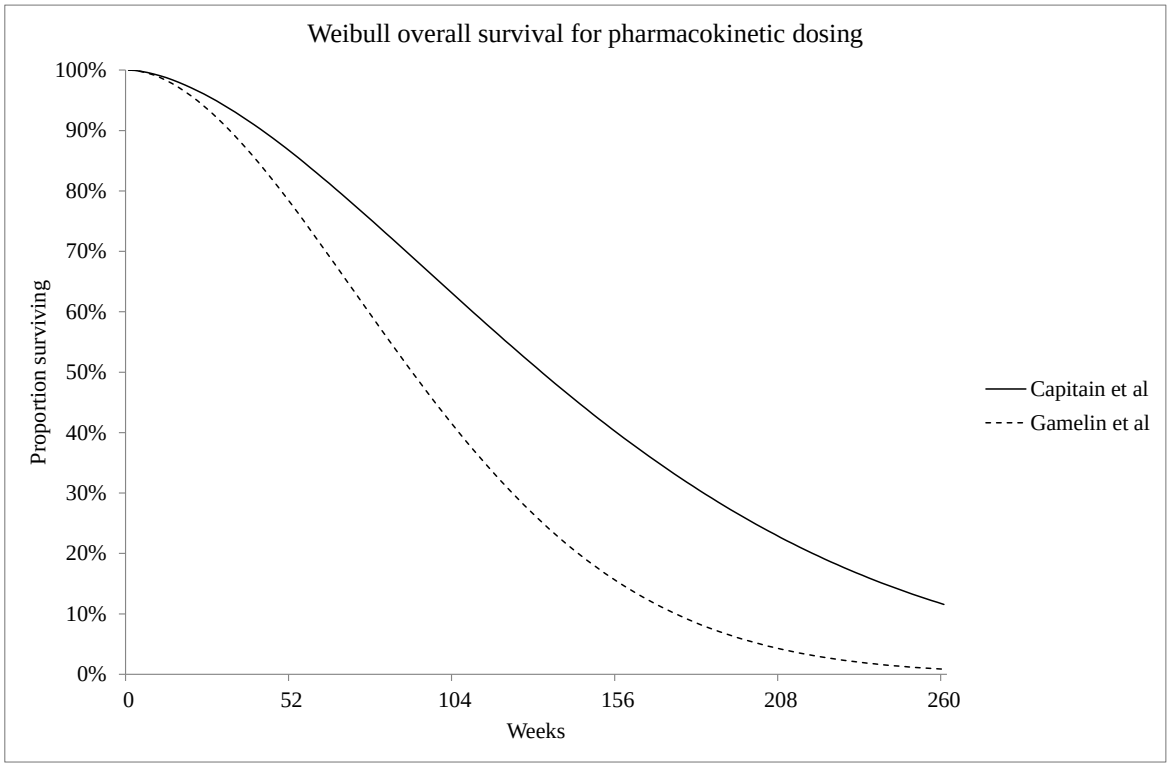


Figure 37. Capitain et al. (2012)[119] and Gamelin et al. (2008)[118] PK Weibull OS curves

In the light of this, two strands of analysis will be presented: one based upon FOLFOX6 studies and one based upon 5-FU + FA studies. Within the strand based upon FOLFOX6 studies a sensitivity analysis applying the hazard ratio for overall survival derived from Gamelin et al. (2008)[118] will be performed as a bridge. Note that within the strand based upon 5-FU + FA studies, due to the regimens not being current standard UK practice the drug costs will be based upon FOLFOX6 for 1st line and FOLFIRI for 2nd line.

The clinical effectiveness section concluded that an assumption of equivalence between My5-FU dose adjustment and pharmacokinetic dose adjustment by more traditional methods was justified reasonable assumption. As a consequence, the economic modelling will assume that the pharmacokinetic dosing curves of the literature are equally applicable to My5-FU dose adjustment. If this assumption is not valid, none of the results of the economic modelling hold.

6.2.4.3 FOLFOX studies analyses

The base case will apply the parameterised Weibull overall survival curve and overall progression free survival curve estimated from the pharmacokinetic dose adjustment arm of Capitain et al. (2012)[119] to the My5-FU arm. The Weibull overall survival curve and overall progression free survival curve for the BSA arm will be those estimated from the medians reported in Capitain et al. (2012),[119] coupled with an assumption of them having the same shape parameter as the corresponding pharmacokinetic dose adjustment curve. This is reported in more detail in Table 19 and Table 23 of the clinical effectiveness section.

Due to Capitain et al. (2012)[119] only reporting the median overall survival for the BSA arm, a scenario analysis will be presented that applies the proportionate hazard of overall survival derived from Gamelin et al. (2008)[118] of 0.829255, as reported in greater detail in the clinical effectiveness section 5.5.4.3.4.

Due to the concerns around the size and derivation of the BSA control arm within Capitain et al. (2012)[119] and that only medians are reported, a range of scenario analyses that apply curves for the BSA arm derived from the wider literature will be presented. The studies underlying these estimates are reported in more detail in sections 5.7.3.5 and 5.7.3.6 of the clinical effectiveness section.

A scenario analysis will apply the Weibull overall survival curve estimated by combining the data from the five BSA studies (Seymour et al., 2007,[165] COIN et al., 2011,[34] Hochster et al., 2008,[167] Ducreux et al., 2011,[168] Tournigand et al., 2004[169]) and the progression free survival curve estimated

by combining the data from the three BSA studies of FOLFOX (COIN 2011,[34] Ducreux 2011,[168] Tournigand 2004[169]). The curves of the base case will be retained for the My5-FU arm.

Two further scenario analyses will apply the Weibull overall survival curves and progression free survival curves estimated from (a) Ducreaux et al. (2011)[168] and (b) Tournigand et al. (2004).[169] The curves of the base case will be retained for the My5-FU arm.

The analysis of the clinical effectiveness section suggests that the survival in the UK based studies is somewhat worse than that of the other studies. This might imply that any analysis based upon pooling data from single arms for the BSA arm that includes the UK studies may tend to bias the analysis in favour of My5-FU. A fairer comparison with the pharmacokinetic curves of Capitain et al. (2012)[119] might be to pool the data from single arms for the BSA arm but excluding the UK studies. This will be undertaken as a final sensitivity analysis.

This leads to the following base case analyses and scenario analyses (Table 45).

Table 45. Base cases and scenario analyses: FOLFOX Studies

	Source	Scale	Shape	Mean (mths)
Base Case				
OS My5-FU	Capitain et al., 2012	λ=0.00233	γ=1.66906	33.76
OS BSA	Capitain et al., 2012: from median	λ=0.00398	γ=1.66906	24.49
PFS My5-FU	Capitain et al., 2012	λ=0.02438	γ=1.13668	25.06
PFS BSA	Capitain et al., 2012: from median	λ=0.05060	γ=1.13668	13.19
Scenario analysis 01				
OS My5-FU	Capitain et al., 2012	λ=0.00233	γ=1.66906	33.76
OS BSA	Gamelin et al., 2008 0.829255 HR	..	..	30.17
PFS My5-FU	Capitain et al., 2012	λ=0.02438	γ=1.13668	25.06
PFS BSA	Capitain et al., 2012: from median	λ=0.05060	γ=1.13668	13.19
Scenario analysis 02				
OS My5-FU	Capitain et al., 2012	λ=0.00233	γ=1.66906	33.76
OS BSA	Pooled 5 BSA studies*	λ=0.00942	γ=1.50343	20.09
PFS My5-FU	Capitain et al., 2012	λ=0.02438	γ=1.13668	25.06
PFS BSA	Pooled 3 BSA studies**	λ=0.03194	γ=1.40082	10.65
Scenario analysis 03				
OS My5-FU	Capitain et al., 2012	λ=0.00233	γ=1.66906	33.76
OS BSA	Ducreux et al., 2010	λ=0.00183	γ=0.03058	21.91
PFS My5-FU	Capitain et al., 2012	λ=0.02438	γ=1.13668	25.06
PFS BSA	Ducreux et al., 2010	λ=1.96532	γ=1.38097	11.41

Scenario analysis 04				
OS My5-FU	Capitain et al., 2012	λ=0.00233	γ=1.66906	33.76
OS BSA	Tournigand et al., 2004	λ=0.01411	γ=0.03568	28.19
PFS My5-FU	Capitain et al., 2012	λ=0.02438	γ=1.13668	25.06
PFS BSA	Tournigand et al., 2004	λ=1.24954	γ=1.35822	10.66
Scenario analysis 05				
OS My5-FU	Capitain et al., 2012	λ=0.00233	γ=1.66906	33.76
OS BSA	Non-UK pooled 3 BSA studies***	λ=0.00570	γ=1.57760	23.75
PFS My5-FU	Capitain et al., 2012	λ=0.02438	γ=1.13668	25.06
PFS BSA	Pooled 3 BSA studies	λ=0.03194	γ=1.40082	10.65
* COIN (2011), Ducreux et al. (2010), Hochster et al. (2008), Seymour et al. (2007), Tournigand et al. (2004)				
** COIN (2011), Ducreux et al. (2010), Tournigand et al. (2004)				
*** Ducreux et al. (2010), Hochster et al. (2008), Tournigand et al. (2004)				

6.2.4.4 5-FU + FA studies analyses

Note that the following analyses still assume current UK practice in terms of the drug costs for 1st line therapy being those of FOLFOX. The 5-FU + FA studies analyses apply the curves from the 5-FU + FA studies, this being motivated in part by the only RCT of pharmacokinetic dosing being a 5-FU + FA study.

Due to Gamelin et al. (2008)[118] not presenting the progression free survival curves, the base case will adopt the most conservative approach. It will apply the parameterised Weibull overall survival curves estimated from Gamelin et al. (2008),[118] but it will assume equivalence between My5-FU and BSA dose adjustment for progression free survival, and apply the Weibull progression free survival curve estimated by combining the arms of the three main BSA studies.

Two scenario analysis will apply the Weibull progression free survival curves inferred from the durations of response reported in Gamelin et al. (2008)[118] as reported in more detail in 5.5.4.3.5, while retaining the other curves of the base case.

A further scenario analysis will apply the Weibull progression free survival curve estimated from Gamelin et al. (1998)[139] for the My5-FU arm, while retaining the other curves of the base case.

A further scenario analysis will apply the Weibull overall survival curve estimated by pooling the results of Gamelin et al. (2008),[118] Gamelin et al. (1998)[139] and Capitain et al. (2008)[135] in the My5-FU arm, while retaining the other curves of the base case.

A further scenario analysis will apply the Weibull overall survival curve estimated by pooling the results of Gamelin et al. (2008),[118] Gamelin et al. (1998)[139] and Capitain et al. (2008)[135] in the My5-FU arm, the progression free survival curve estimated from Gamelin et al. (1998)[139] in the My5-FU arm while retaining the curves of the base case for the BSA arm.

A final scenario analysis will apply the Weibull overall survival curve estimated by pooling the results of Gamelin et al. (2008),[118] Gamelin et al. (1998)[139] and Capitain et al. (2008)[135] in the My5-FU arm, the progression free survival curve estimated from Gamelin et al. (1998)[139] in the My5-FU arm, the Weibull overall survival curve estimates from pooling five BSA studies and the Weibull progression free survival curve estimates from pooling three BSA studies in the BSA arm.

This leads to the following base case analyses and scenario analyses (Table 46).

Table 46. Base cases and scenario analyses: 5-FU + FA Studies

	Source	Scale	Shape	Mean (mths)
Base case				
OS My5-FU	Gamelin et al., 2008	λ=0.00270	γ=1.82786	22.59
OS BSA	Gamelin et al., 2008	λ=0.00865	γ=1.54066	19.65
PFS My5-FU	Pooled 3 BSA studies*	λ=0.05541	γ=1.35834	7.71
PFS BSA	Pooled 3 BSA studies	λ=0.05541	γ=1.35834	7.71
Scenario analysis 01				
OS My5-FU	Gamelin et al., 2008	λ=0.00270	γ=1.82786	22.59
OS BSA	Gamelin et al., 2008	λ=0.00865	γ=1.54066	19.65
PFS My5-FU	Gamelin et al., 2008: resp. dur. A	λ=0.02047	γ=1.82786	7.46
PFS BSA	Gamelin et al., 2008: resp. dur. A	λ=0.05378	γ=1.54066	6.00
Scenario analysis 02				
OS My5-FU	Gamelin et al., 2008	λ=0.00270	γ=1.82786	22.59
OS BSA	Gamelin et al., 2008	λ=0.00865	γ=1.54066	19.65
PFS My5-FU	Gamelin et al., 2008: resp. dur. B	λ=0.00798	γ=1.82786	12.49
PFS BSA	Gamelin et al., 2008: resp. dur. B	λ=0.03280	γ=1.54066	8.27
Scenario analysis 03				
OS My5-FU	Gamelin et al., 2008	λ=0.00270	γ=1.82786	22.59
OS BSA	Gamelin et al., 2008	λ=0.00865	γ=1.54066	19.65
PFS My5-FU	Gamelin et al., 1998	λ=0.08197	γ=0.99089	12.54
PFS BSA	Pooled 3 BSA studies	λ=0.05541	γ=1.35834	7.71
Scenario analysis 04				
OS My5-FU	Pooled 3 PK studies**	λ=0.01089	γ=1.38189	24.05
OS BSA	Gamelin et al., 2008	λ=0.00865	γ=1.54066	19.65

PFS My5-FU	Pooled 3 BSA studies	λ=0.05541	γ=1.35834	7.71
PFS BSA	Pooled 3 BSA studies	λ=0.05541	γ=1.35834	7.71
Scenario analysis 05				
OS My5-FU	Pooled 3 PK studies	λ=0.01089	γ=1.38189	24.05
OS BSA	Gamelin et al., 2008	λ=0.00865	γ=1.54066	19.65
PFS My5-FU	Gamelin et al., 1998	λ=0.08197	γ=0.99089	12.54
PFS BSA	Pooled 3 BSA studies	λ=0.05541	γ=1.35834	7.71
Scenario analysis 06				
OS My5-FU	Pooled 3 PK studies	λ=0.01089	γ=1.38189	24.05
OS BSA	Pooled 5 BSA studies***	λ=0.00942	γ=1.50343	20.09
PFS My5-FU	Gamelin et al., 1998	λ=0.08197	γ=0.99089	12.54
PFS BSA	Pooled 3 BSA studies	λ=0.05541	γ=1.35834	7.71
* Kohne et al. (2003), Kohne et al. (2005), Cunningham et al. (2009) ** Gamelin et al. (2008), Gamelin et al. (1998) and Capitain et al. (2008) *** Kohne et al. (2003), Kohne et al. (2005), Cunningham et al. (2009), Gamelin et al. (2008), Seymour et al. (2007)				

For the probabilistic modelling a Cholesky decomposition of the parameters' variance-covariance matrix is applied.

6.2.4.4.1 2nd line therapy: survival estimates

The progression free survival among those receiving 2nd line chemotherapy is assumed to follow that of the 2nd line FOLFIRI of Tournigand et al. (2004).[169] (Figure 38) Analysis of this data suggests that both the lognormal and the log-logistic provide reasonable fits to this data (Table 47). But there may be some concerns about extrapolating using these forms due to the relatively long tails they involve when extrapolating beyond the trial data. As a consequence, the base case will apply the Weibull parameterisation of the 2nd line FOLFIRI progression free survival curve, partly in order to increase consistency with the other curves that are being applied. But the impact of this is likely to be slight, with all three parameterisations suggesting a mean progression free survival of around 0.34 years.

Table 47. Goodness of fit estimates for parameterisations of 2nd line FOLFIRI PFS

		Log likelihood				
	Obs	**H_0**	**H_1**	**d.f.**	**AIC**	**BIC**
exponential	111	-135.781	-135.781	1	273.562	276.271
weibull	111	-119.699	-119.699	2	243.397	248.816
gompertz	111	.	-127.887	2	259.774	265.193
lognormal	111	.	-116.960	2	237.920	243.339
loglogistic	111	.	-116.364	2	236.727	242.146

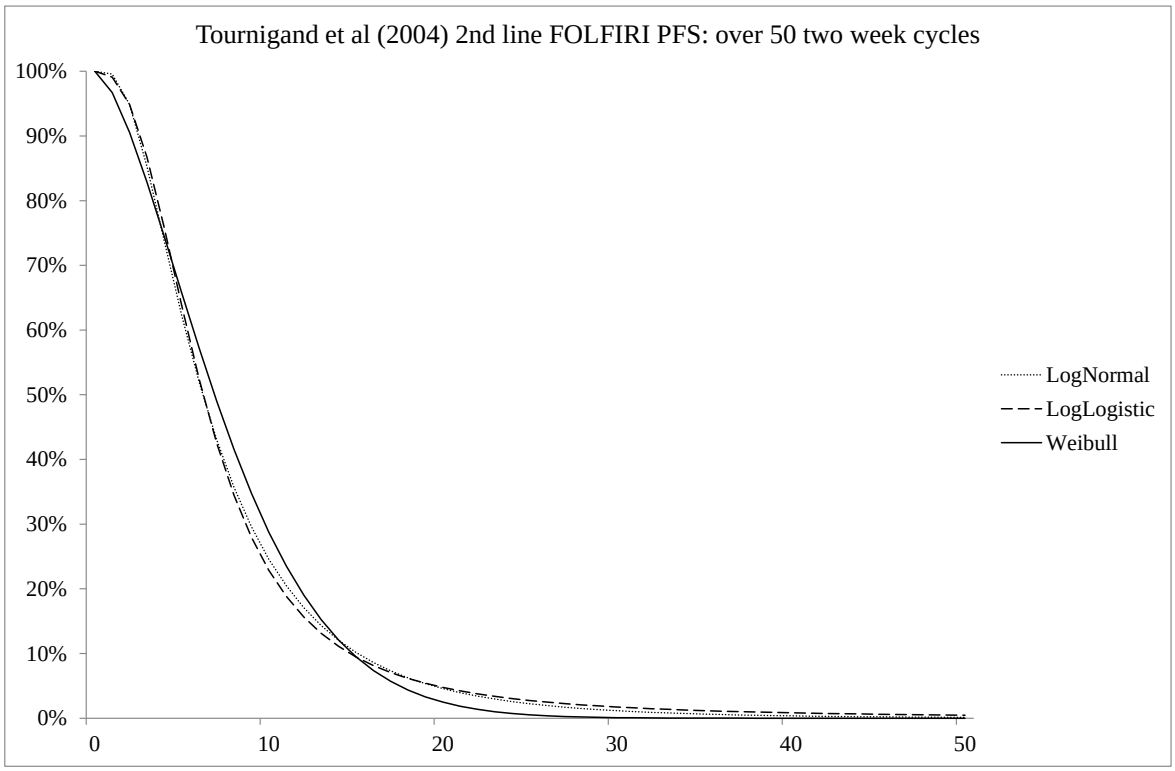


Figure 38. Lognormal, log-logistic and Weibull for 2nd line FOLFIRI PFS

Note that within this the duration, effect and cost of 2nd line therapy is treated as being independent of the duration, effect and cost of 1st line therapy. This may not be accurate for even the deterministic analysis. If My5-FU increases progression free survival from first line therapy compared to BSA dosing, this may also affect the duration, effect and cost of second line therapy. The base case assumption is that it does not. There is also no obvious data that would enable alternative assumptions about this to be parameterised.

Even with the base case assumption that any increase in progression free survival from first line therapy due to My5-FU dosing does not affect the duration, effect and cost of second line therapy, a further problem may arise within the probabilistic modelling from modelling first line effects and

second line effects independently. For some of the iterations of the probabilistic modelling the first line progression free survival curve may be simulated as being quite close to the overall survival curve. This would squeeze the time spent in post first line progression free survival, such that for some iterations there is insufficient time to accrue the simulated duration, effect and cost of second line therapy. However, the mean 2nd line progression free survival of around 0.34 years is sufficiently short compared to the mean survival subsequent to 1st line progression free survival for this not to be a concern.

6.2.4.5 Adverse events: rates

Adverse events rates are drawn from the key comparative papers. It should be borne in mind that these appear to report the proportion of patients experiencing events rather than the numbers of actual events. As a consequence, modelling underestimates the number of events to some degree, which could tend to bias the analysis.

As Capitain et al. (2012)[119] did not distinguish between grade III and grade IV adverse events, where this distinction is required this balance will be drawn from the Gamelin et al. (2008)[118] data.

6.2.4.6 Progression free survival and survival with progression quality of life

As previously reviewed in the section on quality of life values in NICE mCRC assessments, augmented with the results of the systematic review of Appendix 16, the results of Farkkila et al. (2013)[192] and those used in the modelling of TA176[182] and TA212[183] are reasonable estimates. Both suggest a similar quality of life decrement of around 0.18 for the move from progression free survival to progressive disease, though it has to be recognised that the Farkkila et al. (2013)[192] 0.643 relates to mCRC patients receiving only palliative care. In the light of this, the current assessment will apply quality of life values of 0.820 for progression free survival and 0.643 for survival with progression as drawn from Farkkila et al. (2013).[192] The values of 0.80 and 0.60 from TA176[182] and TA212[183] are also applied as a reasonable sensitivity analysis, while the general public values of 0.51 and 0.21 of Best et al. (2010)[190] are applied as a further sensitivity analysis.

6.2.4.7 Adverse events: Quality of life

With the exception of CG131,[7] the quality of life impacts of adverse events have not been separately modelled within previous NICE mCRC assessments. CG131[7] included QALY decrements for adverse events of 0.103 for grade 3/4 diarrhoea, 0.150 for febrile neutropenia and 0.116 for hand foot syndrome, as drawn from the Lloyd et al. (2006)[196] study of metastatic breast cancer.

In the light of this, a systematic literature review of the quality of life impacts of chemotherapy related adverse events was undertaken, the results of this being reported in full in Appendix 22. This literature review updated and widened the literature review reported in Shabaruddin et al. (2013).[171] Based upon just the values reported in this literature review, the following quality of life decrements for grade III/IV adverse events appear reasonable. Cardiac toxicity has not been further considered due the only differences between the arms in Gamelin et al. (2008)[118] being for grade I/II cardiac adverse events, these being asymptomatic.

Table 48. Literature review based grade III/IV adverse event quality of life decrements

Grade III/IV adverse event	QoL dec.	Source
Diarrhoea Nausea/vomiting Mucositis	0.074 0.074 0.074	Lloyd et al. (2006),[196] and informed by Boyd et al. (2011)[197] and Shiroiwa et al. (2009)[193]
Hand-foot	0.085	Lloyd et al. (2006),[196] and informed by Shiroiwa et al. (2009)[193]
Leukopenia	0.090	Frederix et al. (2013)[198]
Neutropenia	0.073	Informed by Tolley et al. (2013)[199] but conditioned by the relationship of the other Tolley estimates with those of the broader literature
Febrile neutropenia	0.112	Lloyd et al (2006),[196] and informed by Shiroiwa et al. (2009)[193]
Thrombocytopenia	0.081	Swinburn et al. (2012)[200]

Due to the range of sources being drawn from for the above, clinical expert opinion was sought on the face validity of these estimates and their relative magnitudes. This can be summarised as viewing the quality of life decrements for leukopenia, neutropenia and thrombocytopenia as too high. Apparently even for grade III/IV events, much of the leukopenia and neutropenia is asymptomatic. Similarly, thrombocytopenia was viewed as being unlikely to significantly affect quality of life unless it led to bleeding. The probability of requiring platelet transfusion for thrombocytopenia was also viewed as being very small, suggesting that any quality of life decrement associated with thrombocytopenia should perhaps be only applied to a small percentage of patients.

There was a suggestion that diarrhoea would have a larger quality of life decrement than nausea/vomiting, while mucositis might have a smaller impact. Febrile neutropenia was agreed to have the largest quality of life decrement.

The literature review identified the abstract by Boyd et al. (2011)[197] which reports the interim results from an analysis of the MRC funded SCOT trial of patients with fully resected stage III colorectal

cancer or full resected high risk stage II disease. This presents the EQ-5D quality of life decrements associated for a subset of both grade I/II and grade III/IV adverse events. The interim analysis has been verbally presented in more detail by the author, with EQ-5D data being collected from 1,292 patients at baseline, every cycle, 9, 12, 18, 24 months and annually thereafter. This data has been further analysed within a univariate analysis, with the following results [*personal communication: Kathleen Boyd*] (Table 49).

Table 49. SCOT trial EQ-5D grade III/IV adverse event quality of life decrements colorectal cancer

	No AE	Grade I/II			Grade III/IV		
	N	N	QoL Dec.	s.e.m.	N	QoL Dec.	s.e.m
Alopecia	2,082	246	-0.0477	0.0317	8	n.a.	n.a.
Anaemia	2,082	757	-0.0202	0.0149	3	n.a.	n.a.
Anorexia	2,083	315	-0.0600	0.0209	22	0.1584	0.2033
Constipation	2,084	512	-0.0521	0.0166	11	-0.1166	0.2033
Diarrhoea	2,081	1,190	-0.0400	0.0125	94	-0.0900	0.0379
Fatigue	2,081	1,826	-0.0280	0.0103	60	-0.0800	0.0615
Hand & Foot	2,082	383	-0.0132	0.0268	21	-0.3255	0.2035
Mucositis Clinical	2,082	181	-0.0860	0.0320	60	n.a.	n.a.
Mucositis Functional	2,082	506	-0.0525	0.0173	18	-0.0375	0.1438
Nausea	2,081	1,117	-0.0460	0.0123	29	-0.1410	0.0769
Neuropathy sensory	2,081	2,220	-0.0290	0.0096	33	-0.1970	0.0910
Neutropenia	2,081	305	0.0214	0.0245	85	-0.0607	0.0457
Photophobia	2,083	43	0.0103	0.0832	20	0.0000	0.0080
Rash	2,082	161	-0.0963	0.0309	15	n.a.	n.a.
Taste Alteration	2,082	723	-0.0445	0.0157	20	0.1585	0.2030
Thrombocytopenia	2,083	324	-0.0309	0.0325	8	n.a.	n.a.
Vomiting	2,081	257	-0.0520	0.0224	22	-0.0170	0.0910
Watery eye	2,083	241	-0.0638	0.0283	20	n.a.	n.a.

The n.a. values for the grade III/IV events were due to insufficient numbers of events: none for alopecia and photophobia, one for rash and watery eye, two for anaemia and mucositis clinical and six for thrombocytopenia.

The univariate analysis regressed the adverse events against quality of life individually. A multivariate analysis was also undertaken in which all adverse events were simultaneously regressed against quality of life. The multivariate analysis led to inconclusive results, with the individual adverse events being highly correlated with one another. Dropping some adverse events from the

multivariate analysis still led to inconclusive results. In the effective absence of multivariate results, the authors recommend using the results of the univariate analysis.

The multi-collinearity between the adverse events of Boyd et al. (2011)[197] would appear to raise the possibility that within the univariate analyses the estimated quality of life decrements for an adverse event are picking up not only the impact of the adverse event under consideration, but also some of the impacts of the adverse events with which it is highly correlated. As a consequence the univariate values should perhaps be treated with some caution, with there being the possibility of double counting the quality of life impacts of adverse events. My5-FU.

The Boyd et al. (2011)[197] data still appears to be the best data in terms of robustness and alignment with NICE methods, but Lloyd et al. (2006)[196] also seems a credible source and unaffected by the problems of multi-collinearity. In the light of this, the quality of life impacts of adverse events have been calculated on the following basis. For grade III/IV adverse events:

- Diarrhoea taken directly from the SCOT trial univariate estimates
- Nausea/vomiting taken as the mean of the SCOT trial univariate estimates
- Hand-foot assumed to be greater than the diarrhoea decrement by the Best et al. (2010)[190] proportion
- Mucositis taken from the SCOT trial univariate estimates
- Neutropenia taken from the SCOT trial univariate estimates
- Leukopenia assumed to be as per neutropenia
- Thrombocytopenia taken from Swinburn et al. (2012)[200]

But in the light of expert opinion neutropenia, leukopenia and thrombocytopenia are assumed to have no quality of life impact for the base case.

Table 50. Adverse event quality of life decrements Grade III/IV

	Grade I/II	**Grade III/IV**
Diarrhoea	-0.040	-0.090
Nausea/vomiting	-0.035	-0.079
Hand & Foot	-0.013	-0.103
Mucositis	-0.053	-0.038
Neutropenia*	..	-0.061
Leukopenia*	..	-0.061
Thrombocytopenia*	..	-0.081
*Only applied as a sensitivity analysis		

The above Table 50 includes quality of life decrements for the grade I/II adverse events. These are largely driven by the SCOT trial estimates, but as with the estimates for grade III/IV adverse events they are also informed by the other estimates within the literature. For analyses based upon the adverse event rates of Gamelin et al. (2008)[118] the quality of life estimates for grade I/II adverse event rates were applied within sensitivity analyses. There remain concerns with the SCOT trial estimates for grade I/II adverse events given the issues around multi-collinearity.

6.2.4.8 Adverse event: Durations

There is a paucity of data on the duration of adverse events within the literature. The duration of adverse events is as an important a driver of the QALY impact of adverse events as the quality of life decrements outlined above. As already noted, there is duration data for grade III and grade IV adverse events within the COIN trial data set, but it was not possible to arrange an intellectual property agreement with the UCL.

Expert opinion suggests that the following may be reasonable (Table 51).

Table 51. Adverse event durations of quality of life impacts (days)

	Grade I/II	Grade III/IV
Diarrhoea	18	5
Nausea/vomiting	12	5
Hand & Foot	15	5
Mucositis	12	3
Neutropenia	..	7
Leukopenia	..	5
Thrombocytopenia	..	3

The above Table 51 durations for grade III/IV events are broadly in line with those reported for the average length of stay associated with adverse events as reported in Twelves et al. (2001)[201] as summarised in Appendix 21. Whether the adverse events have completely resolved at discharge may be a moot point, but it might be anticipated that any remaining quality of life impacts would be somewhat below their peak effect.

6.2.5 My5-FU costs

The costs (ex VAT), volumes and shelf lives once opened for the My5-FU elements as supplied by Saladax are:

- £60 per stabiliser kit, and 20 stabilisers per kit
- £835 per assay kit, 100 assays per kit and a shelf life of 30 days

- £75 per quality control kit, sufficient for 40 quality control runs and a shelf life of 90 days
- £200 per calibration kit and a shelf life of 90 days

Laboratory staff timings are based upon expert opinion (*Personal communication: Andrew Teggert at South Tees Foundation Hospitals NHS Trust Helen Haley at South Durham NHS*): 2 minutes of a Band 3 for sample receipt and preparation, 2 minutes of a Band 6 per quality control run and 2 minutes of a Band 6 per calibration. These are costed using the 2013 NHS pay scale[202] coupled with a percentage mark-up for overheads drawn from the 2013 PSSRU Unit Costs of Health and Social Care[203] costing for a hospital pharmacist.

The staff costs incurred obtaining a blood sample are based upon 30 minutes of health visitor time face to face with the patient [*personal communication: Delyth Mcentee, Christie Hospital 28 March 2014*], costed using the 2013 PSSRU Unit Costs of Health and Social Care.[203] An alternative would be to have the blood taken at an outpatient appointment. The 2012-13 NHS reference costs[204] give the following: Nurse-led outpatient WF01A 370 medical oncology, non-admitted face to face follow up appointment £102.

The cost per completed My5-FU assay is sensitive to:

- The number of assays per kit. Saladax suggests that each assay kit contains 100 assays. The Middlesborough laboratory was achieving around 200 assays per assay kit on their platform (*Personal communication: Andrew Teggert at South Tees Foundation Hospitals NHS Trust Helen Haley at South Durham NHS*).
- Whether assays are batched weekly or daily. Each batch requires quality control which involves both staff time and three additional assays. Given the fortnightly cycle length for FOLFOX, Saladax argues that weekly batching would be clinically feasible. Weekly batching of samples would if anything be simpler to implement within the laboratory, provided that this met clinical needs. (*Personal communication: Andrew Teggert at South Tees Foundation Hospitals NHS Trust Helen Haley at South Durham NHS*).
- The annual laboratory throughput. If throughput is low a proportion of the assay kit has to be thrown away due to the 30 day shelf life of the assay kit once opened. The following assumes that My5-FU is only used for treating mCRC patients. The patient numbers identified in TA118[179] can be coupled with the proportions of mCRC patients receiving infusional 5-FU both 1st line and 2nd line. For the North Tees and Hartlepool NHS Trust population of 365,000 this suggests perhaps around an annual 30 mCRC patients receiving infusional 5-FU regimes

at 1st line and at 2nd line[2]. Coupling these with the median number of cycles for 1st line and 2nd line of 12 and 7 as reported in Tournigand et al. (2004)[169] suggests around an annual 500 cycles of infusional 5-FU for mCRC patients. Expert opinion suggests that this approximately correct, though may be a little low (*Personal communication: Nick Wadd, North Tees and Hartlepool Trust*). Saladax suggests around 4 My5-FU assays will be required per patient, which assuming the assays are repeated at switch to 2nd line FOLFIRI would result in an annual throughput of around 250 My5-FU assays. More continuous monitoring would tend to raise this.

As shown below (Table 52), at throughputs below an annual 500, the cost per test is quite sensitive to the annual throughput. Once the annual throughput has risen to above 1,000 the cost per test has largely stabilised (Figure 39).

Table 52. Cost per My5-FU assay and annual throughput: by kit volume and batch frequency

	Weekly	Weekly	Daily	Daily
Annual	**100/kit**	**200/kit**	**100/kit**	**200/kit**
100	£86.77	£68.39	£180.03	£120.35
200	£67.47	£56.19	£114.73	£82.17
300	£61.03	£52.12	£92.96	£69.44
400	£57.82	£50.09	£82.08	£63.08
600	£54.60	£48.05	£71.19	£56.71
800	£52.99	£47.03	£65.75	£53.53
1,000	£52.18	£46.42	£62.49	£51.62
1,200	£51.72	£46.02	£60.31	£50.36
1,500	£51.26	£45.61	£58.13	£49.15

[2] Note that this results in some inconsistency between the costing and the modelling, since due to the available clinical effectiveness evidence the modelling is only of pharmacokinetic dose adjustment of 1st line therapy.

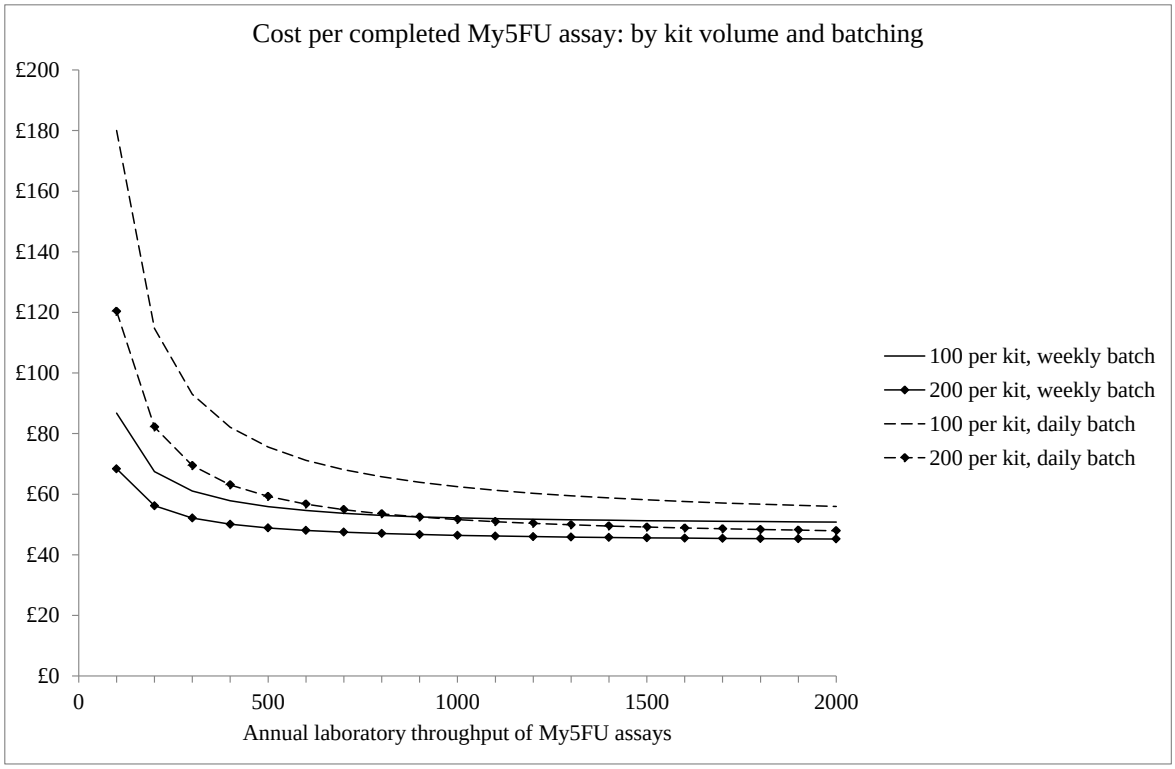


Figure 39. Cost per My5-FU assay and annual throughput: by kit volume and batch frequency

In the light of the above, the base case will assume an annual throughput of 300 with weekly batching and 100 assays per kit. This results in a cost per completed My5-FU assay of £61.03 as outlined in greater detail below (Table 53).

Table 53. Base case My5-FU assay cost

Stabiliser	£3.00
Staff input calibration	£0.05
Staff input QC	£0.38
Staff input initial handling	£1.30
My5-FU assay	£17.78
Calibration	£2.70
QC	£0.33
Total laboratory per test	£25.53
HV cost of taking sample	£35.50
Total cost	**£61.03**

A sensitivity analysis that assumes 200 assays per assay kit will be performed, this resulting in a cost per test of £52.12. Further sensitivity analyses of annual throughputs of 500 and 1,000 will be performed, as will sensitivity analyses that assume 200 assays per assay kit. For the 500 throughput this results in costs per test of £55.89 and £48.86, and for the 1,000 throughput this results in costs per test of £52.18 and £46.42.

Note that within the above there is no allowance for the capital cost of the analyser. These typically have a daily capacity of between 1,200 and 1,800, though this may not be fully utilised. Service costs for this element are to some degree commercial in confidence. The underlying assumption is that the marginal analyser capital cost per additional assay is small to the point of insignificance. But it has to be acknowledged that the analysers are expensive, and a multi-year laboratory service contract may well stretch into seven figures.

6.2.5.1 My5-FU assays per patient

[redacted] Expert opinion suggests that testing would initially be until stabilisation had occurred, and then perhaps every third cycle or when there was unexpected toxicity.

Capitain et al. (2012)[119] report that 64% (n=75/118) of patients in the pharmacokinetic dosing arm had increased their dose by at least 10% at 3 months, with a range of 10% to 40% and a mean increase of 20%. 36% (n=42/118) increased their dose by at least 20%, among whom the range was 20% to 40% with a mean increase of 26%. Unfortunately, Capitain et al. (2012)[119] do not present any data on the number of adjustments that were required. The dose adjustment algorithm permits dose adjustments of as little as 5%, but adjustments may be somewhat larger than this, depending upon how far from the target range the plasma concentration is.

Similarly, Capitain et al. (2012)[119] report that 18% (n=22/118) had a dose reduction of at least 10%, with a range of 10% to 40% and a mean of 20%. 12% (n=14/118) had a dose decrease of at least 20%, with a range of 20% to 40% and a mean of 26%.

In total, within the Capitain et al. (2012)[119] study the vast majority of patients in the pharmacokinetic dose adjustment arm had their dose adjusted: 82%. These patients would require a minimum of 3 My5-FU assays for stability; i.e. two consecutive results within the target range, to have been established.

Given an assumption that final bandings were all at 10% increments to the initial dose, this is consistent with 28% (n=33/118) having a dose increase of 10%, 17% (n=20/118) having a dose increase of 20%, 15% (n=18/118) having a dose increase of 30% and 3% (n=4/118) having a dose increase of 40%. For the proportion having their dose reduced, this is consistent with 7% (n=8/118) having a dose reduction of 10%, 6% (n=7/118) having a dose reduction of 20%, 5% (n=6/118) having a dose reduction of 30% and 1% (n=1/118) having a dose reduction of 40%.

The steps taken to get to these dose reductions is unknown. Some may have been in steps of 5%, some in steps larger than 10%. To some extent the likelihood of these different sized steps may tend to be cancelled out by the larger number patient only having a relatively small overall adjustment of 10% compared to the smaller number having a larger overall adjustment of 30% or 40%. With this in mind, as a working assumption a common step of 10% can be assumed across all patients can be assumed. In other words, those with:

- 0% adjustment would require 2 My5-FU assays
- 10% adjustment would require 3 My5-FU assays
- 20% adjustment would require 4 My5-FU assays
- 30% adjustment would require 5 My5-FU assays
- 40% adjustment would require 6 My5-FU assays

Applying these suggests an average initial requirement of 3.23 My5-FU assays, broadly in line with the Saladax figure. If the adjustment to 10% is more usually done in 5% increments as may occur under the Gamelin et al. (2008)[118] dose adjustment algorithm, so resulting in a minimum requirement for 4 My5-FU assays for these patients, the average initial requirement rises to perhaps around 4.4 My5-FU assays. But it should also be borne in mind that the minimum step in the Kaldate et al. (2012)[96] dose adjustment algorithm is around 10% of the initial dose.

The base case will assume an average initial requirement of 3.23 My5-FU assays per patient. Sensitivity analyses will vary this to [redacted] and to 4.4 My5-FU assays per patient. The other extreme of assuming all adjustment occurs after the first test can also be assumed, capping the number of initial My5-FU assays per patient at a maximum of 3.

Dose adjustment will also require further staff time to calculate the appropriate dose and communicate this to pharmacy. There is some uncertainty around what is reasonable to assume for this, but the base case will assume 10 minutes of consultant time per adjustment [*personal communication: Nick Wadd*]. The base case applies this only in the My5-FU arm. It can be argued that it should also be applied to the 4% reported by Capitain et al. (2012)[119] who had their dose reduced in the BSA arm, though this would have little impact upon results.

But there remains some uncertainty as to how many further My5-FU assays would be required over the course of chemotherapy. Gamelin et al. (2008)[118] reported an average of 4 cycles to get the plasma concentration in range, though the relevance of this may be reduced by the initial 5-FU dose employed within Gamelin et al. (2008).[118] Kline et al. (2013)[156] also suggested that as the number of cycles increases the ability to metabolise 5-FU fall which may tend to increase plasma concentrations and so result in an ongoing need for testing using My5-FU.

Expert opinion suggests that unexpected toxicity could lead to more being assays being used, or that there might be routine monitoring every third cycle post-stabilisation. This will be explored as a sensitivity analysis.

6.2.5.2 Chemotherapy costs

The cost of line insertion is common to both arms and so has not been included.

Iveson et al. (1999)[205] estimate a cost for a disposable pump for 5-FU inclusive of all disposables and pharmacist time of £62 [£105] though there is some ambiguity as to whether this is per cycle or per week within a two week cycle. This is broadly in line with the £35 [£38] per pump of TA212[183] and the £37 [£39] per pump of Shabarrudin (2011),[206] when these are coupled with the £38 [£47] pharmacist time for the 5-FU infusion of TA93[30] and TA118.[179] In the light of this a cost per disposable pump, exclusive of pharmacist time, of £39 will be applied.

Drug costs have been sourced from the CMU EMIT database[207] in line with the 2013 NICE methods guide.[208] Note that though pharmacokinetic dosing results in 5-FU dose changes, the ingredient cost of the 5-FU is so small that the costs of the change in the 5-FU being administered has not been factored into the analysis.

Pharmacy preparation costs have been taken from TA93,[30] uprated for inflation. A point worth bearing in mind is that some hospital pharmacies contract out the 5-FU preparation. This approach has not been taken into account in the analysis, and it would be difficult to do so given considerations around commercial confidentiality.

The administration cost is based upon the outpatient cost for a complex prolonged infusion: SBZ14Z [*personal communication: Helen Haley, South Tees NHS Trust*].

Staff costs for flushing the line at the end of each cycle are based upon 40 minutes of health visitor time face to face with the patient [*personal communication: Delyth Mcentee, Christie Hospital 28*

March 2014], costed using the 2013 PSSRU Unit Costs of Health and Social Care.[203] Some areas recall patients for an outpatient appointment for termination of their cycle. As a consequence, the £102 for a Nurse-led outpatient WF01A 370 medical oncology, non-admitted face to face follow up appointment can be used for a sensitivity analysis.

This results in the following cost per cycle for FOLFOX and FOLFIRI Table 54.

Table 54. Chemotherapy costs for mCRC

	FOLFOX	FOLFIRI
Administration	£286.60	£286.60
Pharmacy	£189.06	£189.06
Folinic acid	£6.17	£6.17
Oxaliplatin	£18.12	
Irinotecan		£29.02
5-FU bolus	£1.27	£1.27
5-FU infusion	£3.70	£3.70
Pump	£38.96	£38.96
Line flush	£40.67	£40.67
Total	**£584.54**	**£595.44**

6.2.5.3 Other ongoing costs

Ongoing monthly costs have been drawn from Kerr et al (1999) as reported in TA118[179]: consultations £80 [£128], tests £65 [£103] and primary care costs £10 [£17].

6.2.5.4 Adverse events: Resource use

The systematic literature review of adverse events costs in sterling, as summarised in Appendix 21 found relatively little of use for current purposes.

Leese et al. (1993)[209] reviewed patient notes and estimated febrile neutropenia to cost £2,445 [£4,428] for patients with haematological disorders but no solid tumours. Leese et al. (1994)[210] which was based upon expert opinion suggested an estimate of £1,542 [£2,793] for patients with solid tumours.

Smith et al. (2002)[211] provide cost estimates for a number of grade III/IV adverse events. The following estimates appear to be implied:

- £1,000 [£1,532] for stomatitis
- £1,016 [£1,557] for diarrhoea
- £600 [£920] for hand-foot syndrome
- £1,100 [£1,686] for nausea/vomiting

- £200 [£307] for neutropenia
- £780 [£1,196] for sepsis/fever
- £780 [£1,196] for anaemiathrom/bocytopenia

But there is a lack of detail within the paper.

In the light of the above, adverse events will be costed as either an inpatient episode or as a prescribed drug therapy.

The costs of adverse events will be mainly driven by the proportion of adverse events requiring hospitalisation. Expert opinion suggests that the following might be approximately reasonable (Table 55), though considerable uncertainty surrounds these estimates and there was a suggestion by one of the experts that the estimates may be on the high side. There was also disagreement on whether neutropenia would lead to admission, the following assuming that admission would only occur if it progressed to be febrile neutropenia.

Table 55. Hospital admission rates for adverse events

	Grade I	Grade II	Grade III	Grade IV
Diarrhoea	0%	5%	50%	100%
Vomiting/nausea	0%	5%	50%	100%
Mucositis	0%	5%	50%	100%
Hand foot syndrome	0%	5%	50%	100%
Leukopenia	0%	0%	0%	0%
Neutropenia	0%	0%	0%	0%
Thrombocytopenia	0%	0%	0%	5%

6.2.5.5 Adverse events: Unit costs

The health resource groups (HRGs) for hospitalisations have been taken from the NHS reference cost grouper (Table 56).[212] Colorectal cancer suggest a CC score of 2 leading to the following HRG and costs. The inpatient costs are taken from non-elective short stay and non-elective long stay as a weighted average of all admissions, and not limited to general medicine or oncology admissions.

Table 56. Hospitalisation costs for adverse events: Non-Elective

	HRG	Description	Mean
Diarrhoea	FZ91M	Non-Malignant Gastrointestinal Tract Disorders, without Interventions, with CC Score 0-2	£798
Vomiting/nausea	FZ91M	Non-Malignant Gastrointestinal Tract Disorders, without	£798

		Interventions, with CC Score 0-2	
Mucositis	CZ23Y CZ23X	Major Head, Neck and Ear Disorders, without CC Major Head, Neck and Ear Disorders, with Intermediate CC	£663 £781
Hand foot syndrome	JD07J	Skin Disorders without Interventions, with CC Score 2-5	£1,102
Leukopenia	SA35D	Agranulocytosis with CC Score 2-4	£1,490
Neutropenia	SA08J	Other Haematological or Splenic Disorders, with CC Score 0-2	£921
Thrombocytopenia	SA12J	Thrombocytopenia with CC Score 2-4	£1,453

Those not treated as inpatients are assumed to be identified during routine follow-up and prescribed medication:

- Diarrhoea: loperamide [BNF[213] £1.74, eMIT[207] £0.28], codeine, antibiotics if felt to be infective
- Nausea/Vomiting: domperidone [BNF[213] £1.39, eMIT[207] £0.32], metoclopramide, ondansteron
- Mucositis: benzydamine [BNF[213] £6.45], vaseline on lips
- Hand-foot: simple creams such as diprobase [BNF[213] £6.32], topical antibacterial
- Thrombocytopenia: a small percentage of serious events may get platelet transfusion, with Varney et al. (2003) as reported in TA145[214] suggesting a cost of £84.22 [£101.08].

6.2.5.6 Summary of main parameter input values to the base cases

The main parameter inputs that result from the above are summarised below (Table 57 to Table 60).

Table 57. Main parameter input values to the base cases: survival estimates

Clinical effectiveness FOLFOX		
PK λ OS	0.00233	Inferred from Captain et al. (2012)
PK γ OS	1.66906	Inferred from Captain et al. (2012)
BSA λ OS	0.00398	Inferred from Captain et al. (2012)
BSA γ OS	1.66906	Inferred from Captain et al. (2012)
PK λ PFS	0.02438	Inferred from Captain et al. (2012)
PK γ PFS	1.13668	Inferred from Captain et al. (2012)
BSA λ PFS	0.05060	Inferred from Captain et al. (2012)
BSA γ PFS	1.13668	Inferred from Captain et al. (2012)
Clinical effectiveness 5-FU + FA		
PK λ OS	0.00270	Inferred from Gamelin et al. (2008)
PK γ OS	1.82786	Inferred from Gamelin et al. (2008)
BSA λ OS	0.00865	Inferred from Gamelin et al. (2008)
BSA γ OS	1.54066	Inferred from Gamelin et al. (2008)
PK λ PFS	0.05541	Inferred from pooled 3 studies
PK γ PFS	1.35834	Inferred from pooled 3 studies
BSA λ PFS	0.05541	Inferred from pooled 3 studies

BSA γ PFS	1.35834	Inferred from pooled 3 studies

Table 58. Main parameter input values to the base cases: adverse events

FOLFOX AE rates				Grade III/IV	
Diarrhea PK				2%	Captain et al. (2012)
Neutropenia PK				18%	Captain et al. (2012)
Mucositis PK				1%	Captain et al. (2012)
Thrombocytopenia PK				12%	Captain et al. (2012)
Diarrhea BSA				12%	Captain et al. (2012)
Neutropenia BSA				25%	Captain et al. (2012)
Mucositis BSA				15%	Captain et al. (2012)
Thrombocytopenia BSA				10%	Captain et al. (2012)
5-FU + FA AE rates	Grade I	Grade II	Grade III	Grade IV	
Diarrhea PK	9%	3%	4%	0%	Gamelin et al. (2008)
Mucositis PK	2%	1%	1%	1%	Gamelin et al. (2008)
Hand-foot syndrome PK	30%	21%	10%	1%	Gamelin et al. (2008)
Leukopenia PK	0%	0%	0%	0%	Gamelin et al. (2008)
Diarrhea BSA	14%	28%	15%	3%	Gamelin et al. (2008)
Mucositis BSA	2%	1%	1%	1%	Gamelin et al. (2008)
Hand-foot syndrome BSA	16%	22%	7%	0%	Gamelin et al. (2008)
Leukopenia BSA	0%	2%	1%	1%	Gamelin et al. (2008)

Table 59. Main parameter input values to the base cases: Quality of life

Quality of life values	PFS	SWP			
Farrkila	0.820	0.643			Farrkila et al (2013)
TA176	0.800	0.600			TA176
Best	0.515	0.213			Best et al (2010)
Adverse event QALYs	Grade I	Grade II	Grade III	Grade IV	
Diarrhoea	-0.0020	-0.0020	-0.0012	-0.0012	MRC SCOT trial + opinion
Nausea/vomiting	-0.0012	-0.0012	-0.0011	-0.0011	MRC SCOT trial + opinion
Hand & Foot	-0.0005	-0.0005	-0.0014	-0.0014	MRC SCOT trial + opinion
Mucositis	-0.0017	-0.0017	-0.0003	-0.0003	MRC SCOT trial + opinion
Neutropenia	0.0000	0.0000	-0.0012	-0.0012	MRC SCOT trial + opinion
Leukopenia	0.0000	0.0000	-0.0008	-0.0008	MRC SCOT trial + opinion
Thrombocytopenia	0.0000	0.0000	-0.0007	-0.0007	MRC SCOT trial + opinion

Table 60. Main parameter input values to the base cases: Costs

Costs of My5-FU					
Cost My5-FU	£61.03				Saladax plus NHS staffing costs
Number of My5-FU assays	3.23				Inferred from Captain et al.(2012)
Number dose adjustments	1.58				Inferred from Captain et al. (2012)
Cost dose adjustments	£23.17				10 minutes consultant time
Chemotherapy costs					
FOLFOX per cycle	£591.21				CMU EMIT plus NHS ref. costs
FOLFIRI per cycle	£602.11				CMU EMIT plus NHS ref. costs
Adverse event costs	Grade I	Grade II	Grade III	Grade IV	
Diarrhoea	£1.74	£41.54	£399.78	£797.82	CMU EMIT plus NHS ref. costs
Nausea/vomiting	£1.39	£41.21	£399.61	£797.82	CMU EMIT plus NHS ref. costs
Hand & Foot	£6.32	£61.09	£554.07	£1,101.81	CMU EMIT plus NHS ref. costs
Mucositis	£6.45	£45.16	£393.53	£780.61	CMU EMIT plus NHS ref. costs
Neutropenia	£0.00	£0.00	£0.00	£0.00	CMU EMIT plus NHS ref. costs
Leukopenia	£0.00	£0.00	£0.00	£0.00	CMU EMIT plus NHS ref. costs
Thrombocytopenia	£0.00	£0.00	£4.21	£76.65	CMU EMIT plus NHS ref. costs

6.2.5.7 Results: FOLFOX studies analyses

For the FOLFOX studies base case, the following deterministic results apply for the two scenarios of treatment for 12 cycles and treatment until progression (Table 61).

Table 61. FOLFOX base case: Deterministic results

	My5-FU	BSA	Net
LY	2.63	1.95	0.69
QALY	2.07	1.47	0.60
Costs			
My5-FU	£197	£0	£197
Adjustment	£37	£0	£37
FOLFOX	£6,560	£6,092	£467
FOLFIRI	£2,442	£2,578	-£136
Monitoring	£7,895	£5,847	£2,047
AEs	£15	£144	-£129
Total	£17,145	£14,663	£2,483
ICER			£4,148

Apparent in the above is that the 2nd line FOLFIRI provides a reasonably large cost offset: sufficient for two My5-FU test costs in the treatment for 12 cycles scenario. This appears to mainly arise due to the progression free survival curve for My5-FU crossing over, and so being assumed to follow, the overall survival curve. As 2nd line FOLFIRI is only administered upon entering survival with progression after 1st line FOLFOX the proportion of patients receiving 2nd line FOLFIRI within the My5-FU arm is not only later than in the BSA arm, it is also less. This may be more an artefact of the model structure than a reasonable assumption, and argues for a sensitivity analysis that excluded the impact of 2nd line FOLFIRI.

The probabilistic modelling of 10,000 iterations coincidentally results in the same central estimate of cost effectiveness: £4,148 per QALY. The probabilistic modelling results in the following scatterplot (Figure 40) and CEAC (Figure 41).

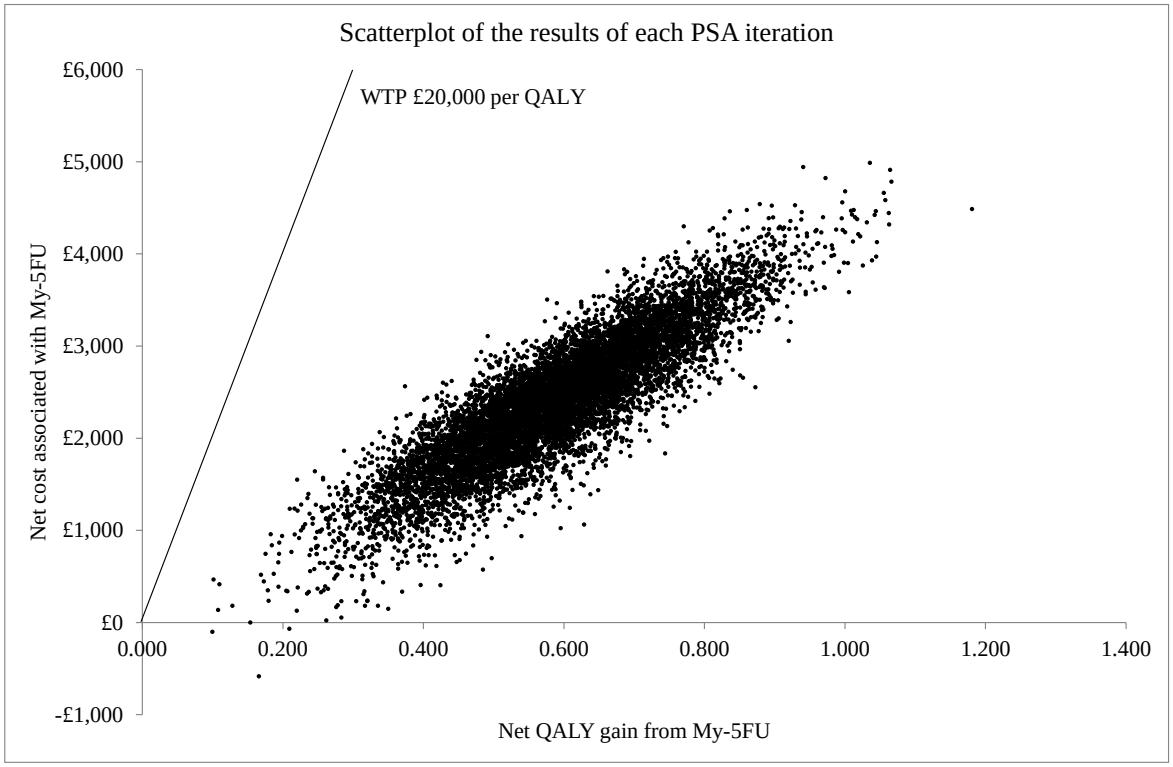


Figure 40. FOLFOX base case: Cost Effectiveness Plane Scatterplot

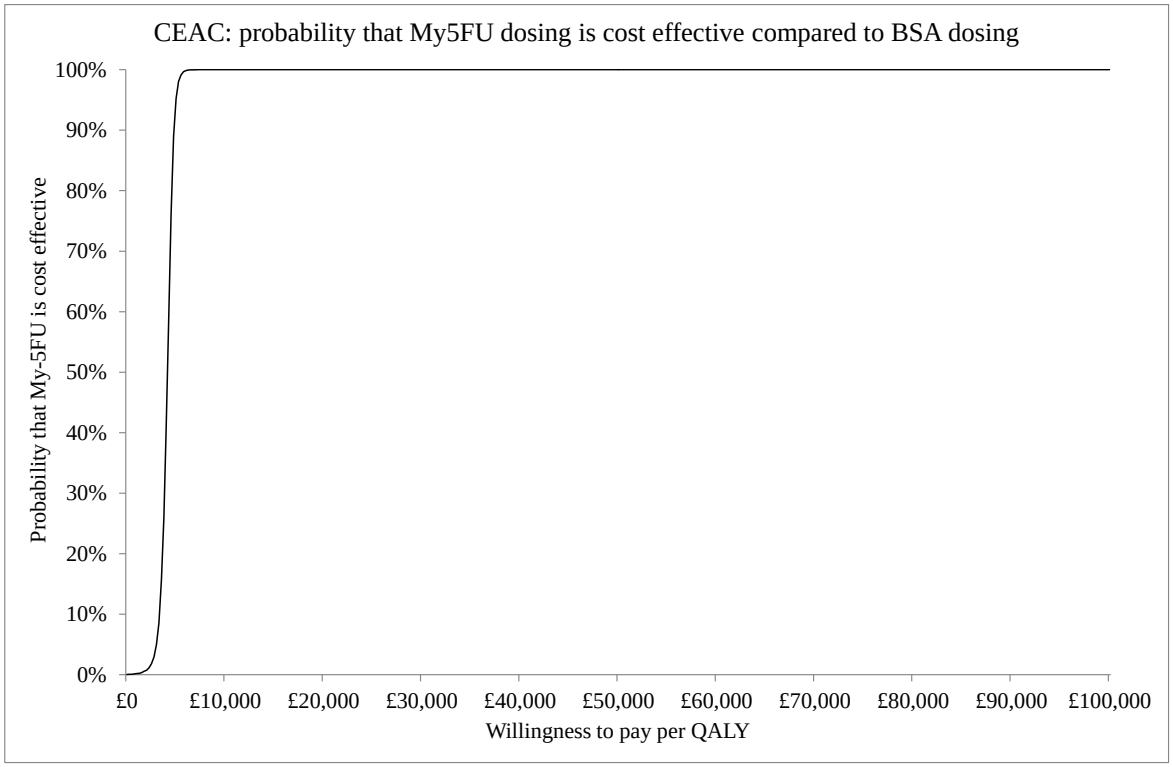


Figure 41. FOLFOX base case: Cost Effectiveness Acceptability Curves

For the scenario analyses applying BSA curves from a range of studies within the literature, the following results apply (Table 62).

Table 62. FOLFOX scenario analyses: Deterministic results

Scenario analysis 01

	My5-FU	BSA	Net
LY	2.63	2.37	0.26
QALY	2.07	1.74	0.32
Total	£17,145	£15,933	£1,213
ICER			£3,740

Scenario analysis 02

	My5-FU	BSA	Net
LY	2.63	1.61	1.03
QALY	2.07	1.22	0.85
Total	£17,145	£13,783	£3,362
ICER			£3,950

Scenario analysis 03

	My5-FU	BSA	Net
LY	2.63	1.76	0.88
QALY	2.07	1.32	0.74
Total	£17,145	£14,281	£2,864
ICER			£3,850

Scenario analysis 04

	My5-FU	BSA	Net
LY	2.63	2.20	0.44
QALY	2.07	1.60	0.47
Total	£17,145	£15,492	£1,653
ICER			£3,514

Scenario analysis 05

	My5-FU	BSA	Net
LY	2.63	1.89	0.75
QALY	2.07	1.40	0.67
Total	£17,145	£14,624	£2,521
ICER			£3,762

The first scenario analysis of applying the hazard ratio from Gamelin et al (2008) to the Weibull for overall survival derived from the pharmacokinetic dosing arm of Capitain et al 2012 in order to derive the Weibull for overall survival in the BSA dosing arm improves the cost effectiveness of My5-FU from the £4,148 of the base case to £3,740 per QALY.

This may initially seem a perverse result. The change increases discounted survival in the BSA arm to 2.37 years. As there is no change to the progression free survival curve in the BSA arm, all this survival is modelled as being experienced at the survival with progression quality of life of 0.643, resulting in total QALYs in the BSA arm of 1.74: an increase of 0.27 over the base case. But this additional survival involves an increase in ongoing treatment and monitoring costs from £5,847 to £7,117: an increase of £1,269 compared to the base case. This can be interpreted as a cost per QALY of £4,626. In other words while there are additional ongoing costs from the increased survival in the BSA dosing arm there is no suggestion that the increase in survival is not cost effective, even if it is only experienced at the survival with progression quality of life.

But the key point here is that £4,626 per QALY for this additional survival in the BSA dosing arm lies above the base case £4,168 per QALY for My5-FU compared to BSA. As a consequence, the change improves the cost effectiveness estimate for My5-FU compared to BSA. Had the cost effectiveness for My5-FU compared to BSA dosing been somewhat higher than £4,626 per QALY, applying the hazard ratio of Gamelin et al to derive the BSA overall survival curve would have somewhat worsened the cost effectiveness estimate for My5-FU compared to BSA dosing.

This sensitivity analysis is also dependent upon the model structure and it forcing the additional survival to be evaluated at the survival with progression quality of life of 0.643. Had it been evaluated at the progression free survival quality of life of 0.820, the cost effectiveness of My5-FU would have worsened to £4,876 per QALY.

Changing the source of the BSA progression free survival estimates and overall survival estimates as in scenario analysis 02 from those inferred from the Capitain et al. (2012)[119] medians to those derived from pooling BSA arms within the literature has relatively little impact upon cost effectiveness results. Similarly, changing the source to Ducreux et al. (2011)[168] improves the ICERs slightly further.

Changing the source of the BSA progression free survival estimates and overall survival estimates as in scenario analysis 04 from those inferred from the Capitain et al. (2012)[119] medians to those derived from Tournigand et al. (2004)[169] again slightly improve the ICER but the effect is not dramatic.

The last scenario analysis explored the impact of applying the BSA overall survival curve derived from non-UK studies. The justification for this is that the UK studies may suggest a worse overall survival. In order to compared like with like, the estimates from Capitain et al for PK dosing can be

compared with the estimates from the pooled non-UK studies for BSA dosing. The impact upon results is again not large.

In short, if hazard ration for overall survival derived from Gamelin et al (2008) is applied, under a plausible scenario this may slightly worsen the cost effectiveness estimate. But in the main, applying the curves derived from single arms within the literature has relatively little impact upon results.

6.2.5.8 Results: 5-FU + FA studies analyses

For the 5-FU + FA studies base case, the following deterministic results apply (Table 63).

Table 63. 5-FU + FA base case: Deterministic results

	My5-FU	BSA	Net
LY	1.81	1.57	0.23
QALYs	1.30	1.15	0.15
Costs			
My5-FU	£197	£0	£197
Adjustment	£37	£0	£37
FOLFOX	£5,751	£5,751	£0
FOLFIRI	£2,619	£2,614	£5
Monitoring	£5,433	£4,738	£695
AEs	£111	£161	-£50
Total	£14,147	£13,264	£883
ICER			£5,853

The probabilistic modelling of 10,000 iterations results in a very similar central estimate of cost effectiveness: £5,852 per QALY. The probabilistic modelling results in the following scatterplot (Figure 42) and CEAC (Figure 43).

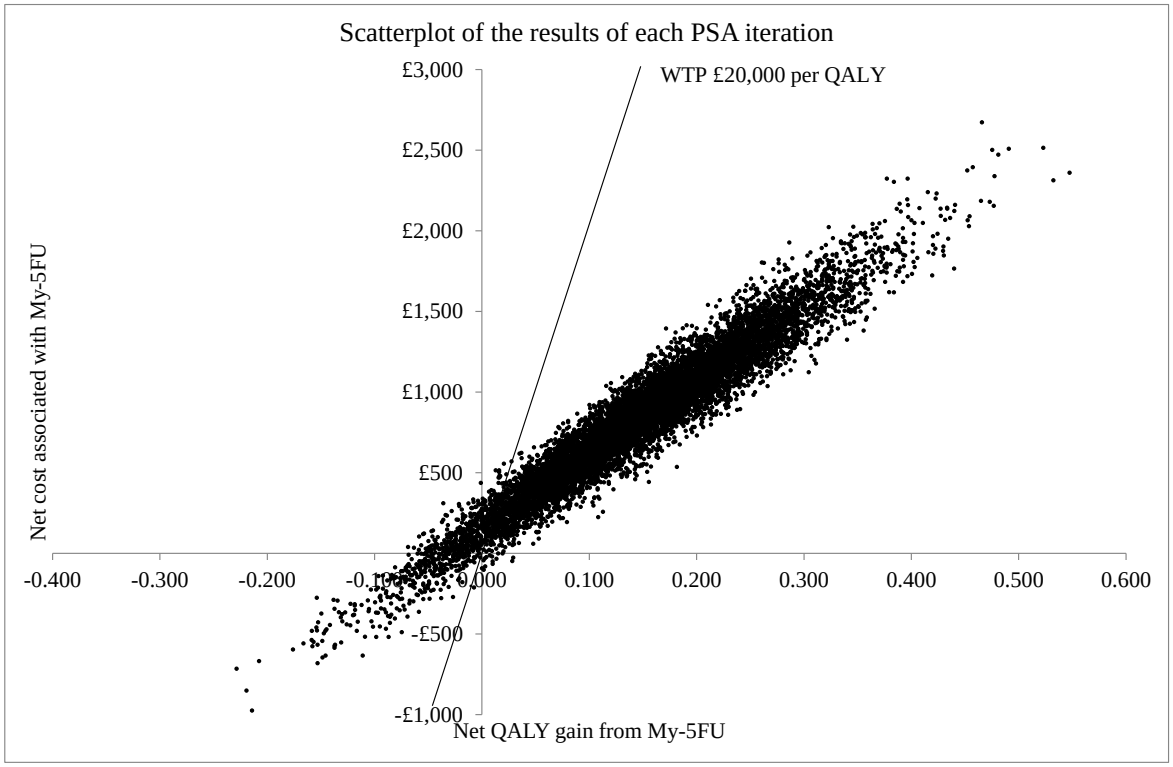


Figure 42. 5-FU + FA base case: Cost Effectiveness Plane Scatterplot

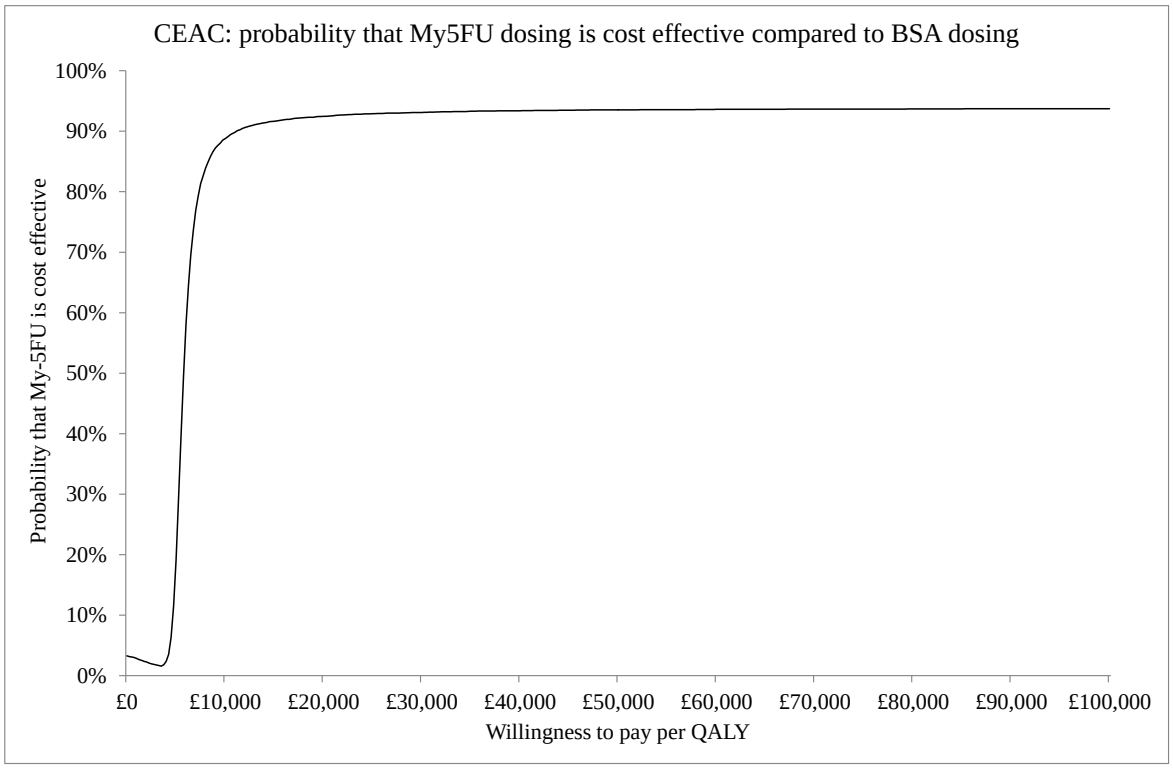


Figure 43. 5-FU + FA base case: Cost Effectiveness Acceptability Curves

For the scenario analyses applying BSA curves from a range of studies within the literature, the following results apply (Table 64).

Table 64. 5-FU + FA scenario analyses: Deterministic results

Scenario analysis 01

	My5-FU	BSA	Net
LY	1.81	1.57	0.23
QALY	1.30	1.13	0.17
Total	£14,540	£13,059	£1,480
ICER			£8,615

Scenario analysis 02

	My5-FU	BSA	Net
LY	1.81	1.57	0.23
QALY	1.37	1.16	0.21
Total	£15,024	£13,558	£1,466
ICER			£6,965

Scenario analysis 03

	My5-FU	BSA	Net
LY	1.81	1.57	0.23
QALY	1.37	1.15	0.22
Total	£14,127	£13,264	£862
ICER			£3,989

Scenario analysis 04

	My5-FU	BSA	Net
LY	1.90	1.57	0.33
QALY	1.37	1.15	0.21
Total	£14,427	£13,264	£1,163
ICER			£5,459

Scenario analysis 05

	My5-FU	BSA	Net
LY	1.90	1.57	0.33
QALY	1.43	1.15	0.28
Total	£14,427	£13,264	£1,163
ICER			£4,165

Scenario analysis 06

	My5-FU	BSA	Net
LY	1.90	1.44	0.46
QALY	1.43	1.07	0.36
Total	£14,427	£12,864	£1,564
ICER			£4,291

For the first two scenario analysis that apply the progression free survival estimates derived from Gamelin et al. (2008)[135] response duration data, the cost effectiveness of My5-FU is estimated to worsen compared to the base case. This appears to be due to a modelled increase in the proportion of patients receiving ongoing 1st line FOLFOX6 tending to outweigh the quality of life gains from an increased duration of progression free survival. This effect appears to work in reverse for the scenario analysis that applies the progression free survival curve of Gamelin et al (1998) in the My5-FU

The remaining scenario analyses that pool results for a range of curves from a number of one arm studies have only a limited impact upon results.

6.2.5.8.1 Sensitivity analyses: FOLFOX studies

As previously discussed, sensitivity analyses around the cost per My5-FU assay can be conducted (Table 65). These assume annual throughputs of 500 and 1,000, and also that assume 200 assays per kit, and finally the throughput and assays per kit of the base case but with daily batches.

Expert opinion suggests that between 10% and 20% of patients that started a 12 cycle course of FOLFOX6 might, after a treatment holiday start another course of FOLFOX6. This can be explored by assuming that 40% of those remaining in progression free survival at the end of the first year start another course of FOLFOX6.

As also discussed above, a sensitivity analysis excluding 2nd line FOLFIRI appears justified due to the My5-FU progression free survival curve crossing and so being modelled as following the overall survival curve after a certain point.

The modelling has not considered end of life costs, since all patients will be modelled as incurring these costs. But they will incur them at different times and discounting may have an effect. As a consequence, an admittedly arbitrary end of life cost of £3,000 for each incident death can be modelled.

It is unclear whether there is sufficient health visitor capacity for blood samples to always be taken in the community. In the light of this, the cost of a nurse led outpatient appointment can be assumed for the taking of the blood sample.

The alternative sources of quality of life values for the main health states can also be explored.

The number of My5-FU assays required per patient for initial stabilisation can be raised to [redacted] and 4.4. Based upon expert opinion, it can also be assumed that there will be a need for ongoing monitoring using My5-FU subsequent to initial stabilisation in one third of FOLFOX administrations.

Changing the source of adverse event estimates to be Gamelin et al. (2008)[118] can also be explored. The extent to which the overall survival estimates and the progression free survival estimates drive results can be explored by excluding them, leaving only the differences in adverse event costs and effects and the additional costs of My5-FU testing.

Table 65. Univariate sensitivity analyses: FOLFOX studies

Sensitivity analysis	Δ QALY	Δ Cost	ICER
Base case	0.599	£2,483	£4,148
500 throughput, 100 per kit	0.599	£2,466	£4,120
1,000 throughput, 100 per kit	0.599	£2,454	£4,100
300 throughput, 200 per kit	0.599	£2,454	£4,100
500 throughput, 200 per kit	0.599	£2,443	£4,082
1,000 throughput, 200 per kit	0.599	£2,436	£4,069
Daily My5-FU batches	0.599	£2,586	£4,320
10% 2nd course FOLFOX6	0.599	£3,156	£5,272
No 2nd line FOLFIRI	0.600	£2,618	£4,363
£3,000 End of life cost	0.599	£2,410	£4,026
Quality of life: TA176	0.589	£2,483	£4,214
Quality of life: Best et al (2010)	0.413	£2,483	£6,016
[redacted]	[redacted]	[redacted]	[redacted]
4.4 My5-FU assays	0.599	£2,554	£4,267
Single adjustment/extra assay	0.599	£2,465	£4,118
Ongoing 1/3rd My5-FU assays used	0.599	£2,610	£4,361
OP visit for blood test	0.599	£2,697	£4,506
AEs from Gamelin et al (2008)	0.599	£2,562	£4,277
Same OS and PFS	0.000	£104	£435,819

Cost effectiveness estimates are relatively insensitive to the throughputs that are assumed, provided that weekly batching is possible. They are more sensitive to whether batching is weekly or daily, but again the difference is not dramatic.

Assuming that a proportion of patients remaining in progression free survival at 12 months would receive a second course of FOLFOX6 has a reasonable impact upon the cost effectiveness estimate, worsening it to £5,272 per QALY.

Excluding 2nd line FOLFIRI has a relatively minor impact, as do end of life costs.

The source of the quality of life values is rather more important, as might be anticipated. The values of TA176[182] worsen the cost effectiveness estimates to a degree. The values of Best et al. (2010)[190] have a rather larger impact as might be anticipated due to valuing the additional survival less highly.

Increasing the number of My5-FU assays to [redacted] and to 4.4 for the initial stabilisation has only a limited impact. Assuming ongoing monitoring while on treatment has only a minor impact due to the base case assuming only 12 cycles of treatment.

Costing the taking of the blood sample at the outpatient visit rate has a reasonable impact, worsening the cost effectiveness estimate to £4,506 per QALY.

The source of adverse events has only a limited impact.

Equalising overall survival and progression free survival between the arms shows the extent to which the cost effectiveness of My5-FU rests upon these. The costs effectiveness estimates increase dramatically, as would be expected. These cost effectiveness estimates would further worsen if, after the initial stabilisation period, further ongoing monitoring with My5-FU was required.

6.2.5.8.2 Sensitivity analyses: 5-FU + FA studies

A similar set of sensitivity analyses to those presented above for the analyses based upon FOLFOX studies can be undertaken for the analyses based upon 5-FU + FA studies, only the last changing the source of adverse event estimates to be Capitain et al. (2012)[119] (see Table 66).

Table 66. Univariate sensitivity analyses: 5-FU + FA studies

Sensitivity analysis	Δ QALY	Δ Cost	ICER
Base case	0.151	£883	£5,853
500 throughput, 100 per kit	0.151	£866	£5,743
1,000 throughput, 100 per kit	0.151	£854	£5,663
300 throughput, 200 per kit	0.151	£854	£5,662
500 throughput, 200 per kit	0.151	£844	£5,593
1,000 throughput, 200 per kit	0.151	£836	£5,540
Daily My5-FU batches	0.151	£986	£6,535
10% 2nd course FOLFOX6	0.151	£883	£5,853
No 2nd line FOLFIRI	0.151	£878	£5,820
£3,000 End of life cost	0.151	£859	£5,693

Quality of life: TA176[182]	0.141	£883	£6,270
Quality of life: Best et al. (2010)[190]	0.051	£883	£17,485
[redacted]	[redacted]	[redacted]	[redacted]
4.4 My5-FU assays	0.151	£954	£6,324
Single adjustment/extra assay	0.151	£865	£5,736
Ongoing 1/3rd My5-FU assays used	0.151	£990	£6,559
OP visit for blood test	0.15	£1,098	£7,274
AEs from Capitain et al. (2012)[119]	0.150	£804	£5,344
Same OS and PFS	0.000	£104	£435,804

The pattern of results for the sensitivity analyses based upon the 5-FU + FA studies mirrors that of the sensitivity analyses based upon the FOLFOX studies. The main sensitivity analysis of interest is the application of the Best et al. (2010)[190] quality of life values, this worsening the cost effectiveness estimate to £17,485 per QALY. If this is coupled with an outpatient visit being required for the taking of the blood sample the cost effectiveness estimate would worsen further to £21,732 per QALY.

6.2.6 The cost effectiveness of pharmacokinetic dose adjustment using My5-FU in head and neck

6.2.6.1 Modelling approach

Blanchard et al. (2013)[50] undertook a meta-analysis of studies comparing induction chemotherapy using a taxane plus cisplatin and 5-FU (TPF) with induction chemotherapy using cisplatin and 5-FU alone (PF). They noted that the rates of radiotherapy and concomitant chemotherapy differed significantly following TPF induction and PF induction: 85% of patients received their planned radiotherapy, 49% received concomitant chemotherapy as planned and only 31% did not received any of the planned concomitant chemotherapy after TPF induction compared with 81%, 43% and 38% after PF induction. This may suggest that one of the main causes of the increased survival following TPF induction compared to PF induction was a better response to induction permitting more patients to undergo their planned chemo-radiotherapy.

This might suggest an approach of modelling an increase in responses rate to induction therapy leading to an increase in the proportion of patients receiving chemo-radiotherapy as planned, with survival and progression free survival being modelled as a function of the proportion receiving chemo-radiotherapy. Fety et al. (1998)[157] provide response rates for pharmacokinetic dose adjustment of PF induction therapy compared to BSA adjustment of PF induction therapy. Blanchard et al. (2013)[50] go on to note that "*No data on tumour response was collected*", but two of the papers underlying Blanchard et al. (2013)[50] do present some data on response rates. Hitt et al. (2005)[215] present both complete response rates and partial response rates. Pointreau et al. (2009)[216] present

overall response rates. But Posner et al. (2007)[217] and Vermorken et al. (2007)[218] do not present response rates.

As previously reviewed, Buyse et al. (2000)[185] in a meta-analysis of 25 RCTs raised concerns that response rates are quite poor predictors of overall survival within advanced CRC. The number of data points for a similar analysis based upon Hitt et al. (2005)[215] and Pointreau et al. (2009)[216] for head and neck cancer would be very considerably less than that available to Buyse et al.[185] Any resulting mapping from differences in induction chemotherapy response rates to differences in overall survival is likely to be questionable and subject to very high degree of uncertainty. Mapping from induction chemotherapy response rates to radiotherapy and concomitant chemotherapy treatment rates, and then on to survival would also seem to be questionable and subject to very high degree of uncertainty.

In the light of this, modelling survival in head and neck cancer as a function of response rates to induction chemotherapy has not been explored further. But the impact that response rates to induction chemotherapy might have upon the rates of administration of subsequent chemo-radiotherapy is explored in the following section.

Given the relative paucity of data for head and neck cancer, an exploratory analysis can be conducted that explores the cost and QALY impacts of the adverse events that Fety et al. (1998)[157] report for pharmacokinetic dosing compared to BSA dosing for induction chemotherapy for locally advanced head and neck cancer.

As requested during the ASG, this can be coupled with a threshold analysis which examines what impact My5-FU monitoring would be required to have upon overall survival for it to be cost effective at conventional NICE thresholds. However, it should be borne in mind that induction chemotherapy and its effects are likely to work through somewhat different channels than FOLFOX in mCRC. If the main impact of induction chemotherapy is to permit more patients to undergo chemo-radiotherapy, an analysis of the required overall survival hazard ratio may be a rather poor guide as to the required effectiveness of My5-FU monitoring.

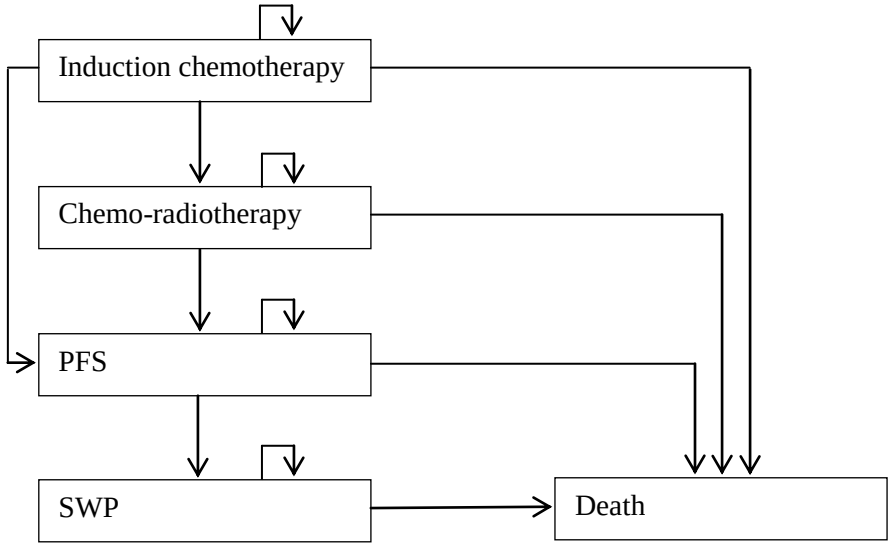
In the light of this, the modelling for locally advance head and neck cancer will attempt to identify:

- The progression free survival and overall survival of current therapy
- Adverse event rates, differentiated by arm
- The quality of life associated with advanced head and neck cancer
- The number of My5-FU assays that might be applied during induction therapy
- The costs of induction therapy

- The costs of subsequent chemo-radiotherapy
- The proportion of patients going forward for chemo-radiotherapy, differentiated by arm
- The ongoing costs having completed treatment

This gives rise to the following model structure (Figure 44).

Figure 44 Model structure for locally advanced head and neck cancer



6.2.6.1.1 Induction chemotherapy response rates and subsequent therapy rates

Blanchard et al. (2013)[50] did not meta-analyse response rates, noting that "*No data on tumour response was collected*" but going on to note that "*among patients who did start chemo-radiotherapy, there was no difference in compliance with concomitant chemotherapy (p=0.51)*". The papers underlying Blanchard et al. (2013) do report some data on response rates to induction chemotherapy and rates of subsequent therapy, as summarised below.

Hitt et al. (2005)[215] compared patients who received either cisplatin 100mg/m2 on day 1 plus FU 1,000 mg/m2 continuous infusion on days 1 through 5 (n=193) or paclitaxel 175mg/m2 on day 1, cisplatin 100mg/m2 on day 2 plus FU 1,000 mg/m2 continuous infusion on days 2 through 6 (n=189). Patients with complete response (CR) or partial response of greater than 80% in primary tumour received additional CRT of cisplatin 100mg/m2 on days 1, 22 and 43 plus 70 Gy. The following response rates to induction chemotherapy were observed (Table 67).

Table 67. Hitt et al (2005)[215] response rates to induction chemotherapy

	CF n=193		PCF n=189	
CR	26	13.5%	63	33.3%
PR	105	54.4%	89	47.1%
of which > 80%	69	35.8%	66	34.9%

Hitt et al. (2005)[215] go on to note that 39.4% (n=76) went on to receive per-protocol chemo-radiotherapy in the CF arm compared to 60.3% (n=114) in the PCF arm. While a simplification, if it is assumed that all those achieving a complete response to induction chemotherapy received subsequent chemo-radiotherapy, this would imply that 50 of the 69 partial responders with more than 80% response received it in the CF arm and 51 of the 66 in the PCF arm: reasonably constant proportions of 72.5% and 77.3% respectively.

Pointreau et al. (2009)[216] undertook a phase III trial with the specific aim of larynx preservation in patients with invasive squamous cell carcinoma. This compared three cycles of induction chemotherapy comparing TPF with PF. TPF consisted of docetaxel at 75mg/m2 on day 1, cisplatin at 75mg/m2 on day 1 and 5-FU at 750mg/m2 by 24 hour continuous infusion for 5 days. PF consisted of cisplatin at 100mg/m2 on day 1 and 5-FU at 1000mg/m2 by 24 hour continuous infusion for 5 days. Patients whose cancer responded well with either complete response of partial response (Table 68) with normal larynx mobility were treated with radiotherapy, which could be augmented with chemotherapy. The specific treatment according to protocol was delivered to 90% of the TPF group with 63% receiving complete treatment without delay or dose reduction, compared to 80% and 32% of the PF group.

Table 68. Pointreau et al (2009) [216] response rates to induction chemotherapy

	PF n=103		TPF n=110	
CR	31	30.1%	53	48.1%
PR	30	29.1%	42	38.2%

Radiation therapy was performed in 76% (n=84) of patients in the TPF group all of whom were responders. For the PF group 61% (n=63) of patients received radiotherapy, though Pointreau et al. (2009)[216] note that 57 patients responded to induction therapy and 6 had refused surgery. This could be seen as suggesting that complete responders received radiotherapy, while perhaps between 70% and 80% of partial responders received radiotherapy.

Posner et al. (2007)[217] compared TPF (n=255) with PF (n=246). The docetaxel dose was 75mg/m2 followed by cisplatin at 100mg/m2 followed by 5-FU at 1000mg/m2 per day as a continuous 24 hour infusion for 4 days. Those in the PF arm received cisplatin at 100mg/m2 followed by 5-FU at 1000mg/m2 per day as a continuous 24 hour infusion for 5 days. Three cycles of induction chemotherapy were administered.

Posner et al. (2007)[217] do not report response rates to induction therapy, only noting that 79% (n=202) received radiotherapy in the TPF arm compared to 75% (n=184) in the PF arm. Progressive disease is noted as one of a number of reasons for discontinuation of therapy, but the reporting of this does not appear to distinguish between progressive disease during induction therapy from that during the entire course of therapy.

Vermorken et al. (2007)[218] compared TPF (n=177) with PF (n=181) where TPF involved docetaxel at 75mg/m2 followed by cisplatin 75mg/m2 on day 1 and 5-FU at 750mg/m2 per day by continuous infusion for days 1 to 5. The PF regime increased the dose of cisplatin to 100mg/m2 on day 1, and also involved 5-FU at 750mg/m2 per day by continuous infusion for days 1 to 5. Up to four cycles were delivered. Patients without progressive disease and without a number of adverse events and adequate bone marrow function underwent radiotherapy.

More patients completed their induction chemotherapy in the TPF group76% (n=134) than in the PF group, 66% (n=119). But rates of completion of radiotherapy were more similar between the groups: 73% (n=129) for TPF and 66% (n=120) for PF. Vermorken et al. (2007)[218] do not separately report induction chemotherapy response rates.

While quite uncertain, the above could be taken as indicating that all complete responders to induction TPF will receive chemo-radiotherapy, while only 70% of partial responders to induction chemotherapy will receive chemo-radiotherapy. Fety et al. (1998)[157] report the following response rates which, if coupled with the assumptions about the rates of subsequent chemo-radiotherapy, imply the following (Table 69).

Table 69. Fety et al. (1998) induction chemotherapy response rates

	BSA dosing	**Subs. CRT**	**PK dosing**	**Subs. CRT**
Complete response	33% (19/57)	33%	29% (14/49)	29%
Partial response	44% (25/57)	31%	53% (26/49)	37%
Total	77% (44/57)	64%	82% (40/49)	66%

The relatively small differences in overall response rates could be taken as suggesting that while BSA dosing has a slightly lower overall response rate the differences in the proportions of patients receiving subsequent chemo-radiotherapy will be quite small: 2%. The extent of this difference may be slightly skewed in the above by the higher mean rate of complete response in the BSA dosing arm. It may be more reasonable to assume equivalence in terms of complete response and attribute any differences to changes in partial response. If so the additional 5% response rate in the pharmacokinetic dose adjustment arm could translate into perhaps an additional 3% receiving subsequent chemo-radiotherapy. While these differences seem slight, the chemo-radiotherapy costs per patient will be very much larger than the direct My5-FU tests costs.

The limited differences in overall response rates may also help illuminate how likely it is that the required threshold for the hazard ratio for overall survival and associated mean overall survival gain from My5-FU dose adjustment will be reached.

6.2.6.1.2 My5-FU administrations

Fety et al. (1998)[157] used a regimen in which 5-FU was administered over 96 hours, with the adjustment being based on the AUC during 0-48 hours. The AUC was measured during the first cycle. This led to any dose adjustment requirements for the following cycles, though the dose during the first cycle was only adjusted if the AUC during 0-48 hours was unusually high. The second cycle and the third cycle also had their AUC measured during 0-48 hours, with any required dose adjustment occurring at mid cycle.

Fety et al. (1998)[157] also report the following numbers of patients receiving treatment at each cycle (Table 70):

Table 70. Fety et al. (1998)[157] patients treated each cycle

	Cycle 1	Cycle 2	Cycle 3
BSA	57 100%	52 91%	49 86%
PK	49 100%	45 92%	41 84%

This suggests a total of 2.8 My5-FU assays over the three cycles.

Fety et al. (1998)[157] also report quite high dose adjustments during cycles 2 and 3. Within the BSA arm 3.9% received a 5-FU dose reduction during cycle 2 and 20.9% received a dose reduction during cycle 3. Within the pharmacokinetic arm 66.6% received a dose reduction during cycle 2 and 78.0% received a dose reduction during cycle 3. Also within the pharmacokinetic arm 8.8% received dose

increases during cycle 2 and 4.8% received dose increases during cycle 3. These dose adjustments will be costed assuming an additional 10 minutes consultant time.

6.2.6.2 Progression free survival and overall survival: BSA dosing

Due to the Blanchard et al. (2013)[50] curves not being Kaplan-Meier plots, they have no steps and as a consequence are not suitable for the Guyot et al. (2012)[125] method. As a consequence, parameterised curves have been fitted to the Blanchard et al. (2013)[50] TPF overall survival and progression free survival curves using ordinary least squares (Figure 45 and Figure 46).

EAG statistical opinion suggests that the fitted curves are likely to extrapolate too high a long term survival. In particular, the observed data appears to exhibit something of a downturn towards the end of both the overall survival curve and the progression free survival curve. For this reason the base case will apply a linear extrapolation using the last five values of the observed data. Applying this means that there are minimal differences between the parameterised curves up to this point (Figure 47). The Weibull will be applied.

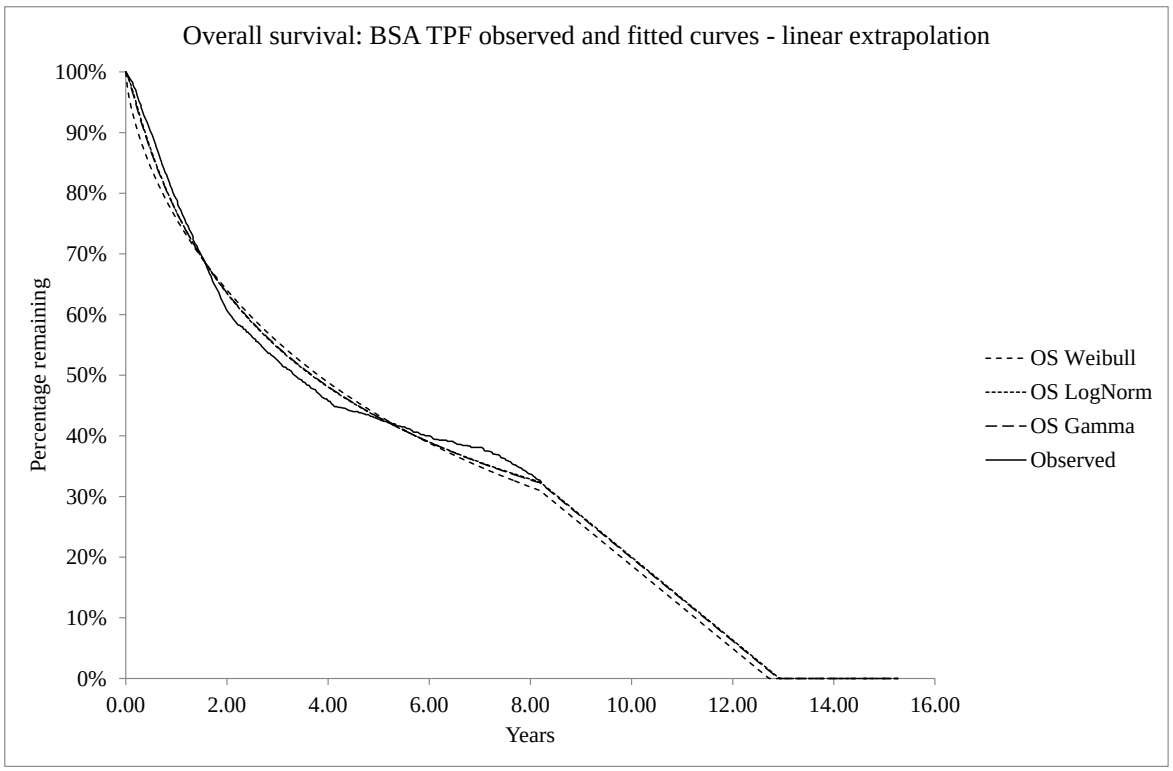


Figure 45. Blanchard et al. (2013)[50] OS observed values and fitted curves

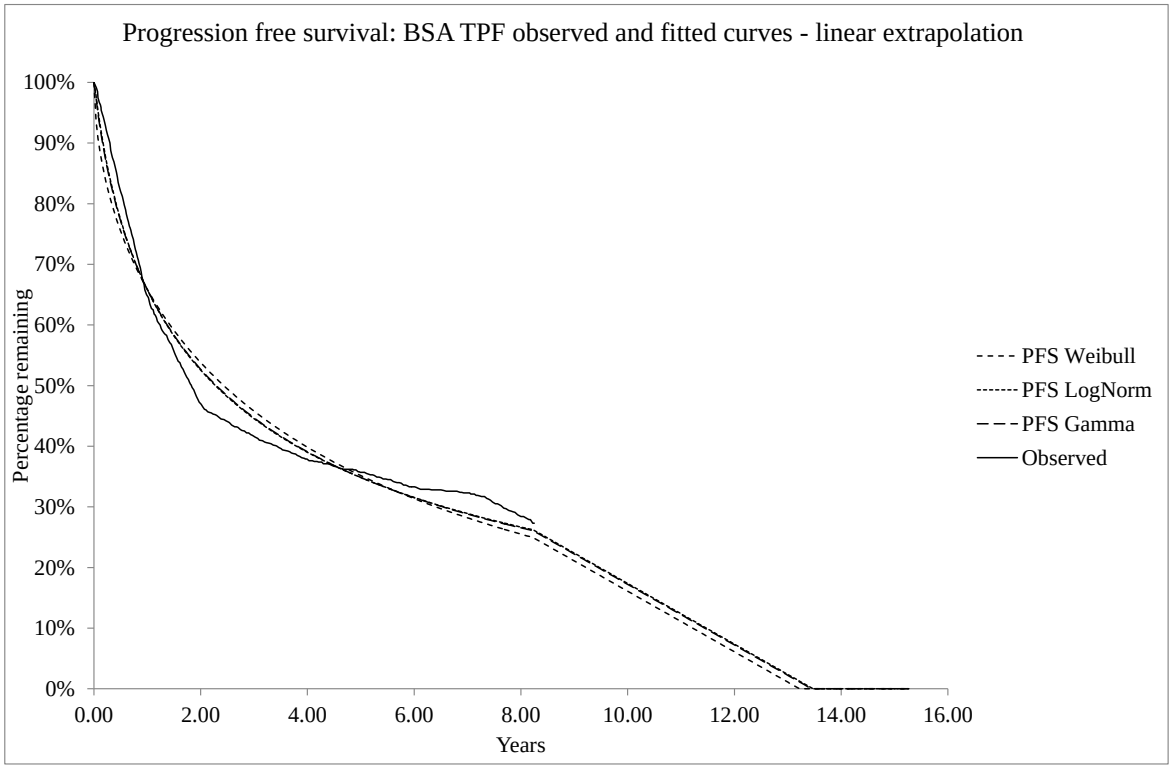


Figure 46. Blanchard et al. (2013)[50] PFS observed values and fitted curves

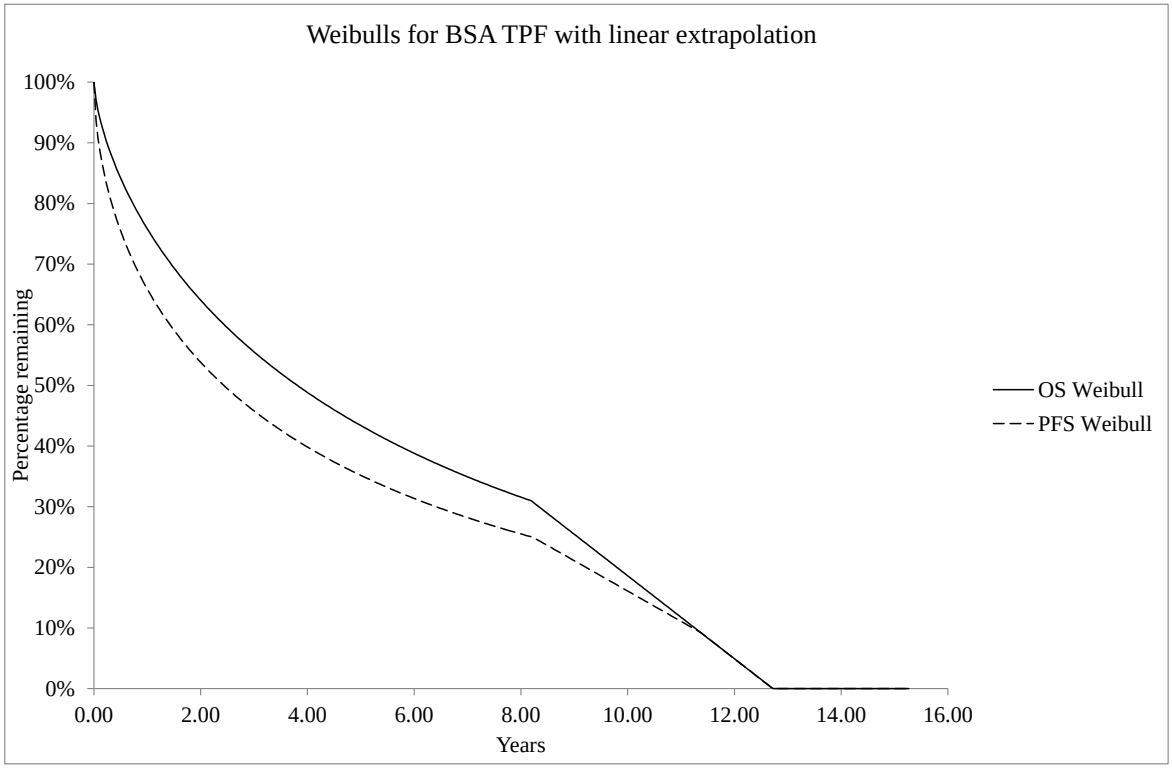


Figure 47. Blanchard et al. (2013)[50] Weibull curves with linear extrapolation applied

6.2.6.3 Adverse events rates

The clinical effectiveness estimates of Fety et al. (1998)[157] are based upon pharmacokinetic monitoring of the 5-FU dose within the context of cisplatin+5-FU induction chemotherapy (PF): with dosing of 100mg/m^2 and a starting dose of 4,000mg/m^2 for 5-FU, with the 5-FU being administered as a continuous infusion over 4 days. Current induction chemotherapy is 5-FU in combination with a taxane, either docetaxel or paclitaxel, in combination with cisplatin and 5-FU (TPF): dosing would typically be 75mg/m^2, 75mg/m^2 and 750mg/m^2 per day for the 5-FU, with the 5-FU being administered for 4-5 days. In some instances, cisplatin plus 5-FU (PF) may also be given as induction chemotherapy: dosing would typically be 100mg/m^2 and 1,000mg/m^2. Blanchard et al. (2013)[50] meta-analysed studies comparing TPF with PF.

Given the difference between current practice (TPF) and the regime of Fety et al. (1998)[157] (PF), the following assumes that the relative risks of Grade III/IV adverse events for pharmacokinetic dosing compared to BSA dosing reported by Fety et al. (1998)[157] for PF are equally applicable to TPF. Fety et al. (1998)[157] also only report the proportion of cycles at which the grade III/IV adverse events of neutropenia/thrombocytopenia, mucositis and digestive tract were experienced. The relative risk for neutropenia/thrombocytopenia is applied equally to the baseline risks for neutropenia and thrombocytopenia for TPF induction chemotherapy as reported in Blanchard et al. (2013),[50] and the papers underlying Blanchard et al.[50] Similarly, the relative risk of digestive tract toxicity is applied equally to the baseline risks for vomiting, nausea and diarrhoea as reported in Blanchard et al.[50], and the papers underlying Blanchard et al.[50]

Fety et al. (1998)[157] report grade III/IV adverse events as a proportion of the total number of cycles. This can be coupled with the data on the numbers of patients receiving treatment to suggest the following numbers of events per patient (Table 71).

Table 71. Fety et al. (1998)[157] grade III/IV adverse events per patient

	BSA	PK
Neutropenia/thrombocytopenia	0.49	0.20
Mucositis	0.14	0.00
Digestive tract	0.14	0.22

The split between neutropenia and thrombocytopenia and the split of digestive tract adverse events into diarrhoea and nausea/vomiting can be made in proportion to the rates reported in the studies underlying Blanchard et al. (2013).[50] This suggests the following

Table 72).

Table 72. Fety et al. (1998)[157] grade III/IV adverse events per patient reattributed

	BSA	PK
Neutropenia	0.47	0.20
Thrombocytopenia	0.02	0.01
Mucositis	0.14	0.00
Diarrhoea	0.06	0.10
Nausea/vomiting	0.08	0.13

As there is no split between grade III and grade IV adverse events, for costing purposes the split that was used for the mCRC modelling has been applied.

The costs and QALY impacts estimated for each adverse events within the mCRC modelling have been reapplied.

6.2.6.3.1 Quality of life values

Appendix 18 summarises the quality of life values used in previous NICE assessments of treatments for locally advanced head and neck cancer. Both of these assessments were STAs and as a consequence, the values used should be read with a degree of caution. TA145 commissioned an EQ-5D study among oncology nurses which suggested a value of 0.659 for while on treatment and 0.129 for post treatment progressive disease. TA172 mapped patient level EORTC QLQ-C30 data onto EQ-5D scores using the algorithm developed by Kind et al. (2005).[219] This resulted in values of 0.65 for progression free survival under standard treatment and 0.52 for survival with progression.

The values from TA172 appear to be more in line with the NICE methods guide. The values are also more in line with those used in the mCRC modelling, though being different diseases there is no particular reason that they should be entirely aligned. As a consequence, the modelling will apply quality of life values of 0.65 for progression free survival and 0.52 for survival with progression. It will be further assume that those on treatment have the progression free survival quality of life.

But note that Appendix 19 summarises the broader quality of life literature in head and neck cancer. This suggests that remission or being recurrence free may be associated with a somewhat higher quality of life. This again suggests that some scepticism should be applied to the following relatively crude modelling of head and neck cancer, and that inferences made from the mCRC may not hold.

6.2.6.3.2 Cost of induction chemotherapy

Each cycle of induction chemotherapy is assumed to consist of docetaxel 75mg/m^2, cisplatin 75mg/m^2 and a daily total of 750mg/m^2 5-FU over four days. The 5-FU is assumed to be administered as two sequential 48 hour infusions using a balloon elastomer pump [*personal communication: Janice Szulc*

James Cook University NHS Trust]. This results in the following costs per cycle of induction chemotherapy (Table 73).

Table 73. Costs of induction chemotherapy

Induction chemotherapy	Cost
Pharmacy	£189.06
Administration 1st	£238.39
Administration subsequent	£255.06
Docetaxel	£34.29
Cisplatin	£20.50
5-FU	£3.70
Elastomer pump	£38.96
Line flush	£47.33
Total per cycle	£827.29
Total per course	£2,481.86

In line with Fety et al. (1998)[157] and expert opinion it is assumed that three cycles of induction chemotherapy are planned, though some UK practise is apparently to aim for four cycles. Progression and deaths limit the number of induction chemotherapy cycles that are applied within the model to some degree.

6.2.6.3.3 Cost of chemo-radiotherapy

Chemo-radiotherapy is assumed to consist of cisplatin 100mg/m^2 at the start of weeks 1, 4 and 7 coupled with 70Gy radiation therapy delivered in equal daily doses Monday to Friday for 7 weeks. The pharmacy and administration costs for chemotherapy are drawn from the same sources as the mCRC modelling with the cisplatin cost being drawn from the CMU EMIT database.

The costs of planning radiotherapy are based upon a weighted average of the 2012-13 NHS references costs of outpatient planning codes SC40Z to SC52Z, excluding codes related to total body imaging SC42Z to SC44Z. Note that this assumes that there is only one preparation and imaging session per patient. These costs would increase substantially were it to be required e.g. weekly. The weighted average outpatient cost of £552 only increases slightly to £557 if day cases are included.

The costs of administering radiotherapy are based upon a weighted average of the 2012-13NHS reference costs of outpatient delivery of a fraction of radiotherapy codes SC12Z to SC28Z, excluding the code SC25Z for a fraction of total bod irradiation. This results in a cost per fraction of £117. Note that including day cases had little impact upon the weighted average, only increasing it to £120.

This results in the following costs (Table 74).

Table 74. Costs of chemo-radiotherapy

Radiotherapy	Cost
Planning	£551.67
Administration - per fraction	£117.03
Administration - total	£4,095.91
Total per course - radiotherapy	£4,647.58
Concurrent chemotherapy	
Pharmacy	£47.27
Administration	£238.39
Cisplatin	£27.18
Total per administration	£312.83
Total per course - chemotherapy	£938.50
Overall total per course	£5,586.08

Note that it is assumed that once having started chemo-radiotherapy patients receive the full course. This is not entirely realistic, as some patients will die and some patients will cease therapy. In particular, it appears that a number of patients will cease chemotherapy while perhaps continuing with radiotherapy.

This assumption is made in order to avoid perhaps artificially differentiating the BSA arm from the My5-FU arm. The alternative of assuming that only those modelled as remaining in progression free survival as per the parameterised Weibulls would continue to receive chemo-radiotherapy could well be equally objectionable.

6.2.6.3.4 Costs of progression

TA145 specifies a range of costs associated with treating patients who have progressed: nursing costs, salvage surgery, secondary radiotherapy and secondary systemic therapy. These are costed at an average of £1,099 which when uprated to 2013-13 prices yields a cost of £1,318.

6.2.6.3.5 Ongoing costs

TA145 also specifies various frequencies of repeat follow up visits depending upon the length of time since treatment ranging from weekly up to five weeks from end of therapy, monthly thereafter for the first year, every two months for the second year and every three months thereafter. These have been costed using the 2012-13 NHS reference cost for medical oncology consultant led follow up appointment: £139.22.

6.2.6.3.6 Results

As outlined in the below (Table 75), if there is no survival advantage associated with My5-FU there are only minimal quality of life gains associated with its adverse event profile, though this does give rise to some small cost offsets. But given the net costs, only a very small improvement in either progression free survival or overall survival is required to render My5-FU cost effective.

Table 75 ***Base case results head and neck modelling***

HR PFS = 0.966, HR OS = 1.000

	My5-FU	BSA	Net
QALYs			
PFS	2.454	2.386	0.068
SWP	0.297	0.351	-0.054
AEs	0.000	-0.001	0.000
Total	2.750	2.736	0.014
Costs			
My5-FU	£168	£0	£168
Adjust.	£37	£6	£31
Induction	£2,283	£2,283	£0
CRT	£5,083	£4,916	£167
AEs	£102	£149	-£47
SWP	£1,000	£1,034	-£34
Ongoing	£5,179	£5,179	£0
Total	£13,851	£13,567	£285
ICER			£20,586

HR PFS = 1.000, HR OS = 0.990

	My5-FU	BSA	Net
QALYs			
PFS	2.387	2.386	0.001
SWP	0.366	0.351	0.015
AEs	0.000	-0.001	0.000
Total	2.752	2.736	0.016
Costs			
My5-FU	£168	£0	£168
Adjust.	£37	£6	£31
Induction	£2,283	£2,283	£0
CRT	£5,083	£4,916	£167
AEs	£102	£149	-£47
SWP	£1,039	£1,034	£5
Ongoing	£5,189	£5,179	£10
Total	£13,901	£13,567	£335
ICER			£20,601

6.2.6.3.7 Sensitivity analyses

The base case assumes that constant proportions of patients receive induction chemotherapy and subsequent chemoradiotherapy, the latter being 3% higher in the My5-FU arm than in the BSA arm. An alternative assumption is to assume that only those modelled as being in progression free survival receive induction chemotherapy and chemoradiotherapy (Table 76). The alternative in the opposite direction is to equalise the proportions receiving subsequent chemotherapy.

Table 76. Sensitivity analysis head and neck modelling: only PFS treated

HR PFS = 0.981, HR OS = 1.000

	My5-FU	BSA	Net
QALYs			
PFS	2.424	2.386	0.038
SWP	0.321	0.351	-0.030
AEs	0.000	-0.001	0.000
Total	2.744	2.736	0.008
Costs			
My5-FU	£174	£0	£174
Adjust.	£37	£6	£31
Induction	£2,353	£2,350	£2
CRT	£4,784	£4,770	£14
AEs	£102	£149	-£47
SWP	£1,016	£1,034	-£18
Ongoing	£5,179	£5,179	£0

HR PFS = 1.000, HR OS = 0.995

	My5-FU	BSA	Net
QALYs			
PFS	2.386	2.386	0.000
SWP	0.358	0.351	0.008
AEs	0.000	-0.001	0.000
Total	2.744	2.736	0.008
Costs			
My5-FU	£173	£0	£173
Adjust.	£37	£6	£31
Induction	£2,350	£2,350	£0
CRT	£4,770	£4,770	£0
AEs	£102	£149	-£47
SWP	£1,037	£1,034	£3
Ongoing	£5,184	£5,179	£5

Total	£13,643	£13,487	£156
ICER			£19,909

Total	£13,653	£13,487	£165
ICER			£20,064

Assuming therapy to be equal to the proportion remaining progression free results in a smaller cost differential than assuming that 3% more patients would progress to chemo-radiotherapy in the My5-FU arm than in the BSA arm. As a consequence, the required treatment effect falls (Table 77).

Table 77. Sensitivity analysis head and neck modelling: same CRT rate between arms

HR PFS = 0.984, HR OS = 1.000

	My5-FU	BSA	Net
QALYs			
PFS	2.418	2.386	0.032
SWP	0.325	0.351	-0.025
AEs	0.000	-0.001	0.000
Total	2.743	2.736	0.007
Costs			
My5-FU	£168	£0	£168
Adjust.	£37	£6	£31
Induction	£2,283	£2,283	£0
CRT	£4,916	£4,916	£0
AEs	£102	£149	-£47
SWP	£1,019	£1,034	-£15
Ongoing	£5,179	£5,179	£0
Total	£13,704	£13,567	£137
ICER			£20,740

HR PFS = 1.000, HR OS = 0.995

	My5-FU	BSA	Net
QALYs			
PFS	2.386	2.386	0.000
SWP	0.358	0.351	0.008
AEs	0.000	-0.001	0.000
Total	2.744	2.736	0.008
Costs			
My5-FU	£168	£0	£168
Adjust.	£37	£6	£31
Induction	£2,283	£2,283	£0
CRT	£4,916	£4,916	£0
AEs	£102	£149	-£47
SWP	£1,037	£1,034	£3
Ongoing	£5,184	£5,179	£5
Total	£13,727	£13,567	£160
ICER			£19,463

As would be anticipated, removing the 3% higher rate of chemo-radiotherapy in the My5-FU arm lessens the treatment effect that is required for My5-FU to be cost effective at a willingness to pay of £20,000 per QALY.

But in short, given the additional costs associated with My5-FU and the relatively long survival among locally advanced head and neck patients only small treatment effects upon progression free survival or overall survival are required for My5-FU to be cost effective.

6.2.6.4 Discussion and conclusions

6.2.6.4.1 The costs of My5-FU testing

Based upon an annual throughput of 300 and 100 assays being available per assay kit, the cost per My5-FU assay is around £61. This includes a staff cost of £35 for 30 minutes of health visitor time to take the blood sample. The cost per assay would rise further were My5-FU to require a dedicated outpatient appointment for the taking of the blood, this doubling the total cost per assay.

This does not include the costs of dose adjustment. Within the modelling, based upon expert opinion, each dose adjustment associated with My5-FU has been assumed to involve a additional 10 minutes of consultant time

All of the economic modelling depends upon equivalence of My5-FU with HPLC and LC-MS being a reasonable assumption. If this is not a reasonable assumption, the cost effectiveness estimates which are presented are not a reflection of the cost effectiveness of My5-FU. If My5-FU has a worse performance than the other methods upon which most of the clinical effectiveness evidence rests, the cost effectiveness estimates that are presented will be systematically biased in favour of My5-FU. There is no obvious means of exploring this assumption or conducting sensitivity analyses around it.

6.2.6.4.2 Modelling the cost effectiveness of My5-FU dose adjustment in mCRC

The modelling is hampered by the trials that underlie the estimates of overall survival and progression free survival treating patients until progression or unacceptable toxicity. Expert opinion suggests that current UK practice appears to have switched to 12 FOLFOX cycles followed by a treatment holiday, with only a minority of patients recommencing a second course of FOLFOX. Some centres may aim for 6 cycles of FOLFOX before taking a treatment holiday. Another key assumption is that the survival estimates are unaffected by the move to intermittent dosing and treatment holidays. This is supported by the results of the COIN trial.

The analysis of adverse events suggests that given their short duration any differences between adverse events rates for My5-FU compared to BSA dose adjustment will result in minimal QALY differences between the arms. The costs of hospitalisations for grade III/IV are more important, and provide some cost offset to the My5-FU assay costs. But changes in the adverse event profile appear unlikely to be sufficient in themselves to render My5-FU cost effective.

The analyses based upon the FOLFOX studies are hampered by a lack of a proper BSA dosing control arm, with Capitain et al. (2012)[119] only reporting medians for the BSA dosing arm. Inferring the BSA dosing overall survival and progression free survival curves from the reported data suggests a gain of an additional overall survival of 0.770 years from pharmacokinetic dosing. This translates into an estimated gain of 0.599 QALYs. Given the additional survival, total routine ongoing monitoring and treatment costs are higher in the My5-FU arm. There are also additional costs of more FOLFOX treatments within the My5-FU arm of £467. This results in an additional total cost arising from My5-FU dose adjustment of £2,483, and in turn into a cost effectiveness estimate of £4,148 per QALY.

The probabilistic modelling results in a similar central estimate with a reasonably tight cost effectiveness acceptability curve.

The above estimates include a cost offset from reduced use of 2nd line FOLFIRI in the My5-FU arm. This appears to occur due to a quirk of the modelling, in that the My5-FU progression free survival curve touches the overall survival curve and is then assumed to follow the overall survival curve. As a consequence a smaller proportion of patients in the My5-FU arm are modelled as receiving 2nd line FOLFIRI compared to the BSA arm. It is probably more sensible to exclude these cost offsets, but doing so only revises the cost effectiveness estimate to £4,363 per QALY.

These cost effectiveness estimates are reasonably stable as the source of parameterised curves is varied. While the net QALYs gained varies between the scenarios the net costs vary in a similar proportion, resulting in quite similar cost effectiveness estimates. This arises mainly due to any changes in overall survival in the BSA dosing arm being associated with increased ongoing monitoring and treatment costs. When coupled with the additional survival being valued at the survival with progression quality of life, this approximately results in the BSA cost effectiveness point travelling along the line joining the old BSA point and the My5-FU point on the cost effectiveness plane.

This stability of results also applies to the scenario analysis that derives the overall survival curve for My5-FU from Capitain et al (2012), but derives the BSA overall survival curve by assuming that the hazard ratio for My5-FU compared to BSA dosing of 0.829255 derived from Gamelin et al (2008) applies. Gamelin et al (2008), while a study of 5-FU + FA, can be seen as the comparative study with the best randomisation.

Provided that the survival gain of the base case is a reasonable estimate, the cost effectiveness of My5-FU is relatively insensitive to the laboratory throughput and varying the number of My5-FU assays per patient from the 3.23 of the base case to [redacted] and to 4.4. If the estimated survival gain is too large, results are likely to be more sensitive to the laboratory throughput and assay numbers.

A sensitivity analysis that assumed around 10% of patients would commence a second course of 12 cycles of FOLFOX had a reasonable impact upon the cost effectiveness estimate, worsening it to £5,272 per QALY.

The base case assumes that the blood sample for the My5-FU assay is taken in the community by a health visitor. Some expert opinion suggests that this may be difficult to source at times, leading to the

blood test requiring a dedicated outpatient visit. If this is the case, the cost effectiveness estimate worsens to £4,506 per QALY.

Applying the quality of life values of CG131[7] rather than those of Farkkila et al. (2013)[192] has a reasonable impact upon the cost effectiveness estimate, worsening it to £6,016 per QALY.

However, these sensitivity analyses rely upon My5-FU resulting in quite a large overall survival gain: 0.770 years. This estimate is based upon Capitain et al. (2012),[119] the BSA dosing arm of which was a historical control group that was somewhat smaller than the pharmacokinetic dose adjustment group. Also, only the median for the overall survival for the BSA dosing arm was reported. The overall survival in the BSA dosing arm was inferred from this relatively limited data, and as a consequence is subject to considerable uncertainty.

The cost effectiveness modelling based upon the 5-FU + FA studies is motivated in part by these containing the main comparative study with reasonable randomisation: Gamelin et al. (2008).[118] In the light of UK practice typically being fortnightly cycles of FOLFOX, the costs of FOLFOX are retained for these analyses. They provide further scenario analyses around which parametric curves should be applied, and what additional survival gain might be anticipated.

The overall survival curves of Gamelin et al. (2008)[118] suggest a survival gain from My5-FU of 0.247 years. When this is coupled with a common progression free survival curve estimated from the three pooled studies, it results in a net gain of 0.151 QALYs. Due to the assumption of a common progression free survival curve, there are no additional FOLFOX treatment costs associated with My5-FU. As a consequence, the additional costs are largely limited to the costs of My5-FU, partly offset by adverse event costs, and the additional routine ongoing monitoring and treatment costs associated with the longer survival. These net additional costs of around £883 result in a cost effectiveness estimate of around £5,853 per QALY.

Changing the source of the parameterised curves for progression free survival to those inferred from the mean durations of response reported in Gamelin et al (2008)[118] worsens the cost effectiveness estimate. Depending upon the method used to infer progression free survival, the cost effectiveness estimate worsens to between £6,965 per QALY and £8,615 per QALY. This appears to be due to a relative increase in the costs of 1st line treatment.

The 5-FU + FA studies based cost effectiveness analyses show similar sensitivities to univariate parameter change as the FOLFOX studies based cost effectiveness analyses. The only sensitivity

analysis that differs is the application of the quality of life values of CG131[7] rather than those of Farkkila et al. (2013)[192]. This has a rather larger impact upon the cost effectiveness estimate based upon the 5-FU + FA studies, worsening it to £17,485 per QALY. If this is coupled with an outpatient visit being required for the taking of the blood sample the cost effectiveness estimate would worsen further to £21,732 per QALY.

6.2.6.4.3 Modelling the cost effectiveness of My5-FU in locally advance head and neck cancer

There is minimal clinical information to inform a cost effectiveness analysis of My5-FU during induction chemotherapy for locally advance head and neck cancer. What data there is is largely limited to that of Fety et al (1998). Adverse event rates, response rates and dose adjustments are reported but there is no information about survival.

Progression free survival and overall survival estimates are available for TPF induction therapy from the meta-analysis of Blanchard et al. (2013).[50] The modelling approach is to apply the costs of induction chemotherapy and subsequent chemo-radiotherapy, the costs and quality of life impacts of adverse events and the ongoing costs of monitoring. The modelling can then estimate what hazard ratio is required for either progression free survival or for overall survival for My5-FU to be cost effective at a threshold of £20,000 per QALY.

The studies underlying Blanchard et al. (2013)[50] can also be read as suggesting that rates of subsequent chemo-radiotherapy tended to increase with response rates to a limited degree. An informal estimate of My5-FU resulting in an additional 3% of patients receiving subsequent chemo-radiotherapy has been included in the base case modelling, though excluding this is explored in a sensitivity analysis.

The base case results suggest that given the relatively long survival among patients with locally advance head and neck cancer compared to mCRC patients, the hazard ratios required for My5-FU to be cost effective in induction therapy for locally advance head and neck cancer differ only slightly from unity. With a hazard ratio of 0.966 for progression free survival and no gain in overall survival there is an estimated net gain of 0.014 QALYs and an estimated cost increase of £285, resulting in a cost effectiveness estimate of £20,586 per QALY. With a hazard ratio of 0.990 for overall survival and no gain in progression free survival there is an estimated gain of 0.016 QALYs and an estimated net cost of £335, resulting in a cost effectiveness estimate of £20,601 per QALY.

Sensitivity analyses around the proportion of patients receiving subsequent chemo-radiotherapy suggest that a hazard ratio of around 0.980 for progression free survival or of around 0.995 for overall

survival would be sufficient to justify the costs of My5-FU during induction therapy for locally advance head and neck cancer.

The EAG views these estimates as quite speculative. While the estimates are considerably less than the hazard ratio for overall survival of 0.829255 derived for mCRC from Gamelin et al. (2008),[118] they are also in an entirely different context: induction chemotherapy for locally advance head and neck cancer rather than what could be described as palliative chemotherapy for mCRC, The overall survival estimates for the two groups of patients are also very different. Given an absolute cost difference, the longer the survival the smaller the relative treatment effect has to be to justify the additional cost. But the required treatment effect also becomes more speculative, and difficult to practically identify and attribute.

7 DISCUSSION

In current clinical practice the dose of 5-FU-containing regimens given to cancer patients is based on the patient's BSA, with downward adjustment in case of severe toxicity. However, it has been suggested that about 40%–50% of patients receiving 5-FU in this way may be under-dosed. It has been hypothesised that dose adaptation might improve outcomes such as response rates and overall survival without increasing toxic side effects, by achieving optimal 5-FU exposure. The My5-FU assay in conjunction with dose adaptation algorithms offers a potential means to achieve more appropriate 5-FU exposure. In this assessment we investigated to what extent dose adjustment fulfils this aim of improved outcomes and if this approach is cost effective.

7.1 Decision problem and objectives

Our overall objective was to undertake a clinical and cost-effectiveness analysis of the pharmacokinetic dose adjustment of 5-FU in cancer patients treated with 5-FU containing chemotherapy regimens in the metastatic and adjuvant setting. We aimed to systematically review the literature on the accuracy of the My5-FU assay compared to gold standard methods (HPLC and LC-MS); the effectiveness of My5-FU PK dosing or of HPLC and/or LC-MS PK dosing compared with BSA dosing and the generalizability of published My5-FU and PK studies. We also aimed to identify evidence relevant to the costs of using My5-FU and to develop a cost effectiveness model.

7.2 Summary of Methods and Findings

7.2.1 Clinical Effectiveness

We searched a number of databases including MEDLINE, EMBASE and the Science Citation Index. Two reviewers independently screened titles and abstracts and discrepancies were resolved through discussion. Quality assessment was undertaken. In the absence of IPD, we used the method of Guyot et al. to reconstruct Kaplan-Meier plots for PFS and OS for comparison of BSA and PK dosing in two regimens.

We found 3,751 records of which 35 papers (representing eight unique studies) were included. We found a high correlation between My5-FU, HPLC and LC-MS/MS but the Bland-Altman plots showed considerable variability. Personal communication with a clinical advisor suggested that the range of values (-18% to +30%) could be considered clinically equivalent; however we remain cautious about outliers.

The evidence on PK versus BSA dosing in the treatment of CRC and H&N cancer patients is weak in both quantity and quality. Evidence for My5-FU was sparse with only one study of clinical outcomes which compared BSA with PK dose adjustment using the My5-FU assay and this study was at risk of selection bias. Of three CRC comparative studies identified, only one was an RCT but unfortunately it used an unrepresentative 8-h infusion regimen. Single arm studies were heterogeneous, of poor design, and severely limited in ability to deliver useful data for comparison of PK versus BSA dosing. There was no RCT evidence about the effectiveness of PK-directed dose adjustment for any currently used 5-FU regimen for any cancer type.

We reconstructed IPD of single arms from studies from a variety of sources and combined data to undertake a comparison of PK dosing with BSA. Overall PK appeared to confer a benefit in both regimens for which any comparative data were available. (Median overall survivals were 19.6 months (95% CI: 17.0 – 21.0) PK versus 14.6 months (95% CI: 14.1 – 15.3) BSA for 5-FU + FA and 27.4 months (95% CI: 23.2 – 38.8) PK versus 20.6 months (95% CI: 18.4 – 22.9) BSA for FOLFOX6 in metastatic colorectal cancer). However these apparent benefits should be viewed with extreme caution because of the quality of the evidence. For H&N cancer, only two studies both more than 15 years old were identified but they used regimens no longer in current use.

We found no useful evidence on stomach, pancreatic or any other cancers where 5-FU regimens are used and no evidence to allow meaningful analysis of the following subgroups:

- People with DPD deficiency;
- People with impaired renal function;
- People with impaired liver function;
- People whose body surface area is outside the standard range for dosing 5-FU;
- People with a less favourable performance status who may be undertreated in current practice.

We found the generalizability of the studies reporting PK versus BSA dosing to be acceptable.

7.2.2 Cost Effectiveness

A comprehensive search of the literature for published economic evaluations, utility studies and cost studies was performed. A de novo model was developed to assess the impact of pharmacokinetic dose adjustment using My5-FU compared to BSA dosing, using the outcomes identified from the clinical effectiveness reviews in terms of PFS and OS and drawing on previous NICE assessments in the area. For the base case, the progression free survival curves and overall survival curves were derived by fitting Weibull curves to the Capitain et al. (2013) data. This was hampered by a relatively poor control arm, for which only median survival estimates were provided.

We used a lifetime (20 year) horizon, a Health and Personal Social Services perspective and a 3.5% discount rate. We incorporated estimates of the impact of My5-FU dose adjustment on test costs, treatment costs, side effect costs and the quality of life impacts of side effects. QALY impact of adverse events was drawn from expert opinion. Costs of grade I/II and grade III/IV adverse events were based on NHS reference costs for those hospitalised and medication costs for those not hospitalised.

4,578 records were identified through electronic searches of which 54 papers were included in the cost effectiveness review. The base case assumed a cost per completed My5-FU assay of £61.03.

The deterministic base case for a FOLFOX regimen for mCRC given over 12 cycles, gave life years gained of 0.770 and a QALY gain of 0.599 at a net additional cost of £2,483 for My5-FU dosing compared to BSA dosing. The additional direct costs of My5-FU made up only a small part of this additional cost, the majority being due to higher 1st line treatment costs and routine ongoing monitoring and treatment costs. The ICER was £4,148 per QALY. Probabilistic results were very similar as were deterministic results using a variety of different scenario analyses. The CEAC showed My5-FU to be 100% likely to be cost effective if the threshold is held at £20,000 per QALY.

The progression free survival curve touched and was then modelled as following the overall survival curve, which means that the costs of 2nd line therapy may have been underestimated in the My5-FU arm. Excluding these costs worsened the cost effectiveness estimate to £4,363 per QALY. Results were reasonably insensitive to the source of parameterised curves that were chosen, although a number of alternatives were explored and the ICERs changed little in relation to sensitivity analyses.

We also explored the hazard ratios for progression free survival and overall survival required for My5-FU to be cost effective for dose adjustment during induction therapy for locally advanced head and neck cancer. Estimated cost increases associated with My5-FU were not large in the context of costs of current induction therapy followed by chemo-radiotherapy. Given the somewhat longer survival among patients with locally advanced head and neck cancer compared to mCRC patients, hazard ratios required to justify the additional cost at a willingness to pay of £20,000 per QALY were not far from unity and a hazard ratio of 0.95 would be modelled as easily justifying the additional cost.

7.3 Strengths and Limitations

We undertook rigorous and comprehensive systematic reviews for both clinical and cost effectiveness and we believe that we identified all relevant publications concerning the effectiveness of PK dose

adjustment in the management of cancer patients treated with 5-FU containing chemotherapies. One of the main problems with this work is that the underlying evidence base for a 'linked evidence' approach is of concern. We found a high correlation between My5-FU, HPLC and LC-MS/MS but the Bland-Altman plots showed considerable variability. All of the economic modelling depends upon equivalence of My5-FU with HPLC and LC-MS being a reasonable assumption. If this is not a reasonable assumption, the cost effectiveness estimates which we have presented are not a reflection of the cost effectiveness of My5-FU.

The evidence base for pharmacokinetic dose adjustment in both colorectal and head and neck cancer is weak. None of the studies we investigated were of high quality; all had important drawbacks in design and methods which, coupled with patchy reporting of key outcomes, limits their validity and the generalizability of the findings. For example we found no randomised evidence on the effect of PK dose adjustment for any currently used 5-FU regimen for any cancer type using either My5-FU or HPLC for dose adjustment.

Further, in order to make best use of published studies we contacted authors in order to obtain IPD. However we were unable to obtain IPD, and in the absence of IPD, we had to reconstruct survival data using the method of Guyot et al. We consistently checked our findings against available empirical data, but nevertheless the process of construction is not as reliable as the use of the original IPD.

We combined reconstructed IPD of single arms from studies from a variety of sources to allow a comparison of PK dosing with BSA. *It should be strongly cautioned that there are many caveats regarding the validity of this procedure including the assumptions of similar treatments and similar populations; furthermore there is a lack of adjustment for potential patient or study level confounders.*

Unfortunately, our work on the My5-FU assay for use in clinical practice with common UK regimens is therefore both indirect and based on non-randomised evidence, drawn together from a small number of non-UK PK versus BSA studies and complemented with data from BSA arms provided by a variety of RCTs which investigated various comparisons of 5-FU treatments but which did not investigate PK adjustment. The single randomised study used an out-of date regimen administered over an obsolete 8h infusion. In addition we used our combined and reconstructed data in our estimations of cost effectiveness. Where the evidence did not directly support a complete "end-to-end" analysis from My5-FU through to overall survival, a linked evidence approach was undertaken, but as our results in relation to comparability of My5-FU and HPLC show there may be some concerns in relation to this approach.

As a consequence, the cost per QALY of My5-FU for mCRC estimate is likely to be subject to considerable uncertainty. The scenario and sensitivity analyses which were undertaken were however mostly reassuring in their similarity to base case findings. For head and neck cancer we were unable to find useful survival data and had to undertake analyses around possible hazard ratios. Again these methods are of concern, although the ratios generated in our calculation generate values which would be modelled as easily justifying the additional cost.

7.4 Practical considerations

7.4.1 Prerequisites for successful PK dose adjustment using My5-FU in clinical practice

Successful pharmacokinetic dose adjustment using My5-FU in clinical practice will depend on:

1) Accurate estimation of plasma 5-FU
2) An appropriate algorithm for dose adaptation
3) An appropriate target plasma 5-Fu level (the target range)

In this section we therefore examine each of these practical issues for consideration in turn.

7.4.1.1 Accurate estimation of plasma 5-FU

No currently available RCT or comparative study used the My5-FU assay for dose adjustment of 5-FU containing chemotherapy regimens in the treatment of any cancer. As a result the current report has relied on comparisons with HPLC. Whilst there is high correlation between My5-FU, HPLC and LC-MS/MS, the small amount of evidence available fond the Bland-Altman plots showed considerable variability. If the range of values (-18% to +30%) found can be considered clinically equivalent. My5-FU has the advantage over HPLC in that it requires only a small amount of plasma, takes less time, is less expensive, requires less training and can be automated.[84]

If PK is adopted for CRC in the UK then there will need to be an expansion of laboratories willing to undertake the assay procedure, and training will be needed for staff and nurses to collect samples correctly.

7.4.1.2 An appropriate algorithm for dose adaptation

No clinical study with known algorithm using My5-FU is currently available to assess the appropriateness of the algorithm best used with My5-FU in the UK.

Of studies using My5-FU for 5-FU monitoring Hendrayana et al. (2012)[151] did not perform dose adjustment, Saam et al. (2011)[220] did not bind physicians to adjust doses according to a specific

algorithm and in Kline et al. (2013)[156] dose adjustment followed an unspecified algorithm supplied by the manufacturer (Myriad Genetic Laboratories).[156] This was unlikely to be the one published by the company[96] as it used a target range of 20 to 24 mg*h/L rather than Kaldate's recommended 20-30 mg*h/L.

Therefore, the evidence on algorithms also comes from an indirect comparison with HPLC studies. Ychou et al. (1999 and 2003)[148] developed adaptation schedules for the bimonthly LV5FU2 (de Gramont) regimen with dose increases up to an AUC of 20 mg*h/l*m^2. The methods of how the algorithm was developed are unclear. Gamelin et al. (2008)[118] used a dose adaptation algorithm developed for the weekly 8h-continous infusion of 5-FU + FA with a target range of 20-24 mg*h/l. The dose adaptation algorithm was based on a regression analysis of the relationship between dose and plasma levels in two groups of patients with different quality of response.[131] They reported differential median overall survival for the PK arm of 22 months compared to 16 months for the BSA arm.[118] Capitain et al. (2012)[119] used protocols based on the Gamelin et al. (2008) algorithm modified for the FOLFOX regimen. These protocols have been commercialised and have not been published. Furthermore, the protocols may not be pure algorithms for 5-FU as they may include other tests/ considerations such as DPD genotyping. It is unclear how such protocols would translate into English services. We therefore conclude that the only algorithms currently available which have been validated in colorectal cancer patients are based on regimens no longer in clinical practice in the UK or are unavailable in the public domain. It is unclear whether the survival gains can be generalised to other treatment regimens that may require alternative and as yet ill-defined adjustment algorithms.[84]

In 2011, Saam reported US experience with My5-FU suggesting that physicians in practice made larger reductions than increases in 5-FU doses.[220] While Gamelin et al. (2008)[118] used an algorithm that allowed 50-70% dose increases for some patients to reach the 5-FU target range; it appears that physicians not bound to an adaptation protocol generally increased doses by only 10-20%, illustrating a cautious attitude towards upward dose adjustment.[220] It is important that dose increases are ruled by algorithms but they will also require clinical judgment. This might result in PK dose adjustment being less effective in clinical practice than in the research environment because different clinicians may apply dose increases more cautiously than in reported studies.

7.4.1.3 An appropriate target plasma 5-FU level (the target range)

Single arm studies investigating PK dose adjustment in colorectal cancer patients used a target range of 20-24 mg*h/L. This target range was established for the 8h 5-FU + FA regimen[131] and was subsequently used for most other regimens.[151, 156, 220] However, Kaldate et al. (2012)[96] developed a new algorithm and argued that newer extended infusion time regimens should use a wider target range

with the upper limit increased to 30 mg*h/L and are less toxic and. No study was identified that made use of this new algorithm. Moreover, a study[156] that was provided by an algorithm by the manufacturer Myriad Genetics Laboratories itself[220] used the 20-24 mg*h/L target range. This introduces some doubts as to the suitability of the Kaldate algorithm.

8 CONCLUSIONS

With an ICER of £4,148, PK dose adjustment using My5-FU appears to be cost-effective for 12 cycles of FOLFOX6 in the treatment of patients with metastatic colorectal cancer. This is based on a survival benefit with questionable plausibility and substantial uncertainties due to limited available evidence. Evidence comes from out of date treatment regimens (e.g., 5-FU on its own in 8 hour rather than 46 hour infusions) and non-randomised comparative studies. In addition there is uncertainty as to the direct applicability of results to UK clinical practice. Uncertainties remain as to how PK dose adjustment should be achieved and how much it will cost the NHS to implement the My-5-FU assay. Our work on H&N cancer suggests that PK dose adjustment is likely to be cost effective at standard willingness to pay thresholds. There was no evidence on 5-FU PK dose adjustment in comparison to BSA based dosing for stomach or pancreatic cancer.

8.1 Recommendations for further research

We are conscious that improved data are becoming available with more information on current practice and experiences of colorectal cancer patients in terms of mechanisms of dosing and adverse events etc. (e.g., from the COIN trial). This will help in assessing cost effectiveness of interventions to improve treatment and survival in colorectal cancer. However given the poor quality of the clinical and cost effectiveness evidence available to us there are a number of research needs including (in priority order) a need for:

- well conducted RCTs of PK versus BSA dosing in
    - metastatic and adjuvant colorectal cancer and in
    - H&N cancer
    - other cancers where a 5-FU regimen is used
- further in depth assessment of the comparability of different methods of current and any newly introduced PK dose adjustment
- randomised assessment of different algorithms for adjusting 5-FU dosing
- research on the QALY impact of adverse events of 5-FU which would be of benefit in any further economic assessments.

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10 Appendix

Appendix 1. Search strategies

Clinical Effectiveness: Objectives A, B and C

Embase Classic+Embase 1947 to 2014 Week 01 (Ovid), searched on 07/01/2014

1	(my5-fu* or My5-FU* or "my5 fu*" or "my 5fu*" or "my 5 fu*").mp.	6
2	ondose.mp.	6
3	saladax.mp.	10
4	1 or 2 or 3	18
5	"myriad genetic*".mp.	125
6	exp immunoassay/	389934
7	(immunoassay* or (immun* adj2 assay*)).mp.	379025
8	6 or 7	474599
9	high performance liquid chromatography/	197019
10	"high performance liquid chromatography".tw.	80851
11	HPLC.tw.	130008
12	"high pressure liquid chromatography".tw.	11005
13	high speed liquid chromatography.tw.	264
14	9 or 10 or 11 or 12 or 13	256728
15	liquid chromatography/ and mass spectrometry/	22033
16	Liquid chromatography-mass spectrometry.tw.	9168
17	LC?MS*.tw.	866
18	HPLC?MS.tw.	42
19	15 or 16 or 17 or 18	27415
20	((pharmacokinetic* or PK) adj2 (dosage* or dose* or dosing or adjust* or adapt* or monitor* or select* or calculat* or guided)).mp.	29883
21	fluorouracil/pk	2869
22	fluorouracil/	105631
23	(fluorouracil* or 5-fluorouracil* or 5fluorouracil*).tw.	37057

24	(5-fu* or 5fu* or fu).tw.	31818
25	22 or 23 or 24	118732
26	exp drug dose/	417095
27	drug monitoring/ or drug clearance/	79769
28	((dose* or dosing or dosage* or fluorouracil* or 5-fluorouracil* or 5fluorouracil* or 5-fu* or 5fu*) adj2 (adjust* or adapt* or monitor* or select* or calculat* or intensi* or escalat* or modif* or reduc* or concentration* or level* or limit* or detect* or measur*)).tw.	160112
29	((drug* or blood or plasma) adj5 (monitor* or concentration* or level*) adj5 (fluorouracil* or 5-fluorouracil* or 5fluorouracil* or 5-fu* or 5fu* or fu)).tw.	652
30	("optimal drug therapy" or ("optimal drug" adj (dosage* or dose* or dosing))).tw.	338
31	26 or 27 or 28 or 29 or 30	604858
32	personalized medicine/ and exp chemotherapy/	865
33	((personal* or individual*) adj2 (chemotherap* or dosage* or dose* or dosing)).mp.	10000
34	32 or 33	10652
35	31 or 34	611253
36	5 and 25	5
37	5 and 35	5
38	36 or 37	8
39	8 and 25 and 35	251
40	((5-fu* or 5fu* or fu) adj "plasma assay*").mp.	2
41	21 and 35	1315
42	4 or 38 or 39 or 40 or 41	1565
43	14 and 25	1263
44	19 and 25	95
45	43 or 44	1331
46	35 and 45	496
47	20 and 25	319
48	42 or 46 or 47	2102

MEDLINE(R) 1946 to November Week 3 2013 (Ovid), searched on 07/01/2014

1	(my5-fu* or My5-FU* or "my5 fu*" or "my 5fu*" or "my 5 fu*").mp.	0
2	ondose.mp.	2
3	saladax.mp.	1
4	1 or 2 or 3	3
5	"myriad genetic*".mp.	92
6	exp Immunoassay/	453924
7	(immunoassay* or (immun* adj2 assay*)).mp.	248384
8	6 or 7	527480
9	Chromatography, High Pressure Liquid/	155449
10	"high performance liquid chromatography".tw.	65042
11	HPLC.tw.	91531
12	"high pressure liquid chromatography".tw.	9702
13	high speed liquid chromatography.tw.	156
14	9 or 10 or 11 or 12 or 13	209442
15	exp Chromatography, Liquid/ and exp Mass Spectrometry/	65715
16	Liquid chromatography-mass spectrometry.tw.	7763
17	LC?MS*.tw.	365
18	HPLC?MS.tw.	5
19	15 or 16 or 17 or 18	68737
20	((pharmacokinetic* or PK) adj2 (dosage* or dose* or dosing or adjust* or adapt* or monitor* or select* or calculat* or guided)).mp.	6441
21	exp Fluorouracil/pk	1533
22	exp Fluorouracil/	42066
23	(fluorouracil* or 5-fluorouracil* or 5fluorouracil*).tw.	29605
24	(5-fu* or 5fu* or fu).tw.	21573
25	22 or 23 or 24	55027
26	Dose-response Relationship, Drug/ or Drug Dosage Calculations/	356879
27	Drug Monitoring/ or Metabolic Clearance Rate/	36771
28	((dose* or dosing or dosage* or fluorouracil* or 5-fluorouracil* or 5fluorouracil* or 5-fu* or 5fu*) adj2 (adjust* or adapt* or monitor* or select*	111057

	or calculat* or intensi* or escalat* or modif* or reduc* or concentration* or level* or limit* or detect* or measur*)).tw.	
29	((drug* or blood or plasma) adj5 (monitor* or concentration* or level*) adj5 (fluorouracil* or 5-fluorouracil* or 5fluorouracil* or 5-fu* or 5fu* or fu)).tw.	549
30	("optimal drug therapy" or ("optimal drug" adj (dosage* or dose* or dosing))).tw.	231
31	26 or 27 or 28 or 29 or 30	476498
32	Individualized Medicine/	4498
33	((personal* or individual*) adj2 (chemotherap* or dosage* or dose* or dosing)).mp.	5704
34	32 or 33	10111
35	31 or 34	484057
36	5 and 25	3
37	5 and 35	4
38	36 or 37	5
39	8 and 25 and 35	172
40	((5-fu* or 5fu* or fu) adj "plasma assay*").mp.	1
41	21 and 35	773
42	4 or 38 or 39 or 40 or 41	942
43	14 and 25	857
44	19 and 25	138
45	43 or 44	904
46	35 and 45	319
47	20 and 25	92
48	42 or 46 or 47	1171

Medline In-Process & Other Non-Indexed Citations January 07, 2014 to November Week 3 2013 (Ovid), searched on 07/01/2014

1	(my5-fu* or My5-FU* or "my5 fu*" or "my 5fu*" or "my 5 fu*").mp.	1
2	ondose.mp.	0
3	saladax.mp.	1
4	1 or 2 or 3	1
5	"myriad genetic*".mp.	11
6	(immunoassay* or (immun* adj2 assay*)).mp.	9114
7	"high performance liquid chromatography".tw.	9130
8	HPLC.tw.	7931
9	"high pressure liquid chromatography".tw.	470
10	high speed liquid chromatography.tw.	25
11	7 or 8 or 9 or 10	14539
12	Liquid chromatography-mass spectrometry.tw.	872
13	LC?MS*.tw.	61
14	HPLC?MS.tw.	0
15	12 or 13 or 14	924
16	((pharmacokinetic* or PK) adj2 (dosage* or dose* or dosing or adjust* or adapt* or monitor* or select* or calculat* or guided)).mp.	365
17	(fluorouracil* or 5-fluorouracil* or 5fluorouracil*).tw.	1413
18	(5-fu* or 5fu* or fu).tw.	1243
19	17 or 18	2089
20	((dose* or dosing or dosage* or fluorouracil* or 5-fluorouracil* or 5fluorouracil* or 5-fu* or 5fu*) adj2 (adjust* or adapt* or monitor* or select* or calculat* or intensi* or escalat* or modif* or reduc* or concentration* or level* or limit* or detect* or measur*)).tw.	6026
21	((drug* or blood or plasma) adj5 (monitor* or concentration* or level*) adj5 (fluorouracil* or 5-fluorouracil* or 5fluorouracil* or 5-fu* or 5fu* or fu)).tw.	19
22	("optimal drug therapy" or ("optimal drug" adj (dosage* or dose* or dosing))).tw.	19
23	20 or 21 or 22	6051
24	((personal* or individual*) adj2 (chemotherap* or dosage* or dose* or	306

	dosing)).mp.	
25	23 or 24	6275
26	5 and 19	1
27	5 and 25	0
28	26 or 27	1
29	6 and 19 and 25	2
30	((5-fu* or 5fu* or fu) adj "plasma assay*").mp.	0
31	4 or 28 or 29 or 30	3
32	11 and 19	47
33	15 and 19	6
34	32 or 33	52
35	25 and 34	9
36	16 and 19	2
37	31 or 35 or 36	12

Cochrane Library (Wiley), searched on 17/01/2014

#1	("my5-fu" or My5-FU* or "my5 fu" or "my 5fu" or "my 5 fu"):ti,ab,kw	0
#2	ondose:ti,ab,kw	0
#3	saladax:ti,ab,kw	0
#4	#1 or #2 or #3	0
#5	(myriad next genetic*):ti,ab,kw	2
#6	[mh immunoassay]	4017
#7	(immunoassay* or (immun* near/2 assay*)):ti,ab,kw	4787
#8	#6 or #7	6316
#9	[mh ^"Chromatography, High Pressure Liquid"]	2376
#10	("high performance liquid chromatography"):ti,ab,kw	2356
#11	HPLC:ti,ab,kw	2450
#12	("high pressure liquid chromatography"):ti,ab,kw	388
#13	("high speed liquid chromatography"):ti,ab,kw	1
#14	#9 or #10 or #11 or #12 or #13	5409
#15	[mh "Chromatography, Liquid"]	2788

#16	[mh "Mass Spectrometry"]	1052
#17	#15 and #16	581
#18	("liquid chromatography-mass spectrometry"):ti,ab,kw	157
#19	("LC-MS" or LCMS* or "LC MS"):ti,ab,kw	443
#20	("HPLC-MS" or HPLCMS* or "HPLC MS"):ti,ab,kw	105
#21	#18 or #19 or #20	651
#22	((pharmacokinetic* or PK) near/2 (dosage* or dose* or dosing or adjust* or adapt* or monitor* or select* or calculat* or guided)):ti,ab,kw	2463
#23	[mh Fluorouracil/PK]	68
#24	[mh Fluorouracil]	3825
#25	(fluorouracil* or 5-fluorouracil* or 5fluorouracil*):ti,ab,kw	5908
#26	("5 fu" or 5fu* or fu):ti,ab,kw	2903
#27	#24 or #25 or #26	7097
#28	[mh "Dose-Response Relationship, Drug"]	24110
#29	[mh "Drug Dosage Calculations"]	66
#30	[mh ^"Drug Monitoring"]	1032
#31	[mh ^"Metabolic Clearance Rate"]	1544
#32	((dose* or dosing or dosage* or fluorouracil* or 5-fluorouracil* or 5fluorouracil* or "5-fu" or 5fu*) near/2 (adjust* or adapt* or monitor* or select* or calculat* or intensi* or escalat* or modif* or reduc* or concentration* or level* or limit* or detect* or measur*)):ti,ab,kw	14997
#33	((drug* or blood or plasma) near/5 (monitor* or concentration* or level*) near/5 (fluorouracil* or 5-fluorouracil* or 5fluorouracil* or "5-fu" or 5fu* or fu)):ti,ab,kw	47
#34	("optimal drug therapy" or ("optimal drug" next (dosage* or dose* or dosing))):ti,ab,kw	44
#35	#28 or #29 or #30 or #31 or #32 or #33 or #34	37921
#36	[mh ^"Individualized Medicine"]	78
#37	((personal* or individual*) near/2 (chemotherap* or dosage* or dose* or dosing)):ti,ab,kw	771
#38	#36 or #37	843
#39	#35 or #38	38431
#40	#5 and #27	1

#41	#5 and #39	0
#42	#40 or #41	1
#43	#8 and #27 and #39	5
#44	(("5-fu" or 5fu* or fu) next (plasma next assay*)):ti,ab,kw	0
#45	#23 and #39	45
#46	#4 or #42 or #43 or #44 or #45	51
#47	#14 and #27	29
#48	#21 and #27	4
#49	#47 or #48	33
#50	#39 and #49	17
#51	#22 and #27	15
#52	#46 or #50 or #51	67

All Results (67)

Cochrane Reviews (0)

Trials (65)

Methods Studies (0)

Technology Assessments (2)

Economic Evaluations (0)

Cochrane Groups (0)

SCI and SSCI via Web of Science searched on 09/01/2014

# 37	#31 OR #35 OR #36 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	399
# 36	#16 AND #19 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	156
# 35	#25 AND #34 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	228
# 34	#32 OR #33 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	731
# 33	#15 AND #19 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	96

# 32	#11 AND #19 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	680
# 31	#4 OR #28 OR #29 OR #30 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	40
# 30	TS=((5-fu* OR 5fu* OR fu) NEAR/1 (plasma NEAR/1 assay*)) Databases=SCI-EXPANDED, CPCI-S Timespan=All years	2
# 29	#6 AND #19 AND #25 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	34
# 28	#26 OR #27 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	3
# 27	#5 AND #25 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	2
# 26	#5 AND #19 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	2
# 25	#23 OR #24 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	131,943
# 24	TS=((personal* OR individual*) NEAR/2 (chemotherap* OR dosage* OR dose* OR dosing)) Databases=SCI-EXPANDED, CPCI-S Timespan=All years	6,959
# 23	#20 OR #21 OR #22 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	127,286
# 22	TS=("optimal drug therapy" OR ("optimal drug" NEAR/1 (dosage* OR dose* OR dosing))) Databases=SCI-EXPANDED, CPCI-S Timespan=All years	186
# 21	TS=((drug* OR blood OR plasma) NEAR/5 (monitor* OR concentration* OR level*) NEAR/5 (fluorouracil* OR 5-fluorouracil* OR 5fluorouracil* OR 5-fu* OR 5fu* OR fu)) Databases=SCI-EXPANDED, CPCI-S Timespan=All years	415
# 20	TS=((dose* OR dosing OR dosage* OR fluorouracil* OR 5-fluorouracil* OR 5fluorouracil* OR 5-fu* OR 5fu*) NEAR/2 (adjust* OR adapt* OR monitor* OR select* OR calculat* OR intensi* OR escalat* OR modif* OR reduc* OR concentration* OR level* OR limit* OR detect* OR measur*)) Databases=SCI-EXPANDED, CPCI-S Timespan=All years	127,025
# 19	#17 OR #18	46,445

	Databases=SCI-EXPANDED, CPCI-S Timespan=All years	
# 18	TS=(5-fu* OR 5fu* OR fu) Databases=SCI-EXPANDED, CPCI-S Timespan=All years	22,299
# 17	TS=(fluorouracil* OR 5-fluorouracil* OR 5fluorouracil*) Databases=SCI-EXPANDED, CPCI-S Timespan=All years	34,612
# 16	TS=((pharmacokinetic* OR PK) NEAR/2 (dosage* OR dose* OR dosing OR adjust* OR adapt* OR monitor* OR select* OR calculat* OR guided)) Databases=SCI-EXPANDED, CPCI-S Timespan=All years	11,242
# 15	#12 OR #13 OR #14 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	38,936
# 14	TS=HPLC$MS* Databases=SCI-EXPANDED, CPCI-S Timespan=All years	2
# 13	TS=LC$MS* Databases=SCI-EXPANDED, CPCI-S Timespan=All years	44
# 12	TS=("liquid chromatography" NEAR/3 "mass spectrometry") Databases=SCI-EXPANDED, CPCI-S Timespan=All years	38,898
# 11	#7 OR #8 OR #9 OR #10 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	185,457
# 10	TS="high speed liquid chromatography" Databases=SCI-EXPANDED, CPCI-S Timespan=All years	300
# 9	TS="high pressure liquid chromatography" Databases=SCI-EXPANDED, CPCI-S Timespan=All years	7,726
# 8	TS=HPLC Databases=SCI-EXPANDED, CPCI-S Timespan=All years	135,862
# 7	TS="high performance liquid chromatography" Databases=SCI-EXPANDED, CPCI-S Timespan=All years	79,350
# 6	TS=(immunoassay* OR (immun* NEAR/2 assay*)) Databases=SCI-EXPANDED, CPCI-S Timespan=All years	158,922
# 5	TS=(myriad NEAR/1 genetic*) Databases=SCI-EXPANDED, CPCI-S Timespan=All years	106
# 4	#1 OR #2 OR #3 Databases=SCI-EXPANDED, CPCI-S Timespan=All years	4
# 3	TS=saladax	2

	Databases=SCI-EXPANDED, CPCI-S Timespan=All years	
# 2	TS=ondose Databases=SCI-EXPANDED, CPCI-S Timespan=All years	2
# 1	TS=((my5-fu*) OR (My5-FU*) OR "my5 fu" OR (my NEAR/1 5fu*) or "my 5 fu") Databases=SCI-EXPANDED, CPCI-S Timespan=All years	1

Clinical Effectiveness: Objective D

mCRC

Limited search below to publication year 2011 onwards to pick up records since the searches were run for CG131 (i.e. 25 February 2011).[7]

Ovid MEDLINE(R) 1946 to April Week 2 2014, searched on 23/04/2014

1	exp Colorectal Neoplasms/	146177
2	((colorect$ or colon$ or rectum$ or rectal$ or rectosigmoid$ or intestin$ or bowel) adj3 (metasta* or neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*)).tw.	143010
3	1 or 2	184392
4	Neoplasms/	268877
5	Carcinoma/	64081
6	Adenocarcinoma/	124609
7	4 or 5 or 6	447733
8	Colonic Diseases/	13498
9	Rectal Diseases/	6964
10	exp Colon/	53847
11	exp Rectum/	29665
12	8 or 9 or 10 or 11	91843
13	7 and 12	4451
14	3 or 13	185328
15	exp Neoplasm Metastasis/	153885

16	metasta*.mp.	350752
17	15 or 16	356332
18	14 and 17	39866
19	exp Fluorouracil/	37468
20	(fluorouracil* or 5-fluorouracil* or 5fluorouracil*).tw.	27174
21	(5-fu* or 5fu* or fu).tw.	19870
22	19 or 20 or 21	49582
23	18 and 22	5623
24	(metaanalys* or "meta analys*" or "meta-analys*").tw.	53902
25	"systematic* review*".mp.	46337
26	meta analysis.pt.	46905
27	24 or 25 or 26	97421
28	23 and 27	94
29	limit 23 to systematic reviews	109
30	28 or 29	131
31	limit 30 to yr="2011 -Current"	32

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 22, 2014, searched on 23/04/2014

1	((colorect$ or colon$ or rectum$ or rectal$ or rectosigmoid$ or intestin$ or bowel) adj3 (metasta* or neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*)).tw.	9793
2	metasta*.mp.	24769
3	1 and 2	2470
4	(fluorouracil* or 5-fluorouracil* or 5fluorouracil*).tw.	1330
5	(5-fu* or 5fu* or fu).tw.	1231
6	4 or 5	2031
7	(metaanalys* or "meta analys*" or "meta-analys*").tw.	7774
8	"systematic* review*".mp.	8702

9	7 or 8	13598
10	3 and 6 and 9	2
11	3 and 6	207
12	limit 11 to (meta analysis or systematic reviews)	5
13	10 or 12	5
14	limit 13 to yr="2011 -Current"	3

Cochrane Library (Wiley), searched on 23/04/2014

#1	MeSH descriptor: [Colorectal Neoplasms] explode all trees	5218
#2	((colorect* or colon* or rectum* or rectal* or rectosigmoid* or intestin* or bowel) near/3 (metasta* or neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*)):ti,ab,kw	8722
#3	#1 or #2	8841
#4	MeSH descriptor: [Neoplasms] this term only	4747
#5	MeSH descriptor: [Carcinoma] this term only	1002
#6	MeSH descriptor: [Adenocarcinoma] this term only	2388
#7	#4 or #5 or #6	8049
#8	MeSH descriptor: [Colonic Diseases] this term only	329
#9	MeSH descriptor: [Rectal Diseases] this term only	232
#10	MeSH descriptor: [Colon] explode all trees	1304
#11	MeSH descriptor: [Rectum] explode all trees	1175
#12	#8 or #9 or #10 or #11	2521
#13	#7 and #12	70
#14	#3 or #13	8863
#15	MeSH descriptor: [Neoplasm Metastasis] explode all trees	3741
#16	metasta*:ti,ab,kw	13237
#17	#15 or #16	13319
#18	#14 and #17	2168
#19	MeSH descriptor: [Fluorouracil] explode all trees	3873
#20	(fluorouracil* or 5-fluorouracil* or 5fluorouracil*):ti,ab,kw	6164
#21	(5-fu* or 5fu* or fu):ti,ab,kw	3150

#22	#19 or #20 or #21	7561
#23	#18 and #22	1057
#24	#23 Publication Date from 2011 to 2014	195

All Results (195)

Cochrane Reviews (2)

All

Review

Protocol

Other Reviews (6)

Trials (181)

Methods Studies (0)

Technology Assessments (1)

Economic Evaluations (5)

Cochrane Groups (0)

H&N

SIGN 90 guideline (2006)[37] - Evidence identified for the guideline covers the period to the end of 2003

NICE Evidence update (2010) *[personal communication: NICE 23 April 2014]* - searches cover 01/01/04 to 30/06/10

NICE Evidence update (2012)[116] - searches cover 01/07/10 to 12/12/11

Limited search below to publication year 2011 onwards to pick up records since the searches were run for NICE evidence update "Improving outcomes in head and neck cancers: Evidence Update May 2012".[116]

Ovid MEDLINE(R) 1946 to April Week 2 2014, searched on 23/04/2014

1	exp "Head and Neck Neoplasms"/	237244
2	(((head adj2 neck) or face or facial or oesophageal or esophageal or oesophagus or esophageal or esophagus or thyroid or salivary or paranasal or "aero digestive" or aerodigestive or aero-digestive or UADT or "nasal cavity" or larynx or laryngeal or glottis or glottic or "oral cavity" or ear or oropharynx or oropharyngeal or nasopharynx or nasopharyngeal or hypopharynx or	128309

	hypopharyngeal or pharynx or pharyngeal or parapharyngeal or mouth) adj3 (metasta* or neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*)).tw.	
3	1 or 2	255655
4	exp Fluorouracil/	37468
5	(fluorouracil* or 5-fluorouracil* or 5fluorouracil*).tw.	27174
6	(5-fu* or 5fu* or fu).tw.	19870
7	4 or 5 or 6	49582
8	3 and 7	4957
9	(metaanalys* or "meta analys*" or "meta-analys*").tw.	53902
10	"systematic* review*".mp.	46337
11	meta analysis.pt.	46905
12	9 or 10 or 11	97421
13	8 and 12	62
14	limit 8 to systematic reviews	57
15	13 or 14	84
16	limit 15 to yr="2011 -Current"	14

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 22, 2014, searched on 23/04/2014

1	(((head adj2 neck) or face or facial or oesophageal or esophageal or oesophagus or esophageal or esophagus or thyroid or salivary or paranasal or "aero digestive" or aerodigestive or aero-digestive or UADT or "nasal cavity" or larynx or laryngeal or glottis or glottic or "oral cavity" or ear or oropharynx or oropharyngeal or nasopharynx or nasopharyngeal or hypopharynx or hypopharyngeal or pharynx or pharyngeal or parapharyngeal or mouth) adj3 (metasta* or neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*)).tw.	8487
2	(fluorouracil* or 5-fluorouracil* or 5fluorouracil*).tw.	1330
3	(5-fu* or 5fu* or fu).tw.	1231
4	2 or 3	2031
5	1 and 4	141

6	(metaanalys* or "meta analys*" or "meta-analys*").tw.	7774
7	"systematic* review*".mp.	8702
8	6 or 7	13598
9	5 and 8	3
10	limit 5 to (meta analysis or systematic reviews)	2
11	9 or 10	3
12	limit 11 to yr="2011 -Current"	3

Cochrane Library (Wiley), searched on 23/04/2014

#1	MeSH descriptor: [Head and Neck Neoplasms] explode all trees	3908
#2	(((head near/2 neck) or face or facial or oesophageal or esophageal or oesophagus or esophageal or esophagus or thyroid or salivary or paranasal or "aero digestive" or aerodigestive or aero-digestive or UADT or "nasal cavity" or larynx or laryngeal or glottis or glottic or "oral cavity" or ear or oropharynx or oropharyngeal or nasopharynx or nasopharyngeal or hypopharynx or hypopharyngeal or pharynx or pharyngeal or parapharyngeal or mouth) near/3 (metasta* or neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*)):ti,ab,kw	7750
#3	#1 or #2	7998
#4	MeSH descriptor: [Fluorouracil] explode all trees	3873
#5	(fluorouracil* or 5-fluorouracil* or 5fluorouracil*):ti,ab,kw	6164
#6	(5-fu* or 5fu* or fu):ti,ab,kw	3150
#7	#4 or #5 or #6	7561
#8	#3 and #7	842
#9	#8 Publication Date from 2011 to 2014	158

All Results (158)

Cochrane Reviews (0)

All

Review

Protocol

Other Reviews (4)

Trials (150)

Methods Studies (0)

Technology Assessments (2)

Economic Evaluations (2)

Cochrane Groups (0)

Cost Effectiveness: Objective E

Cost search 1: Cost effectiveness of PK dosing and 5-FU

Same as search strategies for Clinical Effectiveness: Objectives A, B and C (see above)

Cost search 2: Adverse events of chemotherapy: Quality of life

Search 2a

Reran exactly the same search as Shabarrudin, et al. (2013),[171] limited to those added after their search was run (June 2011).

N.b. their search was run in Medline and Embase at the same time.

Ovid Embase 1980 to 2014 Week 12 and Ovid MEDLINE(R) 1946 to March Week 2 2014, searched 26/03/2014

1	utility.af.	249345
2	util$.af.	1267175
3	value$.af.	3027887
4	valuation$.af.	9190
5	1 or 2 or 3 or 4	4157549
6	time trade-off.af.	1673
7	TTO.af.	1412
8	(time adj2 trade adj2 off).af.	1696
9	time-trade-off.af.	1673
10	6 or 7 or 8 or 9	2350
11	person trade-off.af.	95
12	PTO.af.	1150
13	(person adj2 trade adj2 off).af.	95
14	person-trade-off.af.	95
15	11 or 12 or 13 or 14	1205
16	standard gamble.af.	1403
17	SG.af.	24199
18	(standard adj2 gamble).af.	1424
19	16 or 17 or 18	25136

20	visual analogue scale$.af.	34143
21	VAS.af.	71777
22	(visual adj2 analogue adj2 scale).af.	30245
23	20 or 21 or 22	90806
24	judgement$.af.	24572
25	10 or 15 or 19 or 24	52652
26	cancer.af.	4043795
27	chemotherapy.af.	837929
28	cytotoxic.af.	307572
29	exp cancer/	5688751
30	26 or 27 or 28 or 29	6831544
31	5 and 25 and 30	1537
32	limit 31 to english language	1350
33	limit 32 to human (n.b. 602 from Medline, 589 from Embase)	1191
34	remove duplicates from 33 (n.b. 313 from Medline, 580 from Embase)	893
35	limit 34 to ed=20110601-20140326 [Limit not valid in Embase; records were retained]	656
36	limit 35 to dd=20110601-20140326 [Limit not valid in Ovid MEDLINE(R); records were retained]	276
37	limit 35 to em=201100-201412 [Limit not valid in Ovid MEDLINE(R); records were retained]	269
38	36 or 37	285
39	limit 38 to yr="2011 -Current" (n.b. 124 from Medline, 186 from Embase – includes duplicates)	261

Search 2b

Made improvements to search 2a above and only looked at any extras the improvements retrieved.

N.b. No date limit was applied and cancer and chemotherapy terms were combined with the boolean operator AND

Ovid MEDLINE(R) 1946 to March Week 2 2014, searched 26/03/2014

1	Health Status/	57926
2	exp "Quality of Life"/	114259

3	exp Quality-Adjusted Life Years/	6774
4	(utilit* or disutilit* or (quality adj2 life) or QoL or hrql or hrqol or qaly* or health state* or health status).tw.	265920
5	(value* or valuation*).tw.	1144946
6	1 or 2 or 3 or 4 or 5	1453190
7	((standard adj2 gamble) or SG or (time adj2 trade adj2 off) or TTO or (person adj2 trade adj2 off) or PTO or (visual adj2 analog* adj2 scale*) or VAS or judgement*).tw.	55312
8	chemotherap*.mp.	305412
9	cytotoxi*.mp.	215983
10	antineoplastic*.mp.	350668
11	8 or 9 or 10	655061
12	exp Neoplasms/	2516811
13	(neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*).tw.	2052611
14	12 or 13	2906356
15	6 and 7 and 11 and 14	228
16	limit 15 to english language	194
17	Animals/ not Humans/	3812070
18	16 not 17	187
19	Limit 18 to ed=20110601-20140326	38
20	limit 19 to yr="2011 -Current"	35
21	18 not 19	149

Embase 1980 to 2014 Week 12, searched 26 Mar 2014

1	exp health economics/	601627
2	exp health status/	133750
3	exp "quality of life"/	258706
4	exp quality adjusted life year/	11658
5	(utilit* or disutilit* or (quality adj2 life) or QoL or hrql or hrqol or qaly* or health state* or health status).tw.	392413
6	(value* or valuation*).tw.	1470360
7	2 or 3 or 4 or 5 or 6	1981954
8	((standard adj2 gamble) or SG or (time adj2 trade adj2 off) or TTO or	81071

	(person adj2 trade adj2 off) or PTO or (visual adj2 analog* adj2 scale*) or VAS or judgement*).tw.	
9	exp chemotherapy/	364306
10	chemotherap*.tw.	357534
11	cytotoxi*.mp.	309321
12	antineoplastic*.mp.	300253
13	9 or 10 or 11 or 12	949783
14	exp neoplasm/	3171940
15	(neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*).tw.	2610335
16	14 or 15	3638984
17	7 and 8 and 13 and 16	439
18	limit 17 to english language	392
19	animal/ not human/	1175889
20	18 not 19	391
21	limit 20 to dd=20110601-20140326	160
22	limit 20 to em=201100-201412	157
23	21 or 22	171
24	limit 23 to yr="2011 -Current"	153
25	20 not 23	220

Search 2c

Supplement the above searches 2a and 2b with one that includes generic instruments and AE terms

Ovid MEDLINE(R) 1946 to March Week 4 2014, searched 02/04/14

1	(EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF6D or health utilities index or HUI).tw.	15952
2	chemotherap*.mp.	305766
3	cytotoxi*.mp.	216184
4	exp "Antineoplastic Agents"/	817215
5	antineoplastic*.mp.	351082
6	2 or 3 or 4 or 5	1110394

7	exp Neoplasms/	2518920
8	(neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*).tw.	2054720
9	7 or 8	2908935
10	1 and 6 and 9	228
11	limit 10 to english language	219
12	Animals/ not Humans/	3814327
13	11 not 12	219
14	Diarrhea/	38106
15	(diarrhoea or diarrhea).tw.	66815
16	exp Thrombocytopenia/	38591
17	exp Leukopenia/	31360
18	(leukopenia* or leukocytopenia* or neutropenia* or thombocytopenia* or thrombopenia*).tw.	33614
19	Mucositis/	782
20	mucositis.tw.	5932
21	Stomatitis/	5131
22	stomatitis.tw.	11197
23	Hand-Foot Syndrome/	96
24	Foot Dermatoses/ci [Chemically Induced]	344
25	Hand Dermatoses/ci [Chemically Induced]	1282
26	((hand foot syndrome* or (acral erythema* or palmoplantar erythrodysesthesia*)) adj1 chemotherapy induced).tw.	31
27	exp Heart Diseases/ci [Chemically Induced]	31712
28	((cardiac* or heart*) adj1 (adverse or harm* or side-effect* or toxic* or complication*)).tw.	10899
29	cardiotoxic*.tw.	7809
30	Nausea/	12757
31	Vomiting/	19046
32	(nause* or vomit* or emesis).tw.	62296
33	14 or 15 or 16 or 17 or 18 or 19 or 20 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	280758
34	13 and 33	19

35	exp "Drug-Related Side Effects and Adverse Reactions"/	87091
36	(risk* or safe or safety or adverse or undesirable effect* or harm* or pharmacovigilance or side-effect* or precaution* or warning* or contraindication* or contra-indication* or tolerability or toxic* or complication*).ti.	592138
37	ae.fs.	1328971
38	35 or 36 or 37	1779742
39	13 and 38	59
40	34 or 39	69

Embase 1980 to 2014 Week 13, searched 02/04/14

1	(EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF6D or health utilities index or HUI).tw.	26744
2	"Short Form 36"/	11771
3	1 or 2	31039
4	exp chemotherapy/	369730
5	chemotherap*.tw.	362434
6	cytotoxi*.mp.	312608
7	antineoplastic*.mp.	302930
8	4 or 5 or 6 or 7	960409
9	exp neoplasm/	3205221
10	(neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*).tw.	2641077
11	9 or 10	3676076
12	3 and 8 and 11	601
13	limit 12 to english language	575
14	animal/ not human/	1178623
15	13 not 14	575
16	diarrhea/ or acute diarrhea/ or chronic diarrhea/	156385
17	(diarrhoea or diarrhea).tw.	89281
18	exp Thrombocytopenia/	113656

19	exp Leukopenia/	134764
20	(leukopenia* or leukocytopenia* or neutropenia* or thombocytopenia* or thrombopenia*).tw.	48087
21	mucosa inflammation/	22214
22	mucositis.tw.	9334
23	stomatitis/ or oral mucositis/	19653
24	stomatitis.tw.	12143
25	hand foot syndrome/	6869
26	((hand foot syndrome* or (acral erythema* or palmoplantar erythrodysesthesia*)) adj1 chemotherapy induced).tw.	40
27	cardiotoxicity/	31377
28	((cardiac* or heart*) adj1 (adverse or harm* or side-effect* or toxic* or complication*)).tw.	17851
29	cardiotoxic*.tw.	10452
30	"chemotherapy induced nausea and vomiting"/	1065
31	chemotherapy induced emesis/	5530
32	(nause* or vomit* or emesis).tw.	93341
33	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	499141
34	15 and 33	71

Totals for searches since June 2011:

Shabarrudin, et al. (2013) search updated since June 2011 plus any extras retrieved by improved search and supplementary search since June 2011

Medline	**Embase**	**Total**	**Total after deduplication**
Search 2a (line 39, just Medline): **124** (run 26/03/2014)	Search 2a (line 39, just Embase): **186** (run 26/03/2014)	310	255
Extras to 2a (line 39) in Medline found by search 2b (line 20): **31** (run 26/03/2014)	Extras to 2a (line 39) in Embase found by search 2b (line 24): **123** (run 26/03/2014)	154	122
Extras to 2a (line 39) and 2b	Extras to 2a (line 39) and 2b	52	45

(line 19) in Medline found by search 2c (line 40): **20** (run 02/04/2014)	(line 24) in Embase found by search 2c (line 34): **32** (run 02/04/2014)		

Totals for searches pre June 2011:

Extras retrieved by improved search and supplementary search pre June 2011

Medline	**Embase**	**Total**	**Total after deduplication**
(search 2b (line 21) NOT search 2a (line 33)): **84** (run 26/03/2014)	(search 2b (line 25) NOT search 2a (line 33)): **153** (run 26/03/2014)	237	180 not sifted
(search 2c) NOT search 2a (line 33)): **44** (run 02/04/2014)	(search 2c) NOT search 2a (line 33)): **36** (run 02/04/2014)	80	66

Cost search 3: Adverse events of chemotherapy: Resource use

Ovid MEDLINE(R) 1946 to March Week 3 2014, searched 02/04/2014

1	chemotherap*.mp.	305766
2	cytotoxi*.mp.	216184
3	exp "Antineoplastic Agents"/	817215
4	antineoplastic*.mp.	351082
5	1 or 2 or 3 or 4	1110394
6	exp Neoplasms/	2518920
7	(neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*).tw.	2054720
8	6 or 7	2908935
9	exp Economics/	485325
10	exp "Costs and Cost Analysis"/	178538
11	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	423541
12	("resource use" or resource utili?ation).tw.	8300
13	9 or 10 or 11 or 12	779447
14	5 and 8 and 13	10151
15	limit 14 to english language	9337
16	Animals/ not Humans/	3814327
17	15 not 16	8673

18	&pound.tw.	1910
19	(&pound or pound* or UK or "United Kingdom" or GBP or sterling or "National Health Service" or NHS).tw.	105480
20	17 and 18	49
21	17 and 19	384
22	Diarrhea/	38106
23	(diarrhoea or diarrhea).tw.	66815
24	exp Thrombocytopenia/	38591
25	exp Leukopenia/	31360
26	(leukopenia* or leukocytopenia* or neutropenia* or thombocytopenia* or thrombopenia*).tw.	33614
27	Mucositis/	782
28	mucositis.tw.	5932
29	Stomatitis/	5131
30	stomatitis.tw.	11197
31	Hand-Foot Syndrome/	96
32	Foot Dermatoses/ci [Chemically Induced]	344
33	Hand Dermatoses/ci [Chemically Induced]	1282
34	((hand foot syndrome* or (acral erythema* or palmoplantar erythrodysesthesia*)) adj1 chemotherapy induced).tw.	31
35	exp Heart Diseases/ci [Chemically Induced]	31712
36	((cardiac* or heart*) adj1 (adverse or harm* or side-effect* or toxic* or complication*)).tw.	10899
37	cardiotoxic*.tw.	7809
38	Nausea/	12757
39	Vomiting/	19046
40	(nause* or vomit* or emesis).tw.	62296
41	22 or 23 or 24 or 25 or 26 or 27 or 28 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40	280758
42	20 and 41	2
43	21 and 41	38
44	17 and 41	1074

Cost search 4: mCRC/H&N cancer: Quality of life

Ovid MEDLINE(R) 1946 to March Week 4 2014, searched 03/04/2014

1	exp Colorectal Neoplasms/	145851
2	((colorect$ or colon$ or rectum$ or rectal$ or rectosigmoid$ or intestin$ or bowel) adj3 (metasta* or neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*)).tw.	142669
3	1 or 2	183977
4	Neoplasms/	268242
5	Carcinoma/	63997
6	Adenocarcinoma/	124430
7	4 or 5 or 6	446841
8	Colonic Diseases/	13485
9	Rectal Diseases/	6962
10	exp Colon/	53746
11	exp Rectum/	29617
12	8 or 9 or 10 or 11	91698
13	7 and 12	4442
14	3 or 13	184912
15	exp Neoplasm Metastasis/	153603
16	metasta*.mp.	349948
17	15 or 16	355521
18	14 and 17	39775
19	exp "Head and Neck Neoplasms"/	236849
20	(((head adj2 neck) or face or facial or oesophageal or esophageal or oesophagus or esophageal or esophagus or thyroid or salivary or paranasal or "aero digestive" or aerodigestive or aero-digestive or UADT or "nasal cavity" or larynx or laryngeal or glottis or glottic or "oral cavity" or ear or oropharynx or oropharyngeal or nasopharynx or nasopharyngeal or hypopharynx or hypopharyngeal or pharynx or pharyngeal or parapharyngeal or mouth) adj3 (metasta* or neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*)).tw.	128028
21	19 or 20	255226
22	Health Status/	58289
23	exp "Quality of Life"/	115314
24	exp Quality-Adjusted Life Years/	6850

25	(utilit* or disutilit* or (quality adj2 life) or QoL or hrql or hrqol or qaly* or health state* or health status).tw.	267987
26	22 or 23 or 24 or 25	344340
27	(standard gamble or SG or time trade off or TTO or visual analog* scale* or VAS or EQ5D or EQ-5D or euroqol or euro-qol or SF-36 or SF36 or SF-6D or SF6D or health utilities index or HUI).tw.	57547
28	26 and 27	17183
29	18 and 28 Colorectal Cancer AND metastases terms (may miss some)	21
30	14 and 28 Colorectal Cancer	139
31	21 and 28 Head and Neck Cancer	159
32	30 or 31 Hardly any duplicates so worth keeping lists for each cancer separate to make sifting easier	296
33	limit 30 to english language Colorectal Cancer	133
34	limit 31 to english language Head and Neck Cancer	144
35	limit 29 to english language Colorectal Cancer AND metastases terms (may miss some)	19

Cost search 5: mCRC/H&N cancer: Resource use

Ovid MEDLINE(R) 1946 to March Week 4 2014, searched 03/04/2014

1	exp Colorectal Neoplasms/	145851
2	((colorect$ or colon$ or rectum$ or rectal$ or rectosigmoid$ or intestin$ or bowel) adj3 (metasta* or neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*)).tw.	142669
3	1 or 2	183977
4	Neoplasms/	268242
5	Carcinoma/	63997
6	Adenocarcinoma/	124430
7	4 or 5 or 6	446841
8	Colonic Diseases/	13485
9	Rectal Diseases/	6962
10	exp Colon/	53746
11	exp Rectum/	29617
12	8 or 9 or 10 or 11	91698
13	7 and 12	4442
14	3 or 13	184912
15	exp Neoplasm Metastasis/	153603

16	metasta*.mp.	349948
17	15 or 16	355521
18	14 and 17	39775
19	exp "Head and Neck Neoplasms"/	236849
20	(((head adj2 neck) or face or facial or oesophageal or esophageal or oesophagus or esophageal or esophagus or thyroid or salivary or paranasal or "aero digestive" or aerodigestive or aero-digestive or UADT or "nasal cavity" or larynx or laryngeal or glottis or glottic or "oral cavity" or ear or oropharynx or oropharyngeal or nasopharynx or nasopharyngeal or hypopharynx or hypopharyngeal or pharynx or pharyngeal or parapharyngeal or mouth) adj3 (metasta* or neoplasm* or neoplasia or tumor* or tumour* or cancer* or carcinoma* or malignan* or adenocarcinoma*)).tw.	128028
21	19 or 20	255226
22	exp Economics/	487398
23	exp "Costs and Cost Analysis"/	179191
24	(pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.	425718
25	("resource use" or resource utili?ation).tw.	8363
26	22 or 23 or 24 or 25	783201
27	14 and 26	5330
28	21 and 26	3771
29	limit 27 to english language	4814
30	limit 28 to english language	3271
31	Animals/ not Humans/	3826890
32	29 not 31	4748
33	30 not 31	3237
34	(&pound or pound* or UK or "United Kingdom" or GBP or sterling or "National Health Service" or NHS).tw.	106315
35	32 and 34 Colorectal Cancer	205
36	33 and 34 Head and Neck Cancer	96
37	18 and 26	701
38	limit 37 to english language	602
39	38 not 31	591
40	34 and 39 Colorectal Cancer AND metastases terms (may miss some)	42

Appendix 2. Sample data extraction form for Objective A-1

Name of first reviewer: *Name of second reviewer:*

Study details		
Study ID (Ref man)		
First author surname		
Year of publication		
Country		
Declared Interests		
Aim of the study		
Selection and storage of patients/plasma samples		
Description of method of selection		
Description of method and duration of storage		
Number of patients/healthy volunteers		
Number of samples/patient		
Total number of plasma samples		
Age of participants		
Gender of participants		
Cancer patients or healthy volunteers		
Type of cancer		
Further details of cancer		
Tests	**Reference standard**	**Index test**
Type of test (equipment)		
Further description		
Details of any repeat measurements to check (to check reliability, performance across different analysers or different laboratories)		
Results		
Range of concentrations for reference standard		
Range of concentrations for index test		
For correlation between reference standard and index test:		
Regression method		
Linearity test/cusum test?		
R^2 (95%CI)		
Slope (95%CI)		

Intercept (95%CI)	
From Bland-Altman plot:	
Percent bias (95%CI)	
Upper limit of agreement	
Lower limit of agreement	
Details of outliers	
Visually is there a pattern between the mean value and the difference? (If no pattern then can statistics from Bland-Altman plot are interpretable)	
Authors' conclusion	
Reviewer's conclusion	

Appendix 3. Sample data extraction form for Objective A-2 and single arm studies from Objectives B and C

Name of first reviewer: *Name of second reviewer:*

Study details	
Study ID (Ref man)	
First author surname	
Year of publication	
Country	
Study design	
Publication (full/abstract etc.)	
Study setting	
Number of centres	
Duration of study	
Follow up period	
Cancer type(s)	
Funding	
Aim of the study	
Inclusion/exclusion criteria for patients	
Inclusion criteria:	
Exclusion criteria:	
Participants (characteristics and numbers)	
Item	
Total number of participants	
Sample attrition/drop out	
Age *Mean SD* *Median (range)*	
Sex *Men* *Women*	
Cancer stage *I* *II* *III* *IV*	
Performance status *0* *1*	

2 *3* *4*	
Number of Metastatic sites *1* *2* *3* *4*	
Previous 5-FU treatment	
Treatment	
Item	
Type of dose regimen used	
Other interventions Yes/No	
Cycle number	
Outcomes reported	
Primary outcome(s)	
Secondary outcomes	
Timing of assessments	
Progression free survival Yes/No	
Overall survival Yes/No	
Adverse event (toxicity) Yes/No	
Health related quality of life: Yes/No; which measures used?	
Response	
Length of follow up reported Yes/No	
Proportion progressing to surgery Yes/No	
Study end point	
Overall survival	
Item	
Median survival 95% CI	
Kaplan-Meier plot Yes/No	
Total events	
Total censored	
At risk table yes/no	
Hazard ratio 95% CI	
Log rank test (p value)	

Progression free survival		
Item		
Median survival 95% CI		
Kaplan-Meier plot yes/no		
Total events		
Total censored		
At risk table yes/no		
Hazard ratio 95% CI		
Describe criteria for determining progression:		
Incidence of adverse events / side effects /toxicity; specify time/period =		
Item (Rename as appropriate)		**P value**
Diarrhoea Grade (specify; WHO or NCI CTAE etc.)		
I		
II		
III		
IV		
Nausea Grade (specify; WHO or NCI CTAE etc.)		
I		
II		
III		
IV		
Mucositis Grade (specify; WHO or NCI CTAE etc.)		
I		
II		
III		
IV		
Mouth sore Grade (specify; WHO or NCI CTAE)		
I		
II		
III		
IV		

Hand-foot syndrome Grade (specify; WHO or NCI CTAE etc.)		
I		
II		
III		
IV		
Leucopenia Grade (specify; WHO or NCI CTAE etc.)		
I		
II		
III		
IV		
Neutropenia Grade (specify; WHO or NCI CTAE etc.)		
I		
II		
III		
IV		
Thrombocytopenia Grade (specify; WHO or NCI CTAE etc.)		
I		
II		
III		
IV		
Cardiac toxicity Grade (specify; WHO or NCI CTAE etc.)		
I		
II		
III		
IV		
Conjunctivitis Grade (specify; WHO or NCI CTAE etc)		
I		

II		
III		
IV		
Other (specify)		

Objective Response rate (specify criteria [NR]; specify time:	
Item	**N (%)**
CR (Complete response)	
PR (Partial response)	
Overall response (CR+PR)	
Disease Control (stable disease)	
Disease progression	
Differential response	
Duration of response (mean / median)	
Objective response rate (complete and partial response) of ITT patients [95% CI]	
Disease control rate of ITT patients [95% CI]	
5-FU plasma concentration	
Item	
Method of 5-FU measurement	
Frequency of 5-FU measures	
Plasma concentration	
Range	
Mean	
AUC	
Range	
Mean	
Dose adjustment	
Item	
Dose adjustment Yes/No	
Specify adjustment rule	
Adjustment algorithm specified yes/no	
Algorithm provided yes/no	
Mean 5-FU dose (mg/m^3/wk)	
Dose adjustment for toxicity rule	
Dose adjustment for toxicity n/N	
Target AUC range	
Proportion with 5-FU measures in target range	
Incidence of over and under dosing (specify time)	

Number of patients with dose adjustment	
Frequency of dose adjustment (number adjustment/number of measures)	
Test failure rates	
Other	
Health related quality of life	
Item	
Authors' conclusion	
Reviewer's conclusion	

Supplementary information / data:

Information on new algorithm	
Item	

Appendix 4. Sample data extraction form for Objectives B and C: primary comparative studies

Name of first reviewer: *Name of second reviewer:*

Study details			
Study ID (Ref man)			
First author surname			
Year of publication			
Country			
Study design			
Publication (full/abstract)			
Study setting			
Number of centres (by arm)			
Duration of study			
Follow up period			
Cancer type(s)			
Funding			
Aim of the study			
Inclusion/exclusion criteria for patients			
Inclusion criteria:			
Exclusion criteria:			
Study flow (consort diagram)			
Item	**BSA arm**	**PK arm**	**All**
Screened			
Randomised/Included			
Excluded			
Missing participants			
Withdrawals			
Participants (characteristics and numbers)			
Item	**BSA arm N (%)**	**PK arm N (%)**	**All**
Total number of participants			
Sample attrition/drop out			
Age *Mean SD* *Median (range) years*			
Sex *Men* *Women*			
Cancer stage *I*			

II *III* *IV*			
Performance status *0-1* *2-3* *4*			
Number of Metastatic sites *1* *2* *3*			

Treatment		
Item	**BSA arm**	**PK arm**
Type of dose regimen used		
Other interventions Yes/No		
How many cycles		

Outcomes reported	
Primary outcome(s)	
Secondary outcomes	
Timing of assessments	
Progression free survival Yes/No	
Overall survival Yes/No	
Adverse event (toxicity) Yes/No	
Health related quality of life: Yes/No; which measures used?	
Length of follow up reported Yes/No	
Proportion progressing to surgery Yes/No	
Study end point	

Overall survival			
Item	**BSA arm**	**PK arm**	**All**
Median survival 95% CI months			
Kaplan-Meier plot Yes/No			
Total events			
Total censored			
At risk table Yes/No			
Hazard ratio 95% CI			
Log rank test (P value)			

Progression free survival

Item	BSA arm	PK arm	P value
Median survival 95% CI			
Kaplan-Meier plot Yes/No			
Total events			
Total censored			
At risk table Yes/No			
Hazard ratio 95% CI			
Incidence of adverse events / side effects /toxicity; specify time/period =			
Item (Rename as appropriate)	**BSA arm n/N (%)**	**PK arm n/N (%)**	**P value**
Diarrhoea Grade (WHO)			
I			
II			
III-IV			
Nausea Grade (specify; WHO or NCI CTAE)			
I			
II			
III			
IV			
Vomiting Grade (specify; WHO or NCI CTAE)			
I			
II			
III			
IV			
Mucositis Grade (specify; NCI CTAE)			
I			
II			
III-IV			
Mouth sore Grade (specify; WHO or NCI CTAE)			
I			
II			
III			
IV			

Hand-foot syndrome Grade (specify; WHO or NCI CTAE)			
I			
II			
III			
IV			
Leukopenia Grade (specify; WHO or NCI CTAE)			
I			
II			
III			
IV			
Neutropenia Grade (specify; NCI CTAE)			
I			
II			
III-IV			
Thrombocytopenia Grade (specify; NCI CTAE)			
I			
II			
III-IV			
IV			
Cardiac toxicity Grade (specify; WHO or NCI CTAE)			
I			
II			
III			
IV			
Conjunctivitis Grade (specify; WHO or NCI CTAE)			
I			
II			
III			
IV			
Other (specify)			
Neuropathy			
Severe damage to organ			

Sepsis			
Septic shock			

Objective Response rate (specify criteria RECIST; specify time 3 months and 6 months)				
Item	**BSA arm n/N (%)**	**PK arm n/N (%)**		**P value**
CR (Complete response)				
PR (Partial response)				
Overall response (CR+PR)				
Disease Control				
Disease progression				
Duration of response (mean / median)				

Dose adjustment		
Item (Please define if necessary **)**	**BSA arm**	**PK arm**
Specify adjustment rule		
Method of 5-FU measurement		
Frequency of 5-FU measures		
Adjustment algorithm specified Yes/No		
Algorithm provided Yes/No		
Mean 5-FU dose (mg/m^3/wk) (SD)		
Proportion (%) of patients reached target range		
Dose adjustment for toxicity n/N		
Proportion with 5-FU measures levels in target range		
Incidence of over and under dosing (please specify)		
Frequency of dose adjustment (number of adjustment/number of measures)		
Test failure rates		
Other		

Health related quality of life		
Item		

Authors' conclusion
Reviewer's conclusion

Appendix 5. Sample quality assessment form for Objective A-1: QUADAS-2 tool with index questions adapted to the review

Name of first reviewer: Name of second reviewer:

Phase 1: State the review question

Patients (setting, intended use of index test, presentation, prior testing):
Index test(s):
Reference standard:

Phase 2: Draw a flow diagram for the primary study

Phase 3: Risk of bias and applicability judgements

QUADAS-2 is structured so that four key domains are each rated in terms of the risk of bias and the concern regarding applicability to the review question (as stated in Phase 1). Each key domain has a set of signalling questions to help reach the judgements regarding bias and applicability.

Domain 1: Patient selection

A. Risk of bias	
Describe methods of patient selection:	
Was a consecutive or random sample of patients enrolled?	
Did the study avoid inappropriate exclusions?	
Could the selection of patients have introduced bias? **Risk:**	
B. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting): Range of plasma concentrations:	
Is there concern that the included patients or range of plasma concentrations do not match the review question? **Concern:**	

Domain 2: Index test(s)

A. Risk of bias	
Describe the index test and how it was conducted and interpreted:	
Were the number of failed results and measurement repeats reported?	
Could the conduct or interpretation of the index test have introduced bias? **Risk:**	

B. Concerns regarding applicability Describe the preparation and storage of the sample before the index test was applied:
Is there concern that the index test, its conduct, or interpretation differ from the review question? **Concern:**

Domain 3: Reference standard

A. Risk of bias	
Describe the reference standard and how it was conducted and interpreted:	
Is the reference standard likely to correctly classify the target condition?	
Could the reference standard, its conduct, or its interpretation have introduced bias? **Risk:**	
B. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question? **Concern:**	

Domain 4: Flow and timing

A. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the Bland-Altman plot: Describe the time interval and any interventions between index test(s) and reference standard:	
Was there an appropriate interval between index test(s) and reference standard?	
Were both index test and reference standard conducted on all samples??	
Did patients receive the same reference standard?	
Were all patients included in the Bland-Altman plot?	
Could the patient flow have introduced bias? **Risk:**	

Appendix 6. Sample quality assessment forms for Objectives B and C

First author (year) study ID: *Name of first reviewer:* *Name of second reviewer:*

Reporting	**Rating**
1. Is the hypothesis/aim/objective of the study clearly described? **(Yes/No)**	
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section? **(Yes/No)** *If the main outcomes are first mentioned in the Results section, the question should be answered "No"*	
3. Are the characteristics of the patients included in the study clearly described? **(Yes/No)** *In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be givenFsan*	
4. Are the interventions of interest clearly described? **(Yes/No)** *Treatments and placebo (where relevant) that are to be compared should be clearly described*	
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described? **(Yes/Partially/No)** *A list of principal confounders is provided*	
6. Are the main findings of the study clearly described? **(Yes/No)** *Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions (This question does not cover statistical tests which are considered below)*	
7. Does the study provide estimates of the random variability in the data for the main outcomes? **(Yes/No)** *In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered "Yes"*	
8. Have all important adverse events that may be a consequence of the intervention been reported? **(Yes/No)** *This should be answered "Yes" if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided)*	
9. Have the characteristics of patients lost to follow-up been described? **(Yes/No)** *This should be answered "Yes" where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered "No" where a study does not report the number of patients lost to follow-up*	
10. Have actual probability values been reported (e.g., 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001? **(Yes/No)**	
External validity	**Rating**
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited? **(Yes/No/Unable to determine)** *The study must identify the source population for patients and describe how the patients were selected. Patients would be*	

representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant	
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited? **(Yes/No/Unable to determine)** *The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population*	
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? **(Yes/No/Unable to determine)** *For the question to be answered "Yes" the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered "No" if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend*	
Internal validity – bias	**Rating**
14. Was an attempt made to blind study subjects to the intervention they have received? **(Yes/No/Unable to determine)** *For studies where the patients would have no way of knowing which intervention they received, this should be answered "Yes"*	
15. Was an attempt made to blind those measuring the main outcomes of the intervention? **(Yes/No/Unable to determine)**	
16. If any of the results of the study were based on "data dredging", was this made clear? **(Yes/No/Unable to determine)** *Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer "Yes"*	
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? **(Yes/No/Unable to determine)** *Where follow-up was the same for all study patients the answer should "Yes". If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be "Yes". Studies where differences in follow-up are ignored should be answered "No"*	
18. Were the statistical tests used to assess the main outcomes appropriate? **(Yes/No/Unable to determine)** *The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered "Yes". If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered "Yes"*	
19. Was compliance with the intervention/s reliable? **(Yes/No/Unable to determine)** *Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered "No". For studies where the effect of any*	

misclassification was likely to bias any association to the null, the question should be answered "Yes"	
20. Were the main outcome measures used accurate valid and reliable? **(Yes/No/Unable to determine)** *For studies where the outcome measures are clearly described, the question should be answered "Yes". For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as "Yes"*	
Internal validity - confounding (selection bias)	**Rating**
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? **(Yes/No/Unable to determine)** *For example, patients for all comparison groups should be selected from the same hospital. The question should be answered "Unable to determine" for cohort and case-control studies where there is no information concerning the source of patients included in the study*	
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? **(Yes/No/Unable to determine)** *For a study which does not specify the time period over which patients were recruited, the question should be answered as "Unable to determine"*	
23. Were the subjects randomised to intervention groups? **(Yes/No/Unable to determine)** *Studies which state that subjects were randomised should be answered "Yes" except where method of randomisation would not ensure random allocation. For example alternate allocation would score "No" because it is predictable*	
24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? **(Yes/No/Unable to determine)** *All non-randomised studies should be answered "No". If assignment was concealed from patients but not from staff, it should be answered "No"*	
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? **(Yes/No/Unable to determine)** *This question should be answered "No" for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In nonrandomised studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as "No"*	
26. Were losses of patients to follow-up taken into account? **(Yes/No/Unable to determine)** *If the numbers of patients lost to follow-up are not reported, the question should be answered as "Unable to determine". If the proportion lost to follow-up was too small to affect the main findings, the question should be answered "Yes"*	
Power	**Rating**
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? **(Yes/No/Unable to**	

determine)*	

Appendix 7. Included studies for clinical effectiveness objectives

Objective A
1. Beumer JH, Boisdron-Celle M, Clarke W, Courtney JB, Egorin MJ, *et al.* Multicenter evaluation of a novel nanoparticle immunoassay for 5-fluorouracil on the olympus AU400 analyzer. *Therapeutic Drug Monitoring*. 2009;**31**(6):688-94.
2. Buchel B, Sistonen J, Joerger M, Aebi Y, Schurch S, Largiader CR. Comparative evaluation of the My5-FU immunoassay and LC-MS/MS in monitoring the 5-fluorouracil plasma levels in cancer patients. *Clinical Chemistry and Laboratory Medicine*. 2013;**51**(8):1681-8.
3. Buchel B, Sistonen J, Aebi Y, Largiader CR. Comparative Evaluation of the My5-FU Immunoassay and LC-MS/MS in the Monitoring of 5-fluorouracil levels in cancer patients. *Clinical Chemistry and Laboratory Medicine*. 2012;**50 (5)**:A169-A70.
4. Makihara K, Mishima H, Azuma S, Matsuyama K, Komori K, Hasegawa H, *et al.* A pilot study of pharmacokinetically guided dose management of capecitabine in CRC patients. *Journal of Clinical Oncology*. 2012;**1)**.
5. Kaldate RR, Haregewoin A, Grier CE, Hamilton SA, McLeod HL. Modeling the 5-fluorouracil area under the curve versus dose relationship to develop a pharmacokinetic dosing algorithm for colorectal cancer patients receiving FOLFOX6. *Oncologist*. 2012;**17**(3):296-302.
Objectives B and C
6. Boisdron-Celle M, Craipeau M, Brienza S, Delva R, Guerin-Meyer V, Cvitkovic E, *et al.* Influence of oxaliplatin on 5-fluorouracil plasma clearance and clinical consequences. *Cancer Chemotherapy and Pharmacology*. 2002;**49**(3):235-43.
7. Capitain O, Boisdron-Celle M, Poirier AL, Abadie-Lacourtoiseie S, Morel A, Gamelin E. The influence of fluorouracil outcome parameters on tolerance and efficacy in patients with advanced colorectal cancer. Pharmacogenomics Journal 2008; 8:256-267)
8. Capitain O, Asevoaia A, Boisdron-Celle M, Poirier AL, Morel A, Gamelin E. Individual fluorouracil dose adjustment in FOLFOX based on pharmacokinetic follow-up compared with conventional body-area-surface dosing: A phase II, proof-of-concept study. *Clinical Colorectal Cancer*. 2012;**11**(4):263-7.
9. Cattel L, La Grotta G, Infante L, Passera R, Arpicco S, Brusa P, *et al.* Pharmacokinetic study of oxaliplatin iv chronomodulated infusion combined with 5-fluorouracil iv continuous infusion in the treatment of advanced colorectal cancer. *Farmaco*. 2003;**58**(12):1333-8.
10. Duffour J, Roca L, Bressolle F, Abderrahim AG, Poujol S, Pinguet F, *et al.* Clinical impact of intesified 5-Fluorouracil-based chemotherapy using a prospective pharmacokinetically-guided dosing approach: comparative study in elderly and non-elderly patients with metastatic colorectal cancer. *Journal of chemotherapy (Florence, Italy)*. 2010;**22**(3):179-85.
11. Findlay MPN, Raynaud F, Cunningham D, Iveson A, Collins DJ, Leach MO. Measurement of plasma 5-fluorouracil by high-performance liquid chromatography with comparison of results to tissue drug levels observed using in vivo 19F magnetic resonance spectroscopy in patients on a protracted venous infusion with or without interferon-alpha. *Annals of Oncology*. 1996;**7**(1):47-53.
12. Gamelin E, Boisdron-Celle M, Delva R, Regimbeau C, Cailleux PE, Alleaume C, *et al.* Long-term weekly treatment of colorectal metastatic cancer with fluorouracil and leucovorin: Results of a multicentric prospective trial of fluorouracil dosage optimization by pharmacokinetic monitoring in 152 patients. *Journal of Clinical Oncology*. 1998;**16**(4):1470-8.
13. Gamelin E, Delva R, Jacob J, Merrouche Y, Raoul JL, Pezet D, *et al.* Individual fluorouracil dose adjustment based on pharmacokinetic follow-up compared with conventional dosage: results of a multicenter randomized trial of patients with metastatic

colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2008;**26**(13):2099-105.

14. Gamelin EC, Danquechin-Dorval EM, Dumesnil YF, Maillart PJ, Goudier MJ, Burtin PC, *et al.* Relationship between 5-fluorouracil (5-FU) dose intensity and therapeutic response in patients with advanced colorectal cancer receiving infusional therapy containing 5-FU. *Cancer*. 1996;**77**(3):441-51.
15. Ho YF, Lu WC, Chen RRL, Cheng AL, Yeh KH. Phase I, pharmacokinetic, and bone marrow drug-level studies of trimonthly 48-h infusion of high-dose 5-fluorouracil and leucovorin in patients with metastatic colorectal cancers. *Anti-Cancer Drugs*. 2011;**22**(3):290-8.
16. Jodrell DI, Stewart M, Aird R, Knowles G, Bowman A, Wall L, *et al.* 5-Fluorouracil steady state pharmacokinetics and outcome in patients receiving protracted venous infusion for advanced colorectal cancer. *British Journal of Cancer*. 2001;**84**(5):600-3.
17. Kline CL, Sheikh HS, Scicchitano A, Gingrich R, Beachler C, Finnberg NK, *et al.* Preliminary observations indicate variable patterns of plasma 5-fluorouracil (5-FU) levels during dose optimization of infusional 5-FU in colorectal cancer patients. *Cancer Biology and Therapy*. 2011;**12**(7):557-68.
18. Kline et al. Personalized dosing via pharmacokinetic monitoring of 5-Fluorouracil (5-FU) may reduce toxicity in early or late stage colorectal cancer patients treated with infusional 5-FU-based chemotherapy regimens. Clinical Colorectal Cancer. 2013 online ahead of print
19. Metzger G, Massari C, Etienne MC, Comisso M, Brienza S, Touitou Y, *et al.* Spontaneous or imposed circadian changes in plasma concentrations of 5-fluorouracil coadministered with folinic acid and oxaliplatin: relationship with mucosal toxicity in patients with cancer. *Clin Pharmacol Ther*. 1994;**56**(2):190-201.
20. Milano G, Roman P, Khater R, Frenay M, Renee N, Namer M. Dose versus pharmacokinetics for predicting tolerance to 5-day continuous infusion of 5-FU. *International Journal of Cancer*. 1988;**41**(4):537-41.
21. Patel JN, Deal AM, O'Neil BH, Ibrahim J, Sherrill GB, Davies JM, *et al.* Application of pharmacokinetic (PK)-guided 5-fluorouracil (FU) in clinical practice. *Journal of Clinical Oncology*. 2013;**1)**.
22. Patel JN, O'Neil BH, McLeod HL, Sherrill GB, Olijade O, Inzerillo JJ, *et al.* Investigating the utilization of pharmacokinetic-guided fluorouracil in colorectal cancer. *Journal of Clinical Oncology*. 2012;**1)**.
23. Stremetzne S, Streit M, Kreuser ED, Schunack W, Jaehde U. Pharmacokinetic and 291revue291odynamics comparison of two doses of calcium folinate combined with continuous fluorouracil infusion in patients with advanced colorectal cancer. *Pharmacy World and Science*. 1999;**21**(4):184-9.
24. Ychou M, Duffour J, Kramar A, Debrigode C, Gourgou S, Bressolle F, *et al.* Individual 5-FU dose adaptation in metastatic colorectal cancer: Results of a phase II study using a bimonthly pharmacokinetically intensified LV5FU2 regimen. *Cancer Chemotherapy and Pharmacology*. 2003;**52**(4):282-90.
25. Ychou M, Duffour J, Pinguet F, Kramar A, Joulia JM, Topart D, *et al.* Individual 5FU-dose adaptation schedule using bimonthly pharmacokinetically modulated LV5FU2 regimen: A feasibility study in patients with advanced colorectal cancer. *Anticancer Research*. 1999;**19**(3 B):2229-35.
26. Yoshida T, Araki E, Iigo M, Fujii T, Shimada Y, Saito D, *et al.* Clinical significance of monitoring serum levels of 5-fluorouracil by continuous infusion in patients with advanced colonic cancer. *Cancer Chemotherapy and Pharmacology*. 1990;**26**(5):352-4.
27. Etienne MC, Lagrange JL, Dassonville O, Fleming R, Thyss A, Renee N, *et al.* Population study of dihydropyrimidine dehydrogenase in cancer patients. *Journal of Clinical Oncology*. 1994;**12**(11):2248-53.
28. Fety R, Rolland F, Barberi-Heyob M, Hardouin A, Campion L, Conroy T, *et al.* Clinical

impact of pharmacokinetically-guided dose adaptation of 5- fluorouracil: Results from a multicentric randomized trial in patients with locally advanced head and neck carcinomas. *Clinical Cancer Research*. 1998;**4**(9):2039-45.

29. Fety R, Rolland F, Barberiheyob M, Merlin JL, Conroy T, Hardouin A, *et al.* Clinical randomized study of 5FU monitoring versus standard-dose in patients with head and neck-cancer - preliminary-results. *Anticancer Research*. 1994;**14**(6A):2347-52.
30. Milano G, Etienne MC, Renee N, Thyss A, Schneider M, Ramaioli A, *et al.* Relationship between fluorouracil systemic exposure and tumor response and patient survival. *Journal of Clinical Oncology*. 1994;**12**(6):1291-5.
31. Santini J, Milano G, Thyss A, Renee N, Viens P, Ayela P, *et al.* 5-FU therapeutic monitoring with dose adjustment leads to an improved therapeutic index in head and neck cancer. *British Journal of Cancer*. 1989;**59**(2):287-90.
32. Thyss A, Milano G, Renee N. Clinical pharmacokinetic study of 5-FU in continuous 5-day infusions for head and neck cancer. *Cancer Chemotherapy and Pharmacology*. 1986;**16**(1):64-6.
33. Kim R, Nishimoto N, Inoue H, Yoshida K, Toge T. An analysis of the therapeutic efficacy of protracted infusion of low-dose 5-fluorouracil and cisplatin in advanced gastric cancer. *J Infect Chemother*. 2000;**6**(4):222-8.
34. Ciccolini J, Mercier C, Evrard A, Dahan L, Boyer JC, Duffaud F, *et al.* A rapid and inexpensive method for anticipating severe toxicity to fluorouracil and fluorouracil-based chemotherapy. *Therapeutic Drug Monitoring*. 2006;**28**(5):678-85.
35. Hendrayana T, Kurth V, Krolop L, Kenny P, Hilger RA, Schmidt-Wolf IGH, *et al.* Variability in fluorouracil exposure during continuous intravenous infusion. *International Journal of Clinical Pharmacology and Therapeutics*. 2012;**50**(1):82-4.

Appendix 8. Excluded studies with reasons

a) Excluded studies for Objectives A, B and C

Citation	Reason for exclusion
1. Ackland SP, Garg MB, Dunstan RH. Simultaneous determination of dihydrofluorouracil and 5-fluorouracil in plasma by high-performance liquid chromatography. *Analytical Biochemistry*. 1997;**246**(1):79-85.	Wrong population
2. Adjei AA, Reid JM, Diasio RB, Sloan JA, Smith DA, Rubin J, *et al.* Comparative pharmacokinetic study of continuous venous infusion fluorouracil and oral fluorouracil with eniluracil in patients with advanced solid tumors. *Journal of Clinical Oncology*. 2002;**20**(6):1683-91.	Population <80% included cancers
3. Akiyama S, Nakayama H, Takami H, Gotoh H, Gotoh Y. Pharmacodynamic study of the Saltz regimen for metastatic colorectal cancer in a hemodialyzed patient. *Chemotherapy*. 2007;**53**(6):418-21.	Treatment: bolus
4. Allegra CJ. Dihydropyrimidine dehydrogenase activity: Prognostic partner of 5- fluorouracil? *Clinical Cancer Research*. 1999;**5**(8):1947-9.	Editorial
5. Anderson LW, Parker RJ, Collins JM, Ahlgren JD, Wilkinson D, Strong JM. Gas chromatographic-mass spectrometric method for routine monitoring of 5-fluorouracil in plasma of patients receiving low-level protracted infusions. *Journal of Chromatography – Biomedical Applications*. 1992;**581**(2):195-201.	Technology: GC-MS
6. Au JLS, Rustum YM, Ledesma EJ. Clinical pharmacological studies of concurrent infusion of 5-fluorouracil and thymidine in treatment of colorectal carcinomas. *Cancer Research*. 1982;**42**(7):2930-7.	Wrong treatment
7. Aubert C, Sommadossi JP, Coassolo P, Cano JP, Rigault JP. Quantitative analysis of 5-fluorouracil and 5,6-dihydrofluorouracil in plasma by gas chromatography mass spectrometry. *Biomed Mass Spectrom*. 1982;**9**(8):336-9.	No patients, samples only
8. Azzopardi N, Lecomte T, Ternant D, Boisdron-Celle M, Piller F, Morel A, *et al.* Cetuximab pharmacokinetics influences progression-free survival of metastatic colorectal cancer patients. *Clinical Cancer Research*. 2011;**17**(19):6329-37.	Not 5-FU
9. Bailey H, Wilding G, Tutsch KD, Arzoomanian RZ, Alberti D, Tombes MB, *et al.* A phase I trial of 5-fluorouracil, leucovorin, and dipyridamole given by concurrent 120-h continuous infusions. *Cancer Chemotherapy and Pharmacology*. 1992;**30**(4):297-302.	Population <80% included cancers
10. Baker SD, Verweij J, Rowinsky EK, Donehower RC, Schellens JHM, Grochow LB, *et al.* Role of body surface area in dosing of investigational anticancer agents in adults, 1991-2001. *Journal of the National Cancer Institute*. 2002;**94**(24):1883-8.	Patient group unclear
11. Bamias A, Syrigos K, Fountzilas G, Tzamakou E, Soulti K, Karavasilis V, *et al.* Intensified bimonthly cisplatin with bolus 5-fluorouracil, continuous 5-fluorouracil and high-dose leucovorin (LV5FU2) in patients with advanced gastrointestinal carcinomas: A phase I dose-finding and pharmacokinetic study. *American Journal of Clinical Oncology: Cancer Clinical Trials*. 2004;**27**(5):465-71.	Population <80% included cancers
12. Barberi-Heyob M, Merlin JL, Weber B. Analysis of 5-fluorouracil in plasma and urine by high-performance liquid chromatography. *Journal*	Wrong population

of Chromatography – Biomedical Applications. 1992;**581**(2):281-6.	
13. Ben Fredj, R., et al. (2009). "The dihydrouracil/uracil ratio in plasma, clinical and genetic analysis for screening of dihydropyrimidine dehydrogenase deficiency in colorectal cancer patients treated with 5-Fluorouracil." Pathologie Biologie 57(6): 470-476.	AUC or 5-FU plasma concentration not related to outcomes
14. Beneton M, Chapet S, Blasco H, Giraudeau B, Boisdron-Celle M, Deporte-Fety R, *et al.* Relationship between 5-fluorouracil exposure and outcome in patients receiving continuous venous infusion with or without concomitant radiotherapy. *British Journal of Clinical Pharmacology*. 2007;**64**(5):613-21.	Population <80% included cancers
15. Bergh J. Is pharmacokinetically guided chemotherapy dosage a better way forward? *Annals of Oncology*. 2002;**13**(3):343-4.	Editorial
16. Bertino J, Gamelin E, Milano G. Highlights from: 5-Fluorouracil drug management pharmacokinetics and pharmacogenomics workshop: Orlando, Florida; January 2007 – 5-Fluorouracil drug management: Pharmacokinetics and pharmacogenomics workshop meeting summary. *Clinical Colorectal Cancer*. 2007;**6**(6):407-22.	Meeting highlights
17. Beumer JH, Parise RA, Newman EM, Doroshow JH, Synold TW, Lenz HJ, *et al.* Concentrations of the DNA methyltransferase inhibitor 5-fluoro-2'- deoxycytidine (FdCyd) and its cytotoxic metabolites in plasma of patients treated with FdCyd and tetrahydrouridine (THU). *Cancer Chemotherapy and Pharmacology*. 2008;**62**(2):363-8.	Not 5-FU
18. Biffi M, Petrelli F, Borgonovo K, Cabiddu M, Ghilardi M, Coinu A, *et al.* 5-FU Monitoring in clinical practice: Pharmacokinetic variability. *European Journal of Cancer*. 2013;**49**:S173-S4.	Abstract only – no dose adjustment - excluded
19. Blaschke M, Cameron S, Blumberg J, Wegner U, Ramadori G. Measurements of 5-FU levels in plasma of patients with gastrointestinal cancer. *Journal of Clinical Oncology*. 2012;**1)**.	Population <80% included cancers
20. Blaschke M, Cameron S, Emami K, Blumberg J, Wegner U, Nischwitz M, *et al.* Measurement of 5-FU plasma levels in patients with advanced cancer: Correct approach to practical procedures is essential. *International Journal of Clinical Pharmacology and Therapeutics*. 2011;**49**(1):83-5.	AUC not related to outcomes
21. Blaschke M, Cameron S, Goeschen C, Ramadori G. 5-FU schedules, serum 5-FU levels and their relationship to therapy response and toxicity in patients with gastrointestinal cancer. *Int J Clin Pharmacol Ther*. 2013;**51**(1):56-8.	Population: Lack of information on patient population, patient population unclear
22. Bocci G, Barbara C, Vannozzi F, Di Paolo A, Melosi A, Barsanti G, *et al.* A pharmacokinetic-based test to prevent severe 5-fluorouracil toxicity. *Clinical Pharmacology and Therapeutics*. 2006;**80**(4):384-95.	Treatment: bolus
23. Bocci G, Di Paolo A, Barbara C, Masi G, Fornaro L, Loupakis F, *et al.* Pharmacokinetics, a main actor in a many-sided approach to severe 5-FU toxicity prediction. *British Journal of Clinical Pharmacology*. 2009;**67**(1):132-4.	Letter
24. Bocci, G., et al. (2002). "Severe 5-Fluorouracil toxicity associated with a marked alteration of pharmacokinetics of 5-Fluorouracil and its catabolite 5-fluoro-5,6-dihydrouracil: a case report." European Journal of Clinical Pharmacology 58(9): 593-595.	Treatment: bolus
25. Boisdron-Celle M, Boulanger N, Gamelin E. Pharmacokinetic monitoring. [French] Monitoring pharmacocinetique. *Bulletin du cancer*. 2000;**87**(1):86-92.	Narrative review

26. Boisdron-Celle M, Le Guellec C. Therapeutic drug monitoring of 5-fluorouracil after its administration in high-dose protocols. [French] Niveau de 295revue du suivi therapeutique pharmacologique du 5-fluorouracile au decours de son administration dans le traitement des cancers des voies aerodigestives superieures et du cancer colorectal. *Therapie*. 2010;**65**(3):171-6.	Non English
27. Boisdron-Celle M. Pharmacokinetic adaptation of 5-fluorouracil: Where are we and where are we going? *Pharmacogenomics*. 2012;**13**(13):1437-9.	Editorial
28. Boisdron-Celle, M., et al. (2007). "5-Fluorouracil-related severe toxicity: A comparison of different methods for the pretherapeutic detection of dihydropyrimidine dehydrogenase deficiency." Cancer Letters 249(2): 271-282.	5-FU plasma concentration not related to outcomes
29. Boisdron-Celle, M., et al. (2013). "Prevention of 5-FU-induced toxicities using pretherapeutic DPD deficiency screening: Medical and economic assessment of a multiparametric approach." Journal of Clinical Oncology 1).	AUC or 5-FU plasma concentration not related to outcomes
30. Boisdron-Celle, M., et al. (2013). "Severe fluoropyrimidines toxicities: Screen effectively for DPD deficiencies." Fundamental and Clinical Pharmacology 27: 39-40.	Abstract without dose adjustment following My5-FU measurement
31. Borner MM, Schoffski P, De Wit R, Caponigro F, Comella G, Sulkes A, *et al.* Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: A randomised crossover trial in advanced colorectal cancer. *European Journal of Cancer*. 2002;**38**(3):349-58.	Treatment: bolus
32. Bressolle F, Joulia JM, Pinguet F, Ychou M, Astre C, Duffour J, *et al.* Circadian rhythm of 5-fluorouracil population pharmacokinetics in patients with metastatic colorectal cancer. *Cancer Chemotherapy and Pharmacology*. 1999;**44**(4):295-302.	5-FU plasma concentration not related to outcomes
33. Buchel B, Rhyn P, Schurch S, Buhr C, Amstutz U, Largiader CR. LC-MS/MS method for simultaneous analysis of uracil, 5,6-dihydrouracil, 5-fluorouracil and 5-fluoro-5,6-dihydrouracil in human plasma for therapeutic drug monitoring and toxicity prediction in cancer patients. *Biomedical Chromatography*. 2013;**27**(1):7-16.	Accuracy of other method than My5-FU
34. Buckpitt AR, Longo NS, Londer H, Boyd MR. ASSAY OF 5-FLUOROURACIL (FU) AND 5-FLUORODEOXYURIDINE (FUDR) IN PLASMA AT LOW NANOGRAM LEVEL USING HIGH-PRESSURE LIQUID-CHROMATOGRAPHY (HPLC). *Proceedings of the American Association for Cancer Research*. 1978;**19**(MAR):231-.	No patients, samples only
35. Cai X, Xue P, Song WF, Hu J, Gu HL, Yang HY, *et al.* Role of pharmacokinetic monitoring of serum fluorouracil concentration in patients with local advanced and metastatic colorectal cancer and further improving efficacy of fluorouracil-based chemotherapy. [Chinese]. *Chinese Journal of Oncology*. 2012;**34**(1):39-43.	Non English
36. Cai X, Xue P, Song WF, Hu J, Gu HL, Yang HY, *et al.* The role of pharmacokinetic monitoring of fluorouracil in improvement of efficacy and reduction of adverse reactions for patients with advanced gastric cancer. [Chinese]. *Tumor*. 2011;**31**(10):930-6.	Non English
37. Chan R, Kerr DJ. Can we individualise chemotherapy for colorectal cancer? *Annals of Oncology*. 2004;**15**(7):996-9.	Editorial

38. Cho HK, Lee ES, Lee JW, Park JK, Kang JH, Lee KS, *et al.* Clinical pharmacokinetics of oxaliplatin and 5-fluorouracil administered in combination with leucovorin in Korean patients with advanced colorectal cancer. *Journal of Cancer Research and Clinical Oncology*. 2006;**132**(5):320-6.	5-FU plasma concentration not related to outcomes
39. Cho, H., et al. (2000). "Combined 5-FU and CDDP in a gastric cancer patient undergoing hemodialysis--pharmacokinetics of 5-FU and CDDP. [Japanese]." Gan to kagaku ryoho Cancer & chemotherapy. 27(13): 2135-2138.	Case study
40. Christophidis N, Mihaly G, Vajda F, Louis W. Comparison of liquid- and gas-liquid chromatographic assays of 5-fluorouracil in plasma. *Clinical Chemistry*. 1979;**25**(1):83-6.	Treatment: bolus
41. Ciccolini J, Mercier C, Blachon MF, Favre R, Durand A, Lacarelle B. A simple and rapid high-performance liquid chromatographic (HPLC) method for 5-fluorouracil (5-FU) assay in plasma and possible detection of patients with impaired dihydropyrimidine dehydrogenase (DPD) activity. *Journal of Clinical Pharmacy and Therapeutics*. 2004;**29**(4):307-15.	Patient group unclear
42. Climente-Marti M, Merino-Sanjuan M, Almenar-Cubells D, Jimenez-Torres NV. A Bayesian method for predicting 5-fluorouracil pharmacokinetic parameters following short-term infusion in patients with colorectal cancer. *Journal of Pharmaceutical Sciences*. 2003;**92**(6):1155-65.	5-FU plasma concentration not linked to outcomes
43. Czejka MJ, Jager W, Schuller J, Fogl U, Schernthaner G. Pharmacokinetic aspects of the combination of interferon-alpha-2b and folic acid with fluorouracil. [German] PHARMAKOKINETISCHE ASPEKTE DER KOMBINATION VON INTERFERON-alpha-2b UND FOLINSAURE MIT FLUOROURACIL. *Arzneimittel-Forschung/Drug Research*. 1991;**41**(8):860-3.	Treatment: bolus
44. Czejka MJ, Schuller J, Jager W, Fogl U, Weiss C. Influence of different doses of interferon-alpha-2b on the blood plasma levels of 5-fluorouracil. *European Journal of Drug Metabolism and Pharmacokinetics*. 1993;**18**(3):247-50.	Population: <80% included cancers
45. Daher, G. C., et al. (1990). "The role of dihydropyrimidine dehydrogenase (DPD) and thymidine phosphorylase (dThdPase) in the circadian variation of plasma drug levels of 5-Fluorouracil (FUra) and 5-fluorodeoxyuridine (FdUrd) following infusion of FUra or FdUrd." Annual Review of Chronopharmacology 7: 227-230.	Not 5-FU
46. Danhauser LL, Freimann Jr JH, Gilchrist TL, Gutterman JU, Hunter CY, Yeomans AC, *et al.* Phase I and plasma pharmacokinetic study of infusional fluorouracil combined with recombinant interferon alfa-2b in patients with advanced cancer. *Journal of Clinical Oncology*. 1993;**11**(4):751-61.	Wrong population
47. De Forni M, Gualano V, Canal P, Martel P, Izar-Soum F, Chevreau C, *et al.* Continuous infusion of 5-fluorouracil by double route (intravenous and intraperitoneal) with modulation by folinic acid: Clinical and pharmacokinetic, phase I study in patients with intra-abdominal malignancies. [French] 5-Fluorouracile En Perfusion Continue Double Voie (Intraveineuse Et Intraperitoneale) Module Par L'acide Folinique: Etude Clinique De Phase I Et Pharmacocinetique Chez Des Patients Porteurs De Cancers a Evolution Intra-Abdominale. *Bulletin du Cancer*. 1993;**80**(5):408-17.	Population <80% included cancers
48. de Mattos AC, Khalil NM, Mainardes RM. Development and validation	No patients

of an HPLC method for the determination of fluorouracil in polymeric nanoparticles. *Brazilian Journal of Pharmaceutical Sciences*. 2013;**49**(1):117-26.	
49. DeGregorio MW, Holleran WM, Benz CC, Cadman EC. Quantitative analysis of 5-fluorouracil in human serum by high-performance liquid chromatography. *Analytical Letters*. 1985;**18**(1 B):51-5.	No patients, samples only
50. Di Paolo A, Danesi R, Ciofi L, Vannozzi F, Bocci G, Lastella M, *et al.* Improved analysis of 5-fluorouracil and 5,6-dihydro-5-fluorouracil by HPLC with diode array detection for determination of cellular dihydropyrimidine dehydrogenase activity and pharmacokinetic profiling. *Therapeutic Drug Monitoring*. 2005;**27**(3):362-8.	Treatment: bolus
51. Di Paolo, A., et al. (2001). "Relationship between 5-Fluorouracil disposition, toxicity and dihydropyrimidine dehydrogenase activity in cancer patients." Annals of Oncology 12(9): 1301-1306.	Treatment: bolus
52. Di Paolo, A., et al. (2002). "Relationship between plasma concentrations of 5-Fluorouracil and 5-fluoro-5,6-dihydrouracil and toxicity of 5-Fluorouracil infusions in cancer patients." Therapeutic Drug Monitoring 24(5): 588-593.	Wrong treatment: bolus
53. Dong QM, Huand SH, Zheng WH, He YJ. Clinical significance of 5-FU concentration at steady state in colorectal cancer detected by HPLC method. [Chinese]. *Chinese Journal of Cancer Prevention and Treatment*. 2010;**17**(18):1476-8+81.	Non English
54. Dong, Q. M., et al. (2005). "Relationship of serum level of dihydropyrimidine dehydrogenase and serum concentration of 5-Fluorouracil to treatment response and adverse events in colorectal cancer patients. [Chinese]." Ai zheng = Aizheng = Chinese journal of cancer 24(4): 483-487.	Non English
55. Escoriaza J, Aldaz A, Calvo E, Giraldez J. Simple and sensitive determination of 5-fluorouracil in plasma by high-performance liquid chromatography: Application to clinical pharmacokinetic studies. *Journal of Chromatography B: Biomedical Sciences and Applications*. 1999;**736**(1-2):97-102.	No patients, samples only
56. Etienne MC, Chatelut E, Pivot X, Lavit M, Pujol A, Canal P, *et al.* Co-variables influencing 5-fluorouracil clearance during continuous venous infusion. A NONMEM analysis. *European Journal of Cancer*. 1998;**34**(1):92-7.	Population: <80% included cancers
57. Feng WY, Cai S, Shen JW. Determination of 5-fluorouracil in human plasma by high performance liquid chromatography. [Chinese]. *Chinese Pharmaceutical Journal*. 2003;**38**(4):289-90.	No patients, samples only
58. Fleming RA, Milano G, Thyss A, Etienne MC, Renee N, Schneider M, *et al.* Correlation between dihydropyrimidine dehydrogenase activity in peripheral mononuclear cells and systemic clearance of fluorouracil in cancer patients. *Cancer Research*. 1992;**52**(10):2899-902.	5-FU plasma concentrations not related to outcomes
59. Fleming RA, Milano GA, Etienne MC, Renee N, Thyss A, Schneider M, *et al.* No effect of dose, hepatic function, or nutritional status on 5-FU clearance following continuous (5-day), 5-FU infusion. *British Journal of Cancer*. 1992;**66**(4):668-72.	AUC not related to outcomes
60. Fleming RA, Milano GA, Gaspard MH, Bargnoux PJ, Thyss A, Plagne R, *et al.* Dihydropyrimidine dehydrogenase activity in cancer patients. *European Journal of Cancer Part A: General Topics*. 1993;**29**(5):740-4.	Excluded – case study of 2 patients
61. Fleming, G. F., et al. (2003). "Phase I and pharmacokinetic study of 24-hour infusion 5-Fluorouracil and leucovorin in patients with organ dysfuntion." Annals of Oncology 14(7): 1142-1147.	Population: <80% included cancers

62. Gamelin E, Boisdron-Celle M, Turcant A, Larra F, Allain P, Robert J. Rapid and sensitive high-performance liquid chromatographic analysis of halogenopyrimidines in plasma. *Journal of Chromatography B: Biomedical Applications*. 1997;**695**(2):409-16.	No patients, samples only
63. Gamelin E, Boisdron-Celle M. Dose monitoring of 5-fluorouracil in patients with colorectal or head and neck cancer-status of the art. *Critical Reviews in Oncology/Hematology*. 1999;**30**(1):71-9.	Narrative review
64. Gamelin E, Boisdron-Celle M. Individual dose adjustment in cancer chemotherapy. [French] L'adaptation individuelle de posologie en chimiotherapie anticancereuse. *Revue de Medecine Interne*. 1996;**17**(7):529-33.	Editorial
65. Gamelin E, Gamelin L, Larra F, Turcant A, Alain P, Maillart P, *et al.* Acute cardiac toxicity of 5-fluorouracil: pharmacokinetic correlation. [French] Toxicite cardiaque aigue du 5-fluorouracile: correlation pharmacocinetique. *Bulletin du cancer*. 1991;**78**(12):1147-53.	Non English
66. Gamelin E, Jacob J, Danquechin dorval EM, Pezet D, Delva R, Raoul JL, *et al.* Multicentric randomized trial comparing in weekly treatment of advanced colorectal cancer (crc) intensified 5 fluorouracil and folinic acid (fa) with 5 fu pharmacokinetic monitoring to a constant dose calculated with body surface area. 1998 [cited; Available from: http://0-onlinelibrary.wiley.com.pugwash.lib.warwick.ac.uk/o/cochrane/clcentral/articles/482/CN-00548482/frame.html.	Abstract only – not My5-FU
67. Gamelin E, Metges J, Adenis A, Raoul J, Lam Y, Lecomte T, *et al.* Dose intensity and tolerance improvement of cetuximab, irinotecan, 5-Fu and folinic acid in patients with metastatic CRC ; a pharmacokinetic and pharmacogenetic approach. *Annals of Oncology*. 2008;**19 (S8)**:viii131.	Abstract only – not My5-FU
68. Gamelin, E., et al. (1999). "Correlation between uracil and dihydrouracil plasma ratio, fluorouracil (5-FU) pharmacokinetic parameters, and tolerance in patients with advanced colorectal cancer: A potential interest for predicting 5-FU toxicity and determining optimal 5-FU dosage." Journal of Clinical Oncology 17(4): 1105-1110.	5-FU plasma concentration not related to outcomes
69. Garg MB, Lincz LF, Adler K, Scorgie FE, Ackland SP, Sakoff JA. Predicting 5-fluorouracil toxicity in colorectal cancer patients from peripheral blood cell telomere length: A multivariate analysis. *British Journal of Cancer*. 2012;**107**(9):1525-33.	Treatment: bolus
70. Gonzalez MS, Rebollo J, Escudero V, Valenzuela B, Nalda R, Duart M, *et al.* Pharmacokinetic (pk) guide for dose adjustments in cancer patients (pts) treated with 5-fluoruracil (5-fu) infusions. Preliminary results. *Journal of Clinical Oncology*. 2008;**26**(15).	Abstract only – patient group unknown, not My5-FU
71. Grem JL, Quinn M, Ismail AS, Takimoto CH, Lush R, Liewehr DJ, *et al.* Pharmacokinetics and 298revue298odynamics effects of 5-fluorouracil given as a one-hour intravenous infusion. *Cancer Chemotherapy and Pharmacology*. 2001;**47**(2):117-25.	Wrong treatment
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performance liquid chromatography. *Journal of Chromatography – Biomedical Applications*. 1985;**342**(2):303-13.	
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165. Zhou ZW, Wang GQ, Wan DS, Lu ZH, Chen YB, Li S, *et al.* The dihydrouracil/uracil ratios in plasma and toxicities of 5-fluorouracil-based adjuvant chemotherapy in colorectal cancer patients. *Chemotherapy*. 2007;**53**(2):127-31.	Treatment: bolus
166. Zhou ZW, Wang GQ, Wan DS, Pan ZZ, Li S, Chen G, *et al.* Relationship between dihydropyrimidine dehydrogenase(DPD) activity and toxicity of 5-FU-based adjuvant chemotherapy in colorectal cancer patients. [Chinese]. *Ai zheng = Aizheng = Chinese journal of cancer*. 2004;**23**(11 Suppl):1512-6.	Treatment: bolus
167. Zhu L, Shen GJ, Ding SQ, Hua X. Determination of 5-fluorouracil in 5-fluorouracil injection and human serum by HPLC. *Journal of Food and Drug Analysis*. 2012;**20**(4):947-50+86.	No patients, samples only
168. Zufia L, Egues A, Aldaz A. Validation of an LC/UV Method Based on Accuracy Profiles for Daily 5-Fluorouracil Dose Adjustment in Cancer Patients. *Therapeutic Drug Monitoring*. 2013;**35**(5):727-.	Accuracy of other method than My5-FU

b) Excluded studies for objective D

Citation	Reason for exclusion
1. Asseburg, C., M. Frank, C. H. Kohne, J. T. Hartmann, I. Griebsch, A. Mohr, U. Osowski, J. Schulten and T. Mittendorf (2011). "Cost-effectiveness of targeted therapy with cetuximab in patients with K-ras wild-type colorectal cancer presenting with initially unresectable metastases limited to the liver in a German setting." Clinical Therapeutics **33**(4): 482-497.	Population KRAS WT only
2. Cassidy, J., L. Saltz, C. Twelves, E. Van Cutsem, P. Hoff, Y. Kang, J. P. Saini, F. Gilberg and D. Cunningham (2011). "Efficacy of capecitabine versus 5-fluorouracil in colorectal and gastric cancers: a meta-analysis of individual data from 6171 patients." Annals of Oncology **22**(12): 2604-2609.	Mix of 5-FU therapies versus capecitabine
3. Ling, W., J. Fan, Y. Ma, Y. Ma and H. Wang (2011). "Capecitabine-based chemotherapy for metastatic colorectal cancer." Journal of Cancer Research & Clinical Oncology **137**(6): 927-938.	Mix of 5-FU therapies versus capecitabine
4. Zhang, C., H. Gu, D. Zhu, Y. Li, P. Zhu, Y. Wang and J. Wang (2012). "Capecitabine plus oxaliplatin compared with 5-fluorouracil plus	Mix of 5-FU therapies versus

oxaliplatin in metastatic colorectal cancer: meta-analysis of randomized controlled trials." Oncology Letters **3**(4): 831-838.	capecitabine

Appendix 9. Clinical trials identified from clinical trials.gov, current controlled trials, UKCRN portfolio databases and Saladax

Ongoing

Retrospective Evaluation of 5-FU Exposure Optimization in CRC Patients (5-FU RECORD). NCT02055560 http://clinicaltrials.gov/show/NCT02055560

A single arm study in metastatic colorectal cancer patients treated with pharmacokinetically (PK) dose adjusted weekly or biweekly 5-fluorouracil (5-FU) regimes. - C-5FU-TDM (CESAR C-II-009). EUCTR2011-003553-26-DE http://apps.who.int/trialsearch/Trial.aspx?TrialID=EUCTR2011-003553-26-DE

The Optimization of 5-Fluorouracil Dose by Pharmacokinetic Monitoring in Asian Patients With Advanced Stage Cancer. NCT00943137 http://clinicaltrials.gov/show/NCT00943137

Terminated

Study Comparing Optimized 5-FU Dosing and Standard Dosing in Metastatic Colorectal Cancer Patients Treated With mFOLFOX6 (PROFUSE). NCT01468623 http://clinicaltrials.gov/show/NCT01468623

Appendix 10. Narrative overview of single arm studies and included abstracts

a) Single arm studies for clinical effectiveness review by cancer type

Colorectal Cancer

Boisdron-Celle et al. (2002)[134] investigated in a case series the influence of Oxaliplatin on plasma 5-FU levels by adding it to weekly 5-FU + FA treatment in patients with 5-Fu refractory advanced colorectal cancer. The main finding was that while (1) Oxaliplatin reduces 5-FU plasma clearance and (2) higher plasma concentrations of 5-FU are related to toxicity, Oxaliplatin does not seem to potentiate 5-FU toxicity. 5-FU related toxicities were presented and positively linked to 5-FU plasma concentrations. However, the credibility of the conclusion and extent of toxicity reported is questionable due to considerable discrepancies found in the numbers presented in the paper.

Cattel et al. (2003)[136] studied the pharmacokinetic behaviour of Oxaliplatin in combination with 5-FU in stage IV CRC patients in a prospective case series. The regimen was unusual containing of 14 day continuous 5-FU without FA and chronomodulated Oxaliplatin at three different doses. Omission of FA did not affect the combination effect of Oxaliplatin and 5-FU and PK behaviour was unchanged of both drugs. The focus of this study was on Oxaliplatin rather than 5-FU therefore the two cases of neurotoxicity were related to Oxaliplatin which prompted the dose reduction of Oxaliplatin. The regimen is unusual and therefore the results are of limited interest.

Duffeur et al. (2010)[137] compared in a retrospective database analysis the clinical outcomes of pharmacokinetic dose adjustment in two different age groups (age < or ≥ 65 years) of metastatic CRC patients and concluded that age does not affect the pharmacokinetic behaviour of 5-FU and does not limit intensified chemotherapy. This study included data from two other included studies (Ychou 1999 and 2003)[132, 148] and did not specify how many patients had what dose increase. The first two cycles AUC values from the low toxic (grades 0-2) and severe toxic (≥grade 3) groups did not seem to suggest a significant association between AUC and severe toxicity. However, a significant association seems to be existent between cycle number (<6 / ≥6) and severe toxicity (p = 0.0005).

Findley et al. (1996)[138] measured plasma 5-FU levels and 5-FU levels in liver tissue. They investigated, using a case series, the metabolism of 5-FU with and without interferon-α in patients with colorectal cancer. They concluded that protracted venous infusion may result in greater inter-patient variation of plasma 5-FU levels and addition of interferon-α to 5-FU increases plasma 5-FU levels. Levels of 5-FU correlated with treatment toxicity but not with anti-tumour activity. However,

protracted venous infusion was not specified, i.e., it was unclear how long patients had received 5-FU for and when plasma measurements were taken. The study population was very small and poorly characterised because they were merged from two different studies, therefore it is likely to be retrospective. The grading tool used for toxicity and response was not reported. The link between plasma concentration and outcomes is unlikely to be useful since an arbitrary split of the data was used to compare the data on response / toxicity between two sets of participants with different plasma concentrations (> 5nM and <5nM).

Gamelin et al. (1996)[131] compared the relationship between 5-FU dose intensity and therapeutic response in patients with advanced CRC in a prospective case series and found a wide variation of 5-FU metabolism, whatever the dose, and a clear relationship between 5-FU levels and toxicity and efficacy. This is a thorough study, reporting the relationship between 5-FU plasma levels and outcomes extensively in order to produce a dose adjustment algorithm that is based on previous 5-FU dose and 5-FU plasma levels. The dose adaptation algorithm is based on a regression analysis of the relationship between dose and plasma levels in two groups of patients achieving CR or PR versus MR, SD or PD.

Ho et al. (2011)[140] carried out a prospective case series to determine the maximum tolerated dose and dose-limiting toxicity of 5-FU and folinic acid with modified trimonthly 48-h continuous infusion of high-dose 5-FU/FA (HDFL48) in patients with metastatic colorectal cancer. They recommended a 5-FU dose for future trials of 3,500mg/m^2/48h/week with a fixed dose of FA of 300mg/m^2/48h/week. This study used an unusual HDFL48 regimen. In contradiction to other studies, toxicities did not seem to correlate with high plasma concentrations.

Jodrell et al. (2001)[141] assessed the variability in 5-FU concentrations at steady state during protracted venous infusion (PVI) of 5-FU in CRC patients and attempted to correlate response and toxicity with the 5-FU steady state concentrations in a prospective case series. Due to the lack of a relationship between mean 5-FU plasma concentration and outcomes the study discouraged the use of 5-FU measurements to individualise dosing in patients with PVI 5-FU for advanced colorectal cancer. The lack of a correlation between plasma concentrations and outcomes is inconsistent with other studies; however, the dose regimen is unusual. Outcomes were reported with varying rigour.

Kline et al. (2011)[142] carried out a case series to identify novel and heterogeneous patterns in 5 FU levels, at baseline and during dose adjustment of 5 FU infusions in CRC patients. Based on the findings they call for further studies to investigate physiological and or genetic differences underlying heterogeneity in 5-FU levels during dose optimisation. This paper and the comparative study by

Kline[221] are the only two full papers that used My5-FU for dose adjustment. The paper describes AUCs and adjustments well but does not report overall results needed for data extraction such as mean 5-FU dose and frequency of dose adjustment. Furthermore, the paper fails to specify the adjustment rules for toxicity and AUC values. The results are not linked with any patient outcomes which is why the results are of limited value.

Metzger et al. (1994)[143] analysed in a randomised trial of nine patients the circadian change kinetics of anticancer drugs infused at a constant rate versus circadian rate and concluded that patients with circadian rhythms in 5-FU concentrations were sensitive to 5-FU related toxicity. Chronomodulated 5-FU exposure may permit dose escalation. However, the patient numbers were too small to allow generalisation of conclusions. Adverse events were reported inconsistently and only stomatitis results were linked to AUC values in all nine patients.

Milano et al. (1988)[144] carried out a prospective case series to compare drug dose and individual pharmacokinetics data for their respective ability to predict cycle tolerance for the 5-day continuous infusion schedule in advanced CRC. They reported an AUC threshold of 30,000 ng/ml*h that can be used to predict toxicity using the 5-day continuous infusion schedule of 5-FU.

Stremetzne et al. (1999)[147] compared the pharmacokinetics / pharmacodynamics of two doses of calcium folinate in a randomised trial with random allocation to two different calcium folate concentrations and did not find a significant effect of folinate dose or the day of treatment on pharmacokinetics of 5-FU in advanced CRC patients. The study aimed to evaluate two different doses of folinate, therefore the results are of limited usefulness. High incidence of mucositis might be related to high dose folinate and less dependent on 5-FU levels.

Ychou et al. (1999)[132] applied the concept of 5-FU dose adaptation, using PK parameters, in a prospective case series to the bimonthly LV5FU2 schedule in advanced CRC and established a dose adaptation strategy with a control for toxicity. The adjustment algorithm was solely based on AUC value from first cycle (and toxicity < grade 3). The relationship between plasma 5-FU and response is minimal and not significant. Toxicities were grouped in three categories; digestive, hematologic and cutaneous and only reported for grade III+IV.

Ychou et al. (2003)[148] determined the efficacy and tolerability of the pharmacokinetically adjusted LV5FU2 regimen in the treatment of metastatic colorectal cancers in a prospective case series and concluded that the promising results should be confirmed in a subsequent phase III trial. Patients who did not attain an AUC of at least 15 mg*h/l*m^2 in cycle 2 had an unfavourable PFS as compared to

the other patients. This was a reasonable thorough trial that reports adverse events extensively. However, KM survival functions were not included with the survival data and the relationship between AUC values and outcomes were not reported extensively.

Yoshida et al. (1990)[149] aimed to clarify in a prospective case series whether the dose of 5-FU is related to tumour response and /or toxicity in advanced colonic cancer patients. They cautioned that increased serum concentrations do not always provide therapeutic benefits to patients receiving continuous infusion of 5-FU. However, the author's conclusion is based on a small study sample of 19 patients. They found a significant correlation between plasma concentration / AUC and toxicity but not response. The results presented for adverse events and response were not useful as toxicity was not reported by type of toxicity and non-responders were not divided into stable disease and progressive disease.

Mixed patient group

Ciccolini et al. (2006)[150] aimed to validate a simple and rapid method to determine the DPD status of cancer patients presenting with severe toxicities following 5-FU treatment in a prospective case series. They concluded that systematic detection of DPD-deficient patients prior to 5-FU administration is warranted. The results seem to suggest that DPD activity and plasma 5-FU concentration will not reliably identify all toxic cases, however, plasma concentration was only measured in 6 patients with severe toxicity (grades 3 and 4 only), and therefore, the conclusions are weak.

Hendrayana et al. (2012)[151] explored prospectively in a case series of cancer patients the feasibility of measuring plasma concentrations of 5-FU using My5-FU in routine clinical practice and concluded that 1) BSA dosing results in a large variability in 5-FU exposure and fails to achieve the target exposure in more than 90% of patients and 2) dose adjustment might reduce incidence of diarrhoea and mucositis. This useful study was presented as an extended abstract only and lacks detail on patient characteristics and shows inconsistency in detail of reporting of adverse events.

Head and neck cancer

Etienne et al. (1994)[152] evaluated in a prospective cohort study the incidence of complete and partial DPD deficiency in patients with H&N cancer and concluded that DPD deficiency is rare and that knowledge of DPD status before chemotherapy might not improve the 5-FU dose adaptation strategy but might suggestive of reducing the starting dose in these patients to avoid severe toxicities. The study is of limited interest to the study objective because of the focus on DPD deficiency. Dose adjustment rules and algorithms were not reported either for plasma concentrations or for toxicity.

Toxicities were only reported as mucositis or hematologic toxicities. Toxicity values for toxic and non-toxic values were suggestive of a positive association between AUC and toxicity.
Milano et al. (1994)[153] analysed the link between systemic exposure of 5-FU and tumour response and overall survival in patients with H&N cancer in a prospective case series. They established a positive relationship between plasma exposure and outcomes in terms of response and overall survival and are supportive of individual 5-FU dose adaptation based on pharmacokinetics. This is a useful study reporting overall survival with a Kaplan Meyer function. An AUC threshold of 29,000ng/ml*h was reported for response. However, responses were grouped differently than in other studies and details on adverse events were insufficient (i.e. reported as haematological and digestive).

Thyss et al. (1986)[154] compared patient response and toxicity with individual total 5-FU exposure during treatment with 5-FU plus cisplatin in patients with H&N cancer. This prospective case series demonstrated a close relationship between elevated 5-FU AUC values and the frequency of cycles in which signs of toxicity were observed. The study presented an AUC threshold of 30,000ng/ml*h to be predictive for toxicity. The reporting of adverse events was not useful for the review because they were not reported by type of toxicity. AUC values for cycles were only presented in graphical form and there was no mean AUC per cycle reported.

Gastric cancer

Kim et al. (2000)[155] analysed in a case series the clinical efficacy of a protracted infusion of low-dose 5-FU in combination with cisplatin in the treatment of gastric cancer patients. They considered this to be a useful regimen for patients with advanced gastric cancer pointing out the high response rate and low toxicity and positive results in terms of overall survival. The lack of a relationship between plasma concentration and response was based on seven patients, however details of how the seven patients were selected was not reported. This study considered quality of life in terms of improvement in performance status and improved oral intake both showing a positive trend following treatment.

b) **Included abstracts for the clinical effectiveness review investigating dose adjustment following My5-FU measurement**

Patel et al. (2012)[145]

The aim of this study was to investigate the application and feasibility of pharmacokinetic-guided fluorouracil with 58 patients with CRC from six academic and community sites and provide an assessment of toxicity. The study design was unclear. Patients received mFOLFOX6 (5-FU 2400 mg/m^2 over 46 hours every 2 weeks) with or without bevacizumab. An algorithm to target an AUC of 20-25 mg*h/L was used to adjust 5-FU doses for cycles 2-4. My5-FU was used to determine the

AUCs and peripheral blood was obtained 2-46 hours after the beginning of infusion. This study found the mean AUC post cycle 1 in 39 patients was 19.8 +/- 6.3 mg*h/L with 18% over the AUC target, 31% within, and 51% under. According to cycle 1 findings, the mean dose to achieve AUC 20-25 mg*h/L was estimated to be 2,505 +/- 304 mg/m^2. Nineteen patients were not included due to logistical problems and three hospitalisations following serious adverse events occurred (2 at AUCs > 30). Table 78 shows the most common adverse events was fatigue and diarrhoea for all patients with Neutropenia being the most common adverse event for grade 3/4. In conclusion there was significant heterogeneity noted in 5-FU AUC with BSA-based dosing, with the majority of patients below the 20-25 mg*h/L AUC threshold.

Table 78. Summary of the toxicities for all grades and grades 3/4 (n = 55 patients)

Adverse events	**All grade**	**Grade 3/4**
Diarrhoea	21 (38%)	4 (7%)
Fatigue	24 (44%)	2 (4%)
Mucositis/stomatitis	11 (20%)	2 (4%)
Neutropenia	19 (35%)	15 (27%)

Patel et al. (2013)[146]

In this second study by Patel and colleagues, the aim was to investigate the application of pharmacokinetic-guided 5-fluorouracil in clinical practice.[146] The study design was unclear. Seventy CRC patients from six academic and community sites received mFOLFOX6 (5-FU 2400 mg/m^2 over 46 hours every 2 weeks) with or without bevacizumab. An algorithm to target an AUC of 20-25 mg*h/L was used to adjust 5-FU doses for cycles 2-4. My5-FU was used to determine the AUCs and peripheral blood was obtained 2-44 hours after the beginning of infusion. The primary outcome was the percentage of patients within target AUC by cycle 4 and the secondary outcome was toxicity rates compared to historical data. The percentage of patients within target AUC post cycle 1 and cycle 4 was 30% (95%CI: 18-43%) and 46% (95%CI: 32-61%), respectively (OR=2.16, p = 0.05). For each subsequent cycle, the likelihood of a patients being within target range increased by 28% (p = 0.04). See Table 79 for details of patients below, within, and above the target AUC at cycles 1 to 4. The median dose needed to achieve target AUC at C4 was 2,580 mg/m^2. There were fewer grade 3/4 mucositis and diarrhoea seen compared to historical data (3 v 15% and 6 v 12%, respectively), but no difference in grade 3/4 neutropenia (27 v 33%) compared to historical data. Nine patients were not included due to sampling/processing errors. Overall PK-guided 5-FU resulted in more patients achieving the targeted AUC and fewer patients under-dosed at C4 compared to C1.

Table 79. Patients below (< 20 AUC mg*hr/L), within (20-25 AUC mg*hr/L), and above (>25 AUC mg*hr/L) the target AUC at cycles 1 to 4

AUC mg*hr/L	C1 (n = 57)	C2 (n = 57)	C3 (n = 53)	C4 (n = 52)
<20	30 (53%)	24 (42%)	25 (47%)	17 (33%)
20-25	17 (30%)	21 (37%)	21 (40%)	24 (46%)
>25	10 (17%)	12 (21%)	7 (13%)	11 (21%)

Summary

In summary these two studies by Patel and colleagues demonstrate that individualisation of FU dosing in the front-line, in both community and academic settings appears to be achievable for the treatment of CRC. Due to a paucity of data on PK-guided FU dosing in the clinical setting, a large prospective clinical trial is needed to define the clinical utility of PK-guided FU and more specifically to confirm the promising findings reported to date about dose adjustment following My5-FU measurement with CRC patients.

Appendix 11. Formal quality assessment using an adapted Downs & Black assessment tool[123]

The table below is a summary of the quality assessment for the three CRC comparative studies,[118, 119, 156] the two CRC single arm studies,[135, 139] and two H&N cancer comparative studies.[133, 157, 159] All the studies described the main outcomes to be measured clearly in the introduction or methods and used appropriate statistical tests to assess the main outcomes. In contrast, none of the studies provided sufficient information on the staff, places, and facilities where the patients were treated to allow assessment of whether the patients and their treatments were representative of underlying populations. Furthermore, none of the studies made an attempt to blind those measuring the main outcomes of the intervention. Overall the quality of these studies varied.

Summary table of the formal quality assessment using an adapted Downs & Black assessment:

First author year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Q17	Q18	Q19	Q20	Q21	Q22	Q23	Q24	Q25	Q26	Q27
CRC comparative studies																											
Capitain 2012[119]	Y	Y	N	Y	P	Y	Y	Y	Y	N	UD	UD	UD	NA	N	Y	Y	Y	Y	Y	N	UD	N	N	N	Y	UD
Gamelin 2008[118]	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	UD	UD	UD	N	N	Y	Y	Y	Y	Y	Y	Y	Y	UD	Y	Y	Y
Kline 2013[156]	Y	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	UD	NA	N	Y	Y	Y	Y	Y	Y	Y	N	N	UD	UD	UD
CRC single arm studies																											
Capitain 2008[135]	Y	Y	Y	N	Y	N	Y	Y	Y	Y	UD	UD	UD	NA	N	Y	Y	Y	Y	Y	UD	NA	NA	NA	N	Y	UD
Gamelin 1998[139]	Y	Y	Y	Y	P	Y	Y**	Y	N	Y	UD	UD	UD	NA	N	Y	UD	Y	UD	Y	UD	NA	NA	NA	N	N	UD
H&N cancer comparative studies																											
Fety 1998, 1994[157, 159]	Y	Y	Y	Y	P	Y	Y	Y	Y	Y	UD	UD	UD	N	N	Y	N	Y	Y	N	Y	Y	Y	UD	N	Y	Y
Santini 1989[133]	N	Y	N	Y	N	N	Y	N	Y	N	UD	UD	UD	NA	N	N	UD	Y	Y	N	Y	Y	N	N	Y	Y	UD
Overall ratings																											
y	6	7	5	6	3	4	5	6	5	5	1	1	0	0	0	6	4	7	6	5	4	4	2	0	2	5	2
n	1	0	2	1	1	3	2	1	2	2	0	0	0	2	7	1	1	0	0	2	2	0	3	3	4	1	0
UD	0	0	0	0	0	0	0	0	0	0	6	6	7	0	0	0	2	0	1	0	1	1	0	2	1	1	5
NA	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	0	0	0	0	0	2	2	2	0	0	0
p	0	0	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

****** range rather than IQR and variability in normally distributed data not specified, it was unclear whether "±" was SE or SD

Key: Y=Yes, N=No, P=Partially, CT=Can't tell, UD= Unable to determine, *=number of "partially" responses, NA=not applicable; CRC=colorectal cancer; H&N=head and neck

Appendix 12. Summary of two comparative Head and Neck cancer studies

Fety (1998)(Fety, #510}

Study design

This multicentre RCT assigned 61 patients to a PK adjusted 5-FU regimen and 61 patients to a standard based dose regimen. Patients were assigned to receive induction chemotherapy with cisplatin (100 mg/m^2 on day 1) and 5-FU (96-h continuous infusion), either at standard dose (BSA arm; 4 g/m^2) or at a dose adjusted according to the 5-FU AUC ($AUC_{0\text{-}48h}$; PK arm). Due to 5-FU-related toxicity, three patients (5.2%) in the BSA arm and three patients in the PK arm (6.1%) left the study before completing chemotherapy. The length of follow up was unclear. The primary end point was the incidence of haematological toxicity and the secondary end point was the equivalence of disease response.

Study quality

Randomisation was stratified by centre (three centres were involved). Methods of allocation concealment were not reported. Blinding to treatment was not possible; assessment of response rates was assessed by a panel of two independent radiologists and may have been blinded, but this was not specified. There was some mismatch between the description of methods undertaken and the reported results. There were weaknesses in the clarity and presentation of data. Quality of life, OS and PS were not reported. Adverse event were reported per cycle (counts). It has been previously noted by other authors[85] that the dose adjustment method in this study may have been too complicated, as the 12 protocol violations in the treatment arm (12/61 patients enrolled) were all related to 5-FU dose adjustment miscalculations. Furthermore, since the patients with protocol violations were removed from the analysis and the induction therapy regimen used only two drugs the generalizability to dose adjustment methods in current clinical practice remains questionable. For formal quality assessment, see Appendix 11.

Population

The reported demographic characteristics are summarised in Table **80**. Patients had advanced H&N cancer and most had not received previous chemotherapy. Among the 122 patients randomly assigned to one of the two treatment arms, 16 patients (13%) were found to be "unevaluable" for response and toxicity (4 patients in the BSA arm, and 12 patients in the PK arm).

Table 80. Demographic characteristics before treatment

Item	**Treatment arm**	
	BSA	**PK**

Patient Number		
Total number	61/122 (50%)	61/122 (50%)
Sample attrition/patients not evaluable	4/61 (6.6%)	12/61 (19.7%)
Age (years)		
Mean (SD)	NR	NR
Median	54	55
Range	29-72	36-69
Sex		
Men (%)	52/57 (91.2%)	48/49 (98%)
Women (%)	5/57 (8.8%)	1/49 (2%)
Performance status (%)		
01	16/57 (28.1%)	11/49 (22.4%)
2	34/57 (59.6%)	35/49 (71.4%)
3	7/57 (12.3%)	3/49 (6.1%)
4	0	0
	0	0
Previous therapy (%)	NR	NR
Metastatic sites (%)		
Liver	NA	NA
Lung	NA	NA
Lymph nodes	NA	NA
Others	NA	NA

Summary

The paper by Fety (1998)[157, 159]provides useful information in a randomised design on 5-FU dose adaptation according to pharmacokinetic parameters versus conventional dosing in patients with advanced head and neck cancer. The overall 5-FU exposure in H&N cancer patients was significantly reduced in the dose adjustment arm compared to the fixed-dose arm. This resulted in reduced toxicity, but no improvement in clinical response. The impact on toxicity and efficacy suggests these patients might benefit from individual PK monitoring. The utility of monitoring 5-FU exposure to reduce toxicity was confirmed. It was noted that no link was found between pharmacokinetics and mucositis. As for tumour response, no difference in 5-FU exposure was observed between patients who achieved a CR or PR and patients who had stable disease or progression. This finding was not consistent with previous studies[133, 162] which reported that response and survival were significantly associated with high plasma concentrations in patients with H&N cancer. However, the findings from the study by Fety (1998)[157, 159] should be treated with caution as the methods and overall results were poorly

presented. Fety (1998)[157, 159] also reported that the costs associated with toxicity were considerably reduced for patients receiving 5-FU by a dose-managed approach ($6,803) when compared with those treated with standard 5-FU dosing (at $21,758 this represents approximately 70% reduction in medical costs).

Santini (1989)[133]

Study design

This study involved several study designs at one centre in France. Group 1 (89 patients, 228 cycles) corresponded to a retrospective study during which 5-FU blood concentrations were measured for each individual cycle of 77 patients (177 cycles) which allowed comparison of the distribution of AUC values in relation to response and tolerance to treatment. Group 2 (81 patients, 249 cycles) corresponded to patients entered into a prospective study based on initial data for group 1. For all patients and all cycles of group 2 the $AUC_{0\text{-}3days}$ value was used to determine the extent of reduction of the 5-FU dose for the second half of the cycle. Treatment involved: Day 0, 6h hydration with 5% dextrose (2 litres), NaCl ($6gl^{-1}$), and KCI ($3gl^{-1}$), followed by CDDP ($100mgm^{-1}$) 1 mgmin-1 i.v. in normal saline (0.5 litres) with 1.6% mannitol (0.25 litres), and then 5% dextrose (1 litre), NaCl ($6gl^{-1}$) and KCI ($3gl^{-1}$). Days 1-5, 5-FU 1,000 mg m^{-2} 24 h^{-1} by continuous i.v. infusion with a controlled flow pump. The scheduled protocol called for three courses per patient every three weeks. 5-FU pharmacokinetic measurements were taken on day 3 to adjust the dose for the second half of treatment if required. Median follow up was unclear. The pre-specified primary outcome was unclear although treatment response and toxicity rates were reported.

Study quality

This was a non-randomised study. Inclusion and exclusion criteria were not reported. There was a lack of useful information in the paper due to the poor reporting of both methods and results. Blinding to treatment was not possible. Response was evaluated by the same physician 10 days after completion of the last chemotherapy course, and although they may have been blinded, this was not specified. For formal quality assessment, see Appendix 11.

Population

The reported demographic characteristics for each group are poorly presented. The overall mean age was 61 years (range (36-82) with 145 males and 25 females participating.

Summary

Santini (1989)[133] reported sequential cohorts of patients in whom dose modification was made based on 5-FU exposure. AUC levels greater than 30 mg·h/L were associated with the development of toxicity. There was a statistical difference in complete response rates between group 1 and group 2

and a statistically significant reduction was observed in the incidence of toxic cycles. However, this was a non-randomized study and differences in the tumour stage of patients among the two cohorts may have explained some of the differences in outcomes reported.

Appendix 13. Gamelin 2008 overall survival parametric models

PK: Information criteria

Model	Obs	ll(model)	df	AIC	BIC
exponential	100	-120.817	1	243.6345	246.2397
weibull	100	-100.258	2	204.5161	209.7264
gompertz	100	-104.723	2	213.4463	218.6567
lognormal	100	-99.5674	2	203.1349	208.3452
loglogistic	100	-102.125	2	208.2502	213.4606

BSA: Information criteria

Model	Obs	ll(model)	df	AIC	BIC
exponential	103	-126.959	1	255.9181	258.5528
weibull	103	-113.273	2	230.5459	235.8154
gompertz	103	-119.726	2	243.4518	248.7212
lognormal	103	-108.594	2	221.1878	226.4572
loglogistic	103	-111.199	2	226.3971	231.6665

PK: Model parameters

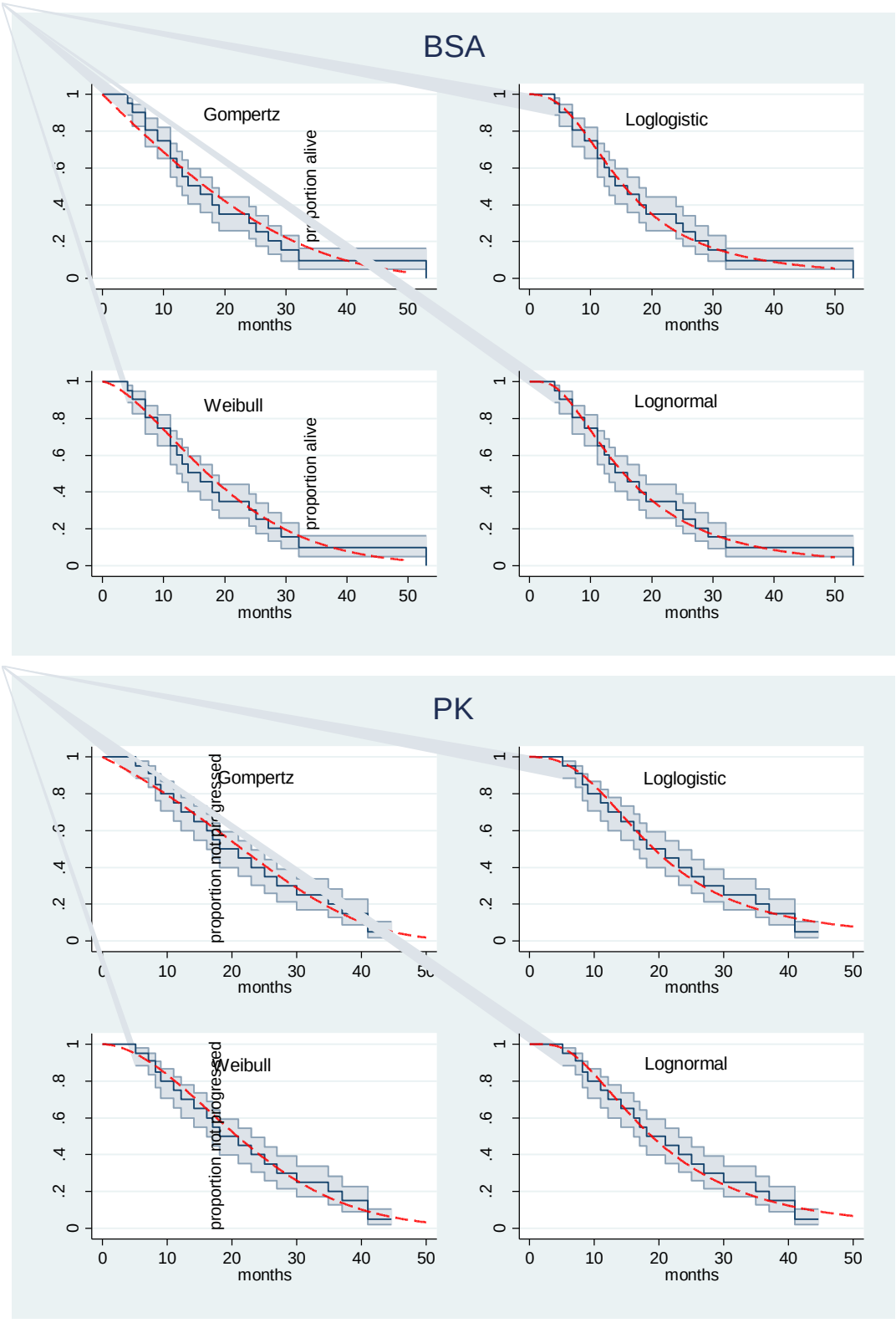
	lognormal		Weibull		Loglogistic *	
	mu	Sigma	lambda	gamma	p	gamma
PK OS	2.937171	0.648108	0.002698	1.827858	0.052014	2.588279
BSA OS	2.737613	0.694454	0.008654	1.540663	0.06445	2.457767

* S = 1 / (1 + (pt)^[1/gamma])

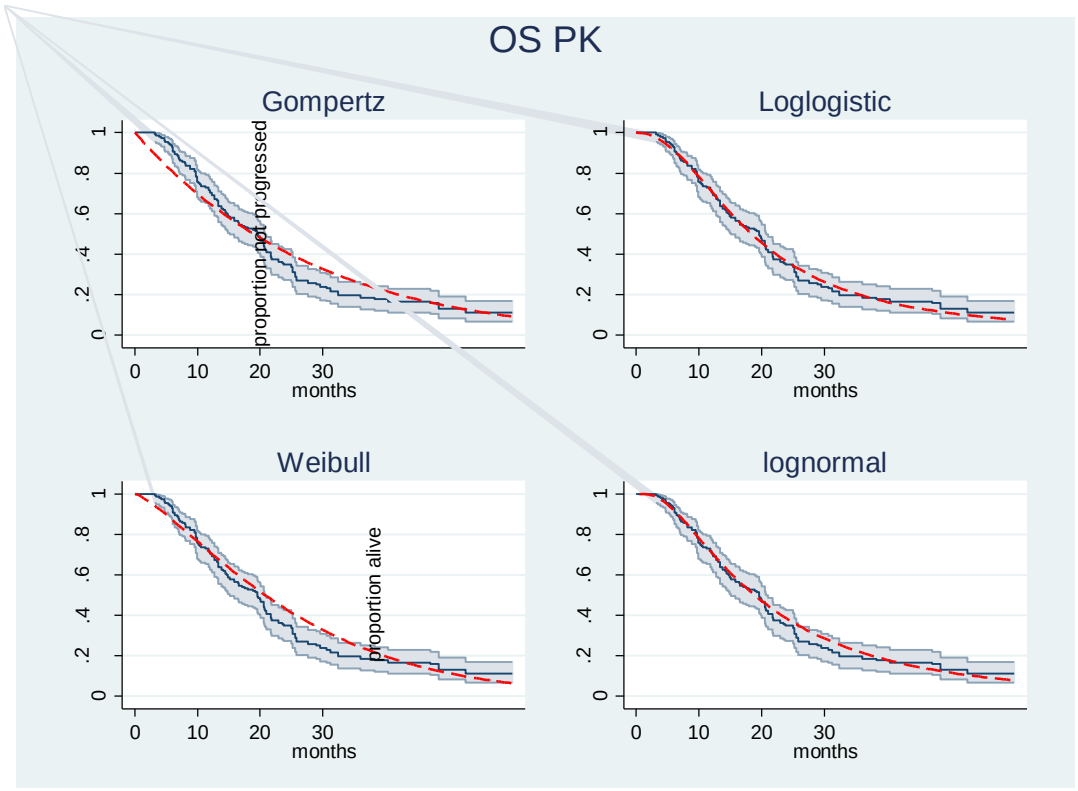
Appendix 14. Parametric fits to reconstructed Kaplan-Meier estimates

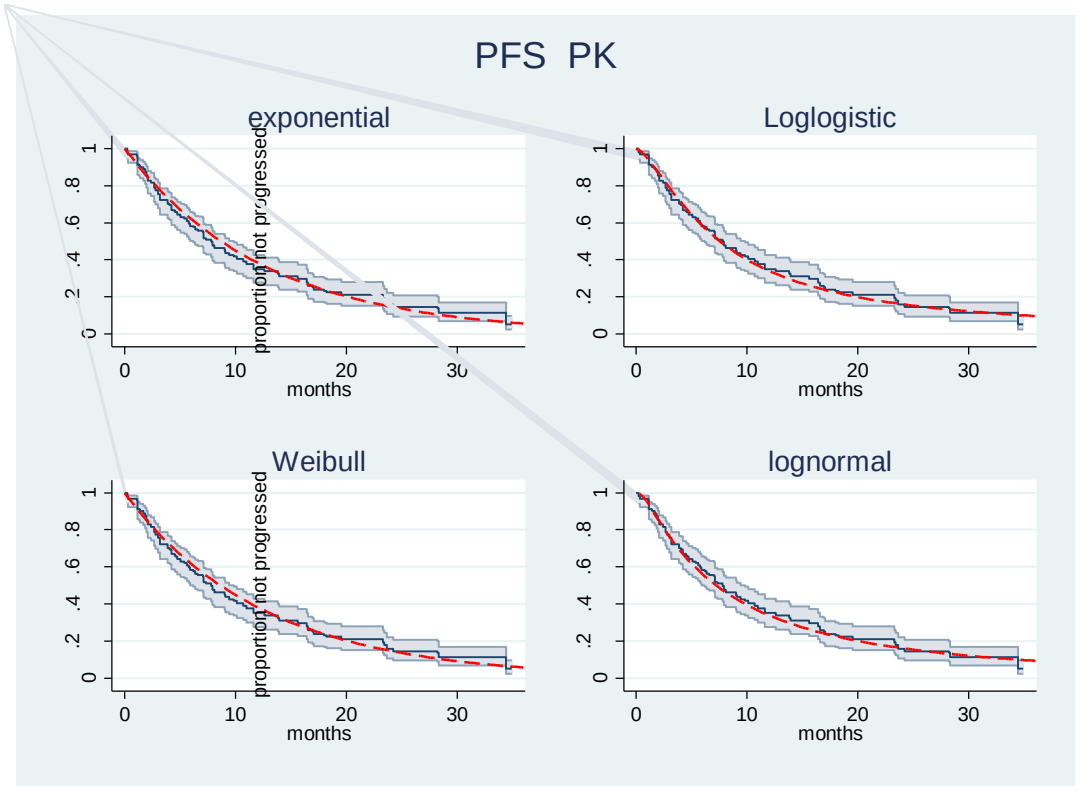
a) FU + FA regimens

Gamelin 2008 Overall survival

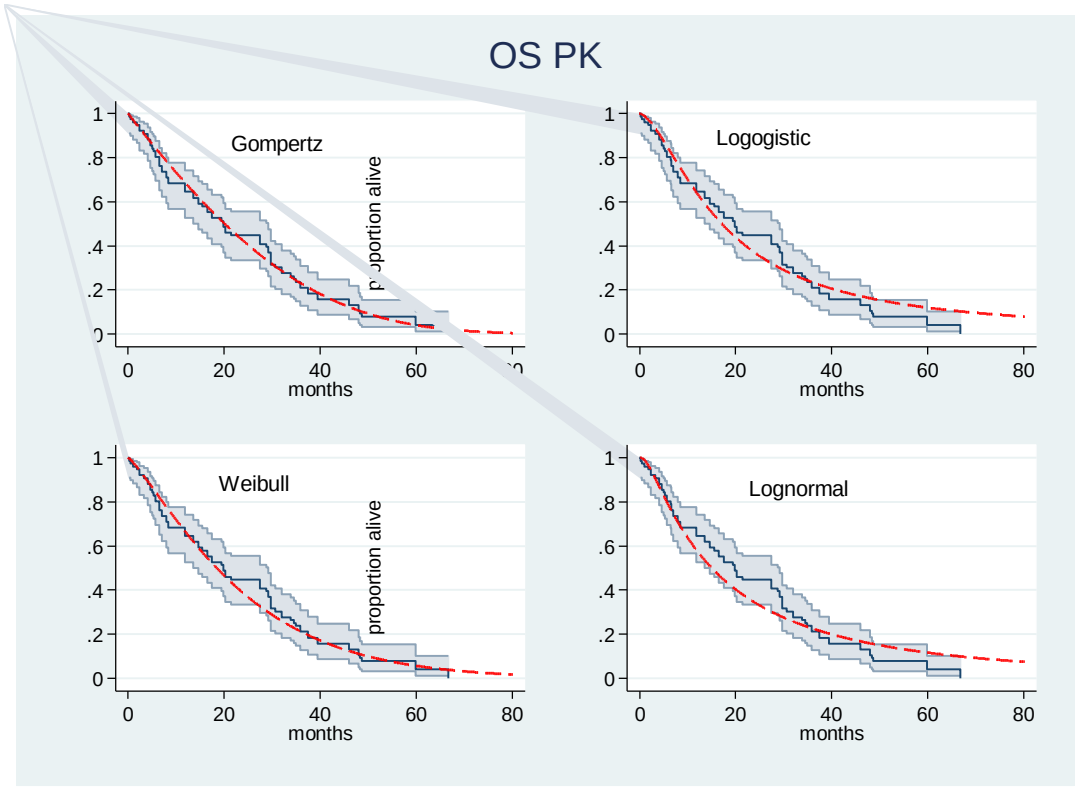


Gamelin 1998

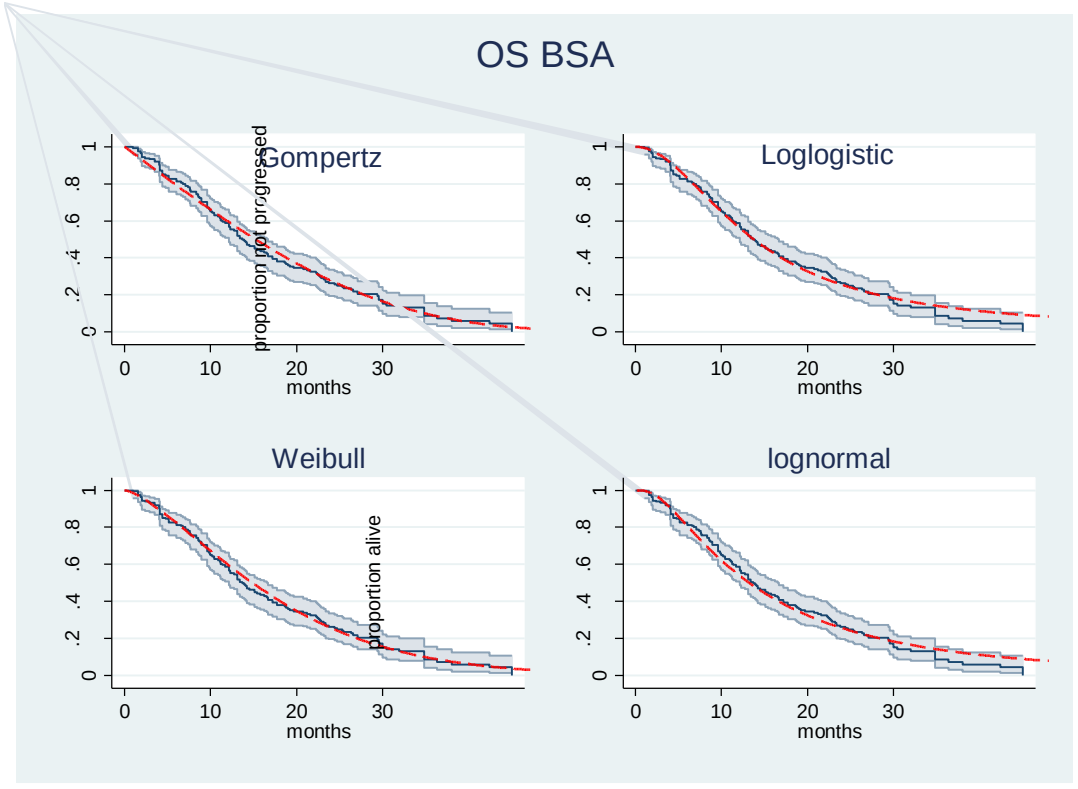




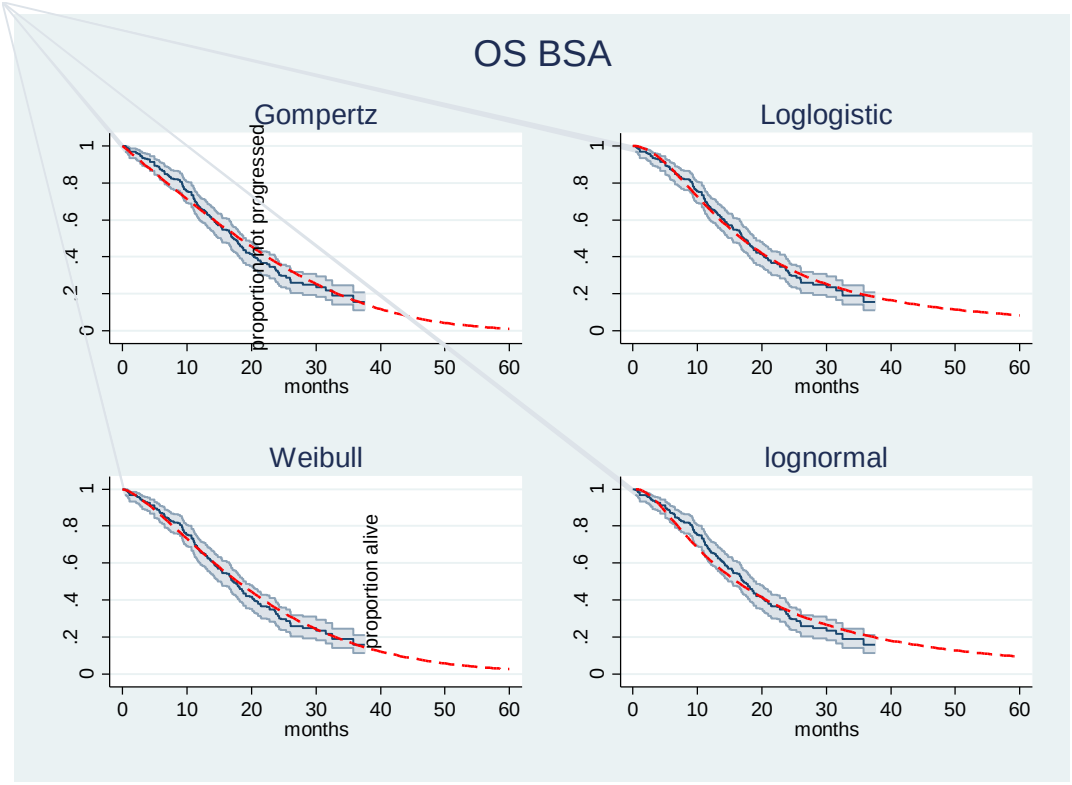
Capitain 2008



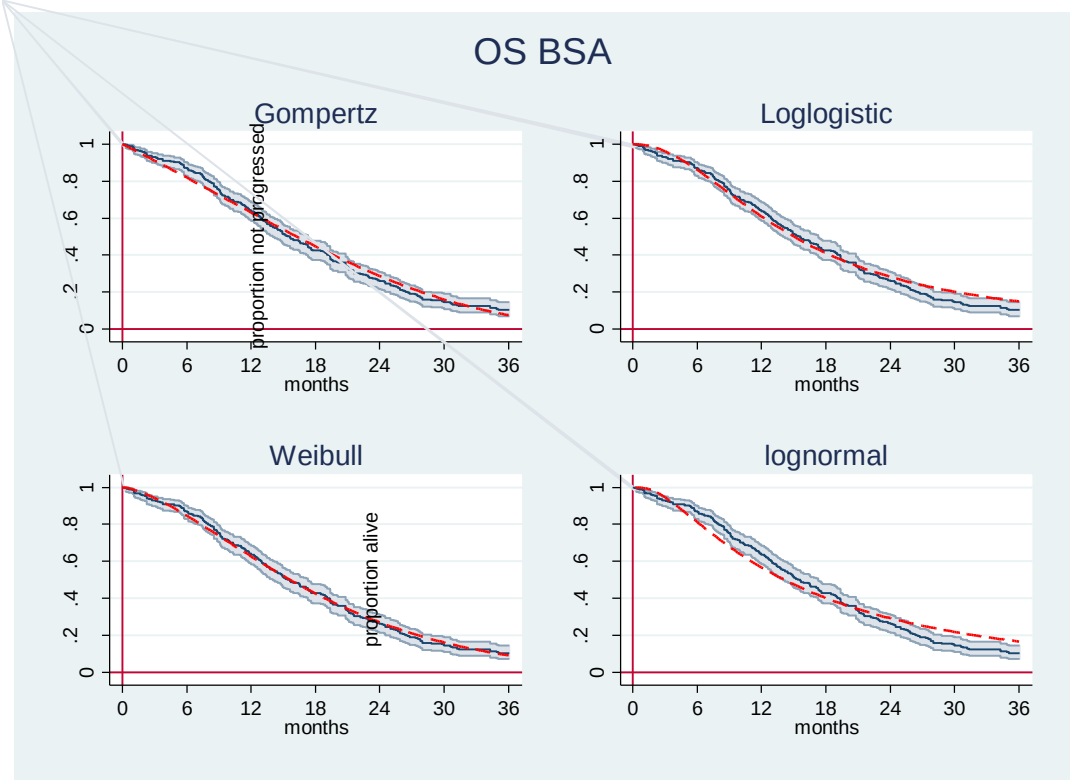
Kohne 2003



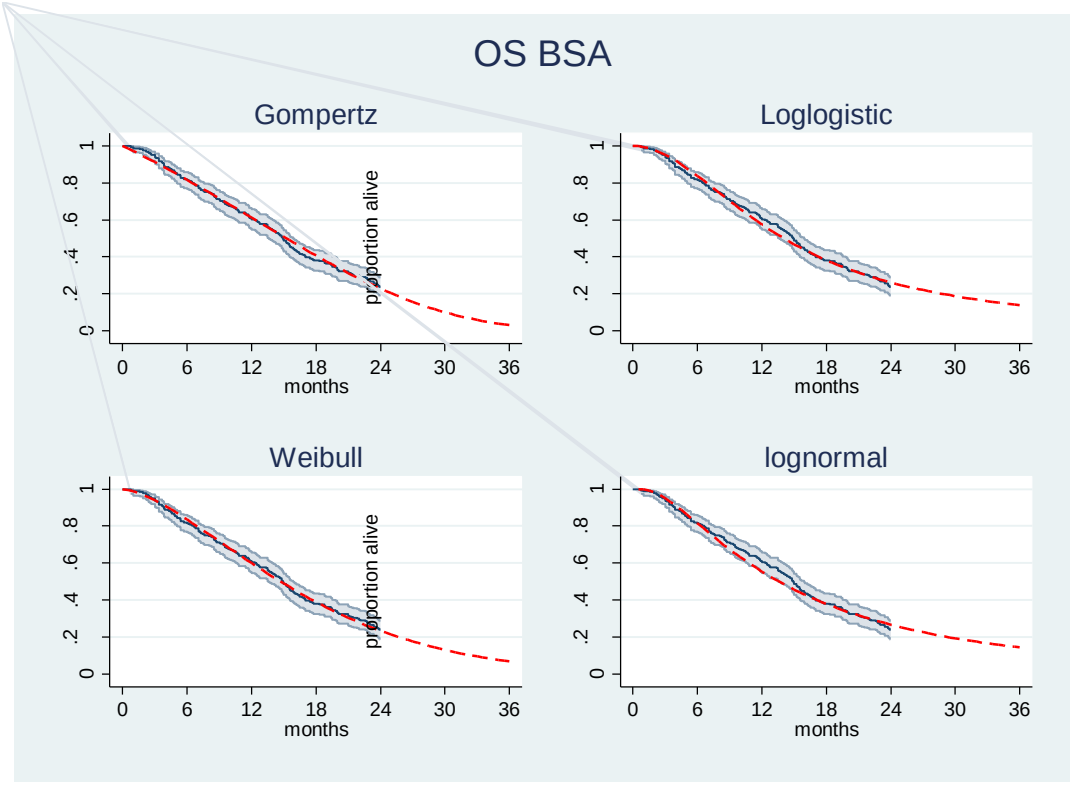
Kohne 2005



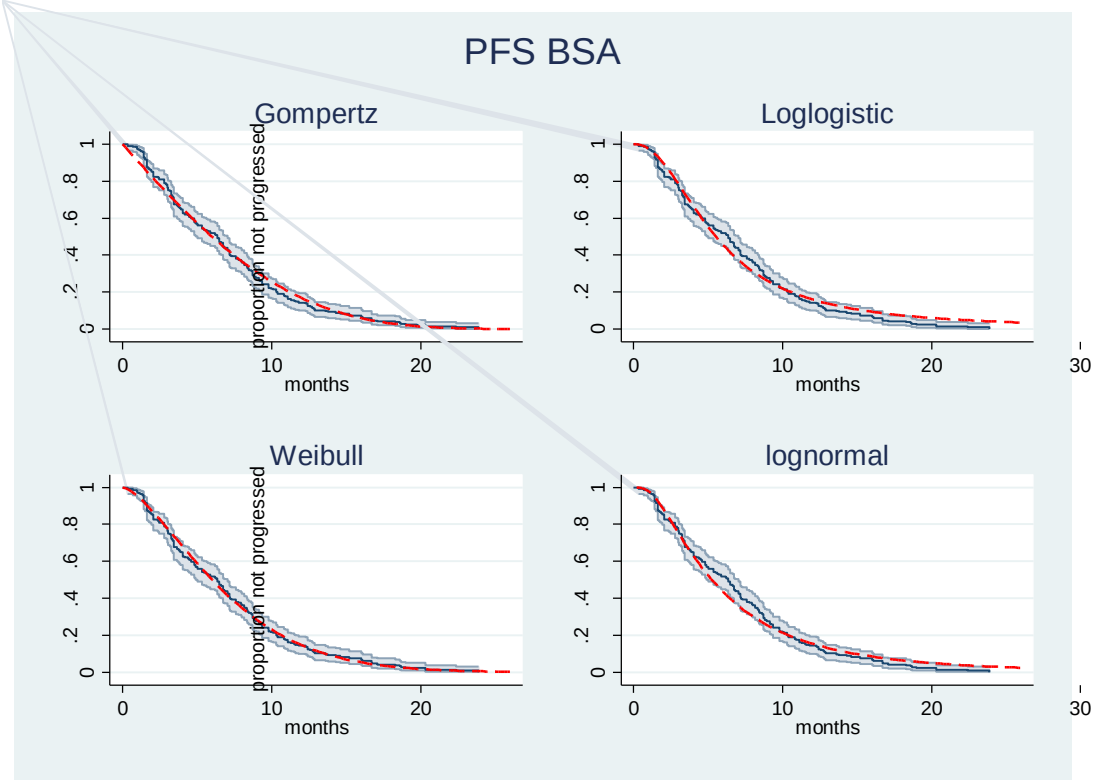
Seymour 2007



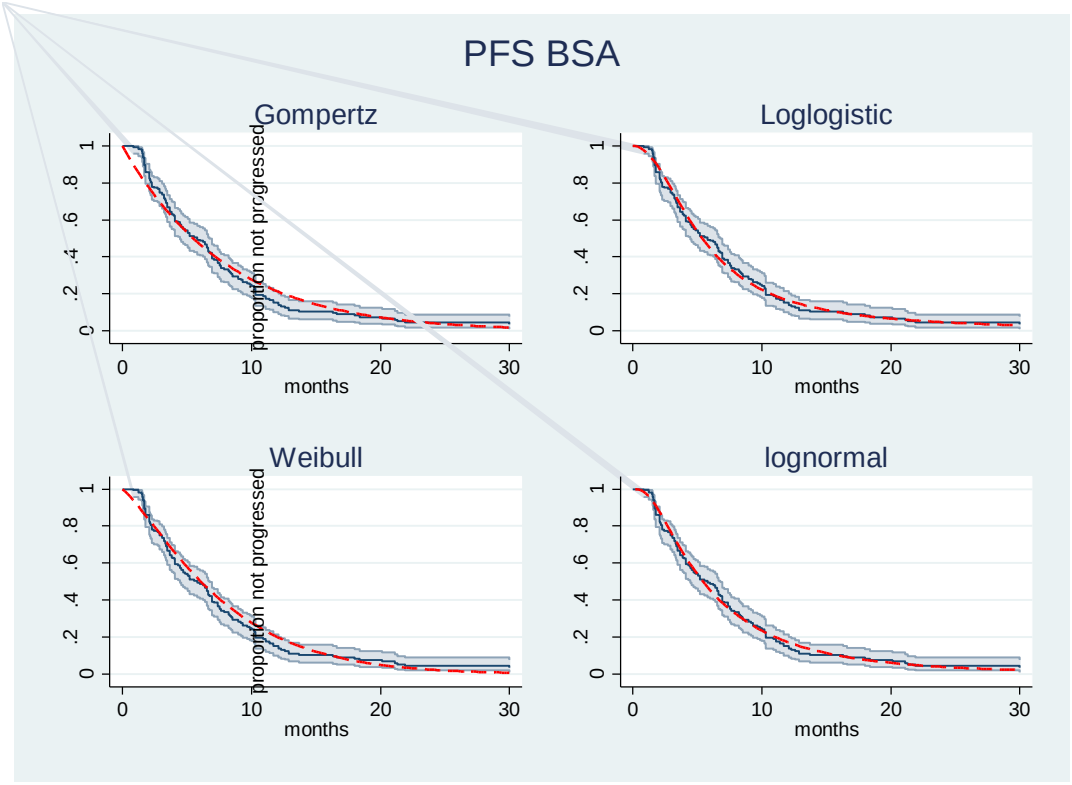
Cunningham 2009



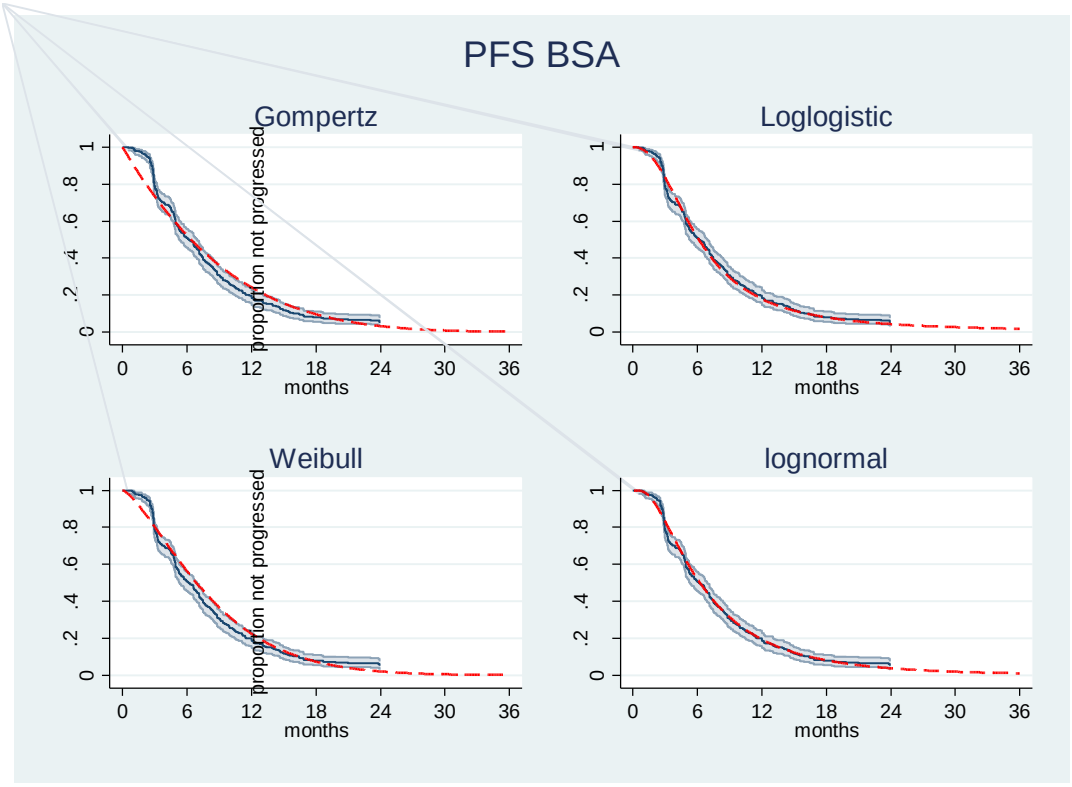
Kohne 2005



Kohne 2003

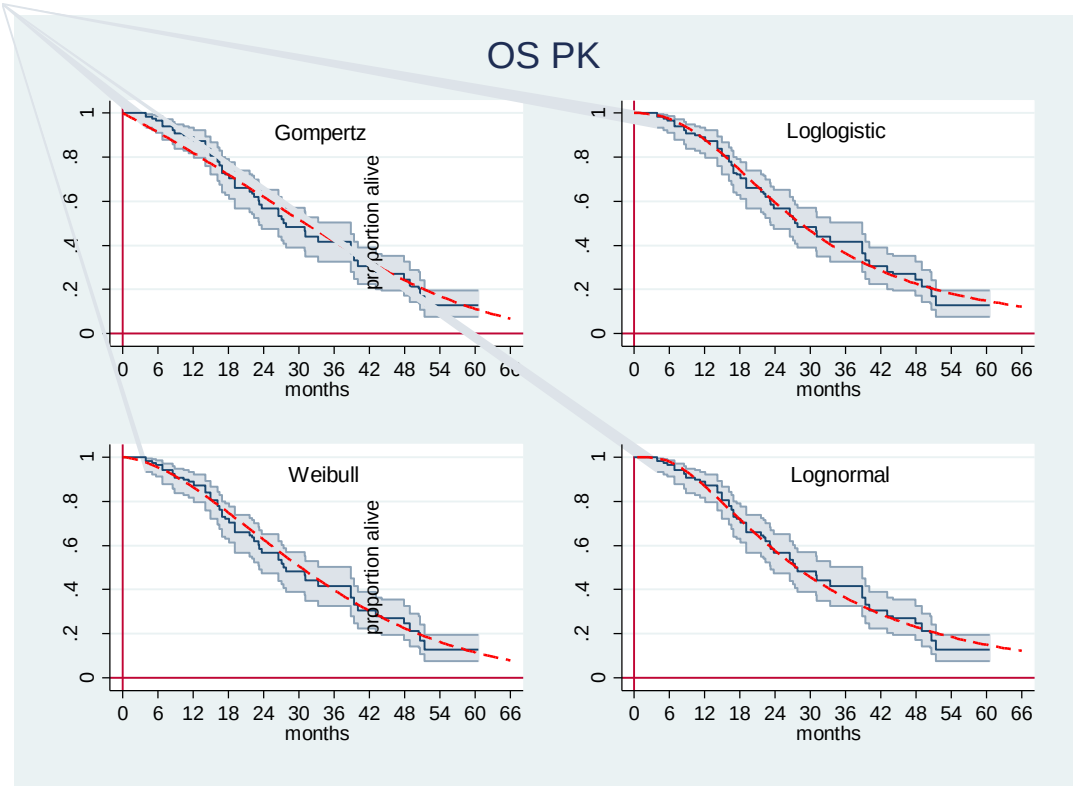


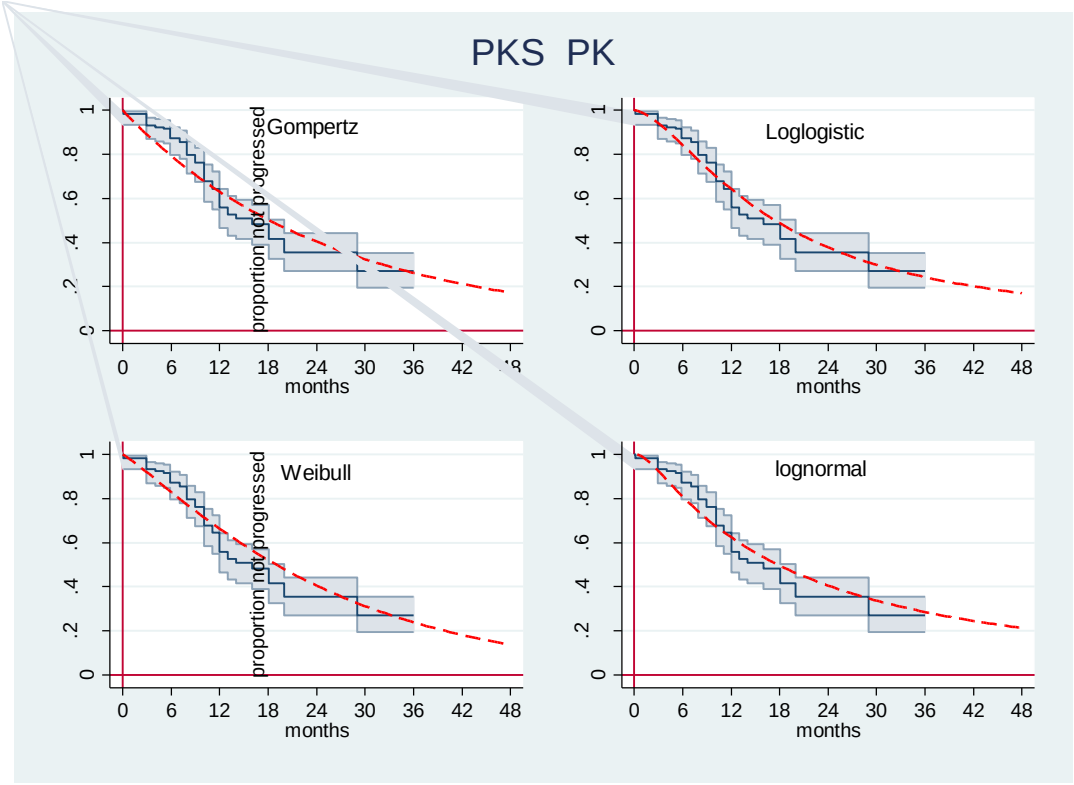
Cunningham 2009



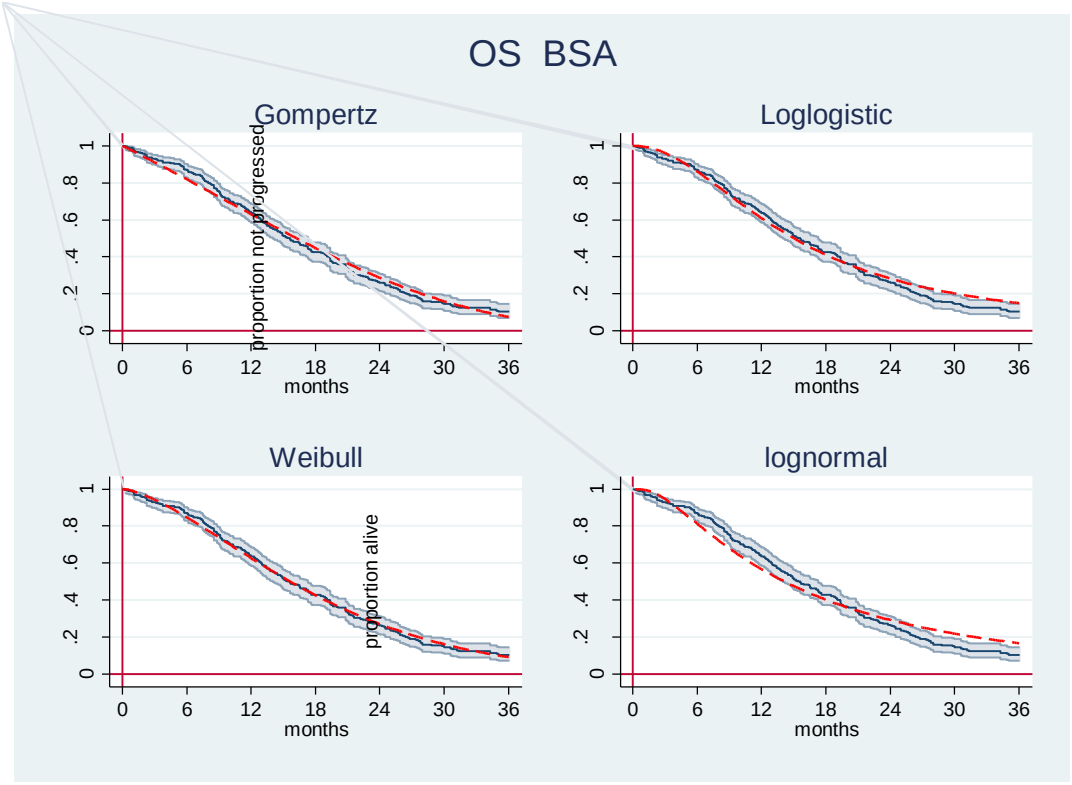
b) FOLFOX6 regimen

Capitain 2012 PK arm

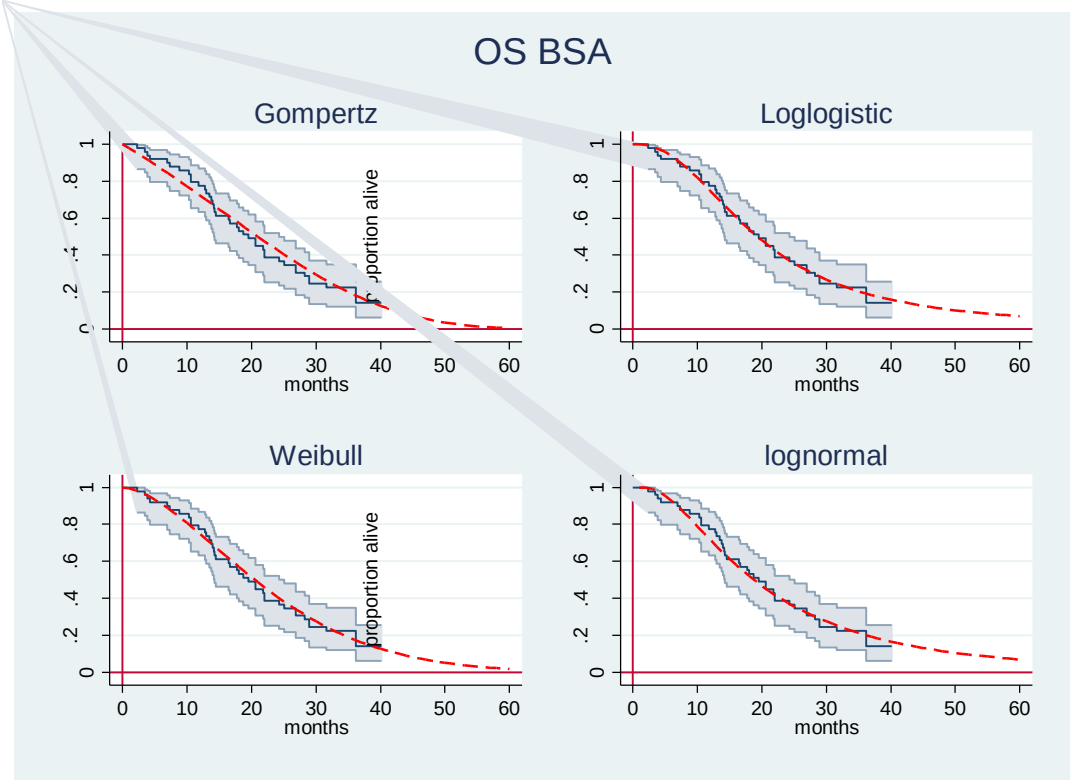




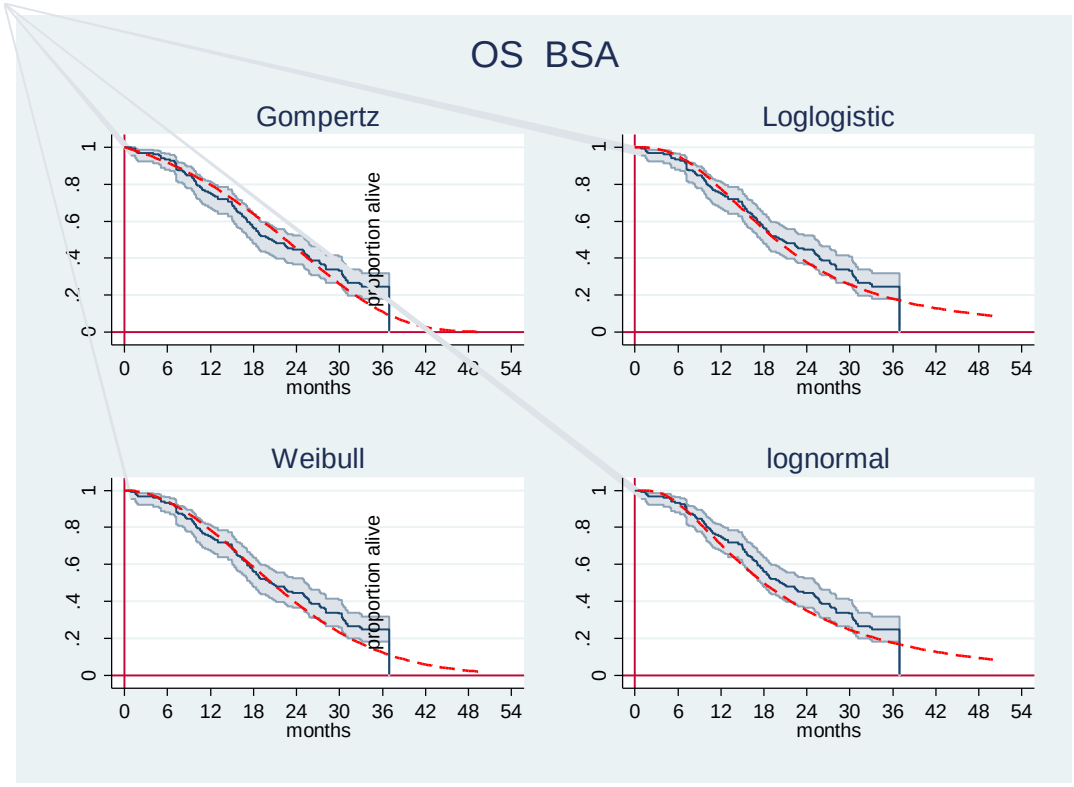
Seymour 2007



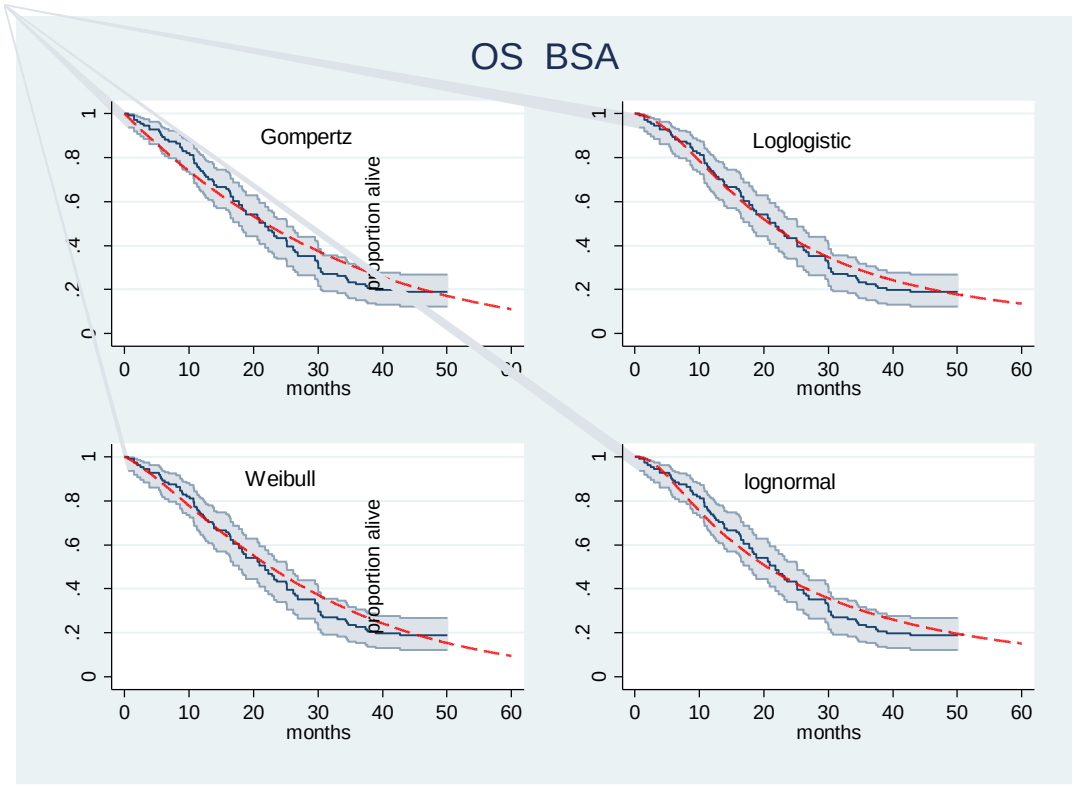
Hochster 2008



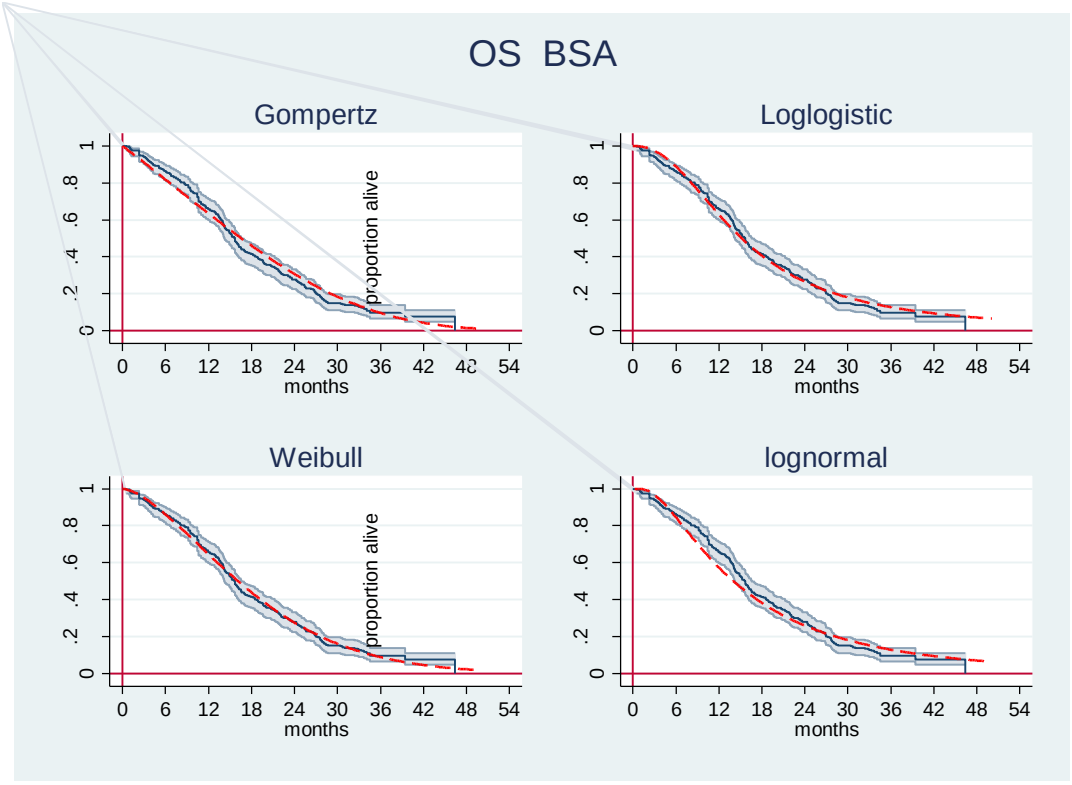
Ducreux 2010



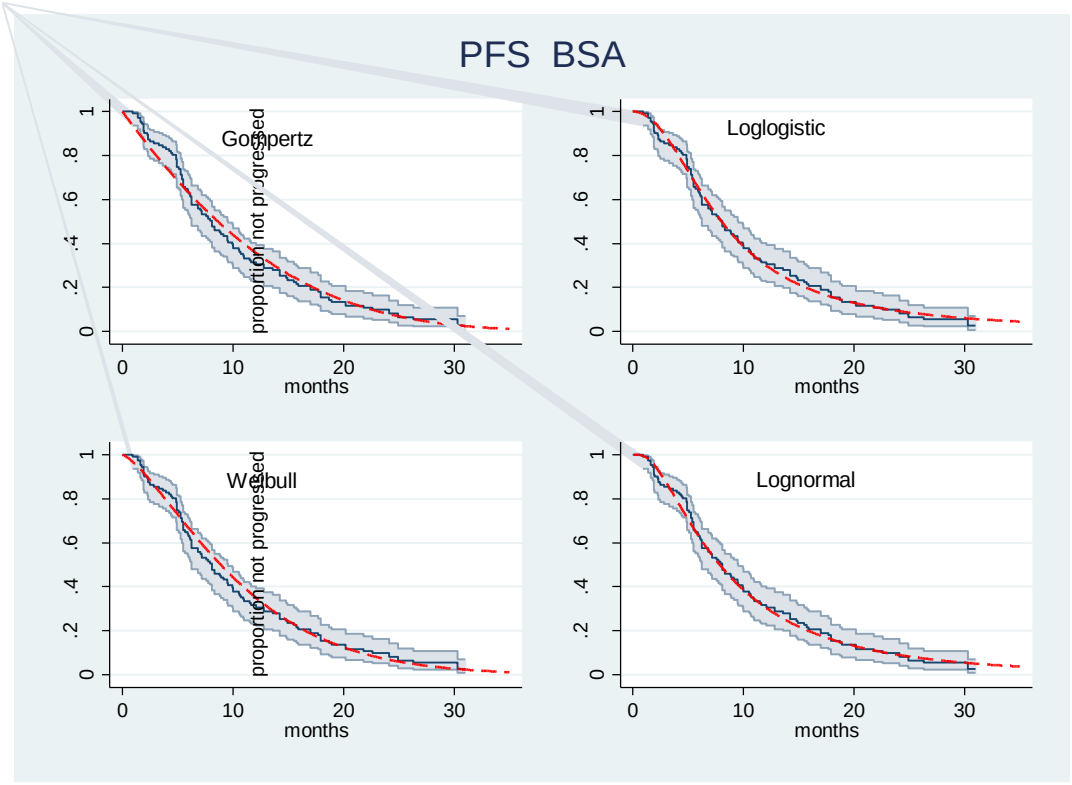
Tournigan d 2004 (FOLFOX first line FOLFIRI second line)



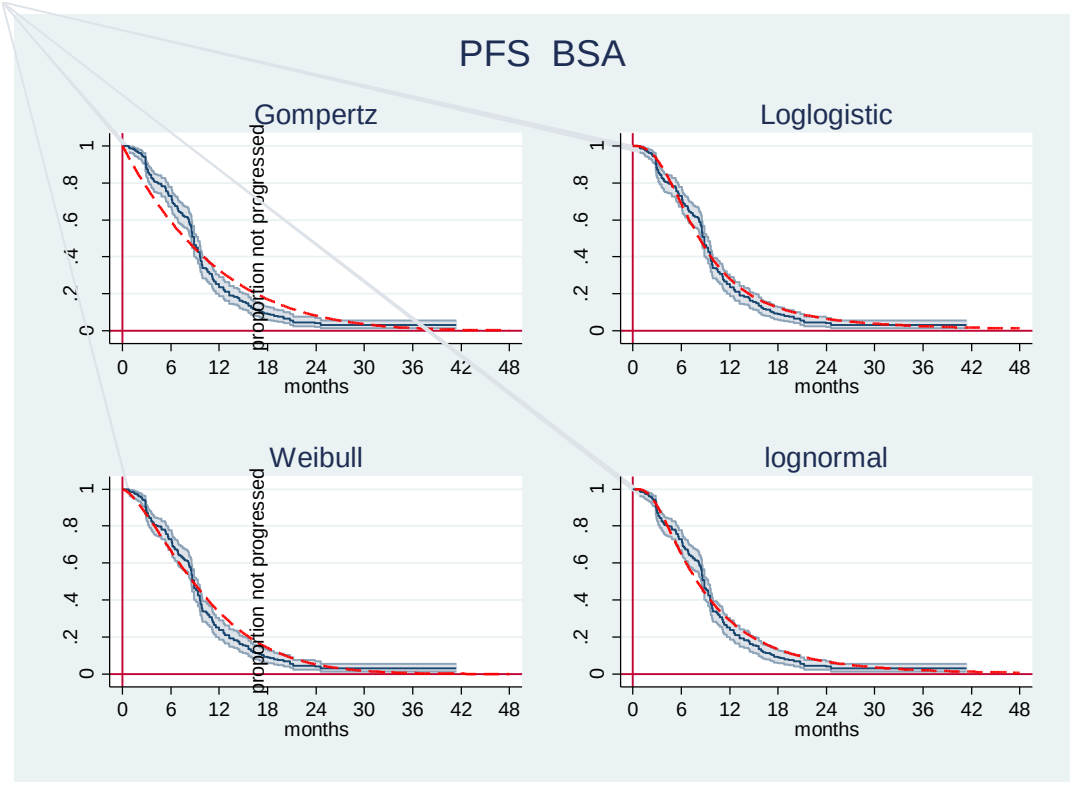
COIN 2011



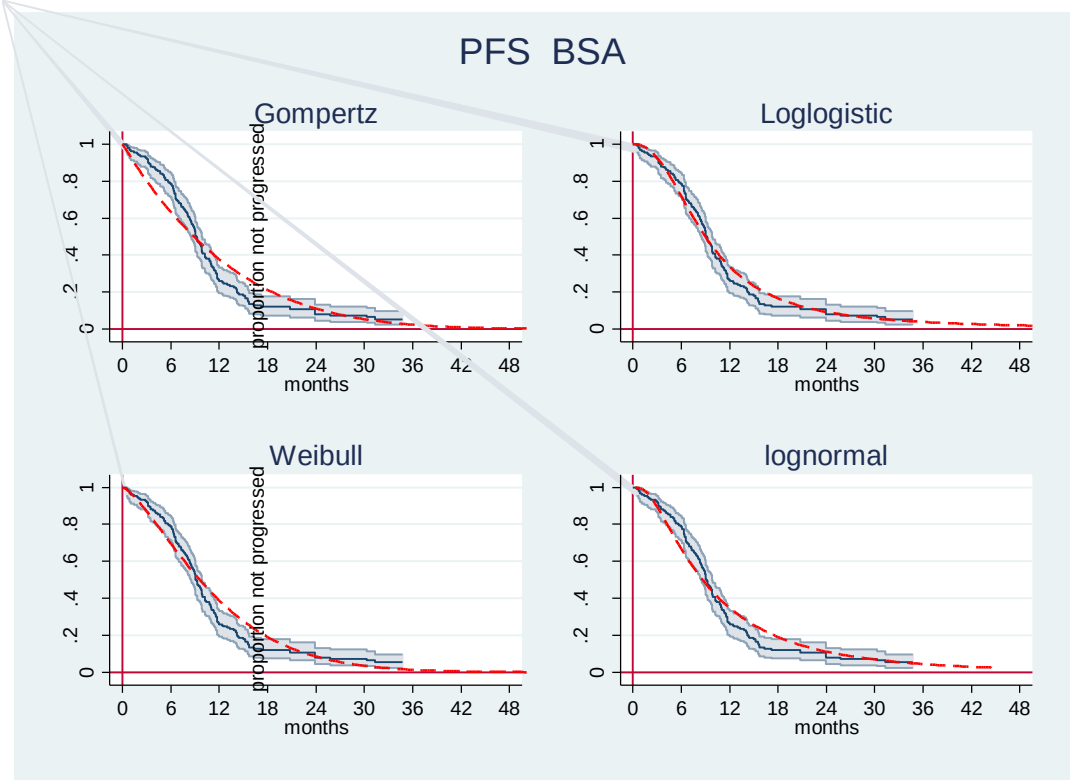
Tournigand 2004



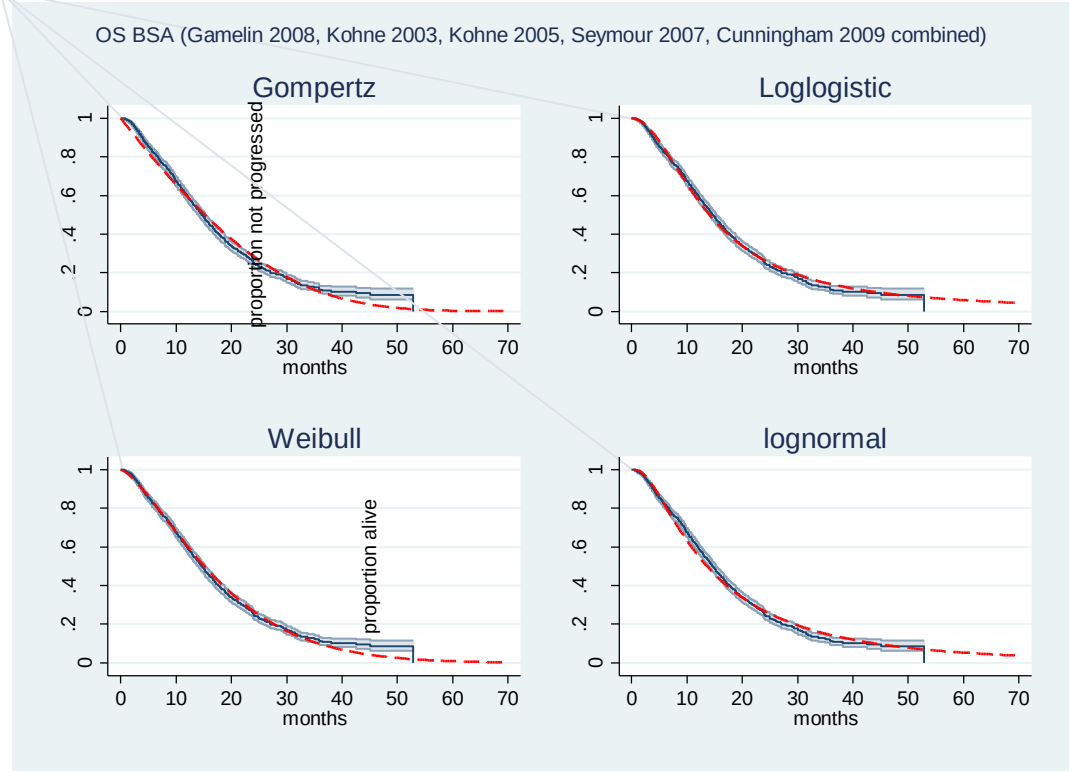
COIN 2011

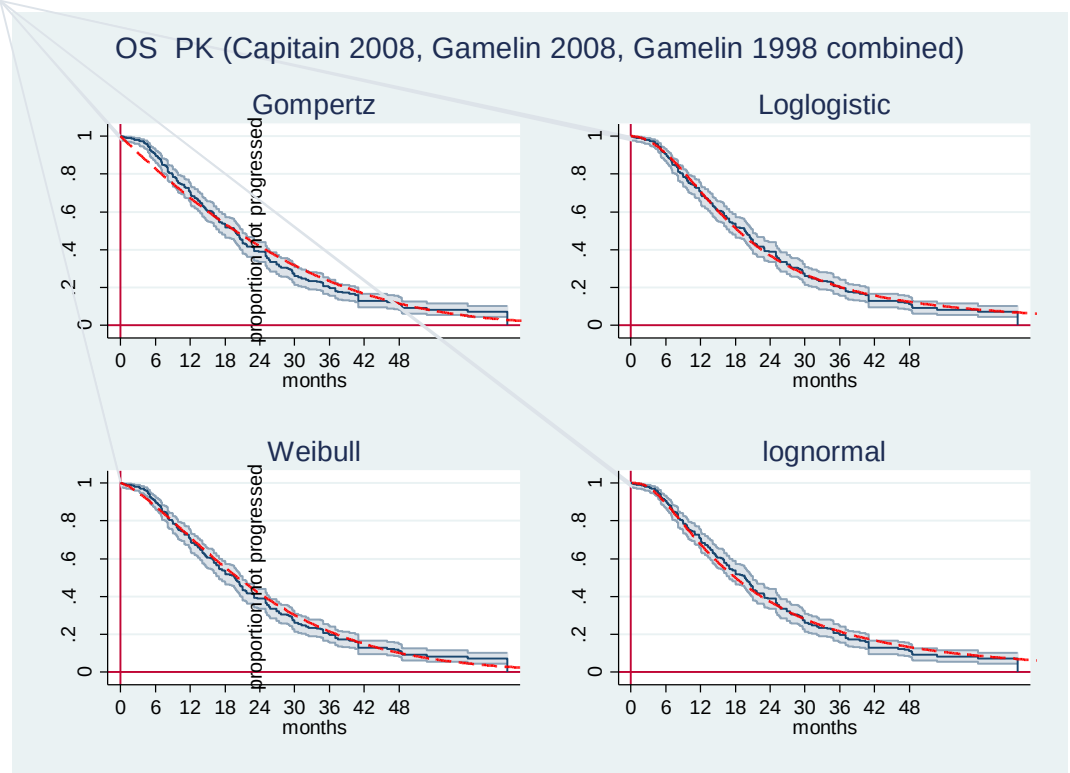


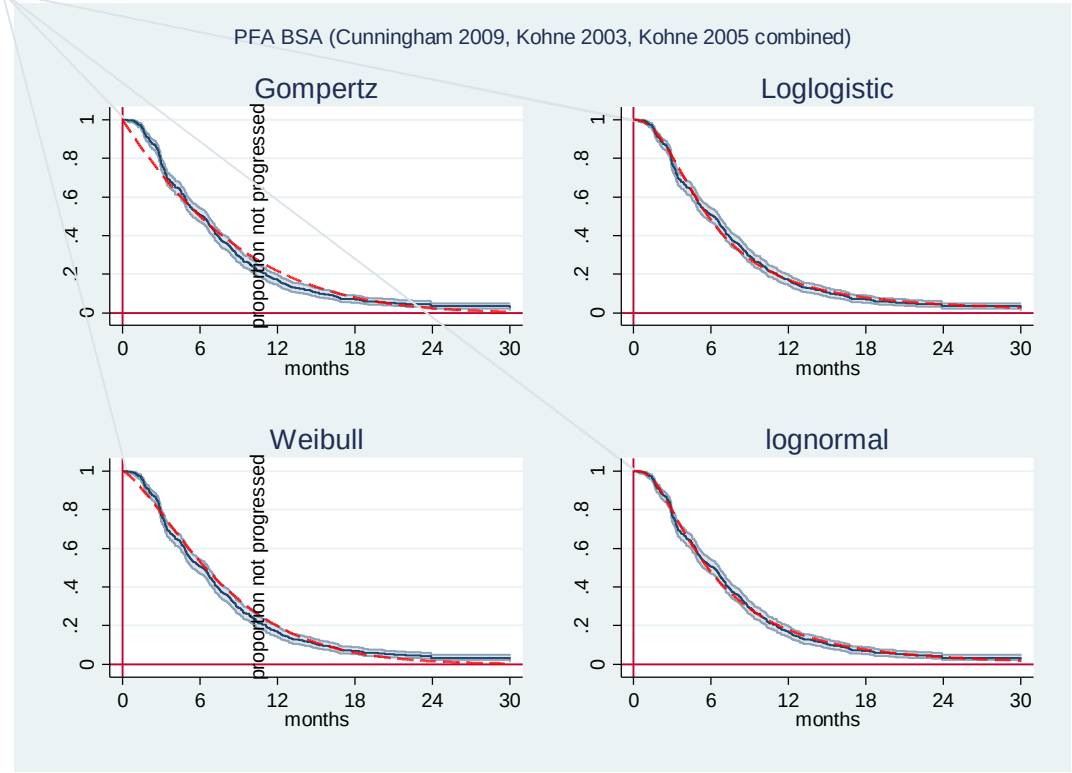
Ducreux 2010



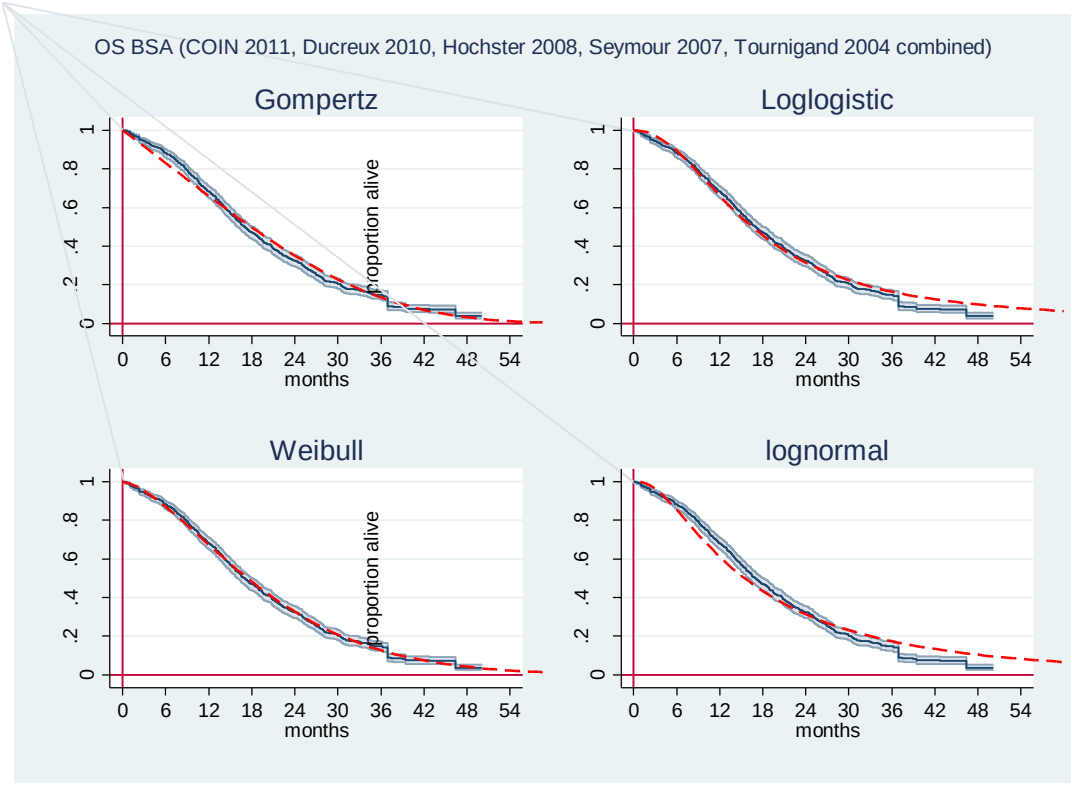
c) Combined FU + FA studies

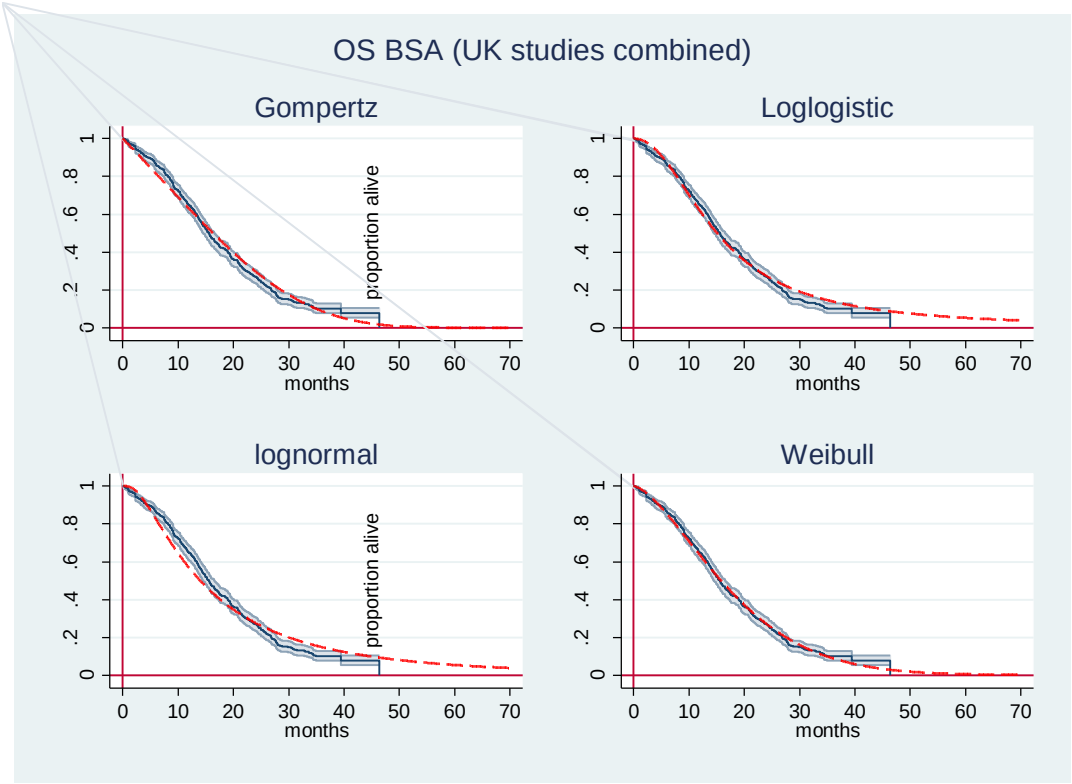




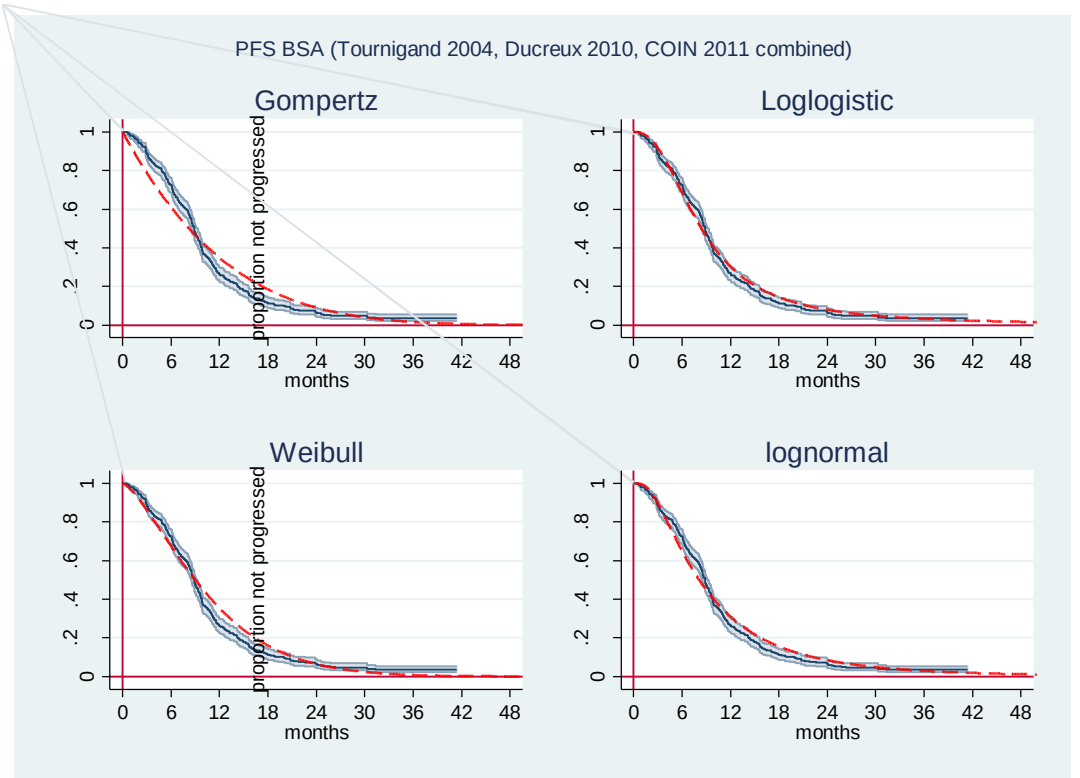

PFA BSA (Cunningham 2009, Kohne 2003, Kohne 2005 combined)
Gompertz
Loglogistic
Weibull
lognormal
proportion not progressed
months
0
.2
.4
.6
.8
1
0
6
12
18
24
30

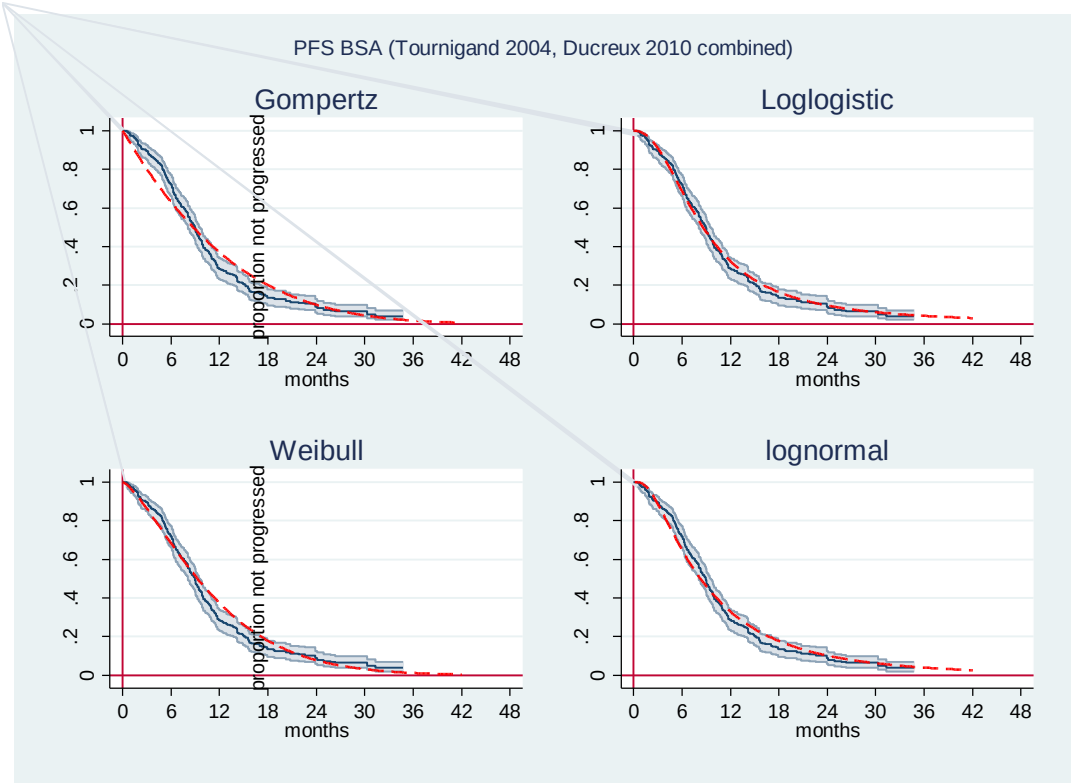
d) Combined FOLFOX6 studies






OS BSA (non UK studies; Ducreux 2010, Hochster 2008, Tournigand 2004 combined)
Gompertz
Loglogistic
Weibull
lognormal
proportion alive
months


PFS BSA (Tournigand 2004, Ducreux 2010, COIN 2011 combined)
Gompertz
Loglogistic
Weibull
lognormal
proportion not progressed
months



e) Weibull and lognormal model parameters for individual studies and combinations of studies

FF6 OS PK	LOGNORMAL	LOGNORMAL	WEIBULL	WEIBULL
	mu	sigma	LAMBDA	GAMMA
STUDY				
Capitain 2012	3.320461	0.7450776	0.0023328	1.669058
FF6 OS BSA	LOGNORMAL	LOGNORMAL	WEIBULL	WEIBULL
	mu	sigma	LAMBDA	GAMMA
STUDY				
Ducreux 2011	2.890615	0.7452636	0.0018259	1.965318
Tournigand 2004	3.018546	1.041158	**0.0141104**	**1.249536**
Coin 2011	2.640272	0.8339556	0.0091487	1.557174
Hochster 2008	2.932136	0.7831604	0.0049491	1.635496
Seymour 2007	2.649206	0.9678668	0.0116269	1.486356
COMBINED	***2.739721***	***0.8999154***	***0.0094214***	***1.503426***
NON UK COMBINED	2.933888	0.850545475	0.0056984	1.5776
UK ONLY COMBINED	2.64068	0.9050935	0.0104068	1.520104

FF6 PFS PK	LOGNORMAL	LOGNORMAL	WEIBULL	WEIBULL
	mu	sigma	LAMBDA	GAMMA
STUDY				
Capitain 2012	2.878827	1.244953	0.0243758	1.136683
FF6 PFS BSA	LOGNORMAL	LOGNORMAL	WEIBULL	WEIBULL
	mu	sigma	LAMBDA	GAMMA
STUDY				
COIN 2011	2.07606	0.736317	0.0310386	1.434147
Ducreux 2011	2.156429	0.838911	0.0305782	1.380975
Tournigand 2004	2.059369	0.834821	**0.0356843**	**1.358216**
COMBINED	***2.095161***	***0.788257***	***0.0319368***	***1.400817***
NON UK COMBINED	2.1151	0.838378	0.03271	1.370594

FU+FA OS PK	LOGNORMAL	LOGNORMAL	WEIBULL	WEIBULL
	mu	sigma	LAMBDA	GAMMA
STUDY				
Gamelin 2008	2.937171	0.6481075	0.0026976	1.827858
Gamelin 1998	2.936224	0.8194655	0.0135412	1.29762
Capitain 2008	2.710242	1.157483	0.0205514	1.20758
COMBINED	2.88818	0.8788956	0.0108903	1.381893
FU+FA OS BSA	LOGNORMAL	LOGNORMAL	WEIBULL	WEIBULL
	mu	sigma	LAMBDA	GAMMA
STUDY				
Gamelin 2008	2.737613	0.694454	0.0086544	1.540663
Cunningham 2009	2.608949	0.913819	0.0119712	1.510307
Kohne 2003	2.582476	0.90816	0.0154912	1.407952
Kohne 2005	2.77669	0.999576	0.0132561	1.373619
Seymour 2007	2.557337	0.914055	0.0178338	1.374292
COMBINED	***2.613328***	***0.915224***	***0.0155657***	***1.396487***
Cunningham 2009	2.608949	0.913819	0.0119712	1.510307
Gamelin 2008	2.737613	0.694454	0.0086544	1.540663
Giacchetti 2000	3.022251	1.047264	0.0149354	1.223547

Kohne 2003	2.582476	0.90816	0.0154912	1.407952
Kohne 2005	2.77669	0.999576	0.0132561	1.373619
Seymour 2007	2.557337	0.914055	0.0178338	1.374292
COMBINED	***2.64079***	***0.930805***	***0.0169611***	***1.350418***

FU+FA PFS PK	LOGNORMAL	LOGNORMAL	WEIBULL	WEIBULL
	mu	sigma	LAMBDA	GAMMA
STUDY				
Gamelin 1998	1.975084	1.220492	0.0819713	0.9908913
FU+FA PFS BSA	LOGNORMAL	LOGNORMAL	WEIBULL	WEIBULL
	mu	sigma	LAMBDA	GAMMA
STUDY				
Cunningham 2009	1.82961	0.759104	0.0485681	1.378005
Giacchetti 2000	1.762772	0.92053	0.0771431	1.151069
Kohne 2005	1.657345	0.813518	0.0499585	1.467809
Kohne 2003	1.692872	0.840886	0.0748098	1.233541
COMBINED	***1.751379***	***0.814365***	***0.0591133***	***1.319453***
Cunningham 2009	1.82961	0.759104	0.0485681	1.378005
Kohne 2005	1.657345	0.813518	0.0499585	1.467809
Kohne 2003	1.692872	0.840886	0.0748098	1.233541
COMBINED	***1.74937***	***0.797924***	***0.0554057***	***1.358335***

Appendix 15. Previous NICE MCRC assessments and DoH report

There have been a number of NICE mCRC assessments:

- TA61: MTA of Capecitabine and Tegafur with Uracil for mCRC: 2002[181]
- TA93: MTA of irinotecan, oxaliplatin and raltitrexed for mCRC: 2005[30]
- TA118: MTA of bevacizumab and cetuximab for mCRC: 2006[179]
- TA176: STA of cetuximab for mCRC: 2008[182]
- TA212: STA of bevacizumab for mCRC: 2009[183]
- CG131: CG for diagnosis and management of colorectal cancer: 2011[7]
- TA242: MTA of cetuximab, bevacizumab and panitumumab for 2nd line treatment of mCRC: 2012[180]

The approach of these assessments and the sources of their inputs are reviewed below, grouped under the following headings.

- The approach to estimating chemotherapy administration costs for infusion regimes
- The approach to modelling the duration of treatment
- The approach to modelling survival
- Quality of life values for disease states and adverse events
- The costs of adverse events

The quality of life summary is supplemented by a brief review of the relevant findings of the Trueman et al. (2007) Bowel Cancer Services report to the DoH, which also conducted a systematic literature review.[222]

Chemotherapy administration costs in NICE assessments for mCRC

This section focuses upon the chemotherapy administration costs for infusion regimes similar to FOLFOX within NICE assessments for mCRC.

TA61: MTA of Capecitabine and Tegafur with Uracil for mCRC: 2002[181]

Administration costs were divided into those only incurred at the start of treatment and those incurred each cycle.

One off costs relevant to the current assessment were the line insertion costs, which for the modified de Gramont regime were costed at £265 [£371] based upon Iveson et al. (1999). Outpatient costs were

taken from the Christie Hospital: £150 [£210] with chemotherapy administration and £80 [£112] without chemotherapy administration.

Per cycle costs included inpatient and outpatient hospital visits, preparatory drugs, community nurse infusion administration and home visits, infusion pumps, pharmacy preparation and materials. Patients on the modified de Gramont regime were assumed to require one outpatient visit to a cancer ward plus two community nurse home visits to disconnect and maintain their infusion lines. The administration cost per 28 days was estimated to be £650 [£910] for the modified de Gramont regime, or £325 [£455] per 2 week cycle.

TA93: MTA of irinotecan, oxaliplatin and raltitrexed for mCRC: 2005[30]

A cost per line insertion of £440 [£595] was drawn from Boland et al. (2003). A cost of £62 [£99] for disposable infusion pumps was taken from Iveson et al. (1999). Inpatient and outpatients costs were taken from the PSSRU unit costs of health care (1999): £356 [£571] per medical oncology inpatient day and £109 [£175] per medical oncology outpatient visit. These were uplifted to 2004 costs using health service inflation indices.

Pharmacy costs of £23 [£30] per simple i.v. infusion and £38 [£49] per complex i.v. infusion were drawn from expert opinion from the Christie Hospital Manchester. For the modified de Gramont regime, the £38 [£49] cost was applied to each of the 5-FU bolus, the 5-FU infusion and the FA infusion resulting in a total pharmacy cost of £114 [£147]. Adding oxaliplatin to this increase the pharmacy cost by a further £38 [£49] to £152 [£195]. FOLFOX6 was assumed to have the same £152 [£195] pharmacy cost.

The modified de Gramont, oxaliplatin plus the modified de Gramont, FOLFOX6, irinotecan plus the modified de Gramont and FOLFIRI were all assumed to require 2 inpatient days if receiving it as inpatients, and 1 outpatient appointment if receiving it as an outpatient. The proportions receiving their treatment as inpatients and outpatients were based upon data from the Aventis submission. This summarised data on 163 UK patients in "*previous chemotherapy trials*": 15 (21%) of 71 modified de Gramont patients receiving inpatient administration, 7 (25%) of 28 irinotecan patients receiving inpatient administration, 3 (7%) of 41 FOLFOX6 patients receiving inpatient administration and 4 (17%) of 23 FOLFIRI patients receiving inpatient administration. Subsequent text suggests that this sample was constructed from the FOCUS trial and the Tournigand trial, though the assessment report notes that "*no information was available concerning how this sample of patients was constructed*".

Additional costs for diagnostic tests of £64.55 [£103.44] were drawn from the Kerr and O'Connor (1999) study of raltitrexed and 5-FU/FA, as were monthly primary care costs of £10.42 [£16.70]. The cost per cycle for clinical consultations of £79.81 [£127.90] was drawn from Iveson et al. (1999).

TA118: MTA of bevacizumab and cetuximab for mCRC: 2006[179]

The administration costs were the same as those used for TA93.[30] The only difference was to assume that no patients had their chemotherapy administered as inpatients due to this increasingly being the case.

TA176: STA of cetuximab for mCRC: 2008[182]

Administration costs were drawn from the NHS 2006 tariff: £123 for a single outpatient infusion based upon HRG 370F Outpatient Adult Follow-Up Attendance Medical Oncology [Attendance without treatment]: Face to Face; and, for a day case chemotherapy administration £277 based upon HRG F98 Day Case Chemotherapy with Digestive System Primary Diagnosis.

TA212: STA of bevacizumab for mCRC: 2009[183]

The administration costs were based upon the pharmacy costs of Tappenden et al. (2007) plus NHS reference costs for administration: for the first day of a cycle £317 [£357] based upon SB14Z Deliver Complex Chemotherapy Including Prolonged Infusional Treatment At First Attendance and for the second day of a cycle £227 [£255] based upon SB15Z Deliver Subsequent Elements Of A Chemotherapy Cycle. Inpatient administration was costed at £1,052 [£1,183] based upon PA44Z: Elective inpatient stay for Neoplasm Diagnoses.

The cost of the elastomer pump was estimated to be £35 [£38] based upon the 48hr pump supplied by Baxter Healthcare. This was assumed to be in addition to the pharmacy on-costs and to the NHS reference costs.

An hour of district nurse time to flush the infusion line at the end of each cycle was also included.

CG131: CG for diagnosis and management of colorectal cancer: 2011[7]

The 2008-09 NHS reference cost of £335 [£363] for SB13Z for the outpatient delivery of more complex parenteral chemotherapy was applied for each FOLFOX administration and for each FOLFIRI administration.

TA242: MTA of cetuximab, bevacizumab and panitumumab for 2nd line treatment of mCRC: 2012[180]

The assessment group assumed a £227 [£246] cost in 2008-09 prices for intravenous infusion of cetuximab monotherapy and panitumumab, drawn from the 2008-09 NHS reference costs for

outpatients HRG SB15Z: Deliver Subsequent Elements Of A Chemotherapy Cycle. This was inflated by an annual 4%, based upon the Hospital and Community Health Services Pay and Prices Index, to give a cost per administration of £255 [£261].
For the additional administration of irinotecan half of the £255 [£261]; i.e. £128 [£131], was added to the £255 [£261] administration cost of cetuximab.

Pharmacy preparation time for each infusion was estimated to cost £15 [£15] for all drugs.

Note that the costs of medical management for progressive disease were taken from Remak and Brazil (2004), a study among breast cancer patients.

The modelling of the duration of treatment in NICE assessments for mCRC

TA61: MTA of Capecitabine and Tegafur with Uracil for mCRC: 2002[181]
The assessment report noted that there was no consistent UK policy about whether treatment should continue to progression or stopped after a fixed period of time. For the modelling it was assumed that patients would be treated for 12 weeks, and that this had no detrimental effect upon survival despite the relevant RCTs treating patients until progression.

A scenario analysis of treating patients until progression was also undertaken. The assessment report noted that a proportion of patients would probably recommence treatment, with the mean treatment duration probably lying between the two extremes that were modelled.

TA93: MTA of irinotecan, oxaliplatin and raltitrexed for mCRC: 2005[30]
The mean number of treatment cycles for 1st and 2nd line therapies within the Tournigand et al. (2004) trial was available to the assessment group from a personal communication from A. Gramont.

TA118: MTA of bevacizumab and cetuximab for mCRC: 2006[179]
For the bevacizumab modelling, the mean number of doses of the 1st line therapies was taken from the trial data reported in the Roche submission to NICE. Similarly, for the cetuximab modelling the mean number of vials administered was taken from the BOND trial as reported in the Merck submission to NICE.

Table 6 of the assessment group report notes that bevacizumab was administered in repeat 8 week cycles. While not specifying treatment duration for trial AVF2107g, trials AVF0780g and AVF2192g both continued treatment to progression or 48 weeks for AVF0780g and 96 weeks for AVF2192g.

Table 18 of the assessment group report does not specify treatment cessation rules for the BOND trial, but other cetuximab trials appear to be until progression or unacceptable toxicity.

TA176: STA of cetuximab for mCRC: 2008[182]

The number of vials used were apparently derived from data for the relevant subset of the CRYSTAL and OPUS trials.

TA212: STA of bevacizumab for mCRC: 2009[183]

The monthly drug costs were based upon the per cycle cost multiplied by the mean number of cycles per month that were observed in the pivotal NO16966 trial: 1.83 for 5-FU based regimes and 1.31 for capecitabine based regimes. Kaplan Meier curves for time to treatment cessation were used to model the time on treatment, though note that these are marked as commercial in confidence.

CG131: CG for diagnosis and management of colorectal cancer: 2011[7]

The numbers of treatment cycles were drawn from the literature. For 1st line treatments, a mean of 8.99 cycles for FOLFOX and a mean of 7.89 cycles for FOLFIRI were applied. For those receiving 2nd line therapies a mean of 7.13 cycles for FOLFOX and 6.00 cycles for FOLFIRI were applied.

TA242: MTA of cetuximab, bevacizumab and panitumumab for 2nd line treatment of mCRC: 2012[180]

For cetuximab plus BSC and cetuximab plus irinotecan patients were assumed to remain on treatment until disease progression. For panitumumab plus BSC a mean of 20 weeks' treatment; i.e. 10 doses, was drawn from data reported by Amado et al. (2008). This data also suggested a progression free survival of 4.0 months when the assessment group's indirect comparison increased this to 5.1 months. The number of doses of panitumumab was proportionately increased to 12.7 doses.

The approach to modelling survival in NICE assessments for mCRC

TA61: MTA of Capecitabine and Tegafur with Uracil for mCRC: 2002[181]

Overall mean survival was based upon Twelves (2002) with the additional assumption of equivalence between the Mayo regime and the modified de Gramont regime. The area under the curve resulted in an estimated mean survival of 15.1 months. What was applied for progression free survival is less clear, though there is reference to a median of 4.7 months within the assessment report.

TA93: MTA of irinotecan, oxaliplatin and raltitrexed for mCRC: 2005[30]

Parametric weibull curves were fitted to Kaplan Meier overall survival curves and progression free survival curves of the FOCUS trial. The modified de Gramont plus irinotecan arm was used as the baseline, with the log-rank hazard ratios for the other arms being estimated. Log-rank hazard ratios

were also estimated for the 1st line FOLFIRI 2nd line FOLFOX6 arm and the 1st line FOLFOX6 2nd line FOLFIRI arm of the Tournigand (2004) study.

Table 66 on page 91 of Hind et al. (2008)[30] reports mean overall survival estimates of 2.28 years for the 1st line FOLFIRI 2nd line FOLFOX6 arm and 2.15 years for the 1st line FOLFOX6 2nd line FOLFIRI arm of the Tournigand (2004) study.

TA118: MTA of bevacizumab and cetuximab for mCRC: 2006[179]

Two models were developed to estimate the cost effectiveness of bevacizumab:

- being added to irinotecan plus 5-FU/FA;
- being added to 5-FU/FA.

Note that these also allowed for 2nd line and 3rd line therapies. For both overall survival and progression free survival parametric weibull curves were fitted to digitised Kaplan Meier curves as reported in Hurwitz et al. (2004) and Kabbinavar et al. (2005)[3]. This resulted in estimates for the mean progression free survival, including progression free survival from 2nd and 3rd line therapies, as 1.27 years for bevacizumab plus irinotecan plus 5-FU/FA compared to 0.97 years for irinotecan plus 5-FU/FA, and 1.16 years for bevacizumab plus 5-FU/FA compared to 0.83 years for 5-FU/FA. Mean overall survival estimates were 1.98 years for bevacizumab plus irinotecan plus 5-FU/FA compared to 1.57 years for irinotecan plus 5-FU/FA, and 1.59 years for bevacizumab plus 5-FU/FA compared to 1.41 years for 5-FU/FA.

One model was developed to estimate the cost effectiveness of cetuximab in combination with irinotecan compared to active supportive care as second line therapy among those EGFR expressing mCRC patients who had failed on irinotecan containing chemotherapy. This was hampered by there being no direct comparative evidence on survival and quality of life. While there was evidence on tumour response rates, the assessment group report notes that "*the impact of cetuximab treatment on HRQoL and overall survival remains unquantified*". Due to this within the primary analysis sought to identify the threshold for the additional overall survival that would render cetuximab cost effective.

For the modelling of the cost effectiveness of adding cetuximab to irinotecan, parametric weibull curves were fitted to Kaplan Meier overall survival curves while the progression free survival was estimated "*using the empirical Kaplan Meier progression free survival curve"* as reported in the BOND trial. The mean overall survival estimate for cetuximab plus irinotecan was 0.79 years.

[3] Note that the section header suggested that this only applied to the non-bevacizumab containing regimes, but figures 13 and 14 suggest that this applied to both arms for the relevant comparison.

A secondary analysis undertook a systematic review of overall survival from active best supportive care. The mean overall survival estimates for active best supportive care were 0.60 years based upon Cunningham et al. (1999), 0.67 years based upon Rao et al. (2004) and 0.77 years based upon Barni et al. (1995).

TA176: STA of cetuximab for mCRC: 2008[182]

The manufacturer submission estimates the effectiveness of the 1st line therapies through parameterised survival curves being fitted to trial data for death before progression and progression free survival. A lognormal curve for death before progression and a weibull curve for progression free survival was fitted for the CRYSTAL trial analysis of cetuximab added to FOLFIRI, while log normal curves were fitted to both death before progression and progression free survival for the OPUS trial analysis of cetuximab added to FOLFOX4. 2nd line time to progression was based upon a log normal fit to data from Tournigand et al. (2004), 3rd line time to progression was based upon a log-logistic fit to data within Jonker et al. (2007). Resection was also incorporated within the model, with an associated survival rate and progression free survival estimated from the data of Adam et al. (2004). But it is not immediately clear how overall survival has been modelled.

Cetuximab plus FOLFIRI was estimated by the manufacturer to result in overall survival of 2.28 years compared to 1.92 years for FOLFIRI. Cetuximab plus FOLFOX4 was estimated by the manufacturer to result in overall survival of 1.89 years compared to 1.41 years for FOLFOX4.

TA212: STA of bevacizumab for mCRC: 2009[183]

The cost effectiveness of bevacizumab added to FOLFOX and added to XELOX was modelled. Parametric curves for progression free survival, the exponential, and for overall survival, the weibull, were fitted to the Kaplan Meier data of the pivotal NO16966 trial[4]. Patients were assumed to follow the Kaplan Meier curves until the median of the relevant curve had been reached, and then to follow the relevant parametric curve.

The estimates of mean progression free survival and overall survival are marked as commercial in confidence.

CG131: CG for diagnosis and management of colorectal cancer: 2011[7]

Parameterised exponential curves were fitted to data drawn from the literature, the exponential form being adopted in large part due to only median survival data being reported for a number of studies.

[4] Based upon Table 23 of the manufacturer submission. Subsequent text suggests that Weibulls may have been used for PFS.

This resulted in mean progression free survival estimates of 11.8 months for 1st line FOLFOX and 10.9 months for 1st line FOLFIRI. The mean progression free survival estimate for 2nd line FOLFOX was 3.6 months, compared to 6.1 months for FOLFIRI. Note that based upon the literature only around 60% of patients were assumed to received 2nd line treatment. The mean overall survival estimates for FOLFOX followed by FOLFIRI was 29.9 months, compared to 31.2 months for FOLFIRI followed by FOLFOX.

TA242: MTA of cetuximab, bevacizumab and panitumumab for 2nd line treatment of mCRC: 2012[180]
Due to a lack of data, the assessment group modelled cost effectiveness among patients with KRAS WT status for 3rd line treatment or beyond.

Progression free survival for BSC was modelled using a parameterised weibull curve fitted to the monthly data points of the relevant Kaplan Meier curve reported within Karapetis et al. (2008) to permit estimation of the weibull shape. This was linked to the mean progression free survival reported in the Merck submission of 2.72 months in order to estimate the scale parameter. The same approach was used to parameterise the weibull curve for overall survival, drawing upon the mean overall survival reported by Merck of 6.2 months.

A similar approach was used for cetuximab plus BSC, based upon means of 4.78 months for progression free survival and 10.0 months for overall survival as reported by Merck.

An indirect comparison for panitumumab plus BSC is undertaken by first characterising the BSC and panitumumab plus BSC area under the curves from the relevant trial, based upon monthly data points from the Kaplan Meier. This resulted in mean progression free survivals of 2.2 months for BSC and 4.0 months for panitumumab plus BSC. The Bucher method was then used in conjunction with the 2.7 months BSC survival estimate from the Merck trial to yield a mean progression free survival estimate of 5.1 months for panitumumab plus BSC. This was then used to fir a parameterised weibull curve.

A similar method was used to parameterise a weibull for overall survival for panitumumab plus BSC, though for this weibull curves were fitted to the four weekly Kaplan Meier data. This resulted in an overall survival estimate of 9.9 months for panitumumab plus BSC and of 9.4 months for BSC. A further adjustment was made to these figures for cross over within the trial. The Bucher method was then used to provide an estimate of a mean of 8.5 months overall survival for panitumumab plus BSC.

The progression free survival for cetuximab plus irinotecan is based upon the median survival estimate, adjusted for KRAS WT status. The same shape parameter as for cetuximab plus BSC is

assumed, to enable characterisation of the scale parameter and the parameterised weibull curve. A similar approach was adopted for overall survival. This resulted in a mean overall survival estimate of 16.6 months for cetuximab plus irinotecan.

Quality of life values used in previous NICE mCRC assessments

TA61: MTA of Capecitabine and Tegafur with Uracil for mCRC: 2002[181]

A cost minimisation analysis was performed due to a lack of convincing evidence of a survival difference between the oral treatments and infusional regimes used in the UK. As a consequence, HRQoL estimates were not required.

TA93: MTA of irinotecan, oxaliplatin and raltitrexed for mCRC: 2005[30]

EQ-5D data from the MRC sponsored FOCUS trial is applied. As outlined in more detail in figure 12 on page 68 of the Hind et al. (2008)[30] HTA monograph, after a slight improvement between baseline and 8 weeks, the average quality of life values applied remain reasonably steady over the period from 8 weeks to 48 weeks. HRQoL values for the various regimens of the FOCUS trial vary between 0.72 and 0.80. The mean HRQoL values across the various regimens of the FOCUS trial of 0.76 was assumed to apply to 1st line FOLFOX6 followed by 2nd line FOLFIRI and for 1st line FOLFIRI followed by FOLFOX6.

But Hind et al. caution that:

> "*...it should be noted that at the time of writing, these data had not been subject to full checking and validation, nor had the data been adjusted for the effects of either informative or uninformative censoring within the trial. Consequently, the resulting cost–utility estimates are presented as a secondary analysis and should be interpreted with caution.*"

The quality of life impacts of adverse events were not separately modelled.

TA118: MTA of bevacizumab and cetuximab for mCRC: 2006[179]

For progression free survival an HRQoL estimate of 0.80 was drawn from the Ramsay et al. (2000) study of quality of life among colorectal cancer survivors. For with progression survival a relative risk of 0.75 was applied to the progression free survival value, resulting in an HRQoL estimate of 0.60. The 0.75 was informed by the estimates of Petrou and Campbelll (1997).

The quality of life impacts of adverse events were not separately modelled.

TA176: STA of cetuximab for mCRC: 2008[182]

The Merck submission for TA176[182] calculated a HRQoL value for progression free survival under 1st line therapy based upon EQ-5D responses by UK patients collected during one of the pivotal trial. EQ-5D was collected at baseline, 8 weeks, 16 weeks, 24 weeks, 32 weeks and 48 weeks.

The submission is slightly ambiguous, but appears to suggest that the EQ-5D may only have been administered among the UK patient subset. The full analysis set consisted of 1,217 patients, while the KRAS wild -type subset Merck stated as being the relevant population subset for the assessment consisted of 348 patients.

37 UK patients completed the EQ-5D at baseline, 22 in the cetuximab + FOLFIRI arm and 17 in the FOLFIRI arm. The numbers of EQ-5D responses at 8 weeks, 16 weeks, 24 weeks, 32 weeks and 48 weeks were 26, 22, 16, 12 and 7 respectively.

The Merck submission for TA176[182] performed an odd averaging exercise that resulted in a HRQoL estimate of 0.777. A more standard weighted averaging would have resulted in a slightly higher HRQoL estimate of 0.790. This estimate may also have been slightly skewed by the one response at week 48 in the FOLFIRI arm resulting in a HRQoL of 0.090 for that patient. Arbitrarily excluding this patient results in a slightly higher weighted average for HRQoL of 0.796.

The weighted average across the 74 respondents in the cetuximab + FOLFIRI arm was 0.790. Across the 46 respondents in the FOLFIRI arm it was also 0.790. Excluding the one response at week 48 in the FOLFIRI arm with a QoL of 0.090 results in a weighted average of 0.805.

The Merck submission also modelled progression to 2nd line therapy and 3rd line therapy. For 3rd line therapy an HRQoL estimate of 0.68 was drawn from the Jonker et al. (2007) study of cetuximab for colorectal cancer. For 2nd line therapy an average of the 0.77 1st line estimate and 0.68 3rd line estimate resulted in an HRQoL estimate of 0.73.

The quality of life impacts of adverse events were not separately modelled.

TA212: STA of bevacizumab for mCRC: 2009[183]

Quality of life values were apparently mainly drawn from TA176: cetuximab for mCRC[182] as summarised above: 0.77 for 1st line progression free survival on treatment, 0.73 for 2nd line progression free survival and 0.67 for survival post progression. An additional state of 1st line

progression free survival post treatment was attributed an HRQoL estimate of 0.79. This appears to have been based upon the 0.77 for 1st line progression free survival post treatment coupled with an adjustment due to expert opinion:

> "*It was deemed that utility values in the PFS post treatment health state would be higher than that of patients receiving first-line treatment given that patients' disease is stable at this point and that they would no longer be experiencing the adverse effects of chemotherapy treatment.*"

The quality of life impacts of adverse events were not separately modelled.

CG131: CG for diagnosis and management of colorectal cancer: 2011[7]

Quality of life values of 0.510 for stable disease and 0.210 for progressive disease were drawn from the Best et al. (2010) study of stage III colon cancer.

QALY decrements for adverse events of 0.103 for grade 3/4 diarrhoea, 0.150 for febrile neutropenia and 0.116 for hand foot syndrome were drawn from the Lloyd et al. (2006) study of metastatic breast cancer.

TA242: MTA of cetuximab, bevacizumab and panitumumab for 2nd line treatment of mCRC: 2012[180]

The quality of life values applied by the EAG were based upon those supplied in the Merck submission to the assessment, with some further adjustments by the EAG. The data underlying these estimates has been published in the Mittman et al. (2009) reporting of the main clinical trial, this reporting HUI3 scores valued using the HUI3 tariff of the Canadian general population sample. The reanalysis by Merck was necessary to align the estimates with the progression free and post progression health states of the model, rather than being averages at specific time points. This resulted in HRQoL estimates of 0.81 for progression free survival and 0.79 for survival with progression in the cetuximab plus best supportive care arm, and of 0.75 for progression free survival and 0.69 for survival with progression in the best supportive care arm.

The EAG noted that these may overestimates due to patients who were less well being less likely to complete the questionnaires. The EAG also noted that it may overestimate the impact of cetuximab being added to best supportive care due to the trial not being blinded.

The EAG revised a number of values in the light of expert opinion and parsimony with other values. Progression free survival had HRQoL values of 0.75 for best supportive care, 0.81 for cetuximab plus

best supportive care, 0.75 for cetuximab plus irinotecan and 0.87 for panitumumab plus best supportive care. Post progression survival was estimated to have a HRQoL of 0.69.
The quality of life impacts of adverse events were not separately modelled.

Trueman et al. (2007) Bowel Cancer Services report to the DoH[222]
In brief, a systematic review for quality of life data was undertaken for the DoH report. This identified the following possible sources: Ko et al. (2003), Ness et al. (1999), Ramsey et al. (2000), Petrou & Campbell (1997), the MRC FOCUS trial, and the Merck MABEL trial. These sources have all been identified within the above NICE assessments.

Adverse event costs used in previous NICE mCRC assessments
TA61: MTA of Capecitabine and Tegafur with Uracil for mCRC: 2002[181]
The report notes that the toxicity profiles were similar, though capecitabine might have a slightly better profile than the Mayo regime with the exception of hand-foot syndrome. The detail of the costings is not presented. The average 28 day adverse event cost is estimated to be £131 [£183] for capecitabine, £170 [£238] for Mayo, and £29 [£41] for the modified de Gramont regimen and £22 [£31]for the inpatient de Gramont regimen.

TA93: MTA of irinotecan, oxaliplatin and raltitrexed for mCRC: 2005[30]
Adverse event costs were split into hospitalisation costs and drug costs. For the base case, the distribution of hospitalisations across specialities was drawn from the Schmitt et al. (1999) study of irinotecan with 5-FU in patients with mCRC after 5-FU failure. This was coupled with PSSRU unit cost data and an assumption of a mean length of stay of 1 day per month. This resulted in an estimate of a monthly hospitalisation cost due to adverse events of £258 [£413].

Drug costs for adverse events were estimated at £9.74 [£15.61] per month, based upon data from the Kerr et al. (1999) study of raltitrexed plus the Mayo regime in advanced colorectal cancer.

These costs were uplifted for inflation using the Health Service Inflation indices and applied to all regimes.

TA118: MTA of bevacizumab and cetuximab for mCRC: 2006[179]
Adverse event costs were split into hospitalisation costs and drug costs, with the costings relying upon the same sources as TA93.[30]

The monthly costs of hospitalisations of £258 [£413] and adverse events of £9.74 [£15.61] per month were increased by a factor of 1.13 for bevacizumab, based upon the relative risk reported in the Roche submission.
These costs were uplifted for inflation using the Health Service Inflation indices.

TA176: STA of cetuximab for mCRC: 2008[182]
Adverse events treated as outpatients are "*Estimated from the UK NHS National Tariff*"; £191 [£221] for a 2nd line outpatient visit for an adverse event, £162 [187] for an outpatient visit for a grade 3/4 adverse event and £166 [£192] for an outpatient visit for a serious adverse event[5]. Quite how these events were distinguished from one another is not clear.

Adverse events treated as inpatients are "*Based on the mapping of the types of adverse events onto the UK HRGs that can likely be assigned to them*"; £1,050 [£1,216] for inpatient treatment of a non-serious adverse event and £1,170 [£1,354] for inpatient treatment of a serious adverse event.

Unfortunately the details of the calculations are in an Appendix to the Merck submission which is not publicly available. It is also not clear what estimates were applied for the balances between outpatient treatment and inpatient treatment for the various adverse events.

TA212: STA of bevacizumab for mCRC: 2009[183]
The following treatment costs were applied to grade III/IV adverse events within the Roche submission.

Table 81. Grade III/IV adverse event costs reported in TA212[183] Roche submission

Adverse event	Unit cost		Reference / comment
Cardiac disorders	£1,201	[£1,300]	Ref costs 2006/7
Diarrhoea	£237	[£257]	LRIG 2006 Erlotinib
Febrile Neutropenia	£1,575	[£1,705]	Ref costs 2006/7
Hypertension	£200	[£217]	Palmer 2004
Infections (excl. Febrile neutropenia)	£1,077	[£1.166]	Ref costs 2006/7
Neurotoxicity	£18	[£19]	LRIG 2006 Erlotinib
Neutropenia / granulocytopenia	£140	[£152]	LRIG 2006 Erlotinib
Hand-foot syndrome	£137	[£148]	York CRD 2004, September 2004
Stomatitis	£819	[£887]	Capri et al. 2003
Venous thromboembolism	£741	[£802]	Ref costs 2006/7

[5] Note that these values are taken from table H28 of the Merck submission, which is not entirely in line with the values reported in table H30 of the Merck submission.

Vomiting / nausea	£240	[£260]	Ref costs 2006/7

Only the calculation of the reference cost related adverse events was documented within the submission, with the apparent additional assumption that all would be treated as inpatients. Those related to Palmer 2004, LRIG 2006 Erlotinib, York CRD 2004, September 2004 and Capri et al. 2003 were not documented, and the full citations were not supplied in the submission's list of references. The ERG noted in its report that it asked for details of the procedure/treatment/drugs which were included in these costs, but that none were provided by Roche.

CG131: CG for diagnosis and management of colorectal cancer: 2011[7]

The cost of £388 [£420] for grade 3/4 diarrhoea was based upon the NHS reference cost FZ45C: Short Stay Non-Elective Inpatient: Non-Malignant Large Intestinal Disorders. The cost of £6,278 [£6,797] for febrile neutropenia was based upon the PbR tariff PA45Z: Febrile Neutropenia with Malignancy. The cost of hand foot syndrome was assumed to be zero due to it typically being treated through treatment cessation and/or dose reduction.

TA242: MTA of cetuximab, bevacizumab and panitumumab for 2nd line treatment of mCRC: 2012[180]

The assessment group based their estimates of the costs of treating adverse events upon the Merck submission. Costs for adverse events of £2,760 [£2,824] for best supportive care, £3,671 [£3,757] for cetuximab plus best supportive care, £880 [£901] for panitumumab plus best supportive care, and £3,671 [3,757] for cetuximab plus irinotecan were estimated by Merck. The EAG revised the £880 [£901] for panitumumab plus best supportive care upwards to be equal to the £2,760 [£2,824] for best supportive care. This was in the light of the estimates for the rates of grade 3/4 adverse events typically being higher for panitumumab plus best supportive care than for best supportive care.

The EAG considered that Merck had performed an extensive analysis of these costs based upon their main trial, noted that they had found no logical flaw in the calculations and that the adverse event costs are very small compared to other costs.

Appendix 16. Quality of life papers and MCRC

Literature within previous mCRC NICE assessments

Best et al. (2010)[190] undertook a time trade off study among 49 Californian colorectal cancer patients and 49 members of the general US public to estimate quality of life values for stage III colorectal cancer. The method of recruitment from the general public is not clear, but efforts were apparently made to recruit respondents who were similar to the patient group. The mean age of patients was 60 years, and the mean age of respondents from the general public was 61 years. Seven health states were involved:

- Adjuvant chemotherapy, no neuropathy
- Adjuvant chemotherapy, moderate neuropathy
- Adjuvant chemotherapy, severe neuropathy
- Remission
- Metastatic stable disease
- Metastatic progressive disease

Neuropathy was included due to it being a potential side effect of oxaliplatin. The health state vignettes included descriptions of the rates and severity of both diarrhoea and fatigue, with some health states also including descriptions of vomiting and loss of weight. Both adjuvant chemotherapy and metastatic disease were associated with intravenous treatment at hospital for a few hours one or two times a fortnight. Each respondent only rated four of the above health states: remission, two of the adjuvant health states and one metastatic health state, plus their own health.

7 patients and 16 members of the general public stated a preference of zero year of perfect health to spending the rest of their life in at least one of the chronic health states. This covered 51 TTO values: 19 for metastatic progressive disease, 5 for metastatic stable disease, 11 for adjuvant chemotherapy with severe neuropathy and the other 16 spread over the other four health states. As far as can be gleaned from the paper, these 51 zero TTO values were included in the statistical analysis.

Results were presented as the raw averages and also as averages adjusted for age, education and current health status. The following table reports the raw mean TTO value, the adjusted mean TTO values, for the adjusted TTO values compared to the remission health state and the standard error of the means of the coefficients.

Table 82. TTO QoL values of Best et al. (2010)[190]

	Patient respondents				General public respondents			
	Raw	**Adj.**	**coef**	**s.e.m.**	**Raw**	**Adj.**	**coef**	**s.e.m.**
Remission	0.87	0.83			0.83	0.82		
Adjuvant, no neuropathy	0.67	0.61	-0.221	0.063	0.62	0.60	-0.223	0.054
Adjuvant, mild neuropathy	0.65	0.61	-0.224	0.075	0.52	0.51	-0.310	0.060
Adjuvant, moderate neuropathy	0.55	0.53	-0.309	0.075	0.48	0.46	-0.362	0.056
Adjuvant, severe neuropathy	0.48	0.48	-0.352	0.073	0.35	0.34	-0.475	0.060
Metastatic, stable	0.46	0.40	-0.433	0.076	0.54	0.51	-0.305	0.055
Metastatic, progressive	0.38	0.37	-0.464	0.074	0.21	0.21	-0.607	0.058
s.e.m. calculated on the basis of the coefficient divided by the reported t-statistic								

The authors noted a potential limitation in that their elicitation method did not allow for states worse than death, so potentially biasing their estimates upwards. This could also be the reason behind the quite high number of zero rated TTO values within the analysis. But there would also seem to be some concerns around the zero rated TTO values, particularly for the 16 responses spread over health states other than adjuvant chemotherapy with severe neuropathy or metastatic disease. It should also be noted that within the vignettes neuropathy was not time delimited so was assumed to last for the entire duration of the health state.

Ramsey et al. (2000)[187] undertook a survey using the FACT-C and the Health Utilities Index version III questionnaires among 173 adult US patients who had survived for a minimum of one year since being diagnosed with colorectal cancer. Suitable respondents were identified from the NCI's cancer surveillance system of western Washington State, stratified by stage. A first phase recruited 74 respondents for face to face interviews, from a pool of 450 who were contacted, to design a self-administered survey. A second phase recruited a further 193 respondents, of whom 98 completed the self-administered survey by post. The mean HUI scores (s.d.) were as below.

Table 83. Ramsey et al. (2000)[187] mean HUI index

	Time since diagnosis				
	13–24 mths	**25–36 mths**	**37–60 mths**	**> 60 mths**	**Mean**
Stage	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
I	0.72 (0.27)	0.89 (0.11)	0.90 (0.06)	0.89 (0.05)	0.84 (0.17)
II	0.85 (0.15)	0.87 (0.13)	0.79 (0.18)	0.91 (0.11)	0.86 (0.14)
III	0.82 (0.15)	0.95 (n=1)	0.79 (0.25)	0.92 (0.05)	0.85 (0.14)
IV	0.95 (n=1)	0.92 (0.04)	0.76 (0.11)	0.84 (0.13)	0.84 (0.12)
Mean	0.80 (0.20)	0.88 (0.12)	0.84 (0.14)	0.90 (0.09)	0.85 (0.15)

Respondents were also further split by whether they survived for the year subsequent to being surveyed or died during it. Of the survivors on 7% were in stage IV when surveyed, while those who died were reasonably equally split across the four stages when surveyed. Among the 161 survivors the mean HUI index was 0.85, while among the 10 who died it was 0.65 (p=0.002). Ramsey et al. conclude that the time since diagnosis is a predictor of HRQoL, the longer the survival since diagnosis the higher HRQoL tends to be among those surviving.

Petrou and Campbell[6] (1997)[188] surveyed 30 UK oncology nurses using the standard gamble. This valued partial response, stable disease and progressive disease with the median reported HRQoL values for these being 1.000, 0.950 and 0.575 respectively. Grade 3/4 adverse events were also rated. Hand-foot syndrome and an episode of febrile neutropenia were reported as not having a significant quality of life impact, with a detriment of between 0.200 and 0.250. Diarrhoea was rated as having a moderate impact upon quality of life, with a detriment of between 0.325 and 0.500. Nausea/vomiting was seen as more serious, with a detriment of between 0.550 and 0.625, while mucositis was rated as having a detriment of between 0.575 and 0.625. Petrou and Campbell noted in the discussion that the quality of life detriments from the grade 3/4 adverse events did not take into account any difference in the likely durations of the adverse events. Their main conclusion was that there was little evidence for a major difference in HRQoL between partial response and the stable disease, but clear evidence for a preference for these over the progressive disease health state.

Ness et al. (1999)[223] identified 166 US patients who had previously had colorectal adenoma removed, identified using the endoscopy clinical database of the Indiana University Medical Centre. Some could not be contacted, refused to be interviewed or did not attend, leaving 90 respondents of whom nine were excluded. The mean respondent age was 54 years, with respondents being equally split between men and women.

Seven health states were developed based upon the stage of colorectal cancer, method of treatment, presence of serious side effects and presence of ostomy. Health state vignettes were developed, splitting effects into the short term of 18 months and the long term of 30 years though terminal health states were limited to 18 months. These were valued using the standard gamble, which resulted in the following mean HRQoL values. Due to the two stage III colon cancer health states never being compared directly and the difference between them not being statistically significant (p=0.093) these were combined. This also applied to the two stage IV metastatic health states (p=0.595).

[6] Sponsored by an educational grant from Rhone-Poulenc Rorer, which apparently became a part of Sanofi-Aventis. The article also includes text boxes referring to irinotecan, which is manufactured by Pfizer.

Table 84. Ness et al. (1999)223 mean standard gamble utilities

	N	Mean (95% CI)	
Stage I rectal or stage I/II colon, resected	81	0.74 (0.69, 0.78)	0.74 (0.69, 0.78)
Stage III colon, resect+chemo, no significant AEs	40	0.70 (0.63, 0.77)	0.67 (0.62, 0.72)
Stage III colon, resect+chemo, significant AEs	41	0.63 (0.56, 0.70)	
Stage II/III rectal, resect/chemo/radio	81	0.59 (0.54, 0.64)	0.59 (0.54, 0.69)
Stage II/III rectal, resect/chemo/radio, with ostomy	81	0.50 (0.44, 0.56)	0.50 (0.44, 0.56)
Stage IV metastatic/unresectable no ostomy	41	0.24 (0.16, 0.32)	0.25 (0.20, 0.31)
Stage IV metastatic/unresectable with ostomy	40	0.27 (0.18, 0.36)	

Ko et al. (2003)[224] analysed the US nationwide 1998 National Health Interview Survey database, extracting all patients identified with melanoma, breast, colon of lung cancer. These patients had had the Health and Activities Limitation Index administered, for which there is a standard scoring algorithm for conversion to a single utility index. 169 colon cancer patients were identified of mean age 61 years and broad balance between men and women. 32 patients were within one year of diagnosis and had a mean utility of 0.67 (s.d. 0.21), 80 patients were between one year and 5 years from diagnosis and had a mean utility of 0.68 (s.d. 0.22) and 80 patients were more than 5 years since diagnosis and had a mean utility of 0.71 (s.d. 0.25).

Mittmann et al. (2009)[191] in a cost effectiveness study of adding cetuximab to best supportive care for the treatment of mCRC analysed Health Utility Index version 3 quality of life data from a publicly funded Canadian RCT. 575 patients were recruited to the trial, with HUI3 data being collected at baseline, 4 weeks, 8 weeks, 16 weeks and 24 weeks. The HRQoL values resulting from this are as below.

Table 85. Mittmann et al. (2009)190 HUI quality of life values

	Cetuximab+BSC			BSC		
	N	Mean	s.d.	N	Mean	s.d.
Baseline	263	0.72	0.23	260	0.71	0.24
Week 4	220	0.73	0.26	184	0.68	0.26
Week 8	190	0.73	0.24	149	0.66	0.28
Week 16	119	0.73	0.24	72	0.63	0.30
Week 24	82	0.77	0.22	36	0.70	0.24

CG131 Adverse events

Lloyd et al.[7] (2006)[196] surveyed 100 members of the UK general public of average age 40 years and equally split between men and women. They assessed the HRQoL of various health states associated with metastatic breast cancer using the standard gamble, with 969 observations being analysed. The method of recruitment of respondents is not clear. Respondents were not told that the health states were related to metastatic breast cancer. A mixed model where the HRQoL was equal to the exponent of the sum of the relevant coefficients divided by one plus the exponent of the sum of the relevant coefficients was applied.

Health state vignettes were developed from a rapid literature review, expert opinion, a focus group with oncology nurses. A further content validation study of the health states was conducted by interviewing three clinical oncologists. The health states were designed to describe a three week period. Two base health state vignettes were developed: one for responding metastatic breast cancer and one for stable metastatic breast cancer.

The parameter estimates of the mixed model for treatment response, treatment progression and all the adverse events were all significant at the 1% level. They resulted in the following HRQoL value for the base state of stable disease with no toxicity, and HRQoL increments and decrements.

Table 86. Lloyd et al. (2006)195 HRQoL values for metastatic breast cancer

Health state	HRQoL
Stable with no toxicity	0.715
Treatment response	+0.075
Disease progression	-0.272
Febrile neutropenia	-0.150
Diarrhoea and vomiting	-0.103
Hand-foot syndrome	-0.116
Stomatitis	-0.151
Fatigue	-0.115
Hair loss	-0.114

mCRC QoL literature review update

Farkkila et al. (2013)[192] reviewed the EQ-5D data of 580 Finnish CRC patients, a proportion of whom had metastatic disease. All patients with colorectal cancer treated at the Helsinki University Central Hospital were invited to participate by post, with non-responders receiving one reminder. The EQ-5D

[7] Employed by United Biosource Corporation. Also co-authored by J Watkins, an employee of Eli-Lilly and Company Ltd.

was scored using the UK social tariff. Local disease patients were divided into those in primary treatment, deemed to be within 6 months of diagnosis, those in rehabilitation, being 6 to 18 months from diagnosis and those in remission, being more than 18 months from diagnosis. How reasonable these categories are is open to question, particularly given the possibility of survivor bias. Advanced colorectal cancer patients were divided into the metastatic who were still receiving oncological care and those who were receiving only palliative care. This resulted in the following EQ-5D quality of life estimates.

Table 87. Farkkila et al. (2013)191 EQ-5D QoL values for colorectal cancer

	N	EQ-5D	s.e.m.	95% CI
Local disease				
Primary treatment	61	0.760	0.030	0.699-0.823
Rehabilitation	79	0.835	0.023	0.777-0.881
Remission	217	0.850	0.014	0.828-0.882
Advanced disease				
Metastatic disease	110	0.820	0.019	0.783-0.858
Palliative care	41	0.643	0.049	0.546-0.747

Odom et al.[8] (2011)[195] analysed EQ-5D data from a phase III trial of panitumumab plus best supportive care versus best supportive care among chemotherapy refractive mCRC patients (n=463). EQ-5D data was measured at baseline and monthly thereafter until disease progression. Unfortunately, this was evaluated using a US valuation of EQ-5D health states. Baseline EQ-5D scores were 0.72 (s.d. 0.24) in the panitumumab arm (n=188) and 0.68 (s.d. 0.25) in the best supportive care arm. (n=175). The changes from baseline appear to be reasonably linear, with the change at 17 weeks in the best supportive care arm being around -0.5 with a 95% confidence interval of around -0.3 to -0.7.

Shiroiwa et al. (2009)[193] in what appears to be a paper prior to that reported in greater detail in the literature review of adverse events QoL impact undertook a time trade-off study among members of the Japanese general public. This assessed the quality of life of hypothetical mCRC patients undergoing chemotherapy and with a range of grade III/IV adverse events. The number of respondents surveyed was considerably smaller than that of the paper reported in the literature review of adverse events QoL impact. This resulted in the following quality of life values being reported. Given the different quality of life scores for being treated with XELOX and with FOLFOX, it appears that the quality of life values for the adverse events were estimated in isolation from these.

[8] Funded by Amgen

Table 88. Shiroiwa et al. (2009)[193] TTO quality of life values

	N	QoL	95% CI
XELOX No AE	191	0.59	0.55-0.64
FOLFOX No AE	183	0.53	0.49-0.57
Grade III/IV AEs			
Febrile neutropenia	175	0.39	0.36-0.42
Nausea/vomiting	192	0.38	0.35-0.42
Diarrhoea	188	0.42	0.39-0.45
Hand-foot	174	0.39	0.36-0.42
Fatigue	185	0.45	0.41-0.48
Peripheral neuropathy	176	0.45	0.41-0.48
Stomatitis	202	0.42	0.39-0.45

Wang et al.[9] (2011)[194] undertook a Q-Twist analysis of data from a phase III open label trial comparing panitumumab plus best supportive care against best supportive care among patients with chemotherapy refractive mCRC. Survival in both arms was partitioned into time without symptoms of disease of a grade III/IV toxicity, time with toxicity, and relapse or disease progression. The duration of grade III/IV toxicities was recorded within the trial, with the mean duration of toxicity across all patients being 3.47 weeks in the panitumumab arm and 1.09 weeks in the best supportive care arm. EQ-5D data was collected during the trial, but unfortunately the paper does not make clear the valuation method. It resulted in the following quality of life values.

Table 89. Wang et al. (2011)[194] EQ-5D quality of life values for 2nd line chemotherapy for mCRC

	Panitumumab (n=124)		BSC (n=119)	
	N	EQ-5D	N	EQ-5D
No symptoms or toxicity	104	0.768	103	0.663
Toxicity: Grade III/IV AE	37	0.601	13	0.441
Relapse/progression	68	0.632	63	0.641

[9] Funded by Amgen

Appendix 17. MCRC UK resource use literature review

Beard et al. (2000)[225] undertook a cost effectiveness of resection for liver metastases compared with standard nonsurgical chemotherapy among mCRC patients. 100 liver resections performed at the Royal Hallamshire Hospital between 1997 and 1999 were analysed. A mean operating time of 3.5 hours was recorded, coupled with a mean length of stay of 10.3 days. The average cost per resection was estimated to be £6,742 [£10,334]. The average cost of chemotherapy was estimated as £2,223 [£3,408] per month.

Cassidy et al. (2006)[226] undertook a cost effectiveness analysis of capecitabine compared to 5-FU plus folinic acid based upon the X-ACT trial. The drug use for adverse events was recorded, with the text noting capecitabine reducing the use of fluconazole for stomatis, 5-HT3 antagonists for nausea/vomiting and cytokines for vomiting. But individual costs per event are unfortunately not given. Note that they also drew quality of life values of 0.86 for stable disease, 0.86 for when undergoing chemotherapy and 0.59 for progressive disease from Ramsey et al. (2000).

Cunningham et al. (2002)[227] undertook a cost effectiveness analysis of adding irinotecan for 5-FU/FA among mCRC patients. A cost per disposable pump inclusive of disposables and pharmacist time of £62 [£87] was estimated. Total adverse events costs in the FOLFIRI arm were estimated to be £1,480 [£2,072] compared to £1,147 [£1,606] in the 5-FU/FA arm. Unfortunately, no breakdown of costs by adverse event was given.

Hale et al. (2002)[92] undertook an analysis of the costs of the de Gramont, the Lokich and raltitrexed chemotherapy among a subsample of 68 patients taking part in an MRC funded chemothrerapy trial among 905 mCRC patients. Costs were not sufficiently disaggregated to be useful for current purposes, with the possible exception of primary care costs. The 12 week costs of care for the de Gramong, Lokich and raltitrexed were £2,672 [£4,282], £983 [£1,575], and £1,305 [£2,091] for chemotherapy, £1,699 [£2,722], £666 [£1,067] and £814 [£1,304] for hospitalisations and £114 [£182], £126 [201] and £152 [£244] for primary care. Societal costs of £914 [£1,465], £762 [£1,221] and £404 [£647] were also estimated, these being mainly composed of carer time.

Hoyle et al. (2013)[228] undertook a cost effectiveness analysis of cetuximab in conjunction compared to among other things panitumumab. Little by way of resource use is provided, other than to note that progression free survival was assumed to require a consultant visit every two weeks.

Iveson et al. (1999)[205] analysed the data from a clinical trial of irinotecan versus infusional 5-FU to estimate their relative cost effectiveness. Line insertion was estimated to cost £250 [£423], while disposable pumps inclusive of pharmacist time was costed at £62 [£105]. Unplanned hospitalisations were recorded during the trial and were costed using 1996/97 NHS reference costs. Total costs appear to relate to the patient survival though this is not entirely clear: a median of 10.8 months in the irinotecan arm and 8.5 months across the 5-FU arms. Hospitalisations were costed at £2,810 [£4,763] for the irinotecan arm and £3,416 [£5,788] for the 5-FU arms. Hospital consultations were costed at £357 [£605] and £393 [£666], GP visits £23 [£39] and £13 [£22], district nurse visits £39 [£65] and £23 [£39] and tests £19 [£32] and £8 [£13].

Starling et al. (2007)[229] undertook a cost effectiveness analysis of cetuximab/irinotecan compared to best supportive care for the treatment of mCRC among patients having failed previous chemotherapy. The data was apparently trial based, with the data for best supportive care coming from 43 eligible patients who were not enrolled due to recruitment having been completed. Ignoring the chemotherapy drug and administration costs for cetuximab/irinotecan, these patients incurred an additional £59.70 [£69.09] per week treatment costs while on chemotherapy. The average weekly cost when not on therapy was £50.00 [£57.87], the same as that for other costs incurred in the best supportive care arm whether receiving chemotherapy or not. Of the 31% of best supportive care patients who received additional palliative chemotherapy, the mean drug cost was £5,327 [£6,165] and the mean administration cost £1,482 [£1,715]. Startling et al. note that the mean survival in the best supportive care arm was 5.2 months but it is unclear what proportion of this time the best supportive care patients received palliative chemotherapy.

Appendix 18. Previous NICE assessments in head and neck

As in Appendix 15, the following reviews the previous NICE assessments in head and neck cancer, examining:

- The approach to estimating chemotherapy administration costs for infusion regimes
- The approach to modelling the duration of treatment
- The approach to modelling survival
- Quality of life values for disease states and adverse events
- The costs of adverse events

Chemotherapy administration costs for infusion regimes

TA145: cetuximab for locally advanced squamous head and neck cancer[214]

The intravenous infusion of cetuximab was apparently costed as a medical oncology outpatient visit using NHS reference costs: £178.66 for the initial visit and £124.66 thereafter. The ERG noted the intravenous infusion administration cost, but did not particularly comment upon it.

TA172: cetuximab for recurrent and/or metastatic squamous head and neck cancer[230]

A weighted average of inpatient and outpatient administration was drawn from Hopper et al. (2004).[231] These were costed using the NHS 2007-08 tariff for X99OST: solid tumour cancer chemotherapy: all drugs at £296.00, and the NHS reference costs 2004 for a medical oncology outpatient visit of £124.66.

The approach to modelling the duration of treatment

TA145: cetuximab for locally advanced squamous head and neck cancer[214]

The cost of radiotherapy and cetuximab was drawn from individual patient data in the pivotal trial. Three radiotherapy regimens were possible, with cetuximab being added to these. The maximum duration of treatment was eight weeks.

TA172: cetuximab for recurrent and/or metastatic squamous head and neck cancer[230]

The cost of cetuximab was drawn from individual patient data in the pivotal trial. The pivotal trial permitted up to six 21 day cycles of therapy. Some of the regimen drugs could be withdrawn if not tolerated. Study treatment was discontinued early if there was unacceptable toxicity or progressive disease.

The approach to modelling survival

TA145: cetuximab for locally advanced squamous head and neck cancer[214]

For those deemed to be cured, UK life tables coupled with a proportionate hazard of 2.786 were used to model mortality. For the remainder, progression free survival and overall survival was modelled by fitting log-normal parametric curves to the Kaplan Meier data.

The ERG comments upon the modelling of survival appeared to mainly be with its treatment in the probabilistic modelling, the large uncertainty around the extrapolated survival not be reflected within this and the probabilistic results.

TA172: cetuximab for recurrent and/or metastatic squamous head and neck cancer[230]

Parameterised weibull curves were fitted to the trial Kaplan Meier data for progression free survival and overall survival.

Quality of life values for disease states and adverse events

TA145: cetuximab for locally advanced squamous head and neck cancer[214]

The manufacturer commissioned a utility valuation study from M-TAG Ltd. This aimed to estimate utility values for a series of health states describing a range of side effects and post-treatment outcomes among patients with locally advanced squamous cell head and neck cancer. A literature search identified how the adverse event profiles changed with the addition of cetuximab to radiotherapy. This informed the choice of adverse events that should be included in the study:

- Stomatis/mucus membrane disorders
- Nausea/vomiting
- Haematological toxicities
- Rash/acne
- Late onset peripheral neuropathy
- Late onset ototoxicity

Seven health states were used to describe different toxicity grades, based upon the National Cancer Institute Common Toxicity Criteria. Two further health states described the late toxicities of peripheral neuropathy and ototoxicity, and a further two health states described the final outcomes of treatment success and treatment failure.

50 UK oncology nurses were recruited for the study, as it was thought unethical to recruit patients. These were screened before being accepted into the study in order to ensure they were familiar with the area, having:

- a minimum of two years working as an oncology nurse;
- a minimum of 11 patients in clinic with locally advanced squamous cell head and neck cancer in the last three months; and,
- experience in treating patients with radiotherapy, chemotherapy or concomitant chemoradiation therapy.

They rated the eleven health states using the EQ-5D and the EQ-5D VAS, and also ranked the various health states from one to eleven. This resulted in the following utility estimates.

Table 90. TA145213 EQ-5D Nurse estimates of QoL for head and neck

		Mean (s.d.)		
State	**Description**	**EQ-5D**	**EQ-5D VAS**	**Rank**
A	On treatment, range of AEs <= 1	0.659 (0.131)	73.5 (17.14)	2.6 (1.57)
B	A plus mucositis 3 / 4	0.062 (0.299)	23.5 (17.17)	8.8 (1.85)
C	A plus mucositis 2	0.608 (0.310)	52.3 (16.55)	5 (1.52)
D	A plus nausea 3 / 4	0.108 (0.350)	30.7 (16.72)	8 (1.71)
E	A plus nausea 2	0.573 (0.247)	55.1 (17.37)	4.6 (1.56)
F	A plus acne/rash 3 or 4	0.226 (0.404)	40.2 (20.11)	7.3 (1.7)
G	A plus haematological 4	0.101 (0.392)	30.7 (19.17)	8.2 (1.96)
H	Post treatment peripheral neuropathy	0.473 (0.266)	57 (14.43)	4.9 (2.10)
I	Post treatment ototoxicity	0.657 (0.239)	60.9 (17.63)	4.2 (2.38)
J	Post treatment loco regional control	0.862 (0.019)	82.6 (15.23)	1.8 (1.94)
K	Post treatment progressive disease[10]	0.129 (0.266)	10.8 (11.81)	10.5 (1.13)

These values needed to be coupled with the mean times in the health states. For treatment duration as defined by the acute phase this was differentiated by arm. For the adverse events for health states B through to G these were calculated based upon the average time spent with the adverse event pooled across the arms. To do this, health states B to G were ordered according to the ranking of the utility study. For patients experiencing more than one of the health states B to G, the QALY impact of the adverse events was determined by the mean EQ-5D utility for the worst health state experienced multiplied by the mean duration of the adverse event during the pivotal trial. The submission is not quite clear about how the mean durations of the adverse events were calculated, but it appears to be across all events observed during the trial without any similar ranking for multiple events being

[10] Note that Table 1 of the executive summary of the M-TAG report gives the EQ-5D values for this health state as 0.284 (0.040). The values given here are those of table 5 of the M-TAG report, as replicated in table 10 of the manufacturer technical appendix 1.

applied. The ERG report in its assessment of the costing of adverse events further suggests that overlapping adverse events were ignored in the calculation of the mean durations of adverse events.

Table 91. TA145213 adverse event QALY decrements

		EQ-5D		Duration	QALY
State	**Description**	**Mean**	**Decrement**	**Days**	**Decrement**
A	On treatment, range of AEs <= 1	0.659			
B	A plus mucositis 3 / 4	0.062	0.597	55.43	0.0907
C	A plus mucositis 2	0.608	0.051	34.46	0.0048
D	A plus nausea 3 / 4	0.108	0.551	13.14	0.0198
E	A plus nausea 2	0.573	0.086	29.82	0.0070
F	A plus acne/rash 3 or 4	0.226	0.433	72.92	0.0865
G	A plus haematological 4	0.101	0.558	44.32	0.0678

The ERG noted that given the absence of other studies for locally advanced squamous cell carcinoma of the head and neck, the nurses were reasonable patient proxies given their experience. The ERG also noted that not taking into account multiple adverse events could have tended to lessen the estimated impact of adverse events within the modelling, though it is not clear whether this is a criticism of the estimated utilities and QALY losses for the given health states per se. The ERG also noted that censoring could have tended to reduce the estimated duration of adverse events and so their estimated QALY impact.

TA172: cetuximab for recurrent and/or metastatic squamous head and neck cancer[230]

Individual patient EORTC QLQ-C30 data were mapped onto EQ-5D scores using the algorithm developed by Kind et al. (2005)[219] study among pancreatic cancer patients where:

$$HRQoL = 0.633 + 0.047 * Q29 - 0.124 * Q3 - 0.167 * Q5 - 0.102 * Q20 - 0.082 * Q26$$

This resulted in HRQoL values of 0.69 for stable/response with cetuximab, 0.65 for stable/response with standard treatment and 0.52 for progressive disease. Unfortunately, the detail of this is given in an Appendix to the submission that is not publicly available. Quality of life values for adverse events were not separately calculated.

The ERG noted the uncertainty inherent in the mapping function, and the lack of any statistically significant difference for health states between the arms. The ERG also noted that adverse events had not been explicitly considered, and also that these would not have been captured within the mapping function of Kind et al. (2005).[219] It felt that some elements of the mapping function for EORTC QLQ-C30 in lung cancer of Baghust et al. (2001)[232] could have proxied for those elements not within Kind et al. (2005).[219]

The cost of adverse events

TA145: cetuximab for locally advanced squamous head and neck cancer[214]

Some adverse events were grouped into a single category for costing purposes: mucositis/stomatitis/dysphagia, acne/rash and nausea/vomiting. An expert panel was convened to estimate the proportion of adverse events that would result in a hospital admission, and the medication that would be administered for both those who were and were not admitted. NHS reference costs were applied to the proportion that were assumed to be admitted, these costs being assumed to cover all relevant procedures. Thrombocytopenia was associated with the cost of a platelet transfusion, the estimate for this being drawn from Varney et al. (2003).[233] Medication costs were conditioned by the duration of events as estimated from trial data, and described in greater detail in the section on quality of life above. No primary care costs were included presumably due to it being assumed that ongoing routine hospital follow-up identified and prescribed medication for the adverse events.

An ERG expert suggested that the grouping of adverse events for costing purposes into mucositis/stomatitis/dysphagia, acne/rash and nausea/vomiting was reasonable. The ERG also noted the possibility of bias arising from censored data and questioned the elimination of overlapping adverse events from the analysis in order to estimate the mean durations of individual adverse events.

TA172: cetuximab for recurrent and/or metastatic squamous head and neck cancer[230]

The adverse event costs as estimated in TA145[214] were applied.

Table 92. TA145213 and TA172230 adverse event costs

Adverse event	Grade	Medication	Cost	Admit	HRG for NELIP	Cost	Total
Mucositis/stomatitis/dysphagia	2	Anti-fungal mouth rinse	£4.01	5%	C37 – Complex major head, neck or ear diagnoses: no compl.	£1,818	£95
Mucositis/stomatitis/dysphagia	3	Anti-fungal mouth rinse	£4.01	10%	C36 – Complex major head, neck or ear diagnoses with compl.	£3,036	£308
Mucositis/stomatitis/dysphagia	4	n.a. as 100% admitted		100%	C36 – Complex major head, neck or ear diagnoses with compl.	£3,036	£3,036
Nausea/vomiting	2	Anti-emetics	£4.86	10%	F47 – General abdominal disorders no compl.	£702	£75
Nausea/vomiting	3	Anti-emetics	£4.86	30%	F46 – General abdominal disorders with compl.	£1,099	£335
Nausea/vomiting	4	n.a. as 100% admitted		100%	F46 – General abdominal disorders with compl.	£1,099	£1,099
Weight loss	3 or 4	None		0%	n.a.	n.a.	£0
Dry mouth	3 or 4	None		0%	n.a.	n.a.	£0
Fatigue	3 or 4	None		0%	n.a.	n.a.	£0
Dehydration	3 or 4	n.a. as 100% admitted		100%	K09 – Disorders of nutrition	£1,519	£1,519
Acne/rash	3 or 4	Top./oral anti-bacterial	£21.24	0%	n.a.	n.a.	£42
Thrombocytopenia	3 or 4	Platelet transfusion	£84.22	0%	n.a.	n.a.	£84
Febrile neutropenia	3 or 4	n.a. as 100% admitted		100%	P23 – Blood cell disorders	£1,337	£1,337
Leukopenia	3 or 4	None		0%	n.a.	n.a.	£0
Anaemia	3 or 4	n.a. as 100% admitted		100%	S06 – Red blood cell disorders without compl.	£930	£930
Fever/Infection	3 or 4	Anti-pyretic		50%	P05 – Major infections	£2,207	£1,103

Appendix 19. Head and neck other QoL literature review

Gerson et al. (2007)[234] surveyed 130 US patients with Barrett's oesophagus using the time trade off. Few of the health states were relevant to the current assessment. But patients were asked to value oesophageal cancer using the time trade off, and reported a mean value of 0.67 (s.d. 0.19).

Llewellyn-Thomas et al. (1993)[235] surveyed 66 US patients with cancer of the larynx using the time trade off prior to a four week course of radiotherapy. The majority were stage I/II with only a third being stage III/IV. Three hypothetical health states were developed as outlined below.

Table 93. Llewellyn-Thomas et al. (1993)[235] health states laryngeal cancer

Severity	Mouth/throat pain	Usual activities	Talking
Low	None	Enough energy	As usual
Moderate	Moderate	Fatigue reduced	Minimally
Severe	Severe	Fatigue stopped	None

Subsequent to treatment patients were asked to rate their own health state as being closest to either low, moderate or severe and again asked to rate the health states using the time trade off. This resulted in the following mean time trade off values and standard deviations, where pre is pre-treatment and post is post treatment.

Table 94. Llewellyn-Thomas et al. (1993)[235] TTO QoL for laryngeal cancer

	Outcome group post treatment			
	Mild (n=24)	Moderate (n=36)	Severe (n=6)	Pooled
Mild				
Pre-treatment	0.721 (0.262)	0.750 (0.199)	0.750 (0.241)	0.739
Post-treatment	0.735 (0.235)	0.757 (0.190)	0.866 (0.075)	0.759
Moderate				
Pre-treatment	0.629 (0.269)	0.644 (0.229)	0.700 (0.270)	0.644
Post-treatment	0.571 (0.264)	0.667 (0.218)	0.758 (0.150)	0.640
Severe				
Pre-treatment	0.352 (0.283)	0.344 (0.253)	0.233 (0.227)	0.337
Post-treatment	0.429 (0.292)	0.381 (0.267)	0.408 (0.390)	0.401

Somewhat to the authors' surprise, they concluded that patients' valuations of health states remained reasonably consistent through time.

McNamee et al. (2004)[236] surveyed 56 UK patients who had received curative treatment for oesophageal cancer. These were surveyed using both the standard gamble and the time trade off, with 28 patients being randomly allocated to each assessment mechanism. Five health states were developed, as outlined below.

Table 95. McNamee et al. (2004)[236] health states for oesophageal cancer

	Solid foods	Usual Eating	Usual activities	Symptoms
HS1	Fine	Usual	No problems	1 of pain, short breath
HS2	Difficult	Less	Some	1+ of pain, short breath, vomiting
HS3	None	A lot less	Frequent problems	2+ of pain, short breath, vomiting, sore muscles, taste loss, bad breath
HS4	Liquid diet	Little	Lot of problems	3+ of pain, short breath, vomiting, sore muscles, taste loss, bad breath
HS5	..	None	None	4+ of pain, short breath, vomiting, sore muscles, taste loss, bad breath + others

McNamee et al. (2004)[236] also defined three possible treatments, with patients experiencing frequent problems carrying out their usual activities across all three treatments. The first involved one trip to hospital, a stay of two nights and moderate pain for a few days after treatment; the second involved one trip to the hospital without admission and having moderate pain for two weeks after treatment; and, the third involved making two or three trips to hospital with each involving a night's stay and each having mild pain for a few days after each treatment.

The quality of life values that resulted are as below.

Table 96. McNamee et al. (2004)[236] TTO and SG QoL for oesophageal cancer

	TTO mean (95% CI)	SG mean (95% CI)
HS1	0.66 (0.50,0.81)	0.78 (0.66,0.89)
HS2	0.45 (0.31,0.60)	0.49 (0.35,0.63)
HS3	0.35 (0.21,0.50)	0.27 (0.15,0.40)
HS4	0.25 (0.13,0.38)	0.20 (0.08,0.31)
HS5	0.08 (0.00,0.17)	0.08 (0.00,0.17)
Treatment 1	0.64 (0.50,0.78)	0.60 (0.47,0.74)
Treatment 2	0.54 (0.40,0.69)	0.61 (0.48,0.74)
Treatment 3	0.62 (0.50,0.76)	0.59 (0.45,0.74)

While there were some differences in the mean quality of life values reported using the standard gamble compared to the time trade off, none were statistically significant.

Ringash et al. (2000)[237] surveys 114 Canadian larynx cancer patients who had been treated with radiotherapy with the previous six months using the time trade off. Most (83%) were stage I/II. Of the 114 patents 2 did not complete the time trade off. A further 18 patients were excluded for not preferring perfect health. Among the remaining 84 patients the mean quality of life was estimated to be 0.878, with a standard deviation of 0.174.

Rogers et al. (2006)[238] surveyed 348 US oral/oropharyngeal cancer patients who had previously been treated by primary surgery using the EQ-5D. 224 patients returned evaluable forms, with the EQ-5D being evaluated using the UK social tariff. The mean quality of life was 0.75, with a standard error of 0.02.

Shenfine et al. (2009)[239] apparently applied the EQ-5D among 215 UK patients with inoperable oesophageal cancer during a trial of palliative therapies. There is mention of the UK social tariff, with the reported EQ-5D values range between 6.82 and 8.04 so appear to be of little use.

Stalmeier et al. (2005)[240] surveyed 45 Dutch oesophageal patients six months after surgery for their tumour using both the VAS and the standard gamble. No details of the stage of patients are given within the paper. Seven health states were developed, all reflecting differing degree of recovery after surgery for oesophageal cancer.

Table 97. Stalmeier et al. (2005)[240] health states for oesophageal cancer

	Eating	Weight loss	Usual activities	Tired	Walking	Pain	Other
2 recurrence-free at home	Small meals	..	..	A little	..	..	..
3 recovery at home	Difficult	Some	Not much	Yes	..	Slight	..
4 in hospital	..	..	..	..	No	..	Dependent
5 in hospital with pneumonia	..	..	..	..	..	..	Dependent
6 recurrence in neoesophagus	Difficult	Not hungry	..	Yes	..	..	Depressed
7 skeletal metastases	..	Not hungry	..	Yes	..	Yes	Depressed
8 unresectable primary tumor	Difficult	Not hungry	..	Yes	..	..	Depressed

This resulted in the following utility values.

Table 98. Stalmeier et al. (2005)[240] VAS and SG QoL values for oesophageal cancer

	Rank	VAS		Standard Gamble	
Health State	Mean	Mean	s.d.	Mean	s.d.
1 own health	2.30	0.77	0.14	0.97	0.06
2 recurrence-free	2.98	0.77	0.11	0.96	0.07
3 recovery at home	4.47	0.55	0.19	0.92	0.15
4 in hospital	4.60	0.54	0.17	0.90	0.15
5 in hospital with pneumonia	5.84	0.39	0.16	0.82	0.25
6 recurrence in neoesophagus	7.60	0.18	0.13	0.41	0.31
7 skeletal metastases	8.22	0.16	0.13	0.35	0.30
8 unresectable primary tumor	8.33	0.11	0.10	0.34	0.31

Wildi et al. (2004)[241] surveyed 50 US patients with oesophegal cancer using the time-trade of, the visual analogue scale and the EQ-5D. It appears that the EQ-5D was converted to utilities using the US mapping. All patients were staged using spiral CT scans and endoscopic ultrasound. The following HRQoL values by SEER stage were derived.

Table 99. Wildi et al. (2004)[241] VAS, TTO and EQ-5D QoL values for oesophageal cancer

		VAS		TTO		EQ-5D	
Stage	N	Mean	s.d.	Mean	s.d.	Mean	s.d.
0	3	0.83	0.18	0.99	0.00	0.93	0.12
1	11	0.56	0.14	0.80	0.30	0.60	0.29
2	24	0.57	0.19	0.54	0.39	0.71	0.21
3	12	0.58	0.21	0.52	0.31	0.69	0.35

Appendix 20. Head and neck other UK resource use literature review

Coyle and Drummond (1997)[242] undertook a costing analysis of data from two distinct but concurrent trials comparing conventional radiotherapy with continuous hyper-fractionated accelerated radiotherapy (CHART). These recruited patients from 10 UK centres and 3 European centres, with 212 head and neck patients receiving conventional radiotherapy and 314 head and neck patients receiving CHART. The head and neck patients were roughly equally split between TI/II and TIII/IV, but the majority (68%) were N0. A societal costing perspective was adopted, though the non NHS-PSS costs appear to be limited to patient travel costs and MacMillan nurse support.

For the head and neck patients conventional treatment was given 5 days per week to the large volume (44Gy in 22 fractions) and then to the small volume (22 Gy in 11 fractions) resulting in a treatment over 33 days or 6.5 weeks. CHART saw radiotherapy given three times on each of 12 consecutive days, including the weekend with an interval of at least 6 hours between each administration. The large volume received a total dose of 37.5 Gy in 25 fractions and the small volume 16.5 Gy in 11 fractions. This resulted in the following resource use estimates.

Table 100. Coyle et al. (1997)[242] radiotherapy resource use

		CHART		Conventional	
Hospital days					
	Ward	20.6	(15.4)	12.3	(19.7)
	Hostel	2.3	(5.0)	1.6	(7.0)
	Total	22.8	(13.9)	13.8	(20.2)
Radiotherapy treatments					
	Before normal working hours	6.8	(4.6)	0.0	(0.0)
	During normal working hours	13.2	(5.0)	33.0	(0.3)
	After normal working hours	9.8	(1.4)	0.0	(0.1)
	Weekends	6.1	(1.1)	0.0	(0.2)
	Total	35.8	(2.3)	33.0	(0.3)
Hospital outpatient appointments		1.7	(1.4)	1.5	(1.3)
GP consultations		1.5	(1.8)	1.3	(2.9)
Other community service consultations		4.9	(14.4)	5.4	(21.9)
Miles travelled for treatment		42.6	(52.3)	795.1	(801.0)

Which in turn resulted in the following cost estimates.

Table 101. Coyle et al. (1997)[242] radiotherapy costs

	Radiotherapy		Other hospital		Total hospital		Community		Patient	
CHART	£1171	[£2120]	£2153	[£3898]	£3325	[£6017]	£84	[£152]	£6	[£11]
s.d.	£407	[£736]	£1492	[£2701]	£1633	[£2956]	£196	[£354]	£12	[£22]
Conventional	£587	[£1062]	£1557	[£2818]	£2144	[£3881]	£93	[£169]	£85	[£154]
s.d.	£120	[£217]	£2045	[£3702]	£2041	[£3695]	£395	[£714]	£129	[£233]

The large standard deviations for the societal elements suggest highly skewed data.

Farndon et al. (1998)[243] report the median NHS costs of treatment per month of survival over a three year period among 132 UK oesophageal cancer patients, mainly seeking to compare resection with palliation costs. After three years around 36% of the resection patients survived, compared to none in the palliation group. Few details of the costing are presented, with the median costs being estimates £8070 [£13,444] for resection compared to palliation costs of radiotherapy of £4720 [£7,863], brachytherapy of £1790 [£2,982], laser of £3540 [£5,897], intubation of £2450 [£4,081] and no treatment of £1390 [£2,315]. After the initial treatment costs, the costs per remaining month of survival were more similar being £457 [£761] for resection compared to between £342 [£569] and £1125 [£1,874] for palliation.

Hopper et al.[11] (2004)[231] in a cost effectiveness analysis of Foscan photodynamic therapy compared to palliative chemotherapy for advanced head and neck cancer estimated a cost for four cycles of palliative chemotherapy of £9,924 [£13,425].

Kim et al. (2011)[43] undertook a retrospective data analysis of the inpatient and outpatient records of 11,403 UK patients with resected squamous cell carcinoma of the head and neck, accessed through the Health Episode Statistics. Among survivors the mean costs per year rapidly declined after the first year and continued to decline thereafter as shown below.

[11] Funded by Biolitec Pharma

Table 102. Kim et al. (2011)[43] postoperative annual costs for UK SCCHN patients

	Year 1		Year 2		Year 3		Year 4		Year 5	
N	11,403		9,697		8,433		7,774		7,399	
2nd Surgery	£208	[£217]	£45	[£47]	£27	[£28]	£29	[£30]	£19	[£20]
Recon, surgery	£2,275	[£2,377]	£85	[£89]	£49	[£51]	£55	[£57]	£38	[£40]
Radiotherapy	£187	[£195]	£4	[£4]	£6	[£6]	£1	[£1]	£2	[£2]
Chemotherapy	£67	[£70]	£17	[£18]	£10	[£10]	£11	[£11]	£8	[£8]
AE	£144	[£150]	£23	[£24]	£13	[£14]	£7	[£7]	£5	[£5]
Inpatient stay	£16,448	[£17,185]	£1,050	[£1,097]	£536	[£560]	£378	[£395]	£230	[£240]
Total inpatient	£19,330	[£20,196]	£1,224	[£1,279]	£641	[£670]	£482	[£504]	£302	[£316]
Outpatient visits	£414	[£433]	£249	[£260]	£198	[£207]	£163	[£170]	£143	[£149]
Radiotherapy	£34	[£36]	£4	[£4]	£7	[£7]	£5	[£5]	£8	[£8]
Chemotherapy	£1	[£1]	£0	[£0]	£1	[£1]	£3	[£3]	£3	[£3]
Total outpatient	£448	[£468]	£254	[£265]	£206	[£215]	£172	[£180]	£153	[£160]
Total cost	£19,778	[£20,664]	£1,477	[£1,543]	£847	[£885]	£653	[£682]	£455	[£475]

Parthan et al.[12] (2009)[244] in a cost effectiveness analysis of docetaxel for induction chemotherapy prior to chemo-radiotherapy among patients with locally advances squamous cell carcinoma of the head and neck provide resource use estimates for both the induction phase and the chemo-radiotherapy phase as below, coupled with resource use for surgery and for long-term follow-up to death.

Table 103. Parthan et al. (2009)[244] resource use for locally advance SCCHN

	Induction	Chemoradiation	Surgery	Follow-up
Number of 3 wk cycles	3.00	2.00	1.00	..
Inpatient days (med onc.)	4.00 (3.20–4.80)	6.00 (4.80–7.20)	..	..
Surgery	..	..	1.00	..
ICU stay [days]	..	4.00 (3.20–4.80)	1.00 (.80–1.20)	..
Inpatient (surgical)	..	..	20.00 (16.00–24.00)	..
Consultant oncologist [h]	1.00 (.80–1.20)	..	..	..
Chemotherapy nurse [h]	5.00 (4.00–6.00)	2.00 (1.60–2.40)	..	..
Clinical nurse specialist [h]	0.50 (.40–.60)	0.50 (.40–.60)	3.30 (2.64–3.96)	0.35 (.28–.42)
Radiologist [h]	..	0.50 (.40–.60)	..	..
Blood test [test]	1.00 (.80–1.20)	1.00 (.80–1.20)	1.00 (.80–1.20)	..
Biochemistry [test]	1.00 (.80–1.20)	1.00 (.80–1.20)	..	..
CT scan [test]	0.50 (.40–.60)	1.00 (.80–1.20)	..	..
Endoscopy [test]	0.50 (.40–.60)	1.00 (.80–1.20)	..	..
Dietician [h]	1.25 (1.00–1.50)	2.00 (1.60–2.40)	6.00 (4.80–7.20)	0.43 (.34–.52)

[12] Funded by Sanofi-Aventis

Speech therapy	1.75 (1.40–2.10)	0.50 (.40–.60)	2.50 (2.00–3.00)	0.69 (.55–.83)
Surgery-related outpatient	..	..	1.00 (.80–1.20)	..

An estimate for palliative chemotherapy of £11,058 [£11,973] is also given.

Appendix 21. Adverse events and resource use

Buxton & O'Brien[13] (1992) in an economic evaluation of ondansteron note that "*No empirical data exists on the costs of emetic episodes*". As a consequence, they estimate a cost per "significant" episode of £30 [£] based upon 2 hours of nursing time, 20 minutes of junior doctor time and a 10% probability of requiring a day's stay, plus some additional disposables. This appears to be a cost estimate for an inpatient.

Flynn et al.[14] (1999)[245] analysed trial data from 29 patients receiving G-CSF plus amphotericin B and 30 patients receiving amphotericin B for neutropenia with suspected deep seated fungal infection. Case note review provide resource use estimates, an average LoS of 9.4 days for G-CSF patients and 14.6 days for non-G-CSF patients being recorded. Inpatient days were costed at £273 [£437], which with other costs resulted in a total costs of £11,247 [£18,023] for G-CSF patients and of £14,317 [£22,943] for non-G-CSF patients.

Leese et al.[15] (1994)[210] analysed the cost of treating febrile neutropenia with malignant blood disorders. Febrile neutropenia is defined as a neutrophil count of less than $1.5x10^9$/L, and Leese et al. note that the standard treatment is hospitalisation and antibiotic therapy. Leese et al. collected data from patients admitted to a district general hospital with febrile neutropenia, or who developed febrile neutropenia while receiving inpatient chemotherapy. Only patients with haematological disorders were included; there were no patients with solid tumours. Patients were required to have a neutrophil count of less than $1.5x10^9$/L and sustained pyrexial illness in excess of 37.5^oC. 46 episodes of febrile neutropenia were recorded among 27 patients. The average length of stay was 17 days. There was also some use of ITU which further increased costs. Mean test costs were £400 [£725], mean drug costs were £631 [£1,143], mean inpatient costs were £1413 [£2,559], resulting in a total mean cost of £2,445 [£4,428].

Leese (1993)[209] surveyed six oncologists from six English hospitals to estimate the cost of treating febrile neutropenia in patients with solid tumours. Mean lengths of stay of 6.3 days in routine care were estimated, with 2.2% of patients requiring critical care of 5.3 days, these ranging in cost between £640 to £1317, with a mean cost of £960 [£1,738]. Drug and pharmacy ranged between £161 [£292] and £489 [£886], averaging £297 [£538]. Diagnostic tests added a further £210 [£380]. This resulted in a total cost estimate ranging between £1,049 and £1,993, with a mean of £1,542 [£2,793].

[13] Funded by Glaxo holdings
[14] Funded by Amgen
[15] Funded by Amgen Roche

Schlenz et al. (2012)[246] undertook a prospective observational study at the regional cancer centre of the Norfolk and Norwich University Hospital. All adult patients admitted with febrile neutropenia during 2007 were identified. A cost per patient was estimated based upon their length of stay and their probable use of antibiotics and G-CSF based upon defined daily doses. 32 patients were identified all of whom had had prior chemotherapy, with 7 patients receiving G-CSF. Unfortunately, average lengths of stay are not given, but an average hospitalisation cost of £2,159 [£2,499] is estimated. Antibiotics added a further £194 [£225] to take the total to £2353 [£2,723], while among those receiving G-CSF this added a further £189 to take the total to £2542 [£2,942].

Twelves et al. (2001)[201] present a range of resource use data from a phase III trial of capecitabine versus 5-FU/FA for advanced or metastatic CRC. Patients were recruited from 59 countries which may lessen the relevance of the resource use data to the UK setting, but hospital lengths of stay for adverse events were as reported below. The Twelves data also suggests that multiple hospitalisations for adverse events did not occur.

Table 104. Twelves et al. (2001)[201] hospital admissions for AEs and mean LoS per AE

	Capecitabine (n=297)				5-FU/FA (n=299)				Pooled (n=596)			
	Patients	Admissions	Total Days	Mean LoS	Patients	Admissions	Total Days	Mean LoS	Patients	Admissions	Total Days	Mean LoS
Dehydration	5	5	50	10.0	0	0	0	..	5	5	50	10.0
Diarrhoea	13	13	112	8.6	14	14	106	7.6	27	27	218	8.1
Hand-foot syndrome	2	2	3	1.5	0	0	0	..	2	2	3	1.5
Infection/Sepsis	1	1	11	11.0	10	10	106	10.6	11	11	117	10.6
Neutropenia	1	1	5	5.0	2	2	19	9.5	3	3	24	8.0
Stomatitis	1	1	32	32.0	11	11	129	11.7	12	12	161	13.4
Vomiting	1	1	4	4.0	1	1	5	5.0	2	2	9	4.5

Report breakdown of countries when get other Twelves reference.

Whyte et al.[16] (2011)[247] developed a cost effectiveness model of the use of G-CSF for the prophylaxis of febrile neutropenia in breast cancer. One off investigations were costed at £47.86 [£55.39] with additional daily investigations of £9.27 [£10.73], while the average duration of hospitalisation for febrile neutropenia was 8 (s.d. 0.2041) days.

[16] Funded by Amgen

Wolowacs et al.[17] (2008)[248] in a cost effectiveness analysis of docetaxel for early node-positive breast cancer drew a range of costs for grade III/IV adverse events from clinical opinion and the literature. Clinical opinion suggests costs per episode of stomatis of £390 [£439]. Other costs drawn from Smith et al. (2002)[211] and Twelves et al. (2001)[201] were £1,965 [£2,210] for anaemia, £2,527 [£2,842] for diarrhoea and £2,209 [£2,485] for vomiting.

Smith et al.[18] (2002)[211] undertook a cost minimisation analysis of pegylated liposomal doxorubicin for ovarian cancer, based upon data from an RCT coupled with UK unit costs. Of the European patients analysed, 49% were from the UK. Rates of grade III/IV adverse events are given in figure 1 of the paper when coupled with the data in table 3 of the paper and an assumption of the trial being randomised on a 1:1 basis between the arms suggests estimates of £1,000 for stomatitis [£1,532], £1,016 [£1,557] for diarrhoea, £600 [£920] for hand-foot syndrome, £1,100 [£1,686] for nausea/vomiting, £200 [£307] for neutropenia, £780 [£1,196] for sepsis/fever and £780 [£1,196] for anaemia/thrombocytopenia. This assumes that the same cost is applied per adverse event regardless of arm. It also places greater weight upon the arm in which more events occur in an attempt to reduce rounding errors from what are in some case quite rare events. No real details of the calculations underlying these estimates are given within the paper.

[17] Funded by Sanofi-Aventis
[18] Funded by Schering Plough

Appendix 22. Literature review of quality of life and adverse events

Summary

This literature review updates and expands the literature review of Shabaruddin et al. (2011 and 2013).[171, 206] A summary of the main results of interest to the My5-FU DAR is reported below, followed by a more detailed presentation of the results from the identified papers. Note that of the papers identified within the literature review of Shabaruddin et al, seven[19] have not been summarised here due to either repetition of previous work, insufficient detail or adverse event categories too broad to be useful for assigning utility decrements to individual adverse events. An additional ten papers identified through the update and expansion of the literature review of Shabaruddin et al are also summarised. This summary covers the main adverse events reported in the mCRC papers, coupled with the comparative BSA versus pharmacokinetic dosing papers.

[19] Franic et al (2003), Grunberg et al (2002), Hess et al (2010), Hutton et al (1996), Leung et al (1999), Ness et al (1999) and Tosh et al (2011)

Table 105. Grade I/II adverse events quality of life decrements

Paper	Bennett	Bennett	Beuerstein	Beuerstein	Beuerstein	Boyd	Havrilesky	Havrilesky	Ossa	Szabo	TA145
Year	2011	2011	2009	2009	2010	2011	2009	2009	2007	2012	2005
Country	..	..	UK	Australia	UK	UK	US	US	UK	Canada	UK
Cancer	mCRC	mCRC	aMelanoma	aMelanoma	CLL	CRC	Ovarian	Ovarian	anaemia	H&N	H&N
Qualifier	1st line	2nd line	..	..	..	..	..	..	..	..	..
N patients	656	530	..	..	..	n.r.	13	..	..	..	..
N nurses	..	..	..	..	..	..	..	..	..	..	50
N clincians	..	..	..	..	..	..	..	..	..	..	..
N public	..	..	63	77	93	..	..	37	110	106	..
TTO	..	..	TTO	TTO	..	..	TTO	TTO	TTO	..	..
SG	..	..	..	..	SG	..	..	..	..	SG	..
EQ-5D	EQ-5D	EQ-5D	..	..	..	EQ-5D	..	..	..	..	EQ-5D
Industry funded	Yes	Yes	Yes	Yes	Yes	..	..	..	Yes	Yes	Yes
Grade I/II											
diarrhoea			0.06	0.11	0.08	0.04					
nausea			0.07	0.12	0.05	0.05	0.35	0.24			0.086
vomiting			0.07	0.12	0.05	0.05	0.35	0.24			
mucositis											0.051
stomatitis			0.10	0.14			0.12	0.09			
hand-foot	0.042	0.077	0.03	0.08						0.050	
leukopenia											
fatigue						0.02					
anaemia									0.08		
neutropenia											

febrile neutropenia			0.09	0.13							
infection/sepsis											
haematological											
cardiac											
alopecia			0.03	0.03			0.10	0.16			
CLL: Chronic lymphocytic leukaemia											

Table 106. Grade III/IV adverse events quality of life decrements

Paper	Bennett	Bennett	Beuerstein	Boyd	Frederix	Frederix	Havrilesky	Havrilesky	Lloyd	Lloyd	Nafees
Year	2011	2011	2010	2011	2013	2013	2009	2009	2006	2006	2008
Country	..	..	UK	UK	Sweden	Dutch	US	US	UK	UK	UK
Cancer	mCRC	mCRC	CLL	CRC	aBreast	aBreast	Ovarian	Ovarian	mBreast	mBreast	NSCLC
Qualifier	1st line	2nd line	..	..	..	..	..	..	..	..	..
N patients	656	530	..	n.r.	..	..	13	..	..	..	..
N nurses	..	..	..	..	..	..	..	..	..	..	..
N clincians	..	..	..	..	..	..	..	..	..	..	..
N public	..	..	93	..	100	100	..	37	100	100	100
TTO	..	..	..	..	TTO	TTO	TTO	TTO	..	..	..
SG	..	..	SG	..	..	..	..	..	SG	SG*	SG
EQ-5D	EQ-5D	EQ-5D	..	EQ-5D	..	..	..	..	..	..	..
Industry funded	Yes	Yes	Yes	..	..	..	..	..	Yes	Yes	Yes
Grade III/IV											
diarrhoea				0.09	0.29	0.19			0.103	0.074	0.047
nausea				0.14			0.40	0.37			0.048
vomiting							0.40	0.37	0.103	0.074	0.048
mucositis											
stomatitis									0.151	0.113	
hand-foot	0.017	0.056			0.23	0.15			0.116	0.085	0.032
leukopenia					0.23	0.09					
thrombocytopenia											
fatigue					0.17	0.13	0.34	0.42	0.115	0.084	0.073

anaemia			0.09		0.12	0.10					
neutropenia							0.30	0.36			0.090
febrile neutropenia							0.46	0.44	0.150	0.112	0.090
infection/sepsis											
haematological											
CLL: Chronic lymphocytic leukaemia											

Table 107. Grade III/IV adverse events quality of life decrements ctd.

Paper	Ossa	Shiroiwa	Shiroiwa	Swinburn	Szabo	Tolley	Tam	TA145
Year	2007	2009	2009	2012	2012	2013	2013	2005
Country	UK	Japan	Japan	UK	Canada	UK	Canada	UK
Cancer	anaemia	mCRC	mCRC	Neuroend.	H&N	CLL	mPancreatic	H&N
Qualifier	..	..	..	..	..	..	..	..
N patients	..	..	..	..	..	..	..	..
N nurses	..	..	..	..	..	..	..	50
N clincians	..	..	..	..	..	..	60	..
N public	110	1,582	1,582	100	106	100	..	..
TTO	TTO	TTO	..	TTO	..	..	..	..
SG	..	..	SG	..	SG	TTO	..	..
EQ-5D	..	..	..	..	..	..	EQ-5D	EQ-5D
Industry funded	Yes	..	..	Yes	Yes	Yes	..	Yes
Grade III/IV								
diarrhoea		0.054	0.056	0.171			0.212	
nausea		0.090	0.090	0.061	0.100		0.194	0.551
vomiting		0.090	0.090	0.061	0.100		0.194	

mucositis					0.100			0.597
stomatitis		0.055	0.034		0.100		0.441	
hand-foot		0.084	0.084	0.188	0.120		0.311	0.433
leukopenia								
thrombocytopenia				0.081		0.108		
fatigue		0.027	0.046				0.473	
anaemia	0.38				0.060			
neutropenia						0.163		
febrile neutropenia		0.082	0.042				0.131	
infection/sepsis						0.195		
haematological					0.070			0.558

CLL: Chronic lymphocytic leukaemia

Methods and results of individual papers

Bennett et al[20] (2011)[249] analysed EQ-5D data from a panitumumab mCRC trial among the wild –type KRAS subset. EQ-5D data from 576 of 656 1st line patients and from 530 of 597 2nd line patients was analysed, and was valued using the UK social tariff. Around 95% of 1st line patients and of 2nd line patients were of ECOG performance score 0-1. The mean baseline quality of life for 1st line patients was 0.778 (0.247, n=284) in the panitumumab + FOLFOX4 arm and 0.756 (0.244, n=292) in the FOLFOX arm. The mean baseline quality of life for 2nd line patients was 0.769 (0.230, n=263) in the panitumab + FOLFIRI arm and 0.762 (0.252, n=267) in the FOLFIRI am. In a further analysis the quality of life decrements associated with grade II and grade III+ skin toxicities were estimated for 1st line and for 2nd line patients. These estimates do not appear to have controlled for the impact of other comorbidities, which if correlated with skin toxicities could bias the analysis.

Table 108. Bennett et al. (2011)[249] patient EQ-5D QoL decrements for mCRC skin toxicity

	1st line patients		2nd line patients	
Grade II	0.042	(-0.012, 0.095)	0.077	(0.014, 0.140)
Grade III+	0.017	(-0.038, 0.071)	0.056	(-0.003, 0.116)

Best et al. (2010)[190] surveyed 49 CRC patients and 49 members of the US general public using TTO, to elicit quality of life values for stage III CRC and the quality of life decrements associated with mild, moderate and severe neuropathy. The raw TTO mean scores were reported, alongside mean scores adjusted for education and current health for a typical 60 year old.

Table 109. Best et al. (2010)[190] US patient and public TTO QoL for mCRC

	Patients				Public			
	Raw	Adjusted	Adj. decrement		Raw	Adjusted	Adj. decrement	
	mean	mean	mean	s.e.m.	Raw	Adjusted	mean	s.e.m.
Remission	0.87	0.83			0.83	0.82		
Adjuvant, no AE	0.67	0.61	-0.221	0.063	0.62	0.60	-0.223	0.054
with mild neuropathy	0.65	0.61	-0.224	0.075	0.52	0.51	-0.310	0.060
with mod neuropathy	0.55	0.53	-0.309	0.075	0.48	0.46	-0.362	0.056
with sev. neuropathy	0.48	0.48	-0.352	0.073	0.35	0.34	-0.475	0.060
Metastatic, stable	0.46	0.40	-0.433	0.076	0.54	0.51	-0.305	0.055
Metastatic, progressive	0.38	0.37	-0.464	0.074	0.21	0.21	-0.607	0.058

[20] Supported by Amgen

Beuerstein et al[21] (2009)[250] surveyed 63 members of the UK general public and 77 members of the Australian general public using the standard gamble to elicit quality of life values for advanced melanoma and the side effects of treatment. Health state vignettes were developed using the NCI CTCAE definitions.

Table 110. Beuerstein et al (2009)[250] UK and Aus. public SG QoL for advanced melanoma

	All		Australia		UK	
	Mean	s.e.	Mean	s.e.	Mean	s.e.
Clinical response states						
Partial response	0.88	0.01	0.91	0.01	0.85	0.02
Stable disease	0.80	0.01	0.83	0.01	0.77	0.02
Progressive disease	0.52	0.02	0.47	0.03	0.59	0.02
Best supportive care	0.52	0.02	0.46	0.03	0.59	0.02
Utility decrement for grade I/II AEs						
Hair loss	-0.03	0.01	-0.03	0.01	-0.03	0.01
Skin reaction	-0.06	0.01	-0.08	0.01	-0.03	0.01
Diarrhoea	-0.09	0.01	-0.11	0.01	-0.06	0.01
Nausea/vomiting	-0.10	0.01	-0.12	0.01	-0.07	0.01
Flu-like syndrome	-0.11	0.01	-0.13	0.01	-0.09	0.01
Stomatitis	-0.13	0.01	-0.14	0.01	-0.10	0.02
Symptomatic melanoma	-0.16	0.01	-0.20	0.02	-0.11	0.02
Utility decrements for grade III/IV AEs						
Day case/ OP for grade III/IV AE	-0.13	0.01	-0.14	0.01	-0.11	0.02
2-5 day IP for grade III/IV AE	-0.17	0.01	-0.20	0.02	-0.13	0.02

Beuerstein et al.[22] (2010)[251] surveyed 93 members of the UK general public using the standard gamble to elicit quality of life values for chronic lymphocytic leukaemia. 4 respondents were excluded due to illogical responses. Within the health state vignettes, the adverse event elements were added to the base health state of "*No change*".

[21] Funded by Bristol-Myers Squibb
[22] Funded by Napp Pharmaceuticals

Table 111. Beuerstein et al. (2010)[251] UK public SG QoL for chronic lymphocytic leukaemia

			95% CI		Decrement	
	Mean	s.d.	Lower	Upper	Mean	s.d.
Complete Response	0.91	0.11	0.88	0.93	..	..
Partial Response	0.84	0.14	0.81	0.87	..	..
No Change	0.78	0.14	0.75	0.82	..	..
and Nausea grade I/II	0.73	0.17	0.69	0.76	-0.05	0.02
and Nausea/Vomiting grade I/II	0.73	0.16	0.69	0.76	-0.05	0.02
Second-line Treatment	0.71	0.17	0.68	0.75	..	..
and Diarrhea grade I/II	0.70	0.19	0.66	0.74	-0.08	0.02
and Anaemia grade III/IV	0.69	0.18	0.65	0.72	-0.09	0.02
Progressive Disease	0.68	0.20	0.64	0.72	..	..
and Pyrexia grade III/IV	0.67	0.17	0.63	0.70	-0.11	0.02
Third-line Treatment	0.65	0.22	0.60	0.69	..	..
and Pneumonia grade III/IV	0.58	0.19	0.54	0.62	-0.20	0.02

Boyd et al. (2011)[197] report interim results from an analysis of the MRC SCOT trial of patients with fully resected stage III colorectal cancer or full resected high risk stage II disease. Limited data is presented but the quality of life impact of a number of grade I/II and grade III/IV adverse events measured by the EQ-5D is summarised as below. This seems likely to have used the UK social tariff. No measures of uncertainty around the central estimates were presented.

Table 112. Boyd et al. (2011)[197] UK patient EQ-5D QoL for stage II and stage III colorectal cancer

	Grade I/II	Grade III/IV
Diarrhoea	-0.04	-0.09
Fatigue	-0.02	
Nausea	-0.05	-0.14
Neuropathy sensory	-0.02	-0.19
Vomiting	-0.05	

Brown et al[23] (2001)[252] surveyed 30 UK oncology nurses using the standard gamble for a cost effectiveness study of docetaxel for advanced breast cancer. No further details are provided in the paper.

[23] Funded by Aventis

Table 113. Brown et al. (2001)[252] UK nurse SG QoL for advanced breast cancer

	Mean	s.d.	Decr.
Start of second-line therapy	0.64	0.15	
Partial/complete response	0.84	0.12	
with peripheral neuropathy	0.62	0.16	0.22
with severe oedema	0.78	0.15	0.06
with severe skin condition	0.56	..	0.28
Stable disease	0.62	0.22	
Progressive disease	0.33	0.24	
Terminal disease	0.13	0.12	
Infection without hospitalisation	0.48	..	
Febrile neutropenia and hospitalised	0.24	0.12	

Frederix et al. (2013)[198] recruited 100 members of the Swedish and 100 members of the Dutch general public for a TTO study. Within their results the authors noted the differences between the Swedish and Dutch responses, but for reasons that are unclear the age profiles of the two samples which were noticeably different: Swedish respondents were typically over 50 while Dutch respondents were typically under 50 and very much younger. All Swedish respondents were female, while only 50% of Dutch respondents were female. Health state vignettes for HER2+ advanced breast cancer were developed for stable disease and for progressive disease, and for a range of grade III/IV adverse events. Frederix et al. (2013)[198] are not explicit about the health state vignettes, and in particular whether adverse events are in conjunction with stable disease or with progressive disease. In the light of the values reported, to calculate the decrements associated with the adverse events it has been assumed that adverse events are in conjunction with stable disease.

Table 114. Frederix et al (2013)[198] Swedish and Dutch public TTO QoL for advanced breast cancer

	Swedish (n=100)			Dutch (n=100)		
	Mean	(s.d.)	Dec.	Mean	(s.d.)	Dec.
Stable disease	0.81	(0.23)		0.69	(0.25)	
Diarrhea	0.52	(0.31)	0.29	0.50	(0.25)	0.19
Fatigue	0.64	(0.30)	0.17	0.56	(0.27)	0.13
Anemia	0.69	(0.29)	0.12	0.59	(0.26)	0.10
Leukopenia	0.58	(0.31)	0.23	0.60	(0.26)	0.09
Anorexia	0.56	(0.30)	0.25	0.66	(0.24)	0.03
Skin rash	0.58	(0.31)	0.23	0.54	(0.27)	0.15
Decrease in LVEF	0.54	(0.29)	0.27	0.47	(0.25)	0.22

Progressive disease	0.61	(0.34)	0.20	0.49	(0.31)	0.20
LVEF: left ventricular ejection fraction						

Grunberg et al (2009)[253] surveyed 96 US patients receiving chemotherapy for either breast cancer or lung cancer, using the standard gamble. Six health states were constructed: perfect health; no nausea or vomiting per cycle; limited vomiting of 3 episodes per cycle; limited nausea of 3 days of nausea per cycle; limited nausea and vomiting of 3 days of nausea and 3 episodes of vomiting per cycle; and, continuous nausea and vomiting. Perfect health was anchored at 1.00, with the mean for continuous nausea and vomiting being rated at zero. The intermediate health states varied 0.59 for no nausea and vomiting to 0.51 for limited nausea.

Havrilesky et al. (2009)[254] surveyed 13 ovarian cancer patients and 37 female members of the US general public to estimate quality of life values for ovarian cancer. Health state vignettes based upon the NCI CTCAE were drawn up, and subsequently amended by a focus group of clinicians. The paper reports a range of quality of life values for ovarian cancer states. It then separately reports a range of quality of life values for adverse events, graphing these against perfect health. While unclear from the text, in the light of the values reported it appears that the adverse events may have been in effect added to the state of perfect health. The decrements reported below for the individual adverse events are calculated on this basis.

Table 115. Havrilesky et al. (2009)[254] US patient and public TTO QoL values for ovarian cancer states

	Mean	SD
Ovarian cancer-clinical remission	0.83	0.25
Early ovarian cancer—newly diagnosed	0.81	0.26
Newly diagnosed ovarian cancer—chemotherapy/grades I/II toxicity	0.60	0.31
Recurrent ovarian cancer—responding to chemotherapy/grades III/IV toxicity	0.61	0.24
Recurrent ovarian cancer—responding to chemotherapy/grades I/II toxicity	0.50	0.34
Advanced ovarian cancer—newly diagnosed	0.55	0.29
Newly diagnosed ovarian cancer—chemotherapy/grades III/IV toxicity	0.49	0.36
Recurrent ovarian cancer—progressive/grades III/IV toxicity	0.47	0.34
Recurrent ovarian cancer—progressive/grades I/II toxicity	0.40	0.33
End stage ovarian cancer	0.16	0.25

Table 116. Havrilesky et al. (2009)[254] US patient and public TTO QoL values for ovarian cancer AEs

	Patients				Public			
	n	Mean	SD	Decr.	n	Mean	SD	Decr.
Alopecia—grade II	12	0.90	0.15	0.10	14	0.84	0.29	0.16
Peripheral neuropathy—grades I/II	13	0.95	0.04	0.05	15	0.81	0.29	0.19
Stomatitis—grade II	13	0.88	0.14	0.12	14	0.91	0.08	0.09
Myalgia/pain—grades I/II	13	0.86	0.15	0.14	15	0.89	0.12	0.11
Nausea/vomiting—grades I/II	12	0.65	0.38	0.35	15	0.76	0.28	0.24
Myalgia/pain—grades III/IV	13	0.72	0.30	0.28	15	0.46	0.39	0.54
Neutropenia—grade IV	13	0.70	0.30	0.30	16	0.64	0.36	0.36
Peripheral neuropathy—grades III/IV	13	0.73	0.27	0.27	14	0.65	0.31	0.35
Nausea/vomiting—grades III/IV	13	0.60	0.40	0.40	16	0.63	0.30	0.37
Fatigue grades III/IV	13	0.66	0.35	0.34	13	0.58	0.33	0.42
Febrile neutropenia	13	0.54	0.33	0.46	15	0.56	0.34	0.44

Jewell et al. (2013)[255] in a US study recruited 15 cervical cancer survivors and 45 women without a cancer diagnosis and undertook a TTO exercise to estimate the quality of life living with a range of grade III/IV adverse events. Health state vignettes were developed using the NCI CTCAE, which were subsequently reviewed by clinical experts. Unfortunately, Jewell et al. (2013)[255] did not estimate a utility for a baseline health state to which the adverse events were added to, meaning that utility decrements associated with the adverse events cannot be identified.

Table 117. Jewell et al (2013)[255] US TTO patient and public QoL for gynaecological cancer

	All			Patients			Volunteers		
	Mean	Med.	SD	n	Mean	Med.	n	Mean	Med.
Infection	0.92	1.00	0.18	13	0.86	0.93	23	0.96	1.00
Pyleonephritis	0.87	1.00	0.25	13	0.91	1.00	24	0.85	1.00
Thrombosis	0.87	0.97	0.25	13	0.87	0.97	24	0.87	0.97
Vaginal stenosis	0.86	0.97	0.23	13	0.88	0.90	24	0.84	0.97
Neutropenia	0.86	0.97	0.26	13	0.83	0.87	24	0.88	1.00
Lymphedema	0.84	0.95	0.26	13	0.88	0.93	23	0.81	0.97
Bladder dysfunction	0.83	0.93	0.28	13	0.86	0.93	23	0.81	0.93
Radiation cystitis	0.86	0.93	0.21	13	0.80	0.90	24	0.69	0.85
Anaemia	0.83	0.93	0.28	13	0.84	0.93	24	0.83	0.97
Genitourinary fistula	0.76	0.90	0.31	13	0.84	0.90	24	0.72	0.89
Bowel obstruction	0.79	0.89	0.29	13	0.77	0.83	23	0.80	0.93
Hydroureter	0.75	0.87	0.30	13	0.76	0.87	24	0.75	0.87

Radiation proctitis	0.72	0.87	0.32	13	0.80	0.90	24	0.69	0.85
Genital-intestinal fistula	0.66	0.83	0.31	13	0.75	0.87	24	0.61	0.67

Kuchuk et al[24] (2013)[256] in a Canadian study used the standard gamble among 102 women with breast cancer who were undergoing chemotherapy. Health state vignettes for the adverse events were based upon the CTC grading criteria and patients' own descriptions. Of the 102 women, only 69 responses were analysed due to a variety of problems such as illogical responses with the others. Unfortunately, as with Jewell et al, Kuchuk et al did not estimate a utility for a baseline health state to which the adverse events were added to, meaning that utility decrements associated with the adverse events cannot be identified. However, the additional decrement associated with a grade III/IV event compared to a grade I/II event can be calculated.

Table 118. Kuchuk et al. (2013)[256] Canadian SG QoL for breast cancer adverse events

	Grade I/II		Grade III/IV	
	Mean	s.d.	Mean	s.d.
Diarrhoea	0.760	0.168	0.677	0.221
Hand-foot	0.754	0.167	0.700	0.189
Mucositis/stomatis	0.747	0.179	0.739	0.179
Nausea	0.730	0.130	0.621	0.222
Neuropathy (sensory)	0.725	0.189	0.694	0.191
Neuropathy (motor)	0.715	0.145	0.725	0.151
Fatigue	0.719	0.214	0.717	0.181
Myalgia	0.715	0.145	0.704	0.138
Alopecia	0.716	0.225		

Lloyd et al[25] (2006)[196] surveyed 100 members of the UK general public using the standard gamble to estimate quality of life values for metastatic breast cancer health states and grade III/IV adverse events. Health state vignettes were developed through a rapid literature review coupled with expert opinion. The mean values were reported, together with the coefficients of a mixed model analysis. All coefficients were significant with the exception of the intercept. Note that there is not an immediate read across from the TTO utilities and decrements and the mixed model coefficients because utilities from the mixed model are derived according to exp(sum_coefs)/(1+ exp(sum_coefs)).

[24] Funded by Eisia Pharmaceuticals
[25] Funded by Eli Lilly

Table 119. Lloyd et al. (2008)[257] UK public SG QoL for metastatic breast cancer and grade III/IV AEs

	Mean	Mixed model	
	TTO	Coef	s.e.
Intercept	..	0.0089	0.3196
Age	..	0.0239	0.0069
Stable disease with no toxicity	0.715	..	
Treatment response	+0.075	0.4063	0.0552
Disease progression	-0.272	-1.1477	0.1031
Febrile neutropenia	-0.15	-0.6603	0.0850
Diarrhoea and vomiting	-0.103	-0.4629	0.0993
Hand-foot syndrome	-0.116	-0.5184	0.0993
Stomatitis	-0.151	-0.6634	0.0993
Fatigue	-0.115	-0.5142	0.0993
Hair loss	-0.114	-0.5086	0.0993

Lloyd et al.[26] (2008)[257] surveyed 26 oncology patients and 83 members of the UK general public using the TTO to derive quality of life values for different severities of anaemia. Slightly unusually, anaemia was defined by haemoglobin levels with seven different haemoglobin bands being evaluated. Trial data was used to map between the haemoglobin bands and FACT-An responses. The FACT-An responses that showed little difference between haemoglobin bands were discarded. The tables of the paper report the "95% CI" but include only one value for this. As a consequence, it is unclear quite what this is: the s.d. or 1.96*s.d.

Table 120. Lloyd et al. (2008)[257] UK patient and public TTO QoL for anaemia

	Public		Pats	
Haemoglobin	Mean	"95%CI"	Mean	"95%CI"
7.0–8.0 g/dL	0.583	0.067	0.297	0.127
8.0–9.0 g/dL	0.608	0.064	0.360	0.126
9.0–10.0 g/dL	0.640	0.060	0.408	0.125
10.0–10.5 g/dL	0.642	0.062	0.446	0.122
10.5–11.0 g/dL	0.661	0.061	0.454	0.111
11.0–12.0g/dL	0.703	0.056	0.545	0.105
12.0+ g/dL	0.708	0.057	0.611	0.112

[26] Funded by OrthoBiotec

Nafees et al.[27] (2008)[258] surveyed 100 members of the UK general public using the standard gamble to estimate quality of life values for metastatic NSCLC and grade III/IV adverse event. Health state vignettes were developed through a rapid literature review coupled with expert opinion. The resulting utilities were analysed using a fixed effect repeated measure model, resulting in the following coefficients.

Table 121. Nafees et al. (2008)[258] UK public SG QoL for NSCLC and grade III/IV AEs

	Coef	s.e.m.
Intercept (stable disease)	0.65320	0.02223
Progressive	-0.17980	0.02169
Response	0.01930	0.00656
Neutropenia	-0.08973	0.01543
Febrile Neutropenia	-0.09002	0.01633
Fatigue	-0.07346	0.01849
Nausea & vomiting	-0.04802	0.01618
Diarrhoea	-0.04680	0.01553
Hair loss	-0.04495	0.01482
Rash	-0.03248	0.01171

Nguyen et al. (2010)[259] surveyed 24 members of the US general public using the standard gamble to estimate quality of life values for testicular cancer. The development of the health state vignettes used for this is not described in the paper, and it is unclear what severity of adverse events was involved. As a consequence, the resulting utility values are of questionable value for health economic modelling.

Table 122. Nguyen et al. (2010)[259] US public SG QoL for testicular cancer

	Mean	s.e.m.
Untreated cancer	0.92	0.03
Peripheral neuropathy	0.94	0.02
Ototoxicity	0.96	0.02
Cardiovascular disease	0.91	0.02
Secondary malignant neoplasm	0.77	0.05
Small bowel obstruction	0.94	0.02
Infertility	0.98	0.01

[27] Funded by Eli Lilly

Ossa et al.[28] (2007)[260] surveyed 110 members of the UK general public using the TTO to estimate the quality of life impact of chemotherapy induced anaemia, within the context of a cost effectiveness analysis of recombinant erythropoietin. Health states vignettes for no, mild, moderate and severe chemotherapy induced anaemia were developed, based upon the elements of the FACT-An questionnaire supplemented with information from the general literature. Three oncologists and six cancer patients subsequently reviewed the vignettes. Results were derived from 106 respondents.

Table 123. Ossa et al. (2007)[260] UK public TTO QoL for anaemia

	Mean	s.e.m.	Decr.
No anaemia	0.86	0.014	
Mild anaemia	0.78	0.016	0.08
Moderate anaemia	0.61	0.020	0.25
Severe anaemia	0.48	0.020	0.38

Shih et al. (2012)[261] applied the standard gamble among 20 Singaporean oncology nurses with a minimum of two years' experience to estimates the quality of life among breast cancer patients undergoing hormonal therapies.

Table 124. Shih et al. (2012)[261] Singapore nurse SG QoL values for breast cancer

	Mean	Decr.	Median
No recurrence and no side effect	0.678	..	0.775
with hip fracture	0.504	0.174	0.475
with wrist fracture	0.533	0.145	0.500
with spine fracture	0.458	0.220	0.463
with vaginal bleeding	0.554	0.124	0.500
with deep vein thrombosis	0.515	0.163	0.475
with pulmonary embolism	0.463	0.215	0.475
with cataract	0.519	0.159	0.475
with ischemic cerebrovascular events	0.408	0.270	0.425
with common side effects—musculoskeletal disorder	0.510	0.168	0.500
with common side effects—hot flushes	0.588	0.090	0.550
with endometrial cancer	0.501	0.177	0.475
New contralateral breast cancer	0.443	..	0.425
Locoregional recurrence and no side effects	0.473	..	0.438
with side effects—general	0.438	0.035	0.425
Distant recurrence and no side effects	0.470	..	0.450

[28] Funded by Roche

with side effects—chemotherapy	0.458	0.012	0.413
with side effects—hormonal therapy	0.445	0.025	0.413

Shiroiwa et al. (2009)[193] surveyed 1,582 members of the Japanese general public using both the TTO and the standard gamble to estimate the quality of life associated with mCRC and grade III/IV events. The development of health state vignettes was based upon the literature, expert opinion and the NCI CTCAE. Respondents were recruited through a large on-line panel of the Japanese public, with respondents also completing the questionnaire on-line. Statistical analysis computed the mean utility decrements associated with: receiving FOLFOX compared to receiving XELOX, experiencing an adverse event compared to not experiencing an adverse event and receiving chemotherapy compared to having completed chemotherapy. The mean estimates coupled with their 95% confidence limits are presented below.

Table 125. Shiroiwa et al. (2009)[193] Japanese public TTO and SG for mCRC and grade III/IV events

	SG			TTO		
	Mean	CI low	CI high	Mean	CI low	CI high
Analysis 1						
Chemotherapy	0.0535	0.0087	0.0983	0.0636	0.0187	0.1084
Stoma	0.0926	0.0484	0.1369	0.1099	0.0655	0.1543
Analysis 2						
Febrile neutropenia	0.0424	0.0008	0.0841	0.0816	0.0425	0.1208
Nausea/vomiting	0.0898	0.0479	0.1316	0.0898	0.0505	0.1292
Diarrhoea	0.0558	0.0134	0.0981	0.0538	0.0139	0.0936
Hand-foot syndrome	0.0841	0.0423	0.1258	0.0839	0.0446	0.1231
Fatigue	0.0464	0.0047	0.0882	0.0269	-0.0124	0.0662
Peripheral neuropathy	0.0345	-0.0080	0.0770	0.0257	-0.0143	0.0656
Stomatitis	0.0341	-0.0078	0.0760	0.0552	0.0157	0.0946
Stoma	0.0463	0.0255	0.0671	0.0404	0.0209	0.0600
Analysis 3						
Chemotherapy	0.0603	0.0121	0.1085	0.0661	0.0175	0.1146
Stoma	0.2063	0.1581	0.2545	0.1281	0.0795	0.1767

Swinburn et al.[29] (2012)[200] used TTO among 100 members of the UK general public to estimate quality of life values for health states associated with neuroendocrine tumours. Health state vignettes were developed based upon the literature, clinician and patient interviews and five pilot interviews to

[29] Funded by Novartis

check the appropriateness of the descriptions. The text is ambiguous and it may be that only diarrhoea was explicitly at grade III/IV, but it seems likely that all adverse events were grade III/IV.

Table 126. Swinburn et al. (2012)[200] UK public TTO QoL for neuroendocrine tumours

	Mean	s.d.	95% CI		Decr.
Stable no AE	0.771	0.20	0.731	0.810	
with diarrhoea	0.600	0.25	0.546	0.645	0.171
with hand-foot syndrome	0.583	0.23	0.538	0.627	0.188
with hyperglycaemia	0.781	0.19	0.743	0.818	-0.010
with nausea/vomiting	0.710	0.21	0.668	0.752	0.061
with pneumontis	0.612	0.26	0.561	0.662	0.159
with rash	0.623	0.23	0.578	0.668	0.148
with stomatis	0.557	0.24	0.509	0.604	0.214
with thrombicytopenia	0.690	0.24	0.643	0.737	0.081
Progressive	0.612	0.24	0.564	0.659	

Szabo et al.[30] (2012)[262] in a Canadian study applied the standard gamble among 106 members of the Canadian general public to estimate quality of life values for head and neck cancer. Health state vignettes were drawn up based upon a literature search, supplemented by EORTEC of a phase III trial. 101 responses were used for the statistical analysis. This undertook a mixed regression analysis with random intercepts to allow for individuals contributing multiple responses.

Table 127. Szabo et al. (2012)[262] Canadian public SG QoL regression for head and neck cancer

	Coef	s.e.m
Intercept	0.610	0.070
Age	0.000	0.001
Sex		
Male	..	
Female	-0.080	0.043
Stage		
Locoregional	..	
Metastatic	-0.110	0.013
Recurrent	-0.050	0.013
Type		
Nonlaryngeal	..	
Laryngeal	0.000	0.009
Post-progression	-0.280	0.013

[30] Funded by Bristol-Myers Squibb

Skin reactions Grade I/II	-0.050	0.021
Grade III/IV adverse events		
Haematological	-0.070	0.021
Anaemia	-0.060	0.021
Nausea/vomiting	-0.100	0.021
Mucositis/somatitis	-0.100	0.021
Peripheral neuropathy	-0.090	0.021
Anorexia/weight loss	-0.090	0.021
Skin reactions	-0.120	0.021
Hospitalisation due to toxicity	-0.160	0.021
Treatment cessation due to toxicity	-0.060	0.021

Tolley et al.[31] (2013)[199] apply the TTO among 100 members of the UK general public to elicit quality of life values for late stage chronic lymphocytic leukaemia. A range of health state vignettes were developed using the literature and expert clinical opinion, the aim being to reflect an average patient of 70 years of age. Adverse event descriptions were guided the NCI CTCAE criteria. An anchor state representative of a patient that has received two prior lines of therapy and is about to start another was developed: night sweats, being very tired all the time, weight loss and loss of appetite, swollen glands, chest infections and sore throat, and can walk short distances. From the health state vignettes it appears that the adverse events were grade III/IV, though this is not unambiguous for neutropenia.

Table 128. Tolley et al. (2013)[199] UK public TTO QoL for late stage chronic lymphocytic leukaemia

	TTO	s.d.	95% CI	Decr.
Anchor state	0.549	(0.231)	0.506, 0.592	..
PFS responder	0.671	0.236)*	0.627, 0.715	..
with AE: thrombocytopenia	0.563	(0.108)	0.516, 0.610	-0.108
with AE: neutropenia, no infection	0.508	0.163)*	0.464, 0.551	-0.163
with AE: severe infection	0.476	0.195)*	0.432, 0.519	-0.195
PFS non-responder	0.394	0.219)*	0.353, 0.435	..
with AE: severe infection	0.333	0.061)*	0.294, 0.372	-0.061
Disease progression	0.214	(0.18)*	0.180, 0.247	..
* p<5% for difference with anchor state				

Tam et al. (2013)[263] in a cost effectiveness study of therapies for metastatic pancreatic cancer surveyed 60 Canadian oncologists using the EQ-5D. Health state vignettes were developed for a hypothetical 60 year old man with metastatic pancreatic cancer. The quality of life values were

[31] Funded by GlaxoSmithKline

derived from the 33 respondents, though the mapping used for estimating these from the EQ-5D data is not clear. From the health state descriptors is appears that the adverse event health states are broadly supplemental to the stable disease health state.

Table 129. Tam et al. (2013)[263] Canadian clinical EQ-5D QoL for metastatic pancreatic cancer

	Mean	s.d.	Decr.
Stable disease	0.720	0.185	
Stable disease with grade III/IV			
nausea and vomiting	0.526	0.235	0.194
diarrhoea	0.508	0.207	0.212
stomatitis	0.279	0.231	0.441
febrile neutropenia	0.589	0.171	0.131
fatigue	0.247	0.239	0.473
rash	0.626	0.166	0.094
hand-foot syndrome	0.409	0.210	0.311
neuropathy	0.494	0.177	0.226
Supportive care	0.136	0.184	0.584

While not peer reviewed and officially published the manufacturer submission for TA145:[214] cetuximab for locally advanced squamous head and neck cancer included a utility elicitation study commissioned from M-TAG Ltd. A literature search identified the main adverse events associated with head and neck cancer. Seven health states based upon the NCI CTCAE were developed and rates using the EQ-5D by 50 UK oncology nurses of a minimum of 2 years' experience.

Table 130. TA145 (2005)[214] UK nurse QoL for head and neck cancer

	Mean	s.d.	Decr.
On treatment, range of AEs <= 1	0.659	0.131	
plus mucositis grade III/IV	0.062	0.299	0.597
plus mucositis grade II	0.608	0.310	0.051
plus nausea grade III/IV	0.108	0.350	0.551
plus nausea grade II	0.573	0.247	0.086
plus acne/rash grade III/IV	0.226	0.404	0.433
plus haematological grade IV	0.101	0.392	0.558
Post treatment peripheral neuropathy	0.473	0.266	
Post treatment ototoxicity	0.657	0.239	
Post treatment loco regional control	0.862	0.019	
Post treatment progressive disease[1]	0.129	0.266	